Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection

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Abstract

Background: Beginning in 1994, Vancouver experienced an explosive outbreak of HIV infection among injection drug users (IDUs). The objectives of this study were to measure the prevalence and incidence of hepatitis C virus (HCV) infection in this context and to examine factors associated with HCV seroconversion among IDUs.

Methods: IDUs recruited through a study site and street outreach completed interviewer-administered questionnaires covering subjects' characteristics, behaviour, health status and service utilization and underwent serologic testing for HIV and HCV at baseline and semiannually thereafter. A Cox proportional hazards model was used to identify independent correlates of HCV seroconversion.

Results: As of Nov. 30, 1999, 1345 subjects had been recruited into the study cohort. The prevalence of anti-HCV antibodies was 81.6% (95% confidence interval [CI] 79.6% to 83.6%) at enrolment. Sixty-two HCV seroconversions occurred among 155 IDUs who were initially HCV negative and who returned for follow-up, for an overall incidence density rate of 29.1 per 100 person-years (95% CI 22.3 to 37.3). The HCV incidence remained above 16 per 100 person-years over 3 years of observation (December 1996 to November 1999), whereas HIV incidence declined from more than 19 to less than 5 per 100 person-years. Independent correlates of HCV seroconversion included female sex, cocaine use, injecting at least daily and frequent attendance at a needle exchange program.

Interpretation: Because of high transmissibility of HCV among those injecting frequently and using cocaine, the harm reduction initiatives deployed in Vancouver during the study period proved insufficient to eliminate hepatitis C transmission in this population.

Beginning in 1994, Vancouver experienced an explosive outbreak of HIV infection among injection drug users (IDUs).[1,2] HIV incidence was estimated in 1997 to be 18.6 per 100 person-years.[2] HIV seroconversion was associated with lower levels of education, unstable housing, commercial sex work, borrowing syringes, a longer history of injection drug use and frequent attendance at a needle exchange program.[2,3]

Of almost as much concern as these high rates of HIV transmission was the high rate of infection with hepatitis C virus (HCV) among IDUs.[2] Elsewhere, the prevalence of HCV infection among IDUs has been reported at 30% to 98%,[4–18] whereas incidence has ranged from 4.2 to 22.0 per 100 person-years.[4,6,12,16,19–22] Among populations receiving treatment for drug abuse, prevalence and incidence of HCV infection are lower.[16] At a population level, the use of injection drugs is the single most important risk factor for acquiring HCV infection in developed countries.[23]

The objectives of this study were to measure the prevalence and incidence of HCV infection among a cohort of IDUs in Vancouver and to identify predictors of seroconversion. The study of HCV in parallel with HIV allowed comparison of inci-

dence trends and of sociodemographic and behavioural factors associated with each virus during an outbreak of HIV.

Methods

The Vancouver Injection Drug User Study (VIDUS) is an open cohort study that began recruitment in May 1996.[2] IDUs residing in the greater Vancouver area who had injected at least once in the previous month were enrolled. Baseline and semiannual visits included serological screening for anti-HCV and anti-HIV antibodies and a questionnaire administered by a trained interviewer blinded to HIV and HCV serostatus. The questionnaire covered information on subjects' characteristics, injection and non-injection drug use, borrowing and lending of syringes and other paraphernalia, incarceration, housing, health care utilization, sexual behaviour, and drug and alcohol treatment.

At each visit, counselling was provided before and after the serological testing, and medical and treatment referrals were made as requested. These referrals included sending subjects to clinics that provide immunization against hepatitis A and B.

HCV antibody was assayed by enzyme-linked immunosorbent assay (ELISA) at the University of British Columbia Virology Laboratory according to a modified testing algorithm.[24] Briefly, a third-generation synthetic peptide-based ELISA (HCV enzyme immunoassay (EIA) 4.0, United Biomedical Inc., Haupagge, NY) was used to screen all sera. Samples that tested negative underwent no further testing. Those testing positive were retested with a third-generation ELISA containing recombinant antigens (HCV 3.0, Ortho Diagnostic Systems, Rochester, NY). Samples that tested positive in both assays were classified as positive and underwent no further testing. Samples that gave discordant results were tested by immunoblot assay (RIBA III, Ortho Diagnostic Systems). No indeterminate results were encountered in the immunoblot assay. Therefore, all sera were classified definitively with this algorithm.

Participants who were seropositive for HCV at baseline were compared with those who were seronegative at baseline by means of univariate techniques, including contingency table analysis for categorical variables and Wilcoxon's rank-sum test for continuous variables.

HCV incidence was calculated by the incidence density approach and is expressed here in terms of person-years of observation. All 95% confidence intervals (CIs) were based on the Poisson distribution.

To identify factors associated with HCV seroconversion, persistently seronegative subjects were frequency matched for the duration of follow-up with subjects who had seroincident HCV infection. These 2 groups were compared by means of univariate techniques, as described above. Factors independently correlated with seroconversion to anti-HCV antibody positive status were assessed by Cox proportional hazards modelling. Variables measuring exposures or behaviour in the 6 months before a newly positive test result for HCV (and that were significant at the 5% level in univariate analyses) were entered into the multivariate models. All possible 2-way interactions were evaluated in the final model.

Results

As of Nov. 30, 1999, 1345 subjects had been recruited into the study cohort. The prevalence of anti-HCV anti-bodies at enrolment was 81.6% (95% CI 79.6% to 83.6%). HCV-seropositive IDUs were older than HCV-seronegative participants (median age 35 v. 25 years). IDUs who had been incarcerated, who reported 20 or more sexual partners in their lifetime or who were HIV positive were significantly more likely to be HCV seropositive (Table 1). HCV-seropositive subjects reported injecting for a median of 14 years, whereas seronegative subjects had been injecting for a median of only 3 years. Female IDUs who had been paid for sex had significantly higher rates of HCV infection at enrolment than those who had not been paid for sex. Similarly, IDUs who had borrowed or lent used syringes, who had attended needle exchange programs, who had been enrolled in a methadone maintenance program or who had accessed some other form of addiction therapy had significantly higher rates of HCV infection at enrolment.

Sixty-two HCV seroconversions were documented among the 155 subjects who were initially HCV seronegative and who returned for follow-up visits. The mean interval to follow-up was 16.1 months, and the overall incidence density rate was 29.1 per 100 person-years (95% CI 22.3 to 37.3). The incidence of HIV infection was high at the beginning of the study (19.4 per 100 person-years) but declined to between 2 and 5 per 100 person-years after the first 2 semesters of the study (Fig. 1). The incidence of HCV was also highest during the earlier follow-up periods, yet it remained above 16 per 100 person-years for the duration of the study (Fig. 1).

On univariate analysis, HCV seroconversion occurred more frequently among females than among males (53% v. 34%, $p = 0.03$, Table 2) and among Aboriginals and white people than among those with other ethnic backgrounds (58%, 43% and 26% respectively, $p = 0.02$). Subjects who participated in the sex trade, borrowed or lent syringes, attended needle exchange programs frequently, injected cocaine or "speedballs" (a combination of cocaine and heroin), or accessed some form of addiction therapy (all within the previous 6 months) were significantly more likely to experience HCV seroconversion, as were those who injected frequently (at least once daily). HIV seroconversion was marginally higher among those who experienced HCV seroconversion.

Independent predictors of HCV seroconversion, according to the Cox proportional hazards model, were female sex, injection of cocaine alone or as a component of speedballs, frequent injection and frequent attendance at a needle exchange program (Table 3). Interaction terms did not remain significant when entered in models containing these variables, and sex-specific modelling did not significantly affect the variables associated with HCV seroconversion.

Interpretation

We documented a sustained high incidence of HCV among IDUs and found that seroincident infection was independently associated with female sex, cocaine use, fre-

quent injection and frequent attendance at a needle exchange program.

The relation between HIV and HCV seropositivity among IDUs is not always consistent, but it has been hypothesized that positive associations are likely where the prevalence of both pathogens is high.[25] This dual high-prevalence condition is satisfied in the VIDUS cohort, in which there was a clear association between prevalences of

Table 1: Factors associated with seropositive status for hepatitis C virus (HCV) at enrolment, for a cohort of injection drug users (IDUs) in Vancouver

Variable	All subjects $n = 1345$	HCV status; no. of subjects (and % across row*)		*p* value
		Positive $n = 1098$	Negative $n = 247$	
All subjects	1345	1098 (82)	247 (18)	
Sex				0.08
Male	889	714 (80)	175 (20)	
Female	456	384 (84)	72 (16)	
Median age (and range), yr	34 (15–58)	35 (16–58)	25 (15–56)	0.001
Ethnic background				0.001
White	808	666 (82)	142 (18)	
Aboriginal	338	306 (91)	32 (9)	
Other	199	126 (63)	73 (37)	
Education less than high school	242	189 (78)	53 (22)	0.12
Ever incarcerated				0.001
Yes	1019	882 (87)	137 (13)	
No	326	216 (66)	110 (34)	
Ever been paid for sex (women only; $n = 456$)				< 0.001
Yes	336	297 (88)	39 (12)	
No	120	87 (72)	33 (28)	
No. of lifetime sex partners				0.003
< 20	467	359 (77)	108 (23)	
≥ 20	878	739 (84)	139 (16)	
HIV status				0.001
Positive	288	275 (95)	13 (5)	
Negative	1057	823 (78)	234 (22)	
Median period of injecting (and range), yr	11 (0–42)	14 (0–42)	3 (0–38)	0.001
Ever borrowed or lent a used syringe				0.001
Yes	883	762 (86)	121 (14)	
No	462	336 (73)	126 (27)	
Ever attended a needle exchange program				0.001
Yes	1205	1017 (84)	188 (16)	
No	140	81 (58)	59 (42)	
Ever had methadone therapy				0.001
Yes	231	212 (92)	19 (8)	
No	1114	886 (80)	228 (20)	
Ever had any addiction therapy				0.001
Yes	754	644 (85)	110 (14)	
No	591	454 (77)	137 (23)	
Calendar year of enrolment				0.001
1996	920	802 (87)	118 (13)	
1997	203	150 (74)	53 (26)	
1998	120	77 (64)	43 (36)	
1999	102	69 (68)	33 (32)	

*Except where indicated otherwise.

HIV and HCV infection at baseline. However, the study documents interesting comparative trends in the rates of HIV and HCV seroincidence among IDUs. Although HIV incidence was high at study inception, it subsequently declined, as had been predicted through mathematical modelling.[26] In contrast, despite a prevalence of 81.6% at baseline, HCV incidence remained above 16 per 100 person-years over the 3-year period of observation. High rates of incidence for HCV are well documented among young and new IDUs,[15,27] such that 80% become infected within 4 years of initiating injection drug use.[28]

High rates of HCV transmission are explained by a combination of high risk of infection for each syringe-sharing contact and high infectivity throughout much of the natural history of an infection (and consequent high prevalence among syringe lenders), as well as the frequency of syringe-sharing contacts in a given community.[29] The infection rate following needlestick exposure to HCV appears to be at least an order of magnitude greater than that following similar exposure to HIV.[30]

Factors associated with HCV seroconversion in this study resemble those previously shown to predict HIV infection in the same cohort[2] and include frequent injection and use of cocaine either alone or combined with heroin as a speedball. Higher frequency of injection and more chaotic drug use have been associated with cocaine use in a number of cohort studies. Although borrowing used syringes is the most likely operative mechanism of infection and a widely reported predictor of HCV infection among IDUs,[13] socially desirable responses may explain why it was not a more significant direct measure of risk in this study. Measures of high frequency of injection may be a better, albeit surrogate, measure of this core risk behaviour. Conversely, other researchers have reported that practices such as sharing other injection paraphernalia (e.g., cookers, cotton or water) and "front-end loading" (syringe-mediated drug sharing) may contribute to transmission above and beyond that associated with simple syringe sharing.[14,20,31] This finding suggests that prevention messages aimed at IDUs must go beyond simply advising against sharing needles and should discourage sharing of any injection equipment.

The association of HCV seroincidence with female sex suggests a higher vulnerability to parenteral exposure, an important role for sexual exposure or both. Romanowski and associates[13] also reported associations between high prevalence of HCV infection and the sex trade, but these associations did not remain significant on multivariate analysis. Sexual transmission of HCV has been documented but appears relatively inefficient.[32–34] In studies of HCV transmission, associations with numbers of partners, condom use and commercial sex have been less consistently demonstrated in populations of IDUs than in other affected populations.[8,35]

We and others have previously reported an association between HIV infection and frequent attendance at needle exchange programs.[2,21,36] We now report a similar association for HCV infection, an association that may result from unmeasured confounders — factors promoting transmission that are common among those frequently attending needle exchange programs. However, such findings have also been interpreted as suggesting that needle exchange programs may actually promote HIV transmission.[37,38] It should be noted that a close analysis of the association between HIV and frequency of attendance at needle exchange programs for the Vancouver IDU cohort did not support a hypothesis of causality.[3]

High and increasing rates of HCV infection have been documented in Canadian prison populations.[39] Our study illustrates that IDUs who have been incarcerated are especially likely to be infected with HCV.

This study had several limitations. Because of high HCV prevalence at enrolment and limited follow-up to date, the statistical power to determine incidence and associated risk factors was low. Participants who were initially HCV seronegative returned for follow-up less frequently
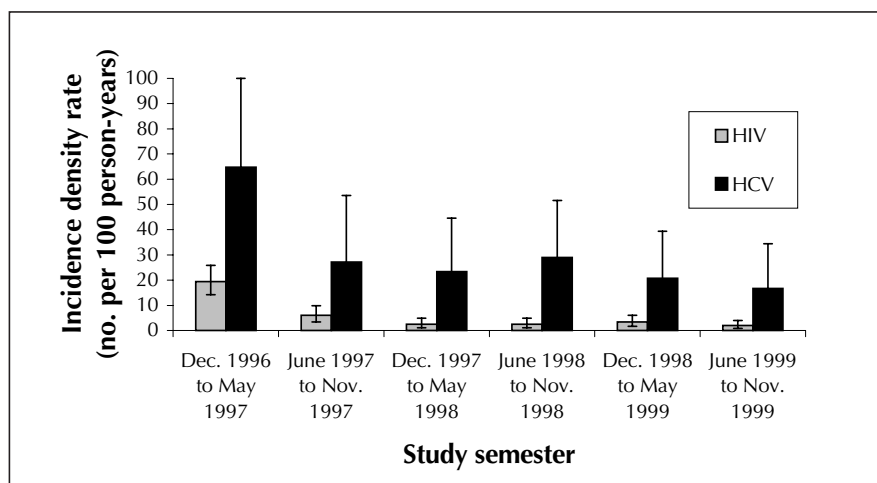

Fig. 1: Incidence density rate (and 95% confidence interval) for hepatitis C virus and HIV over 3 years of the Vancouver Injection Drug User Study.

Table 2: Factors associated with HCV seroconversion among IDUs who were HCV negative at baseline

| | | HCV status; no. of subjects (and % across row*) | | |
Variable	All subjects n = 1345	HCV seroconversion n = 62	HCV negative at follow-up n = 93	p value
All subjects	155	62 (40)	93 (60)	
Sex				0.03
Male	108	37 (34)	71 (66)	
Female	47	25 (53)	22 (47)	
Median age (and range), yr	28 (15-55)	29 (15–55)	27 (16–53)	0.83
Ethnic background				0.02
White	84	36 (43)	48 (57)	
Aboriginal	24	14 (58)	10 (42)	
Other	47	12 (26)	35 (74)	
Education less than high school	31	13 (42)	18 (58)	0.81
Unstable housing†‡	86	37 (43)	49 (57)	0.39
Incarceration‡	41	18 (44)	23 (56)	0.55
Involved in sex trade‡				0.001
Yes	16	13 (81)	3 (19)	
No	139	49 (35)	90 (65)	
No. of sex partners‡				0.04
< 3	114	40 (35)	74 (65)	
≥ 3	41	22 (54)	19 (46)	
HIV positive at baseline	5	1 (20)	4 (80)	0.65
HIV seroconversion				0.05
Yes	12	8 (67)	4 (33)	
No	143	54 (38)	89 (62)	
Median period of injecting (and range), yr	7	4 (0–38)	3 (0–26)	0.63
Borrowed syringes‡				0.04
Yes	41	22 (54)	19 (46)	
No	114	40 (35)	74 (65)	
Lent syringes‡				0.03
Yes	36	20 (56)	16 (44)	
No	119	42 (35)	77 (65)	
Frequent attendance at needle exchange program‡§				0.001
Yes	75	41 (55)	34 (45)	
No	80	21 (26)	59 (74)	
Drugs injected‡				
Heroin	98	44 (45)	54 (55)	0.06
Cocaine	84	42 (50)	42 (50)	0.006
Speedballs (cocaine plus heroin)	35	23 (66)	12 (34)	0.001
Frequent injection¶				0.001
Yes	84	46 (55)	38 (45)	
No	71	16 (22)	55 (77)	
Methadone therapy‡	16	4 (25)	12 (75)	0.20
Addiction therapy‡				0.007
Yes	21	14 (67)	7 (33)	
No	134	48 (36)	86 (64)	

*Except where indicated otherwise.

†Unstable housing defined as living primarily in a single-room occupancy hotel, boarding room, hostel, transition house, jail or on the street in the previous 6 months.

‡Behaviour in the previous 6 months.

§At least once per week.

¶At least once per day.

Table 3: Cox proportional hazards model of independent predictors of HCV seroconversion among IDUs

Variable	Univariate hazard ratio (and 95% CI)	Adjusted hazard ratio (and 95% CI)
Female sex	1.69 (1.02–2.80)	2.29 (1.35–3.89)
Use of cocaine or speedballs (or both)	3.60 (1.88–6.90)	2.42 (1.22–4.79)
Frequent injection*	3.54 (2.03–6.20)	2.02 (1.09–3.77)
Frequent attendance at needle exchange program†	3.69 (2.12–6.43)	2.56 (1.37–4.79)

*At least once per day.

†At least once per week

than did study subjects in general. It is plausible that some HCV-negative IDUs were not highly street entrenched (i.e., were not involved in a chronic and intractable way with the street scene) and were therefore less likely to return for a follow-up visit. Indeed, some of the participants who were negative for HCV at baseline were deported from Canada during the follow-up period. Also, the study instrument did not address the practices of tattooing and body piercing, which have been associated elsewhere with HCV infection.[35,40–42] Observations in this study were made over the course of a documented outbreak of HIV. This and the unique characteristics of the Vancouver injection drug use scene may limit the generalizability of the results.

HCV infection represents a major cause of morbidity and stands as a sensitive marker for activities that may transmit HIV parenterally. Because this and other studies indicate extreme pressure toward HCV transmission among seronegative IDUs, resulting from both high prevalence and high infectivity, it appears that the prevention efforts must be expanded yet further.

Mathematical models suggest that even in populations with a high prevalence of HCV infection, there is hope that a drop in syringe sharing will reduce the incidence of such infection.[43] However, such reductions have been hard to realize. Because of high transmissibility of HCV among those injecting frequently and using cocaine, we conclude that the harm reduction initiatives deployed in Vancouver during the study period proved insufficient to eliminate hepatitis C transmission in this population. In addition to promoting behavioural change and harm reduction among established users, researchers and prevention workers urgently need to focus on primary prevention of injection drug use, early intervention with and treatment of non-injection and injection drug users, and altering the social determinants that predispose people to engage in these activities.

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