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Direct-acting antiviral treatment for hepatitis C, reinfection and mortality among people attending an inner-city community health centre in Victoria, Canada

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ABSTRACT

Background: Direct-acting antiviral (DAA) treatment for hepatitis C virus (HCV) has been shown to be effective among PWID, but more real-world data on treatment outcomes is needed. The aim of this analysis was to assess the efficacy of DAA therapy, and the rate of reinfection and mortality among people attending an inner-city community health centre in Victoria, Canada.

Methods: In this retrospective study, patients treated with DAA therapy between November 2014 and Dec 31, 2017 were included. Retrospective chart review was performed to assess recent injecting drug use (IDU, previous six months) or receipt of opioid agonist treatment (OAT). The primary endpoint was Sustained Virologic Response (SVR12). Secondary endpoints included HCV reinfection and mortality.

Results: Of 270 patients who initiated DAA treatment (31% female), 20% (n = 54) had HIV/HCV coinfection, 32% (n = 84) had cirrhosis, 67% (n = 181) had genotype 1, 6% (n = 15) had genotype 2, 26% (n = 69) had genotype 3. 46% (n = 125) of patients were receiving OAT and 49% (n = 132) reported recent IDU. 98% (n = 265) completed treatment; two people stopped due to mental health, two people died, and one was non-adherent. 92% (249 of 270) achieved SVR12. 16 patients with End of Treatment (EOT) response did not have a SVR12; 7 were lost to follow-up; 2 people refused bloodwork; 2 people died; 1 had reinfection; and 4 had viral relapse. There was no difference in SVR12 by OAT (OAT, 93% vs. no OAT, 91%, $P = 0.435$), recent injecting drug use (yes, 92% vs. no, 92%, $P = 0.904$), or HIV status (HIV, 92% vs. no HIV, 94%, $P = 0.498$). Eight cases of HCV reinfection were observed over 253 person-years of follow up (3.2 cases per 100 person-years; 95% CI 1.6-6.3). Twenty people died (6.3 per 100 person-years; 95% CI 3.9-10.3), including two during therapy (drug overdose, n = 2) and 18 following therapy completion (drug overdose, n = 7).

Conclusion: This study demonstrates that DAA treatment is effective among a marginalized population receiving care in an inner-city community health centre. The high mortality in this study highlights the importance of integrating HCV care within a framework addressing drug-related harms, preventing overdose mortality, addressing social inequalities, and improving the health of PWID.

Introduction

Hepatitis C virus (HCV) infection is a major public health problem among people who inject drugs (PWID) (Degenhardt et al., 2017; Grebely, Larney et al., 2018). Among the 71 million people living with HCV globally, there are 6.1 million people who have recently injected drugs (representing 8.5% of all people living with HCV) (Grebely, Larney et al., 2018). The availability of safe and effective direct-acting antiviral therapy (DAA) represents a major opportunity to reverse the rising burden of HCV-related liver disease in many countries (Aspinall et al., 2015). However, some providers are still reluctant to provide HCV treatment to people with ongoing injecting drug use, based on concerns of medication prices, response to therapy, and risk of HCV reinfection (Asher et al., 2016).

Treatment for HCV infection with DAA-based therapies has been shown to be effective among people receiving opioid agonist treatment

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(OAT) and people with recent or ongoing injecting drug use (Hajarizadeh et al., 2018). Lower responses to therapy have been observed in "real-world" observational studies as compared to clinical trials, mainly due to an increased loss to follow-up between the end of treatment and sustained virological response (SVR) (Hajarizadeh et al., 2018). However, the majority of clinical trials and real-world studies to date have been limited by the small numbers of people with recent or ongoing injecting drug use, people with HCV genotype 3 infection, people with advanced liver disease and people with HIV/HCV co-infection. Further, there are little data on post-SVR outcomes, including HCV reinfection and mortality. Understanding drug-related mortality among people receiving HCV treatment is important, particularly in settings such as North America, where there has been a significant increase in opioid-related drug overdoses (Centers for Disease Control & Prevention, 2017; Hedegaard, Minino, & Warner, 2018; Public Health Agency of Canada, 2018; Rigg, Monnat, & Chavez, 2018).

Strategies to enhance HCV testing, linkage to care and treatment among people who inject drugs will be critical to achieve HCV elimination globally (Grebely, Dore, Morin, Rockstroh, & Klein, 2017). Community health centres represent a logical venue for expansion of HCV care beyond existing tertiary HCV treatment centres to facilitate HCV care for people who inject drugs (Bruggmann & Litwin, 2013).

The primary aim of this study was used to evaluate the proportion of patients with response to DAA therapy for HCV infection and associated factors among people attending an inner-city community health centre. Secondary aims included an evaluation of the incidence of HCV re-infection following successful therapy and incidence of mortality among patients receiving DAA therapy for HCV infection.

Methods

Study design and participants

This study was a retrospective chart review of patients receiving DAA therapies at an inner-city community health centre, the Cool Aid Community Health Centre, in Victoria, Canada. All participants who initiated DAA therapy between November 1, 2014 (first availability of DAA therapy in British Columbia) and December 31, 2017 were eligible for inclusion in this study and all participants who received at least one dose of therapy were included. The choice of DAA regimen was at the discretion of the treating physician. During this period, a fibrosis stage & > F2 (determined by Transient Elastography [FibroScan®], AST to Platelet Ratio Index (APRI score), fibrosis 4 (FIB-4), or liver biopsy) was required for the government reimbursement of HCV DAA therapy in the province of British Columbia.

Study setting

The Cool Aid Community Health Centre is an inner-city, interdisciplinary primary health care centre serving over 4400 clients living with chronic mental health co-morbidity, substance use and homelessness. The health centre provides low barrier access to HCV screening, treatment and follow-up, integrated within primary care services. The health centre has developed a nurse-led HCV treatment program to effectively reach the population traditionally labelled "hard to reach" and treat these individuals living with HCV in a context of complex health and social issues. The Cool Aid Community Health Centre uses an equity-based, harm reduction framework, striving to provide culturally safe, competent, flexible, low barrier access to care.

The HCV treatment program is supported by an interdisciplinary team of physicians, nurse practitioners, registered nurses, counsellors, dietician and an on-site dispensary, including OAT services, and connections to income assistance and housing. The program incorporates dedicated nurse and physician time, weekly nursing assessment, direct support in nutrition, medication adherence, side effect management, emotional and mental health support, and advocacy.

A peer-facilitated group with both patients who have successfully completed treatment and those contemplating or currently in treatment encourages learning and support that is ongoing and patient-centered. The group provides an efficient point of contact with HCV patients, enabling nurses to provide supports and case-management through treatment. Patients are encouraged and reminded to follow up post treatment for SVR12 visits. Patients who currently use injection drugs or have other risk factors have HCV RNA testing added to regular blood work yearly as part of their care plan.

Study assessments

A retrospective clinical assessment and chart review collected information on HCV testing, assessment for an initiation of HCV treatment and drug current use and history and the reasons for treatment discontinuation, supplementing a case management database that collected relevant information toward patient HCV treatment and SVR outcomes. Drug use and OAT prescription were assessed based on prescriptions on file and clinician documentation in the electronic medical record. Patient assessments before treatment include HCV RNA, HCV genotype, standard laboratory and clinical testing, and FibroScan®. Assessments during treatment included physical examinations, measurements of HCV RNA levels (performed at local laboratories), and standard laboratory testing. HCV RNA levels for evaluation of the primary endpoint (SVR12) were measured on plasma samples tested locally with the Abbott Realtime Assay (lower limit of detection < 12 IU/mL). HCV genotype/subtype was determined by sequencing or the Abbott RealTime HCV genotype assay at the British Columbia Centre for Disease Control as previously described (Rossi et al., 2018).

Stage of liver fibrosis was assessed by liver stiffness measurement (FibroScan® or APRI). For liver stiffness measurements, the chosen cut-offs for significant liver fibrosis and cirrhosis were 7.1 kPa and 12.5 kPa, respectively (Castera et al., 2005). APRI was calculated using aspartate aminotransferase (AST) and platelet count: [(AST [U/L]/upper limit of normal)/platelet count (109/L)] × 100. APRI > 1.0 and > 2.0 defined significant liver fibrosis and cirrhosis, respectively.

Study outcomes

The primary endpoint was the proportion of patients who achieved SVR12, defined as an HCV RNA level below the limit of quantification 12 weeks after the end of treatment in all participants who received at least one dose of medication (ITT population). If HCV RNA was not assessed at 12 weeks post-treatment, the result of the next available HCV RNA assessment was used to calculate SVR. Secondary endpoints included the incidence of HCV reinfection following successful DAA therapy and the incidence of mortality during and following DAA therapy.

Reinfection was defined by the presence of quantifiable HCV RNA after an end of treatment among those who were negative at SVR12. Reinfection was distinguished from relapse using viral genotyping where a genotype or subtype switch had occurred. In the absence of a genotype switch, any case of virological recurrence following a negative test at SVR12 was considered a reinfection given the low likelihood of virological relapse at twelve weeks following therapy. Date and cause of death were determined through coroner's reports, hospital records or retrospective chart review.

Statistical analyses

Baseline characteristics were tabulated on patients initiating DAA therapy at the Cool Aid Community Centre up until December 31, 2017. Overall participant characteristics were determined by the data distribution and summarized using appropriate summary statistics stratified by injecting drug use [mean (SD), median (IQR), n(%)].

Point estimates for the proportion of participants with SVR were calculated, including two-sided 95% exact confidence intervals using the Clopper-Pearson method. SVR was stratified by key factors that were hypothesized to be associated with HCV treatment outcomes including age (stratified by median), gender (male, female), current OAT (any, methadone, buprenorphine, morphine), recent drug use (excluding cannabis use, past 6 months), recent injecting drug use (including heroin, cocaine, methamphetamine, and other opioids, past 6 months), HCV genotype (including mixed HCV infection), treatment regimen, liver disease stage (F0-1, F2-3, F4), previous HCV treatment experience (any, DAA experience, IFN experience), and HIV infection (yes, no).

Unadjusted logistic regression analyses were performed to identify predictors of SVR12 and to estimate crude odds ratios (OR) and corresponding 95% confidence intervals (95% CI). Since no factors associated with SVR12 in unadjusted analyses were observed, adjusted logistic regression analyses were not performed.

Demographic, behavioural and clinical characteristics among those with HCV reinfection and those who died during study follow-up were described. Rates of HCV reinfection and mortality were calculated using person-time of observation. The estimated date of reinfection was calculated as the midpoint between the dates of the last undetectable HCV RNA test and the first detectable HCV RNA test. Time at risk for reinfection commenced at the date of undetectable HCV RNA at end of treatment for all patients who achieved SVR12 and ended at the estimated date of re-infection, or at the last available study visit with HCV RNA testing. Time at risk for mortality commenced at the date of HCV treatment initiation and ended at the estimated time of death, or at the last available study visit. Rates of HCV reinfection and mortality were also stratified by recent injecting drug use. Confidence intervals for reinfection and mortality rates were calculated using a Poisson distribution.

For all analyses, statistically significant differences were assessed at a 0.05 level; p-values were two-sided. All analyses were performed using Stata v14.0 (StataCorp, College Station, Texas).

Study oversight

The retrospective chart review was approved by Western Institutional Review Board and was conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP) guidelines.

Results

Participant characteristics

Of 270 patients who received at least one dose of study medication, the median age was 48 years, 31% were female, 20% were co-infected with HIV/HCV, 67% had genotype 1a, and 32% had cirrhosis (Table 1). Most patients had a history of injection drug use (94%), 64% of patients had recently used drugs (previous six months), 49% had recently injected drugs (previous six months), and 46% were receiving OAT. Overall, 11% had previously received HCV treatment.

Overall HCV treatment completion and outcomes

Among patients who initiated therapy (n = 270), the majority received either sofosbuvir and ledipasvir (35%), sofobusvir and velpatasvir (30%) or elbasvir and grazoprevir (17%) (Table 1). Overall, 98% (265 of 270) completed treatment. Of the patients who did not complete treatment (Fig. 1), two discontinued due to pre-existing mental health co-morbidity, one discontinued due to non-adherence at the discretion of the treating physician, and two died of illicit drug overdose.

In ITT analysis, 92% (249 of 270, 95% CI: 88%, 95%) had an SVR12. Among those patients who completed treatment but did not have an SVR (n = 16), reasons for not achieving an SVR included lost to follow-up (n = 7), refused bloodwork (n = 2), virologic relapse (n = 4), death (n = 2) and reinfection (n = 1).

In the first patient with viral relapse (genotype 3a), the patient had been previously treated with pegylated interferon with ribavirin and discontinued as a non-responder. HCV RNA level was 67,965 IU/mL at the time of treatment initiation. At the time of virologic relapse (SVR12), the HCV RNA level was 232,070 IU/mL and post hoc sequencing demonstrated no resistance. In the second patient with viral relapse (genotype 1a), HCV RNA level was 1,032,147 IU/mL at the time of treatment initiation. Patient was non-adherent to treatment and then lost to follow-up. At the time of virologic relapse seven months after EOT, the HCV level with 2,457,752 IU/mL. No resistance analysis was available. In the third patient with viral relapse (genotype 1a), HCV RNA level was 6,508,399 IU/mL at the time of treatment initiation. At

Table 1
Baseline characteristics.

Characteristic	Overall (n = 270)	No recent injecting drug use (n = 138)	Recent injecting drug use (n = 132)
Age, median (25%, 75%)	54 (47-60)	57 (50-62)	51 (44-57)
Female sex, n (%)	85 (31)	43 (31)	42 (32)
History of drug use, n (%)			
Recent drug use*, n (%)	173 (64)	41 (30)	132 (100)
History of injecting drug use, n (%)	255 (94)	123 (89)	132 (100)
Recent injecting drug use*, n (%)	132 (49)	0 (0)	132 (100)
Receiving OAT, n (%)	125 (46)	38 (28)	87 (66)
Methadone[a]	102 (82)	33 (87)	69 (79)
Buprenorphine/ naloxone[a]	14 (5)	5 (13)	9 (10)
Morphine[a]	9 (7)	0 (0)	9 (10)
HCV genotype, n (%)			
1	181 (67)	91 (66)	90 (68)
2	15 (6)	12 (9)	3 (2)
3	69 (26)	32 (23)	37 (28)
4	1 (0)	1 (1)	0 (0)
Mixed	3 (1)	1 (1)	2 (2)
HIV infection, n (%)	54 (20)	15 (11)	39 (30)
Stage of liver disease, n (%)			
No or mild fibrosis (F0-F1)	67 (25)	35 (26)	32 (25)
Moderate or advanced fibrosis (F2-F3)	114 (43)	53 (39)	61 (47)
Cirrhosis (F4)	84 (32)	47 (35)	37 (28)
Previous HCV therapy[b], n (%)	30 (11)	17 (12)	13 (10)
Previous DAA therapy	9 (3)	4 (3)	5 (4)
Previous interferon-based therapy	24 (9)	14 (10)	10 (8)
DAA treatment, n (%)			
Sofobuvir/ledipasvir	95 (35)	47 (34)	48 (36)
Sofosbuvir/velpatasvir	80 (30)	42 (30)	38 (29)
Elbasvir/grazoprevir	46 (17)	28 (20)	18 (14)
Sofosbuvir	19 (7)	11 (8)	8 (6)
Paritaprevir/ritonavir/ ombitasvir and dasabuvir	18 (7)	6 (4)	12 (9)
Sofosbuvir and elbasvir/grazoprevir	8 (3)	2 (1)	6 (5)
Pegylated interferon and telaprevir	2 (1)	1 (1)	1 (1)
Simeprevir and sofosbuvir	1 (0)	0 (0)	1 (1)
Sofosbuvir/velpatasvir/ voxilaprevir	1 (0)	1 (1)	0 (0)

Data are n (%), or median (IQR). OAT = opioid agonist therapy.

[a] Percentages are among those receiving OAT ‡F0–F1 < 7·1 kPa, F2–F3 7·1–12·49 kPa, F4 ≥ 12·5 kPa.

[b] Three people had a history of both DAA and interferon-based treatment.

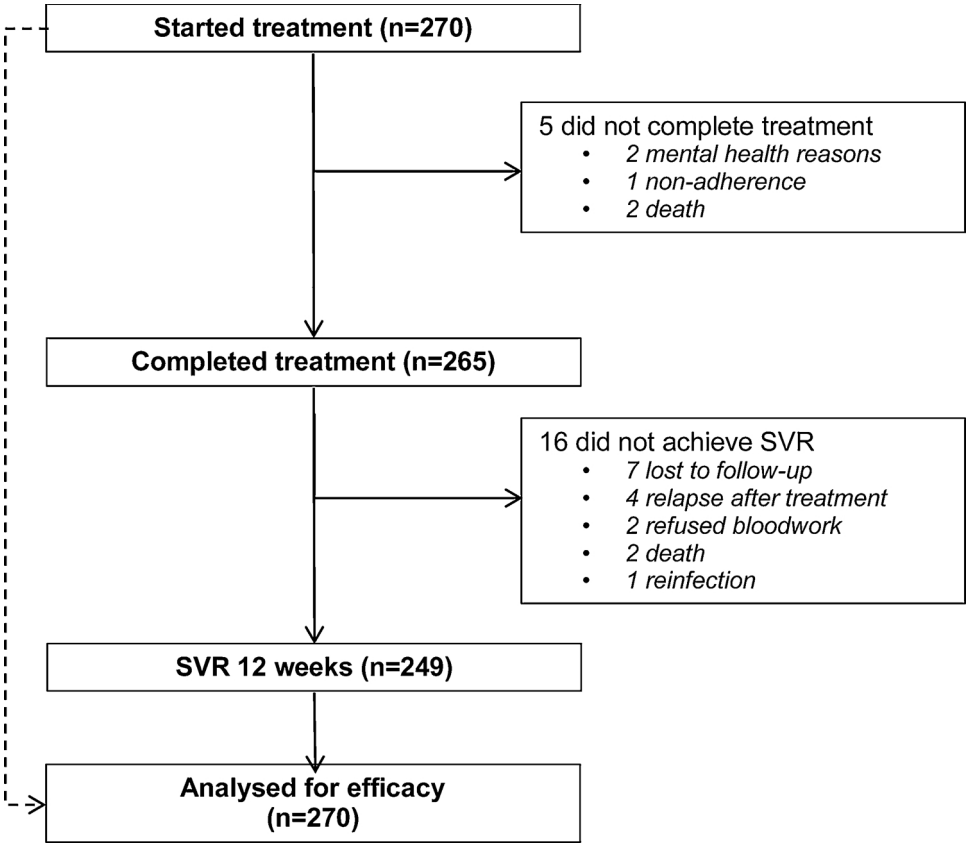

Fig. 1. Study profile.

the time of virologic relapse (SVR12), the HCV RNA level was 1,886,512 IU/mL and post hoc sequencing demonstrated the presence of resistance associated substitutions in the NS3 (V36 L, Q80 K and E357 G) and NS5A (MS8A and Q30 H) regions. In the fourth patient with viral relapse (genotype 3a), HCV RNA level was 2,623,570 IU/mL at the time of treatment initiation. At the time of virologic relapse (SVR12), the HCV RNA level was 4977 IU/mL and post hoc sequencing demonstrated the presence of resistance associated substitutions in the NS3 (Q168Q), and NS5A (S62T and Y93H/R) regions.

SVR stratified by key demographic and clinical characteristics

The proportion with SVR stratified by key characteristics is shown in Table 2 and Fig. 2. There was no difference in SVR between those with and without recent (previous 6 months) drug use (P = .797), recent injecting drug use (P = 0.904), current OAT (P = 0.435), or HIV infection (P = 0.498).

Reinfection

Among the 251 participants eligible to be followed for reinfection (including 124 people with recent injecting drug use), there were eight cases of HCV reinfection (253 person-years of follow-up; reinfection rate 3.2 cases per 100 person-years; [95% CI 1.6–6.3]) (Table 3). Among people who reported recent injecting drug use at baseline (n = 124), the rate of HCV reinfection was 5.9 cases per 100 person-years; (95% CI 2.9–11.7; 8 reinfections; 136 person-years of follow-up). Among people who reported recent injecting drug use following treatment (n = 91), the rate of HCV reinfection was 7.7 cases per 100 person-years (95% CI 3.8–15.3; 8 reinfections; 105 person-years of follow-up). All patients with reinfection were reported to be injecting ≥ daily both in 6 months prior to treatment and after treatment. Stimulant use was most common as main drug (methamphetamine, n = 5, cocaine n = 2, fentanyl = 1) while five participants were receiving OAT.

Deaths

Including the two deaths during treatment, 20 patients died following treatment initiation (322 person-years of follow-up) representing a mortality incidence of 6.3 cases per 100 person-years [95% CI 3.9–10.3]. Nine deaths were due to drug overdose (2.8 cases per 100 person-years [95% CI 1.5–5.4]). The other causes for death included: liver cancer (n = 1), liver disease (n = 1), subarachnoid hemorrhage (n = 1), heart failure (n = 4), respiratory failure (n = 1), COPD (n = 1), sudden natural event (n = 1) and unknown (n = 1).

Among people with recent injecting drug use at the time of HCV treatment initiation (n = 132), 15 patients died following treatment initiation (171 person-years of follow-up) representing a mortality incidence of 8.8 cases per 100 person-years (95% CI 5.3–14.6) and overdose incidence of 5.3 cases per 100 person-years (95% CI 2.7–10.1).

Discussion

In this retrospective study of people attending an inner-city community health centre for HCV DAA treatment in Victoria, Canada, the response to HCV DAA treatment was 92%. There was no difference in SVR12 by HIV status, fibrosis stage, current OAT or recent injecting drug use. The rate of HCV reinfection was low, but somewhat higher among those with ongoing injecting drug use during follow-up. These outcomes following DAA therapy in a real-world setting demonstrates how effective HCV clinical management can be for people who inject drugs with a multidisciplinary team with clinician and nursing clinical assessment and monitoring, OAT provision, psychiatric services, and social support services including peer support (Grebely et al., 2015).

Table 2
SVR12 (95% CIs), stratified by key characteristics.

	n	SVR	no SVR	SVR % (95% CI)	Unadjusted OR (95% CI)	P
Age						
≤54	139	127	12	91.4 (85.4-95.5)	1.00	
> 54	131	122	9	93.1 (87.4-96.8)	1.28 (0.52-3.15)	0.590
Sex						
Female	85	77	8	90.6 (82.3-95.8)	1.00	
Male	185	172	13	93.0 (88.3-96.2)	1.37 (0.55-3.45)	0.498
Current OAT at baseline						
No	145	132	13	91.0 (85.2-95.1)	1.00	
Methadone	102	95	7	93.1 (86.4-97.2)	1.34 (0.51-3.48)	0.552
Buprenorphine/naloxone	14	13	1	92.9 (66.1-99.8)	1.28 (0.15-10.58)	0.819
Morphine	9	9	0	100.0 (66.4-100.0)	NA	NA
Recent drug use at baseline (last 6 months)						
No	97	90	7	92.8 (85.7-97.0)	1.00	
Yes	173	159	14	91.9 (86.8-95.5)	0.88 (0.34-2.27)	0.797
Recent injecting drug use at baseline (last 6 months)						
No	138	127	11	92.0 (86.2-96.0)	1.00	
Yes	132	122	10	92.4 (86.5-96.3)	1.06 (0.43-2.58)	0.904
HCV genotype						
1	181	166	15	91.7 (86.7-95.3)	1.00	
2	15	14	1	93.3 (68.1-99.8)	1.27 (0.16-10.29)	0.826
3	69	65	4	94.2 (85.8-98.4)	1.47 (0.47-4.59)	0.509
4	1	0	1	0.0 (0.0-97.5)	NA	NA
Mixed	3	3	0	100.0 (29.2-100.0)	NA	NA
Liver Fibrosis						
F0-F1	67	60	7	89.6 (79.7-95.7)	1.00	
F2-F3	114	107	7	93.9 (87.8-97.5)	1.78 (0.60-5.33)	0.300
F4	84	77	7	91.7 (83.6-96.6)	1.28 (0.43-3.86)	0.657
HIV infection						
No	216	198	18	91.7 (87.1-95.0)	1.00	
Yes	54	51	3	94.4 (84.6-98.8)	1.55 (0.44-5.45)	0.498
HCV treatment experience						
No	240	222	18	92.5 (88.4-95.5)	1.00	
Yes	30	27	3	90.0 (73.5-97.9)	0.73 (0.20-2.64)	0.631
DAA treatment, n (%)						
Sofobuvir/ledipasvir	95	89	6	93.7 (86.8-97.6)	1.00	
Sofosbuvir/velpatasvir	80	73	7	91.3 (82.8-96.4)	0.70 (0.23-2.18)	0.542
Elbasvir/grazoprevir	46	40	6	87.0 (73.7-95.1)	0.45 (0.14-1.48)	0.188
Sofosbuvir	19	18	1	94.7 (74.0-99.9)	1.21 (0.14-10.70)	0.862
Paritaprevir/ritonavir/ombitasvir and dasabuvir	18	18	0	100.0 (81.5-100.0)	NA	NA
Sofosbuvir and elbasvir/grazoprevir	8	8	0	100.0 (63.1-100.0)	NA	NA
Pegylated interferon and telaprevir	2	2	0	100.0 (15.8-100.0)	NA	NA
Simeprevir and sofosbuvir	1	1	0	100.0 (2.5-100.0)	NA	NA
Sofosbuvir/velpatasvir/voxilaprevir	1	0	1	0.0 (0.0-97.5)	NA	NA

The successes in this equity-based model that focus on harm-reduction, flexible health care delivery and stigma reduction (Harris & Rhodes, 2013) can inform models of service delivery and international guidelines in the management of HCV infection among people who have recently injected drugs.

In this study, treatment completion (98%) and SVR (92%) were similar to that reported in a systematic review and meta-analysis of DAA treatment outcomes among people with recent injecting drug use (treatment completion, 96.9%; SVR, 87.4%), and those receiving OAT (treatment completion, 97.5%; SVR, 90.7%) (Hajarizadeh et al., 2018). However, the majority of studies to date have included small numbers of people with recent injecting drug use, HIV, and advanced liver disease (Grebely, Dore et al., 2016; Grebely, Hajarizadeh, & Dore, 2017; Grebely, Mauss et al., 2016; Hajarizadeh et al., 2018). The results from this study are impressive, given a high proportion of participants with ongoing injecting drug use (49%), HIV co-infection (20%) and advanced liver disease (32%). Given previous data demonstrating lower response to therapy in "real-world" studies compared to clinical trials, the response to therapy in this "real-world" cohort was favourable. This study adds to the body of knowledge in this area and supports the rationale that ongoing injecting drug use should not be used as a reason for withholding or discontinuing therapy.

One of the successes of this "real world" cohort was the low proportion lost to follow-up following the completion of treatment and evaluable for SVR (7 or 2.6% of ITT population). Engagement after HCV therapy is critical to accurately document SVR, monitor advanced liver disease, and follow for potential HCV reinfection (Nouch et al., 2018). Non-attendance for SVR results (Butner et al., 2017; Morris et al., 2017) or patients attending other primary care appointments in the clinic around their SVR 12 due date, without having lab work drawn (Nouch et al., 2018) are key challenges in the engagement in HCV care. These challenges were addressed in several ways: nursing staff worked with the research coordinator to case manage and document SVR process, leaving reminder messages in the electronic medical record for all clinical staff, pharmacies were called to leave messages for patients on daily dispense OAT when there was no current patient contact information, nursing outreach provided bloodwork at local shelters and housing sites, and patients far overdue for SVR were offered incentives of $20 to complete SVR bloodwork. On site nursing phlebotomy created opportunities for patients with a history of injection drug use to work patiently with nursing staff or the patient themselves to find a vein in difficult blood draws from scarring and overuse. The recent availability of a finger-stick point of care assay to detect HCV RNA in one hour may provide an opportunity to address problems with venous access and simplify the collection of blood, thereby improving follow-up for SVR and HCV reinfection blood work in the real-world (Grebely, Applegate, Cunningham, & Feld, 2017; Grebely, Lamoury et al., 2017; Lamoury et al., 2018).

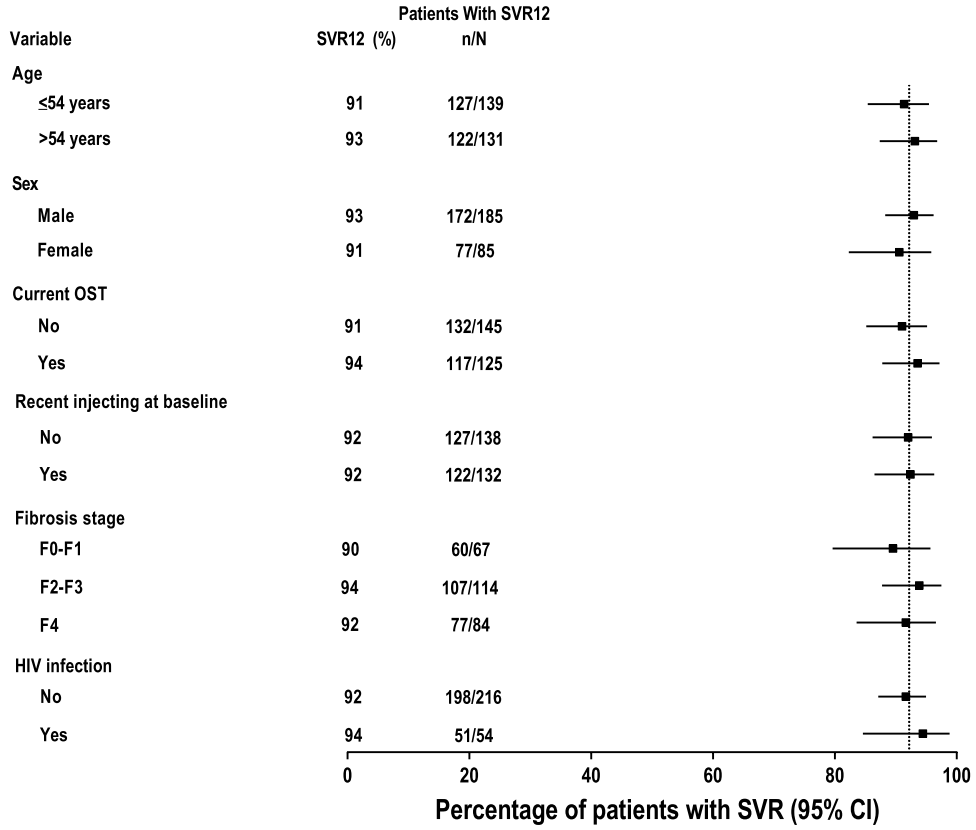

Fig. 2. Forest plot of SVR12, stratified by key characteristics. The dotted line shows the overall SVR12 (92%) in this study.

In this study, there were eight cases of HCV reinfection representing an incidence of 3.2 cases per 100 person-years; (95% CI 1.6–6.3). This study is consistent with studies of reinfection among people followed after DAA-based therapies (2.3–2.6 per 100 person-years) (Dore et al., 2017; Grebely, Conway, et al., 2018; Grebely, Dalgard, et al., 2018) including those with people with ongoing injecting drug use (2.4 per 100 person-years) (Aspinall et al., 2013; Grebely, Dalgard, et al., 2018; Midgard et al., 2016; Young et al., 2017). Although continued injection drug use following successful HCV therapy may lead to reinfection and compromised treatment outcomes (Cunningham et al., 2015), this low rate of reinfection demonstrates the careful efforts of patients in not sharing injecting equipment. Strategies to address HCV reinfection should include efforts to educate people about HCV transmission, re-infection risks, and strategies for mitigating the risk of reinfection (including ready access to sterile needles/syringes) (Martinello, Dore, Matthews, & Grebely, 2018). Further, re-treatment following HCV re-infection should be offered without stigma and discrimination (Martinello et al., 2018). However, the lower rates of re-infection that have been observed to date may assure providers who are still reluctant to provide HCV treatment to people with ongoing injecting drug use (Asher et al., 2016), reducing the HCV-related disease burden in community health care settings.

All-cause mortality rate was 6.2 per 100 py during the study period (8.9 deaths per 100 py among those with recent injecting), and overdose mortality was 2.8 overdose deaths per 100 py (5.3 overdose deaths per 100 py among those with recent injecting), highlighting the competing mortality risk among this population (Mathers et al., 2013). The introduction of a toxic synthetic opioid, fentanyl, into the illicit drug market has dramatically increased drug related overdoses and deaths in Canada and the US (Centers for Disease Control & Prevention, 2017; Rigg et al., 2018). According to the Public Health Agency of Canada, on average, nearly 10 people died each day of an illicit drug overdose in Canada from January 2016 to March 2018 (Public Health Agency of Canada, 2018). In British Columbia, unintentional illicit drug overdose deaths increased from 211 in 2010 to an estimated 1450 in 2017 (BC Coroners' Service, 2018). The loss of patients due to overdose has had a profound impact on community health centres, including both patients and staff. It is critical that HCV care is integrated within a framework that also addresses drug-related harms, prevents overdose mortality, addresses social inequalities, and improves the health of people who

Table 3
Reinfection Characteristics.

Patient	Sex	Age	Co-infect HIV	OST Type	Recent IDU	IDU Post Tx	Highest Frequency	Main Drug
RF001	Female	50	yes	Methadone	yes	yes	≥Daily	Methamphetamine
RF002	Male	23	no	no	yes	yes	≥Daily	Methamphetamine
RF003	Female	56	yes	Methadone	yes	yes	≥Daily	Methamphetamine
RF004	Male	53	no	no	yes	yes	≥Daily	Cocaine
RF005	Male	52	yes	Suboxone	yes	yes	≥Daily	Cocaine
RF006	Female	42	yes	Methadone	yes	yes	≥Daily	Fentanyl
RF007	Male	37	no	Kadian	yes	yes	≥Daily	Methamphetamine
RF008	Male	47	yes	no	yes	yes	≥Daily	Methamphetamine

use drugs (Grebely et al., 2015).

This study has several limitations. The study was conducted as a retrospective chart review, so there is a potential for information bias (those who report certain behaviours will be more likely to be in the medical charts) and social desirability bias (people may answer questions in a manner that will be viewed favourably by clinicians). However, the responses to therapy were high across all sub-populations, including patients who reported (or may have not reported) recent injection drug use, so we do not anticipate that these potential sources of bias had a major impact on the observed findings of this study. This community health centre has experience in providing HCV care and resources for research and study follow up, including some incentives for patients. As such, the results of this study may not be generalizable to all populations of people who inject drugs and/or receiving OAT, and to all HCV treatment settings. However, educating health-care providers on harm-reduction, equity-based and peer-supported HCV treatment strategies may reduce stigma for people who inject drugs and help increase successes in both SVR and reinfection rates. Conclusions about the rate of HCV reinfection should be interpreted with caution, given that patients were only followed up to a total of 253 person-years. Although the low number with reinfection is encouraging, further long-term data are needed to evaluate HCV reinfection, addressing concerns from some clinicians about adherence, efficacy, and safety of DAA therapy for people who have recently injected drugs.

Overall, this study demonstrates that DAA treatment is effective among people receiving care in an inner-city community health centre, including those who are receiving OAT and people with recent injecting drug use. The high mortality in this study highlights the importance of integrating HCV care within a framework addressing drug-related harms, preventing overdose mortality, addressing social inequalities, and improving the health of people who use injection drugs.

Contributors

MS, RM, JG, EC and CF contributed to the study design. CF was the study principal investigator. MS and RM conducted the chart review. RM, AD, TB, KL, KG treated patients and inputted data. JG, EC led the study analyses. All authors contributed to the data interpretation, writing and review of the report.

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