

Incident Hepatitis C Virus in Women with Human Immunodeficiency Virus Infection

M. Augenbraun,¹ J. J. Goedert,³ D. Thomas,⁵ J. Feldman,¹ E. C. Seaberg,⁴ A. L. French,⁵ E. Robison,² M. Nowicki,⁷ and N. Terrault⁸

¹State University of New York–Downstate Medical Center, Brooklyn, and ²Montefiore Medical Center, Bronx, New York; ³Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, and ⁴Johns Hopkins School of Public Health and ⁵Johns Hopkins University, Baltimore, Maryland; ⁶CORE Center Cook County Hospital, Rush Medical College, Chicago, Illinois; and ⁷University of Southern California at Los Angeles and ⁸University of California at San Francisco

Individuals infected with human immunodeficiency virus type 1 (HIV-1) are frequently coinfecting with hepatitis C virus (HCV). Acute HCV infection is often asymptomatic and poorly understood. We conducted a historical prospective study of HCV antibody and viremia in plasma samples obtained during 1994–1999 from a cohort of initially HIV-1–infected, HCV-uninfected women and from HIV-1–HCV–uninfected women. Twenty-two (1.5%) of 1517 experienced seroconversion. Of these, 14 (64%) truly acquired a new infection as assessed by enzyme immunoassay response and new-onset viremia. The incidence rate in HIV-1–infected women was 2.7 cases per 1000 person-years; it was 3.3 cases per 1000 person-years in HIV-1–seronegative women (relative risk, 1.21; $P = .75$). Acquisition of HCV was associated with any history of drug use ($P < .01$). Five of 12 viremic, seroconverting individuals cleared viremia. Incident HCV infection among HIV-1–infected and HIV-1–uninfected women was low. It was linked to drug use and commonly resolved.

An estimated 4 million people in the United States are infected with hepatitis C virus (HCV) [1]. Although the incidence of new infections has decreased as a result of improved screening of the blood supply, it can be anticipated that clinical manifestations of infection (i.e., cirrhosis and hepatocellular carcinoma) in chronically

infected persons will become more common during the next 2 decades [2].

Because most people who acquire HCV are asymptomatic, it has been difficult to characterize some of the features of acute infection. These and other aspects of HCV infection may be further complicated by frequent coinfection with HIV-1 [3]. We studied repository blood specimens obtained from a large cohort of HIV-1–infected women observed prospectively since 1994 to identify and describe cases of newly acquired HCV infection.

PATIENTS AND METHODS

The Women's Interagency HIV Study (WIHS) is a prospective multicenter study of the natural history of HIV infection in women. The WIHS comprises 6 consortia: New York City Consortium (Bronx); State University of New York at Brooklyn; Washington, D.C., Consortium; Los Angeles, Southern California Consortium; San Francisco/Bay Area Consortium; and the Chicago Consortium. The WIHS methods and baseline cohort

Received 8 May 2003; accepted 8 July 2003; electronically published 14 October 2003.

Financial support: National Institute of Diabetes and Digestive and Kidney Diseases (grant 5644201). The Women's Interagency HIV Study is funded by the National Institute of Allergy and Infectious Diseases, with supplemental funding from the National Cancer Institute, the National Institute of Child Health and Human Development (NICHD), the National Institute on Drug Abuse, the National Institute of Dental and Craniofacial Research, the Agency for Health Care Policy and Research, the National Center for Research Resources, and the Centers for Disease Control and Prevention (grants U01-AI-35004, U01-AI-31834, U01-AI-34994, U01-AI-34989, U01-HD-32632 [NICHD], U01-AI-34993, U01-AI-42590, 5-MO1-RR00083, and 5-MO1-RR00079).

Reprints or correspondence: Dr. Michael Augenbraun, SUNY-Downstate Medical Center, Box 1187, 450 Clarkson Ave., Brooklyn, NY 11203 (michael.augenbraun@downstate.edu).

Clinical Infectious Diseases 2003;37:1357–64

© 2003 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2003/3710-0012\$15.00

characteristics have been described elsewhere [4]. From October 1994 through November 1995, 2059 women with HIV-1 infection and 569 HIV-1-seronegative women were enrolled in the WIHS. Women were recruited through HIV primary care sites, drug treatment facilities, and community-based outreach facilities. Women were interviewed and examined at enrollment and at 6-month intervals thereafter. Laboratory studies were also performed at each visit. Data regarding risk factors for HCV acquisition (e.g., injection drug use and sexual history) were collected through a standardized questionnaire administered by study personnel. Risk factors for HIV acquisition in HIV-1-seropositive and HIV-1-seronegative women include injection drug use (34% and 28% of women, respectively), heterosexual exposure (42% and 26%, respectively), and receipt of a transfusion (4% and 3%, respectively). No risk was identified in 20% and 43% of women, respectively. The research protocol was reviewed and approved by the institutional review boards at each facility. At enrollment, all participants (HIV-1-seropositive and HIV-1-seronegative women) were screened for the presence of antibodies to HCV by a second-generation EIA (HCV EIA 2.0; Abbott Laboratories).

Plasma samples from each study visit were stored at -70°C . In 1999, the last plasma study specimen placed in repository for each of the initially HCV-seronegative women was tested for antibody to HCV by a third-generation EIA (HCV EIA 3.0; Ortho-Diagnostic Systems), in accordance with the manufacturer's directions. For women with discordant results between this last specimen and that of the enrollment specimen, antibody testing was repeated (serial HCV EIA 3.0, followed by recombinant immunosorbent assay [RIBA; RIBA HCV 3.0; Chiron]) using specimens in the study repository from all intervening semiannual study visits between the 2. In this way, a study visit within 6 months of apparent HCV seroconversion could be identified. The original negative enrollment specimens were confirmed by HCV EIA 3.0.

In women who demonstrated HCV seroconversion, specimens obtained at each study visit were then tested for the presence of HCV RNA by HCV branched DNA (bDNA) (Quantiplex 2.0 branched chain DNA-enhanced label amplification assay; Chiron). Data from the bDNA testing were converted to international units (IU/mL) by using kit-specific conversion factors provided by the manufacturer. To screen for virus loads of less than the level of detection of the bDNA test, plasma specimens from before and after the initial detection of HCV by bDNA were tested via qualitative RT-PCR (COBAS Amplicor HCV Detection Kit; Roche Diagnostic Systems). Genotyping of HCV isolates was performed using E1 sequences, as described elsewhere [5].

Acute HCV infection was defined as an HCV EIA 3.0 seroreactive test result (confirmed as positive by RIBA) after ≥ 1 seronegative test result, combined with HCV viremia measurable by bDNA or RT-PCR also preceded by a negative test

result. Acute infection was also considered to have occurred only if both the HCV EIA 3.0 and the RIBA result became reactive after negative test results (≥ 2 negative test results separated by 6 months), even if viremia could not be demonstrated. For the purpose of some analyses, the date of seroconversion was considered the first study visit with a reactive HCV EIA 3.0 result. Women who acquired HCV antibody during study follow-up were informed and counseled by study personnel.

To examine changes in CD4 cell count and HIV-1 RNA level around the time of HCV seroconversion, we used a matched, nested, case-control approach in which each HCV seroconverter was matched with 4 patients who did not have seroconversion to HCV by HIV-1 status, age (within ± 1 year), and frequency of study visits at the time of seroconversion. Seroincidence rates over time were estimated by using person-years of observation. Potential confounders were examined by stratification using exact Poisson models. Homogeneity was tested to determine whether there was a common relative risk across strata. If there was no significant heterogeneity, then relative risk was pooled across the strata using StatXact 4 for Windows (Cytel Software). Risk factors presumed to be associated with HCV acquisition included drug use, sexual behavior, and age. Analysis of the case-control data was by conditional logistic regression analysis (EGRET; Cytel Software) or by repeated-measures analysis of variance.

RESULTS

Seroconversion. A total of 2628 women enrolled in the WIHS; 2059 were HIV-1 seropositive (78%), and 569 were HIV-1 seronegative (22%). At enrollment, HCV EIA 2.0 results were nonreactive for 1127 HIV-1-infected women (55%) and 390 HIV-1-uninfected women (69%). Among HCV-seronegative women, at enrollment, the mean age of those who were HIV-1 infected was slightly greater than that for women who were HIV-1 uninfected (34.7 vs. 33.0 years). The rate of drug use of any sort, before or after enrollment, was higher among HIV-1-seronegative women (30% vs. 19%). There were no differences in the rates of injection drug use.

Over a mean of 3.5 years (range, 0.2–59 months), 22 of all women at risk (1.5%) experienced seroconversion, as assessed by HCV EIA 3.0, during follow-up. Of the 22 HCV seroconverters, 12 (55%) developed a reactive EIA result after seronegative results of a test or tests, as well as newly measurable viremia, within 6–12 months before or after the date of seroconversion. Six women (27%) experienced seroconversion (as determined by HCV EIA 3.0) during study follow-up but did not demonstrate viremia either concomitant with or during the study visits preceding or after the seroconversion. Two of these 6 women had seroconversion with strongly positive HCV EIA 3.0 test results along with concomitant RIBA reactivity, suggesting true acute infection, despite the absence of HCV vi-

remia. HCV seroconversion occurred at the last study visit, so determination of subsequent new-onset viremia was not possible. The other 4 had weakly positive HCV EIA 3.0 results with negative or indeterminate RIBA results; these were likely false-positive test results.

Four women who demonstrated HCV EIA 3.0 seroconversion during study follow-up were noted to have viremia at and then after the enrollment visit. In these cases, HCV EIA 3.0 seroconversion did not occur until long after the enrollment visit (range, 18–42 months). All 4 of these women were infected with HIV-1. In sum, 14 of these 22 women with HCV EIA 3.0 seroconversion can be confidently said to have acquired HCV infection during study follow-up (figure 1). These 14 cases form the basis for calculating the incidence of HCV. The incidence rate of new HCV infection for HIV-1–infected women was 2.7 cases per 1000 person-years. For HIV-1–uninfected women, the incidence rate was 3.3 cases per 1000 person-years (table 1). There was no statistical difference between the rates ($P = .76$), with an overall estimated incidence rate of 2.8 cases per 1000 person-years (95% CI, 1.5–4.7 cases per 1000 person-years).

In all but 2 of the patients with seroconversions who had new-onset viremia, RIBA test results became positive at the same visit as the HCV EIA 3.0 test result (i.e., within 0–6 months). In one case, RIBA test results became positive at the visit after the EIA 3.0 seroconversion (i.e., within 6–12 months); in the other case, RIBA test reactivity was detected only 1.5 years later (i.e., within 8–24 months).

Transmission factors. Women with a history of any drug use, either before enrollment or during study follow-up, were more likely to acquire HCV infection than were women who gave no such history (5.3 cases per 1000 person-years vs. 0.7 cases per 1000 person-years; $P = .01$). There was no significant

heterogeneity in drug use between HIV-1–infected and HIV-1–uninfected women ($P = .29$). The overall relative risk was 7.3 (95% CI, 1.8–48.4; $P < .01$). Among the 14 women who acquired a new HCV infection, 6 had a reported history of use of crack, cocaine, or heroin during the study follow-up period. Six other women reported a history of crack, cocaine, or heroin use before but not during the study period. Eighty-six percent of the women who acquired HCV infection reported a history of or current drug use, compared with 22% of 1517 HCV-seronegative women at enrollment ($P < .01$). Birth in Puerto Rico was also associated with HCV acquisition ($P = .02$).

There was no greater association between acute HCV infection and lifetime number of sexual partners, frequency of condom use, or history of sexually transmitted diseases at enrollment, either in comparison with all HCV-seronegative women or with the matched control subjects. Rates of acute HCV infection for these and other demographic characteristics are outlined in table 1.

In the matched-control study, the mean absolute CD4 cell count of all HIV-1–infected women with newly acquired HCV infection at the time of the first reactive HCV EIA 3.0 result was 433 cells/mm³ (range, 89–1355 cells/mm³; median, 344 cells/mm³). For all HIV-1–infected women who did not acquire HCV infection, the mean CD4 count was 385 cells/mm³ (range, 14–1880 cells/mm³; median, 348 cells/mm³; table 2). In women with acute HCV infection, the CD4 cell count increased between the visit preceding and the visit of seroconversion, compared with a decrease in the matched control subjects during the same study visits, whether HIV-1 infected or uninfected ($P < .05$). In a comparison of the same groups, log HIV-1 RNA levels (as determined by PCR) were found to have decreased in both (HCV-seronegative patients, from 4.11 to 3.81 log₁₀

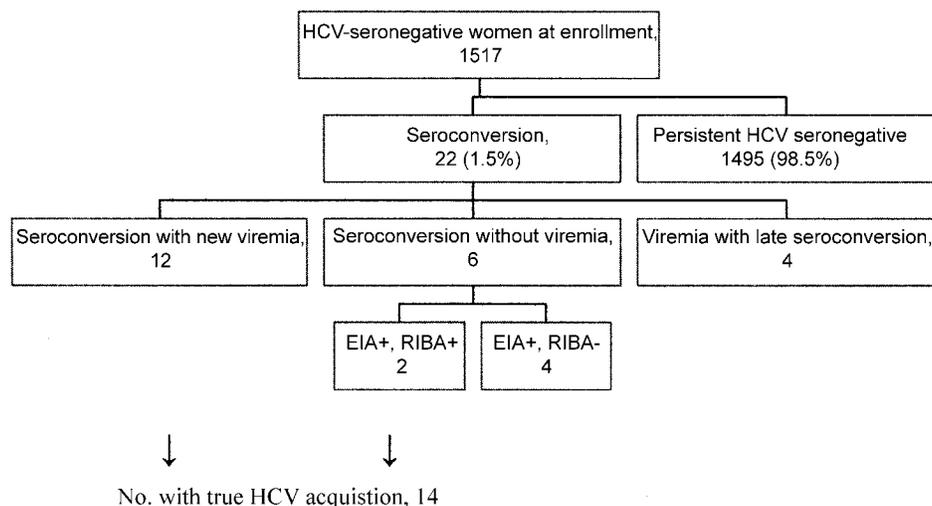


Figure 1. Hepatitis C virus (HCV) antibody acquisition, as determined by HCV EIA 3.0 (Ortho-Diagnostic Systems). RIBA, recombinant immunosorbent assay (RIBA HCV 3.0; Chiron); +, positive; –, negative.

Table 1. Rates of acute hepatitis C virus (HCV) infection in women, by demographic characteristics.

Characteristic	No. of HCV seroconverters	No. of person-years	Incidence	Rate ratio (95% CI)	<i>P</i>
Race					
					.76
African American	6	2669	2.2	1.0 (referent)	
White	3	831	3.6	1.6 (0.3–7.5)	
Hispanic	4	1292	3.1	1.4 (0.3–5.8)	
Other	1	152	6.6	2.9 (0.1–24.1)	
Education					
					.46
Less than high school	3	1627	1.8	1.0 (referent)	
High school	7	1493	4.7	2.5 (0.6–15.2)	
Some college	3	1343	2.2	1.2 (0.2–9.0)	
College or more	1	490	2.0	1.1 (0.02–13.8)	
Any drug use					
					.01
No	2	2684	0.7	1.0 (referent)	
Yes	12	2277	5.3	7.1 (1.6–65.1)	
Ever injected drugs					
					.20
Yes	2	293	6.8	2.7 (0.3–11.9)	
No	12	4668	2.6	1.0 (referent)	
Lifetime no. of sex partners					
					.21
1–4	2	1248	1.6	1.0 (referent)	
5–10	6	1458	4.1	2.6 (0.5–26.0)	
11–100	4	1943	2.1	1.3 (0.2–14.2)	
>100	2	250	8.0	5.0 (0.4–68.9)	
Ever paid for sex					
					.21
Yes	1	1205	0.8	0.2 (0.006–1.6)	
No	13	3727	3.5	1.0 (referent)	
Place of birth					
					.03
United States	12	3803	3.2	1.0 (referent)	
Puerto Rico	2	163	12.3	3.9 (0.4–17.5)	
Other	...	978 (0.0–1.1)	
Age, years					
					.80
<25	2	521	3.8	1.0 (referent)	
25–29	2	1051	1.9	0.5 (0.04–6.8)	
30–35	5	1309	3.8	1.0 (0.2–10.5)	
>35	5	2072	2.4	0.6 (0.1–6.6)	
HIV-1 infected					
					.76
Yes	10	3739	2.7	0.8 (0.2–3.6)	
No	4	1222	3.3	1.0 (referent)	
Total	14	4961	2.8	...	

copies/mL; patients with acute HCV infection, from 4.74 to 3.8 log₁₀ copies/mL; *P* = .12). None of the 9 women infected with HIV-1 were receiving HAART at the visit before seroconversion, compared with 7 (18%) of 40 matched controls (exact *P* = .02). Four women (44%) with new HCV infected and 4 control subjects (10%) were receiving HAART at the time of the index visit (*P* = .18), perhaps accounting for the decrease. There were no discernible trends in HIV-1 RNA level measurements by PCR in the 2–3 visits after HCV seroconversion.

HCV viremia. In only 2 of the 12 cases of seroconversion with new-onset HCV viremia did RT-PCR demonstrate HCV viremia before detection by bDNA. Otherwise, positive test results using these methods were concordant. The first appearance of measurable virus by bDNA or quantitative RT-PCR coincided with HCV EIA 3.0 seroconversion for 9 (75%) of these cases (i.e., within 0–6 months). In 1 case (8%), viremia occurred before HCV EIA 3.0 seroconversion (i.e., 6–12 months). Surprisingly, in 2 cases (17%), HCV EIA 3.0 sero-

Table 2. Mean CD4 cell count before and after acquisition of hepatitis C virus (HCV) infection.

HIV-1 and HCV infection status	No. of patients	CD4 cell count at visit before seroconversion, cells/mm ³		CD4 cell count at first visit after seroconversion, cells/mm ³	
		Mean ± SD	Median	Mean ± SD	Median
HIV-1 uninfected					
HCV uninfected	16	1235 ± 518	1094	1087 ± 403	1101
Acute HCV infection	4	1294 ± 502	1322	1578 ± 315	1447
HIV-1 infected ^a					
HCV uninfected	40	402 ± 362	328	385 ± 328	348
Acute HCV infection ^b	9	328 ± 174	293	433 ± 377	344

^a $P < .05$.

^b Data are missing for 1 patient.

conversion preceded the demonstration of virus by either bDNA or RT-PCR (i.e., a window of 6–12 months). Quantitative virus measurements after first appearance varied widely (table 3). Both the initially measurable HCV bDNA level and the maximal HCV bDNA level for HIV-1–infected HCV seroconvertors were significantly higher than the same measurements for HIV-1–uninfected HCV seroconvertors ($P = .048$ and $P = .008$, respectively, by exact Mann-Whitney test).

The first measured bDNA HCV load in each of the patients ranged from $<42,000$ IU/mL (i.e., the lower limit of detection) to 19 million IU/mL. Eleven of the 12 women were infected with genotypes 1a (8 women) or 1b (3 women). Five of the 12 women (2 HIV-1–seropositive women and 3 HIV-1–seronegative women) lost measurable virus over serial samplings during follow-up, suggesting resolution of infection. No differences in EIA optical density or RIBA pattern at the time of seroconversion were noted between the women who lost virus and those in whom virus persisted.

Four women, all of whom were HIV-1 infected, whose HCV EIA 3.0 result became reactive during the study period were found to have had measurable HCV levels at enrollment. EIA reactivity developed only after a considerable period of follow-up (i.e., 18–42 months). No HCV genotype predominated within this group. Although 1 of these 4 women had persistently measurable virus in excess of 10^7 copies/mL, the others had alternating periods of measurable and unmeasurable virus levels, including 1 period in which no virus was detected at 25–37 months. At the time of seroconversion, 3 of these women were receiving HAART, and this had been initiated during the study period in 2. From the time of enrollment to the time of seroconversion, CD4 counts decreased in 2 of these women (from 426 cells/mm³ to 19 cells/mm³ in one woman, and 500 cells/mm³ to 269 cells/mm³ in the other) and increased in the other 2 (from 118 cells/mm³ to 399 cells/mm³ in one woman, and from 541 cells/mm³ to 619 cells/mm³ in the other).

DISCUSSION

The incident rate of HCV infection in this large group of women with and at risk for HIV-1 infection was low. Incidence rates of HCV in populations at risk, like new injection drug users, may be remarkably high [6–9]. It is likely that those in the WIHS cohort at highest risk for HCV acquisition had already acquired infection before enrollment. Additionally, once enrolled in the study, the WIHS participants were likely to receive standard counseling regarding safe sex practices and risk of ongoing drug use, although the impact of such messages is unclear [10–12].

The majority of women in the WIHS who acquired HCV infection had some history of drug use—distant or current, injection or not—which was considerably out of proportion to the WIHS study cohort overall, supporting the contention that, with the screening of the blood supply, the use of drugs, primarily via injection, is the single most important risk factor for HCV acquisition [13]. Sexual transmission of HCV is plausible, but the association is weak [14–16]. For the few women acquiring HCV in this study who had no history of drug use, we were unable to demonstrate any association with number of sex partners or a history of sexually transmitted diseases. One interesting observation from this small group of HCV seroconvertors is the slight overrepresentation of women born in Puerto Rico, when compared with matched control subjects. Ethnic differences may imply genetic predisposition, cultural practices, or geographic variations, none of which can be demonstrated clearly in this small group but might warrant further investigation.

To a degree, subject serologic and virologic presentations varied. The National Institutes of Health consensus statement on HCV infection states, “The very high sensitivity and specificity of the third generation of EIAs (sensitivity 99%, specificity 99%) obviate the need for confirmatory RIBA in the

Table 3. Serial hepatitis C virus (HCV) levels, measured by branched DNA (bDNA), and qualitative RT-PCR results in seroconverters with viremia.

Patient, test	Study visit				
	1	2 ^a	3 ^b	4 ^c	5 ^d
1					
bDNA, IU/mL	0 ^e	22,378	0	ND	ND
RT-PCR	–	+	–	–	–
2					
bDNA, IU/mL	0	0	0 ^e	ND	ND
RT-PCR	–	+	–	–	–
3 ^f					
bDNA, IU/mL	0	846,860 ^e	4,257,978	ND	ND
RT-PCR	–	+	+	+	+
4 ^f					
bDNA, IU/mL	0	1,429,765 ^e	0	ND	ND
RT-PCR	–	+	–	–	–
5					
bDNA, IU/mL	0 ^e	343,452	281,798	229,820	282,015
RT-PCR	–	+	+	+	+
6 ^f					
bDNA, IU/mL	0	2,693,264 ^e	ND	ND	ND
RT-PCR	–	+	–	–	ND
7 ^f					
bDNA, IU/mL	0	19,042,998 ^e	1,068,908	226,747	2512
RT-PCR	–	+	+	+	+
8 ^f					
bDNA, IU/mL	0	35,428 ^e	ND	ND	ND
RT-PCR	–	+	+	ND	ND
9 ^f					
bDNA, IU/mL	0	5,406,453 ^e	28,994,354	5,310,836	ND
RT-PCR	–	+	ND	ND	ND
10 ^f					
bDNA, IU/mL	0	0 ^e	4,546,904	ND	ND
RT-PCR	–	+	+	ND	ND
11 ^f					
bDNA, IU/mL	0	11,211,843 ^e	1,476,077	1,327,547	1,482,405
RT-PCR	–	+	ND	ND	ND
12					
bDNA, IU/mL	0	0 ^e	ND	ND	ND
RT-PCR	–	+	–	–	–

NOTE. Study visit 1 was the first study visit immediately before detectable viremia. bDNA level determined using Quantiplex 2.0 branched chain DNA-enhanced label amplification assay (Chiron). COBAS Amplicor HCV Detection Kit (Roche Diagnostic Systems) was used for RT-PCR. ND, test not performed; +, positive; –, negative.

^a Mean time after study visit 1, 7.6 months (range, 5–13 months).

^b Mean time after study visit 2, 13.5 months (range, 5–40 months).

^c Mean time after study visit 3, 8.3 months (range, 5–15 months).

^d Mean time after study visit 4, 6 months (range, 4–8 months).

^e Visit with first detectable antibody by HCV EIA 3.0 (Ortho-Diagnostic Systems).

^f HIV-1 seropositive.

diagnosis of individual patients, particularly those with risk factors for HCV" [17]. The entire WIHS cohort could be considered at risk for HCV infection. However, of 22 persons with seroconversion, only 14 with antecedent negative HCV viremia had a new, strongly reactive HCV EIA result with confirmatory RIBA result, and of these persons, 12 subsequently had measurable levels of virus in plasma (positive predictive value, 64%). Four seroconvertors (18%) with weakly reactive HCV EIA, negative RIBA, and repeatedly negative RT-PCR determinations cannot definitively be said to have acquired HCV infection. These may represent false-positive results, although a weak immune response to true exposure cannot be absolutely ruled out. False-positive results could be eliminated by increasing the cut-off values for the EIA.

An additional 4 women (18%) had measurable levels of virus in plasma at enrollment and many months to years before HCV EIA 3.0 seroconversion occurred. These also cannot be described as new infections. The interval between the detection of HCV viremia and the development of HCV antibodies is usually 6–8 weeks, with some cases taking up to 6–12 months [18]. A number of studies have previously suggested that the development of antibody to HCV may be significantly delayed in immunocompromised individuals [18–21]. Beld et al. [22] reported on 5 individuals, none of whom were HIV-1 infected, who had low-grade HCV viremia without seroconversion for a mean of 40.3 months. Although the virus load was low or not detectable in some of the women with a delayed seroconversion in our study, at least 1 of them had an HCV load (determined by RT-PCR) of 40,000,000 copies/mL consistently for ≥ 12 months, and probably for much longer, before mounting an antibody response. In 2 of 4 instances, women with late HCV seroconversion had decreasing CD4 cell counts before the appearance of HCV antibody.

Serial HCV load measurements in our subjects showed no clear patterns. It has been suggested that HCV RNA levels are much higher in immunosuppressed patients than in immunocompetent individuals [23, 24]. Although the number of seroconversions was small, there was a suggestion that HIV-1-infected women who acquired new HCV infections had higher HCV loads. Clearance of infection was also high in our patients. Current estimates suggest that, overall, ~15% of exposed individuals will not have chronic infection [25, 26]. At least 5 (42%) of 12 patients with viremia (2 of whom were HIV-1 infected, and 3 of whom were HIV-1 uninfected), seroconversion, and sufficient follow-up visits after seroconversion appeared to lose virus over repeated 6-month visits. Messick et al. [27] reported that ~25% of a cohort of HIV-uninfected patients with hemophilia lost virus during follow-up. In another cohort, nearly 14% of HIV-uninfected individuals resolved HCV infection during follow-up, whereas rates of resolution in HIV-infected individuals were 5%–8.6%, depending

on the CD4 cell count [22]. Overall, the women here who cleared viremia had lower peak HCV loads.

Conclusions about HCV acquisition and acute infection are limited by the relatively few cases of seroconversion detected. It should also be recognized that follow-up visits in the WIHS were infrequent (i.e., every 6 months) and often offered few time points, both before and after seroconversion, to characterize changes over time with great confidence. Despite these drawbacks, some important observations should be noted. Acute HCV infection is now almost exclusively a problem of individuals with a history of drug use. Although most exposed individuals will predictably develop an antibody response, a certain proportion may not do so for quite some time. Many will also clear viremia, particularly if they are not immunosuppressed, and those who do will do so soon after infection. Clinicians should maintain a high index of suspicion of HCV infection for individuals at risk and consider repeated antibody testing, as well as HCV RNA testing, when such individuals have negative results of a single antibody study.

Acknowledgments

We thank Brad Goebel and Wendell Miley, Scientific Applications International, NCI-Frederick, Maryland, for performing the HCV serological and bDNA assays.

References

1. Kim W. The burden of hepatitis C in the United States. *Hepatology* **2002**; 36(5 Suppl 1):S30–4.
2. Wong J, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* **2000**; 90:1562–9.
3. Sherman K, Rouster S, Chung R, Rajicic N. Hepatitis C virus prevalence among patients coinfecting with human immunodeficiency virus: cross sectional analysis of the US adult clinical trial group. *Clin Infect Dis* **2002**; 34:831–7.
4. Barkan S, Melnick S, Preston-Martin, et al. The Women's Interagency HIV Study (WIHS)—design, methods, sample, cohort characteristics and comparison with reported AIDS cases in US women. *Epidemiology* **1998**; 9:117–25.
5. Villano S, Vlahov D, Nelson K, Cohn S, Thomas D. Persistence of viremia and the importance of long term follow-up after acute hepatitis C infection. *Hepatology* **1999**; 29:908–14.
6. Gostin L, Lazzarini Z, Jones T, et al. Prevention of HIV/AIDS and other blood borne diseases among injection drug users: a national survey on the regulation of syringes and needles. *JAMA* **1997**; 277:53–62.
7. Villano S, Vlahov D, Nelson K, et al. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. *J Clin Microbiol* **1997**; 35:3274–7.
8. van Beek I, Dwyer R, Dore G, et al. Infection with HCV and hepatitis C virus among injection drug users in a prevention setting: retrospective cohort study. *BMJ* **1998**; 317:433–7.
9. Garfein R, Doherty M, Monterosso E, et al. Prevalence and incidence of hepatitis C virus infection among young adult injection drug users. *J Acquir Immune Defic Syndr Hum Retrovirol* **1998**; 18(Suppl 1): S11–9.
10. Wilson TE, Minkoff H, DeHovitz J, Feldman J, Landesman S. The

- relationship of cocaine use and HIV serostatus to incident sexually transmitted diseases among women. *Sex Transm Dis* **1998**;25:70–5.
11. Novotna L, Wilson T, Minkoff H, et al. Predictors and risk taking consequences of drug use among women with HIV-infection. *J Acquir Immune Defic Syndr Hum Retroviro* **1999**;20:502–7.
 12. Wilson T, Massad S, Riesther K, et al. The sexual, contraceptive, and drug use behaviors of women with HIV and those at high risk for infection: results from the Women's Interagency HIV Study (WIHS). *AIDS* **1999**;13:591–8.
 13. Alter M. Epidemiology of hepatitis C. *Hepatology* **1997**;26:62S–65S.
 14. Thomas D, Zenilman J, Alter H. Sexual transmission of hepatitis C virus among patients attending Baltimore sexually transmitted diseases clinic: an analysis of 309 sex partnerships. *J Infect Dis* **1995**;171:768–75.
 15. Van Doornum G, Hookyas C, Cuyppers M, et al. Prevalence of hepatitis C virus infection among heterosexuals with multiple partners. *J Med Virol* **1991**;35:22–7.
 16. Van der Poel CL, Cuyppers HT, Reesink HW. Hepatitis C virus six years on. *Lancet* **1994**;344:1475–9.
 17. Seeff LB, Hoofnagle JH. Appendix: the National Institutes of Health Consensus Development Conference Management of Hepatitis C 2002. *Clin Liver Dis* **2003**;7:261–87.
 18. Maple P, McKee T, Desselberger U, Wreghitt T. Hepatitis C virus infections in transplant patients: serological and virological investigations. *J Med Virol* **1994**;44:43–8.
 19. Schmidt WN, Wu P, Cederna J, Mitros FA, LeBrecque DR, Stapleton JT. Surreptitious hepatitis C virus (HCV) infection detected in the majority of patients with cryptogenic chronic hepatitis and negative HCV antibody tests. *J Infect Dis* **1997**;176:27–33.
 20. de Oliveira JM, Rispeter K, Viazov S, Saback FL, Roggendorf M, Yoshida CF. Differences in HCV antibody patterns in haemodialysis patients infected with the same virus isolate. *J Med Virol* **2001**;63:265–70.
 21. Le Pogam S, Le Chapis D, Christen R, Dubois F, Barin F, Goudeau A. Hepatitis C in a hemodialysis unit: molecular evidence for nosocomial transmission. *J Clin Microbiol* **1998**;36:3040–3.
 22. Beld M, Pennin M, van Putten M, et al. Low levels of hepatitis C virus RNA in serum, plasma and peripheral blood mononuclear cells of injecting drug users during long antibody-undetectable periods before seroconversion. *Blood* **1999**;94:1183–91.
 23. Beld M, Penning M, Lukashov V, et al. Evidence that both HIV and HIV induced immunodeficiency enhance HCV replication among HCV seroconvertors. *Virology* **1998**;244:504–12.
 24. Cribier B, Rey D, Schmitt C, et al. High hepatitis C viremia and impaired antibody response in patients coinfecting with HIV. *AIDS* **1995**;9:1131–6.
 25. Alter M, Margolis H, Krawczynski K, et al. The natural history of community acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. *N Engl J Med* **1992**;327:1899–905.
 26. Thomas D, Astemroski J, Rai R, et al. The natural history of hepatitis C infection. *JAMA* **2000**;284:450–6.
 27. Messick K, Sanders J, Goedert J, Eyster M. Hepatitis C viral clearance and antibody reactivity patterns in persons with haemophilia and other congenital bleeding disorders. *Haemophilia* **2001**;7:568–74.