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Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents

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SUMMARY. Despite the availability of effective therapy for hepatitis C virus (HCV) infection, there are little data on the uptake of treatment. We evaluated factors associated with HCV infection and the uptake of HCV treatment in a large community-based inner city cohort in Vancouver, Canada. The Community Health and Safety Evaluation is a cohort study of inner city residents recruited from January 2003 to June 2004. HIV and HCV status and information on prescriptions for HCV treatment were determined through linkage with provincial databases. HCV prevalence was calculated and factors associated with HCV infection were identified. HCV treatment uptake and incidence of HCV infection from January 2000 to December 2004 were expressed in terms of person-years of observation. Among 2913 individuals, HCV antibody testing was performed in 2118 and the HCV seroprevalence was 64.2% (1360 of 2118). In total, 1.1% of HCV antibody-positive individuals (15 of 1360) initiated treatment for HCV infection from January 2000 to December 2004 [0.28 cases per 100 person-years (95% CI, 0.15–0.46)]. Three of 15 (20.0%) treated individuals achieved a sustained virological response. During the same period, the incidence of HCV infection was 7.26 cases (95% CI, 5.72–8.80) per 100 person-years. Overall, the rate of new HCV seroconversions in this cohort in the study period was about 25 times the rate of HCV treatment uptake. There are extremely low rates of HCV treatment initiation and very limited effectiveness, despite a high prevalence of HCV infection in this large community-based cohort of inner city residents with access to universal healthcare.

Keywords: hepatitis C virus, injection drug use, public health, treatment, urban populations.

INTRODUCTION

Hepatitis C virus (HCV) infection constitutes a major public health burden, with a global prevalence of 1–2% [1]. Injection drug use is the predominant mode of HCV transmission in most developed nations, accounting for >50% of existing and >75% of new infections [2]. Individuals with chronic HCV infection are at increased risk of developing cirrhosis, hepatocellular carcinoma and end-stage liver disease [3]. Data suggest that morbidity, mortality and economic costs related to HCV will dramatically increase in the next 15–20 years [4].

Hepatitis C virus prevention efforts targeted towards injection drug users (IDUs) have been limited in effectiveness and the rate of new infections remains high [5]. Decreases in the future HCV prevalence and disease burden can only be accomplished by reducing transmission among high-risk persons and expanding treatment access for those at the greatest risk of disease progression [6].

Current HCV treatment regimens achieve an overall viral clearance rate of approximately 55%, although a number of viral and host factors influence individual treatment success [7]. While historically excluded from treatment, guidelines from the United States in 2002 [8] and Canada in 2004 [9] encourage the inclusion of IDUs in HCV treatment on a case by case basis, given studies demonstrating that HCV treatment in IDUs is effective, when delivered within comprehensive programs [10–18]. As data regarding HCV treatment

Abbreviations: SVR, sustained virological response; HAV, hepatitis A virus; HCV, hepatitis C virus; IDUs, injection drug users.

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coverage in illicit drug users is sparse, we estimated the uptake of treatment in a large community-based inner city cohort in Vancouver, consisting mainly of illicit drug users.

METHODS

Study participants

The Community Health and Safety Evaluation cohort was designed to measure the uptake of health services in the Downtown Eastside of Vancouver, Canada. In an effort to collect a representative sample of residents in this community, venues for recruitment were selected based on census track data from a total population of approximately 16 000 people. Individuals were informed of the project through community-based agency staff, postings in local agencies, door-to-door initiatives, and through word of mouth. A random selection of single room occupancy hotels, social housing units, and health facilities were sampled. Surveys were administered in a variety of settings, including ten community-based agencies, two community health clinics, the Life Skills Centre, the Health Contact Centre, 117 single room occupancy hotels and social housing buildings, and a large space that operates as a needle exchange. By using such a wide range of recruitment venues and strategies the final cohort had the best chance to capture a group of individuals that were representative of this community. All those included in the study had to have their names and personal health numbers verified through the British Columbia Ministry of Health database, ensuring that the participants all had the potential to be linked successfully. Between January 2003 and June 2004, 2913 participants completed a one-time interviewer administered survey and consent to have specific laboratory and treatment records accessed through data linkages using their names and/or personal health card numbers. Study participants received CDN$10 to complete the survey and participants were then followed retrospectively and prospectively through health-related database linkages. Information collected for this study included HCV and HIV serologic testing performed at the British Columbia Centre for Disease Control and the University of British Columbia Virology Department (laboratories responsible for all Provincial virology testing). HCV treatment prescription data was obtained from the British Columbia Ministry of Health PharmaCare database that captures all HCV treatment administered through publicly funded sources. The University of British Columbia/Providence Health Care Research Ethics Board approved this study.

MATERIALS AND METHODS

Laboratory testing

Linked serologic and RNA testing results for HIV and HCV infections were available from January 1991 to December 2004. HCV antibody testing was performed using second- or third-generation enzyme-linked immunosorbent assays including Organon Teknika (UBI) v2.0, v2.1, v4.0 (Organon Teknika, Durham, NC, USA), Ortho EcI (Ortho, Toronto, ON, Canada) and Abbott AxSYM HCV 3.0 (Abbott Diagnostics, Chicago, IL, USA). HCV RNA testing was performed by the qualitative COBAS AMPLICOR HCV Test v2.0 (Roche Diagnostic Systems, Mississauga, Canada).

HCV treatment

Hepatitis C virus treatment was determined by prescriptions for either interferon or peginterferon alpha-2b with ribavirin from January 2000 to December 2004. The index date used for calculating HCV treatment uptake was either (i) 1st January 2000, for individuals who were HCV antibody-positive at this time or; (ii) the date of the first antibody-positive test for individuals with HCV seroconversion after this time. Follow-up was calculated from the index date to either the date of treatment initiation, date of death, or 31st December 2004, whichever occurred first. Sustained virological response (SVR) was evaluated by undetectable HCV RNA testing ≥24 weeks following HCV treatment.

HCV incidence

Hepatitis C virus incidence was determined from HCV antibody testing from January 2000 to December 2004. Individuals with a negative HCV antibody test followed by a positive test were identified as HCV seroconverters. The index date for calculating HCV incidence was either (i) 1st January 2000 for those who were HCV antibody negative at this time or; (ii) the date of the first HCV antibody negative test for individuals with HCV seroconversion after this time. Follow-up for individuals was calculated from the index date to either the estimated date of infection, the date of last antibody negative test, or the date of death. The estimated date of infection was calculated by taking the midpoint between the patient's last antibody negative test and first antibody-positive test date. Individuals with an estimated date of infection prior to the study period (January 1, 2000) were not identified as seroconverters.

Statistical analysis

Variables examined in statistical analyses included age, sex, ethnicity, housing status, income assistance, education, perceived health access, followed by a regular doctor, vaccinations for hepatitis A and B, HIV status, previous HIV treatment, methadone maintenance treatment, recent incarceration, alcohol use and recent noninjection (crack, cannabis, opioids, methamphetamine and benzodiazepines) and injection drug use. Unstable housing was defined as homeless or staying in a temporary shelter or residing in a single occupancy room. Alcohol use was evaluated as

'frequent use' (everyday/most days), or 'nonfrequent use or no use' (<2–3 times/week or less). Recent injection and noninjection drug use (in the previous 6 months) were evaluated as any drug use *vs* none. Vaccination information was collected by self-report. Factors associated with HCV antibody testing (overall cohort), HCV antibody-positive status (among individuals who received HCV antibody testing) and treatment for HCV infection (among HCV antibody-positive individuals) were then assessed. All univariate comparisons were made using χ^2 or Fisher's exact test, as appropriate. Multiple logistic regression models were fit comprised of all variables and subsequently reduced using backwards elimination. The rate of HCV seroconversion and treatment uptake was computed using person-years of observation. Statistically significant differences were assessed at $P < 0.05$; *P*-values are two-sided.

RESULTS

Among 2913 individuals, HCV antibody testing was performed in 2118 (72.7%). The baseline cohort characteristics stratified by HCV testing status are shown in Table 1. Individuals that received testing for HCV antibodies were more often older, female, of Aboriginal ethnicity, were recently receiving income assistance, had recently received methadone maintenance treatment, had a regular doctor, had received vaccinations for hepatitis A and hepatitis B, had recently been to jail, were HIV infected and had recently used noninjection and injecting illicit drugs (Table 1).

Overall, the HCV prevalence was 64.2% (1360/2118) among those where testing was available and the characteristics of these individuals are shown in Table 2. Among HCV antibody-positive individuals, 83% reported usually or

Table 1 Characteristics of individuals overall and among those having and not having received testing for HCV antibodies in a large, community-based cohort of inner city residents in Vancouver

Characteristics	Overall (*n* = 2913) *n* (%)	HCV antibody testing (*n* = 2118) *n* (%)	No HCV antibody testing (*n* = 795) *n* (%)	OR	95% CI	*P*-value
Mean age (SD)	42.5 (10.1)	41.9 (9.1)	44.1 (12.0)	–	–	<0.001
Age						
<35	636 (22)	470 (22)	166 (21)	1.00	–	–
35–39	535 (18)	417 (20)	118 (15)	0.80	0.61–1.05	0.116
40–44	621 (21)	467 (22)	154 (19)	0.93	0.72–1.20	0.605
45–49	504 (17)	379 (18)	125 (16)	0.93	0.71–1.22	0.633
>50	613 (21)	381 (18)	232 (29)	1.72	1.36–2.19	<0.001
Male sex	2068 (71)	1460 (69)	608 (77)	0.68	1.21–1.77	<0.001
Aboriginal ethnicity	895 (31)	675 (32)	220 (28)	1.22	1.02–1.46	0.032
Unstable housing	1801 (62)	1299 (61)	502 (63)	0.92	0.78–1.10	0.387
Education (≥grade 10)	2020 (69)	1465 (69)	555 (70)	0.97	0.82–1.16	0.798
Receiving income assistance	2310 (79)	1746 (82)	564 (71)	1.92	1.59–2.32	<0.001
Methadone treatment (in the previous 6 months)	561 (19)	507 (24)	54 (7)	4.32	3.22–5.79	<0.001
Usually/always has health access	2415 (83)	1762 (83)	653 (82)	1.08	0.87–1.33	0.537
Have a regular doctor	1928 (66)	1460 (69)	468 (59)	1.55	1.31–1.84	<0.001
Hepatitis A virus vaccination	1821 (63)	1408 (67)	413 (52)	1.83	1.55–2.17	<0.001
Hepatitis B virus vaccination	1808 (62)	1402 (66)	406 (51)	1.88	1.59–2.21	<0.001
Jail time (in previous 6 months)	610 (21)	474 (22)	136 (17)	1.40	1.13–1.73	0.002
HIV infection	324 (11)	300 (14)	24 (3)	5.30	3.47–8.10	<0.001
Noninjection illicit drug use (in previous 6 months)	2262 (78)	1725 (81)	537 (68)	2.11	1.75–2.54	<0.001
Heroin	154 (5)	121 (6)	33 (4)	1.40	0.94–2.08	0.113
Crack	1697 (58)	1345 (64)	352 (44)	2.19	1.86–2.58	<0.001
Injection drug use (in previous 6 months)	1114 (38)	918 (43)	196 (25)	2.34	1.95–2.81	<0.001
Injection Heroin	640 (22)	534 (25)	106 (13)	2.19	1.75–2.75	<0.001
Injection cocaine	891 (31)	743 (35)	148 (19)	2.36	1.94–2.88	<0.001

Table 2 Factors associated with HCV antibody-positive status among individuals having receiving HCV antibody testing in a large, community-based cohort of inner city residents in Vancouver

Characteristic	HCV antibody positive (n = 1360) n (%)	HCV antibody negative (n = 758) n (%)	OR	95% CI	P-value
Mean age (SD)	42.1 (8.2)	41.5 (10.6)	–	–	0.218
Age					
<35	263 (19)	207 (27)	1.00	–	–
35–39	281 (21)	136 (18)	0.61	0.47–0.81	<0.001
40–44	327 (24)	140 (18)	0.54	0.42–0.71	<0.001
45–49	271 (20)	108 (14)	0.51	0.38–0.68	<0.001
>50	216 (16)	165 (22)	0.97	0.74–1.28	0.835
Male sex	914 (67)	546 (72)	0.80	0.65–0.97	0.024
Aboriginal ethnicity	448 (33)	227 (30)	1.15	0.95–1.39	0.171
Unstable housing	873 (64)	426 (56)	1.40	1.17–1.68	<0.001
Methadone treatment (in the previous 6 months)	471 (35)	36 (5)	10.63	7.47–15.12	<0.001
Usually/always has health access	1133 (83)	629 (83)	1.02	0.81–1.30	0.895
Have a regular doctor	973 (72)	487 (64)	1.40	1.16–1.69	<0.001
Hepatitis A virus vaccination	966 (71)	442 (58)	1.75	1.46–2.11	<0.001
Hepatitis B virus vaccination	947 (70)	455 (60)	1.53	1.27–1.84	<0.001
Jail time (in previous 6 months)	336 (25)	138 (18)	1.47	1.18–1.84	<0.001
HIV infection	281 (21)	19 (3)	10.13	6.31–16.27	<0.001
HIV treatment	171 (13)	13 (2)	8.24	4.65–14.59	<0.001
Noninjection illicit drug use (in previous 6 months)	1187 (87)	538 (71)	2.81	2.24–3.51	<0.001
Heroin	79 (6)	42 (6)	1.05	0.72–1.55	0.875
Crack	979 (72)	366 (48)	2.75	2.29–3.31	<0.001
Injection drug use (in previous 6 months)	805 (59)	113 (15)	8.28	6.60–10.39	<0.001
Injection Heroin	461 (34)	73 (10)	4.81	3.69–6.28	<0.001
Injection cocaine	663 (49)	80 (11)	8.06	6.25–10.40	<0.001

always having access to health services, 72% reported having a regular doctor and 71 and 70% reported having been vaccinated for hepatitis A and hepatitis B viruses, respectively. The univariate analysis of factors associated with prevalent HCV infection is shown in Table 2. Following multiple logistic regression analysis, the factors independently associated with HCV infection were injection drug use, noninjection drug use, HIV infection, methadone maintenance therapy, hepatitis A vaccination, Aboriginal ethnicity, older age and unstable housing (Table 3).

Table 3 Multiple logistic regression of factors associated with HCV antibody-positive status in a large, community-based cohort of inner city residents in Vancouver

Characteristics	AOR	95% CI	P-value
Injection drug use in the previous 6 months (*vs* none)	6.32	4.89–8.17	<0.001
HIV infection (*vs* no)	6.61	3.52–12.42	<0.001
Methadone maintenance therapy in the previous 6 months (*vs* none)	6.39	4.36–9.37	<0.001
Noninjection drug use in the previous 6 months (*vs* none)	1.55	1.18–2.04	0.002
Hepatitis A virus vaccination (*vs* none)	1.65	1.32–2.07	< 0.001
Aboriginal ethnicity (*vs* other)	1.58	1.25–2.00	< 0.001
Age per 10 year increase	1.44	1.28–1.63	< 0.001
Unstable housing	1.26	1.00–1.57	0.047

AOR, adjusted odds ratio; CI, confidence interval.

Table 4 HCV treatment uptake per 100 person-years by year

	Number of individuals with HCV treatment	Person-years	Incidence of treatment uptake (per 100 person-years)	95% CI
Year				
2000	2	876	0.23	0.03–0.82
2001	4	978	0.41	0.11–1.05
2002	1	1092	0.09	0.00–0.51
2003	2	1199	0.17	0.02–0.60
2004	6	1274	0.47	0.17–1.02
Overall (2000–2004)	15	5420	0.28	0.15–0.46

Among 1360 HCV antibody-positive individuals, 15 (1.1%) initiated HCV treatment resulting in an overall treatment uptake of 0.28 cases per 100 person-years (95% CI, 0.15–0.46, Table 4). As shown in Table 4, the uptake of HCV treatment remained constant between 2000 and 2004. In a univariate analysis, those receiving HCV treatment were more likely to be male ($P = 0.004$) and less likely to be of Aboriginal ethnicity ($P = 0.048$), and be current crack users ($P = 0.036$). Eight (53%) and seven (47%) received treatment with interferon alpha-2b or pegylated interferon alpha-2b with ribavirin, respectively. Among those initiating treatment ($n = 15$), treatment was completed in 4 (27%). An SVR was achieved in 3 of 15 initiating treatment (20%), leading to an SVR in only 3 of 1360 HCV antibody-positive individuals (0.2%).

Between January 2000 and December 2004, 85 HCV seroconversions were observed during a total of 1171 person-years of follow-up, yielding an overall incidence of 7.26 cases per 100 person-years (95% CI 5.72–8.80). Among those with recent injection drug use, 65 HCV seroconversions were observed during a total of 265 person-years of follow-up, for a rate of 24.54 cases per 100 person-years (95% CI 18.58–30.51). Overall, the rate of new HCV seroconversions in this cohort in the study period was about 25 times the rate of HCV treatment uptake.

DISCUSSION

We have documented a high prevalence of HCV infection, but extremely low rates of HCV treatment uptake and response in this large community-based cohort of inner city residents in Vancouver. This is despite a high proportion reporting access to health services in a community with universal healthcare, including free treatment for HCV infection among individuals with low income.

The factors associated with HCV infection identified in this study are well documented [5]. The strong association of noninjection and injection drug use, Aboriginal ethnicity, unstable housing and HIV infection with HCV infection is not surprising, given data demonstrating that these risk factors are associated with HCV [19–23]. The association with methadone maintenance therapy and HCV may be explained by the circumstance that higher risk individuals are likely to be offered methadone maintenance therapy following HCV infection [5,19]. The association between age and HCV status is also not surprising, given the cumulative exposure which may occur with a greater number of years injecting [22,23]. Lastly, the association with hepatitis A virus (HAV) vaccination was likely the result of an ongoing HAV infection vaccination program in the community specifically targeting HCV infected individuals.

Moreover, the low uptake of HCV treatment in Vancouver is consistent with reports from similar cohorts of illicit drug users in the United States and Australia, where only 1–6% have received HCV treatment [24–27]. Although this low observed HCV treatment uptake may not be limited to illicit drug users. In a study from Europe, it was estimated that among 21 countries in the WHO European region, only 1–16% of the overall population estimated to be infected with HCV had received treatment to date with pegylated interferon-based therapy [28]. However, with appropriate programs in place, higher proportions of illicit drug users can be engaged in care. Data from a multidisciplinary clinic providing HCV education, care and peer-support in Vancouver demonstrated that 26% of HCV infected illicit drug users referred to a weekly HCV support group initiated treatment for HCV infection, with two-thirds achieving an end of treatment response [14]. Although the lower uptake of HCV treatment in the community is likely influenced by the fact that HCV is not a priority for illicit drug users, large proportions of HCV-infected illicit drug users (>70%) are interested in receiving HCV treatment [29]. Factors for not seeking treatment include a lack of information, the absence of symptoms and the perceived side effects of treatment [29]. Second, many illicit drug users are deemed ineligible for HCV treatment based on concerns of adherence, medical co-morbidities, treatment side effects, perceived patient unwillingness to receive treatment and re-infection risk [25]. However, when HCV care is delivered within appropriate multidisciplinary care models, treatment outcomes can

resemble those obtained in stable and nonmarginalized community samples [10–13]. Treatment response rates observed in this study, however, were lower than those obtained in other studies with similar populations [10–13]. This can be attributed to the fact that three-quarters of the patients discontinued HCV treatment early. Higher success rates in other studies are likely attributed to the incorporation of strategies to address side-effects and illicit drug use and the delivery of HCV treatment within multidisciplinary models [10–16].

Information on factors associated with response to HCV treatment among IDUs is growing. It is clear that drug abstinence in the six months preceding treatment provides little predictive value in determining who will respond to therapy [10,12,30]. Thus, as recommended by a number of guidelines [8,9,31], the decision to treat HCV infection in IDUs must be made on a case-by-case basis and injection drug use should not be an absolute contraindication for therapy. Factors such as housing status, social support and other medical co-morbidities must also be considered as part of the overall decision of whether to initiate treatment. In fact, adherence to pre-treatment visits may provide a good proxy of engagement in HCV care [32] and response to HCV therapy [11]. It is becoming increasingly clear that frequent, but not occasional, drug use during therapy may impact response [10,12,30]. Lastly, it is encouraging that among IDUs successfully treated for chronic HCV infection, re-infection rates have remained low, with reported incidence rates of 1–4% [17,33,34]. This may be attributed to reduced risk behaviours resulting from HCV risk reduction education prior to or during treatment. As we move forward, improved education of patients about the natural history and treatment of HCV, appropriate patient selection, strategies to address potential side effects, and the delivery of care within multi-disciplinary models may help to identify illicit drug users most motivated to receive treatment, while also increasing the proportion completing and responding to therapy [10–18].

There are a number of limitations to this study. First, testing for HCV antibodies was not completed on a systematic basis, with assays being ordered as clinically indicated. Missing HCV antibody testing information may have led to an underestimation of the number of HCV antibody-positive individuals, thereby overestimating HCV treatment uptake. Second, not all individuals received HCV RNA testing. Given that ~25% of individuals will spontaneously clear HCV, our estimates of the overall treatment uptake and response to therapy may be underestimated. However, given that few individuals were treated, we do not believe this has a significant effect on the estimates. Third, clinical information was limited through the survey instrument and some participants may have had other contra-indications to treatment that were not collected. Fourth, many of the variables were based on patient self-report and may be prone to socially desirable responses. Fifth, we are assuming that no individuals received treatment through private coverage or other settings not covered by our data. We have no reason to believe that this would be occurring among this cohort. Missing HCV treatment data may have led to an underestimation of the overall treatment uptake, although we do not believe this had a significant impact.

In developed nations, HCV infection is overwhelmingly caused by injection drug use. Our study indicates that the uptake of HCV treatment among illicit drug users is unacceptably low. Further, this is in the absence of any financial restrictions which may preclude HCV treatment in other settings, given that HCV treatment is freely available for individuals with low income. It is clear that the passive recruitment approach for engaging illicit drug users in HCV care is insufficient. To make progress, next critical steps need to include efforts towards improved awareness and active referral of illicit drug users with HCV infection to multidisciplinary settings for HCV care. For these programs, strategies will be required to (i) improve patient education about HCV infection; (ii) identify those most motivated to receive treatment; and (iii) improve the proportion completing and responding to therapy. Lastly, for policy makers, it will be important to focus on HCV prevention efforts among high-risk individuals (e.g. young IDUs), HCV education for patients and physicians and HCV treatment for those at greatest risk of disease progression (e.g. HIV co-infected individuals and older IDUs). A coordinated approach will be required if we are to slow down the current HCV epidemic among IDUs and reduce the future burden of HCV infection.

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