MAJOR ARTICLE

Spontaneous Viral Clearance, Viral Load, and Genotype Distribution of Hepatitis C Virus (HCV) in HIV-Infected Patients with Anti-HCV Antibodies in Europe

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(See the editorial commentary by Bruno and Sacchi, on pages 1262–4.)

Background. Variables influencing serum hepatitis C virus (HCV) RNA levels and genotype distribution in individuals with human immunodeficiency virus (HIV) infection are not well known, nor are factors determining spontaneous clearance after exposure to HCV in this population.

Methods. All HCV antibody (Ab)–positive patients with HIV infection in the EuroSIDA cohort who had stored samples were tested for serum HCV RNA, and HCV genotyping was done for subjects with viremia. Logistic regression was used to identify variables associated with spontaneous HCV clearance and HCV genotype 1.

Results. Of 1940 HCV Ab–positive patients, 1496 (77%) were serum HCV RNA positive. Injection drug users (IDUs) were less likely to have spontaneously cleared HCV than were homosexual men (20% vs. 39%; adjusted odds ratio [aOR], 0.36 [95% confidence interval {CI}, 0.24–0.53]), whereas patients positive for hepatitis B surface antigen (HBsAg) were more likely to have spontaneously cleared HCV than were those negative for HBsAg (43% vs. 21%; aOR, 2.91 [95% CI, 1.94–4.38]). Of patients with HCV viremia, 786 (53%) carried HCV genotype 1, and 53 (4%), 440 (29%), and 217 (15%) carried HCV genotype 2, 3, and 4, respectively. A greater HCV RNA level was associated with a greater chance of being infected with HCV genotype 1 (aOR, 1.60 per 1 log higher [95% CI, 1.36–1.88]).

Conclusions. More than three-quarters of the HIV- and HCV Ab–positive patients in EuroSIDA showed active HCV replication. Viremia was more frequent in IDUs and, conversely, was less common in HBsAg-positive patients. Of the patients with HCV viremia analyzed, 53% were found to carry HCV genotype 1, and this genotype was associated with greater serum HCV RNA levels.

The course of hepatitis C virus (HCV) infection varies widely after initial exposure. Although one-third of individuals may clear the infection spontaneously, the remaining persons have persistent viremia and develop chronic hepatitis C [1–6]. In the former group, liver function test results and hepatic tissue remain normal, and HCV antibodies (Abs) are the only evidence of a past encounter with HCV [7]. In contrast, most patients with chronic hepatitis C show elevations in liver enzyme levels as a consequence of hepatic inflammation, and

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many steadily progress to liver cirrhosis [5, 6, 8–10]. Although serum HCV RNA levels and HCV genotype do not seem to significantly influence the natural history of chronic hepatitis C, these virological features largely affect therapeutic outcomes. Individuals with low viral load and those infected with HCV genotype 2 or 3 respond significantly better to pegylated interferon plus ribavirin than do subjects with high HCV RNA levels and infection with HCV genotype 1 or 4 [11, 12].

Because of shared routes of transmission, coinfection with HIV and HCV is relatively common [13–15]. In Western countries, liver disease due to HCV infection has become a leading cause of morbidity and mortality in HIV-infected individuals [16–19]. In this regard, the virological characterization of HIV-infected patients positive for HCV Abs is important, given that this information may help in making appropriate estimations about the burden of liver disease and the costs of treatment in this population, including the need for liver transplantation in a subset of them. The aim of the present study was to virologically characterize HIV-infected patients positive for HCV Abs in the EuroSIDA cohort, in an attempt to establish the current burden of HCV-related disease and the expected clinical and therapeutic outcomes derived from its main virological features.

METHODS

Patients. EuroSIDA is a prospective study of 14,310 HIV-1–infected patients at 93 centers across Europe, Israel, and Argentina; details have been reported elsewhere [20]. Briefly, for each cohort the centers provide data on consecutive patients seen at the outpatient clinics beginning in May 1994 until a predefined number of patients is enrolled from each site. To date, 7 cohorts of patients have been recruited. Data are collected prospectively at clinical sites and are extracted and sent to the coordinating center at 6-month intervals. For cohorts I–III, eligible patients were those who had had a CD4 cell count <500 cells/mm^3 during the previous 4 months. The CD4 cell count restriction was removed for cohorts IV–VII. At recruitment, in addition to demographic and clinical information, a complete antiretroviral treatment history is obtained, together with the most recent CD4 cell count and plasma HIV RNA measurements. At each follow-up visit, details on all CD4 cell counts and plasma HIV RNA values measured since the last follow-up visit are extracted, as are the dates of starting and stopping each antiretroviral drug received and the use of drugs for prophylaxis against opportunistic infections. The dates of diagnosis of all AIDS-defining illnesses, non–AIDS-defining malignancies, and other serious infections are also recorded. The present analysis includes follow-up to a median date of January 2007.

Information on HCV Ab status has been collected since 1997; patients who died or were lost to follow-up before this date did not routinely have information on HCV Ab status collected. Centers that have determined HCV genotype or that have measured HCV RNA level can provide that information to the coordinating center at any time. The EuroSIDA plasma repository was set up in 1997 and collects plasma samples from all HIV-infected patients at 6-month intervals. Patients with unknown HCV Ab status and a stored plasma sample were identified in 2006, and HCV Ab status was determined. Patients who tested positive for HCV Ab were then tested for serum HCV RNA level and genotype in a reference laboratory. In addition, patients with unknown HCV genotype and stored samples were identified, and serum HCV RNA levels were tested and genotyping was performed.

Serum HCV RNA was investigated and quantified in HCV Ab–positive samples by means of the Versant HCV RNA assay (version 3.0; Bayer Diagnostics), which uses a signal amplification procedure with a linear dynamic range of 615 to 1×10^7 IU/mL. This method uses multiple probes to match several sequences of the HCV genome, negating the potential for underestimation of some HCV genotypes due to mismatches caused by genetic polymorphisms [21, 22].

HCV genotyping was performed using the LiPA HCV genotype assay (version 2.0; Innogenetics), which is a line probe assay that simultaneously detects sequences in the 5' untranslated region (UTR) and the core region. The examination of the core region along with the 5' UTR allows more-accurate discrimination between genotypes 1 and 6 and improves subtyping across distinct genotypes [23–25].

Statistical analyses. Descriptive values are expressed as absolute or median values with interquartile ranges. Categorical variables were compared using the χ^2 test, and continuous variables were compared using nonparametric tests. Logistic regression was used to identify which variables were associated with spontaneous HCV clearance and with HCV genotype 1 infection and which genotype was the most common, after adjustment for demographic (age, sex, HIV exposure group, ethnic origin, region of Europe, date of HCV Ab testing, and date of joining EuroSIDA), clinical (prior AIDS, CD4 cell count, and plasma HIV RNA level), and therapeutic factors (antiretroviral therapy). The results are presented using odd ratios (ORs) and adjusted ORs (aORs). All data were analyzed using SAS software (version 9.1).

RESULTS

Of the 14,310 HIV-infected patients enrolled in EuroSIDA, 3375 (24%) were positive for HCV Ab. Stored specimens were not available for 1435 of these patients, who were excluded from further analyses. Excluded patients were more likely to be of white ethnic origin compared with included patients (95% vs. 89%), more likely to originate from southern Europe/Argentina (39% vs. 34%) or eastern Europe (37% vs. 23%), and less likely to have started antiretroviral therapy (63% vs. 84%). No other significant differences were noted between included and ex-

Table 1. Main characteristics of 1940 HIV-infected patients positive for hepatitis C virus (HCV) antibody.

Variable	Total	Serum HCV RNA		*P*
		Positive	Negative	
Patients	1940 (100)	1496 (77)	444 (23)	. . .
Sex				.22
Male	1348 (69)	1050 (78)	298 (22)	
Female	592 (31)	446 (75)	146 (25)	
Age, median, years	37.2	37.5	37.0	.47
Risk group				<.001
IDUs	1399 (72)	1126 (80)	273 (20)	
MSM	181 (9)	111 (61)	70 (39)	
Heterosexuals	233 (12)	164 (70)	69 (30)	
Other	127 (7)	95 (75)	32 (25)	
Ethnicity				.30
White	1734 (89)	1343 (77)	391 (23)	
Other	206 (11)	153 (74)	53 (26)	
Region				<.001
Southern Europe/ Argentina	654 (34)	536 (82)	118 (18)	
Central Europe	466 (24)	339 (73)	127 (27)	
Northern Europe	378 (19)	274 (72)	104 (28)	
Eastern Europe	442 (23)	347 (79)	95 (21)	
Serum HBsAg status				<.001
Positive	137 (7)	78 (57)	59 (43)	
Negative	1483 (76)	1173 (79)	310 (21)	
Unknown	320 (16)	245 (77)	75 (23)	
Antiretroviral therapy				.048
Yes	1685 (87)	1287 (76)	398 (23)	
No	255 (13)	209 (82)	46 (18)	

NOTE. Data are no. (%) of patients, unless otherwise indicated. HBsAg, hepatitis B surface antigen; IDUs, injection drug users; MSM, men who have sex with men.

cluded HCV Ab–positive patients. Samples were not available because the sample had already been used for a different project or because it was not collected at the center, predominantly because the patient had died or was lost to follow-up before the plasma repository was set up.

The main characteristics of the 1940 HCV Ab–positive patients included in the present analyses are shown in table 1. HCV genotype was determined by the central laboratory for 80% of patients. Overall, 1496 patients (77% [95% confidence interval {CI}, 75%–79%]) were positive for serum HCV RNA and/or had a known HCV genotype. For the comparison between the main features of HIV-infected patients with chronic HCV viremia with those who spontaneously cleared HCV, it is remarkable that injection drug users (IDUs) were less likely to spontaneously clear HCV than were men who had sex with men (MSM) (20% vs. 39%), whereas patients who were positive for serum hepatitis B surface antigen (HBsAg) were more likely to clear HCV than were those negative for HBsAg (43% vs. 21%). Finally, patients from southern Europe/Argentina were less likely to have spontaneously cleared HCV than were those from the other regions (18% vs. 22%–27%).

Table 2 shows the univariate and multivariate ORs for spontaneous clearance of HCV. All 26 patients with prior exposure to interferon therapy who subsequently tested negative for HCV RNA were excluded from this analysis. In the multivariate model, females had 39% increased odds of spontaneous HCV clearance compared with males (aOR, 1.39 [95% CI, 1.06–1.81]; $P = .017$). Compared with MSM, any other exposure group had decreased odds of spontaneous HCV clearance. This was particularly true for IDUs, who had 64% reduced odds of HCV clearance compared with MSM (aOR, 0.36 [95% CI, 0.24–0.53]; $P < .001$). Compared with patients from southern Europe/Argentina, subjects from central or northern Europe had increased odds of spontaneous HCV clearance. This was particularly manifest for patients from northern Europe, who had 47% increased odds of HCV clearance compared with those from southern Europe/Argentina (aOR, 1.47 [95% CI, 1.03–2.09]; $P = .032$). Finally, patients who were positive for HBsAg had increased odds of spontaneous HCV clearance compared with those who were negative (aOR, 2.91 [95% CI, 1.94–4.38]; $P < .001$).

Of patients with detectable serum HCV RNA, 786 (53%) were infected with HCV genotype 1, and 53 (4%), 440 (29%), and 217 (15%) were infected with HCV genotype 2, 3, and 4, respectively. Mixed genotypes were recognized in only 4 (0.2%) patients with viremia. Figure 1 shows the geographical distribution of HCV genotypes across the different regions. Although HCV genotype 1 predominated in all regions, the proportion of patients with HCV genotype 3 infection was significantly higher in eastern Europe than in the rest of Europe. HCV genotype 2 was uncommon and was mainly seen in the northern and central European regions. Finally, HCV genotype 4 represented ~15% of infections but was less frequent in the northern Europe region.

Table 3 shows the main characteristics of patients infected with distinct HCV genotypes. The median viral load in patients for whom the HCV genotype was known was 576,812 IU/mL; it was >500,000 IU/mL in 54%. By genotype, the median serum HCV RNA values were 776,015, 685,258, 393,523, and 389,000 IU/mL for HCV genotypes 1, 2, 3, and 4, respectively ($P < .001$).

Table 4 shows the univariate and multivariate odds of having HCV genotype 1 infection compared with any other HCV genotype. In the multivariate model, females had decreased odds of HCV genotype 1 infection compared with males (aOR, 0.76 [95% CI, 0.59–0.99]; $P = .038$), as did patients from eastern Europe compared with those from southern Europe/Argentina (aOR, 0.37 [95% CI, 0.25–0.56]; $P < .001$). Older patients had decreased odds of HCV genotype 1 infection (aOR, 0.80 per 10 years older [95% CI, 0.68–0.94]; $P = .008$). Finally, patients with a higher serum HCV RNA level had increased odds of HCV genotype 1 infection compared with patients with a lower serum HCV RNA level (aOR, 1.60 per 1 log higher [95% CI, 1.36–1.88]; $P < .001$).

Table 2. Variables associated with spontaneous hepatitis C virus (HCV) clearance.

	Univariate		Multivariate	
Variable	OR (95% CI)	*P*	aOR (95% CI)	*P*
Female sex, vs. male	1.17 (0.93–1.48)	.18	1.39 (1.06–1.81)	.017
Older age, per 10 years	1.13 (0.99–1.28)	.069	1.12 (0.96–1.32)	.15
Exposure group				
MSM	1.00 (reference)		1.00 (reference)	
IDUs	0.39 (0.28–0.55)	<.001	0.36 (0.24–0.53)	<.001
Heterosexuals	0.66 (0.43–1.00)	.050	0.65 (0.40–1.06)	.084
Other	0.56 (0.34–0.93)	.024	0.42 (0.24–0.73)	.002
Serum HBsAg status				
Negative	1.00 (reference)		1.00 (reference)	
Positive	2.87 (1.99–4.15)	<.001	2.91 (1.94–4.38)	<.001
Unknown	1.25 (0.93–1.67)	.13	1.34 (0.95–1.89)	.093
Region				
Southern Europe/Argentina	1.00 (reference)		1.00 (reference)	
Central Europe	1.68 (1.25–2.26)	<.001	1.35 (0.95–1.91)	.098
Northern Europe	1.80 (1.32–2.44)	<.001	1.47 (1.05–2.09)	.032
Eastern Europe	1.26 (0.93–1.72)	.14	1.15 (0.75–1.78)	.52

NOTE. The model was adjusted for data source, ethnic origin, prior AIDS diagnosis, date of testing, date recruited to EuroSIDA, CD4 cell count at date of HCV testing, and antiretroviral therapy. aOR; adjusted odds ratio; HBsAg, hepatitis B surface antigen; IDUs, injection drug users; MSM, men who have sex with men; OR, odds ratio.

DISCUSSION

This study reports the rate of HCV infection chronicity, genotype distribution, and viral load in a large group of HIV-infected patients across Europe. In excess of three-quarters of HIV-infected patients positive for HCV Ab showed active HCV replication. In HIV-negative individuals, spontaneous HCV clearance occurs overall in approximately one-third of cases [1–6]. Two factors might explain the higher rate of chronicity we saw in the present HIV-infected population. First, HIV-associated immunodeficiency could impair effective immune control of HCV replication after initial exposure [1, 26, 27], given that it has been shown in other immunocompromised conditions. Second, IDUs represented the largest group of HCV Ab–positive patients in EuroSIDA, and repeated exposure to HCV in them could have favored the establishment of persistent HCV infection. Although innate and adaptive immune responses might partially protect against repeated exposure to HCV [28], they might be less effective for exposure to distinct HCV genotypes or in the setting of HIV infection [29]. Given that HCV viremia was more frequent among HCV Ab–positive IDUs enrolled in EuroSIDA than in HCV Ab–positive subjects infected through sexual contact (whether homo- or heterosexual), we hypothesize that repeated exposure to HCV rather than HIV-associated immunosuppression was the most likely cause of the higher rate of HCV infection chronicity noted on average in EuroSIDA patients. In fact, HCV exposure must have preceded HIV infection in most cases, as has been shown in other studies that have examined the incidence of HCV and HIV infections in high-risk groups [30, 31].

Patients with markers of dual hepatitis B virus (HBV) and HCV infections show a worse liver prognosis [32]. In our study, HCV viremia was less frequent in persons with HBsAg than in the rest of the population (54% vs. 75%). This observation is in agreement with the findings of prior studies, in which viral interference phenomena have been reported to account for reciprocal inhibition of HBV and HCV replication [33, 34]. It is noteworthy that control of HBV replication with antiviral agents does not seem to be associated with HCV rebound, while the contrary may occur [35, 36]. The biological basis for this observation relies on the distinct cell cycles for HBV and HCV infection. Although the genetic material of HBV is relatively stable within infected cells as covalently closed circular DNA, the RNA of HCV can be found replicating in the cytosol only, where it is subject to rapid degradation [37, 38]. Therefore, if HBV overtakes HCV replication, there is a high chance of spontaneous HCV eradication. In contrast, treatment of HCV infection with pegylated interferon plus ribavirin may make previously aviremic HBsAg-positive patients prone to HBV rebound [36].

Of patients with active HCV replication, 53% were infected with HCV genotype 1; this genotype was associated with higher HCV RNA levels and male sex, and it was less prevalent in eastern Europe. Whether subjects infected with HCV genotype 1 have higher serum HCV RNA levels than do those infected with other genotypes has been debated for a while. Only a few studies have claimed such an association, as in a large US cohort of individuals with hemophilia [39] and, more recently, in the RIBAVIC trial [40]. Although it has been claimed that underestima-

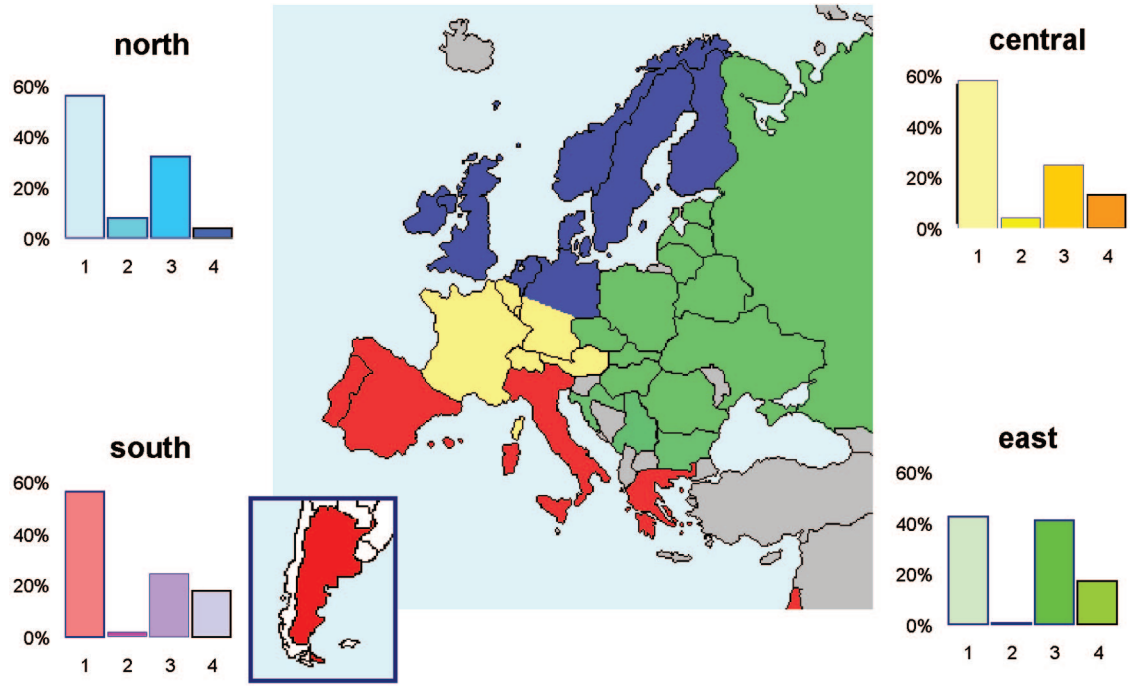

Figure 1. Distribution of hepatitis C virus genotypes in the distinct EuroSIDA regions.

tion of viral load in persons infected with non-1 HCV genotypes is the reason for this observation, at least when some amplification methods are used, in our study serum HCV RNA level was measured by a hybridization technique that uses multiple probes and with which all distinct HCV genotypes seem to be reliably quantified [21, 22]. Therefore, we are confident about our find-

Table 3. Main features of 1496 HIV-infected patients with chronic hepatitis C, stratified by hepatitis C virus (HCV) genotype.

	HCV genotype				
Variable	1	2	3	4	*P*
Patients with genotype	786 (53)	53 (4)	440 (29)	217 (15)	. . .
Male sex	569 (72)	37 (70)	300 (68)	144 (66)	.24
Age, median, years[a]	37.1	40.9	37.7	36.2	.001
Risk group, IDUs	569 (72)	28 (53)	356 (81)	173 (80)	<.001
White ethnicity	695 (88)	49 (92)	409 (93)	190 (88)	.046
Region					<.001
Southern Europe/Argentina	306 (57)	12 (2)	131 (24)	87 (16)	
Central Europe	187 (55)	16 (5)	86 (25)	50 (15)	
Northern Europe	153 (56)	23 (8)	85 (31)	13 (5)	
Eastern Europe	140 (40)	2 (0.6)	138 (40)	67 (19)	
Serum HBsAg positive	38 (5)	4 (8)	21 (5)	15 (7)	.001
Started antiretroviral therapy[a]	693 (88)	45 (85)	353 (80)	196 (90)	<.001
Serum HCV RNA level[b]					
Median, IU/mL	776,015	685,258	393,523	389,000	<.001
Range, IU/mL	728–39,200,000	6772–7,692,310	787–51,999,959	2870–16,399,854	. . .
Level >500,000 IU/mL	444 (62)	31 (61)	183 (45)	84 (43)	<.001
CD4 cell count, median, cells/mm^3	313	349	326	350	.21
Plasma HIV RNA level, median, log copies/mL	2.70	2.30	2.70	2.55	.10

NOTE. Data are no. (%) of patients, unless otherwise indicated. HBsAg, hepatitis B surface antigen; IDUs, injection drug users.

[a] At date of genotyping.

[b] Available only for 719 (91%), 51 (96%), 408 (93%), and 195 (90%) patients for genotypes 1, 2, 3, and 4, respectively.

Table 4. Variables associated with hepatitis C virus (HCV) genotype 1 infection.

	Univariate		Multivariate	
Variable	OR (95% CI)	*P*	aOR (95% CI)	*P*
Female sex, vs. male	1.25 (1.00–1.56)	.050	0.76 (0.59–0.99)	.038
Older age, per 10 years	1.00 (0.88–1.13)	.94	0.80 (0.68–0.94)	.008
Region				
Southern Europe/Argentina	1.00 (reference)		1.00 (reference)	
Central Europe	1.08 (0.82–1.42)	.58	0.83 (0.59–1.16)	.26
Northern Europe	1.05 (0.79–1.41)	.73	0.90 (0.64–1.26)	.54
Eastern Europe	1.97 (1.50–2.59)	<.001	0.37 (0.25–0.56)	<.001
Higher HCV RNA level, per 1 log higher	1.49 (1.29–1.71)	<.001	1.60 (1.36–1.88)	<.001
Prior AIDS, yes vs. no	0.82 (0.65–1.03)	.086	1.22 (0.93–1.59)	.15

NOTE. The model was adjusted for data source, ethnic origin, exposure group, serum hepatitis B surface antigen serostatus, date of HCV genotyping, date recruited to EuroSIDA, and CD4 cell count at the date of HCV testing. aOR, adjusted odds ratio; OR, odds ratio.

ing of higher serum HCV RNA levels in patients infected with HCV genotype 1 than with genotype 3 or 4. Given that baseline HCV load predicts treatment outcome [14], our observation further emphasizes the difficulties of successfully treating HCV genotype 1–infected patients.

Serum HCV RNA levels may vary after antiretroviral exposure, with a trend toward increasing during the first months after the initiation of therapy and decreasing steadily thereafter [41–43]. Moreover, differences may be seen between protease inhibitors (PIs) and nonnucleoside reverse-transcriptase inhibitors, as was recently observed in the RIBAVIC trial [40], in which 379 HIV/HCV-coinfected patients were examined. Multiple linear regression analysis identified HCV genotype 1 and PI-based regimens as independent predictors of higher serum HCV RNA levels. Moreover, it should be noted that antiretroviral therapy in general was independently associated with lower HCV RNA levels in the RIBAVIC analysis [40], a finding that we could not reproduce in our study.

Several limitations of our study should be acknowledged. First, HCV Ab status was not known for all patients, and plasma samples were not available for all patients who were HCV Ab positive. Patients with missing data were more likely to have died or to have been lost to follow-up during the earlier years of the study. Second, 2 different data sources were used, and therefore potential biases might have been introduced. It is important to note that the plasma repository was set up in 1997, and it was unlikely that the decision to send a sample for storage was related to HCV Ab status or genotype. Where data were available from both the case report forms and the central laboratory, results from the latest were used and taken as the most accurate results. All models were adjusted for the data source, and overall sensitivity analyses including only data from the central laboratory showed results similar to those of the main analyses presented here. Finally, we have no information on when patients were infected with HCV, the duration of drug use in IDUs, or whether IDUs were using injection drugs at the time blood was drawn. Despite these limitations, we feel that this study provides a comprehensive overview of the epidemiology of HCV in HIV-infected patients across Europe.

In summary, this extensive virological study of HIV-infected patients positive for HCV Abs enrolled in EuroSIDA has shown that nearly one-quarter of patients spontaneously cleared HCV infection after initial exposure, although this rate was much higher in MSM (39%) than IDUs (20%). Of patients with HCV viremia, 53% were infected with HCV genotype 1, and this genotype was associated with higher serum HCV RNA levels. Altogether, these findings highlight the difficult-to-treat profile of chronic HCV infection in HIV-positive individuals.

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