REVIEW

Hepatitis C and HIV-1 coinfection

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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 coinfecting 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 coinfecting with both HIV-1 and HCV have demonstrated that HCV is the leading non-acquired immunodeficiency syndrome (AIDS) cause of death in coinfecting 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.

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 coinfecting 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 coinfecting 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 coinfecting 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 coinfecting 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.

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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	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 coinfecting 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 coinfecting women comprising 1089 coinfecting 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 coinfecting 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 coinfecting 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 coinfecting mothers.⁴⁰

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

Year, reference	No of coinfecting mothers/HCV infected only	Location	No HCV infected children (%) in coinfecting/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 coinfecting patients

Year, reference	No of coinfecting patients/HCV only infected	Location	Mean/ median CD4 cell count	Absolute increase in HCV viral load in coinfecting 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 × 10 ⁶ copies/ml, p<0.05	Single
1994 ⁴³	17/17	USA	201	25.6 × 10 ⁵ eq genome/ml, p=0.006	Multiple
1995 ⁴⁴	75/75	France	278	101.7 × 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 × 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 coinfecting/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 coinfecting 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 coinfecting 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 coinfecting patients.⁵⁵

Together, these data demonstrate a higher rate of vertical and sexual transmission of HCV in coinfecting 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 coinfecting 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 coinfecting patients.⁶⁷ Similar evidence for liver related deaths was provided by the UK haemophilic cohort of

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

Year, reference	Location	No of coinfectd 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	3.45 (2.0–6.25)	Patients with well controlled HIV-1 replication
1993 ²¹	USA	18/195	—	AIDS	1.72 (1.25–2.36)	—
1999 ⁵⁸	Canada	22/59	17.2 y	AIDS and death	0.3 (0.084–1.07)	Patients with progressive liver disease
2001 ⁷⁵	USA	207	7 y	AIDS	2 (1.06–3.9)	Haemophiliacs
1998 ⁷⁶	France	119/119	3 y	Death	1.66 (1.1–2.51)	—
1995 ⁷⁷	Italy	214/202	30 months	AIDS and death	1.54 (1.03–2.30)	AIDS free cohort with known seroconversion date
					1.64 (1.06–2.06) adjusted for CD4 cell count	
					0.97 (0.52–1.79) adjusted for CD4 cell count	

305 patients of whom 125 were coinfectd. The relative hazard of liver related death, adjusted for age and HCV genotype, was 17.5-fold for coinfectd 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 coinfectd 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×10⁹/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 coinfectd 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 stage⁶⁵ 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 coinfectd 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 activity⁷² 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 coinfectd 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 coinfectd 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 coinfectd, 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 AIDS²⁰; two studies were based on retrospective¹⁵ 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 coinfecting patients

Year, reference	Country	No of patients coinfecting	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 coinfecting 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 cells⁸³ 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 suggested⁹³ 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 coinfecting 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,^{15 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 lipodystrophy in coinfecting 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 coinfecting 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 coinfecting 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 coinfecting 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 coinfecting 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 coinfecting 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 coinfecting 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 infected¹²² 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 coinfecting 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 coinfecting 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.

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