Hepatitis C Virus Reinfection in Injection Drug Users

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Spontaneous clearance of hepatitis C (HCV) may provide protection against reinfection. In a large community-based cohort study of 3,553 inner-city residents (mainly injection drug users), we identified HCV-infected individuals in whom virological clearance had occurred and compared the rate of reinfection in this group with that observed in previously uninfected members of the same cohort. We identified 926 HCV-uninfected and 658 HCV-infected viremic subjects at baseline, with 152 of 658 (23.1%) spontaneously clearing viremia over a median follow-up of 5.2 years (IQR, 2.8-7.4). At baseline, individuals with HCV clearance were more likely to be HIV coinfected ($P < .001$) and to be engaged in frequent illicit drug use ($P = .004$) and injection drug use ($P < .001$). The occurrence of HCV infection was lower in individuals with previous infection (14/152, 9.2%) compared with that in those without previous infection (172/926, 18.6%), with incidence rates of 1.8 (95% CI, 0.9-3.0 cases/100 person-years) and 8.1 (95% CI, 6.9-9.4 cases/100 person-years) cases/100 person-years, respectively, after accounting for follow-up. In a logistic regression analysis, with previous HCV infection assessed as a covariate with other potential confounding variables (age, sex, ethnicity, HIV infection, housing status, and illicit and injection drug use), individuals with previous HCV infection and viral clearance were 4 times less likely to develop infection than those infected for the first time (adjusted odds ratio, 0.23; 95% CI, 0.10-0.51, $P < .001$). In conclusion, individuals with clearance of HCV infection may have a lower risk of acquiring HCV than individuals who have never been infected, despite ongoing exposure to HCV. (HEPATOLOGY 2006;44:1139-1145.)

Hepatitis C virus (HCV) infection constitutes a major public health burden, affecting more than 170 million individuals throughout the world.[1] Injection drug use has emerged as the primary mode of transmission globally, accounting for more than 75% of incident cases.[1] The prevalence of HCV infection in injection drug users (IDUs) is 60%-90%,[2-4] with 80% of these individuals going on to develop persistent, chronic infection.[5]

Pharmacologic advances have led to the development of effective treatment regimens leading to a virological "cure" in 50% of HCV-infected subjects receiving pegylated interferon in combination with ribavirin.[6,7] Although these outcomes have been replicated in active IDUs,[8,9] there is still concern that the risk of HCV reinfection through recurrent parenteral exposure will negate the benefits of treatment.

In fact, reinfection with HCV after spontaneous clearance has been demonstrated to occur in IDUs with ongoing risk behavior,[10,11] as well as in other groups, including polytransfused children with thalassemia[12] and subjects undergoing liver transplantation.[13] Reinfection does occur in chimpanzees rechallenged with HCV after clearance of the original infection,[14-17] but the resistance to subsequent HCV infection is relatively greater, which is likely related to immune protection.[14,18] In humans, preliminary data from one cohort suggested that IDUs who successfully clear HCV are less likely to develop viremia following reexposure to HCV than are previously uninfected individuals.[19] Given that a greater proportion of IDUs are receiving treatment for HCV, a clearer understanding of this protection from reinfection and its determinants is important. With this in mind, we compared the rate of HCV reinfection among individuals who had

Abbreviations: HCV, hepatitis C virus; IDUs, injection drug users; HBV, hepatitis B virus; EIA, enzyme immunoassay; Ab, antibody.

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spontaneous HCV clearance with the rate of primary HCV infection among participants in a large observational, community-based cohort.

Patients and Methods

Study Population. The Community Health and Safety Evaluation (CHASE) project is a prospective open cohort study designed to evaluate health service use in the Downtown Eastside of Vancouver. Between January 2003 and June 2004, 3,553 subjects were recruited via community organizations and door-to-door canvassing of a random sample of single-occupancy hotels in the community, based on census information. Subjects were eligible for inclusion if they lived or utilized health services in the community. Study participants received a CDN$10 stipend to complete a short, interviewer-administered questionnaire that gathered information on demographics, health service utilization, HIV testing, HCV testing, and recent drug use. Subjects were requested to provide time-limited consent for the researchers to link with specific provincial health services databases using subject names and personal health card numbers in order to acquire historical data, including HCV, HIV, and hepatitis B virus (HBV) testing performed at the British Columbia Centre for Disease Control and the University of British Columbia Virology Department at St. Paul's Hospital. The University of British Columbia /Providence Health Care Research Ethics Board approved this study.

Individuals were defined as HCV uninfected if the result of their first linked enzyme immunoassay (EIA) test for HCV antibodies (HCV Ab) was negative. Participants were considered HCV infected if the results of their first recorded EIA test for HCV antibodies was positive. HCV clearance was defined as the presence of HCV antibodies followed by one subsequent negative test for HCV RNA (HCV Ab+/HCV RNA−). HCV persistence was defined as a positive test for HCV antibodies followed by at least one HCV RNA–positive test, with all subsequent tests remaining positive (HCV Ab+/HCV RNA+). Individuals with persistent HCV RNA were excluded from analysis except for the evaluation of demographic characteristics. We then compared the incidence of HCV infection between 1992 and 2005 in individuals with (HCV Ab+/HCV RNA−) and without previous infection (HCV Ab−) in order to evaluate the effect of prior infection on subsequent infection rates.

For the purpose of this study, the index visit by an uninfected subject was considered the date of the first negative HCV antibody test. The incidence of new cases of HCV infection was measured by an HCV-antibody-negative test and a subsequent positive test during follow-up (HCV Ab−/HCV Ab+), with the date of HCV infection estimated as the midpoint between the last HCV-antibody-negative test and the first HCV-antibody-positive test. During the follow-up period, the incidence of HCV reinfection was determined by the detection of HCV RNA following spontaneous clearance of HCV (HCV Ab+/HCV RNA−/HCV RNA+), with the date of HCV reinfection estimated as the midpoint between the last HCV-RNA-negative test and the first HCV-RNA-positive test after clearance. Follow-up for individuals developing viremia was defined as the time from the index visit to the date of reinfection or infection. For individuals who remained clear of viremia, this was defined as the time from the index visit to the date of the most recent negative HCV RNA test or HCV antibody test in previously infected and previously uninfected subjects, respectively.

Laboratory Testing. All virology testing was performed at 2 certified provincial laboratories between 1992 and 2005. HCV antibody testing was performed using first-, second-, or third-generation enzyme-linked immunosorbent assays (May 1992-September 1993: UBI HCV EIA v2.0 [Organon Teknika, Durham, NC]; October 1993-July 1994: UBI HCV EIA v2.1 [Organon Teknika, Durham, NC]; August 1994-March 1997: UBI HCV EIA v4.0 [Organon Teknika, Durham, NC]; April 1997-present: AxSYM HCV v3.0 [Abbott Diagnostics, Chicago, IL]). Specimens reactive for anti-HCV antibodies were retested by a second- or third-generation Recombinant Immunoblot Assay (Chiron, Emeryville, CA) until 1999 to confirm the EIA specificity. Between April 1997 and July 1999, AxSYM HCV 3.0 anti-HCV reactive specimens were retested by UBI HCV v4.0, and from August 1999 to the present time, AxSYM HCV 3.0 reactive samples were retested by Ortho EcI (Ortho Diagnostics, Mississauga, Ontario, Canada). Only specimens reactive by both manufacturers' tests were considered anti-HCV reactive.

The presence or absence of viremia was detected by HCV RNA testing performed when requested by a physician. Since January 1998, HCV RNA testing has been performed by the qualitative COBAS AMPLICOR HCV Test v2.0 (limit of detection: 50 IU/mL, Roche Diagnostic Systems, Mississauga, Ontario, Canada). To ensure specimen integrity, HCV RNA testing was performed using dedicated serum samples separated within 4-6 hours of collection or EDTA plasma separated within 3-5 days of collection. HBV and HIV status were determined by confidential record linkage to the British Columbia Centre for Disease Control virology testing database.

Statistical Analysis. Variables of interest in this analysis included age, ethnicity, housing status, alcohol use,

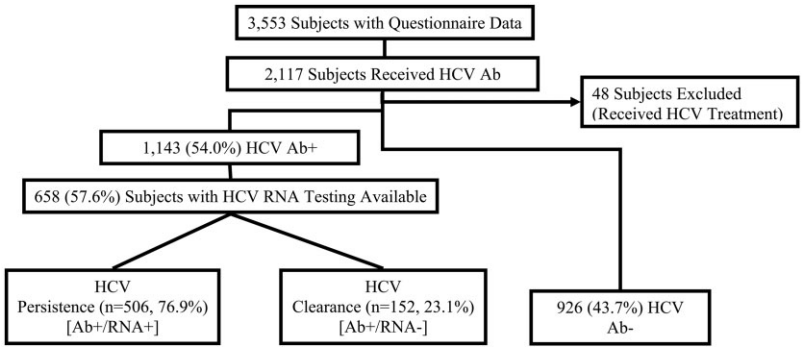

Fig. 1. Subject disposition.

injection drug use, noninjection illicit drug use, previous HBV infection, and HIV status. The age of a participant was determined as the age on the date the questionnaire was administered. Unstable housing was defined as living in a shelter, rooming house, or single-occupancy hotel or as living on the street/being homeless. Illicit drug use behavior was defined as the use of injected cocaine, injected heroin, and injected crystal methamphetamine, as well as the use of heroin, crack cocaine, and crystal methamphetamine though inhalation. Illicit drug use, injection drug use, and alcohol use in the past 6 months were categorized as "frequent," if used everyday/most days; "any," if any reported use in the preceding 6 months; or "none," if no use reported. Exposure to HBV was defined as having had historical positive tests for HBV surface antigen and anti–hepatitis B core total. HIV status was determined by a confidential record linkage to the British Columbia Centre for Disease Control HIV testing database or by subject self-report. We compared characteristics of subjects with and without previous HCV infection using a 2-sample t test for quantitative variables and the χ^2 or Fisher's exact test, as appropriate, for testing differences between 2 proportions. We also compared the characteristics of subjects with and without incident HCV infection using the χ^2 or Fisher's exact test, as appropriate. A multiple logistic regression model comprising potential confounders was used to assess if previous HCV infection was independently associated with reductions in the incidence of HCV infection. Differences were considered statistically significant at $P < .05$, and all reported P values are 2-sided.

Results

Of the 3,553 subjects enrolled in the cohort, 2,117 (59.6%) had HCV antibody testing (Fig. 1). Forty-eight subjects reported having previously received treatment for HCV infection and were excluded from further analysis. At baseline, we identified 926 subjects (43.7%) uninfected with HCV, as documented by negative testing for HCV antibodies. The remaining 1,143 individuals (55.2%) were HCV antibody positive on their first recorded test. HCV RNA test results were available for 658 of these subjects. No significant differences were observed in the demographics between HCV-antibody-positive individuals who did receive HCV RNA testing and those who did not, including age ($P = .87$), male sex ($P = .95$), illicit drug use ($P = .27$), and HIV infection ($P = .32$). However, subjects who did not receive HCV RNA testing were more likely to have engaged in recent injection drug use (62.9% vs. 54.4%, $P = .004$). After identifying 506 individuals with persistent HCV infection on the basis of being HCV RNA positive, we found 152 (23.1%) with spontaneous clearance of viremia.

A comparison of the participants without previous HCV infection with those with HCV clearance is shown in Table 1. The 2 groups were similar in sex ($P = .41$) and housing status ($P = .84$); however, individuals with previous HCV clearance were older (43.7 years vs. 41.2 years, $P < .001$), more likely to be of Aboriginal ethnicity (50.3% vs. 29.0%, $P < .001$), more likely to have previous HBV infection (5.9% vs. 1.3%, $P < .001$), and more likely to be coinfected with HIV (23.5% vs. 7.3%, $P < .001$) than those previously uninfected with HCV. Although there was no difference in the proportion of subjects who engaged in any illicit drug use ($P = .50$), individuals previously infected with HCV were more likely to be engaged in frequent illicit drug use (68.0% vs. 55.2%, $P = .004$) and injection drug use (any; 48.0% vs. 26.0%, $P < .001$, frequent; 24.8% vs. 13.9%, $P < .001$). The median follow-up time beyond the index visit for individuals with clearance of viremia (n = 152) was 5.2 years (IQR, 2.8-7.4) compared to 2.8 years (IQR, 1.4-5.0) for individuals without previous HCV infection (Table 2).

The overall prevalence of HCV infection in this cohort was 63.6% (1,315/2,069), including in 172 previously

Table 1. Characteristics of Participants Without Previous Infection Versus Those With HCV Clearance

Characteristic	Previously Uninfected (HCV Ab−; n = 926), n (%)	HCV Clearance (HCV Ab+/HCV RNA−; n = 152), n (%)	P*
Age in years, mean (SD)	41.2 (11.3)	43.7 (7.7)	< .001
Sex (male)	628 (67.4)	93 (60.8)	.41
Ethnicity			
White	541 (58.4)	69 (45.1)	–
Aboriginal	269 (29.0)	77 (50.3)	< .001
Other	116 (12.6)	7 (4.6)	.089
HIV infected	68 (7.3)	35 (23.0)	< .001
Previous HBV infection	12 (1.3)	9 (5.9)	< .001
Unstable housing	646 (69.8)	105 (68.6)	.84
Illicit drug use			
Any	801 (86.5)	135 (88.9)	.50
Frequent	511 (55.2)	104 (68.0)	.004
Injection drug use			
Any	241 (26.0)	73 (48.0)	< .001
Frequent	129 (13.9)	38 (24.8)	< .001

*Student 2-sample *t* test for age, χ^2 or Fisher's exact test as appropriate for all other comparisons of groups.

uninfected individuals. The occurrence of HCV infection was lower in individuals with previous infection (14/152, 9.2%) than in those without previous infection (172/926, 18.6%). After accounting for duration of follow-up, the incidence of HCV infection was 5 times lower in those previously infected with HCV (1.8 cases/100 person-years; 95% confidence interval [CI], 0.9-3.0 cases/100 person-years) than in those without previous infection (8.1 cases/100 person-years; 95% CI, 6.9-9.4 cases/100 person-years). This occurred despite those with previous HCV infection being at increased risk for HCV acquisition because of higher rates of HIV coinfection, illicit drug use, and injection drug use. The observed difference could not be explained by a lack of follow-up in previously infected individuals, as the median documented time those in this group were without viremia was 5.4 years (range, 0-13.5 years). In a logistic regression of individuals with and without incident HCV infection, with previous HCV infection assessed as a covariate along with other potential confounders (age, sex, ethnicity, HIV infection, housing status, and illicit and injection drug use), individuals with previous HCV infection and viral clearance were still 4 times less likely to develop incident infection than those infected for the first time [adjusted odds ratio, 0.23; 95% CI, 0.10-0.51, $P < .001$].

We also evaluated the occurrence of recurrent HCV viremia in individuals with and without HIV infection and previous viral clearance (Table 3). HCV infection occurred in 8 of 117 HIV-negative individuals with previous HCV infection (6.8%) compared to in 6 of 35 HIV coinfected individuals (17.1%). After accounting for follow-up, the incidence of HCV infection in HIV-negative individuals with previous HCV clearance (1.4 cases/100 person-years; 95% CI, 0.7-2.9 cases/100 person-years) remained 2 times below that in HIV coinfected individuals (2.8 cases/100 person-years; 95% CI, 1.0-6.1 cases/100 person-years).

Of the 14 subjects with HCV reinfection, 13 had ongoing cocaine use, 9 by injection (Table 4), and 6 were HIV positive. HCV viremia was cleared a second time in 4 subjects (29%), despite ongoing cocaine use by all 4. None of these 4 subjects were coinfected with HIV at the time they cleared HCV.

Discussion

In this study of a large community-based cohort of inner-city residents of Vancouver, we have demonstrated that individuals who successfully clear HCV infection have a lower risk of acquiring HCV infection than indi-

Table 2. Occurrence of HCV Viremia in Participants Without Previous Infection Versus in Those With HCV Clearance

Characteristic	Previously Uninfected (HCV Ab−; n = 926), n (%)	HCV Clearance (HCV Ab+/HCV RNA−; n = 152), n (%)
Person-years of follow-up	2127	793
Median follow-up (years)	2.8	5.2
Occurrence of viremia	172/926 (18.6%)	14/152 (9.2%)
Incidence (/100 person-years, 95% CI)	8.1 (6.9-9.4)	1.8 (0.9-3.0)

Table 3. Occurrence of HCV Viremia in HIV-Negative and HIV-Positive Previously HCV Infected Individuals With HCV Clearance (n = 152)

Characteristic	HCV Clearance (HCV Ab+/HCV RNA−) and HIV negative (n = 117)	HCV Clearance (HCV Ab+/HCV RNA−) and HIV positive (n = 35)
Person-years of follow-up	581	212
Median follow-up (years)	5.0	5.4
Occurrence of viremia	8/117 (6.8%)	6/35 (17.1%)
Incidence (/100 person-years, 95% CI)	1.4 (0.7-2.9)	2.8 (1.0-6.1)

viduals without previous HCV infection, despite the former group appearing to be at higher risk of exposure. This protection was tracked over a median of 5 years.

The overall rate of clearance of HCV viremia was 23.1%, which is consistent with published data for non-IDUs.[20] HCV reinfection with viremia occurred in only 10 of 152 subjects (6.6%), despite 90% of them continuing to engage in illicit drug use, including 50% who reported injection drug use. These findings are not surprising, given that reinfection with HCV after spontaneous clearance is well described in IDUs with ongoing risk behaviors.[10,11]

After adjusting for potential confounders, individuals with previous clearance of HCV infection were 4 times less likely to be reinfected with HCV than were individuals infected for the first time. Therefore, we believe these different rates were not associated with epidemiological differences in the 2 populations. In fact, these data are consistent with results from another cohort of IDUs in Baltimore, which showed that over a 2-year period IDUs with HCV clearance had an incidence of infection of 6.0 cases/100 person-years compared to that of previously uninfected IDUs of 10.5 cases/100 person years.[19] Although our patient population may have differed in important ways from that cohort in race and ethnicity, HIV infection, and injection drug use, we observed a similar protection in subjects with previous HCV infection.

HIV-infected subjects with previous HCV clearance were 2 times more likely to demonstrate recurrence of HCV viremia (2.8 cases/100 person-years) than those without HIV (1.4 cases/100 person-years). Although it was not possible to definitively establish the order of HIV and HCV infections for some participants in this study, data suggest that 90%-95% of HIV infections in IDUs occur after HCV infection.[3] As such, this suggests HIV may be affecting the persistence of HCV rather than its initial clearance. HIV infection may decrease circulating HCV-specific CD4 and CD8 T cells, higher levels of which are generally found in individuals with HCV clearance, leading to either reinfection with HCV or the re-emergence of low-level viremia that may have been undetectable by conventional assays for a period.[21]

Our data lend support to the hypothesis that previous exposure to HCV may be protective, possibly on an immunologic basis, despite repeated exposure to HCV. In chimpanzees, reinfection with HCV leads to an attenuated course of infection, with the level and duration of viremia markedly reduced and no evidence of liver disease.[15-17] The level of viremia has been linked to the nature of cellular CD4 and CD8 T-cell responses. The *in vivo* depletion of memory CD4 T cells prior to reinfection results in persistent viremia with a failure to resolve HCV infection,[22] despite functional memory CD8 T-cell responses in the liver. Similarly, *in vivo* depletion of CD8

Table 4. Characteristics of Participants With HCV Reinfection

ID	1995-97	1998	1999	2000	2001	2002	2003	2004	2005	HIV	Drugs
1		Ab+/RNA−	RNA+		RNA+	RNA+	RNA+			Y	Crack
2	Ab+				RNA−	RNA−/RNA+	RNA−			Y	IV cocaine
3	Ab+				RNA−			RNA+/RNA+		Y	Crack
4	Ab+					RNA−	RNA+	RNA−/RNA−		N	IV cocaine/crack
5					Ab+	RNA+/RNA−		RNA+/RNA+		N	IV cocaine
6	Ab+			RNA−		RNA+				Y	IV cocaine
7		Ab+			RNA+	RNA+	RNA−	RNA−/RNA+		N	IV cocaine/crack
8					Ab+/RNA−/RNA+	RNA−		RNA−		N	IV cocaine/crack
9	Ab+		RNA−		RNA+		RNA−			Y	Crack
10			Ab+			RNA−/RNA−	RNA−	RNA+/RNA−	RNA+	N	IV cocaine
11					Ab+		RNA−	RNA+		N	Crack
12	Ab+						RNA−/RNA+			N	IV cocaine
13	Ab+	RNA−						RNA+		N	None
14	Ab+						RNA−	RNA+		Y	IV cocaine/crack

T-cell responses results in prolonged HCV viremia that is not controlled until HCV-specific CD8 T cells recover in the liver.[17] Importantly, it seems that with a rapid, multiantigen T-cell proliferative response, chimpanzees can develop protective immunity that prevents reinfection with the same and with different genotypes of HCV.[16,23] This may also be the case in humans. In one study that considered 3 IDUs with clinical evidence of HCV reinfection and subsequent clearance, it was demonstrated that clearance was associated with more vigorous CD4+ T-cell responses when compared to patients with acute and chronic HCV infection.[24] Further data evaluating viral sequence evolution in IDUs showed that despite ongoing injection drug use during the year of observation, subjects with HCV clearance and HCV persistence demonstrated protection against both reinfection with HCV and superinfection with a different viral genotype, respectively.[25]

There are at least 2 other potential explanations for these results. It has been demonstrated that genetic polymorphisms in some HLA class I and II molecules[26,27] and genes encoding interactions between HLA class I molecules and NK cells[28] are associated with clearance of HCV infection. Thus, it is possible those with HCV clearance are a selected group with genetic characteristics protecting against initial HCV infection and subsequent reinfection. Alternatively, given that this study was originally designed to evaluate health utilization, it lacks detailed information on needle sharing, equipment sharing, and historical drug use. This is important, as individuals previously exposed to HCV may be more experienced and have safer injection routines and thus may be less likely to share injection equipment with others. Such a behavioral difference (which would protect against HCV reinfection) would not be detected in this study. However, given the higher rate of HIV infection in those with previous clearance, it is more likely that those with HCV clearance remain at higher risk of acquiring HCV infection over time.

This report has a number of limitations inherent to large retrospective studies. Virological test results were obtained from a historical database that included antibody assays that changed and improved over time. This is particularly relevant to the HCV antibody tests, which may have been less sensitive prior to 1996. In addition, testing was not systematically done, only on physician request, so subjects who cleared HCV viremia and were later reinfected may have been misclassified as having persistent infection. In some cases, virological clearance was confirmed by a single negative test, which may have represented fluctuating low-level viremia rather than true clearance. This may have overestimated the reinfection rate. Also, some individuals with HCV clearance may have had low-level viremia that was below the limit of detection of the assay (50 IU/mL) and may never have truly cleared their HCV infection. If this were true of some individuals, it would make our analysis a minimum estimate of the difference between the 2 groups. In addition, not all patients received HCV RNA testing, introducing a potential selection bias. However, the similar demographics and HIV status between the 2 groups would indicate similar testing patterns. Further, the incidence of primary HCV infection in individuals without previous infection may also be underestimated because of nonsystematic testing for viremia, once again making our analysis a minimum estimate of the difference between the 2 groups. All these limitations are best addressed in the context of a prospective cohort study with systematic laboratory testing for HCV.

Treatment for HCV infection is often withheld from IDUs because of the perceived high risk of subsequent HCV reinfection after treatment, reducing the impact of treatment on the evolution of the HCV epidemic. However, our data suggest that spontaneous clearance may confer some protection against reinfection. If protection against HCV infection extends to those who have cleared their viremia following antiviral therapy, it could provide a stronger rationale for expanding treatment programs for IDUs, including those who continue to be at risk for HCV exposure. Although preliminary data suggest that lower rates of reinfection are observed after the treatment-induced clearance of HCV infection in IDUs compared to the incidence of HCV infection in uninfected individuals,[29,30] this must be confirmed in prospective cohorts. Given that reinfection can occur, it is critical to educate patients about the risk of HCV reinfection associated with needle and equipment sharing.

In conclusion, further research is required to investigate the mechanism of the effect we have described in order to define its magnitude and to establish how it applies to treated individuals. As IDUs continue to drive the HCV epidemic in developed countries, it is quite clear that any efforts to control this epidemic must include a comprehensive strategy to address the disease in this target population. The results of this study provide some assurance that such strategies could be successfully implemented to limit the impact of HCV in IDUs and in the general population.

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