Haemophilia (2004), **10,** 1–8

REVIEW ARTICLE

HIV and HCV coinfection in haemophilia

J. T. WILDE
Department of Haemotology, University Hospital, Birmingham NHS Trust, Edgbaston, Birmingham, B15 2TH, UK

Summary. A substantial number of haemophilic patients are infected with both human immunodeficiency virus (HIV) and hepatitis C (HCV). HIV has been shown to accelerate the course of HCV chronic liver disease and there is evidence that HCV infection may worsen the prognosis of HIV. As many HIV infected patients are stable on highly active antiretroviral therapy (HAART) HCV should be actively managed in coinfected individuals. Pegylated interferon (Peg-IFN)/ribavirin combination therapy is the treatment of choice for HCV infection and should be considered in patients with stable HIV on or off HAART with CD4 counts >200 $\times$ 10^6/l. Results of on-going trials of combination therapy in coinfected individuals are awaited. For coinfected patients with end stage liver disease who are stable on HAART liver transplantation should be considered.

Keywords: HIV, HCV, Liver Disease, Haemophilia, HAART, Interferon

Introduction

Prior to the development of viral inactivation procedures in the mid-1980s virtually all haemophilic patients who had previously received large pool plasma-derived factor concentrates were infected with hepatitis C virus (HCV). A considerable proportion of these patients were also infected with human immunodeficiency virus (HIV). Before the introduction of highly active antiretroviral treatment (HAART) in the mid-1990s HIV was considered to be the main viral infection in coinfected patients and the importance of HCV infection was underplayed. However, as HIV infection has been so effectively controlled by HAART there has been a heightened awareness of the potentially life-threatening effects of chronic HCV infection in coinfected patients. Consequently management of HCV infection in this cohort is now actively encouraged. This paper will discuss the interactions between HIV and HCV and cover aspects concerning the management of these viruses in coinfected haemophilic patients.

Correspondence: J. T. Wilde, Department of Haemotology, University Hospital, Birmingham NHS Trust, Birmingham, UK.
Tel.: 0121 627 2353; fax: 0121 697 8497;
e-mail: jonathan.wilde@uhb.nhs.uk

Accepted after revision 29 August 2003

Interaction between HIV and HCV

Effect of HIV on HCV

It is well recognized that HIV accelerates the progression of chronic liver disease to liver failure and death in HCV-coinfected patients. HCV liver disease has become a major cause of death in HIV-infected patients stabilized on HAART [1–3]. In one large Spanish study of blood transfusion recipients and intravenous drug users 14.9% of coinfected patients had developed cirrhosis within the first 10 years of acquiring HCV infection compared with only 2.6% of HCV-monoinfected individuals [4].

Makris *et al.* reported a higher rate of progression of HCV liver disease to cirrhosis in HIV-coinfected individuals in a cohort of UK haemophilic patients [5]. This observation was confirmed in a study by Benhamou *et al.* of a larger cohort of coinfected patients [6]. In a study of haemophilic patients Eyster *et al.* reported that progression to HCV-associated liver failure was accelerated by HIV [7]. Telfer *et al.* reported that after a median time from initial exposure to factor concentrate of 15 years coinfected haemophilic patients were 21-fold more likely to develop hepatic decompensation compared with HCV-monoinfected individuals [8]. In 1997 Darby *et al.* published a retrospective study of the UK haemophilia cohort in which as of 1 January 1993

the cumulative deaths from liver disease since first HCV exposure in HIV-infected patients was fourfold that of HIV-negative individuals (6.5% vs. 1.4%, respectively) [9]. In a more recent study of 134 haemophilic patients Lesens *et al.* reported a sevenfold overall increased liver disease-related death rate in coinfected individuals compared with the HCV-monoinfected group with an even higher rate in patients who had progressed to AIDS [10]. Hepatocellular carcinoma is a well-recognized complication of chronic HCV infection and appears to develop after a shorter duration of infection in HIV-infected patients [11].

The exact way in which HIV accelerates chronic HCV liver disease has not been elucidated. As HIV itself does not appear to cause a hepatitis directly the effect is presumably mediated via suppression of the immune response against HCV. However, although there is evidence for this effect in that HCV viraemia tends to be higher in HIV-positive patients compared with those with HCV monoinfection both in haemophilic and non-haemophilic cohorts [12–14], there is no conclusive evidence that the level of HCV viraemia is directly related to the severity of HCV liver disease [15,16].

There is evidence to suggest that more advanced HIV infection is associated with more rapid progression of HCV liver disease [17,18]. However, the level of HIV viraemia is not correlated with severity of HCV liver disease [14]. In a study of 26 coinfected Greek haemophilic patients Delladetsima *et al.* reported no relationship between the stage of HIV infection and liver biopsy evidence of cirrhosis [19]. These authors observed restriction of necroinflammatory hepatitic activity to patients with early HIV infection and concluded that the development of cirrhosis with eventual progression to liver failure is initiated at this stage of HIV disease when immune function is still relatively well preserved.

As in HIV-negative individuals there is evidence to suggest that HCV genotype 1 may be associated with more rapid progression to cirrhosis than other genotypes in coinfected patients [19–21].

Effect of HCV on HIV

Whether or not HCV infection accelerates the progression of HIV infection to AIDS and death remains unclear. One European and two North American studies conducted during the early 1990s concluded that HCV coinfection did not adversely influence survival in HIV-infected individuals [22–24]. Similarly four further studies, one before and three after the advent of HAART, concluded that HCV infection did not accelerate immunological and clinical progression of HIV disease [25–28]. However, Piroth *et al.*, in a French study of 119 HIV- and HCV-coinfected patients and 119 HIV-monoinfected individuals, observed that clinical progression of HIV was more rapid in the coinfected cohort [29]. Overall attrition of CD4 counts with time was not significantly different between the two groups. However, in patients with an initial CD4 count above 600×10^6 L^{-1} there was a significantly more rapid reduction with time in the coinfected patients.

In 2000 Greub *et al.* published the results of the Swiss HIV Cohort Study, a prospective study of over 3000 HIV-positive patients on HAART [30]. At a median follow-up of 28 months 6.6% of HIV-monoinfected patients progressed to AIDS compared with 9.7% and 15% of HCV-seropositive patients who were past or active intravenous drug users, respectively. The relative risk of developing an AIDS-defining illness or death in the coinfected group was 1.7 compared with HCV-seronegative patients. HCV infection was not associated with a reduction in the probability of HIV-infected patients achieving HIV suppression below 400 copies mL^{-1}. However, following initiation of HAART-coinfected patients had impaired CD4 count recovery compared with HIV-monoinfected individuals. In a study of a subset of patients the level of HCV viraemia was not found to be an influencing factor in CD4 cell count recovery. This observation has been confirmed in a similar study on a cohort of UK HIV-infected haemophilic patients commencing HAART [31]. In the Swiss Cohort Study HCV genotype 3 was associated with a more blunted CD4 count recovery. However, in a UK study, Sabin *et al.* reported that HIV-infected haemophilic patients coinfected with HCV genotype 1 had a worse prognosis compared with other genotypes [32].

Following Greub's publication a US study of almost 2000 HIV-infected patients with a similar median follow-up reported that HCV coinfection was not associated with an increased risk of progression to AIDS or death or impairment of the immunological response to HAART [33].

The differences between the Swiss and US studies may be explained by variability in the patient groups [33]. In the Swiss study HCV-infected patients tended to be younger, white and female whereas in the US study patients were older and more likely to be African–American.

Whether HCV infection does worsen the outcome of HIV infection the mechanism has not been elucidated. Possible mechanisms that have been suggested include HCV-mediated direct impairment

of CD4 cell production or sensitization of CD4 cells to apoptosis [34].

In three recent studies, including one of haemophilic patients, the hepatitis G virus (HGV) has been reported to be associated with improved survival in HIV infection [35,36]. It is therefore possible that if HCV does have an adverse effect on the course of HIV, the presence of persistent HGV infection may alleviate this effect to some degree. However, this remains to be proved.

Effect of HAART on HCV infection

Two European studies, one of a cohort of haemophilic patients, reported that the initial period of HAART was not associated with significant elevations in serum transaminase levels and HCV viraemia [37,38]. However, other studies have reported contrary observations. In a study of 21 coinfected haemophilic patients Ragni and Bontempo observed an increase in HCV viraemia in 17 individuals during a 96-week period following commencement of HAART [39]. However, this was not associated with evidence of progression of HCV liver disease, although one patient did progress to liver failure during the first year of HAART. Other studies have observed rises in HCV viraemia and transaminases following commencement of HAART consistent with immune reconstitution-mediated reactivation of HCV liver disease [40–43]. In the study of Vento *et al.*, which included 51 coinfected patients followed up for a 9-month period, there were transient rises in HCV and transaminase levels following commencement of HAART peaking at 1 month. Thirty-one patients who underwent liver biopsy showed an increase in mean Knodell histological score from 8 before HAART to 13 on HAART. This was due to increased necroinflammatory activity consistent with reactivation of an immune-mediated attack on HCV as a consequence of HAART-induced immune reconstitution. Seven of the patients in this study progressed to decompensated liver disease during the study period and had HAART discontinued [42].

Effects of HIV drugs on the liver

If worsening of pre-existing transaminitis or new transaminitis occurs in coinfected patients commenced on HAART direct drug-related toxicity must be considered as a possible cause and not be assumed to be due to an immune reconstitution-mediated exacerbation of HCV infection. Pre-existing liver disease predisposes to HIV drug-induced liver toxicity [44,45]. All the licensed nucleoside reverse transcriptase inhibitor drugs (NRTIs) can cause elevation of liver enzymes and have been associated with the development of hepatitic steatosis with hepatomegaly [46]. Stavudine and didanosine are the most likely of the NRTIs to be associated with hepatic steatosis and accompanying hyperlactataemia or occasionally potentially life-threatening lactic acidosis. Abacavir may be associated with the development of deranged liver function as part of a multi-organ hypersensitivity reaction which may develop within a few days or weeks of commencement. Liver function test abnormalities associated with the other drugs in this group result from direct drug toxicity. The mechanism of this effect is likely to be a consequence of hepatocellular mitochondrial toxicity.

The licensed non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine have also been associated with hepatic toxicity. Efavirenz can cause direct hepatocellular damage with elevation of liver enzymes, especially in patients with hepatitis B or C. Nevirapine can cause derangement of liver function with potentially life-threatening fulminant hepatitis as part of a generalized immune-mediated hypersensitivity reaction which can occur within the first 2 months of treatment [47]. The risk of nevirapine-associated hypersensitivity is directly correlated with the CD4 count, reducing as immune function declines [48]. Nevirapine can also cause direct dose-dependent hepatotoxicity occurring after at least 4 months of therapy, especially in patients with hepatitis C coinfection [45].

Although the earlier protease inhibitor drugs (PIs) indinavir, ritonavir and saquinavir were associated with liver toxicity [42,49] this does not appear to be a problem with the newer agents amprenavir, nelfinavir and lopinavir/ritonavir combination.

All HIV medications should be used with caution in patients with HCV-associated hepatic impairment with regular monitoring of liver function. Patients on NRTIs or NNRTIs should be monitored closely for the possible development of hepatic steatosis, hyperlactataemia and lactic acidosis. Medications should be suspended or permanently discontinued if deterioration in liver function occurs.

Management of HCV in HIV infection

HIV-infected haemophilic patients are likely to have been previously screened for HCV infection using an HCV antibody test. Virtually all will have been found to have a positive test consistent with past exposure to HCV in factor concentrates. However,

around 15% of individuals will naturally eradicate the virus and therefore it is important to determine whether HCV infection is still present by performing a polymerase chain reaction (PCR) test for HCV RNA. If the patient is HCV RNA positive, quantitation of the virus should be performed and the genotype determined. HIV-infected patients who are antibody negative should have an HCV RNA test performed as false negative antibody tests can occur as a consequence of immunosuppression [50].

Coinfected patients with intermittent or persistent transaminitis should be considered for HCV eradication therapy. A liver biopsy is commonly performed in the assessment of HCV infection. There has been concern in the past over the safety of this procedure in haemophilic patients due to the potential for bleeding [51]. However, provided effective factor concentrate replacement protocols are followed the risk does not appear to exceed that of patients who do not have a bleeding disorder [52,53]. Due to the potential for HCV infection to proceed to end-stage liver disease a good case can be made for initiating HCV treatment without information on liver histology. However, histological findings can be very useful in informing management decisions both for the clinician and the patient. Not uncommonly, minimal hepatitic changes may be present making it unlikely that HCV infection will progress at any time in the future to cirrhosis and liver failure. In this circumstance treatment could reasonably be withheld. Equally if advanced cirrhosis is present a decision may be taken not to proceed with treatment due to the reduced chances of HCV eradication.

In HCV RNA-positive patients with persistently normal hepatic transaminases a liver biopsy should be considered as progressive liver disease cannot be excluded. HCV therapy should only be offered if significant liver disease is present on histology [50].

Treatment of HCV in HIV infection

HCV treatment strategy in HIV-infected patients is the same as in immunocompetent patients. Individuals with stable HIV infection and well preserved CD4 counts not on HAART should be strongly advised to consider HCV treatment. The HCV-associated hepatic necroinflammatory process is most active at this stage of HIV infection due to relatively preserved immune function and HCV eradication should be attempted at this stage before significant fibrosis develops. Furthermore, eradication of HCV at this stage will remove the adverse influence of HCV on the course of HIV infection and reduce the risk of HAART drug-induced hepatotoxicity if HIV therapy is required at any time in the future.

HIV-infected patients who are stable on HAART should be assessed on an individual basis. Treatment should be considered in stable patients with CD4 counts $>200 \times 10^6$ L^{-1}. Coinfected individuals with progressive HIV disease and low CD4 counts should have HAART commenced as a priority. HCV treatment should be considered only when HIV infection is stabilized and CD4 counts improve. Patients with advanced HIV infection and hepatic decompensation should not be considered for HCV treatment.

The treatment of choice for HCV is combination therapy with pegylated interferon (Peg-IFN) and ribavirin. Peg-IFN is a formulation of alpha-interferon complexed with polyethylene glycol (Peg). It is administered subcutaneously and the formulation enables sustainment of therapeutic interferon levels which allows a once-weekly dosing schedule. At present there are two preparations: peg-alpha-2b interferon (Pegasys; Roche Products Ltd., Welwyn Garden City, UK) and peg-alpha-2a interferon (PegIntron; Schering-Plough Ltd., Welwyn Garden City, UK). Ribavirin, an analogue of the DNA base guanosine, is taken orally twice daily. To optimize therapy it is important that ribavirin is prescribed at the correct dose for body weight [54]. Patients commenced on combination therapy should be advised to abstain from alcohol.

In HIV-negative patients Peg-IFN/ribavirin combination therapy can achieve HCV eradication rates of just over 40% for HCV genotype 1 and up to 80% for genotypes 2 and 3 [55,56]. Besides eradicating HCV, combination therapy reduces the degree of hepatic fibrosis [56,57]. Even in non-responders a course of interferon therapy can slow fibrosis progression and reduce the risk of end-stage liver disease and the development of hepatocellular carcinoma [58]. In a review of seven studies of HIV/HCV-coinfected individuals with a combined total of 198 patients conventional interferon/ribavirin combination therapy resulted in an overall HCV RNA clearance rate of 25% (ranging from 17% to 40%) [54]. In three studies with a combined total of 63 patients who had failed to respond or had relapsed following a course of interferon monotherapy the overall response to conventional interferon/ribavirin therapy was slightly lower at 22% (ranging from 14% to 35%) [54].

Factors predictive of a favourable response to combination therapy in coinfected patients include a CD4 cell count of $>500 \times 10^6$ L^{-1} and plasma HIV RNA levels of $<10^4$ copies mL^{-1} [59,60]. Poorer

results in patients with lower CD4 counts may be due to the presence of more advanced fibrosis in this group, a known predictive factor of reduced response to IFN [61]. Other favourable predictive factors in common with HCV-monoinfected patients include non-genotype 1 HCV infection, low HCV load ($<3.5 \times 10^6$ copies mL^{-1}), age <40 and abstinence from alcohol [54,62].

The initial study looking at the efficacy of peg-IFN/ribavirin in coinfected patients reported an end-of-treatment response of 65% [54]. Data on the sustained response rate is awaited. Interim analysis of a similar trial reported a 44% response rate to peg-IFN/ribavirin at 24 weeks [63]. A number of larger studies of peg-IFN/ribavirin in coinfected patients are ongoing.

Patients commenced on peg-IFN/ribavirin should have an HCV RNA test performed at 3 and 6 months. Although the majority of responders become HCV RNA negative by 3 months, treatment should be continued in those who remain RNA positive as later responses have been reported [64]. If the 6-month RNA test is positive therapy should be discontinued as a response beyond this time is very unlikely. A recent trial has suggested that persistence of detectable HCV RNA at 3 months is a strong predictor of response failure in coinfected patients [55]. Therefore, a case could be made for discontinuing therapy at this early stage in non-responders, so avoiding unnecessary drug treatment and possible toxicity. Patients with genotype 1 infection who have cleared HCV RNA by 6 months should have treatment continued for a full 12 months to consolidate the response. Responders with non-genotype 1 virus can have treatment discontinued at 6 months [50]. Following cessation of therapy responders should have regular HCV RNA monitoring and if relapse occurs further combination therapy should be considered.

Side-effects of interferon and ribavirin and interactions with HAART drugs

The main side-effects of peg-IFN are similar to conventional preparations and include flu-like symptoms, lethargy, depression and cytopenias. IFN can induce a reduction in CD4 lymphocyte counts in some individuals. This is likely to be a consequence of pooling of the lymphocytes within lymphoid tissue and is usually transient. Occasionally the fall in CD4 count can be severe enough to necessitate cessation of IFN and may be irreversible [65]. Ribavirin is associated with the development of a dose-dependent haemolytic anaemia. Haemoglobin levels can fall below 11 g dL^{-1} in up to 35% of patients [66]. Anaemia is not usually clinically significant but may be severe enough to cause symptoms. This effect of ribavirin may compound zidovudine-induced anaemia in patients on this drug. Symptomatic patients can be effectively treated with recombinant human erythropoietin, which is preferable to reducing the ribavirin dose with the potential reduction in its anti-HCV effect [67].

With regard to interactions with HIV drugs ribavirin is known to inhibit the intracellular phosphorylation of zidovudine, stavudine and zalcitabine *in vitro*. This has the potential to reduce the efficacy of these drugs *in vivo* but there is no evidence that this interaction is clinically significant [68–70]. Ribavirin enhances the phosphorylation of didanosine [54]. Although this may enhance the anti-HIV effect of didanosine there have been reports of an increased incidence of mitochondrial toxicity in patients on both drugs manifesting clinically as weight loss, pancreatitis, hyperlactataemia or at its most extreme lactic acidosis [71,72]. Stavudine and to a lesser extent the other NRTIs appear to have similar interactions with ribavirin [73]. Therefore, patients receiving HCV combination therapy and HAART regimens containing NRTIs should be monitored very closely, and for those on didanosine consideration given to changing to an alternative drug.

Liver transplantation for HCV liver disease in coinfected patients

Patients who develop HCV related liver failure or localised hepatocellular carcinoma who have stable HIV infection on or off HAART should be considered for liver transplantation. Prior to HAART the prognosis in this group of patients was very poor [74]. In the series reported by Gordon et al the one year and three year survival in the six HIV positive haemophilic patients was 67% and 23% respectively which was significantly worse than that of the 19 HIV negative patients (90% and 83% respectively) [75]. However with the marked improvement in the management of HIV infection graft survival rates at one year post liver transplantation in this patient group is now around 80%, similar to that of HIV negative patients [76]. At the time of writing an HIV positive haemophilic patient transplanted in Birmingham UK remains alive and well four years post transplant [77]. A second patient transplanted in early 2003 also remains well. HIV infection should therefore not be considered a contraindication to liver transplantation.

Conclusions

- It is well established that HIV infection worsens the prognosis of HCV liver disease.
- There is also evidence that HCV has a detrimental effect on the course of HIV infection.
- HCV infection should therefore be actively managed in coinfected patients.
- Patients who are considered to require treatment who have stable HIV infection either on or off HAART with CD4 counts >200x106/l should be treated with Peg-IFN / ribavirin combination therapy.
- Close clinical and laboratory monitoring is recommended to screen for possible drug side effects and interactions.
- As in immunocompetent individuals responders with genotype 1 virus should continue treatment for 12 months and those with non-genotype 1 virus for six months.
- Individuals with end stage liver disease with stable HIV infection should be considered for liver transplantation.

References

1 Soriano V, Garcia-Samaniego J, Valencia E, Rodriguez-Rosado R, Munoz F, Gonzalez-Lahoz J. Impact of chronic liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users. *Eur J Epidemiol* 1999; **15**: 1–4.

2 Bica I, McGovern B, Dhar R *et al.* Increasing mortality due to end-stage liver disease in patients with HIV infection. *Clin Infect Dis* 2001; **32**: 492–7.

3 Monga H, Rodriguez-Barradas M, Breaux K *et al.* Hepatitis C virus infection-related morbidity and mortality among patients with HIV infection. *Clin Infect Dis* 2001; **33**: 240–7.

4 Soto B, Sanchez-Quijano A, Rodrigo L *et al.* HIV infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997; **26**: 1–5.

5 Makris M, Preston FE, Rosendaal FR, Underwood JCE, Rice KM, Triger DR. The natural history of chronic hepatitis C in haemophiliacs. *Br J Haematol* 1996; **94**: 746–52.

6 Benhamou Y, Bochet M, Di Martino V. Liver fibrosis progression in HIV and hepatitis C virus coinfected patients. *Hepatology* 1999; **30**: 1054–8.

7 Eyster ME, Diamondstone LS, Lien JM, Ehmann C, Quan S, Goedert JJ for the Multicenter Hemophilia Cohort Study. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. *J AIDS* 1993; **6**: 602–10.

8 Telfer P, Sabin C, Devereux H, Scott F, Dusheiko G, Lee C. The progression of HCV-associated liver disease in a cohort of haemophilic patients. *Br J Haematol* 1994; **87**: 555–61.

9 Darby S, Ewart D, Giangrande P, Dolin PJ, Spooner RJD, Rizza CR. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. *Lancet* 1997; **350**: 1425–31.

10 Lesens O, Deschenes M, Steben M, Belaanger G, Tsoukas CM. Hepatitis C virus is related to progressive liver disease in HIV-positive hemophiliacs and should be treated as an opportunistic infection. *J Infect Dis* 1999; **179**: 1254–8.

11 Garcia-Samaniego J, Rodriguez M, Berenguer J *et al.* Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterol* 2001; **96**: 179–83.

12 Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus RNA levels in haemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. *Blood* 1994; **84**: 1020–3.

13 Telfer PT, Brown D, Devereux H, Lee CA, Dusheiko GM. HCV RNA levels and HIV infection: evidence for a viral interaction in haemophilic patients. *Br J Haematol* 1994; **88**: 397–9.

14 Cribier B, Rey D, Schmitt C, Lang JM, Kirn M, Stoll-Keller F. High hepatitis viremia and impaired antibody response in patients co-infected with HIV. *AIDS* 1995; **9**: 1131–6.

15 Ghany MG, Leissinger C, Laiger R, Sanchez-Pescador K, Lok ASE. Effect of human immunodeficiency virus infection on hepatitis C virus infection in hemophiliacs. *Dig Dis Sci* 1996; **4**: 1265–72.

16 Ahmed MM, Mutimer DJ, Martin B, Elias E, Wilde JT. Hepatitis C viral load, genotype and histological severity in patients with bleeding disorders. *Haemophilia* 1999; **5**: 49–55.

17 Rockstroh J, Spengler U, Sudhop T *et al.* Immunosuppression may lead to progression of hepatitis C virus-associated liver disease in hemophiliacs coinfected with HIV. *Am J Gastroenterol* 1996; **91**: 2563–8.

18 Puoti M, Bonacini M, Spinetti A *et al.* Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and HIV. *J Infect Dis* 2001; **183**: 134–7.

19 Delladetsima J, Katsarou O, Touloumi G, Vgenopoulou S, Hatzakis A, Karafoulidou A. Significance of immune status, genotype and viral load in the severity of chronic hepatitis C in HIV infected haemophilia patients. *Haemophilia* 2002; **8**: 668–73.

20 Garcia-Samaniego J, Soriano V, Castilla J *et al.* Influence of hepatitis C genotypes and HIV infection on histological severity of chronic hepatitis C. *Am J Gastroenterol* 1997; **92**: 1130–4.

21 Yee TT, Griffioen A, Sabin CA, Dusheiko G, Lee CA. The natural history of HCV in a cohort of haemophilic

patients infected between 1961 and 1985. *Gut* 2000; **47**: 845–51.
22 Llibre JM, Garcia E, Aloy A, Valls J. Hepatitis C virus and progression of infection due to human immonudeficiency virus. *Clin Infect Dis* 1993; **16**: 182.
23 Quan CM, Krajden M, Grigoriew GA, Salit IE. Hepatitis C virus infection in patients infected with the human immunodeficiency virus. *Clin Infect Dis* 1993; **17**: 117–9.
24 Wright TL, Hollander H, Pu X *et al.* Hepatitis C in HIV infected patients with and without AIDS: prevalence and relationship to patient survival. *Hepatology* 1994; **20**: 1152–5.
25 Dorrucci M, Pezzoti P, Phillips AN, Cozzi L, Rezza G. Coinfection of hepatitis C virus with immunodeficiency virus and progression to AIDS. *J Infect Dis* 1995; **172**: 1254–8.
26 Macias J, Pineda JA, Leal M *et al.* Influence of hepatitis C virus infection on the mortality of antiretroviral treated patients with HIV disease. *Eur J Clin Microb Infect Dis* 1998; **17**: 167–70.
27 Haydon GH, Flegg PJ, Blair CS, Brettle RP, Burns SM, Hayes PC. The impact of chronic hepatitis C virus infection on HIV disease and progression in intravenous drug users. *Eur J Gastro Hepatol* 1998; **10**: 485–9.
28 Staples CT Jr, Rimland D, Dudas D. Hepatitis C in the HIV Atlanta VA (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. *Clin Infect Dis* 1999; **29**: 150–4.
29 Piroth L, Duong M, Quantin C *et al.* Does hepatitis C virus co-infection accelerate clinical and immunological evolution of HIV-infected patients. *AIDS* 1998; **12**: 381–8.
30 Greub G, Ledergerber B, Battegay M *et al.* for the Swiss HIV Cohort Study. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 2000; **356**: 1800–5.
31 Wilde JT, Collins P, Sabin C, Lee CA. Relationship between hepatitis C viraemia and CD4 cell count recovery in HIV positive haemophilia patients on highly active antiretroviral therapy. *Haemophilia* 2002; **8**: 534.
32 Sabin CA, Telfer P, Phillips AN, Bhagani S, Lee CA. The association between hepatitis C virus genotype and human immunodeficiency virus disease progression in a cohort of hemophilic men. *J Infect Dis* 1997; **175**: 164–8.
33 Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. *JAMA* 2002; **288**: 199–206.
34 Graham CS, Koziel MJ. Why should hepatitis C affect immune reconstitution in HIV-1-infected patients? *Lancet* 2000; **356**: 1865–6.
35 Xiang J, Wunschmann S, Diekema DJ *et al.* Effect of coinfection with GB virus C on survival among patients with HIV infection. *N Engl J Med* 2001; **345**: 707–14.
36 Tillman HL, Heiken H, Knapik-Botor A *et al.* Infection with GB virus C and reduced mortality among HIV-infected patients. *N Engl J Med* 2001; **345**: 715–24.
37 Zylberberg H, Chaise ML, Rubian C *et al.* Triple therapy for human immunodeficiency virus infection does not modify replication of hepatitis C virus in coinfected subjects. *Clin Infect Dis* 1998; **26**: 1104–6.
38 Rockstroh JK, Theisen A, Kaiser R, Sauerbruch T, Spengler U. Antiretroviral triple therapy decreases HIV viral load but does not alter hepatitis C virus (HCV) serum levels in HIV-HCV-coinfected hemophiliacs. *AIDS* 1998; **12**: 829–30.
39 Ragni MV, Bontempo FA. Increase in hepatitis C virus load in hemophiliacs during treatment with highly active antiretroviral therapy. *J Infect Dis* 1999; **180**: 2027–9.
40 John M, Flexman J, French M. Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? *AIDS* 1998; **12**: 2289–93.
41 Rutschmann O, Negro F, Hirschel B, Hadengue A, Anwar D, Perrin L. Impact of antiretroviral treatment with HIV protease inhibitors on hepatitis C viremia in patients coinfected with HIV. *J Infect Dis* 1998; **177**: 783–5.
42 Vento S, Garofano T, Renzini C, Casali F, Ferraro T, Concia E. Enhancement of hepatitis C virus replication and liver damage in HIV co-infected patients on antiretroviral combination therapy. *AIDS* 1998; **12**: 116–7.
43 Lovell R, Collins PW, Wilde JT. The influence of HAART on HCV infection in a cohort of haemophilic patients. *Haemophilia* 2000; **6**: 338.
44 Rodriguez-Rosado R, Garcia-Samaniego J, Soriano V. Hepatotoxicity after introduction of highly active antiretroviral therapy. *AIDS* 1998; **12**: 1256.
45 Nunez M, Lana R, Mendoza JL, Martin-Carbonero L, Soriano V. Risk factors for severe liver toxicity following the introduction of HAART. *J AIDS* 2001; **27**: 426–31.
46 Powderly W. Long-term exposure to lifelong therapies. *J AIDS* 2002; **29**: S28–40.
47 Leitze Z, Nadeem A, Choudhary A, Saul Z, Roberts I, Manthous C. Nevirapine-induced hepatitis treated with corticosteroids? *AIDS* 1998; **12**: 1115–7.
48 Martinez E, Blanco JL, Arnaiz J *et al.* Hepatotoxicity in HIV-1-infected patients receiving nevirapine containing antiretroviral therapy. *AIDS* 2001; **15**: 1261–8.
49 Sulkowski M, Thomas D, Chaisson R, Moore R. Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis B or C virus infection. *JAMA* 2000; **283**: 74–80.
50 Makris M, Baglin T, Dusheiko G *et al.* Guidelines on the diagnosis, management and prevention of hepatitis in haemophilia. *Haemophilia* 2001; **7**: 339–45.
51 Aledort LM, Levine PH, Hilgartner M *et al.* A study of liver biopsies and liver disease amongst haemophiliacs. *Blood* 1985; **66**: 367–72.

52 Ahmed MM, Mutimer DJ, Elias E *et al.* A combined management protocol for patients with coagulation disorders infected with hepatitis C virus. *Br J Haematol* 1996; **95**: 383–8.
53 Evans GD, Woodall T, Lawrence K, Wight D, Baglin TP, Alexander G. Progression of liver disease in hepatitis C infected haemophiliacs assessed by serial liver biopsy. *Br J Haematol* 2003; **121**: 92.
54 Soriano V, Sulkowski M, Bergin C *et al.* Care of patients with chronic hepatitis C and HIV coinfection: recommendations from the HIV-HCV International Panel. *AIDS* 2002; **16**: 813–28.
55 Fried MW, Shiffman ML, Reddy RK *et al.* Peg interferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975–82.
56 Manns MP, McHutchison JG, Gordon SC *et al.* Peg-interferon alfa-2b in combination with ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: results of a randomised trial. *Lancet* 2001; **358**: 958–65.
57 Poynard T, McHutchison J, Davis GL *et al.* Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. *Hepatology* 2000; **32**: 1121–37.
58 Poynard T, Moussalli J, Ratziu V, Regimbeau C, Opolon P. Effect of interferon therapy on the natural history of hepatitis C virus-related cirrhosis and hepatocellular carcinoma. *Clin Liver Dis* 1999; **3**: 869–81.
59 Soriano V, Garcia-Samaniego J, Bravo R *et al.* Interferon alpha for the treatment of chronic hepatitis C in patients with HIV. *Clin Infect Dis* 1996; **23**: 585–91.
60 Torriani F, Soriano F. Chronic hepatitis C in HIV-infected individuals. *AIDS Rev* 2000; **2**: 168–77.
61 Poynard T, Bedossa P, Opolon P *et al.* Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997; **349**: 825–32.
62 Poynard T, McHutchison J, Goodman Z for the ALGOVIRC Projects Group. Is an 'a la carte' combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? *Hepatology* 2000; **31**: 211–8.
63 Chung R, Anderson J, Alston B *et al.* A randomized, controlled trial of pegylated interferon alpha-2a with ribavirin vs. interferon alpha-2a with ribavirin for the treatment of chronic HCV in HIV co-infection: ACTG A5071. *Ninth Conference on Retroviruses and Opportunistic Infections*, Seattle, WA, 2002: abstr LB-15.
64 EASL. International Consensus Conference on Hepatitis C. *J Hepatol* 1999; **30**: 956–61.
65 Soriano V, Rodriguez-Rosado R, Garcia-Samaniego J. Management of chronic hepatitis C in HIV-infected patients. *AIDS* 1999; **13**: 539–46.
66 Jimenez-Nacher I, Soriano V. Interactions of antiretroviral drugs. *AIDS Rev* 2000; **1**: 116–23.
67 Poles M, Dieterich D. Hepatitis C/HIV coinfection: clinical management issues. *Clin Infect Dis* 2000; **31**: 154–61.
68 Landau A, Batisse D, Piketty C, Jian R, Kazatchkine M. Lack of interference between ribavirin and nucleoside analogues in HIV-HCV coinfected individuals undergoing concomitant antiretroviral and anti-HCV combination therapy. *AIDS* 2000; **14**: 1857–8.
69 Morsica G, De Bona A, Uberti C, Sitia G, Finazzi R, Lazzarin A. Ribavirin therapy for chronic hepatitis C does not modify HIV viral load in HIV-1 positive patients under antiretroviral treatment. *AIDS* 2000; **14**: 1656–8.
70 Zylberberg H, Benhamou Y, Lagneaux JL *et al.* Safety and efficacy of interferon-ribavirin combination therapy in HCV-HIV coinfected subjects: an early report. *Gut* 2000; **4**: 608–9.
71 Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. *Lancet* 2001; **357**: 280–1.
72 Kakuda T, Brinkman K. Mitochondrial toxic effects of ribavirin. *Lancet* 2001; **357**: 1802–3.
73 Garcia-Benayas T, Blanco F, Soriano V. Weight loss in HIV-infected patients. *N Engl J Med* 2002; **347**: 1287–8.
74 Gow PJ, Pillay D, Mutimer D. Solid organ transplantation in patients with HIV infection. *Transplantation* 2001; **72**: 177–81.
75 Gordon FH, Mistry PK, Sabin CA, Lee CA. Outcome of orthotopic liver transplantation in patients with haemophilia. *Gut* 1998; **42**: 744–9.
76 Roland ME, Havlir DV. Responding to organ failure in HIV-infected patients. *N Engl J Med* 2003; **348**: 2279–81.
77 Wilde JT, Teixeira P, Bramhall SR, Gunson B, Mutimer D, Mirza DF. Liver transplantation in haemophilia. *Br J Haematol* 2002; **117**: 952–6.

