Prevalence of hepatitis C and hepatitis B infection in the HIV-infected population of France, 2004

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Our objective was to estimate the prevalence of HCV and HBV co-infection among HIV-infected adults in France and describe the epidemiological characteristics of co-infected patients and their clinical management. A one-day national cross-sectional survey was conducted in 2004. A random and proportional probability sample design was used, based on the number of AIDS cases reported since 1999 by hospital wards. Weighted estimations were computed. HIV-infected adults (out/in-patients) were included after consent. Data were collected on demographic criteria, HIV, HCV and HBV infections, as well as on antiviral therapies. Overall, 1849 HIV-infected patients were included. The prevalence of anti-HCV or HCV RNA positivity (HCV co-infection) was 24.3% [95% confidence interval (CI): 21.3-27.6] and varied from 3.1% in men who had sex with men to 92.8% in injecting drug users (IDUs). The prevalence of positive HCV RNA was 17.0% [95% CI:14.7-19.4]. The prevalence of HBs antigen (Ag) or HBV DNA positivity was 7.0% [95% CI: 5.9-8.1] and varied with the continent of birth from 2.1% in Northern Africa to 10.8% in sub-Saharan Africa. The prevalence of HIV-HCV-HBV co-infection was 1.6% [95% CI: 1.0-2.4], mostly IDUs (83.3%). A severe liver disease (cirrhosis or hepatocellular carcinoma) was diagnosed in 24.7% of the positive HCV RNA patients.This study confirmed the burden of HCV infection in French HIV-infected patients and described for the first time in France the epidemiological characteristics of HIV-HBV co-infection. Furthermore, it stresses the severity of liver disease related to HCV in HIV-infected population.

Introduction

The decline of mortality due to opportunistic infections in HIV-infected patients since the introduction of highly active antiretroviral therapy (HAART) has led to an increase in morbidity and mortality related to hepatitis B (HBV) and C (HCV) virus infections, and end-stage liver disease among HIV-infected patients in France [1;2]. As these infections share similar routes of transmission, co-infection with HIV and viral hepatitis B and/or C is common. Approximately one-third of HIV-infected individuals are infected with HCV and 70% of HIV-infected have prior contact with HBV infection [3;4]. Those coinfections lead to an increase risk of cirrhosis and hepatic failure compared to HCV or HBV-monoinfected patients [5]. Therefore determination of HBV and HCV status is crucial for HIV-infected patients care and for allocations of resources in health care programs. In France, although HCV prevalence among HIV-infected persons was estimated at national level in 2001 (28 % [95 % confidence interval (CI): 27-31]) [6], it was not estimated for HBV yet. In June 2004, we conducted a one-day national cross-sectional survey in order to assess the prevalence of HCV and HBV infections among HIV-infected patients, and describe the characteristics of HIV-HCV and HIV-HBV co-infected patients and their clinical management.

Methods

We used the sampling frame of hospital wards (infectious diseases, internal medicine) based on the number of AIDS cases reported through the Mandatory notification at the national level between January 1999 and September 2003. The 207 wards which had notified more than three AIDS cases and 70 wards randomly selected among the 211 having notified three or less AIDS cases were invited to participate on a voluntary basis.

At the time of the survey, every HIV-infected out or in-patient seeking care in one of the selected wards was enrolled after informed consent, and the number of HIV-infected patients refusing to participate was collected. A standardized questionnaire was used to collect data from medical records on socio-demographic characteristics (age, gender, country of birth), HIV infection (HIV transmission group ie: person infected through high-risk heterosexual contacts, man who has sex with men, injecting drug user, transfusion recipient, haemophiliac; clinical classification, CD4 cell count, viral load, antiretroviral therapy), and on alcohol consumption. The alcohol intake was collected using the number of glasses (or drink) of alcohol drunk per week. It is considered that whatever the kind of alcohol (beer, wine, cocktail …) served, it contains 10 grams of pure alcohol (the standard quantity served varies with the type of alcohol). Excessive alcohol intake was defined as the consumption of more than 21 glasses (210 g of alcohol) per week for women, and more than 28 glasses (280 g of alcohol) for men.

Biological markers of hepatitis C (anti-HCV antibody (Ab), HCV RNA), hepatitis B (anti-HBs and anti-HBc Ab, HBs antigen (Ag), HBe Ag, HBV DNA), and hepatitis Delta status (Ab, Ag) were also collected.

HCV co-infection was defined as positive anti-HCV antibodies or HCV RNA, chronic hepatitis C as positive HCV RNA, HBV co-infection as positive HBs Ag or HBV DNA, and chronic hepatitis B as positive HBs Ag.

For patients with chronic hepatitis B or C, we also collected alanine aminotransferase (ALT) levels, presence of clinical complications of cirrhosis (e.g. ascites, portal hypertension…) and diagnosis of hepatocellular carcinoma. To describe the management of co-infected patients, we collected data on the methods used for diagnosis of liver fibrosis (liver biopsy, serum markers), the METAVIR scores [7] and antiviral treatment (past or current).

Cirrhosis was defined by a METAVIR score F4 (liver biopsy or serum markers of fibrosis) or by the presence of complications of cirrhosis. Severe liver disease was defined as cirrhosis or hepatocellular carcinoma diagnosis.

All data were analysed using Stata 8.2 (Stata Corporation, College Station, TX). The sample design was specified mentioning a weight attributed to each individual, equal to the inverse of his inclusion probability and the stratification. Estimates were calculated from the classical Horvitz-Thompson unbiased estimator using the specific survey functions implemented in the Stata software. Confidence intervals were also estimated using unbiased estimators

Results

Of the 277 randomly selected wards, 167 (60.3%) accepted to participate. Among wards which had notified more than three AIDS cases, the median number of cases notified by the participating wards was higher than those notified by the non-participating ones (30 versus 13, respectively; p 10-4). Among the 2054 eligible HIV-infected patients, 205 refused to participate in the study (9% and 13% of out-patients and in-patients, respectively). Of the 1849 patients who agreed, 78.6% [95% confidence interval: 75.3-81.5] were out-patients and 21.4% [95% CI: 18.5-24.7] were in-patients.

Table 1 shows the main characteristics of HIV-infected patients. The estimated mean age was 42.9 years [95% CI: 42.4-43.5]. Excessive alcohol intake was estimated for 5.3% [95% CI: 4.3-6.6] of the patients (unknown: 11%). Those who acquired HIV through injecting drug use (IDUs) were more likely excessive alcohol drinkers than the rest of the population (respectively, 12.3% and 3.8%; p<10-3).

HIV-HCV co-infection

The prevalence of HIV-HCV co-infection (Table 2) was 24.3% [95% CI: 21.3-27.6] and varied depending on HIV transmission groups (maximum for IDU: 92.8%) and continent of birth (maximum for Northern Africa: 35.1%). The prevalence of chronic hepatitis C was 17.0% [95% CI: 14.7-19.4].

Table 1

Characteristics of medical ward-recruited HIV-infected adults in France, 22 June 2004

N = 1849	%	95% CI*
Sex		
Male	68.2	65.3-71.0
Female	31.6	28.8-34.5
Not documented	0.2	0.1-0.5
Age		
≥ 40 years	60.9	58.3-63.4
< 40 years	38.4	35.9-41.0
Not documented	0.7	0.4-1.4
Country/continent of birth		
France	64.9	59.8-69.8
French overseas territories#	3.1	1.6-5.7
Sub-Saharan Africa	17.4	14.2-21.2
North Africa	5.1	4.0-6.3
Other	8.5	6.3-11.3
Not documented	1.0	0.6-1.8
HIV transmission group		
Heterosexual contact	41.4	37.3-45.7
MSM[1]	30.2	26.3-34.4
IDU[2]	18.8	16.0-21.9
Transfusion recipient/haemophiliac	2.7	2.0-3.6
Undetermined	6.9	5.6-8.4
HIV clinical classification		
Primary infection	0.7	0.4-1.5
Asymptomatic	39.4	35.8-43.1
Symptomatic	24.6	21.9-27.4
AIDS	33.5	30.3-36.8
Not documented	1.8	1.2-2.8
CD4 count		
< 350 cells/mm³	49.7	46.4-53.0
≥ 350 cells/mm³	48.5	45.2-51.7
Not documented	1.8	1.2-2.7
HIV viral load		
Detectable	53.3	50.5-56.2
Undetectable	43.4	40.5-46.4
Not documented	3.3	2.4-4.4
Antiretroviral (ARV) therapy		
Yes	75.1	72.3-77.8
Interrupted	6.0	4.8-7.5
No	18.4	15.9-21.1
Not documented	0.5	0.2-0.9

* Confidence interval
[1] Man who has sex with men
[2] Injecting drug user
French Guyana, French West Indies, Reunion Island

Table 2

Prevalence of HBV and HCV infections by group of HIV transmission and continent of birth, France, 22 June 2004

	HBV$		HCV§	
N = 1849	%	95% CI*	%	95% CI*
Overall	**7.0**	5.9-8.1	**24.3**	21.3-27.6
HIV transmission group				
Heterosexual contact	**5.3**	3.9-7.2	**8.6**	6.5-11.2
MSM[1]	**9.2**	7.1-11.8	**3.1**	2.0-4.7
IDU[2]	**7.5**	5.1-11.0	**92.8**	89.0-95.3
Transfusion recipient/ haemophiliac	**5.9**	1.9-16.6	**47.1**	32.3-62.5
Undetermined	**6.6**	3.3-12.5	**18.0**	11.1-27.8
Continent of birth				
Europe[3]	**6.3**	5.2-7.7	**28.2**	24.9-31.8
Northern Africa	**2.1**	0.6-7.4	**35.1**	25.3-46.2
Sub-Saharan Africa	**10.8**	7.7-14.9	**10.2**	7.2-14.4
Asia	**10.0**	2.4-33.1	**15.0**	4.7-38.5
American continent	**7.4**	2.8-17.9	**2.5**	0.5-10.4

* Confidence interval
$ HBs Ag+ or HBV DNA+
§ anti-HCV + or HCV RNA+
[1] Man who has sex with men
[2] Injecting drug user
[3] Including French Guyana, French West Indies, and Reunion Island

Among the HIV-infected patients with chronic hepatitis C, degree of liver fibrosis was assessed either by liver biopsy for 48.5% or by serum markers for 5.3% and both methods were used for 4.0% of the patients; 32.4 % had no available evaluation at the time of the survey (variable not documented: 10%). Severe liver disease defined by the presence of cirrhosis or hepato-cellular carcinoma was diagnosed in 24.7% [95% CI: 19.7-30.5] of the HIV-infected patients with chronic hepatitis C. Severe liver disease was diagnosed in 33.4% of IDUs with excessive alcohol consumption and in 21.8% of those without (p=.05).

Among patients with chronic hepatitis C, 36.4% [95% CI: 30.7-42.6] were (or had been) treated with anti-HCV therapy. This proportion varied whether liver disease was assessed or not (49.8% and 14.6%, respectively: p<10-3). Anti-HCV treated patients were (or had been) under ribavirin and interferon (pegylated or not) in 79.7%, and under interferon alone in 17.0% (not documented in 3.3%).

HIV-HBV co-infection

The prevalence of HIV-HBV co-infection was 7.0% [95% CI: 5.9-8.1] (Table 2), and varied according to the continent of birth (maximum for Sub-Sahara Africa: 10.8 %). The prevalence of negative HBs Ag associated to negative anti-HBc and negative anti-HBs was 27.1% [95% CI: 24.5-30.0] (Table 3).

Among positive HBs Ag patients, HBV-DNA was positive for 48.5% [95% CI: 38.6-58.4], negative in 27.3% and was not documented for 24.2%. HBe Ag was positive for 33.3%, negative for 45.4% and, was not documented for 21.3%. Among positive HBs Ag IDUs, delta virus serostatus was not documented for 77.0%, positive for 19.2% and negative for 3.8%. Delta status was not documented for 66.7% of positive HBs Ag Sub-Saharan Africans, and was positive for 2.8%.

Among positive HBs Ag patients, the severity of liver disease was assessed in 37.1% of them, depending on the ALT level: in 14.3% when ALT level was equal or below the upper limits of the reference values and in 59.3% when ALT level was greater. A severe liver disease was diagnosed in 26.0% and absent in 33.3% of the overall positive HBs Ag patients with abnormal ALT level.

At the time of the survey, 71.2% of the positive HBs Ag patients were treated for hepatitis B: with lamivudine (31.0%), tenofovir (8.4%) or adefovir (3.8%) alone, and 28.0% with lamivudine and tenofovir. The proportion of anti-HBV treatment varied from 81.8% when patients were on antiretroviral therapy to 11.8% when they were not.

HIV-HBV-HCV co-infection

The overall prevalence of HBV-HCV co-infection was 1.6% [95% CI: 1.0-2.4]. HIV-infected patients with HBV-HCV co-infection were mainly (83.3%) injecting drug users. The prevalence of chronic hepatitis B associated with chronic hepatitis C was 0.8% [95% CI: 0.5-1.3].

Discussion

This survey estimated the prevalence of HBV co-infection (7%) among HIV-infected adults in France in 2004. It also estimated for the first time in Europe, the prevalence of HBV-HCV co-infection (1.6%) and of chronic hepatitis B and C (0.8%) in this population. It confirmed the importance of HIV-HCV co-infection (24.3%), mainly in IDUs. The prevalence of HCV and HBV infections was greater among HIV-infected patients than in the French population in 2004 (0.84% and 0.65%, respectively) [8].

Prevalence rates of HBV and HCV infection in our study were close to those reported in European HIV-infected cohorts at inclusion [9;10]. The estimates of HCV co-infection in 2001 (28%) [6] and 2004 (24%) were slightly different. This could possibly be due to a decrease in the proportion of IDUs between the two studies (22% versus 18.8%, respectively).. Interestingly, although cases of acute HCV infection have been described since 2001 in France among men who have sex with men [11], the estimates of HCV co-infection between 2001 (6%) and 2004 (3%) were not different in this group. However, any comparison of the estimates between the two surveys (2001 and 2004) should be interpreted with caution due to different sampling design. The prevalence of HCV co-infection (10%) among patients born in Sub-Saharan Africa, very close to the HBV's (around 11%), could reflect the overall high prevalence estimates (3%) of HCV in Sub-Saharan Africa [12]. Therefore, HCV screening should be also routinely added to HBV testing and repeatedly included in the follow-up of HIV-infected patients originating from this region.

The proportion of patients with chronic hepatitis C who had a liver fibrosis assessment evaluation increased from 49% [6] to 62% in 2001 and 2004, respectively. This could be related to the development and availability of non-invasive markers of liver fibrosis in place of liver biopsy, since 2001 [13].

Severe liver disease among HCV mono-infected patients is associated with excessive alcohol consumption [14]. In our study, the proportion of severe liver disease among IDUs who had reported excessive consumption was higher than among those who had not. However, the overall proportion of heavy drinkers (12.3%) was three times lower than the 41.3% observed in newly referred HIV-infected IDUs with positive anti-HCV attending hepatology reference centers in France, in 2004 [15].

We found that almost one third of the HIV-infected population had negative biological markers for hepatitis B. A better promotion of anti-HBV vaccination targeting this population should be stressed according to the French recommendations [16].

Even though a higher incidence of liver-related cirrhosis [17], and a deleterious impact of hepatitis delta co-infection on liver fibrosis

Table 3

Prevalence of biological markers of HBV infection among HIV-infected adults, France, 22 June 2004

N = 1849				%	95% CI*
HBs Ag (+) or HBV DNA (+)				7.0	5.9-8.1
Negative HBV markers#				27.1	24.5-30.0
HBs Ag (-)	anti-HBc (-)	anti-HBs (+)		9.4	7.5-11-5
HBs Ag (-)	anti-HBc (+)	anti-HBs (-)	*23.7*		
		anti-HBs (+)	*12.6*	37.6	35.0-40.2
		anti-HBs (?)	*1.3*		
Not documented				18.9	

* Confidence interval
\# HBs Ag (-) anti-HBc (-) and anti-HBs (-)

[18] had been observed in HIV-HBV co-infected patients compared to mono HIV-infected, biological markers (HBs Ag, HBV DNA, HBe Ag, Delta status) and the evaluation of liver disease severity related to chronic hepatitis B were too often not documented. Therefore, the overall proportion of severe liver disease (26.0%) related to chronic hepatitis B could be underestimated.

The proportion of patients being treated for chronic hepatitis B was very high (71 %). A possible explanation is that antiviral molecules against HBV were opportunely chosen when HAART was needed. Since then, European guidelines on treatment of viral hepatitis and HIV co-infections have been issued in 2005 [19]. Criteria to decide whether to treat chronic hepatitis B include HBV-DNA level, liver disease activity, and the evaluation of the presence of cirrhosis. Moreover, the development and the use of less invasive techniques than liver biopsy probably contributed to a better diagnosis of severe liver disease by clinicians in this population.

Our study has several limitations. The results relied on data collected from medical records as the viral hepatitis markers were not measured at the time of the survey. The participation of the wards was lower than expected and may have biased the prevalence estimates. However, it is difficult to draw a conclusion on how it may have affected the results (over or underestimation). A small proportion of the patients did not agree to participate. It is unlikely that the non participation may be related to the HCV/HBV infection status and thus had any effect on our estimates. Also, we were not able to take into account the follow-up frequency of the patients. It is possible that patients with chronic hepatitis B or C were more likely to have been included in the study leading to a potential overestimation of the prevalence figures. However, the HCV and HBV prevalence we found was not significantly different from that reported in European cohorts at inclusion [6,7].

Conclusion

With a longer life expectancy for HIV-infected patients, hepatitis B and C associated co-morbidities are becoming major concerns in terms of health care. This study confirms the burden of HCV infection in HIV-infected patients and also emphasises the severity of liver disease linked to viral hepatitis in HIV-infected patients. The assessment of chronic hepatitis B co-infection in HIV-infected definitely needs to be improved, especially screening for hepatitis delta antibodies and evaluation of liver fibrosis. Since 2004, European guidelines for the management and treatment of chronic hepatitis C and B coinfection in HIV-infected adults have been released and should help the clinicians for a better assessment of chronic hepatitis B and C in HIV-infected patients. Furthermore, vaccination against HBV must be promoted among HIV-infected people with negative biological markers for hepatitis B.

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References

1. Lewden C, Salmon D, Morlat P, Bevilacqua S, Jougla E, Bonnet F, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol 2005;34(1):121-30.
2. Rosenthal E, Pialoux G, Bernard N, Pradier C, Rey D, Bentata M, et al. Liver-related mortality in human-immunodeficiency-virus-infected patients between 1995 and 2003 in the French GERMIVIC Joint Study Group Network (MORTAVIC 2003 Study). J Viral Hepat 2007;14(3):183-8.
3. Thio CL. Hepatitis B in the human immunodeficiency virus-infected patient: epidemiology, natural history, and treatment. Semin Liver Dis 2003;23(2):125-36.
4. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-Infected Person. Ann Intern Med 2003;138(3):197-207.
5. Bruno R, Sacchi P, Puoti M, Maiocchi L, Patruno S, Carosi G, et al. Natural history of compensated viral cirrhosis in a cohort of patients with HIV infection. J Acquir Immune Defic Syndr 2007;46(3):297-303.
6. Salmon-Ceron D, Gouezel P, Delarocque-Astagneau E, Piroth L, Dellamonica P, Marcellin P, et al. Co-infection VIH-VHC à l'hôpital. In French. Enquête nationale juin 2001. Med Mal Inf 2003;33:78-83.
7. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24(2):289-93.
8. Meffre C, Le Strat Y, Delarocque-Astagneau E, Antona D, Desenclos JC. Prevalence of hepatitis B and C in France, 2004. InVS, Saint-Maurice 2006
9. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS 2005;19(6):593-601.
10. Weis N, Lindhardt BO, Kronborg G, Hansen AB, Laursen AL, Christensen PB, et al. Impact of hepatitis C virus coinfection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: a nationwide cohort study. Clin Infect Dis 2006;42(10):1481-7.
11. Gambotti L, Acute hepatitis C collaborating group. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. Euro Surveill 2005;10(5):115-7. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=535
12. Madhava V, Burgess C, Drucker E. Epidemiology of chronic hepatitis C virus infection in sub-Saharan Africa. Lancet Infect Dis 2002;2(5):293-302.
13. Cacoub P, Halfon P, Rosenthal E, Pialoux G, Benhamou Y, Perronne C, et al. Treatment of hepatitis C virus in human immunodeficiency virus infected patients in "real life": Modifications in two large surveys between 2004 and 2006. J Hepatol 2008;48(1):35-42.
14. Delarocque-Astagneau E, Roudot-Thoraval F, Campese C, Desenclos JC, The Hepatitis CSSS. Past excessive alcohol consumption: a major determinant of severe liver disease among newly referred hepatitis C virus infected patients in hepatology reference centers, France, 2001. Ann Epidemiol 2005;15(8):551-7.
15. Delarocque-Astagneau E, Pioche C, Desenclos J. National surveillance of Hepatitis C by voluntary hepatology reference centres, 2001-2004. Bull Epidemiol Hebd 2006;51-52:414-8.
16. Delfraissy JF. Co-infections par le virus des hépatites. In: Médecine-Sciences F, editor. Rapport 2004 : Prise en charge thérapeutique des personnes infectées par le VIH.Paris: Ministère de la santé, de la famille et des personnes handicapées, France; 2004. p. 159-76. In French.
17. Thio CL, Seaberg EC, Skolasky R, Jr., Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002;360(9349):1921-6.
18. Lacombe K, Boyd A, Desvarieux M, Serfaty L, Bonnord P, Gozlan J, et al. Impact of chronic hepatitis C and/or D on liver fibrosis severity in patients co-infected with HIV and hepatitis B virus. AIDS 2007;21(18):2546-9.
19. Alberti A, Clumeck N, Collins S, Gerlich W, Lundgren J, Palu G, et al. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. J Hepatol 2005;42(5):615-24.

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