MAJOR ARTICLE

Influence of Hepatitis C Virus Infection on HIV-1 Disease Progression and Response to Highly Active Antiretroviral Therapy

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Objective. To assess hepatitis C virus (HCV) antibody prevalence in the EuroSIDA cohort, along with survival, human immunodeficiency virus (HIV)–1 disease progression, virologic response (plasma HIV-1 RNA load of <500 copies/mL), and CD4 cell count recovery by HCV serostatus in patients initiating highly active antiretroviral therapy (HAART).

Results. HCV serostatus at or before enrollment was available for 5957 patients; 1960 (33%) and 3997 (67%) were HCV seropositive and seronegative, respectively. No association between an increased incidence of acquired immunodeficiency syndrome-defining illnesses or death and HCV serostatus was seen after adjustment for other prognostic risk factors known at baseline (adjusted incidence rate ratio [IRR], 0.97 [95% confidence interval {CI}, 0.81–1.16]). However, there was a large increase in the incidence of liver disease–related deaths in HCV-seropositive patients in adjusted models (IRR, 11.71 [95% CI, 6.42–21.34]). Among 2260 patients of known HCV serostatus initiating HAART, after adjustment, there was no significant difference between HCV-seropositive and -seronegative patients with respect to virologic response (relative hazard [RH], 1.13 [95% CI, 0.84–1.51]) and immunologic response, whether measured as a ⩾50% increase (RH, 0.94 [95% CI, 0.77–1.16]) or a ⩾50 cells/μL increase (RH, 0.92 [95% CI, 0.77–1.11]) in CD4 cell count after HAART initiation.

Conclusions. HCV serostatus did not affect the risk of HIV-1 disease progression, but the risk of liver disease-related deaths was markedly increased in HCV-seropositive patients. The overall virologic and immunologic responses to HAART were not affected by HCV serostatus.

Hepatitis C virus (HCV) coinfection has become one of the most challenging clinical situations to manage in HIV-1–infected individuals. Indeed, at present, end-stage liver disease is the cause of 17%–45% of in-hospital deaths in HIV-1–infected individuals in the West [1–3]. Because of shared routes of transmission, an estimated 30% of HIV-1–infected individuals are coinfected with HCV in the United States [4]. In Europe, epidemiologic differences in the prevalence of HCV infection have been described among countries, with rates of HCV coinfection being >50% in Spain and Italy but <15% in northern European countries, such as Germany and Denmark [5].

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HIV-1 may accelerate HCV-related liver disease, especially when HIV-1–associated immunodeficiency progresses [6, 7]. In support of these observations, liver-biopsy studies have demonstrated higher rates of cirrhosis and more-advanced fibrosis stages in the livers of HIV-1/HCV–coinfected patients than of HCV-monoinfected patients after comparable infection times [8, 9]. However, these studies were conducted before the introduction of highly active antiretroviral therapy (HAART) and, hence, were not able to assess a possible influence of HAART on the course of chronic HCV infection. Of interest, several studies have suggested that HAART has a protective effect with regard to the further development of liver fibrosis and liver disease–related mortality in HIV-1/HCV–coinfected individuals [10–12].

Studies evaluating the influence of HCV infection on HIV-1 disease progression, however, have shown conflicting results. Although some studies have demonstrated an association between HCV infection and faster HIV-1 disease progression (or at least a poorer CD4 cell count response) in coinfected individuals receiving HAART [13–18], other studies have not found such an association [19–22]. To clarify this controversy, we examined the clinical outcome and the virologic and immunologic responses to HAART in a large group of HIV-1–infected patients in the EuroSIDA cohort, comparing patients with and without HCV coinfection.

PATIENTS, MATERIALS, AND METHODS

Patients. EuroSIDA is a prospective, European study of HIV-1–infected patients at 89 centers across Europe, as well as Israel and, now, Argentina; details of the study have been published elsewhere [23]. Briefly, the centers provided data on consecutive patients seen at the outpatient clinics beginning in May 1994 until a predefined number of patients was enrolled from each center. The first group of 3117 patients was defined as EuroSIDA cohort I. Enrollment of a second cohort of 1365 patients (cohort II) began in December 1995. In April 1997, a further 2844 patients were recruited and were defined as cohort III. Cohort IV, which includes 1225 patients, was enrolled beginning in April 1999; Cohort V, which includes 1258 patients, was recruited beginning in September 2001; and cohort VI, which includes 1420 patients, was recruited beginning in November 2003. For cohorts I–III, eligible patients were those who had had a CD4 cell count <500 cells/μL during the previous 4 months. The CD4 cell count restriction was removed for cohorts IV–VI.

At recruitment, in addition to demographic and clinical information, a complete antiretroviral history was obtained, together with the 8 most recent CD4 cell count and plasma HIV-1 RNA load measurements. At each follow-up visit, details on all CD4 cell counts and plasma HIV-1 RNA loads measured since the last follow-up visit were obtained, as were 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, including those diagnosed subsequent to the first diagnosis of such an illness, were also recorded, using the Centers for Disease Control and Prevention's 1993 clinical definition of AIDS [24]. Follow-up was conducted until the autumn of 2004.

HCV antibody testing was performed by use of commercial ELISAs. Only limited numbers of HCV RNA load measurements were performed in Europe and, thus, these data were not routinely available.

Statistical methods. The patients were grouped at recruitment by HCV serostatus—unknown, seronegative, or seropositive. Those patients without prospective follow-up were excluded from all analyses. The characteristics of the patients with and without known HCV serostatus were compared, as were the characteristics of the patients who were known to be HCV seropositive or seronegative at recruitment. Continuous variables were compared by the Wilcoxon rank sum test, and categorical variables were compared by the χ^2 test.

The incidence of clinical HIV-1 disease progression (defined as a new AIDS-defining illness or death by any cause [hereafter, "any death"]) was determined by dividing the number of clinical events by the number of person-years of follow-up (PYFU). The patients were followed either from their date of recruitment into the EuroSIDA cohort or from their first HCV antibody test result (baseline), whichever was later, to either their first AIDS-defining illness or death. Thus, patients who had HCV antibody testing results available after recruitment were included in the analyses from the time of their first available result. Patients with no clinical events were censored at the date of their last follow-up visit. Poisson regression was used to determine the incidence rate ratios (IRRs) of clinical events, comparing HCV-seropositive and HCV-seronegative patients, both in univariable analyses and after adjustment. In one set of multivariable models, only baseline (i.e., fixed) factors were included; in a second set, updated values (i.e., time dependent) were included. Analyses were repeated with and without adjustment for plasma HIV-1 RNA load, because this variable was available only in a smaller group of patients (routine viral load testing was not introduced until 1997). Adjustments were made for CD4 cell count, age, prior AIDS diagnosis, HIV-1 treatment at baseline, baseline date, hepatitis B surface antigen (HBsAg) status, sex, ethnicity, geographic region, and risk group. In the updated-factors multivariable models, CD4 cell count and initiation of HAART were adjusted for as time dependent, and, where AIDS was not part of the end point, the models were further adjusted for diagnosis of a new AIDS-defining illness. HAART was defined as treatment with a protease inhibitor (PI), nonnucleoside reverse transcriptase inhibitor (NNRTI), or abacavir, with at least 2 other nucleoside analogues.

For the analysis of predictors of time to virologic and immunologic responses, we used Cox proportional hazards models, with stratification by center. A virologic response was defined as achieving a plasma HIV-1 RNA load of <500 copies/mL after initiation of HAART, and an immunologic response was defined in 2 ways: (1) an increase of ⩾50% in CD4 cell count after initiation of HAART and (2) an increase of ⩾50 cells/μL in CD4 cell count after initiation of HAART. Patients who did not achieve either response were censored at the date of their last plasma HIV-1 RNA load or CD4 cell count measurement. No adjustments were made for changes to or stopping of the initial HAART regimen. Models were adjusted for factors that have been previously shown to be related to a virologic or immunologic response, including CD4 cell count and plasma HIV-1 RNA load at initiation of HAART, the HAART regimen initiated, prior treatment, risk group, age, and prior diagnosis of an AIDS-defining illness. Both CD4 cell count and plasma HIV-1 RNA load were included as categorical variables, so that patients with missing data at initiation of HAART would be included.

RESULTS

Demographics and characteristics of patients. The patients of unknown HCV serostatus at recruitment were predominantly in the EuroSIDA cohorts recruited beginning in 1994 and 1995, before the implementation of routine HCV testing across Europe. As a consequence, the patients of unknown HCV serostatus at recruitment had lower CD4 cell counts, were more likely to have AIDS, and were more likely to have initiated ART as monotherapy or dual therapy at recruitment into the EuroSIDA cohort.

Table 1 summarizes the main clinical and demographic characteristics of the patients of known HCV serostatus at recruitment into the EuroSIDA cohort. Overall, 3997 (67%) were HCV seronegative, and 1960 (33%) were HCV seropositive. Of the HCV-seropositive patients, 78% had been infected with HIV-1 via injection drug use—and, hence, probably also acquired HCV via this route—and 31% were female (compared with 23% of the HCV-seronegative patients [$P < .0001$]). In contrast, in the HCV-seronegative patients, HIV-1 transmission was mostly related to sexual contact. Although the differences were statistically significant because of the large sample size, the HCV-seropositive patients were broadly comparable to the HCV-seronegative patients with respect to plasma HIV-1 RNA load at recruitment (median, 3.21 log copies/mL [interquartile range {IQR}, 2.19–4.40 log copies/mL] vs. 2.87 log copies/mL [IQR, 1.90–4.28 log copies/mL]; $P = .0020$) and CD4 cell count at recruitment (median, 291 cells/μL [IQR, 160–441 cells/μL] vs. 305 cells/μL [IQR, 170–455 cells/μL]; $P = .035$). In addition, there was a higher proportion of patients with AIDS before or at recruitment into the EuroSIDA cohort in the HCV-seronegative group versus the HCV-seropositive group (27% vs. 21%; $P < .0001$). A small number of patients had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels measured before or at recruitment into the EuroSIDA cohort, and, as was expected, elevated ALT and AST levels were more frequent in the HCV-seropositive group than they were in the HCV-seronegative group ($P < .0001$). Chronic hepatitis B (positivity for serum HBsAg) was more frequent in the HCV-seropositive group than it was in the HCV-seronegative group (9% vs. 7%; $P < .0001$). Treatment for HCV infection was uncommon in the HCV-seropositive patients (2%). There were large variations in rates of HCV seropositivity between Europe regions as well as within the regions (table 2).

Clinical progression. Overall, 917 new AIDS-defining illnesses, 819 any deaths, 109 liver disease–related deaths, and 462 non–HIV-1–related deaths occurred in the patients of known HCV serostatus (table 3). The event rates of all of the end points considered were significantly higher in the HCV-seropositive patients than they were in the HCV-seronegative patients.

However, the event rates shown in table 3 may be confounded by other factors that affect the outcomes assessed. Table 4 summarizes the IRRs by HCV serostatus in both univariable and multivariable analyses. The multivariable models are shown separately after adjustment for (1) fixed factors known at baseline and (2) updated factors for CD4 cell count, initiation of HAART, and, where AIDS was not part of the end point, diagnosis of a new AIDS-defining illness. It is noteworthy that, although the univariable analysis showed a higher incidence of a new AIDS-defining illness or any death in the HCV-seropositive patients than in the HCV-seronegative patients (IRR, 1.44 [95% confidence interval {CI}, 1.29–1.60]; $P < .0001$]), no increased incidence of new AIDS-defining illnesses or any deaths was found in the HCV-seropositive patients after adjustment for either baseline factors (IRR, 0.97 [95% CI, 0.81–1.16]; $P = .72$) or updated factors (IRR, 1.06 [95% CI, 0.89–1.28]; $P = .50$).

In addition, compared with the HCV-seronegative patients, the HCV-seropositive patients had a significantly decreased incidence of AIDS-defining illnesses after adjustment. However, they had a significantly increased incidence of any death in both the fixed-factor and the updated-factor multivariable models (IRR, 1.41 and 1.80; $P = .0024$ and $P < .0001$, respectively), the result of a >10-fold higher incidence of liver disease–related deaths in the HCV-seropositive patients in the fixed-factor multivariable model (IRR, 11.71 [95% CI, 6.42–21.34]; $P < .0001$) and an even higher incidence in the updated-factor multivariable model (IRR, 12.31 [95% CI, 6.77–22.41]; $P < .0001$).

All of the analyses shown in table 4 were repeated with additional adjustment for plasma HIV-1 RNA load either as a fixed factor at baseline or as an updated factor. The results were similar (data not shown). In addition, all univariable and multivariable analyses were repeated separately for injection drug

Table 1. Characteristics of the study population, by hepatitis C virus (HCV) serostatus at recruitment into the EuroSIDA cohort.

Characteristic	HCV seronegative	HCV seropositive	P[a]
Patients	3997 (67.1)	1960 (32.9)	…
Sex			<.0001
Male	3083 (77.1)	1358 (69.3)	
Female	914 (22.9)	602 (30.7)	
Age, median (IQR), years	37.5 (31.8–45.4)	33.9 (29.4–39.0)	<.0001
Ethnicity			<.0001
White	3464 (86.7)	1840 (93.9)	
Other	533 (13.3)	120 (6.1)	
Geographic region			<.0001
Southern Europe/Argentina/Israel	982 (24.6)	695 (35.5)	
Central Europe	1137 (28.5)	293 (15.0)	
Northern Europe	1186 (29.7)	359 (18.3)	
Eastern Europe	692 (17.3)	613 (31.3)	
Mode of HIV-1 acquisition			<.0001
Homosexual contact	2139 (53.5)	129 (6.6)	
Injection drug use	129 (3.2)	1519 (77.5)	
Heterosexual contact	1443 (36.1)	200 (10.2)	
Other	286 (7.2)	112 (5.7)	
Prior AIDS diagnosis	1084 (27.1)	420 (21.4)	…
HIV-1 treatment at recruitment			<.0001
Naive	690 (16.8)	492 (25.1)	
ART	1203 (30.1)	754 (38.5)	
HAART	2124 (53.1)	714 (36.4)	
Plasma HIV-1 RNA load at recruitment			
Data available	3145 (78.7)	1182 (60.3)	<.0001
<500 copies/mL	1424 (45.3)	468 (39.6)	.0080
Median (IQR), log copies/mL	2.87 (1.90–4.28)	3.21 (2.19–4.40)	.0020
CD4 cell count at recruitment			
<50 cells/μL	318 (8.0)	187 (9.5)	.039
Median (IQR), cells/μL	305 (170–455)	291 (160–441)	.035
Hepatitis[b]			
Increased ALT level	639 (55.7)	368 (82.7)	<.0001
Increased AST level	795 (76.4)	446 (92.5)	<.0001
HBsAg status			<.0001
Negative	3434 (85.9)	1552 (79.2)	
Positive	281 (7.0)	177 (9.0)	
Unknown	282 (7.1)	231 (118.8)	
Duration of follow-up, median (IQR), months	45 (15–84)	32 (9–84)	.0032

NOTE. Data are no. (%) of patients, unless otherwise noted. Forty-six HCV-seropositive patients (2.3%) had received treatment of any kind for HCV infection. HAART, highly active antiretroviral therapy; HBsAg, hepatitis B surface antigen; IQR, interquartile range.

[a] For the comparison between the HCV-seronegative patients and the HCV-seropositive patients.

[b] Alanine aminotransferase (ALT) levels at recruitment were available for 1593 patients and were classified as increased when they reached >23 U/L for men and >19 U/L for women, and aspartate aminotransferase (AST) levels at recruitment were available for 1522 patients and were classified as increased when they reached >19 U/L for men and >15 U/L for women.

users (IDUs) and other risk groups. Among IDUs, after adjustment for fixed factors, there was a significantly increased incidence of liver disease–related deaths (IRR, 12.66 [95% CI, 6.76–23.71]; $P < .0001$) in those coinfected with HIV-1 and HCV. A similar trend, although smaller in size and not significant, was observed among non-IDUs (IRR, 6.16 [95% CI, 0.85–44.50]; $P = .072$). However, it should be noted that this analysis had limited power, as is indicated by the wide CIs;

Table 2. Distribution of rates of hepatitis C virus (HCV) seropositivity among patients of known HCV serostatus at recruitment into the EuroSIDA cohort.

Geographic region, country	Patients of known HCV serostatus		IDUs of known HCV serostatus		HCV-seropositive patients who acquired HIV-1 via injection drug use, %
	Total no.	HCV seropositive, %	Total no.	HCV seropositive, %	
Southern Europe					
Italy	743	56.9	373	95.7	84.4
Spain	249	53.0	109	90.8	75.0
Portugal	270	30.4	80	83.8	81.7
Greece	147	5.4	5	80.0	50.0
Central Europe					
Switzerland	188	39.4	70	97.1	94.4
France	496	21.6	66	83.3	51.4
Germany	736	15.6	84	82.1	60.0
Austria	26	15.4	9	44.4	100.0
Luxembourg	88	12.5	7	100.0	63.6
Belgium	87	11.5	4	100.0	40.0
Northern Europe					
Denmark	357	19.9	46	97.8	63.4
The Netherlands	49	20.4	4	100.0	40.0
United Kingdom	526	24.5	121	88.4	82.9
Ireland	85	36.5	30	93.3	90.3
Sweden	205	29.3	47	93.6	73.3
Norway	132	22.7	27	88.9	80.0
Eastern Europe					
Hungary	78	3.9	0	0	0
Czech Republic	59	17.0	5	80.0	40.0
Slovakia	33	3.0	1	100.0	100.0
Poland	484	61.2	255	96.1	82.8
Estonia	80	56.3	38	94.7	80.0
Lithuania	80	51.3	39	94.9	90.2
Rumania	107	3.7	0	0	0
Ukraine	122	71.3	82	97.6	92.0
Serbia and Montenegro	29	24.1	5	80.0	57.1
Latvia	93	66.7	64	87.5	90.3
Belarus	47	70.2	31	96.8	90.9
Russia	93	25.8	17	100.0	70.8
South America, Argentina	152	29.0	24	79.2	43.2
Middle East, Israel	116	5.2	7	71.4	83.3

NOTE. IDU, injection drug user.

there were 67 liver disease–related deaths during 8037 PYFU in IDUs and 42 liver disease–related deaths during 24,084 PYFU in non-IDUs ($P < .0001$).

Effect of HAART by HCV serostatus. A total of 3760 patients from the entire EuroSIDA cohort initiated HAART after enrollment into the study and had some prospective follow-up; of these, 2260 were of known HCV serostatus before initiation of HAART (66% were HCV seronegative and 34% were HCV seropositive). There were no differences between the HCV-seropositive patients and the HCV-seronegative patients with respect to either CD4 cell count (median, 215 vs. 232 cells/μL; $P = .22$) or plasma HIV-1 RNA load (median, 4.25 vs. 4.26 log copies/mL; $P = .45$) at the time when HAART was initiated. The groups were also comparable with respect to the HAART regimen initiated: of the HCV-seropositive patients and the HCV-seronegative patients, 70% in each group initiated a single PI–containing regimen; 15% and 14%, respectively, initiated a dual PI–containing regimen; and 7% and 6%, respectively, initiated an NNRTI-containing regimen ($P = .083$; χ^2 test).

Table 3. Clinical events and event rates, by hepatitis C virus (HCV) serostatus.

Clinical event, HCV serostatus	No. of events	PYFU	No. of events/100 PYFU (95% CI)	*P*
New AIDS-defining illness/any death				<.0001
Seronegative	818	20,293	4.0 (3.8–4.3)	
Seropositive	520	8989	5.8 (5.3–6.3)	
New AIDS-defining illness				.024
Seronegative	603	20,293	3.0 (2.7–3.2)	
Seropositive	314	8989	3.5 (3.1–3.9)	
Any death				<.0001
Seronegative	456	22,221	2.1 (1.9–2.2)	
Seropositive	363	9872	3.7 (3.3–4.1)	
Liver disease–related death				<.0001
Seronegative	20	22,221	0.1 (0.1–0.1)	
Seropositive	89	9872	0.9 (0.7–1.1)	
Non–HIV-1–related death				<.0001
Seronegative	233	22,221	1.0 (0.9–1.2)	
Seropositive	229	9872	2.3 (2.0–2.6)	

NOTE. Person-years of follow-up (PYFU) and clinical events were allocated by current HCV serostatus. CI, confidence interval.

Of the 2015 patients with a plasma HIV-1 RNA load of ⩾500 copies/mL or with an unknown viral load, 1799 (89%) achieved a plasma HIV-1 RNA load of <500 copies/mL after initiation of HAART (89% of the HCV-seronegative patients and 91% of the HCV-seropositive patients) ($P = .20$; χ^2 test). The time to first achieving a plasma HIV-1 RNA load of <500 copies/mL was also comparable between the 2 groups (figure 1), being, on average, 5 months (95% CI, 5–6 months) for the HCV-seronegative patients and 6 months (95% CI, 5–7 months) for the HCV-seropositive patients ($P = .99$; log-rank test). Six months after HAART initiation, 55% (95% CI, 52%–57%) of the HCV-seronegative patients and 51% (95% CI, 47%–54%) of the HCV-seropositive patients were estimated to have a plasma HIV-1 RNA load of <500 copies/mL. After adjustment for relevant variables, there was no significantly decreased frequency of virologic response (plasma HIV-1 RNA load of <500 copies/mL) in the HCV-seropositive patients, compared with that in the HCV-seronegative patients (relative hazard [RH], 1.13 [95% CI, 0.84–1.51]; $P = .42$). Models that excluded patients with missing viral loads at HAART initiation showed very similar results (RH, 1.07 [95% CI, 0.88–1.30]; $P = .49$). Of the 1518 patients with a known plasma HIV-1 RNA load of ⩾500 copies/mL at HAART initiation, 502 (33%) responded with a ⩾50% decrease in plasma HIV-1 RNA load. There was no difference between the HCV-seropositive patients and the HCV-seronegative patients with respect to this proportion (33%, for both groups; $P = .99$), and, after adjustment, there was no difference in the RH of this end point between the HCV-seropositive patients and the HCV-seronegative patients (RH, 0.98 [95% CI, 0.78–1.22]; $P = .83$).

Of the 2215 patients with a known CD4 cell count at HAART initiation, 1823 (82%) achieved a ⩾50% increase in CD4 cell count (83% of the HCV-seronegative patients and 80% of the HCV-seropositive patients ($P = .093$; χ^2 test). The time to immunologic success was not significantly different between the 2 groups (figure 2*A*); the median time to attaining the immunologic-success criteria was 9 months (95% CI, 8–9 months) for the HCV-seronegative patients and was 9 months (95% CI, 8–10 months) for the HCV-seropositive patients ($P = .067$; log-rank test). A total of 2015 patients (91%) achieved a ⩾50 cell/μL increase in CD4 cell count after initiation of HAART (91% of the HCV-seronegative patients and 90% of the HCV-seropositive patients) ($P = .33$; χ^2 test). The time to immunologic success was not significantly different between the 2 groups (figure 2*B*); the median time to attaining the immunologic-success criteria was 6 months (95% CI, 5–6 months) for the HCV-seronegative patients and was 6 months (95% CI, 5–6 months) for the HCV-seropositive patients ($P = .056$; log-rank test). After adjustment for relevant variables, there was no significantly decreased frequency of immunologic response, whether measured as a ⩾50% increase (RH, 0.94 [95% CI, 0.77–1.16]; $P = .58$) or as a ⩾50 cells/μL increase (RH, 0.92 [95% CI, 0.77–1.11]; $P = .40$) in CD4 cell count after initiation of HAART, in the HCV-seropositive patients versus the HCV-seronegative patients. Further analyses that considered the change in CD4 cell count at 6 months after initiation of HAART also revealed no difference in immunologic response between the 2 groups.

DISCUSSION

Of the 5957 patients in the EuroSIDA cohort for whom HCV serostatus at recruitment was known, 33% were HCV seropositive. Given that ~85% of individuals positive for HCV antibod-

Table 4. Incidence rate ratios (IRRs), by hepatitis C virus (HCV) serostatus.

	Univariable		Multivariable			
			Fixed factors		Updated factors	
Clinical event, HCV serostatus	IRR (95% CI)	*P*	IRR (95% CI)	*P*	IRR (95% CI)	*P*
New AIDS-defining illness/any death		<.0001		.72		.50
Seronegative	1.00		1.00		1.00	
Seropositive	1.44 (1.29–1.60)		0.97 (0.81–1.16)		1.06 (0.89–1.28)	
New AIDS-defining illness		.020		.0016		.030
Seronegative	1.00		1.00		1.00	
Seropositive	1.18 (1.03–1.35)		0.70 (0.56–0.87)		0.78 (0.62–0.98)	
Any death		<.0001		.0024		<.0001
Seronegative	1.00		1.00		1.00	
Seropositive	1.79 (1.56–2.06)		1.41 (1.13–1.76)		1.80 (1.44–2.25)	
Liver disease–related death		<.0001		<.0001		<.0001
Seronegative	1.00		1.00		1.00	
Seropositive	10.02 (6.17–16.27)		11.71 (6.42–21.34)		12.31 (6.77–22.41)	
Non–HIV-1–related death		…		…		<.0001
Seronegative	1.00		1.00		1.00	
Seropositive	2.21		…		…	

NOTE. Fixed-factor multivariable models were adjusted for CD4 cell count, age, prior AIDS diagnosis, HIV-1 treatment at baseline, baseline date, hepatitis B surface antigen status, sex, ethnicity, geographic region, and risk group. In the updated-factors multivariable models, CD4 cell count and initiation of highly active antiretroviral therapy were adjusted for as time dependant and, where AIDS was not part of the end point, the models were further adjusted for diagnosis of a new AIDS-defining illness.

ies are chronically infected with HCV [25], our results underscore the clinical importance of concomitant HCV coinfection in HIV-1–infected individuals in Europe. The problem is particularly worrisome in eastern and southern Europe, where HCV coinfection rates are ~50%. However, IDUs are more likely to be tested for HCV than are non-IDUs, suggesting that the percentage of IDUs who test positive for HCV may be higher than the overall prevalence of HCV infection. Indeed, in the present study, there was little variation in rates of HCV seropositivity among IDUs with known HIV-1 infection from all participating countries, with 70%–100% of them being HCV coinfected.

As a limitation of our study, <10% of the HCV-seropositive patients had had HCV RNA loads measured (data not shown), preventing a direct comparison between patients with viremia and those with self-limited HCV infection. However, hepatitis C–associated viral clearance appears to be reduced in patients coinfected with HIV-1 [25], whereas it remains unknown whether HAART affects the rate of clearance of HCV. In addition, we did not include information on treatment for hepatitis C in our analyses. Treatment was uncommon, and neither exclusion of patients receiving treatment nor adjustment for treatment altered any of our findings (data not shown). Another limitation of the present study is the fact that serologic results were not available for all patients in the EuroSIDA cohort, primarily because testing for HCV antibodies had not been routinely introduced across Europe at the time when the study began. It is possible that patients with more-advanced HCV-associated disease died before they could be tested for HCV and were, therefore, excluded from the present analyses. An analysis limited to the patients recruited into cohort III and later cohorts, however, revealed an HCV seroprevalence similar to that found in the overall EuroSIDA cohort as well as similar results throughout (data not shown). This limitation would not affect the assessment of responses to HAART, which was introduced around the time when HCV testing became common. Finally, neither genotype data nor sufficient records on ALT and AST levels were available, which would have allowed further subanalysis in specific patient groups.

Overall, no increased risk of clinical progression to AIDS or death could be found in the HCV-seropositive versus the HCV-seronegative patients. Surprisingly, the HCV-seropositive patients even had a reduced incidence of new AIDS-defining illnesses in the multivariable analyses; however, non–HIV-1–related deaths and liver disease–related deaths were significantly more frequent in the HCV-seropositive patients, suggesting that competing risks led to the observed reduction in AIDS incidence. With better treatment options for HIV-1 infection and an extended duration of HCV infection, coinfected patients obviously become more prone to liver disease. The greater number of non–HIV-1–related deaths among the HCV-seropositive patients may reflect comorbidity from continued active injection drug use in this group or from alcohol use. However, no data on these matters have been collected, thereby preventing further conclusions. In addition, in a further subanalysis, no increase in clinical progression to AIDS was found in the HCV-seropositive IDUs with HIV-1 coinfection, compared with that in the HCV-seropositive IDUs without HIV-1 coinfection. These results are in disagreement with those of the Swiss HIV Cohort

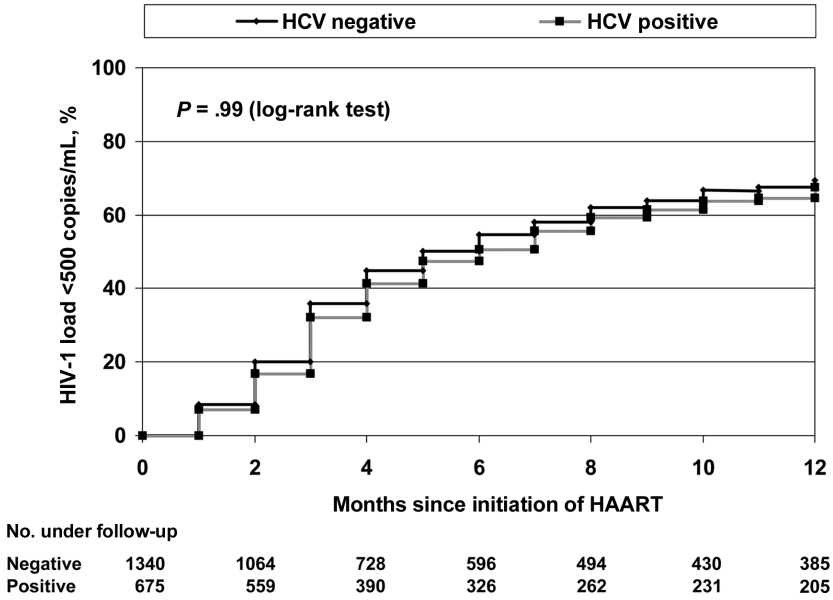

Figure 1. Kaplan-Meier curve showing time to achieving a plasma HIV-1 RNA load of <500 copies/mL after initiation of highly active antiretroviral therapy (HAART), by hepatitis C virus (HCV) serostatus when HAART was initiated.

Study, which showed an independent association between hepatitis C and HIV-1 disease progression and survival, especially in HIV-1/HCV–coinfected IDUs [13]. In contrast, other studies [19, 26] have reported no increased risk of the development of a new AIDS-defining illness in HCV/HIV-1–coinfected persons, once adjustments are made for receipt of HAART and failure to suppress HIV-1 replication. The reason for these discrepancies remain unclear but may be related to demographic differences in the populations studied and the inclusion criteria employed. For instance, the Swiss HIV Cohort Study included only patients receiving HAART [13]. At baseline, there were more patients with prior AIDS, lower CD4 cell counts, and higher plasma viremia in the coinfected group than in the HCV-negative group. The Johns Hopkins cohort, on the other hand, included both treated and untreated individuals [19]. Moreover, differences in duration of HCV infection might play a role.

In the EuroSIDA cohort, we also observed a higher rate of liver disease–related deaths in the HCV-seropositive patients than in the HCV-seronegative patients, but we did not observe a higher rate of opportunistic infections. It should be highlighted, however, that the proportion of all deaths attributable to liver disease in those with hepatitis C remains quite small. Recent studies have suggested that a change occurs in the natural course of hepatitis C in HIV-1–infected patients after HAART initiation, showing a better liver disease–related outcome in coinfected patients receiving HAART [10–12].

Similar to what was observed in the Johns Hopkins cohort, the HCV-seropositive patients in the EuroSIDA cohort were more likely to be treatment naive and less likely to initiate HAART than were the HCV-seronegative patients. In addition, the HCV-seropositive patients were more likely to have received prior monotherapy or double-nucleoside therapy, again reflecting the difficulties of treatment in HIV-1/HCV–coinfected individuals in combination with the comorbidity and problems associated with injection drug use. Possible differences in the time point of HAART initiation as well as in the initial treatment choices may also have affected the different outcomes in the various cohort studies. Moreover, many factors—such as treatment adherence, temporal changes in the way HAART is used, better management of toxicities, and more awareness of liver problems as people live longer—that cannot be measured directly and that, therefore, were either incompletely assessed or not assessed at all in the various cohort studies may also have influenced the outcomes.

Subanalyses within our study examining virologic control in patients initiating their first HAART regimen showed no differences in the percentage of patients achieving as well as in the time to achieve a plasma HIV-1 RNA load of <500 copies/mL between the HCV-seropositive patients and the HCV-seronegative patients. In the Swiss HIV Cohort Study [13], differences in neither the virologic response to HAART nor the virologic failure rate were observed in association with HCV status. However, the study did find a lower CD4 cell count recovery in HCV-positive patients receiving HAART than in HCV-negative patients receiving HAART. This finding was not confirmed in the present study, whether we defined immunologic success as a CD4 cell count increase of $\geqslant$50% or of $\geqslant$50 cells/μL from baseline. A more-recent report from the Swiss HIV Cohort Study, however, mentions that an extended follow-up of their patients (up to 4 years) resulted in a

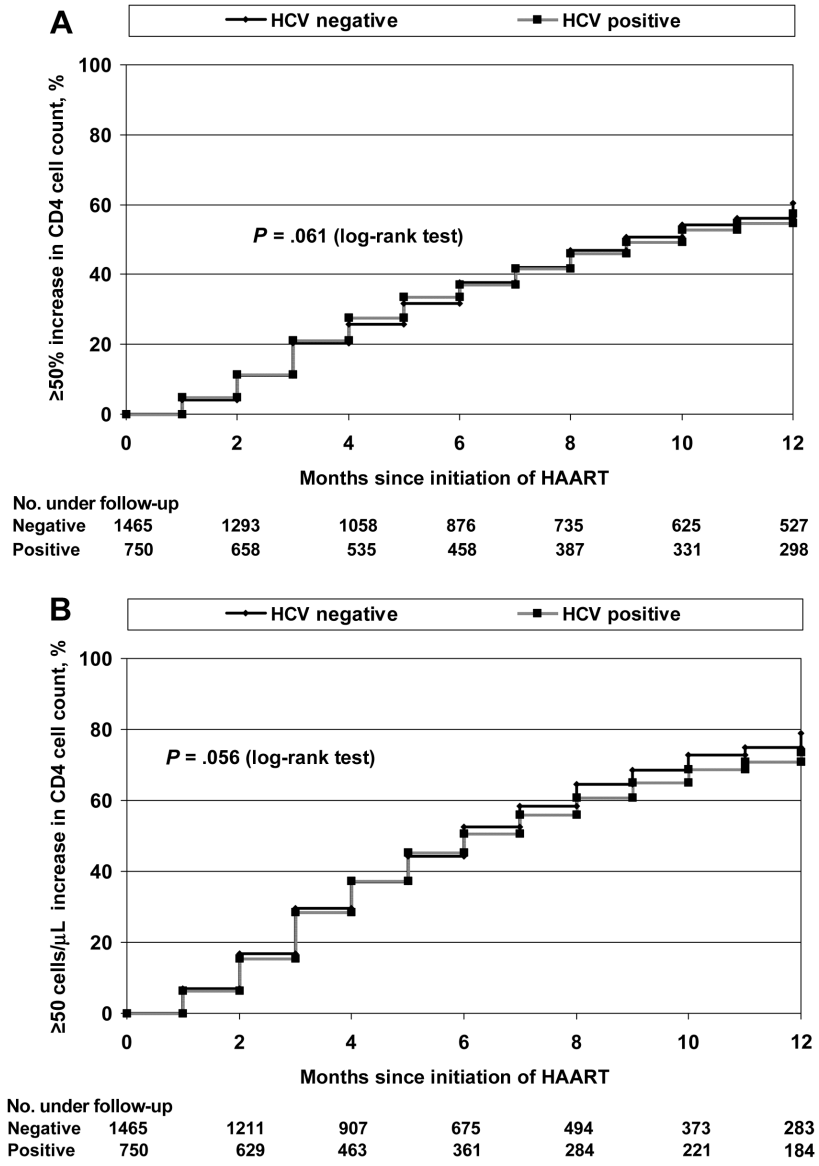

Figure 2. *A,* Kaplan-Meier curve showing time to achieving a ⩾50% increase in CD4 cell count after initiation of highly active antiretroviral therapy (HAART), by hepatitis C virus (HCV) serostatus when HAART was initiated. *B,* Kaplan-Meier curve showing time to achieving a ⩾50 cells/μL increase in CD4 cell count after initiation of HAART, by HCV serostatus when HAART was initiated.

finding of a lack of association between HCV status and immunologic recovery after initiation of HAART [27].

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References

1. Martin-Carbonero L, Soriano V, Valencia E, Garcia-Samaniego J, Lopez M, Gonzalez-Lahoz J. Increasing impact of chronic viral hepatitis on hospital admissions and mortality among HIV-infected patients. AIDS Res Hum Retroviruses **2001**; 17:1467–71.
2. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with HIV infection. Clin Infect Dis **2001**; 32:492–7.
3. Mocroft A, Brettle R, Kirk O, et al. changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. AIDS **2002**; 16:1663–71.
4. Soriano V, Sulkowski M, Bergin C, et al. Care of patients with chron-

ic hepatitis C and HIV-coinfection: recommendations from the HIV-HCV International Panel. AIDS **2002**; 16:813–28.
5. Rockstroh J. Management of hepatitis B and C in HIV-coinfected patients. J Acquir Immune Defic Syndr **2003**; 34(Suppl 1):S59–65.
6. Eyster M, Diamondstone L, Lien J, Ehmann WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection on multitransfused hemophiliacs: effect of coinfection with HIV. J Acquir Immune Defic Syndr **1993**; 6:602–10.
7. Rockstroh J, Spengler U, Sudhop T, et al. Immunosuppression may lead to progression of hepatitis C virus associated liver disease in hemophiliacs coinfected with HIV. Am J Gastroenterol **1996**; 91:2563–8.
8. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenteral acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol **1997**; 26:1–5.
9. Martin-Cabonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus–infected patients with chronic hepatitis C: a European collaborative study. Clin Infect Dis **2004**; 38:128–33.
10. Benhamou Y, DiMartino V, Bochet M, et al. Factors affecting liver fibrosis in human immunodeficiency virus and hepatitis C virus coinfected patients: impact of protease inhibitor therapy. Hepatology **2001**; 34:283–7.
11. Tural C, Fuster D, Tor J, et al. Time on antiretroviral therapy is a predictive factor for liver fibrosis in HIV and hepatitis C virus (HCV) coinfected patients. J Viral Hepat **2003**; 10:118–25.
12. Qurishi N, Kreutzberg C, Lüchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet **2003**; 362:1708–13.
13. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet **2000**; 356:1800–5.
14. De Luca A, Bugarini R, Lepri A, et al. Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects. Arch Intern Med **2002**; 162:2125–32.
15. Lincoln D, Petoumenos, Dore GJ, Australian HIV Observational Database. HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy. HIV Med **2003**; 4:241–9.
16. Martin JC, Castilla J, Lopez M, Arranz R, Gonzalez-Lahoz J, Soriano V. Impact of chronic hepatitis C on HIV-1 disease progression. HIV Clin Trials **2004**; 5:125–31.
17. Piroth L, Duong M, Quantin C, et al. Does hepatitis C virus coinfection accelerate clinical and immunological evolution of HIV-infected patients? AIDS **1998**; 12:381–8.
18. Lesens O, Deschenes M, Steben M, Belanger G, Tsoukas C. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus–positive hemophiliacs and should be treated as an opportunistic infection. J Infect Dis **1999**; 179:1254–8.
19. Sulkowski M, Moore R, Mehta S, Chaisson R, Thomas D. Hepatitis C and progression of HIV disease. JAMA **2002**; 288:199–206.
20. Dorrucci M, Pezzoti P, Phillips A, Cozzi L, Rezza G. Coinfection of hepatitis C virus with immunodeficiency virus and progression to AIDS. J Infect Dis **1995**; 172:1503–98.
21. Macias J, Pineda JA, Leal M, et al. Influence of hepatitis C virus infection on the mortality of antiretroviral-treated patients with HIV-disease. Eur J Clin Microbiol Infect Dis **1998**; 17:167–70.
22. Sabin C, Telfer P, Phillips A, Bahgani S, Lee C. The association between hepatitis C virus genotype and human immunodeficiency virus disease progression in a cohort of hemophilic men. J Infect Dis **1997**; 175:164–8.
23. Mocroft A, Katlama C, Johnson A, et al. AIDS across Europe 1994–1998: the EuroSIDA study. Lancet **2000**; 356:291–6.
24. Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep **1992**; 41:1–19.
25. Thomas D, Astemborski J, Rai R, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA **2000**; 284:450–6.
26. Klein M, Lalonde R, Suissa S. The impact of hepatitis C virus coinfection on HIV-progression before and after highly active antiretroviral therapy. J Acquir Immune Defic Syndr **2003**; 33:365–72.
27. Kaufmann G, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years. The Swiss HIV Cohort Study. Arch Intern Med **2003**; 163:2187–95.