Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study)

Eric Rosenthal, Marilyne Poirée, Christian Pradier[a], Christian Perronne[b], Dominique Salmon-Ceron[c], Loic Geffray[d], Robert P. Myers[e], Philippe Morlat[f], Gilles Pialoux[g], Stanislas Pol[h] and Patrice Cacoub[i] for the GERMIVIC Joint Study Group

Objective: To determine mortality due to end-stage liver disease (ESLD) in a nationwide cohort of HIV-infected patients 5 years after the introduction of highly active antretroviral therapy (HAART) and to compare this with that observed before and during the early years of HAART.

Design and methods: All departments of internal medicine and infectious diseases from the GERMIVIC Study Group prospectively recorded all deaths in HIV-infected patients during 2001. Sixty-five departments, following a total of 25 178 HIV-infected patients, participated in the study. Results were compared with those of previous surveys conducted using similar methodology in 1995 and 1997.

Results: Among 265 deaths observed during 2001, 129 (48.7%) were related to AIDS, 38 (14.3%) to ESLD, and 98 (36.7%) to other causes. Mortality due to ESLD represented 28% of non AIDS-related deaths; 36 of the 38 patients (95%) dying from ESLD had chronic hepatitis C virus (HCV) infection. In 2001, deaths due to ESLD (14.3%) were significantly more frequent than in 1995 (1.5%; $P < 0.01$) and 1997 (6.6%; $P < 0.01$). During this interval, the prevalence of hepatocellular carcinoma as a cause of death increased (1995, 4.7%; 1997, 11%; 2001, 25%; $P < 0.05$), as did alcohol consumption ($P < 0.01$).

Conclusions: In the post-HAART era, ESLD due to HCV is a growing cause of mortality in HIV-infected patients. Increased longevity attributable to HAART, and a higher prevalence of alcohol consumption, are probably involved in this trend.

AIDS 2003, **17**:1803–1809

Keywords: hepatitis C virus, HIV, mortality, morbidity, cirrhosis, hepatocellular carcinoma

From the Service d'Hématologie Clinique, Hôpital Archet, Nice, [a]CISIH, Hôpital Archet, the [b]Service des Maladies Infectieuses, Hôpital Raymond Poincaré, Garches, the [c]Service de Médecine Interne, Groupe Hospitalier Cochin, Paris, the [d]Service de Médecine Interne, Centre Hospitalier Général Bisson, Lisieux, the [e]Service d'Hépato-Gastro-entérologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, the [f]Service de Médecine Interne, Hôpital Saint-André, Bordeaux, the [g]Service des Maladies Infectieuses, Hôpital Tenon, the [h]Service d'Hépatologie, Hôpital Necker, and the [i]Service de Médecine Interne, Groupe Hospitalier Pitié-Salpêtrière, Paris, France. *Joint Study Group on Hepatitis C virus of the French National Society of Internal Medicine and the French Society of Infectious Diseases; see Appendix.

Correspondence to E. Rosenthal, Service d'Hématologie Clinique, Hôpital Archet 1, 151 route de Saint-Antoine de Ginestière, 06202 Nice cedex 3, France.

Received: 27 November 2002; revised: 4 February 2003; accepted: 18 February 2002.

DOI: 10.1097/01.aids.0000072671.21517.44

ISSN 0269-9370 © 2003 Lippincott Williams & Wilkins

Introduction

Coinfection with hepatitis C virus (HCV) and HIV is common as both viruses are transmitted by parenteral routes, i.e., injecting drug use and blood transfusion. In the USA, it is estimated that 30% of the 800 000 HIV-infected individuals are coinfected with HCV [1,2]; similar rates have been reported in Western Europe [3]. Among certain subgroups of HIV-infected patients, such as in injecting drug users and haemophiliacs, the prevalence of coinfection approaches 70–90% [2–4]. HCV infection leads to chronic hepatitis in 85% of HIV-negative patients; approximately 20% will eventually develop cirrhosis of the liver [5,6]. In HIV-positive individuals, chronic hepatitis C is more severe, particularly in those with advanced immunosuppression [7–10]. Regardless of HIV serostatus, time represents a critical factor in determining mortality due to end-stage liver disease (ESLD). In HIV-positive patients, longer survival observed since the introduction of highly active antiretroviral therapy (HAART) may permit the progression of HCV-related liver disease and increase mortality due to complications including liver failure and hepatocellular carcinoma (HCC). Moreover, HAART itself may accelerate the progression of HCV-related liver disease [11]. Several studies have suggested an increased risk of mortality caused by ESLD in HIV–HCV coinfected patients [12–21]. However, most of these studies examined cohorts of haemophilic patients [12,13] or single-centre cohorts of HIV seropositive patients and compared mortality rates during the pre-HAART era with that during the early years of HAART.

Five years following the introduction of HAART, we have examined the mortality associated with HCV-related ESLD in a nationwide cohort of HIV-infected patients in France. The objective of the study was to assess trends in mortality by comparing current data to two previous surveys conducted by our study group in the pre-HAART era (1995) and during the first few years of this therapy (1997) [20].

Patients and methods

Study design

The current study (2001) was a multi-centre prospective survey of French departments of internal medicine and infectious diseases active in the treatment of HIV-infected individuals. In each department, a standardized questionnaire similar to that used in our previous studies [20] was completed prospectively on a quarterly basis. The questionnaire included information regarding the number of HIV-infected patients regularly seen (i.e., at least every 3 months), risk factors for HIV transmission, and the number of deaths during the interval. The causes of death were specified as AIDS-related, ESLD-related (cirrhosis and/or HCC), or other.

A second questionnaire [20] was completed for each patient who died of ESLD indicating the patient's demographic data, mode of HIV transmission, criteria for diagnosis of cirrhosis and/or HCC (considered 'definite' if documented histopathologically or 'probable' if documented clinically, based on raised serum alpha-fetoprotein levels, and/or with imaging), positive test results for HCV (anti-HCV antibody revealed by a third generation ELISA), hepatitis B virus [HBV; HBV surface antigen (HBsAg) revealed by ELISA] and hepatitis D virus (HDV; anti-HDV antibody revealed by ELISA), self-reported daily alcohol consumption, concomitant use of hepatotoxic drugs; previous treatment with interferon alpha (IFN-α); and CD4 cell count, Centers for Disease Control and Prevention (CDC) stage of HIV infection [22], and antiretroviral therapy at the time of death.

Statistical analysis

Kruskall–Wallis, Pearson chi-square, and chi-square for trends were used for comparing HIV characteristics and HCV-related events between the three study periods (1995, 1997, 2001).

Results

Study population

Eighty-two questionnaires were distributed to French departments of internal medicine and infectious diseases; a total of 65 departments (79%) responded. During the year 2001, these departments followed 25 178 HIV-infected patients. The modes of HIV infection were homosexual transmission (31%), injecting drug use (21%), heterosexual transmission (38%), transfusion of blood products (3%), and other or unknown (7%) (Table 1).

Mortality rates

Among the 25 178 HIV-infected patients followed in 2001, 265 deaths were observed, representing a mortality rate of 1.05%. Causes of death were as follows (Table 2): AIDS (n = 129, 48.7%), ESLD (n = 38, 14.3%) and other (n = 98, 37.0%). ESLD represented 27.9% of the non AIDS-related deaths.

Mortality due to ESLD in relation to hepatitis viruses

The main characteristics of the 38 patients who died due to ESLD are outlined in Table 3. These patients were predominantly male (79%) and the mean age was 42 years (range, 32–69 years). HIV transmission occurred predominantly via injecting drug use (76%).

Table 1. Comparison of the risk factors for HIV transmission among the 1995, 1997 and 2001 cohorts.

Variable	1995	1997	2001	*P*
Total HIV-infected patients (n)	17 487	26 497	25 178	
Risk factor for HIV transmission (%)				
Homosexual	39.0	34.7	31.0	< 0.01
Injecting drug use	25.0	18.9	21.0	< 0.01
Heterosexual	24.5	34.6	37.6	< 0.01
Transfusion	2.9	1.4	3.0	< 0.01
Other	8.6	10.4	7.4	< 0.01

Table 2. Comparison of mortality rates from the 1995, 1997 and 2001 surveys.

Variable	1995	1997	2001	P
Total HIV-infected patients (n)	17 487	26 497	25 178	
Total HCV-infected patients [n (%)]	ND	4465 (16.8%)	6168 (24.5%)	
Total deaths [n (annual incidence)][a]	1426 (8.15%)	543 (2.04%)	265 (1.05%)	< 0.01
AIDS-related deaths [n (% of total death)]	1307 (91.6%)	459 (84.5%)	129 (48.7%)	< 0.01
ESLD-related deaths [n (% of total death)]	21 (1.5%)	36 (6.6%)	38 (14.3%)	< 0.01
Other causes of death [n (% of total death)]	99 (6.9%)	48 (8.8%)	98 (36.7%)	< 0.01

[a]Annual incidence was calculated by comparison with the total number HIV-infected patients followed during the interval. HCV, Hepatitis C virus; ESLD, end-stage liver disease.

Among the 38 cases with death due to ESLD, 19 (50%) were considered definite and 19 (50%) probable. Thirty of these patients had HCV-related cirrhosis (including HCC in seven cases), six had cirrhosis due to HBV–HCV coinfection (including HCC in one case), and two had HBV-related cirrhosis (including HCC in one case and HDV coinfection in another). Of the 30 patients who died due to HCV-related cirrhosis (without HBV coinfection), 25 (83%) consumed alcohol. In these patients, daily alcohol consumption was high (> 60 g) in 11 (44%), moderate (30–60 g) in eight (32%), and low (< 30 g) in six (24%). Ten of the 38 patients (26.3%) who died as a result of ESLD had previously received treatment with IFN-α alone (n = 6) or in combination with ribavirin (n = 3). HIV category according to the 1993 revised CDC classification system was determined in 34 patients: seven (21%) were asymptomatic (stage A), nine (26%) were symptomatic (stage B), and 18 (53%) had AIDS (stage C). At the time of death, the mean CD4 lymphocyte count was 200×10^6/l (range, $3–700 \times 10^6$/l), and 28 patients (74%) were receiving HAART.

Comparison with the 1995 and 1997 surveys

The distribution of risk factors for HIV transmission differed between 2001 and the previous cohorts (Table 1). Whereas heterosexual transmission was more common in 2001 (1995, 25% versus 2001, 38%; $P < 0.01$), transmission due to homosexual activity (1995, 39% versus 2001, 31%; $P < 0.01$) and injecting drug use decreased (1995, 25% versus 2001, 21%; $P < 0.01$). Although overall mortality decreased from 1995 to 2001 (8.15% versus 1.05%; $P < 0.01$), the proportion of deaths attributable to cirrhosis and/or HCC increased (1995, 1.5%; 1997, 6.6%; 2001, 14.3%; $P < 0.01$) (Table 2). During the same interval, the percentage of patients who died because of AIDS decreased from 91.6% in 1995 to 48.7% in 2001 ($P < 0.01$). Among the patients who died from ESLD, the percentage of patients with HCV infection (without HBV or HDV coinfection) was higher in 2001 (78.9%) than in 1995 (57.1%) and 1997 (55.5%) ($P < 0.05$; Table 4). HCC as a cause of death also increased over this time interval (1995, 4.7%; 1997, 11.1%; 2001, 25%; $P < 0.05$). The percentages of injecting drug use and alcohol consumption were also higher in 2001 (76% and 66%, respectively) when compared with that observed in the 1995 (29% and 38%, respectively; $P < 0.05$) and 1997 surveys (39% and 33%, respectively; $P < 0.05$). Finally, prescription of HAART was more frequent in 2001 (74%) than in 1997 (42%, $P < 0.01$), and there was a non-significant increase in median CD4 cell counts at death between these time points.

Discussion

As in our previous surveys [20], our current study analysed approximately half of the HIV-related deaths reported to the French Public Health Network (Institut de Veille Sanitaire) in 2001 [23]. During this year, death due to ESLD represented 28% of all non AIDS-related deaths in the HIV-positive population. These findings are in accordance with recent studies from Europe showing the growing importance of liver disease as a cause of mortality in HIV-infected patients

Table 3. Characteristics of the 38 HIV-infected patients with deaths due to ESLD.

Patient number	Sex /age (years)	Viral hepatitis	Alcohol consumption[a]	Diagnosis of cirrhosis[b]	Diagnosis of HCC[b]	Risk factor for HIV transmission	CD4 cell count ($\times 10^6$ cells/l)	CDC stage	Prior HCV treatment	Anti-HIV medications (n)
1	M/51	HCV /HBV	High	Definite	No	IDU	107	C	–	4
2	M/51	HCV	No	Probable	No	Homosexual	58	C	–	3
3	M/42	HCV	High	Probable	No	IDU	24	C	–	3
4	M/43	HCV	Low	Definite	No	IDU	82	C	IFN	3
5	M/37	HBV /HDV	No	Definite	Probable	ND	184	A	–	2
6	M/42	HCV	No	Probable	No	IDU	50	ND	–	3
7	M/45	HCV	High	Definite	No	IDU	310	C	–	3
8	M/42	HCV /HBV	High	Probable	No	IDU	80	ND	–	3
9	F/39	HCV	Mod	Probable	No	IDU	ND	ND	IFN	3
10	F/44	HCV	No	Probable	No	IDU	297	B	IFN	3
11	F/36	HCV	No	Definite	No	IDU	148	B	IFN	3
12	M/44	HCV	High	Definite	No	IDU	158	B	IFN	0
13	F/37	HCV	Mod	Definite	No	IDU	134	C	–	3
14	M/40	HCV /HBV	No	Definite	No	IDU	700	A	–	3
15	M/37	HCV /HBV	Mod	Definite	No	IDU	358	ND	–	3
16	M/34	HBV	No	Definite	No	Heterosexual	178	B	–	3
17	M/36	HCV	High	Probable	No	IDU	297	A	–	3
18	F/40	HCV	Mod	Probable	No	IDU	30	C	–	3
19	M/46	HCV	Low	Definite	No	IDU	129	C	–	3
20	M/37	HCV	High	Probable	No	IDU	64	B	–	2
21	F/37	HCV	Mod	Probable	No	IDU	54	C	–	3
22	M/51	HCV /HBV	High	Probable	No	IDU	437	C	–	3
23	M/50	HCV	No	Definite	No	Hemophilia	326	B	–	3
24	F/41	HCV	Mod	Probable	No	IDU	592	B	–	2
25	M/62	HCV	No	Definite	Probable	Hemophilia	82	C	IFN	2
26	M/47	HCV	No	Definite	No	Heterosexual	160	A	–	2
27	M/44	HCV	High	Definite	No	IDU	184	C	–	0
28	M/36	HCV	Mod	Probable	No	IDU	463	B	IFN−Riba	2
29	M/40	HCV	Low	Probable	No	IDU	370	A	–	3
30	M/51	HCV	Mod	Probable	Probable	IDU	110	C	–	3
31	M/36	HCV	High	Probable	Probable	IDU	44	C	–	3
32	M/32	HCV	Low	Definite	Definite	IDU	90	C	–	3
33	M/38	HCV	No	Definite	Definite	IDU	450	A	IFN	3
34	M/39	HCV /HBV	No	Definite	Definite	Heterosexual	3	C	–	2
35	M/36	HCV	Low	Probable	No	IDU	191	C	IFN-Riba	3
36	M/42	HCV	High	Definite	No	IDU	240	B	PEG-Riba	3
37	F/69	HCV	No	Probable	Probable	Transfusion	180	A	–	3
38	M/51	HCV	Low	Probable	Probable	Homosexual	58	C	–	3

[a]Daily alcohol consumption defined as low (< 30 g), moderate (30–60 g), or high (> 60 g). [b]Definite (histologically proven); probable (clinically, biologically, or ultransonographically proven). ESLD, End-stage liver disease; M, male; F, female; HCV, hepatitis C virus; HBV, hepatitis B virus; HDV, hepatitis delta virus; Mod, moderate; HCC, hepatocellular carcinoma; IDU, injecting drug use; CDC, Centers for Disease Control and Prevention; IFN, interferon; Riba, ribavirin; PEG, pegylated interferon alfa-2b; ND, not determined.

Table 4. Characteristics of patients with deaths due to ESLD in 1995, 1997 and 2001.

Variable	1995 n = 21	1997 n = 36	2001 n = 38	*P*
Mean age [years (range)]	41 (26–66)	42 (31–62)	42 (32–69)	NS
Injecting drug use [n (%)]	6 (28.5%)	14 (38.8%)	29 (76.3%)	0.03
Alcohol consumption [n (%)]	8 (38.0%)	12 (33.3%)	25 (65.7%)	0.01
HCC [n (%)]	1 (4.7%)	4 (11.1%)	9 (25.0%)	0.03
Anti-HCV treatment [n (%)]	4 (19.0%)	3 (8.3%)	10 (26.3%)	NS
Median CD4 cell count [$\times 10^6$/l (IQR)]	113 (27–257)	131 (46–306)	158 (72–303)	NS
HAART [n (%)]	0	15 (41.6%)	28 (73.6%)	< 0.01

ESLD, End-stage liver disease; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HAART, highly active antiretroviral therapy.

Table 5. End-stage liver disease-related mortality among HIV-infected individuals in the pre-highly active antiretroviral therapy (HAART) and HAART eras[a].

	Pre-HAART era		HAART era	
Cohort	Year(s)	% (n)	Year(s)	% (n)
Brescia, Italy [11]	1987	13% (35/305)	1996	35% (16/46)
Boston, USA [14]	1991	11.5% (3/26)	1998–1999	50% (11/22)
Madrid, Spain [10,12]	1991–1995	4.8% (15/312)	2000	45% (9/20)
France (present study)	1995	1.5% (21/1426)	2001	14.3% (38/265)

[a]Mortality figures expressed as number of deaths attributable to end-stage liver disease out of the total number of deaths during the interval.

[24,25]. For example, Camino *et al.* reviewed the causes of death among 1600 HIV-infected patients in Spain during a 21-month period in 1998 and 1999 [24]. Of the 44 deaths registered during this interval, liver disease was responsible for 25%. In another multi-centre study from France, 422 deaths were reported among HIV-infected patients during the year 2000 [25]. HCV coinfection was the most frequent non AIDS-related cause of death, representing 10% of all cases.

Combining our contemporary data with our previous surveys from 1995 and 1997 [20], has allowed us to evaluate temporal trends in the mortality of HIV-infected patients in France. Importantly, unlike previous studies addressing this issue [14–16,18,24], our data were derived from a large population of HIV-infected patients from a national network. All participating centres were involved in three consecutive surveys conducted with similar methodology. Although the annual incidence of death decreased between 1995 and 2001, mortality attributable to ESLD (expressed as a percentage of the total number of deaths) increased progressively from 1.5% in 1995, to 6.6% in 1997, and 14.3% in 2001. These findings confirm those of previous studies of predominantly single-centre cohorts in Europe and North America [14–16,18,24] (Table 5), emphasizing the growing importance of ESLD in HIV-infected patients. Several factors may be implicated in this evolution. First, prior to the HAART era, early mortality due to opportunistic infections probably precluded future deaths related to associated chronic viral hepatitis. Moreover, the progression to cirrhosis and HCC in patients with chronic HCV infection occurs over an average of two or three decades [5,6], potentially leading to a burden of disease over time. Increased longevity of HIV-infected patients in the era of HAART, along with accelerated progression of HCV-related liver disease [26] places this group of patients at extremely high risk for liver disease and its complications in future years.

In the current study, mortality due to ESLD in HIV-infected patients was predominantly related to HCV coinfection (95%). However, additional factors, such as alcohol consumption (66%), HBV coinfection (21%), and the use of hepatotoxic medications, must be considered as potential cofactors in accelerating the progression of chronic liver disease or promoting decompensation in some of these patients. In particular, the use of alcohol was more prevalent among patients who died from ESLD in 2001 (66%) than in those during previous years (1995, 38%; 1997, 33%). In parallel, the proportion of injecting drug users, whom are often co-dependent on alcohol, was higher in 2001 (76%) than in 1995 (29%) and 1997 (39%). As observed in HIV-negative patients with chronic hepatitis C [27], the incidence of HCC as a cause of death increased over the study interval (1995, 4.7%; 2001, 25%). Regardless of its aetiology, cirrhosis *per se* is an important risk factor for HCC [28]. Thus, longer survival of HIV-infected patients with HCV-related

cirrhosis may be implicated in the higher rate of HCC observed in 2001. Similarly, a higher prevalence of alcohol abuse probably played a major factor in the rising proportion of HCC-related deaths [29]. These data emphasize the importance of abstinence from alcohol due to its role in accelerating fibrosis progression [30] and promoting hepatocarcinogenesis in HCV-infected patients.

Our data demonstrate that approximately three-quarters of patients who died from ESLD in 2001 were receiving HAART. This is significantly higher than in 1997 (44%), and parallels the rising prescription of HAART in France during the period. The association of chronic HCV infection with hepatotoxicity during HAART constitutes a potential concern for morbidity and mortality in HIV–HCV coinfected patients [31,32]. In particular, HCV infection is an independent risk factor for HAART-related hepatotoxicity [33], and it has been reported that HAART may increase the severity of hepatic necroinflammatory lesions in patients with chronic hepatitis C [9]. However, other studies have suggested that the use of protease inhibitors may be protective with respect to the progression of HCV-related liver disease [26]. Unfortunately, the design of our study did not allow us to determine the role of HAART in overall or liver-related mortality in our patient population. Nevertheless, a recent study demonstrating that HAART is the strongest predictor of survival in HIV-positive patients [34] suggests that treatment for HIV is more important in terms of overall survival than concerns regarding the potential exacerbation of HCV-related liver disease by these medications.

Our multi-centre, national study demonstrates that ESLD, predominantly due to HCV coinfection, is now a leading cause of mortality in the HIV-infected population. Five years after the introduction of HAART, the importance of liver disease as a cause of death has increased progressively. This finding probably relates to prolonged longevity attributable to HAART, and possibly due to an increased prevalence of alcohol use. These findings emphasize the importance of developing effective strategies for the prevention and treatment of chronic HCV infection and the moderation of alcohol intake in HIV-positive patients.

References

1. Sherman K, Roustrer S, Chung R, Rajicic N. **Hepatitis C: prevalence in HIV-infected patients across sectional analysis of the US ACTG.** *Antiviral Ther* 2000, **5** (suppl1): 64–65.
2. Lauer G, Walker B. **Hepatitis C virus infection.** *N Engl J Med* 2001, **345**: 41–52.
3. Soriano V, Kirk O, Antunes F, Johnson M, d'Arminio Monforte A, Teglbjorg LS, *et al*. **The influence of hepatitis C on the prognosis of HIV: the EuroSIDA study.** *XIII International Conference on AIDS.* Durban, July 2000 [abstract ThOrB655].
4. Hagan H, Thiede H, Weiss N, Hopkins S, Duchin J, Alexander E. **Sharing of drug preparation equipment as a risk factor for hepatitis C.** *Am J Public Health* 2001, **91**: 42–46.
5. Seff LB. **Natural history of hepatitis C.** *Hepatology* 1997, **26** (suppl 1): S21–S28.
6. Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, *et al*. **The natural history of community acquired hepatitis C in the United States.** *N Engl J Med* 1992, **327**: 1899–1905.
7. Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. **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**:602–610.
8. Quan CM, Krajden M, Grigoriew GA, Salit IE. **Hepatitis C infection in patients infected with the human immunodeficiency virus.** *Clin Infect Dis* 1993, **17** (suppl 1):117–119.
9. Soto B, Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengoechea M, Hernandez-Quero J, *et al*. **Human immunodeficiency virus modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis.** *J Hepatol* 1997, **27**:1725–1730.
10. Ragni MV, Belle SH. **Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection.** *J Infect Dis* 2001, **183**:1112–1115.
11. Vento S, Garofano T, Renzini C, Casali F, Ferraro T, **Concia E. Enhancement of hepatitis C replication and liver damage in HIV-coinfected patients on antiretroviral combination therapy.** *AIDS* 1998, **12**:116–117.
12. Darby SC, Ewart DW, Giangrande PL, Dolin PJ, Spooner RJ, Rizza CR. **Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Director's Organisation.** *Lancet* 1997, **350**: 1425–1431.
13. Yee TT, Griffioen A, Sabin CA, Dusheiko G, Lee CA. **The natural history of HCV in a cohort of haemophilic patients infected between 1961 and 1985.** *Gut* 2000, **47**: 845–851.
14. Soriano V, Garcia-Samaniego J, Valancia E, Rodriguez-Rosado R, Munoz F, Gonzalez-Lahoz J. **Impact of chronic liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users.** *Eur J Epidemiol* 1999, **15**: 1–4.
15. Puoti M, Spinetti A, Ghezzi A, Donato F, Zaltron S, Putzolu V, *et al*. **Mortality for liver disease in patients with HIV infection: a cohort study.** *J Acquired Immune Defic Syndr* 2000, **24**: 211–217.
16. Martin-Carbonero L, Soriano V, Valencia ME, Lopez M, Gonzalez-Lahoz J. **Impact of chronic viral hepatitis on hospital admission and mortality in HIV-infected patients.** *AIDS Res Hum Retroviruses* 2001, **17**:1467–1471.
17. Di Pierri G, Raiteri R, Bonora S, *et al*. **Liver failure from HCV as the current leading cause of death in HIV-infected patients in northern Italy.** *Eighth Conference on Retroviruses and Opportunistic Infections.* Chicago, February 2001 [abstract 573].
18. Bica I, McGoven B, Stone D, McGowan K, Scheib R, Snydman DR. **Increasing mortality due to end-stage liver disease in patients with HIV infection.** *Clin Infect Dis* 2001, **32**:492–497.
19. Monga H, Rodriguez-Barradas M, Breaux K, Khattak K, Troisi CL, Velez M, *et al*. **Hepatitis C virus infection-related morbidity and mortality among patients with HIV infection.** *Clin Infect Dis* 2001, **33**:240–247.
20. Cacoub P, Geffray L, Rosenthal E, Perronne C, Veyssier P, Raguin G. **Mortality among HIV-infected patients with cirrhosis or hepatocellular carcinoma due to hepatitis virus C in French departments of Internal Medicine/Infectious Diseases in 1995 and 1997.** *Clin Infect Dis* 2001, **32**:1207–1214.
21. Soriano V, Martin-Carbonero L, Puoti M, Garcia-Samaniego J. **Mortality due to chronic viral liver disease in HIV-infected patients.** *Clin Infect Dis* 2001, **33**:1793–1794.
22. Anonymous. **1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults.** *JAMA* 1993, **269**: 729–730.
23. Anonymous. **Surveillance du sida en France. Situation au 30 septembre 2001.** *BEH* 2001, **47**:207–213.
24. Camino X, Iribarren JA, Arrizabalga J, Rodriguez F, Von Wichmann AM. **Causes of mortality among patients infected with the human immunodeficiency virus in the era of highly active antiretroviral therapy.** *Enferm Infecc Microbiol Clin* 2001, **19**:85–86.

25. Lewden C, Héripret L, Bonnet F, *et al*. **Causes of death in HIV-infected adults in the era of highly active antiretroviral therapy (HAART), the French survey 'Mortalité 2000'.** *Ninth Conference on Retroviruses and Opportunistic Infections*. Seattle, February 2002 [abstract 753].
26. Benhamou Y, Di Martino V, Bochet M, Colombet G, Thinault V, Liou A, *et al*. **Factors affecting liver fibrosis in HIV and hepatitis C coinfected patients: impact of protease inhibitor therapy.** *Hepatology* 2001, **34**:283–287.
27. Deuffic S, Buffat L, Poynard T, Valleron AJ. **Modeling the hepatitis C virus epidemic in France.** *Hepatology* 1999, **29**:1596–1601.
28. Colombo M. **Natural history and pathogenesis of hepatitis C virus related hepatocellular carcinoma.** *J Hepatol* 1999, **31** (suppl 1):25–30.
29. Donato F, Tagger A, Gelatti U, Parrinello G, Boffetta P, Albertini A, *et al*. **Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women.** *Am J Epidemiol* 2002, **155**:323–331.
30. Poynard T, Bedossa P, Opolon P. **Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIR groups.** *Lancet* 1997, **349**:825–832.
31. Lenzo N, Garas B, French M. **Hepatic steatosis and lactic acidosis associated with stavudine treatment in an HIV patient: a case report.** *AIDS* 1997, **11**:1294–1296.
32. Karras A, Rabian C, Zylberberg H, Hermine O, Duchatelle V, Durand F, *et al*. **Severe anoxic hepatic necrosis in an HIV-hepatitis C virus-coinfected patient starting antiretroviral triple combination therapy.** *AIDS* 1998, **12**: 827–829.
33. Soriano V, Sulkowski M, Bergin C, Hatzakis A, Cacoub P, Katlama C, *et al*. **Care of patients with chronic hepatitis C and HIV co-infection: recommendations from the HIV-HCV international panel.** *AIDS* 2002, **16**:813–828.
34. Tedaldi E, Baker R, Moorman A, Alzola CF, Furher J, McCabe RE, *et al*. **Hepatitis viruses: influence on morbidity, mortality and response to antiretroviral therapy.** *Ninth Conference on Retroviruses and Opportunistic Infections*. Seattle, February 2002 [abstract 659].

Acknowledgements

We thank J. N. Mazza (CISIH, Hôpital Archet 1, Nice, France) for data management.

Appendix

Members of the GERMIVIC group from French departments of internal medicine and infectious diseases participating in the Mortavic 2001 study

Amiens: B. Pautard-Huchemblé, J.L. Schmit; Angouleme: M. Bonnefoy; Annecy: J.P. Bru, J. Gaillat; Antibes: L. Lerousseau; Arras: D. Dubois; Avignon: A. Azzedine, A De La Blanchardière, G. Lepeu; Belfort: J.P. Faller; Besancon: P. Balvay, F. Barale, J.M Estavoyer, D. Vuitton; Bobigny: M. Bentata, P. Cohen, L. Guillevin, B. Jarrousse, B. Padrazzi; Bordeaux: J. Beylot, N. Bernard, J. Constans, I. Loury, F. Moreau, P. Morlat, J.M. Ragnaud, J.F. Viaud, D Lacoste; Boulogne Billancourt: A. Baglin, M. Dorra, C. Dupont, T. Hanslik, E. Rouveix; Bourg en Bresse: P. Granier; Brest: A. Cénac; Caen: C. Bazin, P. Hazera; Cebazat: J. Schmidt; Chambery: O. Rogeaux; Charleville: C. Menalba; Clamart: R. Fior, P. Galanaud; Clermont de l'Oise: J. J. Pik; Clermont-Ferrand: H. Laurichesse, M. Ruivard; Colmar: G. Laplatte, B. Audoy, N. Plaisance, C. Bouterra, G. Laylotte; Colombes: E. Delarocque, E. Martier, P. Vinceneux; Creteil: P. Lesprit, A. Schaeffer; Dijon: M. Grappin; Dijon: M.C. Greuzard, M.C. Loudes-Chauvin, H. Portier, M. Vinceneux; Dolle: J. Guillaumie; Eaubonne: P. Dournovo; Garches: C. Perronne; Grenoble: O. Bouchard, M. Micoud, P. Morand; Hyeres: J. Boucher, P. Chambourlier, C. Renou; La Reunion: C. Arvin-Berod, P. Poubeau; La Roche Sur Yon: P. Perre; Lille: E. Hachulla, B. Devulder, P.Y. Hatron; Limoges: V. Loustaud-Ratti; Lons Le Saunier: J.D. Berthou, D. Baborier; Luneville: E. Constant, E. Dufay; Lyon: D. Peyramond; Mantes la Jolie: F. Trémolières; Marseille: S. Chapadaud, H. Gallais, J.L. Perret, A. Bourgeade, J.M. Durand, J. Moreau, J. Soubeyrand; Mende: P. Meissonnier; Menton: R. Hayek; Metz: C. Constant, J.J. Raabe, A. Wang; Montpellier: J. Astruc, F. Blanc, P. Perney, A. Vandôme; Nantes: D. Bautoille, C. Guerbois, C. Loyau, F. Raffi, D. Villers; Nancy: C. Burty, P. Canton, J.D. de Korwin, G. Thibaut, D. Wahl; Nice: P. Dellamonica, J.G. Fuzibet, C. Pradier, E. Rosenthal, J.P. Cassuto; Nimes: C. Raffanel; Paris: Z. Amoura, H. Aumaitre, F. Bani-Sadr, J.F. Bergmann, F. Bissuel, A. Boissonnas, E. Bouvet, F. Bricaire, J. Cabane, A. Cabié, P. Cacoub, R. Caquet, C. Carbon, C. Caulin, K. Chemlal, J.P. Coulaud, T de Beaumont, F. Devars du Mayne, C. Dupont, B. Durand, D. Farge, P. Galanaud, C. Gaudebout, J. Gilquin, C. Goujard, P. Hausfater, C. Katlama, M. Karmochkine, F. Krainik, P. Le Bras, V. Le Moing, C. Leport, J. Modaï, J.M. Molina, G. Pialoux, J.C. Piette, Y. Poinsignon, G. Raguin, W. Rozenbaum, D. Sicard, J. Simon, F. Vachon, A.J. Valleron, J.L. Vildé; Orleans: P. Arsac, G. Calamy, C. Mille; Pessac: P. Mercie, J.L. Pellegrin; Poitiers: B. Becq-Giraudon, J.P. Breux; Rennes: F. Cartier; Reims: I. Beguinot, G. Rémy; Rouen: I. Gueit, F. Borsa-Lebas, G. Humbert; Roubaix: J. Wemeau; St Brieux: C. Hascouet, B. Le Cam; St Denis: M.A. Khuong, D. Mechali, X. Roblin; St Etienne: C. Defontaine, F. Lucht; St Germain en Laye: S. Fégueux; St Laurent du Var: D. Ouzan; Sete: B. Kitschke; Sens: C. Clément-Bertoldo, G. Gonzales; Strasbourg: P. Fischer, J.M. Lang, D. Rey, A. Ruellan, J.L. Schlienger; Suresnes: D. Zucman, O. Blétry; Thonon les Bains: P. Romand; Toulouse: L. Alric, L. Cuzin, M. Duffaut; Tourcoing: F. Ajana, Y. Mouton, Y. Yazdanpanah; Tours: J.C. Borderon, P. Choutet, Y. Guimard; Villeneuve St Georges: O. Patey.