REVIEW

Hepatitis C and HIV-1 coinfection

A H Mohsen, P Easterbrook, C B Taylor, S Norris

Gut 2002;**51**:601–608

Hepatitis C virus (HCV) has emerged as the cause of the second major epidemic of viral infection after human immunodeficiency virus (HIV) within the past two decades, and coinfection of HIV and HCV represents a growing problem for the future. This article reviews the current evidence on the epidemiology and clinical implications of an interaction between HIV-1 and HCV infection, and the current status of the management of patients with combined infection.

Hepatitis C virus (HCV) has emerged as the cause of the second major epidemic of viral infection after human immunodeficiency virus (HIV) within the past two decades. Approximately 3% of the world's population are estimated to be infected,[1] and viraemia persists in over 80%.[2] Hepatitis C is now also recognised as one of the leading causes of chronic liver disease, and as a result mortality attributable to hepatitis C is expected to more than triple over the next two decades and to exceed the number of HIV related deaths.[3] Coinfection with HIV and HCV represents a growing problem for the future. In the USA, it has been estimated that there are 240 000 coinfected subjects.[4] Since the introduction of highly active retroviral therapy (HAART), and the dramatic improvement in the life expectancy of HIV infected subjects, the impact of HCV on mortality and development of hepatocellular carcinoma (HCC) has become more evident.[5–7] More recent studies in those coinfected with both HIV-1 and HCV have demonstrated that HCV is the leading non-acquired immunodeficiency syndrome (AIDS) cause of death in coinfected subjects, and end stage liver disease due to HCV infection accounts for up to 50% of all deaths.[8 9] This article reviews the current evidence on the epidemiology and clinical implications of an interaction between HIV-1 and HCV infection, and the current status of the management of patients with combined infection.

See end of article for authors' affiliations

Correspondence to: Dr A H Mohsen, Academic Department of HIV/GU Medicine, Weston Education Centre, GKT School of Medicine, King's College, University of London, London SE5 9RJ, UK; Abdul.Mohsen@kcl.ac.uk

Accepted for publication 4 December 2001

METHODS

We identified all relevant published articles or conference abstracts relating to the epidemiology, natural history, and treatment of HIV-1 and HCV coinfection over the past nine years. Medline and AIDSLINE databases were first searched using the terms "HIV" and "HCV", "liver disease", and for the treatment section we also used the terms "interferon", "antiretroviral therapy" in combination. Abstracts were included only where complete data were available. For prevalence studies we only included studies with ⩾100 patients. In the section on perinatal transmission, studies were included if they had at least 20 coinfected mothers and used either the presence of positive hepatitis C RNA at any time or HCV antibody detection at 12 months for the diagnosis of HCV infection in newborn babies. For the impact of HIV-1 on HCV progression to fibrosis, cirrhosis, decompensated liver disease, or liver related deaths, we included all studies that investigated the effect of coinfection on any aspect of progression or mortality, including HCV viral load and transaminases. The same criteria were applied to studies examining the impact of HCV on HIV progression to AIDS or death, and on the impact of HCV treatment on HIV and HCV disease progression.

PREVALENCE

We identified 12 published seroprevalence studies based on various HIV-1 infected cohorts from Europe[10–13] and North America,[14–21] as shown in table 1. HCV prevalence ranged between 7% and 57% and these differences in seroprevalence across the different studies were largely determined by the HCV risk factor distribution of the study population. Patients with a current or previous history of drug use had infection rates in excess of 80%[12–14 16 17 20] while the prevalence of HCV in homo/bisexual groups varied between 2.6% and 15.2%.[10 12 13 15–17 20] The majority (98%) of HIV-1 infected haemophiliacs are also coinfected with hepatitis C.[6 22] However, even these data may underestimate the true prevalence of HCV among HIV positive patients as at least 4% of HIV-HCV coinfected patients have no detectable antibodies in the presence of HCV viraemia,[24 25] or as a result of immunosuppression may subsequently lose detectable antibodies from serum despite persistent viraemia.[26]

> "The majority (98%) of HIV-1 infected haemophiliacs are also coinfected with hepatitis C"

The consistently high prevalence of HCV infection observed in HIV-1 infected individuals supports the routine screening for HCV in these patients, especially among haemophiliacs and drug users. Where HCV is suspected in the setting of negative antibody screening, detection of HCV RNA by polymerase chain reaction is recommended.

Abbreviations: HCV, hepatitis C virus; HAART, highly active retroviral therapy; HCC, hepatocellular carcinoma; HIV-1, human immunodeficiency virus 1; AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 1 Prevalence of hepatitis C virus (HCV) in human immunodeficiency virus 1 infected patients

Year, reference	Study size	Location	Characteristics of study population	% HCV positive
Europe				
2000[6]	125*	UK	Haemophiliacs	98%
1998[10]	3048	Europe (central, northern and southern)	43% MSM, 27% IDU, 2.4% transfusion	33% (MSM 6%, IDU 91%, transfusion 59%)
1999[11]	204	Spain	77% male, 26% MSM, 61% IDU	57%
2000[12]	3111	Switzerland	65.6% male, 35.6% IDU, 33% MSM	37.2% (IDU 87.7%, MSM 3.7%)
2000[13]	394	Netherlands	80% male, 58% MSM, 9% IDU	15% (MSM 2.6%, IDU 97%)
North America				
1991[14]	101	Sacramento, USA	91% male, 30% IDU, 75% sexual promiscuity, 7% transfusion	7% (IDU 16%, transfusion 29%)
1994[15]	512	San Francisco, USA	98% male, 83% MSM, 7% IDU, 8.5% transfusion	14% (MSM 11.7%, IDU 40%, transfusion 31.6%)
1998[16]	934	New York, USA	37% MSM, 37% IDU, 4% transfusion	40% (MSM 12%, IDU 81%, transfusion 78%)
1997[17]	587	Hawaii, USA	93.2% male, 75% MSM, 14% IDU	17% (MSM 6.6%, IDU 95%)
1998[18]	511	NIH, USA	All women	32%
1999[19]	3134	Texas, USA	Outpatients and prisoners	43%
1999[20]	350	Georgia, USA	98.6% male, 47% MSM, 20% IDU	33% (MSM 14%, IDU 83%)
1993[21]	226	Toronto, Canada	94% male, 61% of HCV positive were IDU, 44% were MSM, and transfusion 22%	8%
1993[22]	382*	USA	Haemophiliacs	98%

MSM, men having sex with men, either homosexual or bisexual; IDU, previous or current intravenous drug use.
*Only two haemophiliac studies were included.

TRANSMISSION

HIV and HCV viruses share common routes of transmission, especially the parenteral route, and as a result coinfection rates in intravenous drug users and haemophiliacs are particularly high (60–90%).[6 22 23] Other non-parenteral routes of transmission are also important,[2 27 28] and there is now increasing evidence that sexual[15 27 29 30] and mother to child HCV transmission is facilitated by HIV infection.[18 31–35] In a study of 662 homosexual men, patients with HIV infection were three times more likely to be HCV positive compared with those who were HIV negative (9% *v* 3%; p<0.001).[30] In addition, independent sexual transmission of HCV among homosexual men accounted for approximately 50% of these cases.[30]

> "There is now increasing evidence that sexual[15 27 29 30] and mother to child HCV transmission is facilitated by HIV infection"

Similarly, there is a two to threefold higher maternal fetal transmission rate in coinfected mothers compared with a transmission rate of less than 6% in HIV negative mothers.[18 31–39]

Table 2 summarises 10 studies of mother to child transmission in coinfected women comprising 1089 coinfected mothers. The vertical transmission rate ranged from a low of 5.8% in one study from the UK to 36% in a large study from Italy. Several factors were associated with a higher rate of HCV transmission in coinfected patients. These included a higher HCV viral load,[18 31] vaginal delivery,[32 34 35] and in one study breastfeeding increased HCV transmission by fourfold (p=0.002) even after adjusting for mode of delivery.[35] In contrast, caesarean section reduced the rate of HCV transmission,[32 34 35] although this has not been corroborated in studies of HIV uninfected/HCV positive mothers, and cannot currently be recommended for management.[35] Few studies have addressed the converse issue of the impact of HCV on HIV transmission in coinfected mothers. However, one study of 487 HIV infected mothers of whom 161 were also HCV infected found a 1.82-fold increased rate of mother to child HIV transmission (95% confidence interval (CI) 1.12–2.95) in coinfected mothers.[40]

Table 2 Risk of hepatitis C virus (HCV) in mother to child transmission in HCV-human immunodeficiency virus (HCV-HIV) coinfected patients

Year, reference	No of coinfected mothers/HCV infected only	Location	No HCV infected children (%) in coinfected/HCV infected only (%)	Definition of HCV infection in the child	Factors associated with higher transmission
1998[18]	41/112	USA	7 (17.1%)/6(5.4%)	PCR positive at 6 months	HIV (p=0.04), HCV viral load (p<0.001)
1995[31]	22/94	Italy	8 (36%)/0(0%)	PCR positive at 12 months	HIV (p<0.001), HCV viral load (p=0.05)
1997[32]	165/80	Italy	25 (15.1%)/3(3.7%)	PCR or HCV antibody positive at 18 months	HIV (p=<0.01), VD (p=0.06)
1998[33]	23/52	Italy	4 (17.4%)/2(3.8%)	PCR positive at 6 months	HIV (p=0.06)
2000[34]	22/328	UK, Ireland	4 (18.6%)/21(6.4%)	PCR positive at 1 month	HIV (p=0.06), VD with emergency CS *v* elective CS (p=0.04)
2001[35]	503/971	EU	70 (13.9%)/60(6.6%)	PCR or HCV antibody positive at 18 months	OR (95% CI) for HCV transmission: HIV, OR 3.76 (CI 1.89–7.41)
1993[36]	51/15	UK	3 (5.8%)/1(6.6%)	PCR positive at 12 months	HIV (NS)
1995[37]	53/17	Italy	12 (23%)/2(12%)	PCR positive at any time	HIV (p=0.277) VD, p<0.05
1995[38]	20/17	Italy	4 (20%)/2(12%)	PCR positive at any time	HIV (NS)
1998[39]	73/49	USA	5 (7%)/2(4%)	PCR positive at 18 months	HIV (NS)

CS, caesarean section; VD, vaginal delivery; PCR, polymerase chain reaction.

Table 3 Impact of human immunodeficiency virus on hepatitis C virus (HCV) viral load in coinfected patients

Year, reference	No of coinfected patients/HCV only infected	Location	Mean/ median CD4 cell count	Absolute increase in HCV viral load in coinfected related to HCV only infected	Based on evaluation at single or multiple time point
2001[25]	107/112	USA	235	0.8 $\log_{10}$ copies/ml, p=0.001	Single
1996[41]	42/37	USA	>200	Only significant difference when CD4 <200	Multiple
1993[42]	13/30	USA	292–1024	26.5 $\times 10^6$ copies/ml, p<0.05	Single
1994[43]	17/17	USA	201	25.6 $\times 10^5$ eq genome/ml, p=0.006	Multiple
1995[44]	75/75	France	278	101.7 $\times 10^5$ eq genome/ml, p<0.0001	Single
1996[45a]	27 (seroconverters)	USA	>200	0.59 $\log_{10}$ copies/ml, p<0.0001	Multiple
1996[45b]	80/20	USA	200	0.33 $\log_{10}$ copies, p=0.021	Multiple
1999[46]	39/15	Italy	206	0.53 $\times 10^6$ copies/ml, p=0.01	Single
1998[47]	9/10	Netherlands	739	1.08 $\log_{10}$ copies/ml, p<0.0001	Multiple
1999[48]	22/48	USA	222	0.5 $\log_{10}$ copies/ml, p=0.02	Single
2000[49]	39/69	Japan	320	>2-fold increase in mean, p=0.02	Multiple
2001[50]	175/77	USA	416	0.57 $\log_{10}$ copies/ml, p<0.001	Multiple
2001[51]	107/112	USA	235	0.91 $\log_{10}$ copies/ml, p<0.00001	Single
2000[52]	31/38	France	652	0.5 $\log_{10}$ copies/ml, p=0.016	Single
1995[53]	11/9	Spain		10-fold higher, p=0.07	Single
1996[54]	22/21	Germany	325	No effect	Single

Table 4 Impact of human immunodeficiency virus 1 on hepatitis C virus (HCV) progression

Year, reference	No of coinfected/HCV only infected patients	Location	Mean follow up	Study outcome	OR/RR (95% CI)	Comment
1997[5]*	1218/3647	UK	—	LRD	3.21 (1.89–5.44) unadjusted	Haemophiliacs
2000[6]	125/173	UK	13.3 y	LRD	17.51 (5.8–52.7), adjusted for age, duration of HCV genotype	Haemophiliacs
1994[15]	74/438	USA	28 months	Survival	0.78 (0.5–1.2), unadjusted	44% had AIDS (selected group)
1999[20]	115/235	USA	141 months	Survival	0.98 (0.7–1.3) unadjusted	70% had AIDS, retrospective cohort
1999[46]	39/15	Italy	—	DLD	12.8% *v* 0%	All patients had severe coagulopathy
1995[53]	32/44	Spain	—	Cirrhosis	4.83 (0.93–24.9) unadjusted	Histology based
1996[56]	36/102	UK	18.8 y	Cirrhosis	3.9 (1.4–10.8), adjusted for age, haemophilia severity	Haemophiliacs
1998[57]	52/462	France	—	Cirrhosis	2.6 (1.1–5.9), adjusted for age, duration of HCV, alcohol	Cross sectional, histology based
1999[58]	81/53	Canada	—	PLD°	7.4 (2.2–25.5), age	Histology based
1999[59]	122/122	France	—	Fibrosis progression	1.221 (1.11–1.33), adjusted for†	Histology based
1994[60]	103/152	UK	—	DLD	21.4 (2.6–174.5), duration of HIV	FU 15.1 y, haemophiliacs
1993[61]	98/58	USA	10 y	DLD	3.2 (0.6–17), adjusted for age, ALT	Haemophiliacs
1997[62]	116/463	Spain	—	Cirrhosis	1.94 (0.92–4.1), duration of HCV	Histology based
1997[63]	22/33	Germany	—	Cirrhosis	1 (0.32–3.14)	Histology based
2001[64]	84/120	Italy and USA	—	Fibrosis stage 3, cirrhosis	3.2 (1.1–9.2), adjusted for age, alcohol, duration of HCV	CD4 <500, histology based
1997[65]	48/11	Spain	—	Fibrosis	17.9 (2.5–129), adjusted for genotype, duration of HCV	Histology based
1996[66]	144/72	Germany	63.9 months	LRD	7% *v* 0%	—

*Patients with HIV were considered coinfected with hepatitis C if they were exposed to high risk blood products.
†Severe immunosuppression (CD4 <200 cells), sex, alcohol, age at HCV infection.
PLD, progressive liver disease; LRD, liver related death; FU, follow up; OR, odds ratio; RR, relative risk; 95% CI, 95% confidence interval.

The majority of studies have reported higher HCV viral loads by a magnitude of 0.3–1.08 log RNA copies/ml in coinfected patients[25 41–53] compared with HIV-1 negative HCV infected subjects (table 3), and this is likely to mediate the higher transmission of HCV in the setting of HIV infection. However, one report suggests that this may be the case only in patients infected with HCV genotype 1.[54] An association between serum HCV viral load and saliva HCV viral load has also been recently demonstrated, which may have major implications for HCV transmission in coinfected patients.[55]

Together, these data demonstrate a higher rate of vertical and sexual transmission of HCV in coinfected patients, and that HIV is a cofactor for HCV transmission.

IMPACT OF HIV ON HCV PROGRESSION

Prior to HAART, the majority of deaths in HIV infected patients were AIDS related, and data on HCV related morbidity and mortality were lacking.[15] However, since HAART became widely available in the last five years and extended life expectancy, the management of concurrent illnesses has attracted more attention. Table 4 summarises data from 17 studies[5 6 15 20 46 53 56 66] on the impact of HIV infection on HCV progression, comprising a total of 2509 coinfected patients. A recent meta-analysis included eight of these studies[56–63] and showed a combined adjusted relative risk of 2.92 (95% CI 1.70–5.0) for progression to cirrhosis or decompensated liver disease in coinfected patients.[67] Similar evidence for liver related deaths was provided by the UK haemophiliac cohort of

Table 5 Impact of hepatitis C virus (HCV) infection on human immunodeficiency virus (HIV) progression

Year, reference	Location	No of coinfected patients/HIV infected alone	Duration of follow up	Outcome	OR/RR (95% CI)	Comment
2001[7]	Canada	78/104	42 months	Death	1.59 (1.06–6.32) unadjusted	—
1994[15]	USA	74/438	84 months	Death	0.85 (0.30–2.4) unadjusted	Selected group
1999[20]	USA	122/228	141 months	AIDS and death	No effect	70% had AIDS
2000[12]	Switzerland	528/1068	28 months	AIDS and death Clinical progression	3.45 (2.0–6.25) 1.72 (1.25–2.36)	Patients with well controlled HIV-1 replication
1993[21]	USA	18/195	—	AIDS	0.3 (0.084–1.07)	—
1999[58]	Canada	22/59	17.2 y	AIDS and death	2 (1.06–3.9)	Patients with progressive liver disease
2001[75]	USA	207	7 y	AIDS Death	1.66 (1.1–2.51)) 1.54 (1.03–2.30)	Haemophiliacs
1998[76]	France	119/119	3 y	AIDS and death	1.64 (1.06–2.06) adjusted for CD4 cell count	—
1995[77]	Italy	214/202	30 months	AIDS	0.97 (0.52–1.79) adjusted for CD4 cell count	AIDS free cohort with known seroconversion date

305 patients of whom 125 were coinfected. The relative hazard of liver related death, adjusted for age and HCV genotype, was 17.5-fold for coinfected patients (95% CI 5.8–52.7) compared with those infected with HCV alone.[6] More recently, the UK National Haemophilia Register has reported that men with haemophilia exposed to HCV and HIV are 4.6-fold more likely to progress to liver related death (6.5%; range 4.5–9.5%) compared with HIV-1 uninfected men (1.4%; range 4.5–9.5%).[5]

"Men with haemophilia exposed to HCV and HIV are 4.6-fold more likely to progress to liver related death compared with HIV-1 uninfected men"

Identification of factors influencing HCV disease progression in HIV coinfected patients has been based mainly on haemophiliac cohorts and has not been assessed adequately in other HIV risk groups. Level of CD4 immunosuppression has emerged as one of the most important determinants of progression to liver fibrosis, and patients with CD4 cell counts less than 500 cells$\times 10^9$/l are 3.2 times (95% CI 1.1–9.2) more likely to have advanced liver fibrosis on liver biopsy.[64] Patients with a low CD4 count or who had an AIDS diagnosis were also at increased risk for severe liver disease.[59–61 64] Other host factors associated with more rapid HCV disease progression include older age at infection and excess alcohol intake.[59] As for HCV transmission, the impact of HIV on HCV progression is likely to be partly mediated through the increased HCV viral load (table 3). A higher HCV viral load was shown in three studies to correlate with increased hepatic inflammation, as defined by a higher alanine aminotransferase (ALT) value[43 49 50] but this has not been confirmed in other studies.[25 41 42 45 46 48 51 54] In addition, an association between HCV viral load and fibrosis progression has not been clearly demonstrated even in HIV-1 uninfected HCV patients, and a positive correlation with histological grade and stage of disease is lacking.[68] There are conflicting data on the impact of HCV genotype on disease progression in coinfected patients. Two studies have shown no effect of genotype on progression[57 64] while a further two have shown the presence of genotype 1 to be associated with more advanced fibrosis stage[65] and liver related death.[6] Other potential risk factors such as mode of acquisition, past hepatitis B infection, and HCV viral load have not been assessed in coinfected populations.

HCV is a known carcinogen,[69] and the rising prevalence of infection has been implicated as a major contributing factor to the recent increase in incidence of hepatocellular carcinoma (HCC) in the USA.[70] The precise mechanism by which HCV induces carcinogenesis is unclear, but animal studies in transgenic mice have implicated the core protein,[71] which has been reported to downregulate p53 promoter activity[72] and repress p21 promoter activity through the p53 pathway.[73] These events may form the basis for the direct role of HCV in the induction of HCC. It has recently been reported that HCC occurs at a younger age in coinfected patients compared with those infected with HCV alone.[74] While further follow up data are needed, this trend is expected to continue over the coming years as the impact of HCV related liver injury in HIV infected subjects gains further attention.

"HCC occurs at a younger age in coinfected patients compared with those infected with HCV alone"

The consensus from these studies is that HIV-1 is clearly associated with accelerated liver disease and reduced survival in HCV infected patients. In altering the rate of fibrosis progression, HIV-1 may further alter the natural history of HCV infection resulting in an aggressive course to end stage liver disease and liver failure.

IMPACT OF HCV ON HIV-1 PROGRESSION

The impact of HCV infection on the course of HIV disease has become evident in recent years, and the findings of nine studies are summarised in table 5,[7 12 15 20 21 58 75–77] four of which were conducted before the widespread availability of triple combination of antiretroviral therapy. In five studies HCV infection appears to have a significant effect on the progression of HIV to AIDS defining illness and AIDS related mortality.[7 12 58 75 76] In the largest study reported to date, based on a Swiss HIV cohort of patients with well controlled HIV-1 replication, 1593 of whom were coinfected, the risk of progression to AIDS defining illness or death was 3.54 (95% CI 2.0–6.25) compared with HCV uninfected individuals. Daar *et al* have also reported a detrimental effect of HCV viral load on HIV progression. For every 10-fold increase in baseline HCV viral load, the relative risk for clinical progression to AIDS was 1.66 (95% CI 1.1–2.51), and the relative risk for AIDS related mortality was 1.54 (95% CI 1–2.3), even after controlling for $CD4^+$ cell count and HIV-1 RNA level.[75] The evidence from these studies confirms that HCV is an independent factor associated with HIV progression to AIDS and AIDS related death. However, four studies failed to demonstrate a negative effect of HCV on HIV progression.[15 20 21 77] In one study, 70% of patients already had AIDS[20]; two studies were based on retrospective[15] or cross sectional analyses,[21] and in a further study the follow up was 30 months.[77] Reasons for the adverse effect of HCV on HIV disease are unknown. One possible explanation is that patients with coinfection, the majority of whom have acquired their infection through injection drug use, may have reduced compliance with HIV therapies.

Table 6 Relationship between hepatitis C virus (HCV) viral load (VL) and CD4 count in coinfected patients

Year, reference	Country	No of patients coinfected	Mean CD4 cell count/median	Results
1996[41]	USA	42	>200	*r*=0.34, p=0.04
1994[43]	USA	17	201	*r*=–0.56, p=0.006
1996[45]	USA	27	>200	0.36 log HCV-VL increase for every log increase in CD4
1999[46]	Italy	39	206	*r*=–0.23, p=0.08
1998[47]	Netherlands	9	696	*r*=–0.22, p<0.05
2000[49]	Japan	39	320	*r*=–0.34, p=0.07
2001[50]	USA	175	416	For every 100 cell increase HCV-VL decreased by 0.19 $\log_{10}$, p=0.002
1997[62]	Spain	116	CD4 <500 cells	*r*=–0.323, p=0.07
2001[25]	USA	112	235	No relation
1993[42]	USA	13	292–1024	No relation
1995[44]	France	75	278	No relation
1999[48]	USA	22	222	No relation
1996[54]	Germany	22	325	No relation

r, correlation.

"HCV is an independent factor associated with HIV progression to AIDS and AIDS related death"

Thirteen studies have examined the impact of HCV viral load on CD4 cell counts (table 6); eight of these have highlighted an inverse correlation between HCV viral load and CD4 count[41 43 46 47 49 50 62] while five studies have shown no relationship,[25 42 44 48 54] and one study reported a positive correlation.[45] It has been suggested that this inverse relationship between HCV viral load and CD4 count may be explained on the basis of immune dysregulation of HCV replication.[49 75]

PATHOGENESIS OF HIV-1-HCV INTERACTION

Several lines of evidence suggest that liver injury in HCV patients is due to the immune response to HCV rather than a direct viral effect. Strong HCV specific T helper 1 cell responses and T helper cell recognition of multiple core epitopes are associated with clearance of HCV naturally and after interferon therapy.[78–80] Furthermore, HCV specific CD4+ and CD8+ T cells have been shown to persist as biomarkers for prior HCV exposure and recovery, even if HCV antibodies decline and become undetectable.[81] HIV-1 infects CD4 cells which leads to impaired response of both the infected CD4+ T cells and the uninfected CD8+ T cells, and this functional loss eventually leads to profound immune dysregulation.[82] The impaired immune response to HCV in the setting of HIV infection may explain the inability of coinfected patients to clear HCV infection naturally, and possibly also the poor response to current treatment.

"The mechanism by which HCV influences HIV-1 progression remains speculative"

The mechanism by which HCV influences HIV-1 progression remains speculative. HCV may downregulate proliferation of T cells[83] or increase apoptosis of T cells by apoptotic pathways.[84] Patients with HCV infection express Fas on peripheral blood mononuclear cells and HCV-RNA has preferentially been detected in these Fas positive cells.[85] This may form the basis for a synergistic effect of HIV-1 and HCV on CD4 positive cells both in terms of production and apoptosis which in turn could explain the negative impact of HCV on HIV progression.

IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL HIV THERAPY ON HCV PROGRESSION

A total of eight studies examined the impact of HAART on HCV progression. Five studies found no evidence for an effect of HAART on HCV replication[86–90] while two studies have reported significant transient increases in HCV viral load[91 92] and transaminases (ALT, aspartate aminotransferase (AST)) following introduction of HAART. A protective effect of HAART on fibrosis progression has also been suggested[59] but needs to be confirmed in large prospective studies. One report has also shown a significant increase in HCV viral load at 96 weeks post HAART compared with baseline, although samples taken at 24 weeks post HAART did not show a significant increase.[93] The mechanism for the higher HCV-RNA levels with HAART despite immune restoration is unclear but is probably not associated with HIV related immune dysfunction. However, the increase in transaminases is associated with an improving immune response as shown by a correlation with a reduction in HIV viral load and increase in CD4 cell count.[90–92 94] In one study, multivariate logistic regression analysis demonstrated that a HAART induced CD4 cell count increase of 50 cells or more was independently associated with severe hepatotoxicity (odds ratio 3.6; 95% CI 1.0–12.9) in coinfected patients.[94]

A number of studies have also identified HCV as a strong predictor of the development of hepatotoxicity (elevation of AST and ALT of over 1.25 times from baseline) with HAART,[13 94–97] in addition to other factors such as ritonavir use[94 97] and hyperbilirubinaemia associated with indinavir treatment. Of 138 HIV patients treated with indinavir, hyperbilirubinaemia occurred in 56 (40.6%), and HCV was an independent predictor of hepatotoxicity.[98] Hepatotoxicity has also been observed with the use of reverse transcriptase inhibitors which can cause mitochondrial toxicity and microsteatosis, and which may also lead to lethal hepatotoxicity.[99] More recently, HCV was shown to be a confounding factor for the development of lipoatrophy in coinfected patients (p=0.003), and in a multivariate analysis HCV was independently associated with insulin resistance, body mass index, and peripheral fat wasting.[100]

In conclusion, there is no definitive evidence to support a clear effect of HAART on the natural history of HCV infection but HCV infection appears to be an independent predictor of hepatotoxicity following the introduction of HAART. The relationship of liver toxicity to antiretroviral therapy depends on the specific antiretroviral agent and the degree of immune reconstitution.

IMPACT OF HCV TREATMENT ON HIV DISEASE PROGRESSION

Treatment of HCV infection has evolved over the last decade with an increasingly higher percentage of patients achieving sustained viral clearance (defined as HCV RNA negative at six months after stopping therapy) following the introduction of combination based therapies with interferon and ribavirin, and more recently pegylated interferon.[101–104] Of note, HCV-HIV coinfected patients were all excluded from placebo controlled trials with interferon alpha. However, the results of nine non-placebo controlled trials[6 52 105–111] showed an equivalent percentage who had a sustained response to HCV therapy in coinfected compared with HCV only infected individuals. This ranged between 8% and 29%, although the interferon dosage and duration varied considerably across the different studies (from 3 to 9 million units weekly for 6–12 months). Side effects of interferon in coinfected patients were comparable with HIV uninfected patients.[52] Over 90% of patients were able to complete their treatment course indicating that interferon is well tolerated even when used in conjunction with antiretroviral therapy. A 5% drop in CD4 cell count occurred in less than 5% of patients treated, and occurred in the first 10 weeks of therapy. However, this decline in CD4 count may be clinically significant and contribute to the subsequent development of opportunistic infections.[52 112 113]

Combination therapy with interferon alpha and ribavirin is the current gold standard in the treatment of HCV infection.[103 104] Based on three studies, 80 coinfected patients treated with interferon and ribavirin showed a comparable sustained viral response rate and incidence of side effects to HIV uninfected patients,[114–116] and the results of several large studies are awaited. Five cases of mitochondrial toxicity have been reported in coinfected patients receiving interferon and ribavirin and were thought to relate to the interaction of ribavirin with didanosine[117 118] as a result of enhanced phosphorylation of didanosine which reached toxic levels.[119] In all studies published thus far, the HIV viral load did not change when ribavirin was commenced in patients who were already receiving antiretroviral therapy.

> "The development of a helicase inhibitor, which is anticipated in the near future, together with other novel approaches, are antisense genes, ribozymes, and HCV specific protease inhibitors"

The recent introduction of pegylated interferon in combination with ribavirin appears to further improve the rate of sustained viral response and patient compliance. Preliminary data report that the regimen is well tolerated with 65% achieving viral clearance at six months.[120] The development of a helicase inhibitor which is anticipated in the near future, together with other novel approaches, are antisense genes, ribozymes, and HCV specific protease inhibitors. Immunotherapy may also have a place in the future. Schlaak *et al* showed HCV viral clearance in two (28.6%) of seven coinfected patients treated with interleukin 2.[121] Future HCV therapy is therefore likely to include multiple combinations similar to those used in HIV therapy.

TRANSPLANTATION

In the past, the presence of HIV infection was generally considered a contraindication for liver transplantation. This was partly related to the ethical debate over allocation of limited health care resources and the difficulty in justifying the use of live related donors when life expectancy was limited for other reasons. However, following the introduction of HAART and subsequent prolonged survival of HIV patients, organ transplantation as a treatment strategy for HCV infection is being evaluated in a number of centres. At King's College Hospital, 1000 liver recipient transplants were performed between 1995 and 2001, of which 10 patients were HIV infected[122] and five had HIV-1-HCV coinfection. Three presented with fulminant liver failure, in two due to hepatitis B infection, in one due to non-A non-B infection (although he was also infected with hepatitis B), and in one due to end stage alcoholic liver disease. All survived the postoperative period and were discharged home. Four patients died subsequently at 3, 6, 15, and 25 months following transplantation, and the cause of death in these patients was hepatitis C complications as a result of reinfection.

> "Organ transplantation as a treatment strategy for HCV infection is being evaluated in a number of centres"

None of the patients with hepatitis B developed graft reinfection post transplant, and six patients are currently alive with the longest survival now over 42 months. Only one patient developed complications related to HIV infection. The treatment related immunosuppressive drugs were well tolerated and infective complications and HIV progression were uncommon. Thus liver transplantation may be an option in carefully selected patients.

INTERACTION OF HCV-HIV-1 COINFECTION AND HEPATITIS A AND HEPATITIS B

There are no available data on vaccination in coinfected patients and therefore vaccination of HCV-HIV infected patients remains controversial. Acute hepatitis A has been shown to be more severe and associated with higher mortality in patients infected with HCV and especially in those with advanced liver disease.[123] However, other groups have not confirmed this finding.[124] The response of hepatitis A vaccination in HIV positive patients is high, with up to 88% mounting an antibody response and without adverse effect.[125]

> "Vaccination of HCV-HIV infected patients remains controversial"

Selective hepatitis A vaccination may be indicated in HIV-HCV coinfected patients who have not been exposed previously. Past hepatitis B exposure as defined by hepatitis B core antibody positive in HIV uninfected patients has also been shown to be a strong predictor of severe liver disease.[2] This observation was confirmed by paired liver biopsies where past hepatitis B infection was an independent marker of progression. Furthermore, hepatitis B is associated with more advanced liver disease in patients with chronic hepatitis C.[126] Patients with HIV-HCV coinfection who have not been exposed to hepatitis B should therefore be vaccinated. Currently, combined hepatitis A and B vaccination is available and will facilitate more convenient delivery of protective vaccination.

Authors' affiliations
A H Mohsen, P Easterbrook, Academic Department of HIV/GU Medicine, King's College, University of London, London, UK
C B Taylor, Department of Sexual Health, King's College, University of London, London, UK
S Norris, Department of Hepatology, King's College, University of London, London, UK

REFERENCES

1 **WHO**. Hepatitis C: Global Update. *Wkly Epidemiol Rec* 1997;**72**:341–4.
2 **Mohsen AH**, Trent HCV Study Group. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. *Gut* 2001;**5**:707–13.
3 National Institutes of Health Consensus Development Conference Panel Statement: management of hepatitis C. *Hepatology* 1997;**26**:2–10S.
4 **Sulkowski MS**, Mast EE, Seeff LB, *et al*. Hepatitis C virus infection as an opportunistic disease in persons infected with human immunodeficiency virus. *Clin Infect Dis* 2000;**30**(suppl 1):S77–84.

5 **Darby SC**, Ewart DW, Giangrande PL, *et al.* Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. *Lancet* 1997;**15**:350:1425–31.
6 **Yee TT**, Griffioen A, Sabin CA, *et al.* The natural history of HCV in a cohort of haemophilic patients infected between 1961 and 1985. *Gut* 2000;**47**:845–51.
7 **Klein MB**, Lalonde RG, Suissa S. Hepatitis C coinfection is associated with increased morbidity and mortality among HIV-infected patients. *8th Conference on Retroviruses and Opportunistic Infections* 2001, abstract 569.
8 **Bica I**, McGovern BH, Dhar R, *et al.* Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001;**32**:492–7.
9 **Soriano V**, Garcia-Samaniego J, Valencia E, *et al.* 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.
10 **Binfield T**, Cent C. Hepatitis C in the EuroSIDA cohort of European HIV-infected patients: prevalence and prognostic value. *12th World AIDS Conference*, Geneva, Switzerland, Geneva, Switzerland, 1998: abstract 22261.
11 **Negredo E**, Domingo P, Sambeat M, *et al.* Influence of coinfection with hepatitis virus on human immunodeficiency plasma viral load. *Arch Med* 1999;**59**:2367–8.
12 **Greub G**, Ledergerber B, Battegay M, *et al.* 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.
13 **Brinker MD**, Wit FWNM, Dillen PMEW, *et al.* Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS* 2000;**14**:2895–902.
14 **Hayashi PH**, Flynn N, McCurdy SA, *et al.* Prevalence of hepatitis C virus antibodies among patients infected with human immunodeficiency virus. *J Med Virol* 1991;**33**:177–80.
15 **Wright TL**, Hollander H, Pu X, *et al.* Hepatitis C in HIV-infected patients with and without AIDS: prevelance and relationship to patients survival. *Hepatology* 1994;**20**:1152–5.
16 **Merrick ST**, Sepkowitz KA, Boyle BA, *et al.* Seroprevalence of hepatitis C antibody and hepatitis B surface antigenemia in a large urban HIV clinic. *12th World AIDS Conference*, Geneva, Switzerland, 1998: abstract 22263.
17 **Vogt RL**, Richmond-Crum S, Diwan A. Hepatitis C infection in human immune deficiency virus-positive cohort in Hawaii. *J Infect Dis* 1997;**176**:542–3.
18 **Thomas DL**, Villano SA, Riester KA, *et al.* Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. Women and Infants Transmission Study. *J Infect Dis* 1998;**177**:1480–8.
19 **Pollard RB**. Analogy of human immunodeficiency virus to hepatitis C virus: the human immunodeficiency model. *Am J Med* 1999;**107**(suppl):41–4.
20 **Staples CT Jr**, Rimland D, Dudas D. Hepatitis C in the HIV Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. *Clin Infect Dis* 1999;**29**:150–4.
21 **Quan CM**, Krajden M, Grigoriew GA, *et al.* Hepatitis C virus infection in patients infected with human immune deficiency virus. *Clin Infect Dis* 1993;**17**:117–9.
22 **Troisi CL**, Hollinger FB, Hoots WK, *et al.* A multicenter study of viral hepatitis in a United States hemophilic population. *Blood* 1993; **81**:412–18.
23 **Centers for Disease Control and Prevention**. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Morb Mortal Wkly Rep* 1998;**47**(RR-19):1.
24 **Bonacini M**, Lin HJ, Hollinger FB. Prevalence of HCV RNA in HIV-infected patients. *J Hepatol* 1999;**30**(suppl 1):135.
25 **Bonacini M**, Lin HJ, Hollinger FB. Effect of coexisting HIV-1 infection on the diagnosis and evaluation of hepatitis C virus. *J Acquir Immune Defic Syndr* 2001;**26**:340–4.
26 **Chamot E**, Hirchel B, Wintsch J, *et al.* Loss of antibodies against hepatitis C virus in HIV-seropositive intravenous drug users. *AIDS* 1990;**4**:1275–7.
27 **Soto B**, Rodrigo L, Garcia-Bengoechea M, *et al.* Heterosexual transmission of hepatitis C virus and the possible role of coexistent human immunodeficiency virus infection in the index case. A multicentre study of 423 pairings. *J Intern Med* 1994;**236**:515–19.
28 **Green ST**, Mohsen AH, McKendrick MW, *et al.* Potential for hepatitis C transmission among non-needle/syringe sharing Sheffield drug injectors through the sharing of drug preparation paraphernalia. *Commun Dis Public Health* 2001;**4**:38–41.
29 **Thomas DL**, Zenilman JM, Alter HJ, *et al.* Sexual transmission of hepatitis C virus among patients attending sexually transmitted diseases clinics in Baltimore—an analysis of 309 sex partnerships. *J Infect Dis* 1995;**171**:768–75.
30 **Craib KJP**, Sherlock CH, Hogg RS, *et al.* Evidence of sexual transmission of hepatitis C virus (HCV) in a cohort of homosexual men. *8th Conference on Retroviruses and Opportunistic Infections*, Chicago, 2001: abstract 561.
31 **Zanetti AR**, Tanzi E, Paccagnini S, *et al.* Mother-to-infant transmission of hepatitis C virus. *Lancet* 1995;**345**:289–91.
32 **Tovo PA**, Palomba E, Ferraris G, *et al.* Increased risk of maternal-infant hepatitis C virus transmission for women coinfected with human immunodeficiency virus type 1. *Clin Infect Dis* 1997;**25**:1121–4.
33 **Mazza C**, Ravaggi A, Rodella A, *et al.* Prospective study of mother-to-infant transmission of hepatitis C virus (HCV) infection. *J Med Virol* 1998;**54**:12–19.
34 **Gibb DM**, Goodall RL, Dunn DT, *et al.* Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000;**356**:904–7.
35 **European Paediatric Hepatitis C Virus Network**. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. *Br J Obstet Gynaecol* 2001;**108**:371–7.
36 **Lam JPH**, McOmish F, Burns SM, *et al.* Infrequent vertical transmission of hepatitis C virus. *J Infect Dis* 1993;**167**:572–6.
37 **Paccagnini S**, Principi N, Massironi E, *et al.* Perinatal transmission and manifestation of hepatitis C virus infection in a high risk population. *Pediatr Infect Dis J* 1995;**14**:195–9.
38 **Zuccotti GV**, Ribero ML, Giovannini M, *et al.* Effect of hepatitis C genotype on mother-to-infant transmission of virus. *J Pediatr* 1995;**127**:278–80.
39 **Granovsky MO**, Minkof HL, Tess BH, *et al.* Hepatitis C virus infection in the mothers and infants cohort study. *Pediatrics* 1998;**102**:355–9.
40 **Hershow RC**, Riester KA, Lew J, *et al.* Increased vertical transmission of human immunodeficiency virus from hepatitis C viruscoinfected mothers. *J Infect Dis* 1997;**176**:414–20.
41 **Ghany MG**, Leissinger C, Lagier R, *et al.* Effect of human immunodeficiency virus infection on hepatitis C virus infection in haemophiliacs. *Dig Dis Sci* 1996;**41**:1265–72.
42 **Sherman KE**, O'Brien J, Gutierrez AG, *et al.* Quantitative evaluation of hepatitis C virus RNA in patients with concurrent human immunodeficiency virus infection. *J Clin Microbiol* 1993;**31**:2679–82.
43 **Eyster ME**, Fried MW, Di Bisceglie AM, *et al.* Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to HIV infection and liver disease. *Blood* 1994;**84**:1020–3.
44 **Cribier B**, Rey D, Schmitt C, *et al.* High hepatitis C viremia and impaired antibody response in patients coinfected with HIV. *AIDS* 1995;**9**:1131–6.
45 **Thomas DL**, Shih JW, Alter HJ, *et al.* Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. *J Infect Dis* 1996;**174**:690–5.
46 **Dragoni F**, Cafolla A, Gentile G, *et al.* HIV-HCV RNA loads and liver failure in coinfected patients with coagulopathy. *Haematologica* 1999;**84**:525–9.
47 **Beld M**, Penning M, Lukashov V, *et al.* Evidence that both HIV and HIV-induced immunodeficiency enhance HCV replication among HCV seroconverters. *Virology* 1998;**244**:504–12.
48 **Bonacini M**, Govindarajan S, Blatt LM, *et al.* Patients coinfected with human immunodeficiency virus demonstrate higher levels of hepatic HCV RNA. *J Viral Hepat* 1999;**6**:203–8.
49 **Yokozaki S**, Takamatsu J, Nakano I, *et al.* Immunologic dynamics in hemophiliac patients infected with hepatitis C virus and human immunodeficiency virus: influence of antiretroviral therapy. *Blood* 2000;**96**:4293–9.
50 **Daar ES**, Lynn H, Donfield S, Gomperts E, *et al.* Hemophilia Growth and Development Study. Relation between HIV-1 and hepatitis C viral load in patients with hemophilia. *J Acquir Immune Defic Syndr* 2001;**26**:466–72.
51 **Boncini M**, Lin HJ, Hollinger B. Effect of coexisting HIV-1 infection on the diagnosis and evaluation of hepatitis C virus. *J Acquir Immune Defic Syndr* 2001;**26**:340–4.
52 **Causse X**, Payen JL, Izopet J, *et al.* Does HIV influence the response of chronic hepatitis C to interferon treatment? *J Hepatol* 2000;**32**:1003–10.
53 **Sanchez-Quijano A**, Andreu J, Gavilan F, *et al.* Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. *Eur J Clin Microbiol Infect Dis* 1995;**14**:949–53.
54 **Berger A**, Prondzinski MVD, Doerr HW, *et al.* Hepatitis C viral load is associated with HCV genotype but not with HIV coinfection. *J Med Virol* 1996;**48**:339–43.
55 **Rey D**, Fritsch S, Schmitt C, *et al.* Quantitation of hepatitis C virus RNA in saliva and serum of patients coinfected with HCV and human immunodeficiency virus. *J Med Virol* 2001;**63**:117–19.
56 **Makris M**, Preston FE, Rosendaal FR, *et al.* The natural history of chronic hepatitis C in haemophiliacs. *Br J Haematol* 1996;**94**:746–52.
57 **Pol S**, Fontaine H, Carnot F, *et al.* Predictive factors for development of cirrhosis in parenterally acquired chronic hepatitis C: a comparison between immunocompetent and immunocompromised patients. *J Hepatol* 1998;**29**:12–19.
58 **Lesens O**, Deschenes M, Steben M, *et al.* Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive haemophililiacs and should be treated as an opportunistic infection. *J Infect Dis* 1999;**179**:1254–8.
59 **Benhamou Y**, Bochet M, Di Martino, *et al.* Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. *Hepatology* 1999;**30**:1054–8.
60 **Telfer P**, Sabin C, Devereux H, *et al.* The progression of HCV-associated liver disease in a cohort of haemophilic patients. *Br J Haematol* 1994;**88**:397–9.
61 **Eyster ME**, Diamondstone LS, Lien JM, *et al.* Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. *J Acquir Immune Defic Syndr* 1993;**6**:602–10.
62 **Soto B**, Sanchez-Quijano A, Rodrigo L, *et al.* Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997;**26**:1–5.

63 **Bierhoff E**, Fischer HP, Willsch E, *et al.* Liver histopathology in patients with concurrent chronic hepatitis C and HIV infection. *Virchows Arch* 1997;**430**:271–7.
64 **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 human immunodeficiency virus. *J Infect Dis* 2001;**183**:134–7.
65 **Garcia-Samaniego J**, Soriano V, Castilla J, *et al.* Influence of hepatitis C virus genotypes and HIV infection on histological severity of chronic hepatitis C. *Am J Gastroenterol* 1997;**92**:1130–4.
66 **Rockstroh JK**, 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.
67 **Graham CS**, Baden LR, Yu E, *et al.* Influence of human immunodeficiency virus infection on the course of hepatitis c virus infection: a meta-analysis. *Clin Infect Dis* 2001;**33**:562–9.
68 **Di Bisceglie A**. Hepatitis C. *Lancet* 1998;**351**:351–5.
69 **International Interferon-Hepatocellular Carcinoma Study Group**. Effect of interferon on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study. *Lancet* 1998; **351**:1535–9.
70 **El-Serag H**, Mason A. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;**340**:745–50.
71 **Moriya K**, Fujie H, Shintani Y, *et al.* The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. *Nat Med* 1998;**4**:1065–7.
72 **Ray RB**, Steele R, Meyer K, *et al.* Transcriptional repression of p53 promoter by hepatitis C virus core protein. *J Biol Chem* 1997;**272**:10983–6.
73 **Ray RB**, Steele R, Meyer K, *et al.* Hepatitis C virus core protein represses p21WAF1/Cip1/Sid1 promoter activity. *Gene* 1998;**208**:331–6.
74 **García-Samaniego J**, Rodríguez M., Berenguer J, *et al.* Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterol* 2001;**96**:179–83.
75 **Daar ES**, Lynn H, Donfield S, *et al.* Hepatitis C virus load is associated with human immunodeficiency virus type 1 disease progression in hemophiliacs. *J Infect Dis* 2001;**183**:589–95.
76 **Piroth L**, Duong M, Quantin C, *et al.* Does hepatitis C virus coinfection accelerate clinical and immunological evolution of HIV-infected patients? *AIDS* 1998;**12**:381–8.
77 **Dorrucci M**, Pezzotti P, Phillips AN, *et al.* Coinfection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. Italian Seroconversion Study. *J Infect Dis* 1995;**172**:1503–8.
78 **Lasarte JJ**, Garcia-Granero M, Lopez A, *et al.* Cellular immunity to hepatitis C virus core protein and the response to interferon in patients with chronic hepatitis C. *Hepatology* 1998;**28**:815–22.
79 **Diepolder HM**, Zachoval R, Hoffmann RM, *et al.* Possible mechanism involving T response to non-structural protein 3 in viral clearance in acute hepatitis C virus infection. *Lancet* 1995;**346**:1006–7.
80 **Rehermann B**, Chisari FV. Cell mediated immune response to the hepatitis C virus. *Curr Top Microbiol Immunol* 2000;**242**:299–325.
81 **Takaki A**, Wiese M, Maertens G, *et al.* Cellular immune responses persist and humoral responses decrease two decades recovery from a single-source outbreak of hepatitis C. *Nat Med* 2000;**6**:578–82.
82 **Mcmichael AJ**, Rowland-Jones S. Cellular immune response to HIV. *Nature* 2001;**410**:980–7.
83 **Graham CS**, Koziel MJ. Why should hepatitis C affect immune reconstitution in HIV-1-infected patients? *Lancet* 2000;**356**:1865–6.
84 **Lai MM**. Hepatitis viruses and signal transduction: true to the core? *Hepatology* 2000;**32**:427–9.
85 **Taya N**, Torimoto Y, Shindo M, *et al.* Fas-mediated apoptosis of peripheral blood mononuclear cells in patients with hepatitis C. *Br J Haematol* 2000;**110**:89–97.
86 **Gavazzi P**, Richallet G, Morand P, *et al.* Effects of double and triple antiretroviral agents on the HCV viral load in patients coinfected with HIV and HCV. *Pathol Biol* 1998;**46**:412–5.
87 **Zylberberg H**, Chaix ML, Rabian C, *et al.* Tritherapy for human immunodeficiency virus infection does not modify replication of hepatitis C virus in coinfected subjects. *J Infect Dis* 1998;**26**:1104–6.
88 **Rockstroh JK**, Theisen A, Kaiser R, *et al.* 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.
89 **Garcia-Samaniego J**, Bravo R, Castilla J, *et al.* Lack of benefit of protease inhibitors on HCV viremia in HIV-infected patients. *J Hepatol* 1998;**28**:526–7.
90 **Gavazzi G**, Bouchard O, Leclercq P, *et al.* Change in transaminases in hepatitis C virus- and HIV-coinfected patients after highly active antiretroviral therapy: differences between complete and partial virologic responders? *AIDS Res Hum Retroviruses* 2000;**20**;16:1021–3.
91 **Rutschmann OT**, Negro F, Hirschel B, *et al.* Impact of treatment with human immunodeficiency virus (HIV) protease inhibitors on hepatitis C viremia in patients coinfected with HIV. *J Infect Dis* 1998;**177**:783–5.
92 **Vento S**, Garofano T, Renzini C, *et al.* Enhancement of hepatitis C virus replication and liver damage in HIV-coinfected patients on antiretroviral combination. *AIDS* 1998;**12**:116–17.
93 **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.
94 **Sulkowski M**, Thomas DL, Chaisson RE, *et al.* Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA* 2000;**283**:74–80.
95 **Karras A**, Rabian C, Zylberberg H, *et al.* Severe anoxic hepatic necrosis in an HIV-1 hepatitis C virus coinfected patient starting antiretroviral triple combination therapy. *AIDS* 1998;**12**:827–9.
96 **Rodriguez-Rosado R**, Garcia-Samaniego J, Soriano V. Hepatotoxicity after introduction of highly active antiretroviral therapy. *AIDS* 1998;**12**:1256.
97 **Arribas JR**, Ibanez C, Ruiz-Antoran B, *et al.* Acute hepatitis in HIV-infected patients during ritonavir treatment. *AIDS* 1998;**12**:1722–4.
98 **Rodriguez-Resado R**, Garcia-Samaniego J, Soriano V, *et al.* Hepatotoxicity after introduction of highly active antiretroviral therapy (HAART). Presented at the *12th World AIDS Conference*, Geneva, 1998: abstract 12288.
99 **Brinkman K**, ter Hofstede HJM, Burger DM, *et al.* Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS* 1998;**12**:1735–44.
100 **Duong M**, Petit JM, Piroth L, *et al.* Association between insulin resistance and hepatitis C virus chronic infection in HIV-hepatitis C virus-coinfected patients undergoing antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001;**27**:245–50.
101 **Heathcote EJ**, Shiffman ML, Cooksley WG, *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000;**343**:1673–80.
102 **Zeuzem S**, Feinman SV, Rasenack J, *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;**343**:1666–72.
103 **Poynard T**, Marcellin P, Lee SS, *et al.* Randomised trial of interferon alpha-2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998;**352**:1426–32.
104 **McHutchison JG**, Gordon SC, Schiff ER, *et al.* Interferon alpha-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 1998;**339**:1485–92.
105 **Boyer N**, Marcellin P, Degott C, *et al.* Recombinant interferon- for chronic hepatitis C in patients positive for antibody to human immunodeficiency virus. *J Infect Dis* 1992;**165**:723–6.
106 **Mariott E**, Navas S, del Romero J, *et al.* Treatment with recombinant-interferon of chronic hepatitis C in anti-HIV positive patients. *J Med Virol* 1993;**40**:107–11.
107 **Mauss S**, Klinker H, Ulmer A, *et al.* Response to treatment of chronic hepatitis C with interferon alpha in patients infected with HIV-1 is associated with higher CD4+ cell count. *Infection* 1998;**26**:16–19.
108 **Del Pozo MA**, Arias JR, Pinilla J, *et al.* Interferon alpha treatment of chronic hepatitis C in HIV-infected patients receiving zidovudine: efficacy, tolerance, and response related factors. *Hepatogastroenterology* 1998;**45**:1695–701.
109 **Soriano V**, Rodriguez-Rosado R, Garcia-Samaniego J. Management of chronic hepatitis C in HIV-infected patients. *AIDS* 1999;**13**:539–46.
110 **Soriano V**, Bravo R, Garcia-Samaniego J, *et al.* A pilot study on the efficacy of escalating dosage of alpha-interferon for chronic hepatitis C in HIV-infected patients. *J Infect* 1997;**35**:225–30.
111 **Mauss S**, Heintges T, Adams O, *et al.* Treatment of chronic hepatitis C with interferon-alpha in patients infected with the human immunodeficiency virus. *Hepatogastroenterology* 1995;**42**:528–34.
112 **Vento S**, Di Perri G, Cruciani M, *et al.* Rapid decline of CD+ cells after IFN- treatment in HIV-1 infection. *Lancet* 1993;**341**:958–9.
113 **Pesce A**, Taillan B, Rosenthal E, *et al.* Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1-infected patients. *Lancet* 1993;**341**:1597.
114 **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;**47**:694–7.
115 **Landau A**, Batisse D, Duong Van Huyen JP, *et al.* Efficacy and safety of combination therapy with interferon-2b and ribavirin for chronic hepatitis C in HIV-infected patients. *AIDS* 2000;**14**:839–44.
116 **Nasti G**, Gennaro GD, Rizzardini G, *et al.* Chronic hepatitis C in HIV-coinfected patients: feasibility and efficacy of interferon-alpha2b and ribavirin combination therapy. *J Acquir Immune Defic Syndr* 2001;**26**:299–300.
117 **Lafeuillade A**, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. *Lancet* 2001;**357**:280.
118 **Kakuda TN**, Brinkman K. Mitochondrial toxic effects and ribavirin. *Lancet* 2001:**357**:1803–4.
119 **Hoggard PG**, Kewn S, Barry MG, *et al.* Effects of drugs on 29,39-dideoxy-29,39-didehydrothymidine phosphorylation in vitro. *Antimicrob Agents Chemother* 1997;**41**:1231–6.
120 **Soriano V**, Garcia-Samaniego J, Perz-Olmeda M, *et al.* Pegylated interferon plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. *1st IAS Conference on HIV Pathogenesis and Treatment*, Buenos Aires, Argentina, July 8–11, 2001:abstract 42.
121 **Schlaak JF**, Zum B, Gerken G, *et al.* Sustained HCV eradication after interleukin-2 therapy in patients with HIV/HCV coinfection. *Association for the Study of Liver Disease* Dallas, Texas, 1999:abstract 431A.
122 **Boyd AE**, Tayler C, Norris S, *et al.* Liver transplantation and HIV—a case series of 7 patients. *8th Conference on Retroviruses and Opportunistic Infections*, Chicago, 2001:abstract 578.
123 **Vento S**, Garofano T, Renzini C, *et al.* Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998;**338**:286–90.
124 **Mele A**, Tosti ME, Stroffolini T. Hepatitis associated with hepatitis A superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998;**338**:1771.
125 **Neilsen GA**, Bodsworth NJ, Watts N. Response to hepatitis A vaccination in human immunodeficiency virus-infected and-uninfected homosexual men. *J Infect Dis* 1997;**176**:1064–7.
126 **Roudot-Thoroval F**, Bastie A, Pawlotsky JM, *et al.* Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: French survey of 6664 patients. *Hepatology*1997;**26**:485–90.