Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: The French national Mortalité 2005 study.

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Abstract

Background

Longer exposure to hepatitis C (HCV) or B virus (HBV) and the increased use of hepatitis treatment might have an impact on liver-related deaths in patients co-infected with the Human Immunodeficiency Virus (HIV). We describe the proportion of liver-related deaths among HIV-infected patients in 2005 compared with 2000.

Methods

In a nationwide survey (341 hospital departments involved in HIV management), all deaths of HIV-infected patients were prospectively notified. Deaths from either cirrhosis, hepatocellular carcinoma or fulminant hepatitis were defined as liver-related deaths.

Results

Of the 898 deaths reported in 2005, liver-related causes accounted for 15.4%; this is compared to 13.4% in 2000. Among liver-related deaths, hepatocellular carcinoma increased from 15% to 25% (p=0.04). Among hepatocellular carcinoma-related deaths: in 2000, 10% were HCV-infected; in 2005, 25% were HCV-infected (p=0.03). Half of the HCV-related deaths had been treated for HCV but 98% remained HCV-RNA positive at time of death. The proportion of HBV-related deaths remained stable between 2000 and 2005.

Conclusions

Liver-related deaths, mainly liver cancers, have increased in HIV-infected patients in France despite wide access to HCV treatment. The stability of HBV-related deaths might be explained by the use of dually active antiretroviral drugs in co-infected patients.

MESH Keywords Adult ; Carcinoma, Hepatocellular ; epidemiology ; mortality ; Female ; France ; epidemiology ; HIV Infections ; epidemiology ; Hepatitis B ; epidemiology ; Hepatitis C ; epidemiology ; Heterosexuality ; Homosexuality ; Humans ; Liver Cirrhosis, Alcoholic ; mortality ; Liver Neoplasms ; epidemiology ; mortality ; Male ; Middle Aged ; Substance Abuse, Intravenous ; epidemiology

INTRODUCTION

In recent years, end stage liver disease has become a major cause of morbidity and mortality in patients chronically infected with the Human Immunodeficiency Virus (HIV) who are coinfected with hepatitis C (HCV) or B virus (HBV) (1–4). This trend may be explained by a prolonged exposure to viral hepatitis, because most patients were infected with HCV in the 1980s. This time interval is compatible with the occurrence of cirrhosis and its late complications, as accelerated fibrosis and cirrhosis are observed in more HCV-HIV coinfected patients compared to HCV mono-infected patients (5, 6).

In parallel, thanks to the widespread use of combination antiretroviral therapy (cART) in industrialised countries, the incidence of Acquired Immune Deficiency Syndrome (AIDS) morbidity and related mortality has dramatically decreased, resulting in an increased life expectancy. However, this has also meant that the causes of death have shifted to predominantly non AIDS-related diseases, with a high proportion of end-stage liver diseases being observed (2, 7–10). These major hepatic complications have emerged in the context of excessive alcohol use – metabolic issues such as steatosis (11) and portal hypertension (12) may also be related to antiretroviral treatment toxicity but their role in liver mortality remains to be defined.

On the other hand, treatments for viral hepatitis are now widely available in industrialised countries and viral eradication is achieved in 25 to 40% of HCV-HIV coinfected patients treated with a peginterferon and ribavirin combination (13–16), while anti-HBV treatment is a part of cART. However, the best treatment strategy for HCV in patients with an indication for cART remains controversial.

Several studies including the French national survey, "Mortalité 2000", have shown that complications of HCV and HBV are the second most frequent underlying cause of death after AIDS in HIV-infected patients, accounting for around 10% of deaths (1–4).

One of the aims of the "Mortalité 2005" survey, was to identify and describe the characteristics of HIV-infected patients who died from end-stage liver disease. These patients were then compared to the population identified in 2000.

METHODS

Data collection

All hospital wards and networks known to be involved in the management of HIV infection in France were contacted and invited to participate in the "Mortalité 2005" survey; this included those that participated in the "Mortalité 2000" survey and physicians involved in penitentiary medicine. Moreover, French societies of intensive care, pneumology and hepatology specialists were contacted and they asked their members to participate (17).

Physicians prospectively reported deaths in HIV-infected adults (18 years or older) every three months in 2005, together with a short abstract describing the potential cause of death. Each case was then documented using a standardized questionnaire that collected information on the potential contributing causes of death, diseases present at time of death and included a global assessment of the underlying cause of death. One physician was especially dedicated to the survey in the coordinating team and oversaw harmonization of data collection. Duplicate reports were identified by cross-matching dates of birth and death. In addition, all participating wards estimated the number of HIV-infected patients seen at least once in 2004 in order to approximate the coverage of the survey.

In the present study, we analysed only those deaths with a known status for HCV and HBV. HCV infection was defined as the presence of serum HCV-antibody or HCV-ribonucleic acid (RNA), HBV infection by that of serum hepatitis B surface antigen or HBV-deoxyribonucleic acid (DNA), and hepatitis delta virus (HDV) infection by that of serum HDV-antibody. An excessive alcohol consumption was defined as daily alcohol intake higher than 50 grams and/or five glasses, and poor socio-economic conditions were defined as the patients having no health insurance, no employment, no accommodation, income below 535 € per month and/or immigrant in illegal situation.

Determination of the underlying cause of death

Information contained in the questionnaire was used to determine the underlying cause of death according to the International Classification of Diseases, tenth revision (ICD-10) rules: the underlying cause of death was the disease or injury, which initiated the train of morbid events leading to death (1). The algorithm of determination was adapted to specific concerns in HIV infection (3) and allowed categorization of deaths as follow: AIDS-related causes according to the 1993 Centers for Disease Control (CDC) clinical classification (18); liver disease including infection with HCV and/or HBV as well as hepatocellular carcinoma, cancers attributable neither to AIDS nor to HCV/HBV infection, cardiovascular diseases, or other causes.

The underlying cause of death was classified as liver disease if the patient died from cirrhosis (ie, ascites, variceal bleeding, encephalopathy, spontaneous bacterial peritonitis, hepatocellular insufficiency), hepatocellular carcinoma or fulminant hepatitis, regardless of the potential relationship to HCV or HBV infection, alcohol or another cause. Patients with hepatocellular carcinoma who died from liver failure were classified as dying from hepatocellular carcinoma, to remain consistent with the definition of an underlying cause of death according to the ICD-10 classification.

Statistical analysis

We compared a) the underlying cause of death categorized in five categories (AIDS, liver disease including viral hepatitis, non-hepatitis and non-AIDS related cancer, cardiovascular disease, other cause) between 2005 and 2000; b) the characteristics of patients who died from a liver-related cause versus another cause, in 2005.

Among HIV-infected individuals with a liver-related cause of death, we compared the distribution of the following variables between 2000 and 2005: a) characteristics of cases; b) type of hepatic events leading to death; c) the proportion of HCV, HBV/HCV co-infections, and excessive alcohol consumption.

Between-group comparisons were performed using Chi-2 and Fisher tests for categorical variables, and the Kruskal-Wallis test for quantitative variables, using α=0.05. A logistic regression model was used to compare characteristics of deaths from liver-related diseases to other deaths and included: age at time of death, gender, viral infection (HBV alone, HCV alone, both, no HBV or HCV infection), latest CD4 cell count < 200/mm3, CDC stage C and excessive alcohol consumption.

Statistical Analysis System (SAS) software version 9.1.3 was used for all analyses.

RESULTS

The Mortalité 2000 and 2005 surveys involved 185 and 341 clinical wards, respectively. These wards estimated that their coverage was around 78,000 HIV-infected patients in 2005 versus 64,000 patients in 2000. A total of 1042 deaths were notified in 2005 as compared to 964 in 2000 and amongst them, the hepatitis virus status was known in 898 and 822 cases, respectively.

Underlying causes of deaths in 2005 and characteristics of cases (Figure 1, Table 1)

Amongst the deaths that occurred in 2005, most were men in their forties with more a known duration of HIV infection of >10 years (Table 1). Forty-four percent of patients who died were coinfected with at least one hepatitis virus, predominantly HCV.

In cases with known hepatitis status, the relative proportion of the five main underlying causes of death changed significantly between 2005 and 2000 ($p < 0.0001$): the percentage of AIDS-defining illness decreased, whereas the proportion of liver-related causes of death and non-hepatitis and non-AIDS related cancers increased (Figure 1). HCV and HBV as causes of death represented 10.9% and 1.8% of deaths, respectively. Underlying causes of deaths did not differ between patients with known and unknown hepatitis status ($p=0.52$).

Characteristics of cases dying from liver-related diseases (Table 1, Table 2)

In 2005, 138 liver-related deaths were notified. Excessive alcohol consumption was significantly more frequent among those dying from liver-related causes than in those dying from other causes (Table 1). Excessive alcohol consumption was more frequent among HCV and HCV/HBV co-infected cases (47% and 83%, respectively) than among HBV co-infected cases (36%) ($p=0.03$). Compared with patients dying from other causes in 2005, patients dying from liver-related causes were significantly older, were more frequently infected by HCV or HBV, and were more likely to be excessive alcohol consumers (using logistic regression). The group dying liver-related deaths had progressed to AIDS less frequently than the group dying from other causes, but did not differ in CD4 count at time of death.

In 2005, the median age of patients at the time of death from liver-related causes was higher than the median age of those dying from liver-related causes in 2000 (Table 2). Furthermore, the time between diagnosis of HIV and death from liver-related diseases was longer in 2005 than in 2000 (Table 2). Amongst these liver-related deaths, virological suppression was greater in 2005 than in 2000, whereas the slightly higher median value of the latest CD4 cell count in 2005 was not significantly different to the value in 2000 (Table 2).

Hepatic disease leading to death

In 2005, the underlying liver-related cause of death was decompensated cirrhosis in 91 cases (66%), hepatocellular carcinoma in 35 cases (25%) (unifocal lesions in 6 cases and multifocal lesions in 16, unspecified in 17 cases), other complications of HCV (3 cases, 2%) including two adverse effects related to interferon treatment, HBV reactivation (1 case, 0.7%), and other causes (8 cases, 6%).

Among patients that died from hepatocellular carcinoma, 80% of them were male, 41% excessive alcohol consumers, 60% tobacco smokers, and 9% diabetic. Patients that died from hepatocellular carcinoma were older than those who died from other liver diseases (48 versus 46 years, $p = 0.04$), whereas other patient characteristics did not differ between these 2 subgroups.

Among liver-related deaths, hepatocellular carcinoma increased from 16/110 cases (15%) in 2000 to 35/138 cases (25%) ($p=0.04$) in 2005. In addition, most deaths from hepatocellular carcinoma were HCV-infected (69%), or HBV-infected (17%), or HCV and HBV-infected (11%), while excessive alcohol consumption alone was reported in a single case (Figure 2).

Respective part of HCV, HBV, alcohol and other causes among liver-related deaths (Table 3)

In 2005, 138 liver-related deaths were notified versus 110 in 2000. Most of them were attributed to HCV infection in both 2005 and 2000, and less frequently to HBV infection, a dual HCV and HBV co-infection, an excessive alcohol consumption, or another cause.

HCV infection

In 2005, 98 patients died from HCV-related liver disease. These patients had a median age of 47 years and a median duration of 14.6 years since HIV diagnosis. The patients died in a state of moderate immunosuppression: median CD4 level at 231/mm^3 (versus 168 CD4/mm^3 in 2000) and HIV-RNA <500 copies/ml in 62% of cases. HCV genotype was available in 70 cases: genotype 1 or 4 (n=47, 67%), and genotype 2 or 3 (n=23, 33%). Fifty percent had previously been treated for HCV infection and 98% of them had positive HCV-RNA at time of death. Forty-seven percent of HCV-infected patients that died in 2005 were excessive alcohol consumers. Among liver-related deaths, the proportion of HCV-infected cases did not differ in 2000 and 2005 (p=0.16), whereas the proportion of hepatocellular carcinoma in HCV-infected patients increased from 10% (7/68 patients) in 2000 to 26% (25/98 patients) in 2005 (p=0.03), The other lethal hepatic events were: decompensated cirrhosis in 70 cases; and other causes in 3 cases including two interferon-related lethal events (as described below).

HBV infection

In 2005, 16 liver-related deaths were HBV-infected, were a median of 43 years old, and the median duration since HIV diagnosis was 15.4 years. Thirty-six percent of these patients were excessive alcohol consumers. All patients that were HBV-infected when they died received antiretroviral treatment and they died in a state of moderate immunosuppression: median CD4 level at 235/mm^3, and HIV-RNA <500 copies/ml in 8 cases (50%).

The proportion of patients that died from hepatocellular carcinoma among those that were HBV-infected at the time of death was 54% (7/13 cases) in 2000 versus 38% (6/16 patients) in 2005. Other lethal hepatic events were attributed to decompensated cirrhosis in 9 cases, and to the consequence of HBV reactivation in 1 case.

HBV/HCV co-infection

In 2005, 7 cases died from HBV/HCV-related liver diseases; the hepatic event leading to death was decompensated cirrhosis in 4 cases, and hepatocellular carcinoma in 3 cases (versus 2/16 cases in 2000).

Alcohol

In 2005, 9 cases died from an isolated alcohol-related liver disease (versus 12 in 2000). The hepatic events leading to death were decompensated cirrhosis in 6 cases, a hepatocellular carcinoma in 1 case, and undetermined causes in 2 cases. However, excessive alcohol consumption was notified in 63 of the 138 cases who died from a liver-related causes in 2005.

Contributing role of treatments in liver-related deaths

Amongst 138 cases who died from liver disease in 2005, some form of treatment was involved in 9 cases (7%): antiretroviral treatment in 3 cases, interferon in 3 cases (1 IFN-induced autoimmune hepatitis, 1 severe thrombocytopenia, 1 sudden death in a patient with depressive symptoms), and other drugs in 3 cases.

DISCUSSION

In this national survey of deaths occurring in HIV-infected patients in 2005, liver diseases represented the third most frequent underlying cause of death (15.4% vs 13.4% in 2000). This finding has already been underlined in a few surveys such as the D:A:D international collaboration, which reported a similar proportion of liver-related diseases among the causes of death in HIV-infected patients in the cART era, with an estimation of liver-related mortality of 0.24% person-years of follow-up, This echoes the findings of our study which did, however only record deaths (2, 4).

Over the 1995–2003 period, the French Mortavic group performed consecutive surveys that showed a dramatic decline in the proportion of AIDS–related deaths from pre-cART periods (92% to 46.9%) and an increase in the proportion of end stage liver disease, as cause of death (1.5% to 12.6%) (2).

We believe that these results may not be explained by the fact that the wards targeted in 2005 slightly differed from those targeted in 2000, since the proportion of liver-related deaths and patients' characteristics did not differ between wards that participated in both the 2000 and 2005 surveys and wards that participated only in 2005 (17). Moreover, hepatology wards that participated only in 2005 reported only 3% percent of all liver related causes of deaths.

In our study, liver-related death occurred mainly in HCV-infected patients representing 71% of patients with liver-related mortality. In this population, the proportion of hepatocellular carcinoma increased by a factor of 3 over this 5-year period. This increase in the proportion of hepatocellular carcinoma occurred despite better control of HIV infection (median CD4 count at 231/mm3 in 2005 versus 157/mm3 in 2000) and may be the result of a longer exposure to HCV infection. Indeed, although the majority of infections occurred in the late 1980s, the efficacy of cART could have increased survival in cirrhotic patients, which has thus allowed the time for more cases of hepatocellular carcinoma to develop. As all hepatocellular carcinoma cases were symptomatic at the time of death as also shown in a

recent study (19), we believe that the recent improvement in the diagnostic accuracy of hepatocellular carcinoma did no play an important role in the increased number of cases observed between 2000 and 2005. The known duration since HIV diagnosis in patients who died from hepatocellular carcinoma, that can be extended to duration since HCV diagnosis, was significantly longer than in patients who died from non-liver-related causes (median: 15.8 years versus 10.8 years). Apart from HCV infection, known risk factors for hepatocellular carcinoma include male gender, age older than 60 years, HBV infection, excessive alcohol consumption, tobacco, diabetes, and high body mass index (19–22). Some of these co-morbidities were frequent in our series of HIV-infected patients dying with hepatocellular carcinoma, like HCV infection (69%), chronic HBV co-infection (17%), excessive alcohol consumption (41%), and tobacco use (60%). The important role of hepatocellular carcinoma in HCV infected patients may be related to a high rate of treatment failure, especially since genotypes 1 and 4 represented 67% of HCV liver deaths in our study, and efficacy of pegylated interferon and ribavirin combination is known not to exceed 15% in patients with such genotypes (13–16).

Conversely, the proportion and the number of HBV-related deaths remained low and stable between 2000 and 2005 and the rate of hepatocellular carcinoma as a cause of death among HBV-infected patients did not increase (7/13 cases in 2000 versus 6/16 cases in 2005). Moreover, there was probably an underestimated proportion of delta co-infection in HBV-infected patients (two cases documented among six hepatocellular carcinoma related to HBV infection in 2005). As it is now well known in HBV mono-infected patients, HBV-DNA levels are directly correlated to the incidence of long-term complications of cirrhosis, hepatocellular carcinoma and deaths. In HBV-HIV co-infected patients, anti-HBV active cART makes it possible to achieve suppression of HBV replication and anti-hepatitis B early antigen seroconversion in a substantial proportion of patients particularly those who have a complete HIV suppression and a satisfactory immune recovery (23). Lamivudine has been widely available since 1996, and if there was a beneficial impact of this therapy then this would have been observed before 2000. The design of our study, therefore, did not allow for exploration of the effect of lamivudine. The widespread use of tenofovir, one of the most promising drugs against HBV in these patients, may rather explain this favourable evolution. Moreover, in cirrhotic patients with long-term suppression of HBV replication under tenofovir treatment, improvement in hepatic functions has been observed, creating hope for a potential reversal of end-stage liver disease, and for a survival benefit in this population (24, 25).

Our study has also pointed out the emergence of new, albeit rare, causes of liver disease leading to death. Among them, cART was directly or indirectly associated in three cases including one case of didanosine-associated lactic acidosis in a patient with pre-existing cirrhosis, and two cases of portal hypertension. Although cART has significantly improved the prognosis of HIV infection, long-term complications of these drugs are increasingly recognized as significant causes of morbidity and mortality. Non-alcohol related fatty liver disease, which can evolve into non-alcohol related steatohepatitis, cirrhosis and ultimately hepatic failure, has been recently described as a complication due to multiple factors that co-exist in HIV-infected patients including metabolic abnormalities, chronic inflammation, concurrent infection with HCV (12). Among them, stavudine and didanosine have proven to be commonly implicated in the occurrence of mitochondrial abnormalities and of lactic acidosis.

More recently, some cases of non-cirrhotic portal hypertension have been described in HIV-infected patients (26–29). In such cases, liver biopsy usually showed vascular lesions presenting as nodular regenerative hyperplasia. Patients underwent the significant complications of portal hypertension, such as variceal bleeding and refractory ascites. It has been hypothesised that these lesions were related to either exposure to didanosine (30) and/or intrahepatic microthrombosis, as two studies have shown coagulation test abnormalities like protein S deficiency, elevated homocysteinemia and a constitutional elevation of plasma factor VIII coagulant activity (12). The protease inhibitor treatment may have played a role in increasing the thromboembolic risk.

In conclusion, while the proportion of deaths related to HBV end-stage liver disease seems stabilized with effective drugs as part of a cART, there is still an increase in deaths related to HCV end-stage liver disease for which therapeutic options remain limited. The incidence of hepatocellular carcinoma is approximately 2–5% per year in HCV-HIV infected patients with cirrhosis. In the absence of new therapeutic options, an exponential burden of deaths from decompensated cirrhosis or hepatocellular carcinoma in HCV-HIV infected subjects is expected in the near future (31, 32). To avoid such a scenario, anti-HCV treatment should be widely proposed even in patients with cirrhosis provided that they have no decompensation as early HCV viral kinetics predicts 3-month sustained virological response and allows stopping therapy in cases of insufficient viral load decrease. As in HBV infection, regression of liver fibrosis has been observed in HCV-HIV co-infected patients after treatment with pegylated interferon plus ribavirin (33). Active promotion of alcohol and smoking cessation programs should be widely implemented. Regular screening for hepatocellular carcinoma should be performed in order to detect small unifocal lesions accessible to surgery. Moreover, evaluation of new therapeutic strategies including new drugs (protease inhibitors, polymerase inhibitors) and high doses of ribavirin in patients who failed to respond to a first treatment as recently demonstrated in the PRESCO trial (34), are urgently needed, and trials must be developed early in HIV-infected patients in parallel to those initiated in HCV mono-infected patients. Lastly, one must remain vigilant about potential new liver complications which may be related to antiretroviral therapy.

Ackowledgements:

Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS) through a grant from the CSS5 (Scientific Sector-based Group number°5)

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Figure 1

Distribution of the underlying cause of death (p <0.0001) and latest CD4 cell count between 2000 (N = 822) and 2005 (N = 898) in deceased HIV-infected patients with a known status for viral hepatitis C and B - Mortalité 2000 and Mortalité 2005 surveys, France

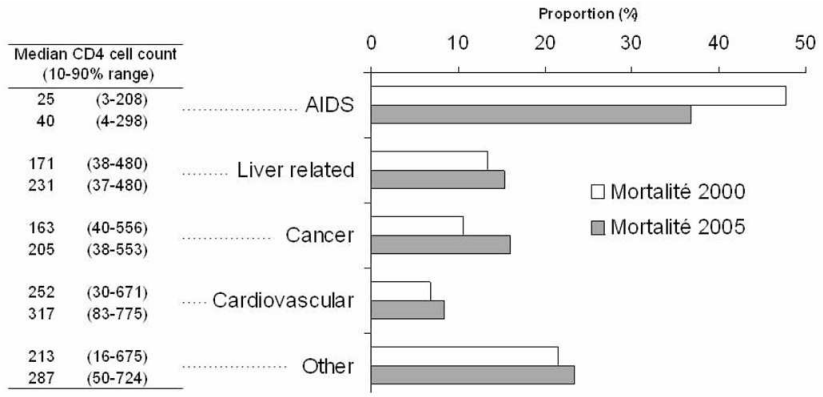

Figure 2

Hepatocellular carcinoma-related deaths in 2000 (N = 16) and in 2005 (N = 35) according to hepatitis co-infections – Mortalité 2000 and Mortalité 2005 surveys, France. HCV: Hepatitis C Virus; HBV: Hepatitis B Virus

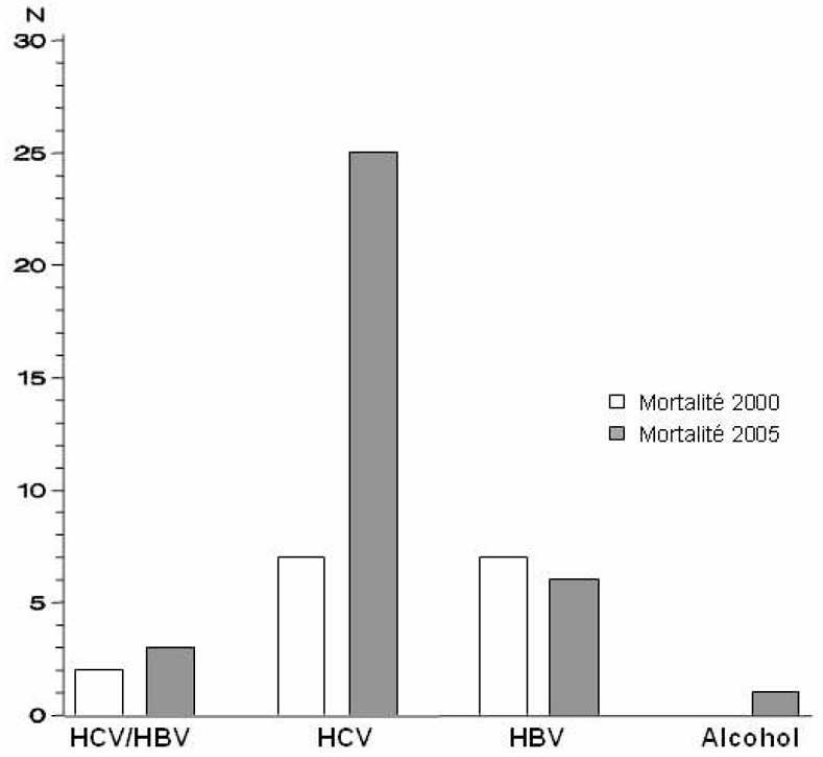

Table 1

Characteristics of liver-related deaths: comparison with deaths from other causes in HIV-infected patients - Mortalité 2005 survey, France.

Mortalité 2005 survey	Total N = 898	Liver-related deaths N = 138	Deaths from other causes N = 760
Median age (years) *	46	47*	45*
Male gender (%)*	75	78*	74*
Transmission risk group (%)			
heterosexual	32	14	36
homosexual	26	11	28
intravenous drug use	30	63	24
Viral infection (%)*			
HCV alone	32	68	25
HBV alone	7	10	7
HCV + HBV	5	12	4
Median known duration since HIV diagnosis (years)	11.8	14.8	10.8
CDC clinical stage C (%)*	65	45*	68*
Median latest CD4 cell count (/mm^3)	159	231	138
Latest CD4 <200/mm^3 (%)	55	44	57
Median latest HIV-RNA ($\log_{10}$ copies/mL)	3.2	2.0	3.5
History of antiretroviral therapy (%)	88	96	87
Excessive alcohol consumption (%)*	28	50*	24*
Smoking status (%)	55	69	53
Poor socio economic conditions (%)	30	25	31
Death in hospital (%)	77	88	75

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; CDC: Centers for Disease Control; HIV: Human Immunodeficiency Virus; RNA: RiboNucleic Acid.

* The distribution of this variables was significantly different ($p<0.01$) in a logistic regression comparing liver-related deaths with deaths from other causes, adjusted for age, gender, presence of HBV or HCV infection, CDC stage and excessive alcohol consumption.

Table 2

Characteristics of liver-related death cases: comparison of their characteristics in 2000 and 2005, Mortalité 2000 and Mortalité 2005 surveys, France

	Mortalité 2000 N = 110	Mortalité 2005 N = 138	p-value
Median age (years)	40	47	**<0.001**
Male gender (%)	76	78	0.72
Median known duration since HIV diagnosis (years)	10.7	14.8	**<0.001**
CDC clinical stage C (%)	41	45	0.52
Median latest CD4 cell count (/mm^3)	171	231	0.21
Latest CD4 <200/mm^3 (%)	56	44	0.06
Median latest HIV-RNA (Log_{10} copies/mL)	3.3	2.0	**<0.001**
Previous cART (%)	75	90	**0.002**
Duration of cART (years)	2.8	7.4	**<0.001**
Excessive alcohol consumption (%)	59	50	0.16
Smoking status (%)	72	69	0.58
Death in hospital (%)	93	88	0.21
% of specialities involved in death declaration			0.19
Infectious diseases and medicine* (%)	98	96	
Hepatology (%)	0	3	
Intensive care unit (%)	2	1	
Others (%)	0	0	

CDC: Centers for Disease Control; HIV: Human Immunodeficiency Virus; RNA: RiboNucleic Acid; cART: combination AntiRetroviral Therapy; HCV: Hepatitis C Virus.

* Pneumology, dermatology, Nephrology, Immunology, oncology, haematology units

Table 3

Underlying cause of liver-related deaths - Mortalité 2000 and Mortalité 2005 surveys, France

		Mortalité 2000 N = 110	Mortalité 2005 N = 138
HCV	n (%)	68 (62)	98 (71)
HBV	n (%)	13(12)	16(12)
HCV + HBV	n (%)	16(14)	7(5)
Alcohol	n (%)	12(11)	9(6)
Other	n (%)	1(1)	8(6)
Cholangiocarcinoma			2
Portal hypertension			2
Fulminant hepatitis			1
Auto-immune hepatitis			1
Drug toxicity			1
Other hepatitis			1

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus.