Patterns of Drug and Alcohol Use and Injection Equipment Sharing Among People With Recent Injecting Drug Use or Receiving Opioid Agonist Treatment During and Following Hepatitis C Virus Treatment With Direct-acting Antiviral Therapies: An International Study

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Background. In many settings, recent or prior injection drug use remains a barrier to accessing direct-acting antiviral treatment (DAA) for hepatitis C virus (HCV) infection. We examined patterns of drug and alcohol use and injection equipment sharing among people with recent injecting drug use or receiving opioid agonist treatment (OAT) during and following DAA-based treatment.

Methods. SIMPLIFY and D3FEAT are phase 4 trials evaluating the efficacy of DAA among people with past 6-month injecting drug use or receiving OAT through a network of 25 international sites. Enrolled in 2016–2017, participants received sofosbuvir/velpatasvir (SIMPLIFY) or paritaprevir/ritonavir/dasabuvir/ombitasvir ± ribavirin (D3FEAT) for 12 weeks and completed behavioral questionnaires before, during, and up to 2 years posttreatment. The impact of time in HCV treatment and follow-up on longitudinally measured longitudinally measured behaviors was estimated using generalized estimating equations.

Results. At screening, of 190 participants (mean age, 47 years; 74% male), 62% reported any past-month injecting 16% past-month injection equipment sharing, and 61% current OAT. Median alcohol use was 2 (Alcohol Use Disorders Identification Test—Consumption; range, 1–12). During follow-up, opioid injecting (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.92–0.99) and sharing (OR, 0.87; 95% CI, 0.80–0.94) decreased, whereas no significant changes were observed for stimulant injecting (OR, 0.98; 95% CI, 0.94–1.02) or alcohol use (OR, 0.99; 95% CI, 0.95–1.04).

Conclusions. Injecting drug use and risk behaviors remained stable or decreased following DAA-based HCV treatment. Findings further support expanding HCV treatment to all, irrespective of injection drug use.

Clinical Trials Registration. SIMPLIFY, NCT02336139; D3FEAT, NCT02498015.

Keywords. DAA; drug use; hepatitis C; injecting drug use; PWID.

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Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease, cirrhosis, and liver cancer, affecting more than 71 million people globally [1, 2]. The burden of HCV infection is disproportionately high among people who inject drugs (PWID) currently or formerly, such as those receiving opioid agonist treatment (OAT) for the management of opioid dependence [3–5]. The development of direct-acting antiviral (DAA) therapies, which are considerably more efficacious and tolerable than previous interferon-based combinations, makes HCV infection a curable disease in nearly all patients with access to treatment. Several studies, including some conducted

by our group, have demonstrated high efficacy of DAA therapy among PWID, irrespective of whether or not they receive OAT or report recent injection [6]. However, uptake of treatment is low [7–9].

The high cost of DAA therapies led to restricted reimbursement in many settings [10–12]. Despite clinical guidelines that recommend DAA treatment for nearly all patients with HCV [13, 14], recent drug and/or alcohol use persists as a restriction to accessing therapy [10–12]. Even in settings where such restrictions do not exist, many physicians are hesitant to treat people who are actively injecting drugs or receiving OAT given concerns regarding continuing or increasing injecting risk behaviors with a consequent risk of HCV reinfection [15].

To date, no study has examined whether and how patterns of drug use and injection risk behaviors change following DAA treatment. Three studies, all conducted in the pre-DAA era, reported stable or decreasing drug-related behaviors during and in the immediate period posttreatment with pegylated interferon alpha ($\pm$ ribavirin) [16–18]. Among 124 people with a history of injecting in Australia, injection drug use remained stable and ancillary injection equipment sharing decreased during and 6 months posttreatment [17]. Among 87 PWID in Montreal, Canada, those who engaged in HCV treatment were less likely to report injecting drug use at 1-year follow-up compared to those who chose not to engage in care [16]. Finally, among 93 PWID followed in an international multicenter clinical trial, drug injecting and alcohol use decreased during and/or 6 months posttreatment, yet no changes were noted for sharing behaviors [18]. In addition to being limited by a short follow-up posttreatment, these investigations only reported average changes in drug use behaviors within the population and over time. Exploring whether and how trends evolve differently for some patients can help clinicians tailor therapeutic actions to optimize health outcomes. Therefore, our aim in this study was to examine longitudinal patterns of drug and alcohol use and injection equipment sharing among people with recent injecting drug use or receiving OAT during and following DAA-based treatment for chronic HCV infection.

METHODS

Study Design and Sample

This study is a pooled analysis of 2 international, multicenter, open-label, single-arm, phase 4 trials to evaluate the efficacy and safety of HCV DAA treatment and its impact on clinical and nonclinical outcomes in HCV-infected people with recent injecting drug use or currently receiving OAT: SIMPLIFY and D3FEAT. Study procedures are similar across the 2 studies and have been previously published along with efficacy and safety findings [19, 20]. Briefly, participants received sofosbuvir/velpatasvir once daily (SIMPLIFY) or paritaprevir/ritonavir/dasabuvir/ombitasvir $\pm$ ribavirin twice daily (D3FEAT) for 12

weeks. Recruitment was conducted through a network of drug and alcohol, hospital, and community clinics and private practices at 25 sites in Australia ($n = 7$), Canada ($n = 6$), France ($n = 2$), New Zealand ($n = 2$), Norway ($n = 1$), Switzerland ($n = 4$), the United Kingdom ($n = 1$), and the United States ($n = 1$). Recruitment occurred between March 2016 and October 2016 in SIMPLIFY and June 2016 and February 2017 in D3FEAT. Participants had to be aged >18 years, have chronic HCV infection, and be HCV treatment-naïve. In SIMPLIFY, participants must have injected drugs in the last 6 months. In D3FEAT, participants must have injected drugs in the last 6 months or be receiving OAT. A total of 190 participants were recruited (SIMPLIFY, $N = 103$; D3FEAT, $N = 87$).

Procedures

Participants completed a self-administered behavioral questionnaire on a tablet computer at screening (pretreatment assessment), baseline (treatment commencement), every fourth week during treatment (weeks 4, 8, 12 [end of treatment]), weeks 24 (sustained virological response [SVR]12) and 36 (SVR24), and 6-month intervals thereafter (weeks 60, 84, and 108) for a total of 10 visits. Questionnaires were developed through focus-testing with PWID and have been used by our group previously in the ACTIVATE study [21]. They collected information on demographics, drug and alcohol use, injecting equipment sharing, and drug treatment. In addition to behavioral surveys, study visits included standard laboratory testing (eg, liver function tests, full blood count), an assessment of adverse events, and, at prespecified select intervals, physical examinations (screening, baseline, weeks 4 and 12), HCV RNA testing (screening, baseline, weeks 12 and 24), HCV genotyping, and fibrosis stage (screening). During treatment, participants attended the clinic on a weekly basis to receive their medication supply. Study nurses and physicians provided counseling and access to ancillary services (eg, injection equipment, OAT) as per the standard of care in their country. All participants provided written informed consent to participate and received the equivalent of AUS\$20 reimbursement for their time at each visit. The study protocol was approved by the St Vincent's Hospital, Sydney Human Research Ethics Committee and local ethics committees at all study sites and was conducted according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines.

Measures

The following 5 behavioral outcomes were evaluated in relation to HCV treatment: injection drug use (any), opioid and stimulant injection, injection equipment sharing, and alcohol use. Opioids included heroin or prescription opioids, and stimulants included cocaine or amphetamine. Injection equipment sharing was defined as receptive sharing of needles, syringes, spoons or mixing containers, drug solution, water, or filters. Alcohol

use was assessed using the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C; score range, 1–12) [22]. Scores of 3 or more (women) and 4 or more (men) indicate hazardous consumption or active alcohol use disorders [22]. Receipt of OAT was also evaluated in relation to HCV treatment and defined as treatment with methadone, buprenorphine, or buprenorphine-naloxone. Noninjected opioids and stimulants were examined as secondary outcomes, given their limited connection to HCV infection and liver-related outcomes. Except for alcohol, all variables were assessed on a binary scale (yes/no) with respect to the previous month (drugs) or currently (OAT). Alcohol use was evaluated in count form.

Statistical Analyses

Descriptive statistics were used to summarize participants' characteristics at screening. Main analyses involved estimating average changes in behaviors over time using a generalized estimating equation (GEE) extension of logistic regression. GEE models were specified using a binomial family function and a logit link for binary variables and an identity family function and a Poisson link for count variables. Models estimated the effect of time since screening on each outcome using the odds ratio (OR) and 95% confidence interval (CI). The time effect was assessed in incremental study visits, irrespective of varying time lapses between visits. To control for behavioral changes attributed to changing OAT patterns over time, models were adjusted for this factor as a time-varying covariate. Fixed covariates (eg, age, sex) had no influence on parameter estimates and were therefore not included in the models.

Since assessment of average behavioral patterns could mask heterogeneity among individuals over time, in secondary

analyses, group-based trajectory modeling was used to visually inspect the presence of distinct longitudinal patterns. This method is used to identify relatively homogeneous clusters of trajectories of stability or change over time in the presence of repeated observations [23, 24]. For each behavioral outcome, the number of groups and their shape were informed by previous studies examining drug use trajectories [25, 26] and several statistical criteria [23, 24]. We considered models with up to 4 and 5 groups for binary and count outcomes, respectively. For each outcome, the final number of groups was determined by selecting the model that maximized the Bayesian information criteria as long as the Bayes factor was <0.1 and membership in each trajectory group was more than 5%. To describe the shape of trajectories, quadratic and cubic polynomials were considered sufficiently flexible for binary and count variables, respectively. We then obtained more parsimonious models by excluding polynomial terms that did not attain statistical significance at the 5% level.

At the time of this analysis (November 2018), follow-up was still ongoing, and analyses were conducted on available data. To minimize the potential for selection bias due to losses to follow-up while accounting for participants who had yet to come back for a study visit, we developed a conservative definition of study retention a priori and refitted the GEE models among individuals who met this criterion. Study retainment was defined as having completed all 5 visits of screening and during treatment and an additional any 2 afterward. Overall, 151 (79.5%) met our predefined criteria for study retention.

Missing values due to participant nonresponse were infrequent (<4% for any one variable) and were left as is. Analyses were performed in SAS 9.4 (SAS Institute Inc, Cary, NC) and the traj macro [25].

Table 1. Descriptive Characteristics at Study Entry for People With Recent Injection Drug Use or Receiving Opioid Agonist Treatment Recruited and Followed in SIMPLIFY and D3FEAT

Variable	Total (N = 190)	SIMPLIFY (n = 103)	D3FEAT (n = 87)
Age, mean (standard deviation), y	47 (9)	47 (9)	47 (10)
Male sex	141 (74%)	74 (72%)	67 (78%)
Completed high school education	92 (49%)	50 (49%)	42 (49%)
Unstable housing, past 6 months	33 (18%)	23 (22%)	10 (12%)
Any injection drug use, past month	117 (62%)	77 (75%)	40 (47%)
Opioid injection, past month	88 (47%)	58 (56%)	30 (35%)
Stimulant injection, past month	58 (39%)	39 (39%)	19 (23%)
Noninjecting opioid use, past month	42 (23%)	26 (26%)	16 (19%)
Noninjecting stimulant use, past month	48 (26%)	28 (28%)	20 (24%)
Sharing of injection equipment, past month	28 (16%)	22 (22%)	6 (8%)
Currently receives opioid agonist treatment	114 (61%)	53 (52%)	61 (72%)
Alcohol use score, ^a median (interquartile range)	2 (0–4)	2 (0–4)	1 (0–4)
≥Advanced fibrosis ^b	32 (18%)	18 (19%)	14 (16%)

Except for age and gender, data were unavailable for 2 participants recruited in D3FEAT. Missing values are reflected in the frequency distributions for each variable.

^a Measured using the Alcohol Use Disorders Identification Test–Consumption.

^b Advanced fibrosis was defined as having a METAVIR score of F3 or higher.

RESULTS

Characteristics of Study Participants

Table 1 presents the characteristics of the 190 participants at screening. Overall, nearly three-quarters of participants were male (74%) with mean age of 47 years (standard deviation, 9). Most had injected drugs in the past month (62%) and were receiving OAT (61%). Major drug classes injected were opioids (47%) and stimulants (32%). Sixteen percent reported sharing injection equipment in the past month. The median alcohol use score, evaluated using the AUDIT-C test, was 2 (interquartile range [IQR], 0–4). Although similar in age and gender distribution, compared to participants recruited in D3FEAT, those enrolled in SIMPLIFY were more likely to report recent unstable housing (22% vs 12%), drug use (eg, injection drug use: 75% vs 47%), and injection equipment sharing (22% vs 8%) and were less likely to be receiving OAT (52% vs 72%), consistent with study inclusion criteria.

Average Behavioral Changes During and Following HCV Treatment

During follow-up, participants had a median of 8 visits (IQR, 7–9) and contributed to a total of 1471 observations. Figure 1 presents the overall proportion of participants reporting each behavioral outcome and their median alcohol use at each visit. Table 2 presents the results of GEE analyses. As ORs remained unchanged after adjusting for OAT, only adjusted estimates are presented. A modest decrease was noted for any injection drug use; each additional study visit was associated, on average, with a 4% decrease in odds of past-month injecting. When examining classes of injected drugs separately, only opioid injecting decreased over time, whereas stimulant injecting did not. For sharing of injection equipment, a more pronounced decrease was noted; each additional study visit was associated, on average, with a 13% decrease in odds of past-month sharing. Alcohol use, receipt of OAT, and noninjecting stimulant use did not appear to change during follow-up. A modest and nonstatistically significant decrease was observed for noninjecting opioid use.

Trajectories of Behavioral Outcomes During and Following HCV Treatment

Figure 2 presents results of group-based trajectory analyses for 4 behavioral outcomes: opioid and stimulant injecting, injection equipment sharing, and alcohol use. Supplementary Table 1 presents the model selection process. For opioids, 3 distinct injection probability trajectories were identified: no (40%), sustained (33%), and decreasing (27%) injection. Among participants presenting with a decrease in opioid injecting, the decline was gradual and persistent throughout treatment and during the 2-year follow-up period. For stimulant injecting, 3 trajectories were identified: no (60%), sustained (22%), and inconsistent (18%) injection. For injection equipment sharing, a 2-trajectory group was identified, 1 of no sharing (89%) and 1 of decreasing sharing (11%). As with opioids, the decline in

Figure 1. Proportion of participants reporting injecting drug use and sharing of injection equipment (A), median alcohol use (B), and proportion receiving opioid agonist treatment (OAT) and noninjecting drugs (C) at each visit, during and following direct-acting antiviral treatment for hepatitis C virus infection among people with recent injection drug use or receiving OAT recruited and followed in SIMPLIFY and D3FEAT (N = 190). Drug use outcomes and OAT refer to the past month and current period, respectively. Baseline visit refers to the date of treatment initiation. Follow-up periods 1, 2, and 3 correspond to weeks 60, 84, and 108 since treatment initiation, respectively. At screening, the sample size was 188 rather than 190 because behavioral data were unavailable for 2 participants recruited in D3FEAT. Abbreviations: BL, baseline; ETR, end of treatment; FU, follow-up; SCR, screening; SVR, sustained virological response; W, week.

sharing probability was gradual and persistent across the follow-up period. For alcohol, 4 distinct trajectories were identified, all of which remained stable during and following HCV treatment: no (31%), low (20%), moderate (33%), and high (16%) use. Trajectories for OAT receipt and noninjecting

Table 2. Changes in Behavioral Outcomes During and Following Direct-acting Antiviral Treatment for Hepatitis C Virus Infection Among People With Recent Injection Drug Use or Receiving Opioid Agonist Treatment Recruited and Followed in SIMPLIFY and D3FEAT, by Incremental Study Visits

Variable	Adjusted Odds Ratio (95% Confidence Interval) ^{a,b}	P Value
Injection drug use, past month	.96 (.92–.99)	.02
Opioid injection, past month	.95 (.92–.99)	.01
Stimulant injection, past month	.98 (.94–1.02)	.33
Sharing injection equipment, past month	.87 (.80–.94)	<.01
Alcohol use, past month	.99 (.95–1.04)	.75
Current opioid agonist treatment	.99 (.97–1.02)	.45
Noninjecting opioid use, past month	.96 (.91–1.01)	.16
Noninjecting stimulant use, past month	1.00 (.97–1.03)	.94

^aAdjusted for opioid agonist treatment at each visit.

^bThe estimated odds ratio indicates the average behavior change across 2 consecutive visits, irrespective of time lapses between visits.

Figure 2. Trajectories of behavioral outcomes during and following direct-acting antiviral treatment for hepatitis C virus infection among people with recent injection drug use or receiving opioid agonist treatment recruited and followed in SIMPLIFY and D3FEAT (N = 190). Solid lines represent the estimated probability of each behavioral outcome for each group, and dashed lines represent 95% confidence intervals. Behaviors refer to the past month period. Baseline visit refers to the date of treatment initiation. Follow-up periods 1, 2, and 3 correspond to weeks 60, 84, and 108 since treatment initiation, respectively. At screening, the sample size was 188 rather than 190 because behavioral data were unavailable for 2 participants recruited in D3FEAT. Example of interpretation: for stimulant injecting, 22% of participants injected stimulants at nearly all visits, 18% oscillated between injecting and noninjecting patterns, and 60% never injected. Abbreviations: BL, baseline; AUDIT-C, Alcohol Use Disorders Identification Test–Consumption; BL, baseline; ETR, end of treatment; FU, follow-up; SCR, screening; SVR, sustained virological response; W, week.

opioid and stimulant use remained stable throughout follow-up (Supplementary Figure 1).

Retention in Follow-up

With the exception of being slightly older (mean age, 47 vs 44 years; $P = .09$), participants classified as retained in follow-up ($n = 151$) were similar to those who were not ($n = 39$) with respect to all other characteristics (Supplementary Table 2). In

GEE analyses restricted to participants retained in follow-up, ORs remained largely unchanged (Supplementary Table 3).

DISCUSSION

This pooled analysis of 2 international multicenter studies evaluated longitudinal patterns of drug use behaviors during and following DAA-based HCV treatment among people with recent injecting drug use or receiving OAT, who often face difficulties

accessing treatment [10–12, 15]. Our study has 2 main findings. First, drug and alcohol use remained stable during follow-up or decreased slightly. Second, sharing of injection equipment underwent a gradual decrease over time. These findings are encouraging, given that sharing behaviors are the main driver of HCV reinfection among PWID [27]. Importantly, behavioral patterns were not transient but appeared to be persistent during the 2-year follow-up. Taken together, our findings do not support concerns of increasing injection drug use or risk behaviors following DAA-based HCV treatment and further endorse the removal of barriers to access for all infected PWID, irrespective of ongoing injection drug use.

The introduction of DAA treatment marks a shift away from the demanding therapeutic engagements of injectable interferon-based treatments to the relatively simple management of well-tolerated, all-oral regimens [28]. While previous studies, conducted in the interferon-era, showed some decreases in drug use and/or injection equipment sharing following treatment [16–18], concerns have arisen that the simplified treatment provision with DAAs may diminish opportunities to have a positive impact on nonclinical outcomes such as risk behaviors [28] or possibly even lead to increases [15]. Our study does not support this. Rather, it seems that for the majority of DAA-treated patients, engagement in treatment is unlikely to modify their drug use patterns. For some, however, it may be a cue to prompt motivation to decrease HCV risk behaviors and injection drug use. This finding underscores the importance of providing counseling and access to ancillary services alongside HCV treatment to ensure that patients have access to all the tools necessary to support them in making broader drug use changes.

Aside from a potential impact of treatment, it is also possible that the stable or decreasing drug use patterns observed reflect a moment in time when individuals were ready to make broader health changes, which in turn motivated HCV treatment-seeking. Supporting this premise is the stable OAT pattern observed throughout follow-up in those reporting OAT at screening, which contrasts with more common patterns of cycling-in and cycling-out of addiction treatment [29]. In a study that examined determinants of DAA treatment initiation among PWID, participants identified similar circumstances as “the right time for treatment” [30]. For more vulnerable and marginalized populations, HCV treatment is situated within a context of competing every day concerns [31]. It is therefore important that personal attitudes be considered in decisions around HCV treatment readiness and that any opportunity for engagement in care is fully seized upon.

While most participants reported low or moderate levels of alcohol use, approximately 16% reported heavy use, according to AUDIT-C criteria [22], and this pattern remained consistent throughout follow-up. Among people with chronic hepatitis C, heavy alcohol use has been linked to excess mortality [32].

While additional research is needed to document its impact on liver-related outcomes among people who achieved viral eradication, there is some evidence that suggests that liver complications post-SVR are lowest in people who do not drink alcohol [33]. Clinical practice guidelines on the management of HCV recommend that all patients who undertake treatment be offered counseling and support to avoid harmful alcohol consumption [13, 14, 34].

Our study has several limitations. First, given the absence of a comparison group of PWID not receiving DAA treatment, we cannot attribute behavioral changes to HCV treatment or any one intervention. Second, behavioral outcomes were based on self-reported data, which are prone to socially desirable responding and recall error. Although behaviors may be underestimated, self-reported information on drug use has been shown to be reliable and valid, particularly if assessed through computer-assisted surveys [35, 36]. Third, even though follow-up was fairly high for a drug-using population and no differences in drug use patterns were found among participants who were and were not retained, our data may have been influenced by losses to follow-up. Long-term changes should be interpreted with caution given the smaller number of participants followed up in later years.

Our findings may not be generalizable to the broader population of current and former PWID. Our study sample was fairly well engaged in health services, and a relatively modest proportion (16%) reported sharing behaviors compared to the prevalence typically reported among community-recruited PWID [37, 38]. Despite a broad geographic distribution of study participants, all were recruited in high-income settings, where there is typically greater capacity for HCV and addiction care delivery relative to low- and middle-income countries. Finally, participants had weekly contacts with healthcare professionals while on treatment, and it is unclear whether findings would be similar in the context of a simplified monitoring strategy, for which there is growing interest [39]. However, even if simplified HCV treatment options become available, many PWID may continue to benefit from regular monitoring and support while on treatment [40].

CONCLUSIONS

Our study results indicate that drug and alcohol use remains stable or decreases slightly and injection equipment sharing decreases during and following DAA-based HCV treatment among people with recent injecting or receiving OAT. These findings further support expanding HCV treatment to all infected PWID, irrespective of ongoing injection drug use. More broadly, our results suggest that even in the era of simplified DAA therapies, there are ways to enhance the delivery of treatment to afford opportunities for harm reduction. Additional research is needed to elucidate which interventions during HCV treatment can promote reductions in injection equipment

sharing. While the majority of people who undergo HCV DAA treatment will achieve cure, reductions in sharing behaviors and risk of HCV reinfection posttreatment will likely not be achieved unless treatment services include HCV counseling and are integrated with addiction treatment and harm-reduction services.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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