Characterizing risk behaviour and reinfection rates for successful programs to engage core transmitters in HCV elimination (C-RESPECT)

Brian Conway MD1, Dan Smyth MD2, Réjean Thomas MD3, Alex Wong MD4, Giada Sebastiani MD5, Curtis Cooper MD6, Hemant Shah MD7, Ritesh Kumar PhD8, Gretty Deutsch MD9, Ted Watson PhD9, for the C-RESPECT Investigators

ABSTRACT

BACKGROUND: Development of robust treatment programs among core transmitters (CT) of hepatitis C virus (HCV) are needed, including strategies to address reinfection risk. The aim of this study was to describe the effectiveness of direct-acting antiviral (DAA) treatment in CT versus non-CT populations and assess reinfection rates after successful treatment. METHODS: Characterizing Risk Behaviour and Reinfection Rates for Successful Programs to Engage Core Transmitters in HCV Elimination (C-RESPECT) was a prospective, observational study of HCV-infected Canadian adult patients (genotypes 1, 3, and 4) treated with DAAs between 2017 and 2020. RESULTS: The full analysis set included 429 participants (259 CT, 170 non-CT). Key differences were observed in baseline profiles: CT participants were younger (mean 42.3 [SD 11.2] y versus 55.0 [SD 11.1] y, respectively) and reported higher rates of social assistance (35.7% versus 14.8%), smoking (83.7% versus 52.4%), low socioeconomic status (yearly income <$15,000: 69.6% versus 43.9%), illicit drug use (83.7% versus 34.3%), and previous incarcerations (62.7% versus 36.9%). DAA treatment adherence was similar; 93.5% versus 98.3% of CT versus non-CT participants completed the assigned treatment duration. Cure rates (sustained virologic response) were comparable, ranging from 94.9% to 98.1%. All reinfections were among CT participants, with a rate of 13.8/100 person-years (95% CI 9.2–20.8) with mean time to reinfection of 24.6 (SD 0.6) months; CONCLUSIONS: CT and non-CT participants respond equally well to DAA treatment; however, with some reinfections among CT participants. Innovative multidisciplinary programs must be developed to mitigate this risk in this key population.

KEYWORDS: Canada; core transmitter; cure; direct-acting antivirals; HCV; hepatitis C virus; observational; real-world evidence; reinfection; sustained virologic response

Author Affiliation

1Vancouver Infectious Diseases Centre, Vancouver, British Columbia, Canada; 2Centre for Research, Education and Clinical Care of At-Risk Populations (RECAP), Moncton, New Brunswick, Canada; 3Clinique L’Actuel, Montreal, Quebec, Canada; 4Saskatchewan Health Authority, Regina, Saskatchewan, Canada; 5McGill University Health Centre, Montreal, Quebec, Canada; 6Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; 7University Health Network, Toronto, Ontario, Canada; 8Merck & Co., Inc., Kenilworth, New Jersey, USA; 9Merck Canada Inc., Kirkland, Quebec, Canada

Correspondence: Brian Conway, Vancouver Infectious Diseases Centre, 201-1200 Burrard Street, Vancouver, British Columbia V6Z 2C7 Canada. Telephone: 604-642-6429. E-mail: brian.conway@vidc.ca
INTRODUCTION

The widespread availability of safe, all-oral, highly effective hepatitis C virus (HCV) therapies has resulted in a reduction in incidence rates in the general population (1). However, a disproportionately higher incidence of HCV remains among high-risk populations such as people who inject drugs (PWID) and men who have sex with men (MSM). Of the approximately 8,000 new HCV cases reported in Canada every year, 83% are estimated to occur in the population of PWID (2), with prevalence rates reported to be 69% in this group (3–6). For the population of MSM, prevalence rates range from 1% to 7% for noninjection drugs users to 25% to 50% reported for those with a history of injecting drugs (7). It has also been reported that HIV-positive MSM have a 4.1 times higher risk for acquiring HCV (8). Moreover, among PWID, MSM have been found to be 1.3 times more likely to be HCV seropositive than men who have sex with women (7).

Acting as core transmitters (CTs) of HCV, PWID and MSM with high-risk behaviours constitute an important viral reservoir. The elimination of HCV as a public health concern is therefore dependent on the control of HCV transmission in these sub-populations. Previous Canadian treatment guidelines have excluded several participant groups from HCV treatment algorithms on the basis of concerns related to poor adherence, exacerbations of previous substance abuse, psychiatric comorbid conditions, and increased risk of reinfection (9). Instead, efforts have focused on the implementation of harm reduction programs that aim to prevent HCV transmission among CT participants primarily by providing drug substitution (opioid agonist therapy) and sterile injecting equipment through needle exchange programs and supervised injection sites (9,10). Evidence has shown that uptake of harm reduction programs reduces the risk of HCV transmission (5,10,11). However, a substantial reduction in HCV prevalence among PWID cannot be achieved by these programs alone, and mathematical modelling studies have suggested that large-scale HCV treatment among PWID (and other CTs) will be required and could be beneficial and cost-effective (12,13).

The cost effectiveness of successful HCV treatment relates prevention of long-term sequelae to the reversal of fibrosis, with reduced rates of decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation (14–17).

In this context, we undertook the current study to compare the effectiveness of current HCV treatment programs for CT and non-CT participants and to specifically examine one long-term outcome that may limit the effectiveness of such programs—namely, the risk of HCV reinfection after successful treatment has been achieved.

METHODS

Study setting and design

This was a prospective, observational study of Canadian participants with HCV treated with currently recommended direct-acting antiviral (DAA) therapies directed against HCV. The duration of data collection was 3 years (2017–2020) with active enrolment during the first 2 years. Participants were followed from DAA treatment initiation to the end of treatment (EOT) and were assessed for cure 3 months post-EOT (for SVR at 12 wk post-treatment, or SVR12, as assessed per standard of care), 6 months post-EOT (for SVR at 24 wk post-treatment, or SVR24, if part of routine care at participating sites), and every 6 months thereafter if cure was achieved. Participants were followed until virologic failure or the end of the study, up to a maximum of 3 years. Participants with reinfection were followed for a minimum of 6 months for assessment of spontaneous clearance. The decision to treat with a DAA for the management of HCV infection was established before and independent of study enrolment on the basis of the treating physician’s judgment. Duration of treatment was also at the discretion of the treating physician according to HCV genotype, presenting clinical characteristics, and relevant Canadian guidelines and recommendations.

All participants provided informed consent before their participation in the study, and the study received ethics approval from research ethics boards as per institutional or clinical requirements (Health Research Ethics Board, Nova Scotia Health Authority Research Ethics Board, Ottawa Health Science Network Research Ethics Board, Le Comité d’éthique de la recherche de CHU de Québec-Université Laval, Hamilton Integrated Research Ethics Board; the Conjoint Health Research Ethics Board, University Health Network Research Ethics Board, Western University Health Sciences Research Ethics Board, Horizon Health Network Research Ethics Board, Regina Qu’Appelle Health
Region Research Ethics Board, Research Ethics Board of the Research Institute of McGill University Health Centre, University of British Columbia Research Ethics Board; Institutional Research Board [IRB] Services, Advarra IRB, and Health Research Ethics Board of Alberta).

**Study population**
The study population consisted of adult (≥18 y) DAA-treated participants with a diagnosis of chronic HCV infection (detectable HCV RNA for ≥6 mo) and confirmed genotypes 1, 3, or 4. Participants were excluded if they were enrolled in a clinical trial of an investigational treatment that was not approved by Health Canada, they were unable or unwilling to provide informed consent for participation in the study, the treating physician felt that study participation might interfere with their overall care or well-being, or they were women who were breastfeeding or pregnant. HIV coinfection did not preclude participation in the study. Participants were stratified into two distinct subgroups, namely CT, which included PWID and MSM participants, and non-CT. The terminology adopted to characterize CTs into PWID and MSM groups is purely epidemiological; no stigmatism or reductionism is meant, and we acknowledge the unique and nuanced experiences, preferences, and identities of all individuals who participated.

**Outcome measures**
The main outcome measure was the incidence rate of HCV reinfection in the post-treatment observation period, defined by detectable HCV RNA after a cure had been documented. The difference between relapse and reinfection was determined by genetic testing, when available; in the absence of genetic testing, reinfections were determined by investigator opinion. The consideration of the observation period before SVR was based on the results of the C-EDGE CO-STAR study, which demonstrated that many reinfections may occur between EOT and SVR12 (18).

Secondary outcomes included achievement of cure (undetectable HCV RNA ≥12 wk after treatment completion), treatment adherence, treatment failure (defined as detectable HCV RNA at EOT or afterward, without a cure having been achieved), treatment discontinuation, participation in a harm reduction program, risk behaviour profile, and substance use.

**Sample size**
Given the descriptive nature of the study, sample size calculations were based on the precision of the estimate for the primary outcome measure, specifically the rate of HCV reinfection. The reinfection rate among CT participants was previously reported to range between 4.3% and 9.2% (19–22). Taking the midpoint between these two values, we assumed a reinfection rate of 7% in the CT group. To have a 95% confidence interval (CI) width of ±3%, a total of 278 CT participants were required for enrolment. For non-CT participants, we assumed a reinfection rate of 1%. With 278 participants per group, the study had 95% power to detect this difference (7% versus 1%) as statistically significant with an α level of 0.05.

**Statistical methods**
Analyses were based on the full analysis set (FAS), defined as all participants who received at least one dose of DAA treatment. The per protocol (PP) population, a subset of the FAS, defined as all participants who met the inclusion criteria and completed their DAA treatment regimen, was used in a secondary analysis of the effectiveness outcome measures, as well as the population in which treatment failure was assessed. The following participants were also included in the PP population and classified as treatment failures: (1) participants who discontinued before study completion with the reason reported as “standard of care”; (2) participants with documented virologic failure with genotypes 1, 3, or 4 during treatment or follow-up; and (3) participants discontinued from the study for any reason.

Demographic and baseline clinical characteristics were tabulated using summary statistics, including mean and standard deviation for continuous variables and number and percentage for discrete variables among patients with available (non-missing) data.

To assess reinfection and treatment failure, the incidence density rate (IDR), defined as the number of reinfections per 100 person-years (PYs) of follow-up, along with the 95% CI, was calculated. For reinfection, IDR was also calculated by post-EOT period (0–3, 3–6, and 6–12 mo post-EOT). Time to reinfection was assessed with the Kaplan–Meier estimator of the survival function and was compared between CT and non-CT participants using the Breslow–Day log-rank test.
Treatment failure and achievement of cure (SVR12, SVR24, SVR12/24) were described with the proportion of participants, along with the 95% CI calculated using the Clopper–Pearson method; between-groups comparisons were conducted using a binomial test for proportions.

Adherence to treatment, participation in a harm reduction program, engagement in risk behaviour, substance use, and by-visit rates of treatment failure (EOT, SVR12, SVR24, and every 6 mo post-SVR) were assessed in patients with available data, using descriptive summary statistics.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Participant disposition
Among 455 screened participants, 429 were considered eligible for study enrolment and were included in the FAS, with 259 participants in the CT group and 170 participants in the non-CT group. The PP population consisted of 291 participants, 172 in the CT group and 119 in the non-CT group. More than half of the CT (54.8%) and non-CT (62.9%) participants completed the study. The most common reason for study discontinuation for both CT (26.6%) and non-CT (24.1%) participants was loss to follow-up.

Demographic and participant profiles and medical history
Participant profiles at baseline differed between participant groups and are summarized in Table 1. CT participants were younger than non-CT participants (mean 42.3 [SD 11.2] y versus 55.0 [SD 11.1] y, respectively) and had lower BMI (mean 25.8 [SD 6.1] kg/m² versus 27.1 [SD 8.0] kg/m², respectively). Ethnicity differed between CT and non-CT groups, with key differences noted for the proportion of Caucasian (74.1% versus 82.8%, respectively) and Indigenous–First Nations or Métis participants (21.2% versus 7.7%). CT participants were also more likely to be on social assistance (35.7% versus 14.8%) and medical disability (27.5% versus 16.0%) than non-CT participants. Of CT participants, 83.7% smoked tobacco compared with 52.4% of non-CT participants. Illicit drug use was documented among 83.7% of CT participants. Among non-CT participants, 34.3% had a remote history of illicit drug use but were included in the non-CT cohort by the site investigators. Education

| Table 1: Demographic and clinical characteristics at baseline |
|-------------------------------------------------------------|
| Characteristic         | CT participants (n = 259) | Non-CT participants (n = 170) |
|------------------------|---------------------------|-------------------------------|
| Age, y, mean (SD)      | 42.3 (11.2)               | 55.0 (11.1)                   |
| BMI, kg/m², mean (SD)  | 25.8 (6.1)                | 27.1 (8.0)                    |
| Gender, male           | 167 (64.5)                | 122 (71.8)                    |
| Ethnicity              |                           |                               |
| Caucasian              | 192 (74.1)                | 140 (82.8)                    |
| Indigenous, First Nations or Métis | 55 (21.2) | 13 (7.7) |
| African American       | 2 (0.8)                   | 1 (0.6)                       |
| Asian                  | 1 (0.4)                   | 8 (4.7)                       |
| Other                  | 9 (3.5)                   | 7 (4.1)                       |
| Missing                | 0                         | 1                             |
| Current employment status |                         |                               |
| Employed               | 33 (12.8)                 | 54 (31.9)                     |
| Unemployed             | 51 (19.8)                 | 37 (21.9)                     |
| In school              | 5 (1.9)                   | 2 (1.2)                       |
| Social assistance      | 92 (35.7)                 | 25 (14.8)                     |
| Medical disability     | 71 (27.5)                 | 27 (16.0)                     |
| Other                  | 6 (2.3)                   | 24 (14.2)                     |
| Missing                | 1                         | 1                             |
| Socioeconomic status, $/y |                     |                               |
| ≤15,000                | 172 (69.6)                | 72 (43.9)                     |
| 15,001–25,000          | 38 (15.4)                 | 18 (11.0)                     |
| 25,001–50,000          | 14 (5.7)                  | 27 (16.5)                     |
| 50,001–75,000          | 3 (1.2)                   | 15 (9.1)                      |
| 75,001–100,000         | 1 (0.4)                   | 11 (6.7)                      |
| ≥100,001               | 0                         | 4 (2.4)                       |
| Unknown                | 19 (7.7)                  | 17 (10.4)                     |
| Missing                | 12                        | 6                             |
| Alcohol use            |                           |                               |
| Yes                    | 111 (43.0)                | 77 (45.6)                     |
| No                     | 147 (57.0)                | 92 (54.4)                     |
| Missing                | 1                         | 1                             |
| Smoking (tobacco)      |                           |                               |
| Yes                    | 216 (83.7)                | 86 (52.4)                     |
| No                     | 42 (16.3)                 | 78 (47.6)                     |
| Missing                | 1                         | 6                             |
| Medical insurance coverage |                     |                               |
| Private insurer        | 11 (4.2)                  | 23 (13.6)                     |
| Provincial Insurance   | 208 (80.3)                | 133 (78.7)                    |

(Continued)
### Table 1

| Characteristic                      | Treatment group, no. (%) |  |
|-------------------------------------|--------------------------|---|
|                                      | **CT participants** (n = 259) | **Non-CT participants** (n = 170) |
| NIHB                                | 30 (11.6)                | 7 (4.1)                      |
| Compassionate drug supply           | 9 (3.5)                  | 2 (1.2)                      |
| Other                               | 1 (0.4)                  | 4 (2.4)                      |
| Missing                              | 0                       | 1                            |
| **Education level**                 |                          |                              |
| Did not complete high school        | 104 (40.9)               | 53 (31.5)                    |
| Completed high school               | 92 (36.2)                | 48 (28.6)                    |
| Partial college or university or CEGEP | 48 (18.9)               | 35 (20.8)                    |
| Undergraduate degree                | 9 (3.5)                  | 25 (14.9)                    |
| Graduate degree                     | 1 (0.4)                  | 7 (4.2)                      |
| Missing                             | 5                       | 2                            |
| **Current home ownership status**   |                          |                              |
| Owned                               | 20 (7.8)                 | 46 (27.2)                    |
| Rented                              | 162 (62.8)               | 100 (59.2)                   |
| Shelter                             | 30 (11.6)                | 9 (5.3)                      |
| Prison or jail                      | 3 (1.2)                  | 0                            |
| Detox or therapy                    | 13 (5.0)                 | 2 (1.2)                      |
| Homeless                            | 12 (4.7)                 | 1 (0.6)                      |
| Other                               | 18 (7)                   | 11 (6.5)                     |
| Missing                             | 1                       | 1                            |
| **Housing or food insecurity**      |                          |                              |
| Yes                                 | 102 (40.2)               | 34 (21.9)                    |
| No                                  | 152 (59.8)               | 121 (78.1)                   |
| Missing                             | 5                       | 15                           |
| **Incarceration status (ever)**     |                          |                              |
| Yes                                 | 160 (62.7)               | 62 (36.9)                    |
| No                                  | 95 (37.3)                | 106 (63.1)                   |
| Missing                             | 4                       | 2                            |
| **Province of residence**           |                          |                              |
| Alberta                             | 19 (7.3)                 | 34 (20.1)                    |
| British Columbia                    | 66 (25.5)                | 50 (29.6)                    |
| New Brunswick                       | 31 (12.0)                | 5 (3.0)                      |
| Nova Scotia                         | 22 (8.5)                 | 6 (3.6)                      |
| Ontario                             | 29 (11.2)                | 24 (14.2)                    |
| Quebec                              | 39 (15.1)                | 44 (26.0)                    |
| Saskatchewan                        | 53 (20.5)                | 6 (3.6)                      |
| Missing                             | 0                       | 1                            |

(Continued)

*Unless otherwise indicated

CT = Core transmitter; NIHB = Non-Insured Health Benefits for First Nations; CEGEP = Collège d’enseignement général et professionnel

also varied between groups, with CT participants reporting higher rates of incomplete high school education (40.9% versus 31.5%). Insecurity about both housing and food (40.2% versus 21.9%) and history of incarceration (62.7% versus 36.9%) were more common among CT participants. Gender and alcohol use were comparable between groups.

### HCV disease characteristics at baseline

HCV disease characteristics at baseline are summarized in Table 2. Among both CT and non-CT participants, predominant HCV genotypes were 1a (56.0% and 57.1%, respectively), 3 (37.5% and 20.0%), and 1b (4.2% and 12.9%).

Liver fibrosis was comparable between groups, with F0 or F1 the most common stage for both CT (63.5%) and non-CT (54.2%) participants. F2–F3 stages were reported by 13.7%–11.4% and 15.8%–12.5% of CT and non-CT participants, respectively. Rate of cirrhosis (F4) was slightly higher for non-CT participants (17.5% versus 11.4%). Mean FibroScan score at baseline was 8.8 (SD 6.5) and 10.6 (SD 9.9) kPa and mean APRI scores were 0.5 (SD 0.4) and 0.7 (SD 0.6), respectively, for CT and non-CT participants.

Baseline HCV resistance testing was carried out in 8.9% of CT and 9.0% of non-CT participants; types of HCV mutations identified were NS3 (82.6% and 71.4%), NS5B (47.8% versus 28.6%), and NS5A (30.4% versus 64.3%) for CT and non-CT participants, respectively.

### Current HCV treatment regimen at baseline

Current HCV treatment regimen is described in Table 3. At baseline, the majority of participants in both groups were prescribed sofosbuvir–velpatasvir—63.7% of CT participants and 57.6% of non-CT participants.
Table 2: HCV disease characteristics at baseline

| Disease characteristic        | Treatment group, no. (%)* |
|------------------------------|---------------------------|
|                              | CT participants (n = 259) | Non-CT participants (n = 170) |
| **HCV genotype†**            |                           |                             |
| 1a                           | 145 (56.0)                | 97 (57.1)                    |
| 1b                           | 11 (4.2)                  | 22 (12.9)                    |
| 1 (other)                    | 1 (0.4)                   | 6 (3.5)                      |
| 3                            | 97 (37.5)                 | 34 (20.0)                    |
| 4                            | 1 (0.4)                   | 5 (2.9)                      |
| Mixed                        | 2 (0.8)                   | 0 (0.0)                      |
| Other                        | 5 (1.9)                   | 2 (1.2)                      |
| Missing                      | 0                         | 1                             |
| **METAVIR score**            |                           |                             |
| F0 or F1                     | 134 (63.5)                | 65 (54.2)                    |
| F2                           | 29 (13.7)                 | 19 (15.8)                    |
| F3                           | 24 (11.4)                 | 15 (12.5)                    |
| F4                           | 24 (11.4)                 | 21 (17.5)                    |
| Missing                      | 48                        | 50                            |
| **FibroScan score, kPa, mean (SD)** |                       | 8.8 (6.5) | 10.6 (9.9) |
| **FibroTest result, mean (SD)** |                       | 10.9 (4.0) | 10.7 (2.2) |
| **APRI result, mean (SD)**   | 0.5 (0.4)                 | 0.7 (0.6)                    |
| **Resistance testing**       |                           |                             |
| Yes                          | 23 (8.9)                  | 14 (9.0)                     |
| No                           | 235 (91.1)                | 141 (91.0)                   |
| Missing                      | 1                         | 15                            |
| **Resistance-associated variants or substitutions identified‡** | | | |
| NS3                          | 19 (82.6)                 | 10 (71.4)                    |
| NS5B                         | 11 (47.8)                 | 4 (28.6)                     |
| NS5A                         | 7 (30.4)                  | 9 (64.3)                     |
| Other                        | 1 (4.3)                   | 0                             |

*Unless otherwise indicated
†Patients may have reported ≥1 genotype
‡Patients may have reported ≥1 resistance substitution

HCV = Hepatitis C virus; CT = Core transmitter; APRI = Aspartate transaminase to platelet ratio index

participants. Elbasvir–grazoprevir was prescribed for 24.3% and 33.5%, ledipasvir–sofosbuvir for 8.5% and 2.9%, and sofosbuvir–velpatasvir–voxilaprevir for 1.2% and 2.9% of CT and non-CT participants, respectively.

Table 3: Baseline HCV treatment regimen

| Regimen                              | Treatment group, no. (%) |
|--------------------------------------|--------------------------|
|                                      | CT participants (n = 259) | Non-CT participants (n = 170)* |
| Daclatasvir                          | 2 (0.8)                  | 0                          |
| Elbasvir–grazoprevir                 | 63 (24.3)                | 57 (33.5)                  |
| Ledipasvir–sofosbuvir                | 22 (8.5)                 | 5 (2.9)                     |
| Sofosbuvir                           | 2 (0.8)                  | 2 (1.2)                     |
| Sofosbuvir–velpatasvir               | 165 (63.7)               | 98 (57.6)                  |
| Glecaprevir–pibrentasvir             | 2 (0.8)                  | 4 (2.4)                     |
| Sofosbuvir–velpatasvir–voxilaprevir  | 3 (1.2)                  | 5 (2.9)                     |

Note: Patients may have reported >1 baseline HCV treatment (combination treatment regimen)
* Patients could have received a combination of DAAs
HCV = Hepatitis C virus; CT = Core transmitter

Harm reduction, risk behaviour, and substance use of CT participants at baseline

Baseline harm reduction, risk behaviour, and substance use among CT participants are presented in Table 4. At treatment initiation, 11.6% of CT participants were using supervised injection sites, 18.5% were participating in a rehabilitation program, 35.5% were participating in a needle exchange program, 25.6% were participating in a drug paraphernalia exchange program, and 53.4% were receiving opioid agonist therapy. Concerning risk behaviour, 74.4% of CT participants had tattoos or piercings, and 16.3% had exchanged sex for monetary or other gain. Among PWID, the mean time since last injection was 117.3 (SD 160.7) days, and mean number of unprotected sexual partners within the past 3 months was 4.3 (SD 3.4). With respect to subscales of the Brief Addiction Monitor questionnaire, the mean reported for the Use subscale was 3.2 (SD 3.0); 11.2 (SD 5.1) for the Risk Factors subscale; and 9.1 (SD 5.1) for the Protective Factors subscale; the mean for the overall scale was 2.4 (SD 1.4).

Outcome measures

Adherence to treatment

Adherence to treatment was similar between participant groups, with 93.5% of CT participants and 98.3% of non-CT participants completing the
Table 4: Harm reduction, risk behavior, and substance use at baseline (full analysis set)

| Harm reduction type of participation | CT participants (n=259), no. (%) |
|-------------------------------------|----------------------------------|
| Supervised injection site           |                                  |
| Yes                                 | 29 (11.6)                        |
| No                                  | 220 (88.4)                       |
| Missing                             | 10                               |
| Rehabilitation program              |                                  |
| Yes                                 | 46 (18.5)                        |
| No                                  | 203 (81.5)                       |
| Missing                             | 10                               |
| Needle exchange program             |                                  |
| Yes                                 | 89 (35.5)                        |
| No                                  | 162 (64.5)                       |
| Missing                             | 8                                |
| Drug paraphernalia exchange program |                                  |
| Yes                                 | 64 (25.6)                        |
| No                                  | 186 (74.4)                       |
| Missing                             | 9                                |
| Opioid agonist therapy              |                                  |
| Yes                                 | 134 (53.4)                       |
| No                                  | 117 (46.6)                       |
| Missing                             | 8                                |
| Risk behaviour                      |                                  |
| Reported tattoos or piercings       |                                  |
| Yes                                 | 189 (74.4)                       |
| No                                  | 65 (25.6)                        |
| Missing                             | 5                                |
| Exchanged sex for money or other reasons |                          |
| Yes                                 | 40 (16.3)                        |
| No                                  | 205 (83.7)                       |
| Missing or unknown                  | 14                               |
| Time since last injection for PWID participants, d, mean (SD) | 117.3 (160.7) |
| Unprotected sexual partners in past 3 mo, mean (SD) | 4.3 (3.4) |
| Brief Addiction Monitor             |                                  |
| Overall, mean (SD)                  | 2.4 (1.4)                        |
| Use subscale, mean (SD)             | 3.2 (3.0)                        |
| Risk factors subscale, mean (SD)    | 11.2 (5.1)                       |
| Protective factors subscale, mean (SD) | 9.1 (5.1)            |

* Unless otherwise indicated
CT = Core transmitter; PWID = People who inject drugs

Achievement of cure (SVR12, SVR24, SVR12/24)
Cure after DAA treatment (SVR12, SVR24, SVR12/24) is presented in Figures 1a and 1b. No statistically significant or clinically meaningful differences were observed between CT and non-CT participants in the achievement of cure in either analysis population. For the FAS, cure rates ranged from 94.9% to 98.1%, and for the PP population, cure rates ranged from 95.3% to 98.0%.

Treatment failure
The rates of treatment failure are presented in Table 5. The overall proportion of CT participants who failed treatment was 19.0% (95% CI 13.1–26.1) compared with 8.6% (95% CI 4.2–15.3) for non-CT participants (p = 0.017). Over a cumulative 187.9 and 100.9 PYs of follow-up for CT and non-CT participants, respectively, the corresponding incidence rates were found to be 21.8 (95% CI 16.1–29.6) versus 9.9 (95% CI 5.3–18.4) treatment failures per 100 PYs.

Reinfection
The number of reinfections per 100 PYs of follow-up are summarized in Table 6. No reinfections were observed in the non-CT group. In the CT group, reinfection was assessed over a cumulative 166.4 PYs and 157.0 PYs for the FAS and PP populations, respectively. Incidence rate of reinfection was 13.8 (95% CI 9.2–20.8) reinfections per 100 PYs in the FAS and 14.7 (95% CI 9.7–22.1) reinfections per 100 PYs in the PP population. The highest reinfection incidence rates were observed 18–30 months post-EOT—21.8 per 100 PYs (95% CI 10.4–45.8) in the FAS and 21.8 per 100 PYs (9.8–48.6) in the PP population. Mean Kaplan–Meier estimated time to reinfection for CT participants was 24.6 (SE 0.6) months and 24.5 (SE 0.6) months for CT participants in the FAS (Figure 2a) and PP population (Figure 2b), respectively.

Harm reduction, risk behaviour, and substance use over time among CT participants
A summary of harm reduction program, risk, behaviour, and substance use over time among CT participants is presented in Table 7. Post-HCV
treatment, approximately 4.2% of CT participants began and 2.3% ceased participation in a harm reduction program; 9.7% began and 12.0% ceased engagement in risk behaviour; and 13.1% began and 4.6% ceased engagement in substance use.

**DISCUSSION**

The results of this real-world study demonstrate that DAA therapy among CT and non-CT participants results in similar cure rates among individuals who have been provided therapy in a supportive clinical setting, with comparable rates of adherence to treatment between participant groups. However, the reinfection rate among CT participants was significant, whereas no reinfections were documented among non-CT participants.

The observed SVR rates are in agreement with those reported in the literature for both non-CT (23) and CT patients (24). In a recent retrospective
### Table 5: Treatment failure rates (per protocol population)

| Timing of visits | Treatment group, no. (%) | p-value |
|------------------|--------------------------|---------|
| Overall, no. (%) | CT participants (n = 172) | 29 (19.0; 13.1–26.1) | 10 (8.6; 4.2–15.3) | 0.017 |
| By visit† EOT | 10 (7.5) | 7 (6.3) |
| SVR12 | 5 (4.1) | 2 (2.6) |
| SVR24 | 3 (3.3) | 1 (2.0) |
| 6 mo post-SVR | 7 (10.1) | 0 (0.0) |
| 12 mo post-SVR | 2 (4.0) | 0 (0.0) |
| 18 mo post-SVR | 1 (2.5) | 0 (0.0) |
| 24 mo post-SVR | 1 (5.3) | 0 (0.0) |

*Unless otherwise indicated
†Proportions based on patients with available data at each visit

CT = Core transmitter; EOT = End of treatment; SVR = Sustained virologic response

### Table 6: Reinfection incidence rates after end of treatment

| Timing of visits | Treatment group | p-value |
|------------------|-----------------|---------|
| Overall, IDR (95% CI) | 13.8 (9.2–20.8) | 0 (NA) |
| By visit, IDR (95% CI) | 12.0 (4.5–32.0) | 0 (NA) |
| 0–3 mo post-EOT | 4.2 (0.6–29.9) | 0 (NA) |
| 3–6 mo post-EOT | 6.4 (1.6–25.7) | 0 (NA) |
| 6–12 mo post-EOT | 15.7 (5.9–41.8) | 0 (NA) |
| 12–18 mo post-EOT | 21.8 (10.4–45.8) | 0 (NA) |
| 18–30 mo post-EOT | 21.8 (9.8–48.6) | 0 (NA) |

CT = Core transmitter; IDR = Incidence density rate (no. of reinfections per 100 person years of follow-up); NA = Not applicable; EOT = End of treatment

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analysis of Canadian PWID patients treated with DAAs, 90% achieved SVR12 without any difference between active (currently injecting) and non-active PWID patients, as long as treatment was delivered in an appropriate setting (24).

With respect to reinfection, a Canadian population-based study by Rossi et al reported that reinfection among PWID after DAA therapy, defined as viremia documented after achievement of SVR, ranged between 1.4 per 100 PYs for former PWID and 3.1 per 100 PYs for recent PWID (25), with the highest rates observed for recent PWIDs aged younger than 45 years (10.4 per 100 PYs). A recent meta-analysis by Hajarizadeh et al, conducted in similar CT populations, reported reinfection incidence rates of 5.9 per 100 PYs among participants reporting recent injectable or non-injectable drug use, 6.2 per 100 PYs among participants recently injecting drugs, and 3.8 per 100 PYs among participants receiving opioid antagonist therapy (26).

The higher incidence rates of reinfection reported in this study likely relate to the fact that our definition of reinfection did not necessitate a confirmation with genetic testing, which is not always the standard of routine care. Although this may have led to an overestimation of incidence, we believe that in the context of this real-world study, limiting the definition of reinfection to genetic confirmation would have resulted in a non-representative underestimate of the true incidence of this important phenomenon. Considering that the mean age of our CT cohort was 42.3 years, the reported incidence is, however, in line with that reported by Rossi et al in younger patients.

An additional factor related to the reinfection rates observed was inclusion of the observation period before SVR. This inclusion was based on the results of the C-EDGE CO-STAR study, which found that many reinfections occur between EOT and SVR (27). Moreover, our assessment must also consider the lack of systematic intervention programs to reduce the rate of reinfection in our CT population once treatment is completed. This is
Risk behaviour and reinfection in HCV core transmitters

Figure 2: Kaplan–Meier time to reinfection for CT participants: (a) full analysis set (mean time to reinfection in CT participants = 24.6 [SD 0.6] mo); (b) per protocol population (mean time to reinfection in CT participants = 24.5 [SD 0.6] mo)

*Note: Median was not estimable for CT group; no reinfections were reported for non-CT group*

*CT = Core transmitter*

Table 7: Harm reduction, risk behaviour, and substance use over time

| Characteristics                  | CT participants | Began | Ceased |
|----------------------------------|-----------------|-------|--------|
| Harm reduction program           |                 | 11 (4.2) | 6 (2.3) |
| Engagement in risk behaviour     |                 | 25 (9.7) | 31 (12.0) |
| Engagement in substance use      |                 | 34 (13.1) | 12 (4.6) |

*CT = Core transmitter*

exemplified by the fact that during the follow-up, a subset of patients resumed high-risk behaviours and substance use. Incidence rates of reinfection were also highest 18–30 months post-EOT, with mean time to reinfection approximately 24 months post-EOT. This suggests that although intervention throughout treatment may encourage initial behavioural modification leading to therapeutic success, long-term solutions are required to ensure that patients remain supported beyond the duration of their treatment regimen to prevent resumption of behaviours that promote reinfection.

Recently, international and Canadian guidelines have shifted to include the recommendation of HCV treatment for CT patients as a priority population (27,28). However, treatment uptake in this high-risk population still remains relatively low, with a recent Canadian study demonstrating that disparities still exist with respect to access to DAA treatment with substantial social–structural and behavioural barriers to care (30). Additional barriers to HCV treatment in this patient group have been linked to both physician reluctance to treat and patient reluctance to be treated (30,31). However,
the between-groups similarities in adherence to treatment observed in our study indicate that once treatment is initiated with CT patients, it can be successfully maintained until completion with obvious short-term benefits to these patients.

A major advantage of this study is the unselected inclusion of CT patients, because this high-risk HCV population has typically been excluded from previous clinical trials, especially ones of this size. In addition, the real-world nature of this study enhances the external validity of our results for both the CT and the non-CT HCV populations. Conversely, an important limitation relates to selection bias, more specifically that CTs who are ready and willing to seek and adhere to treatment may not be representative of the spectrum of CT patients living with HCV, which would include individuals who regularly engage in high-risk behaviours.

In conclusion, despite significant vulnerabilities and comorbid medical and social conditions, CT populations achieve similar HCV cure rates as non-CT populations in a broad range of Canadian clinical centres. Compared with the published medical literature, higher incidence rates of reinfection were observed in our dataset. This speaks to the need for the implementation of programs to reduce the risk of exposure to HCV in the CT population cured of their infection and to maximize the benefits of HCV treatment programs in this key population. These findings should support ongoing initiatives to expand an offer of treatment and long-term engagement in care for a key population for the control of HCV infection in Canada and elsewhere.

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