

# HIV and hepatitis C virus co-infection

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THE LANCET  
Infectious Diseases

Since the decline in HIV-related morbidity and mortality after introduction of highly active antiretroviral therapy (HAART) in 1996, liver disease caused by chronic infection with hepatitis C virus (HCV) has become an increasingly important cause of morbidity and mortality among HIV-infected patients infected parenterally with HCV in more developed countries. A third of HIV-infected individuals in Europe and the USA have HCV co-infection. HIV accelerates HCV liver disease especially when HIV-associated immunodeficiency progresses. With the introduction of pegylated interferon in combination with ribavirin, greatly improved treatment options for patients with HIV and HCV co-infection have become available and have led to sustained virological response rates of up to 40%. Furthermore, recent cohort analyses have shown that immune reconstitution induced by HAART can improve the course of hepatitis C leading to a decline in liver-related mortality. However, patients with HCV co-infection are at increased risk of hepatotoxicity from HAART. Owing to the high rates of HIV and HCV co-infection worldwide, new improved treatment strategies and guidelines for the management of co-infection remain a major future goal.

*Lancet Infect Dis* 2004; 4: 437–44

Morbidity and mortality from infection with hepatitis C virus (HCV) in HIV-positive patients are increasing and have become a major challenge in the management of such patients. In some studies 12% of deaths of patients with HIV infection were due to liver disease, but others have found that end-stage liver disease underlies more than 45% of in-hospital deaths in HIV-infected individuals in more developed countries.<sup>1–5</sup> Owing to shared routes of transmission, an estimated 30% of HIV-positive individuals are co-infected with HCV in the USA and Europe.<sup>6,7</sup>

There is no doubt that HIV accelerates HCV-related liver disease, especially when immunodeficiency progresses.<sup>8,9</sup> Studies on the influence of HCV on progression of HIV disease initially had conflicting results.<sup>10</sup> With long-term observation, however, most recent analyses suggest no negative effect of HCV co-infection on HIV infection when analysis is corrected for use of antiviral therapy.<sup>7,11</sup> Initial trials of hepatitis C treatment with interferon alone or combined with ribavirin showed significantly lower response rates in HIV-positive than in HIV-negative patients. Pegylated interferon in combination with ribavirin has become the cornerstone of therapy for chronic hepatitis C. Recent large trials in patients with HIV and HCV co-infection have shown promising overall sustained response

**Table 1. Average estimated risk of transmission**

Mode	Risk of transmission (%)		
	HIV	HCV	HCV in HIV co-infection
Perinatal	10–50	1–7	1–20
Sexual contact*	1–3	<1	<4
Needle stick injury	0–3	2–8	Unknown

\*Cumulative exposure

rates between 27% and 40%, thereby changing prognosis and guidelines for care of such patients.<sup>12–14</sup> Moreover, beneficial effects of HAART on the long-term course of HCV co-infection have been reported, suggesting that HAART helps to reverse the unfavourable course of hepatitis C in HIV-co-infected individuals.<sup>15,16</sup>

This review aims to clarify how the interactions between HIV and HCV alter results of diagnostic tests, the natural history, and the outcome of antiviral therapy. The current guidelines in practice and management of co-infection are summarised.

## Epidemiology of HIV/HCV co-infection

HIV and HCV infection are global public-health problems. At present, an estimated 40 million people are infected with HIV worldwide, and HCV infection is found in 1–3% of the population in different areas, leading to a worldwide estimate of 60–180 million HCV-infected individuals.<sup>17</sup> HCV and HIV are both transmitted by blood and blood products; HCV is ten times more infectious than HIV. Co-infection is therefore common in people with high exposure to blood. Hepatitis C is found in 60–90% of HIV-positive haemophiliacs and 50–70% of HIV-positive intravenous drug users.<sup>8,18</sup>

By contrast, sexual transmission of HCV is rare, which explains the low frequency (4–8%) of HCV co-infections in homosexual patients with HIV infection. However, small epidemics of acute hepatitis C have been reported in homosexual men from London, UK, and Berlin, Germany, which seem to be associated with a high number of sexual partners and blood-shedding sexual practices.<sup>19,20</sup>

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HCV is detected in 4–8% of infants born to HCV-infected mothers. Dual HCV/HIV infection increases the risk of transmission of both viruses, and high HCV loads in the mother increase the risk of perinatal HCV transmission.<sup>21</sup> However, in HIV/HCV-co-infected mothers receiving HAART and undergoing caesarean-section delivery, the perinatal risk of HCV transmission was less than 1%.<sup>22</sup> The average risk of transmission of HIV and HCV for various settings is summarised in table 1.<sup>23</sup>

### Diagnosis of hepatitis C in HIV-co-infected patients

The presence of HCV can be confirmed serologically through the detection of antibodies to the virus by ELISA. Loss of HCV antibodies, which can be observed in very advanced immunodeficiency in HIV/HCV co-infection, does not necessarily indicate viral clearance. Therefore, a single negative HCV-antibody ELISA does not exclude HCV infection in HIV-positive patients, especially in severe immunodeficiency.

In more than 80% of HIV-infected individuals positive for HCV antibody, HCV is detectable in the blood. Overall, higher concentrations of HCV RNA are found in HIV-seropositive individuals than in HIV-seronegative patients with hepatitis C.<sup>24,25</sup> In a study of haemophilic patients, mean concentrations of HCV RNA increased by 1 log over the first 2 years after HIV seroconversion.<sup>26</sup> The concentration increased eight times faster in HIV-positive individuals than in patients not infected with HIV. Of note, the highest concentrations have been reported in patients who subsequently developed liver failure.<sup>26</sup>

The distribution of HCV genotypes in the HIV-infected population reflects the route of transmission. Genotype 1b accounts for two-thirds of post-transfusion HCV infections and is the predominant genotype in haemophiliacs.<sup>27</sup> By contrast, genotypes 1a and 3a are more common in intravenous drug users. Overall, infections with several genotypes are rare.<sup>28</sup>

In a few studies, the presence of HCV genotype 1 was associated with more severe histopathological findings and more rapid progression to both AIDS and death than for other genotypes.<sup>29,30</sup> However, other studies in haemophiliacs or intravenous drug users with HIV/HCV co-infection did not confirm any relation between severity of chronic liver disease and HCV genotypes.<sup>31–33</sup>

### Natural course of hepatitis C in HIV infection

Hepatitis C in patients with HIV infection is characterised by accelerated progression of HCV-related liver disease. In the American Multicenter Hemophilia Cohort study, liver failure occurred in 9% of multitransfused HCV/HIV-co-infected adult haemophiliacs without an AIDS-defining opportunistic infection or malignant disease.<sup>8</sup> During the same observation period, there were no cases of liver failure among HCV-positive but HIV-negative haemophiliacs. Subsequently, several studies confirmed the unfavourable course of hepatitis C in HIV-co-infected haemophiliacs, particularly in the setting of progressive immunodeficiency and CD4+ cell counts below 100/ $\mu$ L.<sup>9</sup> In addition, the

interval between acquisition of HCV infection and development of cirrhosis was shorter in co-infected than in HIV-seronegative individuals.<sup>34,35</sup> Indeed, within 10–15 years of initial HCV infection 15–25% of HIV-co-infected patients develop cirrhosis compared with 2–6% of HIV-negative patients. Importantly, in co-infected haemophiliacs, the rate of death from advanced liver disease rose 10 years before the increase was observed in HIV-negative haemophiliacs with hepatitis C.<sup>36</sup> Moreover, various reports have highlighted the occurrence of hepatocellular carcinoma at younger ages and after shorter durations of HCV infection in HCV/HIV-co-infected individuals.<sup>37</sup> In a European study of 914 patients co-infected with HCV and HIV who underwent liver biopsy, the distribution of Metavir liver fibrosis stages was F0 in 10% of patients, F1 in 33%, F2 in 22%, F3 in 22%, and F4 in 13%, clearly showing the greater severity of liver fibrosis in this population.<sup>38</sup> The use of antiretroviral therapy (56% receiving HAART) was not associated with severity of liver fibrosis in this cross-sectional analysis.

### Effects of HCV on HIV infection

The issue of whether HCV also adversely affects progression of HIV disease is controversial. In the Swiss cohort, the presence of HCV was independently associated with an increased risk of progression to AIDS and death.<sup>10</sup> The increased risk was mainly attributable to lesser recovery of CD4+ cell counts 1 year after the start of HAART in HIV/HCV-co-infected than in HCV-negative individuals.<sup>10</sup> Subsequent studies in other cohorts, however, did not find any differences in survival when multivariate analysis was applied to correct for use of HAART, baseline viral loads, CD4+ cell counts, age, race, and risk factor for transmission of HIV.<sup>7,11</sup> The EuroSIDA cohort analysis found no difference between HCV-positive and HCV-negative HIV-infected patients responding to newly initiated HAART with a drop in HIV-RNA to less than 400 copies/mL or the time taken for CD4+ cell counts to increase by 50%.<sup>7</sup> Further follow-up data from the Swiss HIV Cohort Study suggest that recovery of CD4+ cell counts did not differ in the extended follow-up between HCV-positive and HCV-negative patients who had received potent antiretroviral therapy.<sup>39</sup> Whereas most cohort studies have found significant increases in liver-related mortality, in that study, there was only a slightly higher rate of liver-related death in the HCV-positive patients than in the HCV-negative participants. This effect was due mainly to the fact that 13 deaths were judged to be only potentially related to end-stage liver disease; only eight were judged definitely related to HCV-associated liver disease. Taken together, extended follow-up in patients with HAART suggests that there are no major differences in HIV-related mortality between HCV-co-infected individuals and patients infected with HIV alone, especially if antiretroviral treatment is given. HAART has been initiated at lower CD4+ cell counts and at later stages of HIV disease in co-infected individuals than in non-HCV-infected patients throughout all reported cohorts. Thus, there seems to be some reservation about offering HAART to HIV/HCV-co-infected patients, probably because HAART is more difficult to manage in these particular patients.

### Pathogenetic mechanisms in HIV/HCV co-infection

Interactions between viral infection and the host are poorly understood in HIV/HCV co-infection. HIV infection might exert a direct cytopathic effect on liver cells.<sup>40</sup> Although pathways of viral entry differ, both viruses can be targeted to the same host cells via binding to shared surface molecules such as DC-SIGN and DC-SIGNR, and the envelope proteins of either virus cooperatively induce hepatocyte apoptosis via an "innocent bystander" mechanism.<sup>41</sup> Moreover, HIV infection seems to facilitate HCV infection of extrahepatic cells.<sup>42</sup> Although such mechanisms might contribute to higher blood HCV viral loads and exaggerated liver damage in HIV-positive patients, most epidemiological data suggest that accelerated progression of liver disease is linked to the loss of CD4+ cells.

Recovery from acute hepatitis C seems to require elimination of HCV-infected cells by virus-specific cytotoxic CD8+ T lymphocytes, the function of which is dependent on sufficient support by virus-specific T-helper cells.<sup>43</sup> In chronic hepatitis C, immune-mediated mechanisms may still be able to control HCV infection partially, in much the same way as cellular immune responses can hold HIV infection in check for some time. Partial containment of HCV infection is likely to be lost when the number of CD4+ cells decreases, and regained when CD4+ cell counts recover. Beyond that, HIV infection might modify cytokine responses to HCV antigens<sup>44,45</sup> leading to the production of fibrogenic factors or to lower concentrations of antifibrogenic factors. Alternatively, HCV could induce secretion of cytokines, such as RANTES, that can counteract HIV infection.<sup>46</sup> Finally, there is an intriguing hypothesis that excessive hepatic HCV loads due to severe loss of CD4+ cells cause the specific type of pathological deterioration that is shown by the syndrome of fibrosing cholestatic hepatitis.<sup>47,48</sup> Although accumulating evidence suggests that HAART can delay accelerated progression of hepatitis C in HIV infection,<sup>16,49</sup> neither antiretroviral drugs nor immune restoration of CD4+ and CD8+ T cells seem to lower rates of HCV replication.<sup>50</sup> Indeed, only a few exceptional reports have described the disappearance of HCV RNA on immune restoration.<sup>50</sup> Higher blood concentrations of HCV RNA and flares of hepatitis simultaneous with restoration of immunity have been observed by several groups.<sup>51,52</sup> These observations have been attributed to substantially increased immune recognition and destruction of HCV-infected hepatocytes after recovery of the immune system. However, direct proof of this hypothesis is still lacking. One patient developed severe cirrhosis and died within 11 months when immune restoration (rise in CD4+ cell count from 10/ $\mu$ L to 150/ $\mu$ L) was achieved with HAART.<sup>53</sup> Thus, meticulous follow-up and better understanding of the underlying mechanism are needed for these patients.

### Course of hepatitis C under antiretroviral therapy

In HIV/HCV co-infected patients, antiretroviral therapy does not seem to induce significant changes in concentrations of HCV RNA during the first 6 months of treatment.<sup>50</sup> However,

a decrease of HCV RNA of about 1 log was seen in HIV/HCV-co-infected individuals receiving 12 months of HAART and having significant immune reconstitution.<sup>54</sup> Other investigators, however, did not observe this decrease in HCV RNA.<sup>55</sup> Moreover, eradication of HCV has been reported in single patients receiving HAART.<sup>56</sup>

There is some evidence that HAART-induced immune reconstitution might reverse the unfavourable accelerated course of hepatitis C in patients with severe HIV-associated immunodeficiency. In a study of 162 individuals with HIV/HCV co-infection who underwent liver biopsy, use of protease inhibitors as part of the HAART regimen was associated with significantly lower rates of progression of fibrosis that could not be explained by other cofactors.<sup>49</sup> These findings are reinforced by a recent long-term cohort analysis, which showed that HIV/HCV-co-infected individuals on HAART had significantly lower liver-related mortality than patients receiving either insufficient (one or two nucleoside reverse transcriptase inhibitors) or no antiretroviral therapy.<sup>16</sup> Overall, the available data suggest that HAART favourably affects the further course of hepatitis C in HIV/HCV-co-infected patients. These benefits seem to outweigh by far the associated risks of increased risk of hepatotoxicity. Thus, HAART should be offered to HIV/HCV-co-infected patients in accordance with the general guidelines for antiretroviral treatment in adult patients.<sup>57</sup>

Short-term and long-term virological success rates of HAART in HIV/HCV co-infection are, however, limited by an increased risk of hepatotoxicity.<sup>58</sup> Various studies have shown that the presence of HCV was independently associated with an increased risk of rises in serum aminotransferases.<sup>59-61</sup> Further studies showed that especially with the protease inhibitor ritonavir (at a dose of 600 mg twice daily) and with the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine there is an increased risk of hepatotoxicity in HIV/HCV co-infection.<sup>62,63</sup> Furthermore, nevirapine-induced liver toxicity is associated with higher nevirapine plasma concentrations and seems not to be limited to the first weeks of therapy.

The use of "d- nucleosides" (didanosine, dideoxycytidine, stavudine), especially the combination of stavudine and didanosine, leads to a higher rate of hepatic steatosis in the co-infected population.<sup>64,65</sup> Therefore, these drugs (especially the combination of stavudine and didanosine) should be avoided in HAART regimens for HIV/HCV-co-infected patients.

A growing body of evidence supports the view that hepatic steatosis has a role in the progression of hepatitis C to fibrosis. HCV proteins, particularly the core protein, can alter the double-membrane structure of mitochondria, impair hepatic oxidation, and affect mitochondrial electron transport leading to oxidative stress and lipid peroxidation.<sup>66,67</sup> Moreover, HCV core targets microsomal triglyceride transfer protein activity, thus interfering with hepatic assembly and secretion of very-low-density lipoproteins.<sup>68</sup> Obesity plays a part in steatohepatitis associated with HCV genotypes 1 and 2 but not genotype 3.<sup>69,70</sup> Several antiretroviral drugs share similar

pathways to cause hepatotoxic side-effects. Thus, infection with HCV genotype 3, extended use of nucleoside analogues, and alcohol misuse are suspected to increase the rate of steatohepatitis in HIV/HCV-co-infected patients. A recent study, however, did not prove this assumption.<sup>64</sup> Nevertheless, steatosis seems to affect the outcome of interferon therapy adversely, independently of the underlying aetiology.<sup>71</sup>

### Therapy of hepatitis C in HIV-co-infected patients

In trials on the efficacy and safety of interferon monotherapy and, later, the combination of interferon  $\alpha$  and ribavirin, response rates in HIV/HCV-co-infected individuals were poor. Overall sustained virological response rates were between 13% and 40% at 24 weeks after the end of combination treatment.<sup>72-76</sup> Moreover, rates of withdrawal owing to adverse events were as high as 29% in the HIV/HCV-co-infected population, which highlights the limitations of this treatment approach in these patients.

The introduction of pegylated interferons enabled better maintenance of effective interferon concentrations for over a week after a single injection. Effective interferon treatment can be achieved by once-weekly subcutaneous injection. The first results of trials on pegylated interferon and ribavirin in HCV-monoinfected patients have clearly shown that this treatment has better virological efficacy than the previous standard treatment, with interferon given on alternate days.<sup>77,78</sup> Hence, various trials have been initiated to study the efficacy and safety of this regimen in HIV/HCV-co-infected patients. The data obtained so far are summarised in table 2.

The best sustained treatment response rate, 40%, was achieved in the APRICOT trial,<sup>12</sup> in which the combination of pegylated interferon  $\alpha$ -2a and ribavirin or placebo was compared with interferon  $\alpha$ -2a plus ribavirin for treatment of hepatitis C in HIV-co-infected individuals. All patients were treated for 48 weeks whatever the HCV genotype. Overall, 880 patients were included, and more than two-thirds of the patients had unfavourable HCV genotypes 1 or 4. The patients were in good immunological condition with a median CD4+ cell count of more than 500 cells/ $\mu$ L. 85% of the patients were receiving HAART. 60% had HIV RNA concentrations of less than 50 copies/mL. Patients with genotype 1 HCV receiving pegylated interferon  $\alpha$ -2a plus ribavirin had a response rate at the end of treatment of 38%

and a sustained virological response rate of 29%. Much better response rates were found for HCV genotypes 2 and 3: that at the end of treatment was 64% and the sustained virological response rate was 62%. The overall low relapse rate for genotypes 2 and 3 suggests that longer treatment periods for this genotype in HIV/HCV co-infection are necessary to avoid later relapse. In pilot studies in which HIV/HCV-co-infected individuals with HCV genotypes 2 or 3 were treated for only 24 weeks, the relapse rates were almost 50%.<sup>63,68</sup> In the RIBAVIC study,<sup>13</sup> the overall virological response rates were significantly lower than those in APRICOT.<sup>13</sup> However, this difference can be explained by the much higher rates of discontinuation owing to toxic effects of regimens including stavudine and didanosine and the greater mitochondrial toxicity (lactacidosis, pancreatitis). We should emphasise here that direct comparisons between APRICOT and RIBAVIC could be misleading as a consequence of differences in study design, baseline characteristics, and approaches to management of treatment-related side-effects.

In the ACTG A5071 trial,<sup>14</sup> only 14% of patients with genotype 1 achieved a sustained virological response rate, whereas the overall rate of sustained virological response was 27%. This finding might be partly explained by the lower ribavirin doses (600 mg/day) given initially; the dose was increased to 1000 mg/day at 12 weeks.

### Therapy of acute hepatitis C in HIV-co-infected patients

Studies in patients with acute HCV monoinfection showed that early treatment with interferon alone for 6 months led to an overall sustained virological response of 98%.<sup>82</sup> Recent retrospective studies investigating the safety and efficacy of interferon alone or with ribavirin in HIV-infected patients with newly detected acute HCV infection also showed much higher sustained virological response rates (>80%) in these patients.<sup>20,21</sup> Since the evidence on this issue is limited and few patients are identified with acute hepatitis C, HIV-infected patients presenting with acute hepatitis C should be treated in prospective clinical trials.

### Ribavirin and HAART in HIV/HCV-co-infected patients

Before the use of ribavirin in patients with HCV infection or HIV/HCV co-infection, there was much concern about drug

**Table 2. Results of trials of pegylated interferon and ribavirin in HIV/HCV-coinfected patients**

Year and reference	Duration of treatment (weeks)	Type of pegylated interferon	Ribavirin dose (mg/day)	n	Virological response at end of treatment	Sustained virological response*	Withdrawals owing to adverse events
2003 <sup>9</sup>	Genotype 1: 48 Genotypes 2 and 3: 24	$\alpha$ -2b	800	68	27 (40%)	19 (28%)	10 (15%)
2003 <sup>30</sup>	Genotype 1: 48 Genotypes 2 and 3: 24	$\alpha$ -2b	800	72	33 (46%)	19 (26%)	12 (17%)
2004 <sup>13</sup>	All genotypes: 48	$\alpha$ -2b	800	205	NA	55 (27%)	77 (38%)
2004 <sup>14</sup>	All genotypes: 48	$\alpha$ -2a	600†	66	27 (41%)	18 (27%)	8 (12%)
2004 <sup>12</sup>	All genotypes: 48	$\alpha$ -2a	800	289	NA	115 (40%)	12%
2004 <sup>81</sup>	All genotypes: 48	$\alpha$ -2b	800	35	14 (40%)	11 (31%)	6 (17%)

\*Negative for HCV RNA 24 weeks after the end of treatment; †increased to 1000 mg/day at 12 weeks. NA=not available.

interactions and dose-dependent anaemia. Ribavirin is a guanosine nucleoside analogue that inhibits intracellular phosphorylation of zidovudine, stavudine, and dideoxycytidine *in vitro*.<sup>83,84</sup> Evidence from the APRICOT trial suggests that no significant inhibition of cellular phosphorylation of zidovudine or stavudine occurs with ribavirin treatment *in vivo*.<sup>85</sup> Ribavirin increases the phosphorylation of didanosine and thereby probably leads to an increased risk of pancreatitis and mitochondrial toxicity in patients receiving concomitant ribavirin and didanosine therapy.<sup>86,87</sup> In the RIBAVIC trial, there was a significantly increased frequency of mitochondrial toxicity in patients receiving ribavirin and didanosine. Therefore, this combination should be avoided. Zidovudine seems to cause severe anaemia in HIV/HCV-co-infected individuals starting anti-HCV combination treatment with ribavirin. However, erythropoietin may help to improve anaemia and allow continuation of the necessary ribavirin dose.<sup>88</sup>

#### Treatment guidelines for initiation of HCV therapy in HIV-co-infected patients

The panel (modified by two papers from Soriano and colleagues<sup>89,90</sup>) summarises the current guidelines for initiation of anti-HCV treatment in HIV-positive patients and guidelines on monitoring the response to therapy in the co-infected population.

The role of liver biopsy for decisions about treatment of hepatitis C in HIV-co-infected individuals is controversial. For those with histological information available and those infected with HCV genotypes 1 or 4, treatment can be deferred if there is no fibrosis (F0) or F1 fibrosis and the patient is willing to undergo a follow-up liver biopsy. In patients infected with HCV genotypes 2 and 3, some physicians treat without taking a biopsy because the overall response rates in this group are higher. In patients with normal concentrations of aminotransferases, liver biopsy should be done before therapy is prescribed.<sup>90</sup> All major trials of pegylated interferon and ribavirin treatment in HIV/HCV-co-infected individuals found that the week 12 time-point was an excellent prediction point for the subsequent probability of sustained virological response. Only patients showing a decline in serum HCV RNA concentrations of more than 2 logs by 12 weeks of therapy had a chance of achieving a sustained response. Therefore, treatment should be discontinued in patients who do not achieve a decline in HCV RNA of this amount within 12 weeks of therapy, because the risk of toxic effects is high and quality of life can be compromised further by anti-HCV-therapy.

The rates of side-effects of anti-HCV therapy in HIV-co-infected individuals are very high; the effects include influenza-like symptoms, haematological abnormalities, neuropsychiatric disorders, local injection reactions, thyroid dysfunction, alopecia, and allergic reactions. Rates of treatment discontinuation in various trials have ranged between 15% and 30%, and in substantial proportions of patients dose reductions of pegylated interferon or ribavirin were needed. The high dropout rates can be partly explained by the initial lack of expertise about the management of HCV-treatment-related side-effects by HIV

#### Recommendations for treatment of hepatitis C in HIV co-infection

HCV treatment should be recommended primarily on the basis of fibrosis (F1–F4) or fibrosis markers in combination with raised serum aminotransferases and positive HCV RNA results

The therapy of choice is the combination of pegylated interferon and ribavirin

Ideal candidates for anti-HCV therapy are patients with CD4-cell counts >350 cells/ $\mu$ L and plasma HIV RNA <50 000 copies/mL, with or without HAART

In patients with CD4-cell counts <350/ $\mu$ L, anti-HCV therapy should be initiated only with caution; ideally HAART should be optimised first

Patients with CD4-cell counts <100–200/ $\mu$ L should receive HAART first before an HCV-specific therapy can be initiated

The treatment duration for all HCV genotypes should be 48 weeks

Early virological response to anti-HCV therapy predicts the chance of sustained response; if there is no decrease in serum concentrations of HCV RNA of >2 log after 12 weeks, treatment can be discontinued because of low likelihood of reaching sustained response

The concomitant use of didanosine and ribavirin should be avoided

Combination of zidovudine or stavudine with ribavirin may increase toxicity; regular follow-up and laboratory safety monitoring are warranted

specialist physicians. Controlled studies suggest that the use of growth factors is helpful in overcoming some of the haematological abnormalities. This approach is especially important in patients infected with HCV genotype 1 because high enough concentrations of ribavirin can be crucial for a sustained virological response. Evidence on the use of colony-stimulating growth factors is still very limited but they should be offered in the presence of neutropenia to maintain the necessary doses of pegylated interferon. The overall decrease in absolute CD4+ cell counts during interferon plus ribavirin therapy reflects the decline in white-blood-cell counts under therapy. However, the relative percentage of CD4+ cells generally remains stable or even increases under interferon plus ribavirin combination therapy.

#### Liver transplantation in HIV/HCV co-infected patients

Before the introduction of HAART liver transplantation in HIV-infected patients was associated with unsatisfactory

**Table 3. Summary of studies on liver transplantation in HIV/HCV-coinfected patients during the HAART era**

Place of research	Year	n	Follow-up (months)	Status
Pittsburgh, USA <sup>92</sup>	1999	1	5	Alive
London, UK <sup>93</sup>	2001	5	4–34 (range)	2 alive
Pittsburgh, USA <sup>94</sup>	2001	5	18 (mean)	2 dead, 3 alive
Miami, USA <sup>95</sup>	2002	7	12.8 (mean)	1 dead, 6 alive
Miami, USA <sup>91</sup>	2002	3	12, 19, 20	All alive
Essen, Germany <sup>96</sup>	2002	5	15.6 (mean)	1 dead, 4 alive
San Francisco, USA <sup>97</sup>	2002	18	10.5 (mean)	4 dead, 14 alive
Pittsburgh, USA <sup>99</sup>	2003	23	36	5 dead, 18 alive
Barcelona, Spain <sup>98</sup>	2004	15	6 (median)	1 dead, 14 alive
Bonn, Germany <sup>100</sup>	2004	6	18 (median)	1 dead, 5 alive
France <sup>101</sup>	2004	11	18 (median)	3 dead, 8 alive

outcomes, because good function of the graft could be maintained in only a small proportion of patients, and most experienced accelerated progression of the HIV infection towards AIDS.<sup>91</sup> However, HIV-infected recipients of liver transplants seem to have much improved short-term and mid-term survival if the HIV infection was effectively controlled after liver transplantation. This change in outcome has prompted several transplantation centres to re-evaluate liver transplantation in the HAART era. Table 3 summarises the experience obtained thus far.

Although there are no consensus recommendations on organ transplantation in HIV-positive patients at present, the criteria used for liver transplantation have been similar in the various centres. In general, candidates were required to have CD4+ cell counts above 100 cells/ $\mu$ L and to have no opportunistic disease. They had to have either no detectable HIV viraemia or at least rational treatment options to control HIV infection successfully after liver transplantation. At least 20 HIV-positive patients have received a liver transplant because of end-stage liver disease due to hepatitis C. 15 are alive up to 2 years after liver transplantation. In the largest series, survival at 1 year and 3 years was similar to that for HIV-negative transplant recipients.<sup>97,99,102</sup> Despite additional immunosuppression caused by the immunosuppressive drugs, the risk of opportunistic diseases remains low in the post-transplant period, as long as HIV infection remains suppressed below detectable amounts. CD4+ cell counts remain stable or even increase with HAART. The immunosuppressive drugs ciclosporin and tacrolimus can inhibit HIV replication *in vitro*,<sup>103</sup> and mycophenolate mofetil has synergistic antiretroviral actions with abacavir, didanosine, and tenofovir.<sup>104</sup> However, the clinical benefit of such interactions remains to be shown. Hepatotoxic effects due to HAART regimens can also be observed in liver allografts, and drugs with a high potential for hepatotoxicity such as stavudine, didanosine, nevirapine, and full-dose ritonavir should be avoided in these patients after liver transplantation.

Therapeutic monitoring of immunosuppressive drugs is mandatory during treatment with antiretroviral agents. Because cytochrome P450 and p glycoprotein are inhibited, there are important pharmacokinetic interactions between antiretroviral drugs (protease inhibitors and NNRTI), and the key immunosuppressive agents ciclosporin and tacrolimus.<sup>105–107</sup> These interactions fundamentally alter pharmacokinetic profiles of calcineurin inhibitors, and the immunosuppressants have to be given in reduced doses or with longer dosing intervals when protease inhibitors, particularly ritonavir-boosted regimens, are part of the antiretroviral therapy after liver transplantation.<sup>100,105,108</sup> By contrast, NNRTI can result in lowered concentrations of immunosuppressive drugs. Such interactions have caused some episodes of acute rejection when protease inhibitors were stopped without adjustment of the doses of calcineurin inhibitors,<sup>102</sup> whereas increased concentrations of immunosuppressive drugs can favour fibrocholestatic hepatitis C

#### Search strategy and selection criteria

Data for this review were identified through searches of the complete PubMed and Medline databases up to April 30, 2004, using the search terms "HCV", "HIV", "liver disease", "HAART", and "genotype" and references from the relevant articles retrieved. Only human studies were selected and preference was given to prospective, peer-reviewed, clinical trials.

and rapid progression towards end-stage liver disease in patients who become reinfected with HCV after transplantation.<sup>109–111</sup>

Recurrence of chronic hepatitis C in the liver graft is very common in HIV-positive patients, and leads to cirrhosis within 5 years in about 20% of patients after transplantation. This rapid progression of HCV-related liver disease to end-stage disease is a major reason for the low life expectancy of HIV-infected liver recipients with hepatitis C. At present, combination anti-HCV therapy with interferon and ribavirin early after liver transplantation (1–3 months) seems to be the best management option in this situation. However, doses of anti-HCV drugs need to be modified to take into account reduced glomerular filtration rates after liver transplantation; our own preliminary data suggest that intensified and longer-term anti-HCV treatment may be needed.

#### Conclusions and future prospects

A third of HIV-infected patients in Europe and the USA have concomitant HCV infection. HIV accelerates the course of HCV-associated liver disease, so there is an urgent need for treatment strategies in this specific group of patients. The introduction of pegylated interferon and ribavirin combination therapy has greatly improved treatment options for HIV/HCV-co-infected patients, leading to sustained virological response rates of up to 40%. Newer cohort analyses also suggest that use of HAART versus no therapy leads to an overall decline in liver-related mortality. Nevertheless the proportion of patients not treatable at all or developing relapse remains high, especially in those infected with HCV genotype 1. Therefore the development of new agents with activity against HCV and treatment maintenance strategies that at least help to prevent further progression of fibrosis are eagerly awaited. In view of the high rate of HIV and HCV co-infections, the development of novel, more effective treatment strategies and guidelines for the management of HIV/HCV-co-infection remains an important future goal.

#### Acknowledgments

Jürgen Rockstroh and Ulrich Spengler were supported by the German Competence Network on HIV/AIDS (grant number 01 KI0211) and the German Competence Network on hepatitis (project number 8.1.2).

#### Conflicts of interest

Jürgen Rockstroh has received consultation or lecture fees from Abbott, Boehringer-Ingelheim, Bristol-Myers-Squibb, Gilead, GlaxoSmithKline, Roche, Schering-Plough. Ulrich Spengler has received lecture fees from Essex and Roche.

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