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The progression of HCV-associated liver disease in a cohort of haemophilic patients

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Summary. We have studied morbidity and mortality related to hepatitis C virus infection in haemophilic patients treated at our centre. 11/255 HCV seropositive patients have developed hepatic decompensation. 20 years after first exposure to lyophilized clotting factor concentrate the risk of hepatic decompensation is estimated to be 10·8% (95% CI 3·8–17·8%). There is a significantly increased risk associated with HIV infection, and also with increased age. For HIV seropositive patients the rates of decline in CD4 lymphocyte count and the development of p24 antigenaemia are significant risk factors for hepatic decompensation. Cirrhosis was seen in 9/19 HIV seropositive patients at post mortem. There was an association of cirrhosis with increased age but not with CD4 count, p24 antigenaemia, or AIDS. In conclusion, HCV infection is associated with serious liver disease in haemophilic patients, but so far this has been restricted to a minority of those at risk. HIV co-infection accelerates progression to hepatic decompensation, and we speculate that this is probably due to enhanced HCV replication in the presence of immune deficiency.

Keywords: haemophilia, hepatitis C, HIV, AIDS, liver disease.

Haemophilia treatment was revolutionized in the 1970s by the introduction of lyophilized large donor pool clotting factor concentrates. Home treatment of bleeding episodes enabled people with severe haemophilia to live relatively normal lives, and permitted surgery to be undertaken safely in the majority. However, the early concentrates were not subjected to a viral inactivation procedure during preparation and their use was associated with a high prevalence of non-A, non-B hepatitis (Cederbaum *et al*, 1982) and with transmission of the human immunodeficiency virus (HIV) (Lee *et al*, 1989). Hepatitis C virus (HCV) is now known to be the major cause of post-transfusion non-A, non-B hepatitis (Choo *et al*, 1989; Kuo *et al*, 1989). Early studies in haemophilia patients using first-generation anti-HCV enzyme immunoassays (EIAs) reported seroprevalence rates between 59% and 80% (Ludlam *et al*, 1989; Makris *et al*, 1990; Noel *et al*, 1989; Roggendorf *et al*, 1989; Rumi *et al*, 1990). With more sensitive second-generation anti-HCV assays it has been shown that the prevalence of HCV infection in those treated with unsterilized large donor pool clotting factor concentrates is close to 100% (Watson *et al*, 1992).

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Whilst patients infected with HCV usually experience a mild acute hepatitis, at least 50% develop chronic hepatitis and some progress to severe liver disease including cirrhosis, hepatocellular carcinoma and hepatic decompensation (Dusheiko, 1992). Haemophilia centres have been collecting clinical information on liver disease for over two decades, but there is still insufficient information to be clear about the natural history and relevant risk factors. Histological studies reported in the mid-1980s drew attention to the presence of severe and in some cases progressive histological changes (Hay *et al*, 1985; Aledort *et al*, 1985; Mannucci *et al*, 1982). One recent study (Eyster *et al*, 1993) suggests that HIV seropositivity is associated with a more rapid disease progression.

In this paper we have retrospectively studied the clinical data on all patients with congenital coagulation disorders registered at our centre who have been treated with clotting factor concentrates and who are HCV seropositive. We have attempted to define the risk of developing symptomatic liver disease, and to identify factors which are associated with disease progression.

METHODS

Clinical assessment. Records of all patients registered at the

Royal Free Hospital Haemophilia Centre were reviewed from 1979 up to August 1993. Over this period, patients with severe haemophilia (factor VIIIc < 1 unit/dl) were seen 6-monthly and those with moderate (factor VIIIc 1–4 units/dl) and mild (factor VIIIc 5–25 units/dl) haemophilia annually. From 1985 onwards, HIV seropositive patients were seen every 3 months. Assessment included medical history, review of home- and in-patient treatment records, physical examination, and a standard panel of blood tests. Since 1979, a serum sample taken at each visit was stored at −40°C. For 183 patients the date of first exposure to large donor pool concentrates was known; these are referred to as 'cohort' patients. Computerized treatment records were started in 1979. The mean annual usage of concentrate was calculated over the 10 years prior to the last clinic visit, or, in the case of deceased patients, over the 10 years prior to death. Serum aspartate transaminase (AST) levels were analysed over the 5 years prior to August 1993, or, in the case of deceased patients, over the 5 years prior to death. AST levels were classified as persistently abnormal if all values over this period were raised, intermittently abnormal if raised on at least one occasion, and normal if values were consistently below the upper limit of normal. Histological specimens were processed and stained by conventional methods. The diagnosis of hepatic decompensation required evidence of at least two of the following: ascites (clinical or radiological) with hypoalbuminaemia, clinical evidence of jaundice, encephalopathy, and prothrombin time prolongation beyond our laboratory normal range (12–16 s). Variceal bleeding and hepatocellular carcinoma were diagnosed on standard clinical and histological criteria.

Virology and immunology. Fresh or stored serum from patients who had received any blood product therapy since 1979 was tested for antibody to HCV by second-generation EIA (Ortho); RIBA-2 confirmation was not required. Hepatitis B surface antigen (HBsAg) was tested by EIA (Murex Diagnostics); antibodies to HIV by EIA (Wellcozyme), and confirmed by gelatin particle agglutination (Mast Diagnostics and Abbott); HIV p24 antigen was tested by EIA (Abbott or Dupont).

The date of HIV seroconversion was taken as the midpoint of the interval between the last negative and the first positive result on stored serum samples. In some cases there was no sample available which tested negative, and for these patients we took the date midway between 1 January 1979 (the first possible presumed date that contaminated blood products were administered) and the first positive test (Lee *et al*, 1989).

Analysis of CD4-positive lymphocyte counts was started in 1982 and has been described previously (Phillips *et al*, 1991).

Statistical methods. Comparisons of categorical variables between groups were made using the Chi-squared test or Fisher's Exact test; comparisons of continuous variables by the Mann-Whitney U test, because of the expected non-normality of these variables (Altman, 1991). Transaminase abnormality was treated as a categorical variable (persistent/intermittent/normal).

Clinical progression to hepatic decompensation was modelled using standard survival analysis methods. In the absence of hepatic decompensation, patient follow-up was censored at 1 August 1993 or death. The baseline date was taken as the date of the first exposure to large donor pool clotting factor concentrate. Kaplan-Meier progression rates and 95% confidence intervals (Kaplan & Meier, 1958) were calculated at 10 and 20 years after exposure to concentrate. Cox Proportional Hazards Models (Cox & Oakes, 1984) were used to compare survival between groups, with haemophilia diagnosis, concentrate usage and age at first exposure to concentrate being treated as fixed covariates at baseline. In the survival analysis, the age was taken to be that at the time of the first exposure to concentrate. Effects of concentrate usage were studied by comparison of those using more and those using less than the median annual usage in the cohort. Seroconversion to HIV and, in HIV seropositive patients only, CD4 counts, the development of p24 antigenaemia and progression to AIDS, were treated as time-dependent covariates, a patients' status being allowed to change as follow-up increased.

Table I. Clinical characteristics of 255 HCV seropositive patients and 183 HCV seropositive 'cohort' patients.

	HCV seropositive ($n = 255$)	HCV seropositive cohort ($n = 183$)
Age (years) at 1 August 1993 in surviving patients		
Median	32·1	33·6
Range	10·2–82·7	10·2–82·8
Age (years) at death in deceased patients		
Median	40·8	43·9
Range	23·1–81·8	23·1–81·8
Diagnosis		
Haemophilia A	185 (72·5%)	129 (70·5%)
Haemophilia B	42 (16·5%)	36 (19·7%)
Von Willebrand's disease	19 (7·5%)	11 (10·4%)
Other*	9 (3·5%)	7 (3·8%)
Severity		
Severe	164 (64·3%)	120 (65·6%)
Moderate	30 (11·8%)	18 (9·8%)
Mild	61 (23·9%)	45 (24·6%)
Concentrate usage ($\times 10^{-3}$ units/yr)		
Median	28	28
Range	0–290	0–290
HIV seropositive	103 (40·4%)	74 (40·4%)
Hepatitis B surface antigen positive	6 (2·4%)	4 (2·2%)
Transaminase level		
Normal	42 (16·5%)	25 (13·7%)
Intermittently abnormal	96 (37·6%)	67 (36·7%)
Persistently abnormal	117 (45·9%)	91 (49·7%)
Deceased	48 (18·4%)	38 (20·8%)

*Other diagnoses: haemophilia A carrier: seven; hypofibrinogenaemia: one; factor XI deficiency: one. The seven haemophilia A carriers were included in the cohort group.

RESULTS

Clinical characteristics of the HCV seropositive patients

Since 1979, 372 patients have received fresh frozen plasma, cryoprecipitate or lyophilized clotting factor concentrate as blood product replacement therapy for congenital clotting factor deficiencies, and sera from 359 (96·5%) were available for testing. 255 patients (68·5%) were HCV seropositive, including 232/241 (96·3%) who had received unsterilized large donor pool clotting factor concentrate. Clinical characteristics of these HCV seropositive patients are shown in Table I.

HIV seropositivity was significantly commoner in patients with haemophilia A ($\chi^2 = 54{\cdot}9$, 2 d.f., $P < 0{\cdot}0001$), and was associated with higher concentrate usage ($P < 0{\cdot}0001$). There were no significant differences in the age at death in those patients who had died ($P = 0{\cdot}3$), although HIV seropositive patients who were still alive at the end of the follow-up period tended to be younger than HIV seronegative patients who were still alive ($P = 0{\cdot}03$). Transaminase abnormality was associated with haemophilia diagnosis ($\chi^2 = 13{\cdot}6$, 4 d.f., $P = 0{\cdot}009$), increased severity of haemophilia ($\chi^2 = 10{\cdot}08$, 4 d.f., $P = 0{\cdot}04$), increased usage of concentrate ($P = 0{\cdot}001$) and HIV seropositivity ($\chi^2 = 12{\cdot}16$, 2 d.f., $P = 0{\cdot}002$). patients who were alive at the end of the follow-up period and who had abnormal transaminase levels tended to be older than those patients with normal levels ($P = 0{\cdot}02$). As almost all patients who had died had abnormal transaminase levels (46/48, 96%), the association of transaminase levels with age and death was difficult to assess. However, patients with persistently abnormal levels were slightly older at death (median 42·6 years) compared to those with intermittently abnormal levels (median 39·9 years). This difference did not reach statistical significance.

Progression of HCV liver disease

The date of first exposure to concentrate was documented in 183 patients, and this group is referred to as the HCV seropositive cohort. Insufficient documentation was available on the remaining 72 patients largely because they had transferred to our centre from other centres after starting home treatment with concentrate. The distribution of age, diagnoses, average annual concentrate usage and prevalence of HIV and HBV infection in the cohort did not differ significantly from the remaining patients; however, the duration of HIV seropositivity was increased in the cohort compared to the non-cohort patients (median time of seroconversion December 1981 in cohort patients and August 1982 in non-cohort patients, $P = 0{\cdot}01$).

The median duration of follow-up since exposure to concentrate is 15·1 years and the range 3·5–28 years (Fig 1). The shortest follow-up was that of a patient with Type 1 von Willebrand's disease and inherited telangiectases who had an episode of acute hepatitis C in 1990 following exposure to cryoprecipitate.

Hepatic decompensation has been seen in 11 cohort patients and in none of the non-cohort patients ($\chi^2 = 4{\cdot}56$, 1 d.f., $P < 0{\cdot}05$). The clinical details of these patients are shown in Table II. 10 of these patients had a diagnosis of haemophilia A and these were all HIV seropositive. The remaining patient had severe haemophilia B and was HIV seronegative. Two patients, including the latter, were considered to have a high alcohol consumption. Only one of the 11 patients had markers of active hepatitis B infection, having been surface antigen positive, e antigen negative and e antibody positive for many years.

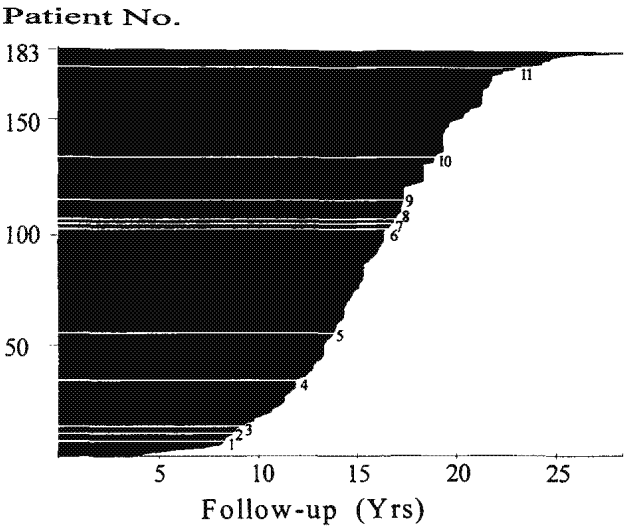

Fig 1. Length of follow-up since first exposure to a large donor pool clotting factor concentrate in 183 cohort patients. Follow-up was censored at death or on 1 August 1993. The white bars indicate follow-up on the 11 patients who progressed to hepatic decompensation.

The median time from first concentrate exposure to hepatic decompensation in these 11 patients was 16·5 years and the range 7·7–22·9 years. The risk of progression to liver failure estimated by Kaplan-Meier analysis in the 183 cohort patients is 1·7% (95% confidence levels 0–3·7%) at 10 years after exposure to concentrate, and 10·8% (95% CI 3·8–17·8%) at 20 years after exposure to concentrate (Fig 2). Using a Cox Proportional Hazards model where the potential effect of HIV comes into effect at the time of HIV seroconversion, the relative hazard of developing liver failure after HIV infection is 21·4 (95% CI 2·6–174·5, $P = 0.004$).

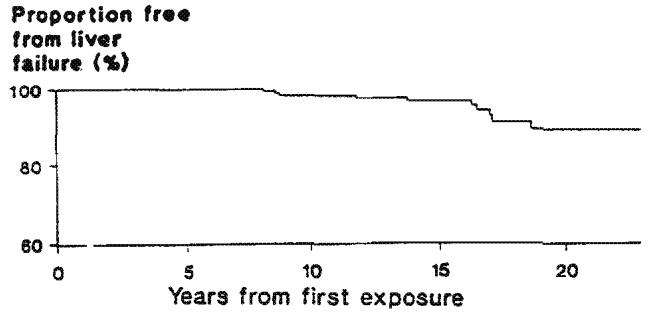

Fig 2. Kaplan-Meier plot showing progression to hepatic decompensation in 183 HCV seropositive haemophilic patients followed since first exposure to a large donor pool clotting factor concentrate.

Table II. Clinical characteristics of HCV seropositive patients developing hepatic decompensation during follow-up.

Patient	Bleeding disorder	Age at diagnosis of HD (yr)	Concentrate usage ($\times 10^{-3}$) units per year)	HIV+	HBsAg	Alcohol	Features of HD	Cause of death	Findings at PM	CD4 count at diagnosis of HD (per mm^3)	CD4 count at death (per mm^3)	Time from exposure to conc. to HD (yr)	Time from HIV sero-conversion to HD (yr)	Time from HD to death (yr)
1	VIIc < 1 u/dl	63	122	Y	N	N	A, E, J, PT, V	HD	PBC, Cirr	ND	ND	8·1	0·3	0·3
2	VIIc < 1 u/dl	55	48	Y	N	N	E, J	Septicae-mia, HD	Cirr	100	100	8·6	6·3	0·3
3	VIIc < 1 u/dl	68	57	Y	N	N	A, E, J	HD	Cirr	ND	600	8·7	4·2	1·1
4	VIIc < 1 u/dl	51	66	Y	N	N	A, J, PT	HD	ND	500	500	11·8	7·2	0·3
5	VIIIc < 1 u/dl +inhibitor	37	51	Y	N	N	J, PT	AIDS, HD, ICH	ND	0	0	13·7	10·0	0·2
6	VIIIc < 1 u/dl	25	30	Y	Y	N	A, J	Pneumonia	ND	0	0	16·3	11·6	0·2
7	VIIIc < 1 u/dl	44	66	Y	N	N	A, E, J, PT, V	HD, ?HCC	Cirr (needle biopsy)	560	840	16·5	9·0	0·7
8	VIIIc < 1 u/dl	38	18	Y	N	Y	A, E, J	HD, ICH	Cirr	0	0	17·0	7·7	0·2
9	VIIIc < 1 u/dl	31	63	Y	N	N	A, J	AIDS, HD	Cirr, hepatic pneumocystis	0	0	17·1	11·1	0·1
10	VIIIc < 1 u/dl	30	115	Y	N	N	A, J, PT	Pneumonia, HD	Cirr	0	0	18·7	8·8	0·3
11	IXc < 1 u/dl	64	63	N	N	Y	A, PT	Alive (1/8/93)	530		22·9			

Abbreviations: A = ascites; Cirr = cirrhosis; E = encephalopathy; HCC = hepatocellular carcinoma; HD = hepatic decompensation; ICH = intracranial haemorrhage; J = jaundice; ND = not done; PBC = primary biliary cirrhosis; PM = post-mortem; PT = prolonged prothrombin time; V = variceal haemorrhage.

The hazard is also increased for those with haemophilia A compared to other bleeding disorders (relative hazard 7·4, 95% CI 0·9–62·0, $P = 0.07$), for those using more than 28 000 units of concentrate per year (the median usage for the cohort) (relative hazard 7·4, 95% CI 0·9–60·0, $P = 0·06$), and in older patients (relative hazard 1·22 per 5-year difference, 95% CI 1·0–1·5, $P = 0·02$).

Amongst the 74 cohort patients who were HIV seropositive, 27 (36·5%) developed p24 antigenaemia, 33 (44·6%) progressed to AIDS, and 32 (43·2%) have died. Restricting the analysis to those who seroconverted to HIV during the study, the risk of developing hepatic decompensation was increased 5 times the after becoming p24 antigen positive (95% CI 1·4–19·1, $P = 0·01$). Each drop of 100 cells/μl in the CD4 lymphocyte count increased the risk of hepatic decompensation by 1·31 (95% CI 1·0–1·7, $P = 0·005$) and there was a raised, although non-significant, risk associated with progression to AIDS (relative hazard 2·3, $P = 0·32$).

Post-mortem histology

During the observation period, 48 HCV seropositive patients died, 39 (81%) of whom were HIV seropositive. The causes of death were AIDS without hepatic decompensation in 25 (52%), AIDS and hepatic decompensation in six (13%), hepatic decompensation without AIDS in four (8%) and other causes in 11 (23%). In two patients there was insufficient information to define the cause of death. Thus, hepatic decompensation contributed to the death of 10 patients (21%). One patient (who died of hepatic decompensation) had evidence of multiple intrahepatic lesions on CT scan shortly before death, and was thought to have hepatocellular carcinoma, but this could not be confirmed by needle biopsy of the liver.

Twenty-two full or limited post-mortems were performed in the HCV seropositive patients. Cirrhosis was diagnosed in nine patients (41%), seven of whom died with liver failure. The remainder showed varying degrees of hepatic fibrosis, but in general there was remarkably little inflammatory infiltrate. Cirrhosis at post-mortem was associated with increased age ($P = 0·04$) and with persistent AST elevation ($P = 0·02$), but there was no significant association with average annual concentrate usage, time between exposure to concentrate and death, CD4 count at death, p24 antigenaemia, or AIDS diagnosis (Table III).

Table III. Clinical characteristics of HCV seropositive patients with post-mortem liver histology.

	Cirrhosis		
	Yes	No	*P* value
All patients	($n = 9$)	($n = 13$)	
Age at death (years)			
Median	54·7	35·4	0·04
Range	29·9–76·5	20·1–56·5	
Concentrate usage ($\times 10^{-3}$ units/yr)			
Median	57	44	0·8
Range	12–122	21–184	
Time between exposure to concentrate and death (years)			
Median	13·6	12·8*	0·72
Range	8·4–18·9	4·24–18·8	
Transaminase levels			
Normal	0 (0)	0 (0)	0·02
Intermittently abnormal	1 (11)	8 (62)	
Persistently abnormal	8 (89)	5 (38)	
HIV seropositive patients only	($n = 9$)	($n = 10$)	
CD4 count at death (cells per mm^3)			
Median	30	70	0·90
Range	0–840	0–840	
p24 antigenaemia	4 (50)†	2 (20)	0·46
AIDS diagnosis	5 (56)	7 (70)	0·82

* Data from nine patients.
† Data from eight patients.

DISCUSSION

In this retrospective single-centre study of the natural history of hepatitis C infection in haemophilic patients, 11 patients have developed hepatic decompensation and the risk in HCV seropositive patients is 10·8% at 20 years after first treatment with large donor pool clotting factor concentrate. HIV seropositive patients are 21 times more likely to develop this complication than HIV seronegative patients, and there is a significant association with p24 antigenaemia and with declining CD4 count. Hepatic decompensation is also commoner in older patients, in heavily treated patients, and in those with a diagnosis of haemophilia A.

Prospective studies involving previously untreated haemophilic patients have demonstrated an almost 100% incidence of non-A, non-B hepatitis following the first infusion of unsterilized large donor pool clotting factor concentrate (Fletcher *et al*, 1983; Kernoff *et al*, 1985). The chronic course of this condition was appreciated in the 1970s when several studies drew attention to the high prevalence of persistent transaminase elevations (Cederbaum *et al*, 1982; Rickard *et al*, 1982; Mannucci *et al*, 1975).

There has been an obvious reluctance to perform liver biopsies in haemophilic patients because of the risk of bleeding complications (Aledort *et al*, 1985); however, a few histological studies have been reported and these document a spectrum of lesions including minimal changes, chronic persistent and chronic active hepatitis and cirrhosis. A worrying feature was the progressive nature of the changes in most, but not all, of those who had repeat biopsies (Hay *et al*, 1985; Aledort *et al*, 1985; Mannucci *et al*, 1982). On the basis of these and other studies it has been estimated that 20% of patients with abnormal transaminase levels will develop cirrhosis within 10 years of infection (Deinstag & Alter, 1986).

There is uncertainty about the risk of progression to symptomatic liver disease and death. Eyster *et al* (1985) found that liver disease was the major cause of death in a cohort of treated haemophilic patients with thrombocytopenia and leucopenia; however, a more recent case-controlled study of post-transfusion non-A, non-B hepatitis in non-haemophilic patients found no difference in mortality between 568 cases and 984 control patients after an average follow-up of 18 years (Seeff *et al*, 1992).

There has been one recent publication on the subject of the natural history of liver disease in haemophilia (Eyster *et al*, 1993), and the findings are similar to our own. This single-centre study reports on the natural history of 156 HCV seropositive patients, 98 (63%) of whom were HIV seropositive. 11/156 HCV seropositive patients developed hepatic decompensation; HIV infection was associated with a 3-fold increased risk and this was estimated to be 42% at 27 years after the first exposure to concentrate.

Our HCV seropositive cohort differs from that of Eyster *et al* (1993), in that we did not exclude patients who were anti-HCV positive by EIA, but negative or indeterminate by RIBA-2. Blood donors with this serological pattern are very unlikely to have active HCV infection, and may have non-specific serological reactivity rather than past infection. Haemophilic patients with this serological pattern, on the other hand, have a very high risk of exposure to HCV and are more likely to have past infection; thus we feel that they should be included in an analysis of the natural history of HCV. Like Eyster *et al* (1993), we used the date of the first exposure to concentrate as an estimate of the time of HCV infection, and accept that this measure is likely to underestimate the true duration of exposure to HCV in some patients. Cederbaum *et al* (1982) demonstrated a similar incidence of abnormal liver function tests in patients heavily treated with cryoprecipitate compared to patients treated with concentrate, and concluded that the risk acquiring non-A, non-B hepatitis is similar in the two groups. Thus, although our patients would almost certainly have been infected with the first dose of concentrate (Fletcher *et al*, 1983; Kernoff *et al*, 1985) the older, heavily treated, patients may have been previously exposed through cryoprecipitate or other blood products.

It is surprising that none of the non-cohort patients have developed hepatic decompensation. Part of the explanation may lie in the shorter median duration of HIV infection in this group. However, the difference is only 6 months, and is unlikely to be the only explanation. These patients had transferred to our centre from other centres after starting home treatment, and perhaps had used less unsterilized concentrate at their original centres than was used at ours.

Eyster *et al* (1985) noted that anti-HIV positivity was associated with the diagnosis of severe haemophilia A, increased age, and greater concentrate usage in their study group. These factors are all potential risk factors for progression of HCV-associated liver disease. We also demonstrated these associations in our study, but by treating HIV seroconversion as a time-dependent covariate we have attempted to model the effect of changed HIV status within each patient independent of other factors. The number of end-points was too small to perform more detailed multivariate analysis.

We have strong evidence that HIV infection accelerates the progression of HCV. Not only is HIV seropositivity associated with an increased risk of developing liver failure, but there is also an association with p24 antigenaemia and decline in CD4 cell count, both of which are prognostic markers of HIV progression in our patients (Lee *et al*, 1989). We found a raised, although non-significant, association with the development of AIDS. The latter finding is not unexpected, as an AIDS diagnosis indicates that the patient has developed some other life-threatening condition from which they are likely to die first. Our histological data did not provide evidence of an association between cirrhosis and HIV progression; however, the applicability of this data to the group as a whole can be questioned. Post-mortem data is liable to selection bias; furthermore there were only 19 samples available and these came from patients with particularly rapid disease progression.

There have been very few other reports of this interaction between HIV and HCV infection. Martin *et al* (1989) describe progression of non-A, non-B hepatitis to liver failure in three HIV seropositive patients within 3 years of the infectious blood transfusion. Our finding of an association of age with HCV progression is consistent with other reports (Di Bisceglie *et al*, 1991), and may reflect diminished immune function with age. The association of greater concentrate usage with hepatic decompensation is also seen in Eyster's study but may reflect the fact that most of the heavy concentrate users are HIV seropositive. We cannot be sure from this study that heavy treatment with factor concentrates is detrimental in HCV liver disease; however, it is likely that patients who received large amounts of unsterilized concentrates from multiple batches were exposed to particularly large innocula of virus and perhaps to multiple HCV genotypes.

Why should patients with both HIV and HCV infections develop hepatic decompensation more rapidly than those with HCV alone? Serious liver disease is unusual in homosexual AIDS patients who are not infected with hepatitis viruses and is usually due to opportunistic infections or tumours (Schneiderman *et al*, 1987). The HIV virus does not seem to be cytopathic to hepatocytes, but it can be demonstrated in Kupffer cells in AIDS patients (Lafon & Kirn, 1992) and could have pathological effects on the liver, for instance by stimulating abnormal production of fibrogenic cytokines. It is more likely that the immunosuppresive effects of HIV infection facilitate HCV replication and mutation, thus resulting in a higher viral load and increased liver damage. Furthermore, hepatic decompensation could be precipitated by AIDS-related opportunistic infections in patients who are already cirrhotic as a result of HCV infection.

We conclude that there is significant morbidity and mortality associated with HCV infection, which is likely to increase in the coming decades. Increased age and HIV infection are significant risk factors, and those with haemophilia A and with high concentrate usage may also be at increased risk. Furthermore, HIV seropositive patients can develop hepatic decompensation before becoming

symptomatic with AIDS. Our findings suggest that anti-viral therapy directed against HCV should be considered in those who are also infected with HIV.

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