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Research paper

Understanding real-world adherence in the directly acting antiviral era: A prospective evaluation of adherence among people with a history of drug use at a community-based program in Toronto, Canada

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ABSTRACT

Background: Direct acting antiviral (DAA) treatments for Hepatitis C (HCV) are now widely available with sustained virologic response (SVR) rates of >90%. A major predictor of response to DAAs is adherence, yet few real-world studies evaluating adherence among marginalized people who use drugs and/or alcohol exist. This study evaluates patterns and factors associated with non-adherence among marginalized people with a history of drug use who were receiving care through a primary care, community-based HCV treatment program where opiate substitution is not offered on-site.

Methods: Prospective evaluation of chronic HCV patients initiating DAA treatment. Self-report medication adherence questionnaires were completed weekly. Pre/post treatment questionnaires examined socio-demographics, program engagement and substance use. Missing adherence data was counted as a missed dose.

Results: Of the 74 participants, who initiated treatment, 76% were male, the average age was 54 years, 69% reported income from disability benefits, 30% did not have stable housing and only 24% received opiate substitution therapy. Substance use was common in the month prior to treatment initiation with, 11% reported injection drug use, 30% reported non-injection drug use and 18% moderate to heavy alcohol use. The majority (85%) were treatment naïve, with 76% receiving sofosbuvir/ledipasvir (8–24 weeks) and 22% Sofosbuvir/Ribarvin (12–24 weeks). The intention to treat proportion with SVR12 was 87% (60/69). In a modified ITT analysis (excluding those with undetectable RNA at end of treatment), 91% (60/66) achieved SVR12. Overall, 89% of treatment weeks had no missed doses. 41% of participants had at least one missed dose. In multivariate analysis the only factor independently associated with weeks with missed doses was moderate to heavy alcohol use ($p = 0.05$).

Conclusion: This study demonstrates that strong adherence and SVR with DAAs is achievable, with appropriate supports, even in the context of substance use, and complex health/social issues.

Background

Recent estimates suggest that there are approximately 71.1 million people worldwide living with chronic hepatitis C (HCV) (Blach, Zeuzem, Manns, & Razavi, 2017). Most new cases of HCV occur among people who use drugs, with global estimates indicating that 67% of people who inject drugs are HCV antibody positive (Nelson et al., 2011). Despite the high prevalence of HCV in this group, treatment uptake has historically been very low (Alavi et al., 2014; Grebely et al., 2009; Iversen et al., 2014). Concerns about adherence have been one of the major barriers to treatment for people who use drugs at the provider level (McGowan & Fried, 2012). In recent years, advances in HCV treatment have drastically improved both the burden of treatment and treatment outcomes; however, all oral therapies introduce the potential for even greater adherence concerns. Although direct acting antiviral (DAA) treatments offer sustained virologic response (SVR) proportions of >90%, their efficacy is dependent primarily on strong adherence

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(Sarpel, 2016). There is little evidence regarding optimal adherence levels or about what factors might be associated with non-adherence among marginalized people who use drugs.

Much of the existing literature on adherence to DAAs among people who use drugs has been determined through secondary analysis of phase 2 or 3 clinical trials. C-EDGE CO-STAR, a randomized, phase 3, placebo-controlled study of grazoprevir/elbasvir among 200 participants who were receiving opiate substation therapy (OST) at community-based clinics, found high adherence rates that matched those of non-drug users (Dore, 2015a). In the study's immediate treatment arm, 77% missed no doses (Dore, 2015b). This study also found that non-adherence rose at treatment weeks 4–6 and again at weeks 10–12 (Dore, 2015b). The SYNERGY study, a phase 2 study of 60 patients with a history of drug use and high rate of psychiatric illness being treated at a community clinic, also found that overall adherence was high initially, but declined after 6 weeks. Although mental health issues did not impact adherence, this study found that recent drug use was a risk factor for non-adherence (Petersen et al., 2016). In contrast, other clinical trials have not found the same association between drug use and non-adherence. A post-hoc analysis of the phase 3 ION-1 study found that drug use during treatment had no impact on non-adherence (Grebely, 2016). These phase 2 and 3 clinical trials provide insight into predictors of non-adherence among people who use drugs, yet adherence patterns in the closely monitored setting of a registered clinical trial may not mirror real-world practice. The RISE II Study, which evaluated real-world adherence to DAAs among 61 patients receiving OST, found that adherence was comparable to registration trials and drug use during treatment was associated with decreased adherence (Litwin, 2016). Although this study provides evidence regarding real-world adherence patterns, the patient population was restricted to those receiving OST and cannot be generalized to the much larger population of people who use drugs yet do not receive OST.

A greater understanding of DAA adherence among people who use substances in real-world settings is instrumental to adequately addressing the current HCV epidemic. The purpose of this study was to evaluate patterns and factors associated with non-adherence among marginalized people who use drugs and/or alcohol and who were receiving DAAs outside of a phase 2 or 3 clinical trial through a community-based, multi-disciplinary HCV treatment program that operates from a harm reduction framework but does not offer on-site OST.

Methods

Program model

The Toronto Community Hep C Program (TCHCP) is a community-based model of HCV care that was designed to provide low-threshold access to HCV treatment for underserved populations. Since 2007, the TCHCP has provided HCV treatment and support for people living in poverty and who use drugs and/or alcohol. The TCHCP is a partnership between three community-based health centres with integrated on-site specialist support. All three health centres have a priority mandate to serve people who are experiencing difficulties accessing conventional medical, social and community services due to low literacy or income levels; housing, family or drug use problems; gender, sexuality, race, culture or mental health issues. HCV care is delivered by nurses, nurse-practitioners and family physicians. Weekly psycho-educational support groups anchor the provision of HCV treatment at each primary care health centre, where clients also have access to case management, harm reduction supplies/programming, counselling, peer support workers, a healthy meal and other services. The program is based on the theories and practices of harm reduction, community development and popular education (Dodd et al., 2016). The program model and its successful treatment/psycho-social outcomes have been detailed previously (Charlebois, Lee, Cooper, Mason, & Powis, 2012; Mason et al., 2015).

Study sample

Any client who was initiating treatment with an interferon-free DAA regimen through the TCHCP was approached to participate in the study starting in July 2015. Participants received sofosbuvir/ledispasvir (1 pill per day), sofosbuvir/daclatasvir (2 pills per day), elbasvir/grazoprevir (1 pill per day) or sofosbuvir and ribavirin (3–4 pills per day); when ribavirin was used in treatment regimens it was dosed twice daily and adjusted based on clients weight ($<$75 kg 1000 mg, $\geq$75 kg 1200 mg). Clients were excluded if they were participating in other HCV treatment studies or if they could not complete the study questionnaires in English. Participants were assessed at baseline (within one month prior or within two weeks of starting treatment) and at treatment completion. Only participants who initiated at least one dose of DAA were included in the analysis. Participants could only be enrolled in the study once. SVR analyses were restricted to only those participants who had reached the SVR12 assessment time point (12 weeks after completion of therapy). SVR proportions were evaluated in both an intention to treat (ITT) and modified intention to treat (mITT) analysis (patients within the ITT population excluding those with an undetectable HCV RNA at end of treatment (end of treatment response (ETR)), yet no SVR12 assessment). Research ethics approval was obtained through Michael Garron Hospital.

Study measures

Medication adherence questionnaires were self-administered and completed weekly. The questionnaire was designed and administered based on best practice quality standards for measuring medication adherence which included: neutral assessment language, a short time frame for adherence estimation and separation of adherence reporting from the health care provider relationship (Williams, Amico, & Womack, 2013). The adherence assessment tool was also piloted with the program's Patient Advisory group and feedback was incorporated in the final version prior to implementation. Each week, participants received an envelope containing the adherence questionnaire from a member of the HCV team with the instruction to return it sealed, once completed. Participants were instructed to "Please tell us what is really happening for you (not what you think we want to hear). Your answers will help us to understand how to better support people who are going through Hep C treatment. Your answers are confidential and will not be shared with any of your Hep C care providers." The questionnaire asked: "During the past 7 days, on how many days have you missed taking any of your Hep C pills?" The questionnaire also contained questions about dose-timing adherence and reason(s) for missed pills.

Pre- and post-treatment questionnaires were administered by a research coordinator who was not part of the clinical care team. Questionnaires examined socio-demographics, program engagement, physical and mental health co-morbidities and substance use. Overall health status was measured using a question from the Canadian Community Health Survey that asked respondents to rate their overall general health on a 5-point scale from poor to excellent (Statistics Canada, 2003). Cognitive health was measured using the Perceived Deficit Questionnaire-Depression (previously known as the MSQLI) (Ritvo et al., 1997; Sullivan, Edgley, & Dehoux, 1990). This tool has been used as a reliable and valid measure in patients with other chronic health conditions (Dilorenzo, Halper, &

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Picone, 2003; Marrie, Miller, Chelune, & Cohen, 2003). Social support was measured using the Medical Outcomes Study – Social Support Survey (MOS-SSS), a 19-item questionnaire that measures perceived availability of four support domains using a 5-point scale item for each. Scores range from 19 to 95 with a high score indicating more support (Sherbourne & Stewart, 1991).

Participants were asked to self-identify gender. Housing status was categorized as stable or unstable based on participant self-report of current living situation. Stable housing included one's own apartment or house. Unstable housing included staying in a rooming/boarding home, friend/relative's place, hotel/motel, shelter/hostel, public place, transitional housing or in an institution. Participants were asked to report the highest level of education they had completed. Anyone who had completed only an elementary school level of education or less was categorized as having a 'low' level of formal education and everyone else was categorized as 'high'. History of incarceration was defined as any time served in either: juvenile detention, provincial/territorial or federal prison. Perceived health care discrimination was derived from a question used in a previous study on the access to health care of homeless adults which asked: "in all the experiences you have had with health care visits in the last 12 months, have you ever felt that the doctor or medical staff you saw judged you unfairly or treated you with disrespect? (yes/no)" (Khandor et al., 2011). Level of group support was determined by asking how often participants attended the weekly psycho-educational support group at the health centre where they received treatment and used a 5-point scale from 'never' to 'always'. Participants were asked about lifetime history of hospitalization for a mental health reason (yes/no), lifetime history of suicide attempt (yes/no), lifetime and past 30-day history of a significant period of depression (yes/no). Participants were also asked about lifetime and past 30-day history of injection drug use (yes/no) and non-injection drug use other than cannabis (yes/no). Receiving OST at baseline was determined by self-report and included methadone or suboxone. Moderate to heavy alcohol use was defined as consuming 'six or more standard drinks on one occasion' weekly or more. Fibrosis scores were collected via chart review and determined by Fibrotest or Fibroscan. Any participant with a fibrosis score of 4 was characterized as having cirrhosis.

Statistical analysis

The primary outcome was whether each treatment week on study contained one or more missed doses. Missing outcome data for a given week (resulting from a missed appointment or incomplete adherence questionnaires) was coded as having at least one missed dose. All univariate and multivariate analyses were performed in the context of Generalized Estimating Equations using an AR-1 correlation structure. The rationale for using this framework was the need to estimate odds ratios for the predictors while accounting for both patient level clustering and the longitudinal nature of the outcome data. Variables of potential importance were specified in advance by the researchers and tested in univariate analyses. Those variables with Wald Test p-values less than or equal to 0.25 in univariate analysis were included in the multivariable model. Alpha = 0.05 was used as the threshold for assessing statistical significance of model parameters. Data were analyzed using the *geepack* package in R version 3.0.2.

Results

A total of 74 participants completed baseline interviews and initiated HCV treatment. There were a total of 948 weekly study visits.

Participant characteristics

The majority of participants identified as male (76%, n = 56) and White/Caucasian (82%, n = 61). Most participants also reported very low incomes and levels of formal education. Nearly one third did not have stable housing (30%, n = 22). More than half (53%, n = 39) rated their overall health as 'fair or poor', 28% (n = 21) as 'good', 18% (n = 13) as 'very good' and only 1% (n = 1) as 'excellent'. The majority (81%, n = 60) reported a lifetime history of depression. All clients had a lifetime history of drug use (injection or non-injection) not including cannabis. Recent injection drug use in the past 30 days was reported by 11% (n = 8). Recent non-injection drug use was reported by 30% (n = 22). Only 24% (n = 18) received OST at baseline. Participant baseline characteristics are presented in Table 1.

Health care engagement

At baseline, 92% (n = 68) of participants "often or always" agreed with the statement "my health care provider and I trust one another" and 99% (n = 71) felt that program staff were "often or always" easy to talk to and encouraged questions. One third (32%) had been with the program or health centre more than 5 years, 42% (n = 31) between 5 years to 1 year, and 26% (n = 19) less than 1 year. A large majority (88%, n = 65) reported that they always or often attend the program's weekly support group. 31% (n = 23) reported that they had experienced perceived discrimination from any health care provider seen in the past year. Not including HCV medication, participants were taking a median of 2 (IQR 1–5) prescriptions. The median length of time since HCV diagnosis was 17 years (IQR 8–23).

HCV treatment outcomes

Most participants (80%, n = 59) were genotype 1; 20% (n = 15) were genotype 2 or 3. One third (32%, n = 24) had cirrhosis and 85% (n = 63) were treatment naive. The majority (76, n = 56) received sofosbuvir/ledipasvir (8–24 weeks); 22% (n = 16) received sofosbuvir and ribarvin (12–24 weeks), 1% (n = 1) sofosbuvir/daclatasvir and 1% (n = 1) elbasvir/grazoprevir. Just over a quarter (27%, n = 20) of participants were on treatment for 8 weeks, 58% (n = 43) for 12 and 15% (n = 11) for 24 weeks.

Client disposition throughout the study is outlined in Fig. 1. Overall, 93% (69/74) of participants were due for their 12-week post treatment assessment (SVR12 visit) at the time of analysis and were included in the treatment efficacy analysis. Of these 69 participants, 97% (67) completed treatment (one discontinued treatment at week two and one died on treatment of unknown cause). The overall ETR was 96% (66 of 69) and ITT SVR12 was 87% (60 of 69). Among the six participants who had anETR, yet did not achieve an SVR12, three participants had detectable HCV RNA at SVR12, two died between ETR and SVR12 (one of drug overdose and one of decompensated liver disease), and one was lost to follow-up. In a modified ITT analysis (excluding those with an undetectable HCV RNA at end of treatment without an SVR12 assessment), 91% (60 of 66) achieved SVR12.

Of the three who had detectable HCV RNA at SVR12, all had risk factors for non-response other than non-adherence. All were male with genotype 3 and two were cirrhotic. Among these three individuals, 1 had no missed doses, 1 had 9 weeks with a missed dose (10 doses missed in total) and 1 had 5 weeks with missed doses (15 doses missed in total). At baseline, two reported recent moderate to heavy alcohol use but no recent drug use and one reported no recent substance use of any kind. Recent injection drug use and recent non-injection drug use was not associated with SVR12 in both the ITT and mITT analysis (all $p > 0.05$). Within the subgroup of participants who reported recent injection drug use

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Table 1
Baseline characteristics of the cohort.

Characteristic	n = 74 (%)
Age (mean, SD)	54 (8)
Gender	
Male	56 (76)
Female	17 (23)
Transgender	1 (1)
Ethnicity	
White/Caucasian (only)	61(82)
Aboriginal	5 (7)
Income source (primary, past month)	
Disability assistance	51 (69)
Social assistance (welfare)	5 (7)
Other government assistance (pension, old age security)	8 (11)
Work (full or part-time)	5 (7)
Other[a]	4 (5)
Education	
Highest level completed—low (elementary or less)	33 (45)
Housing status—unstable	22 (30)
History of incarceration (lifetime)	64 (87)
Social support—MOS-SSS[b] (mean, SD)	61 (21)
Mental health status	
Depression—lifetime	60 (81)
Depression—past 30 days	14 (19)
History of hospitalization for mental health reason	20 (27)
Suicide attempt, lifetime	27 (37)
Cognitive impairment—PDQ-D (mean, SD)[c]	7.4 (4.7)
Substance use	
Any drug use[d]—lifetime	74 (100)
Injection drug use—lifetime	65 (88)
Injection drug use—past 30 days	8 (11)
Non-injection drug use[d]—lifetime	71 (96)
Non-injection drug use[d]—past 30 days	22 (30)
Opiate substation therapy (baseline)	18 (24)
Any alcohol use—past 30 days	39 (53)
Moderate to heavy alcohol use—past 30 days	13 (18)

[a] Other sources of income included: income from spouse, selling drugs, worker's compensation, private insurance injury claim.
[b] Medical Outcomes Study—Social Support Survey.
[c] PDQ-D: Perceived Deficit Questionnaire - Depression.
[d] Does not include cannabis.

(n = 7), all had undetectable HCV RNA at SVR12. Of participants who reported non-injection drug use (n = 21), all but one had undetectable HCV RNA at SVR12. The one without undetectable HCV RNA at SVR12 discontinued treatment at week 2.

Of those who had completed treatment by the time of analysis (n = 72) nearly half (47%, n = 34) reported experiencing a 'stressful life event' while on treatment, such as the death of a friend/family member, having to move, or incarceration. Half reported experiencing side effects (51%, n = 37), however, most side-effects were mild (57%, n = 21). Substance use while on treatment did not change significantly compared to baseline with 20% (n = 14) reporting injection drug use in the last 30 days of treatment, 35% (n = 25) non-injection drug use other than cannabis, 47% (n = 34) reporting any alcohol use and 14% (n = 10) reporting moderate to heavy alcohol use.

Adherence outcomes

At the time of analysis, 72 patients had completed treatment for the prescribed duration, 1 discontinued treatment at week two and

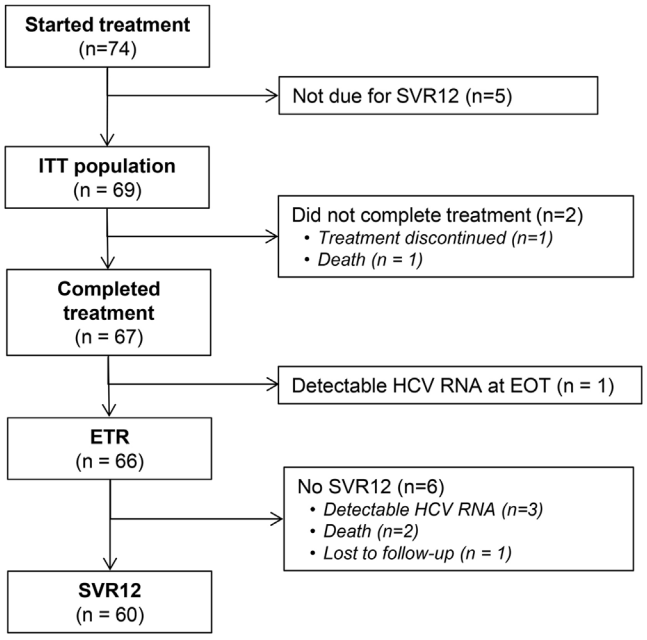

Fig. 1. Patient disposition.
The above figure describes the patient disposition throughout the study.
SVR12 = Sustained virologic response at 12 weeks post treatment completion.
EOT = End of treatment.
ETR = End of treatment response.
ITT = Intention to treat.

1 died while on treatment. All 74 patients were included in the adherence analysis. Overall, only 11% of treatment weeks had any missed doses. Treatment adherence is detailed in Fig. 2. Over one third (41%, n = 30) of participants had at least one missed dose; however, the mean number of missed doses in weeks with a missed dose was only 1.7 (sd = 1.6). Factors associated with weeks with missed doses are displayed in Table 2. In univariate analysis, drug use in the last 30 days (p = 0.01), moderate to heavy drinking in the last 30 days (p = 0.002), depression in the past 30 days (p = 0.03), treatment with an agent other than sofosbuvir/ledipasvir and later week of treatment (p = 0.003) were associated with weeks with missed doses. In the multivariable analysis the only factor independently associated with weeks with missed doses was moderate to heavy alcohol use (OR 2.9, 95% CI 1.0–8.8; p = 0.05).

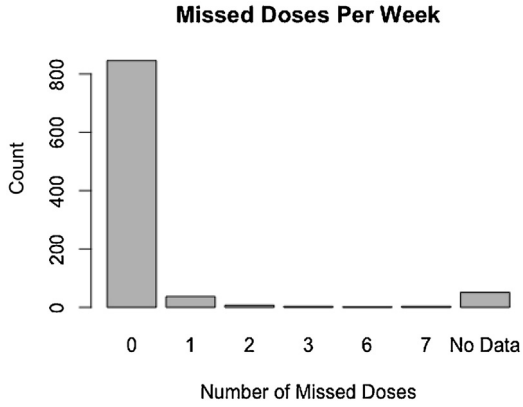

Fig. 2. The distribution of number of missed doses per week on DAA treatment.
The above figure represents a histogram of the number of missed doses each week during the study period. The vast majority of study participants did not report any missed doses during a week of treatment. No data indicates instances when participants missed their appointments or did not return their weekly adherence questionnaire.

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Table 2
Factors associated with weeks with missed doses of DAA among people with a lifetime history of substance use: crude and adjusted odds ratios (ORs) based on generalized estimation equation (GEE) logic models (n = 74 individuals, 948 visits).

	No. of visits (%) or median (IQR)	No. of participants	OR (95% CI)	p-Value	Adjusted OR (95% CI)
Gender					
Male	744 (78.5)	56	1		
Female	196 (20.7)	17	0.38 (0.12–1.2)	0.11	
Other	8 (0.8)	1	0 (0–0)	<0.001	
Education[c]					
Low	459 (48.4)	33	1		
High	489 (51.6)	41	0.58 (0.20–1.7)	0.31	
Housing status					
Stable	661 (69.7)	52	1		
Unstable	287 (30.3)	22	1.1 (0.38–3.2)	0.85	
Depression-past 30 days					
No	739 (78.0)	60	1		1
Yes	209 (22.0)	14	3.6 (1.1–12)	0.03	1.3 (0.4–5.0)
Injection drug use-past 30 days					
No	868 (91.6)	66	1		
Yes	80 (8.4)	8	1.3 (0.33–5.0)	0.72	
Drug use (non IDU)-past 30 days					
No	644 (67.9)	52	1		1
Yes	304 (32.1)	22	3.8 (1.4–11)	0.01	2.1 (0.85–5.3)
Opiate substitutions therapy					
No	748 (78.9)	56	1		
Yes	200 (21.1)	18	1.0 (0.35–3.2)	0.93	
Moderate to heavy drinking-past 30 days					
No	741 (78.2)	61	1		1
Yes	207 (21.8)	13	5.9 (1.9–18)	0.002	3.0 (1.0–8.8)[β]
Treatment type[d]					
Sof/Led	600 (63.3)	56	1		1
Sof/Rib	324 (34.2)	16	4.0 (1.4–11)	0.01	1.9 (0.69–5.2)
Other	24 (2.5)	2	2.4 (0.92–6.1)	0.07	1.4 (0.47–4.2)
Week number	7 (4–11)		1.1 (1.0–1.2)	0.01	1.6 (0.93–2.9)
Cognitive impairment (PDQ-D)[b]	6 (4–11)		1.1 (0.99–1.2)	0.08	1.0 (0.93–1.2)
Social support (MOSS SSS)[a]	58 (45–77)		0.99 (0.97–1.0)	0.24	0.48 (0.048–5.0)

Variables with Wald Test p-values less than or equal to 0.25 in univariate analysis were included in the multivariable model to determine adjusted OR.
[a] Medical Outcomes Study—Social Support Survey.
[b] Perceived Deficit Questionnaire - Depression.
[c] Low education level = completed elementary or less, high education level = completed high school or more.
[d] Sof/led = sofosbuvir/ledipasvir; Sof/Rib = sofosbuvir and ribarvin.
[β] $p \leq 0.05$.

Participants were asked the reasons as to why a dose had been missed and could select more than one response. The top three reported reasons were: forgot (cited 16 times), drug or alcohol use interfered (12 times), could not get to pill for reasons such as housing access, incarceration, or travel (10 times).

Discussion

Our study of DAA therapy for chronic hepatitis C among marginalized people with a history of drug use demonstrates that adherence was excellent and that only moderate to heavy alcohol use was associated with weeks with missed doses. Our study provides valuable insights into real-world adherence patterns and treatment outcomes among people who use drugs outside of OST-based clinical settings.

Overall, adherence was excellent despite multiple and intersectional health and social challenges that can act as barriers to adherence such as poverty, low education levels, mental health issues, and active substance use. Most study participants reported no missed doses and for those who did miss any doses, the mean number of doses missed per week was less than two. In addition, most missed doses were not reported as related to substance use and were unintentional due to forgetfulness or because participants were unable to get to their medication. The reason for the excellent adherence seen in our cohort is likely related, in large part, to the unique structure of the TCHCP. The program's harm reduction approach to substance use and its low barrier, non-judgemental atmosphere likely breached many of the traditional barriers to adherence and promoted strong, therapeutic relationships among clients with peers and care providers. A strong patient–provider relationship is a major factor associated with adherence to medication (Osterberg & Blaschke, 2005). Despite past negative experiences with the health care system reported by nearly one third of participants very high levels of trust with the TCHCP program staff were still observed. A systematic review specific to chronic cardiovascular disease therapies found that at

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the patient-level, poor understanding of one's disease, lack of involvement in treatment decision-making, low health literacy, low family or social support either contributed to or were predictive of non-adherence. At a systems-level, fragmented health care and poor care coordination have also been found to create barriers to adherence (Brown & Bussell, 2011). Our program strives, and has been purposefully designed to reduce many of these above barriers to medication adherence by actively empowering clients to take an active role in their healthcare by providing them with education, peer support and healthcare in a primary care, community-based setting where strong relationships already exist.

Our study of treatment adherence patterns among a group of marginalized people with a history of drug use did not find an association with adherence and recent intravenous or non-intravenous drug use. Past studies of our program have found a similar non-association between drug use and treatment initiation (Charlebois et al., 2012). Other studies have evaluated the association between recent drug use and non-adherence to DAAs with variable results (Dore, 2015a; Grebely, 2016; Litwin, 2016; Petersen et al., 2016). There are several possible reasons for the variability among these numerous studies. First, varying sample sizes and statistical analysis plans led to different statistical power to detect an association among the various studies. In our study we used a GEE model to maximize our statistical power to detect a difference, if one existed, despite our small sample size. Secondly, program structures varied. In the larger multicentre studies such as ION-1 and C-EDGE CO-STAR each clinic provided care according to their own standard practices, while in the single centre studies care was provide in the setting of addictions treatment and OST provision. Our study further suggests that with appropriate support, programmatic structure and principles, concerns about non-adherence for people who use drugs should not be considered as a barrier to more broad provision of DAAs.

Our study did, however, find that moderate to heavy drinking was associated with weeks with missed doses; an association that has similarly been found in studies of HCV treatment prior to the advent of DAAs and in other populations (Marcellin et al., 2011; Tran, Nguyen, Do, Nguyen, & Maher, 2014). Alcohol use and its impact on adherence has been evaluated extensively in the context of highly active antiviral therapy (HAART) for HIV. Although the association between alcohol use and non-adherence has been clearly demonstrated, causality is challenging to determine based on the limitations of the existing literature (Hendershot, Stoner, Pantalone, & Simoni, 2009). In our cohort it is likely that the less than optimal adherence of people who drink moderately to heavily is the result of multiple factors that are not easily explained given the complex social issues of the entire study population and requires further evaluation. When providing HCV therapy for marginalized populations who use substances additional supports for people who drink alcohol moderately to heavily should be considered to optimize adherence but should not be a basis for withholding treatment. This finding is supported by international recommendations and guidelines which highlight that people who use drugs and/or alcohol should not be denied treatment and should be considered for treatment on a case-by-case basis (AASLD-IDSA, 2015; EASL, 2017; INHSU, 2013).

Although DAA treatment efficacy was not the primary focus of our paper, our study demonstrated a mITT SVR comparable to that observed in phase III clinical trials of people with a history of injecting drug use receiving OST (Dore et al., 2016; Grebely et al., 2016) and real-world community-based studies among people with a history of injecting drug use (Read et al., 2017; Morris et al., 2017). In these real-world studies of HCV treatment outcomes among people with a history of injecting drug use, the ITT SVR (80–87%) were lower than the mITT SVR proportions (91%). A significant difference among the studies, however, is the reason for lack of SVR12 assessment data. In our study, clients did not have SVR12 assessment data related primarily to participant death, while in the other papers participants were lost to follow-up. It is unknown what proportion of lost to follow-up participants in the studies by Read et al. and Morris et al. that may have also died. Regardless, the number of participants lost to follow-up drive the substantial drop off in SVRs noted in the mITT and ITT analysis. Although, the provision of antiviral therapy for chronic HCV has been simplified substantially through the development of DAAs, in order to maximize the health impact of SVR, programs that provide HCV treatment should include robust models of post-treatment care to retain clients in care until SVR12 assessment and beyond. The need for supportive and comprehensive care models, as well as an individualized approach to treatment is further highlighted by the high number of study participant deaths in our study which also suggests that people who use drugs should be treated when they are ready (and not only once hepatic fibrosis has progressed) as HCV treatment has the potential to offer opportunities for further health care engagement and improvements to quality of life (Mason et al., 2015; Newman et al., 2013).

Limitations

Due to the voluntary nature of this study our sample likely included participants who are more compliant and thus may be limited by a positive selection bias. In addition, most variables were determined based on self-report and may be subject to recall, social desirability or Hawthorne effect biases. Electronic pill counting was not feasible for this community-driven study and although adherence may be overestimated, this is somewhat mitigated by use of self-report, a short time frame and by our statistical analysis which counted missed data as missed dose. Studies comparing self-report and electronic monitoring of adherence with similar populations have found good correlation (Arnsten et al., 2001; Shi et al., 2010). Recall bias was minimized by using a short-time frame. Social desirability bias was reduced since responses were self-administered outside of the clinician-patient encounter and kept confidential from health care providers. The harm reduction orientation of the program model, which fosters openness, and lack of judgment about substance use likely also supported greater honestly about non-adherence. Missing data was counted as a missed dose in this study. It is possible that missing data does not actually reflect non-adherence and thus non-adherence may be overestimated in some cases. Although our sample size was relatively small it is the largest real-world study to our knowledge to address DAA among marginalized people who use drugs and where OST is not predominate. Additionally, our analysis was conducted to treat each week as a unique event thereby maximizing statistical power to detect factors associated with a week with missed doses. Although our program is not OST based, it provides an intensive level of support that may not be available or generalizable to other settings.

Conclusion

This study provides real world evidence and insight into DAA adherence patterns of marginalized people who use drugs as well as factors associated with weeks with missed doses. It demonstrates that in the context of social marginalization and high rates of substance use, a community-based, supportive model of HCV treatment can promote high levels of adherence and achieve treatment outcomes that are comparable to registered clinical trials. Concerns about non-adherence for people who use drugs should not be a barrier to provision of DAA therapy, however, better supports should be considered to support people who use alcohol

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moderately to heavily. Scaling up appropriate treatment models for marginalized people who use drugs and alcohol will ensure SVR and thereby address the current HCV epidemic among the population that is most impacted. People who use drugs are a diverse group who can, and do, successfully adhere to DAA HCV treatment.

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Conflict of interest

The authors declare no conflict of interests.

References

AASLD/IDSA HCV Guidance Panel (2015). Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*, *62*, 932–954.

Alavi, M., Raffa, J., Deans, G. D., Lai, C., Krajden, M., Dore, G. J., . . . Grebely, J. (2014). Continued low uptake of treatment for hepatitis C virus infection in a large community-based cohort of inner city residents. *Liver International*, *34*(8), 1198–1206.

Arnsten, J. H., Demas, P. A., Farzadegan, H., Grant, R. W., Gourevitch, M. N., Chang, C. J., . . . Schoenbaum, E. E. (2001). Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: Comparison of self-report and electronic monitoring. *Clinical Infectious Diseases*, *33*(8), 1417–1423.

Blach, S., Zeuzem, S., Manns, M. P., & Razavi, H. A. (2017). Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. *The Polaris Observatory HCV Collaborators. Lancet Gastroenterology & Hepatology*, *2*, 161–176.

Brown, M. T., & Bussell, J. T. (2011). Medication adherence: WHO cares? *Mayo Clinic Proceedings*, *86*, 304–314.

Charlebois, A., Lee, L., Cooper, E., Mason, K., & Powis, J. (2012). Factors associated with HCV antiviral treatment uptake among participants of a community-based HCV programme for marginalized patients. *Journal of Viral Hepatitis*, *19*(12), 836–842.

Dilorenzo, T., Halper, J., & Picone, M. A. (2003). Reliability and validity of the multiple sclerosis quality of life inventory in older individuals. *Disability and Rehabilitation*, *25*(16), 891–897.

Dodd, Z., Banga, C. A., Mason, K., Meaney, C., Leszcz, L., & Sockalingam, S. (2016). Engagement in group psychotherapy among marginalized individuals with hepatitis C. *International Journal of Group Psychotherapy*, *66*(3), 338–360.

Dore, G. (2015a). C Edge Co-Star: Adherence and drug use in HCV-infected persons on opioid agonist therapy receiving elbasvir/grazoprevir fixed dose combination for 12 weeks. *Paper presented at the 4th International Symposium on Hepatitis Care in Substance Users*, Presentation retrieved from: https://www.eiseverywhere.com/file_uploads/3f3623614b2115f0d3cf584977e25537_GregDore.pdf.

Dore, G. (2015b). C-EDGE CO-STAR: Efficacy of grazoprevir/elbasvir fixed dose combination for 12 weeks in HCV-infected persons who inject drugs on opioid agonist therapy. *Paper presented at 66th Annual Meeting of the American Association for the Study of Liver Disease*, Presentation retrieved from: http://www.natap.org/2015/AASLD/AASLD_08.htm.

Dore, G. J., Altice, F., Litwin, A. H., Dalgard, O., Gane, E. J., Shibolet, O., . . . on behalf of the C.E.C.O.S.S.G (2016). Elbasvir-grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: A randomized trial. *Annals of Internal Medicine*, *165*(9), 625–634.

European Association for the Study of the Liver (EASL) (2017). EASL recommendations on treatment of hepatitis C 2016. *Journal of Hepatology*, *66*, 153–194.

Grebely, J., Raffa, J. D., Lai, C., Krajden, M., Kerr, T., Fischer, B., & Tyndall, M. W. (2009). Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. *Journal of Viral Hepatitis*, *16*(5), 352–358.

Grebely, J. (2016). On-treatment illicit drug use did not impact treatment outcome during therapy with ledipasvir/sofosbuvir with or without ribavirin in the phase 3 ION-1 study. *Paper presented at The International Liver Congress, European Association for the Study of the Liver*, Presentation retrieved from: http://www.natap.org/2016/EASL/EASL_115.htm.

Grebely, J., Mauss, S., Brown, A., Bronowicki, J. P., Puoti, M., Wyles, D., . . . Dore, G. J. (2016). Efficacy and safety of ledipasvir/sofosbuvir with and without ribavirin in patients with chronic HCV genotype 1 infection receiving opioid substitution therapy: Analysis of phase 3 ION trials. *Clinical Infectious Diseases*, *63*(11), 1405–1411.

Hendershot, C. S., Stoner, S. A., Pantalone, D. W., & Simoni, J. M. (2009). Alcohol use and antiretroviral adherence: Review and meta-analysis. *Journal of Acquired Immune Deficiency Syndrome*, *52*(2), 180–202.

International Network on Hepatitis in Substance Users (INHSU) (2013). Recommendations for the management of hepatitis C virus infection among people who inject drug. *Clinical Infectious Disease*, *57*, 129–137.

Iversen, J., Grebely, J., Topp, L., Wand, H., Dore, G., & Maher, L. (2014). Uptake of hepatitis C treatment among people who inject drugs attending Needle and Syringe Programs in Australia, 1999–2011. *Journal of Viral Hepatitis*, *21*(3), 198–207.

Khandor, E., Mason, K., Chambers, C., Rossiter, K., Cowan, L., & Hwang, S. W. (2011). Access to primary health care among homeless adults in Toronto, Canada: Results from the Street Health survey. *Open Medicine*, *5*(2), e94–e103.

Litwin, A. H. (2016). High rates of sustained virological response in people who inject drugs treated with all-oral direct acting antiviral regimens. *Paper presented at the 5th International Symposium on Hepatitis Care in Substance Users*, Presentation retrieved from: https://www.eiseverywhere.com/file_uploads/ec626d74ab97207d900ddc93eeb18144_166_AlainLitwin.pdf.

Marcellin, P., Chousterman, M., Fontanges, T., Ouzan, D., Rotily, M., Varastet, M., . . . CheObs Study Group (2011). Adherence to treatment and quality of life during hepatitis C therapy: A prospective, real-life, observational study. *Liver International*, *31*(4), 516–524.

Marrie, R. A., Miller, D. M., Chelune, G. J., & Cohen, J. A. (2003). Validity and reliability of the MSQ LI in cognitively impaired patients with multiple sclerosis. *Multiple Sclerosis Journal*, *9*(6), 621–626.

Mason, K., Dodd, Z., Altenberg, J., Meaney, C., Millson, P., & Powis, J. (2015). Beyond viral response: A prospective evaluation of a community-based, multidisciplinary, peer-driven model of HCV treatment and support. *International Journal of Drug Policy*, *26*(10), 1007–1013.

McGowan, C., & Fried, M. (2012). Barriers to hepatitis C treatment. *Liver International*, *32*(1), 151–156.

Morris, L., Smirnov, A., Kvassay, A., Leslie, E., Kavanagh, R., . . . Najman, J. (2017). The impact of integrated community-based hepatitis C treatment for people who inject drugs: Findings from the Queensland Injectors' Health Network. *International Journal of Drug Policy*(in press).

Nelson, P. K., Mathers, B. M., Cowie, B., Hagan, H., Des Jarlais, D., Horyniak, D., & Degenhardt, L. (2011). Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*, *378*(9791), 571–583.

Newman, A., Beckstead, S., Beking, D., Finch, S., Knorr, T., Lynch, C., . . . Shore, R. (2013). Treatment of chronic hepatitis C infection among current and former injection drug users within a multidisciplinary treatment model at a community health centre. *Canadian Journal of Gastroenterology*, *27*(4), 217–223.

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *New England Journal of Medicine*, *353*, 487–497.

Petersen, T., Townsend, K., Gordon, L., Sidharthan, S., Silk, R., Nelson, A., Gross, C., . . . Kohli, A. (2016). High adherence to all-oral directly acting antiviral HCV therapy among an inner-city patient population in a phase 2a study. *Hepatology International*, *10*(2), 310–319.

Read, P., Lothian, R., Chronister, K. J., Gilliver, R., Kearley, J., & Dore, G. J. (2017). Delivery direct acting antiviral therapy for hepatitis C to highly marginalised and current drug injection populations in a targeted primary health care setting. *International Journal of Drug Policy*(in press).

Ritvo, P. G., Fischer, J. S., Miller, D. M., Andrews, H., Paty, D. W., & LaRocca, N. G. (1997). *Multiple sclerosis quality of life inventory: A user's manual*. New York: National Multiple Sclerosis Society.

Sarpel, D. (2016). Non-adherence is the most important risk factor for ledipasvir/sofosbuvir HCV treatment failure in the real world. *Paper presented at the American Association for the Study of Liver Disease Meeting 2016*, Presentation retrieved from: http://www.natap.org/2016/AASLD/AASLD_75.htm.

Sherbourne, C. D., & Stewart, A. L. (1991). The MOS social support survey. *Social Science & Medicine*, *32*(6), 705–714.

Shi, L., Liu, J., Koleva, Y., Fonseca, V., Kalsekar, A., & Pawaska, M. (2010). Concordance of adherence measurement using self-reported adherence questionnaires and medication monitoring devices. *Pharmacoeconomics*, *28*(12), 1097–1107.

Statistics Canada (2003). *Canadian Community Health Survey, Cycle 1.2. Mental health and well-being*. Retrieved from Statistics Canada website: http://www23.statcan.gc.ca/imdb-bmdi/instrument/5015_Q1_V1.eng.pdf. (Accessed 30 November 2016).

Sullivan, M. J., Edgley, K., & Dehoux, E. (1990). A survey of multiple sclerosis. Part I: Perceived cognitive problems and compensatory strategies use. *Canadian Journal of Rehabilitation*, *4*, 99–105.

Tran, B. X., Nguyen, L. T., Do, C. D., Nguyen, Q. L., & Maher, R. M. (2014). Associations between alcohol use disorders and adherence to antiretroviral treatment and quality of life amongst people living with HIV/AIDS. *BMC Public Health*, *14*(27).

Williams, A. B., Amico, K. R., & Womack, J. A. (2013). A proposal for quality standards for measuring medication adherence in research. *AIDS and Behavior*, *1*, 284–297.

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