Interaction between HIV-1 and HCV infections: towards a new entity?

Maria Winnock¹*, Dominique Salmon-Céron², François Dabis¹ and Geneviève Chêne¹

¹INSERM U593, Université Victor Ségalen, 146 rue Léo Saignat, 33076 Bordeaux; ²Department of Internal Medicine, Hôpital Cochin, Paris, France

Since human immunodeficiency virus (HIV) and hepatitis C virus (HCV) share the same modes of transmission, HIV–HCV co-infected patients are relatively common. Until recently, the clinical course of HCV in co-infected patients was overshadowed by the high morbidity and mortality of HIV disease. Recent reductions in morbidity and mortality among HIV-infected patients due to the advent of highly active antiretroviral therapy (HAART), have contributed to the emergence of HCV as a significant viral pathogen in this population. This article reviews the current evidence on the epidemiology and clinical implications of an interaction between HIV-1 and HCV infections.

Keywords: prevalence, epidemiology, fibrosis, liver, HAART

Introduction

A computer-based literature review was undertaken using Medline (PubMed, Pascal, Excerpta Medica) as the primary database. The specific subject heading keywords used for the search strategy were HIV infection (MeSH major topic) and HCV (MeSH terms). Abstracts were systematically reviewed from 2000 to the present and relevant papers were searched manually. Additional references were identified from review articles, from the reference list of articles identified by the Medline search, and by a systematic review of Current Contents (Clinical Medicine and Life Sciences), using ‘Hepatitis’ as keyword.

Epidemiology and transmission

Approximately 40 million people have been infected with human immunodeficiency virus (HIV) worldwide. Hepatitis C virus (HCV) infects an estimated 3% of the world population and represents a viral pandemic that is four to five times more prevalent than HIV infection. In the United States and Europe, 13–43% of HIV-infected persons are also infected with HCV with up to 85% being chronically infected as indicated by the presence of HCV RNA (Table 1).

The prevalence of HIV–HCV co-infection varies markedly depending on the route of HIV infection, being higher among injection drug users and haemophiliacs, compared with homosexual men (Table 2).

The predominant recognized co-infection route is by parenteral exposure to blood. The two groups with the highest risk of acquiring HCV have been blood transfusion recipients and intravenous drug users (IVDU), but their relative importance has changed over the last two decades. Before 1990, blood transfusions accounted for a substantial proportion of HCV transmissions.

Since the advent of routine screening of blood donations, prevalence rates of positive test results for HIV and HCV have declined significantly. In 2002, in the American Red Cross blood donor population, estimates of residual risk in donations among repeat donors, after testing with nucleic acid amplification technology, were reported to be 1 per 1 935 000 and 1 per 2 135 000 for HCV and HIV, respectively.

The implementation of this sensitive technique in Europe will also reduce the residual risk of contaminated blood and blood products as a source of HIV and HCV infections.

Currently, most newly acquired cases of hepatitis C (68%) are related to injecting drug use. Contamination in health workers frequently exposed to blood as well as nosocomial and iatrogenic exposure account altogether for about 5% and a source is not identified in about 10% of cases.

Although both HIV and HCV share the same routes of transmission, the relative efficiency of transmission of these two viruses varies. HCV is approximately 10 times more infectious than HIV by percutaneous blood exposure to small volumes of blood, being transmitted by 15–30 of every 1000 accidental needle-stick injuries, compared with 3 per 1000 for HIV. In contrast, HIV is more transmissible than HCV between heterosexual partners and from a mother to her infant.

The prevalence of anti-HCV antibodies among female sexual partners of HCV-positive men is 3%, whereas the anti-HIV prevalence among female sexual partners of HIV-positive men is four times greater. HIV co-infection in an individual with hepatitis C seems to increase the likelihood of sexual transmission of HCV. Indeed, anti-HCV positivity was observed in 18.7% of subjects who had a steady partner with anti-HIV-positive test results, as opposed to only 1.6% of subjects who had partners presenting only HCV viraemia.
perinatal HIV vertical transmission. Also, the synergic effect of duration of development to end-stage liver disease is very long. The co-infection has been associated with a two- to four-fold increase in mothers. In contrast, the rate of mother-to-infant transmission in women, HIV was transmitted to 20% of infants born to HIV-infected mothers. The interval between infection and the development of cirrhosis can assess due to the lack of early symptoms and by the fact that the fibrosis) and hepatocellular carcinoma.

Infection with HCV can be self-limiting (spontaneous clearance of viraemia), can persist without causing clinical disease (asymptomatic healthy carrier), or can lead to cirrhosis (severe stage of liver fibrosis) and hepatocellular carcinoma.

The natural history of HCV infection has been very difficult to assess due to the lack of early symptoms and by the fact that the duration of development to end-stage liver disease is very long. The interval between infection and the development of cirrhosis can exceed 30 years. In immunocompetent patients, it can be considered that acute infection progresses to chronic infection, as indicated by the presence of HCV RNA in the blood beyond 6 months, in 80% of cases. Among these, up to 20% may develop cirrhosis within 20–30 years, and these patients will further develop hepatocellular carcinoma at an annual rate of 1–4%. Among cirrhotic patients, 6% can be expected to develop hepatic decompensation, and 3–4% can be expected to die or require liver transplantation.

HIV infection appears to adversely affect each stage in the natural history of HCV infection. In a recent study on HCV and HIV dynamics in co-infected subjects, the estimated HIV virion half-life was longer in the latter group, which suggests that co-infection may contribute to a slower clearance of HCV. In haemophilic patients, HCV clearance occurs in only 2–9% of HIV-infected persons. Among cirrhotic patients, 6% can be expected to develop hepatic decompensation, and 3–4% can be expected to die or require liver transplantation.

HIV infection appears to adversely affect each stage in the natural history of HCV infection. In a recent study on HCV and HIV dynamics in co-infected subjects, the estimated HIV virion half-life was longer in the latter group, which suggests that co-infection may contribute to a slower clearance of HCV. In haemophilic patients, HCV clearance occurs in only 2–9% of HIV-infected persons. Among cirrhotic patients, 6% can be expected to develop hepatic decompensation, and 3–4% can be expected to die or require liver transplantation.

Before the administration of antiretroviral therapy to HIV-infected women, HIV was transmitted to 20% of infants born to HIV-infected mothers. In contrast, the rate of mother-to-infant transmission in women with sole HCV viraemia is 4–7%. Maternal HCV infection has been associated with increased perinatal HIV vertical transmission. Also, the synergic effect of co-infection has been associated with a two- to four-fold increase in the rate of HCV transmission to infants of HIV-infected mothers. Indeed, a recent meta-analysis including 10 studies and a total of 2382 infants born to HCV-infected mothers, with and without concomitant HIV infection, showed that HIV co-infection was associated with a 2.8-fold (95% CI: 1.78–4.45) increase in the risk for HCV vertical transmission. Interestingly, in a large cohort report in which HCV-infected mothers were on antiretroviral therapy during pregnancy, the rate of HCV transmission (5%) was not affected by the HIV status of the mother.

### Impact of HIV on HCV

#### Natural history of HCV

Infection with HCV can be self-limiting (spontaneous clearance of viraemia), can persist without causing clinical disease (asymptomatic healthy carrier), or can lead to cirrhosis (severe stage of liver fibrosis) and hepatocellular carcinoma.

The natural history of HCV infection has been very difficult to assess due to the lack of early symptoms and by the fact that the duration of development to end-stage liver disease is very long. The interval between infection and the development of cirrhosis can exceed 30 years. In immunocompetent patients, it can be considered that acute infection progresses to chronic infection, as indicated by the presence of HCV RNA in the blood beyond 6 months, in 80% of cases. Among these, up to 20% may develop cirrhosis within 20–30 years, and these patients will further develop hepatocellular carcinoma at an annual rate of 1–4%. Among cirrhotic patients, 6% can be expected to develop hepatic decompensation, and 3–4% can be expected to die or require liver transplantation.

### Table 1. Prevalence of HCV antibodies in HIV-infected patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Study population</th>
<th>Reference</th>
<th>No. of HIV+ patients</th>
<th>HCV Ab+(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>France</td>
<td>AQUITAINE cohort</td>
<td>1</td>
<td>1935</td>
<td>43</td>
</tr>
<tr>
<td>1999</td>
<td>USA</td>
<td>HAVACS cohort</td>
<td>2</td>
<td>350</td>
<td>33</td>
</tr>
<tr>
<td>2000</td>
<td>Netherlands</td>
<td>University clinic</td>
<td>3</td>
<td>394</td>
<td>14</td>
</tr>
<tr>
<td>2000</td>
<td>Greece</td>
<td>Academic AIDS unit</td>
<td>4</td>
<td>181</td>
<td>14</td>
</tr>
<tr>
<td>2000</td>
<td>Swiss</td>
<td>Swiss HIV cohort</td>
<td>5</td>
<td>3111</td>
<td>37</td>
</tr>
<tr>
<td>2002</td>
<td>USA</td>
<td>US Adult Clinical Trials group (subcohort)</td>
<td>6</td>
<td>213</td>
<td>16</td>
</tr>
<tr>
<td>2003</td>
<td>USA</td>
<td>Cook County Hospital Chicago, IL</td>
<td>7</td>
<td>510</td>
<td>40</td>
</tr>
<tr>
<td>2003</td>
<td>USA</td>
<td>Veterans Aging three-site cohort</td>
<td>8</td>
<td>881</td>
<td>43</td>
</tr>
<tr>
<td>2003</td>
<td>France</td>
<td>French hospitals (one-day survey)</td>
<td>9</td>
<td>1813</td>
<td>28</td>
</tr>
<tr>
<td>2003</td>
<td>USA</td>
<td>Terry Beirn CPCRA</td>
<td>10</td>
<td>2705</td>
<td>17</td>
</tr>
</tbody>
</table>

*CPCRA, Community programs for clinical research on AIDS.

### Table 2. Prevalence of HIV–HCV co-infection as a function of the route of HIV infection

<table>
<thead>
<tr>
<th>Patients</th>
<th>References</th>
<th>Percentage with antibodies to HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVDUs</td>
<td>9,12–18</td>
<td>53–99</td>
</tr>
<tr>
<td>Homosexual men</td>
<td>13,15,16</td>
<td>3–14</td>
</tr>
<tr>
<td>Haemophiliacs</td>
<td>19,20</td>
<td>98</td>
</tr>
<tr>
<td>All patients</td>
<td>1–10</td>
<td>13–43</td>
</tr>
</tbody>
</table>

When HAART is initiated in patients co-infected with HIV and HCV, it could be hypothesized that HCV levels would immediately decrease due to improved immune response. However, the effect of HAART on serum HCV load remains controversial. Most studies have shown no change in HCV RNA titres following HAART, although some studies have a transient or sustained increase in HCV load; yet others have shown a decrease in HCV RNA levels and in some cases even HCV clearance. Discrepancies among the studies could stem from the fact that other factors, such as natural fluctuations over time, severity of liver dysfunction, HIV plasma viraemia levels, CD4 T lymphocyte count, HCV genotype, and the patient’s alcohol consumption have not always been taken into consideration.
HAART therapy has also been reported to reduce intrahepatic HCV load. The impact of protease inhibitors on liver HCV load was investigated in patients who had been treated with protease inhibitors for at least 6 months at the time of the liver biopsy, and compared with that of a group of patients who had never received any PI treatment or had withdrawn for at least 6 months before the liver biopsy. Interestingly, patients under PI therapy had a three- to four-fold lower intrahepatic HCV load than that observed in the other group. No difference was observed in the plasma HCV load between both groups.

Studies on liver fibrosis have compellingly shown that co-infection with HIV worsens the histological course of HCV infection by increasing and accelerating the risk of cirrhosis.

In a cross-sectional study, after 10 years of HCV infection, 15% of HIV-positive patients developed cirrhosis compared with only 3% in the HIV-negative group. The mean time from estimated onset of HCV infection to cirrhosis was significantly longer in HIV-negative (23 years) than HIV-positive patients (7 years). In a longitudinal observation, the 20-year rate of cirrhosis was 37% and 10% in HIV-positive and HIV-negative patients, respectively. This higher rate of cirrhosis and shorter evolution could be explained by a significantly increased rate of the yearly progression of the fibrosis. Indeed, the median fibrosis progression rate of HCV–HIV co-infected patients and patients infected only by HCV is 0.153 and 0.106 fibrosis units per year, respectively. At this rate of fibrosis progression, the median duration from HCV infection to cirrhosis is 26 years in HIV-infected patients and 38 years in non-HIV-infected patients. These results have been confirmed by others, and it was further shown that the observed fibrosis progression in patients for whom paired liver biopsies were available, was even more rapid, with a median of only 14 years from infection to cirrhosis.

In HCV mono-infected patients, the major factors known to be associated with an increased risk of progression to cirrhosis are male gender, older age at HCV infection, and excessive alcohol consumption; viral load and genotype do not seem to influence significantly the progression rate.

Although it is well established that progression of liver fibrosis is accelerated in co-infected patients, factors associated with a more severe progression of liver fibrosis have not yet been well defined in these patients (Table 3). The impact of gender on the course of chronic hepatitis C seems not to be significant in co-infected patients. As in HCV mono-infected patients, older age at HCV infection was significantly associated with severe fibrosis progression; whereas the increased risk of alcohol consumption for cirrhosis was only found in some studies, but not in others.

In the Hepatitis/HIV Spanish Study Group, patients with HCV infection by genotype 1 had a higher histological score, reflecting a higher stage of liver damage; however, other reports failed to confirm the association between HCV genotype and severe liver damage. An independent effect of HCV load on severe liver fibrosis was reported, suggesting that the degree of liver injury could be related to the level of HCV replication, but this was not confirmed by the European Collaborative Study.

As far as HIV-related variables are concerned, an immunodepressed state, expressed by a low CD4 cell count, is systematically associated with severe fibrosis. It has been suggested that chronic use of antiretroviral therapy containing protease inhibitors, together with reduction in alcohol consumption and maintenance of high CD4 count could have a beneficial impact on liver fibrosis progression in HIV–HCV co-infected patients. However, HAART benefit on liver fibrosis was not supported by others.

In HCV mono-infected cirrhotic patients, liver cancer develops after a long period of chronic infection; thus, the age at diagnosis commonly ranges from 65 to 75 years. García-Samaniego et al. analysed the clinical outcome of a small group of HIV-infected individuals diagnosed with HCV-related hepatocellular carcinoma and compared it to that of a control group, matched for age, sex, duration of HCV infection and alcohol consumption. An unusually rapid development of hepatocellular carcinoma in HIV-infected patients was observed in this study, with an age of diagnosis, for 45% of the patients, under the age of 40. In a more recent study, the mean time between exposure to HCV and the development of hepatocellular carcinoma was reported to be about 10 years.

In haemophiliacs, the risk of mortality for liver diseases, including liver cancer, has also been shown to be higher in HIV-infected patients. The risk of death in the 25 years since first exposure to HCV was 6.5% (95% CI, 4.5–9.5) for HIV-1-infected patients, compared to 1.2% (95% CI, 0.7–3.0) for uninfected patients. In 2000, one-fourth of deaths registered among intravenous drug users in the Aquitaine cohort and in the French national survey ‘Mortalité 2000’ were HCV-related. Mortality and morbidity were compared among 263 patients with HIV alone and 166 patients with HCV co-infection. Liver decompensation developed in 100% of patients with co-infection, whereas no liver related deaths or decompensation occurred in patients without co-infection. In a meta-analysis of four published studies that examined the endpoint of decompensated liver disease, the combined adjusted relative risk in co-infected patients, compared to HCV mono-infected patients, is 6.14 (95% CI, 2.86–13.20).

Besides the increase in HCV replication, a faster progression of liver disease, and a higher risk of mortality due to liver disease, HIV infection has also been associated with HCV antibody loss.

In HIV-infected patients, serological assays may fail to detect the presence of HCV antibodies despite active replication of HCV. Loss of reactivity to HCV antigens has also been describing in other forms of immunosuppression such as transplant recipients or patients on chronic haemodialysis.

Bonacini et al. reported that 5.5% of 110 HIV–HCV co-infected, HCV-antibody negative persons were HCV RNA positive in their sera using a commercially available HCV RNA assay (2.0). The median CD4 count of the antibody negative group was significantly lower than that of the HCV antibody-positive group, suggesting that a failure to mount an antibody response was due to immune deficiency. However, when the third-generation assay for anti-HCV testing was used in a large cohort of injection drug users, 97.8% of the 559 HIV-infected participants were anti-HCV positive. Of the remaining 12 anti-HCV-negative subjects, HCV RNA was detected in only one subject, who had recently acquired HCV infection and was undergoing HCV seroconversion. Also, HCV seroreversion is observed more frequently in HIV–co-infected subjects compared to HCV mono-infected patients.

Mechanisms that could explain the accelerated progression of hepatitis C in HIV–positive patients are currently only poorly understood.

The decline of cell-mediated immunity associated with HIV infection could allow greater replication of HCV. In turn, a quantitative increase in HCV viraemia may explain the higher frequency of cirrhosis among HIV-infected patients. However there is no clear correlation between the level of viraemia and the severity of liver disease. HIV infection could contribute to liver injury through...
Table 3. Studies relating the impact of HIV on HCV-induced liver fibrosis

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Reference</th>
<th>Country</th>
<th>Study design</th>
<th>Size (HIV+/HIV–)</th>
<th>Factors associated with severe liver fibrosis in co-infected subjects</th>
<th>Covariates&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benhamou et al., 1999</td>
<td>77</td>
<td>France</td>
<td>retrospective</td>
<td>122/122</td>
<td>Alcohol consumption (&gt;50 g/day), age at HCV infection (&gt;25 years), CD4 cell count (&lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;).</td>
<td>Gender.</td>
</tr>
<tr>
<td>Benhamou et al., 2001</td>
<td>83</td>
<td>France</td>
<td>retrospective</td>
<td>182/–</td>
<td>Absence of PI therapy, alcohol consumption (&gt;50 g/day), CD4 cell count (&lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;) at liver biopsy, age at HCV contamination (&gt;20 years).</td>
<td>Gender, route of HCV infection (IDU versus transfusion), HIV viral load, treatment with NRTI.</td>
</tr>
<tr>
<td>Di Martino et al., 2001</td>
<td>50</td>
<td>France</td>
<td>retrospective</td>
<td>80/80</td>
<td>Age at HCV infection, no interferon therapy, CD4 cell count (&lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;) during follow-up.</td>
<td>HIV coinfection, gender, baseline and continued alcohol consumption (&gt;80 g/day), first Knodell score, end of treatment biochemical response and sustained biochemical response to interferon therapy.</td>
</tr>
<tr>
<td>Martinez-Sierra et al., 2003</td>
<td>54</td>
<td>Spain</td>
<td>cross-sectional</td>
<td>41/147</td>
<td>Age at HCV infection (&gt;20 years), HCV load (&gt;2 × 10&lt;sup&gt;6&lt;/sup&gt; copies/mL), CD4 count (&lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;) at diagnosis of HIV infection.</td>
<td>Gender.</td>
</tr>
<tr>
<td>Moihsen et al., 2003</td>
<td>79</td>
<td>Great Britain</td>
<td>retrospective</td>
<td>55/153</td>
<td>CD4 count at liver biopsy (&lt;200 cells/mm&lt;sup&gt;3&lt;/sup&gt;).</td>
<td>Gender, age at HCV infection (&gt;22 years), duration of HCV (&gt;15 years), alcohol consumption (&gt;20 units/week), route of HCV transmission (IDU versus transfusion), ALAT (&lt;80 IU/L); HCV genotype (1 versus other); HIV load at liver biopsy (&gt;400 copies/mL); antiretroviral treatment (never versus ever).</td>
</tr>
<tr>
<td>Poynard et al., 2003</td>
<td>80</td>
<td>France</td>
<td>retrospective</td>
<td>180/2313</td>
<td>Alcohol consumption (&gt;50 g/day), activity grade (A2–A3).</td>
<td>Gender.</td>
</tr>
<tr>
<td>Martin-Carbonero et al., 2004</td>
<td>81</td>
<td>European Collaborative Study</td>
<td>retrospective</td>
<td>914/–</td>
<td>Age at time of biopsy (&gt;35 years), alcohol consumption (&gt;50 g/day for ≥12 months), CD4 cell count (&lt;500 cells/mm&lt;sup&gt;3&lt;/sup&gt;).</td>
<td>Gender, antiretroviral therapy (HAART versus no treatment), transmission route of HCV transmission (IDU versus other), HCV infection (&gt;15 years), age at time of HCV exposure (&gt;20 years), HCV genotype (1 versus other), plasma HCV RNA load (&gt;8 000 000 IU/mL).</td>
</tr>
</tbody>
</table>

IDU, injection drug user; NIA, necroinflammatory activity; ALAT, alanine aminotransferase.

<sup>a</sup>In univariate or multivariate analyses.

<sup>b</sup>For all patients.
immune or direct viral effects. Mechanisms that are important for tissue damage could be modified in immunocompromised patients, such as the local pattern of cytokine production, expression of adhesion molecules or release of fibrogenic factors.\textsuperscript{95} HIV co-infection has been shown to importantly alter the HCV-specific cytokine response towards a greater production of proinflammatory type 1 cytokines.\textsuperscript{96} Moreover, HIV infection itself may exert a direct cytopathic effect on liver cells independently of other cofactors\textsuperscript{97} since HIV-1 infects not only peripheral blood CD4 cells, but also specialized intrahepatic immune cells such as Kupffer cells, intrahepatic mononuclear cells and hepatocytes.\textsuperscript{98}

**Impact of HCV on HIV**

Hepatitis C may adversely affect HIV infection by accelerating the natural history of infection, or by influencing the response and tolerability to HAART.

**Progression of HIV disease**

Although most studies agree that HIV has a deleterious effect on HIV disease, available data on the impact of HCV infection on HIV progression are not clear. Seven studies are summarized in Table 4.

Before the widespread availability of HAART, co-infection with HCV had been shown to confer an increased risk for progression to AIDS in HIV-infected individuals;\textsuperscript{99,100} however, other studies have failed to demonstrate this increased risk or an adverse effect on survival.\textsuperscript{2,101,102} More recently, in a large Swiss cohort study of 3111 HIV-positive patients starting antiretroviral therapy, Greub et al.\textsuperscript{5} reported that the probability of progression to a new AIDS-defining clinical event or to death was independently associated with HCV seropositivity (hazard ratio 1.7; 95% CI 1.26–2.30), and that HCV seropositivity was also associated with a 21% reduction in the likelihood of increasing the CD4 count by at least 50 CD4 cells/mm\textsuperscript{3}. Also, Daar et al. showed that, after controlling for CD4 cell count and HIV-1 RNA level, HCV RNA was associated with a relative risk for clinical progression to AIDS of 1.66 (95% CI 1.10–2.51) and a relative risk for AIDS-related mortality of 1.54 (95% CI 1.03–2.30). Similar results were reported by De Luca et al.\textsuperscript{103} Conversely, in a study from an urban cohort from the USA, there was no evidence that HCV infection substantially altered the risk of dying, developing AIDS, or responding immunologically to HAART.\textsuperscript{104} Klein et al., in a retrospective cohort study, showed that HCV-positive subjects remained at increased risk for death and hospitalization in the post-HAART era, even after additional adjustment for antiretroviral use and time-updated CD4 cell count and viral measures.\textsuperscript{105}

Two further studies reported that HCV co-infection in HIV patients is not statistically associated with survival.\textsuperscript{106,107}

Furthermore, other studies found that HCV may also impair immune reconstitution after effective anti-HIV therapy.\textsuperscript{5,103} The CD4 cell count increase was significantly smaller in persons with HCV infection than in those without HCV infection. However, three subsequent studies\textsuperscript{99,104,108} evaluating the immunological response to HAART in co-infected subjects found that HCV co-infection did not seem to antagonize the CD4 cell response to HAART.

### Table 4. Studies relating the impact of HCV on HIV progression

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Reference</th>
<th>Country</th>
<th>Study design</th>
<th>Size (HCV+/HCV–)</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al., 1994</td>
<td>102</td>
<td>USA</td>
<td>retrospective longitudinal</td>
<td>74/438</td>
<td>84 months</td>
<td>death</td>
</tr>
<tr>
<td>Dorrucchi et al., 1995</td>
<td>101</td>
<td>Italy</td>
<td>retrospective longitudinal</td>
<td>214/202</td>
<td>30 months</td>
<td>death</td>
</tr>
<tr>
<td>Piroth et al., 1998</td>
<td>99</td>
<td>France</td>
<td>retrospective</td>
<td>119/119</td>
<td>3 years</td>
<td>clinical progression to AIDS</td>
</tr>
<tr>
<td>Lesens et al., 1999</td>
<td>100</td>
<td>Canada</td>
<td>prospective</td>
<td>22/59</td>
<td>17 years</td>
<td>AIDS or death</td>
</tr>
<tr>
<td>Staples et al., 1999</td>
<td>2</td>
<td>USA</td>
<td>retrospective</td>
<td>115/235</td>
<td>141 months</td>
<td>AIDS</td>
</tr>
<tr>
<td>Greub et al., 2000</td>
<td>5</td>
<td>Switzerland</td>
<td>prospective</td>
<td>1157/1068</td>
<td>28 months</td>
<td>AIDS or death</td>
</tr>
<tr>
<td>Daar et al., 2001</td>
<td>39</td>
<td>USA</td>
<td>prospective</td>
<td>207/–</td>
<td>7 years</td>
<td>clinical progression to AIDS</td>
</tr>
<tr>
<td>De Luca et al., 2002</td>
<td>103</td>
<td>Italy</td>
<td>prospective</td>
<td>600/720</td>
<td>37 months</td>
<td>AIDS-related mortality</td>
</tr>
<tr>
<td>Sulkowski et al., 2002</td>
<td>104</td>
<td>USA</td>
<td>prospective</td>
<td>873/1082</td>
<td>70 months</td>
<td>clinical progression to AIDS</td>
</tr>
<tr>
<td>Klein et al., 2003</td>
<td>105</td>
<td>Canada</td>
<td>retrospective</td>
<td>Pre HAART: 42/620</td>
<td>19 months</td>
<td>opportunistic infection death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post-HAART: 83/456</td>
<td>18 months</td>
<td>opportunistic infection hospitalization</td>
</tr>
</tbody>
</table>

*Subgroup with well-controlled HIV-1 viral replication.*
Although HCV may not directly affect the natural history of HIV, its management in co-infected patients may be altered. The Johns Hopkins Cohort Study found that co-infected patients, most of whom were intravenous drug addicts, were less likely to be prescribed antiretroviral therapy, possibly as a consequence of a reduced compliance with anti-HIV therapy in these patients.

Tolerability of HAART

Because the current antiretroviral agents that are available will not eradicate HIV, the goal of therapy is to inhibit HIV replication so that the patient can attain and maintain effective immune responses to most potential microbial pathogens. Three classes of antiretroviral agents are currently combined for the treatment of HIV infection: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). With combination antiretroviral therapy, hepatotoxicity has emerged as an important potential complication.109

NRTI hepatotoxicity has been linked to an increased risk of mitochondrial toxicity due to inhibition of DNA polymerases, in particular DNA polymerase γ, which is the only enzyme responsible for the replication of mitochondrial DNA.110 This inhibition leads to mitochondrial dysfunction with subsequent adverse events ranging from hepatotoxicity and hepatic steatosis to lactic acidosis. Mitochondrial toxicity has been described as occurring at any time in patients receiving NRTIs, whereas lactic acidosis has been described in association with zidovudine, didanosine and stavudine.111-113

The most common mechanisms of toxicity attributed to NNRTIs are hypersensitivity reactions that usually occur early on during the course of treatment as well as later-onset toxicity. These reactions can be observed with all NNRTIs, but are more prominent with nevirapine.114 Clinical features (fever, skin rash, eosinophilia) suggest an immune cytokine-mediated hypersensitivity response, but the triggering mechanisms are at present unknown.115 Although an increase in serum transaminases has been associated with NNRTI use,116 the causal relationship between NNRTI therapy and hepatotoxicity is still unclear.117

Hepatotoxicity associated with PIs is well established.118 All currently available PIs are metabolized in the liver by cytochrome P-450 enzymes,119 and it seems likely that hepatic impairment (hepatitis C, alcohol abuse) may affect their metabolism. PIs can alter the pharmacokinetics of other drugs by acting as P-450 inhibitors or hepatic enzyme inducers,119 thus contributing to hepatotoxicity by increasing plasma concentrations of other drugs. These drug–drug interactions have been beneficially used in PI combination therapy for boosting and maintaining PI plasma concentrations.120

Cohort studies have evaluated the occurrence of hepatotoxicity in patients during antiretroviral therapy.3,116,121-129 In these studies, reported incidence values of liver enzyme elevations vary from 1% to 27%. Co-infection with hepatitis B or C has been consistently identified as the most significant risk factor for the development of significant liver enzyme elevations following HAART. For example, in the Aquitaine Cohort, hepatitis C co-infection was associated with a relative risk for the occurrence of transaminase elevations among HAART-treated patients of 3.2 (95% CI 1.7–6.2); other predictors of hepatotoxicity were baseline transaminase levels and a history of prior severe liver damage.121 The association of hepatitis C coinfection and hepatotoxicity among HAART-treated patients has been largely confirmed, regardless of medication taken.

An explanation of the increased susceptibility to HAART-associated liver toxicity in patients with pre-existing liver disease is a decreased clearance of antiretroviral drugs. Indeed, increased or even toxic drug concentrations have been reported in cirrhotic patients receiving standard doses of PIs or NNRTIs.109 A direct correlation was found between alanine aminotransferase elevation and increase in CD4 cell count in patients with severe hepatotoxicity.130 Increases in transaminases have been interpreted as a reflection of an immune reconstitution syndrome rather than a hepatotoxic effect of antiretroviral therapy.90,130 The increase in cytotoxic CD8 cell counts observed after HAART63,64 and resulting from immune reactivation, would lead to immune destruction of HCV-infected hepatocytes. Further research is necessary to determine the exact mechanisms involved.

HCV treatment in HIV-infected patients

The goal of HCV treatment is to eradicate the virus or at least slow down the progression of hepatic disease in individuals in whom viral eradication is not possible. In HCV-mono-infected patients, combination therapy with pegylated interferon-α (PEG-IFN-α) and ribavirin, a nucleoside analogue, is currently the standard treatment for persistent HCV infection. Pegylated forms of interferon result in improved pharmacokinetics and pharmacodynamics of the drug, allowing a more efficient suppression of virus activity compared to standard interferon. Two forms of PEG-IFN-α have been developed (alfa-2a and alfa-2b), which differ as to physicochemical structure and properties; but, in spite of these differences, the efficacy of both drugs is quite similar.131 The duration of therapy is decided according to HCV genotype. Patients with genotype 2 or 3 should be treated for 24 weeks, whereas those with genotype 1 and, possibly 4, should be treated for 48 weeks.

Manns et al.132 showed that, in naive HCV-mono-infected patients, an optimal dosing due to body weight adaptation (PEG-IFN alfa-2b 1.5 mg/kg + ribavirin > 10.6 mg/kg) results in an overall sustained response rate of 54%, defined as the absence of HCV RNA in peripheral blood 6 months after termination of therapy, with 42% for patients with genotype 1 and 82% for patients with genotype 2/3. In non-responders, in whom viral eradication is not achieved, interferon therapy improves survival of chronic hepatitis C patients by inhibiting development of hepatocellular carcinoma and preventing liver-related deaths.133,134

As the combination of PEG-IFN with ribavirin gives favourable results in patients with chronic hepatitis C, this therapy seems to be an option for co-infected patients in whom HIV infection is controlled with HAART. Available data from prospective studies on HIV-infected patients, show that, in these patients, sustained virological response (SVR), defined as no detectable serum HCV RNA at week 72 of follow-up, is approximately half the response of that observed in HCV-mono-infected patients.138,139 Indeed, recent data on the final results of Ribavine, a randomized, multicentre trial on 412 co-infected patients, comparing the safety, efficacy and tolerability of a 48 week course of standard interferon (alfa-2b, 3 MIU three times a week) to those of PEG-IFN (alfa-2b, 1.5 µg/kg, once a week), both combined with ribavirin (800 mg/day), have shown that an SVR is achieved in 26% of patients treated with PEG-IFN, compared with 18% of patients treated with standard interferon.137 Two further randomized trials, comparing the efficacy of PEG-IFN (alfa-2a, 180 µg weekly) versus interferon (alfa-2a, 6 MIU three times weekly for 12 weeks followed by 3 MIU three times a week for 36 weeks) and ribavirin (600 to 1000 mg/day)138 and a three-arm international trial on 868 patients comparing 48 weeks of treatment with interferon (alfa-2a 3 MIU three times weekly) plus ribavirin (800 mg/day), PEG-IFN
(alfa-2a, 180 µg weekly) plus placebo or Peg-IFN (alfa-2a, 180 µg weekly) plus ribavirin (800 mg/day) shows that an SVR was obtained in 27% and 40% of co-infected patients, respectively. As in HCV mono-infected patients, SVR varies with HCV genotype, being low in genotype 1 or 4 (11–29%) and higher in genotype 3 or others (43–73%) and lack of virological response, or failure to achieve at least a 2 log10 HCV RNA reduction at week 12 are highly predictive of failure to attain a sustained virological response.

Information on the safety and efficacy of combination therapy in co-infected patients is still scarce. An in vitro antagonism has been reported between ribavirin and NRTIs. Indeed, in vitro, ribavirin induces a decrease in the phosphorylation of zidovudine and stavudine. This is a consequence of an increased production of deoxothymidine triphosphate which, by a feedback mechanism, induces a decrease in the thymidine kinase activity. However, a recent randomized trial studying virological and intracellular interactions between stavudine and ribavirin provided evidence that the concomitant use of ribavirin and NRTIs does not induce major changes in the plasma HIV RNA level in the short term as a consequence of a decrease in intracellular concentrations of the active form of the drug in HIV–HCV co-infected patients treated with stavudine as a part of their antiretroviral treatment. On the other hand, data obtained from 68 HIV-infected patients with chronic hepatitis C showed indeed that the treatment with Peg-IFN and ribavirin is relatively well-tolerated in HIV–HCV co-infected patients, new side-effects, including pancreatitis and severe weight loss, may result from the interaction of ribavirin with an antiretroviral drug. Overall, in recent clinical trials, treatment discontinuation occurred in 12–40% of patients.

As far as the proper sequence of HIV and HCV therapies is concerned, an international panel of experts has recently advocated that, when possible, treatment against HCV must precede treatment against HIV since HCV is widely regarded as an opportunistic infection in HIV-infected individuals, the risk of hepatotoxicity is higher in co-infected patients than in HIV mono-infected patients, and HCV may impair the immune reconstitution during HAART. Treatment should be provided to patients with repeated elevated alanine aminotransferase levels, CD4 cell counts greater than 350 cells/mm3, relatively low plasma HIV–RNA levels, no active consumption of illegal drugs or high alcohol intake, and no previous severe neuropsychiatric conditions. The benefit of extending therapy to more than 6 months for HCV genotype 2 or 3, or more than 12 months for genotype 1 or 4 has yet to be examined in clinical trials.

Conclusion
Increasingly, HIV–HCV co-infection is being recognized as a separate entity from HIV or HCV mono-infections. Further research is still needed in order to better understand how the natural history of each virus is modified by the presence of the other, and determine the exact mechanisms of liver toxicity in order to maximize the effectiveness of current therapeutic regimens in co-infected patients.

References
Review


137. Perronne, C., Carrat, F., Bani-Sadr, F. et al. (2004). Final results of ANRS-HC02-RIBAVIC: a randomized controlled trial of pegylated-


