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Intensive Models of Hepatitis C Care for People Who Inject Drugs Receiving Opioid Agonist Therapy:

A Randomized Controlled Trial

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Abstract

Background: Many people who inject drugs (PWID) are denied treatment for hepatitis C virus (HCV) infection, even if they are receiving opioid agonist therapy (OAT). Research suggests that HCV in PWID may be treated effectively, but optimal models of care for promoting adherence and sustained virologic response (SVR) have not been evaluated in the direct-acting antiviral (DAA) era.

Objective: To determine whether directly observed therapy (DOT) and group treatment (GT) are more effective than self-administered individual treatment (SIT) in promoting adherence and achieving SVR among PWID receiving OAT.

Design: Three-group, randomized controlled trial conducted from October 2013 to April 2017. (ClinicalTrials.gov:)

Setting: Three OAT programs in Bronx, New York.

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Participants: Persons aged 18 years and older with genotype 1 HCV infection who were willing to receive HCV therapy on site in the OAT program. Of 190 persons screened, 158 were randomly assigned to a study group and 150 initiated treatment: DOT (n = 51), GT (n = 48), and SIT (n = 51).

Intervention: 2 intensive interventions (DOT and GT) and 1 control condition (SIT).

Measurements: Primary: adherence, measured by using electronic blister packs. Secondary: HCV treatment completion and SVR 12 weeks after treatment completion.

Results: Mean age was 51 years; 65% of participants had positive results on urine drug testing during the 6 months before treatment, and 75% reported ever injecting drugs. Overall adherence, estimated from mixed-effects models using the daily timeframe, was 78% (95% CI, 75% to 81%) and was greater among participants randomly assigned to DOT (86% [CI, 80% to 92%]) than those assigned to SIT (75% [CI, 70% to 81%]; difference, 11% [CI, 5% to 18%]; Bonferroni-corrected P = 0.001). No significant difference in adherence was observed between participants randomly assigned to GT (80% [CI, 74% to 86%]) and those assigned to SIT (difference, 4.7% [CI, −2% to 11%]; Bonferroni-corrected P = 0.29). The HCV treatment completion rate was 97%, with no differences among groups (P = 0.53). Overall SVR was 94% (CI, 89% to 97%); the SVR rate was 98% in the DOT group, 94% in the GT group, and 90% in the SIT group (P = 0.152).

Limitation: These findings may not be generalizable to PWID not enrolled in OAT programs.

Conclusion: All models of onsite HCV care delivered to PWID in OAT programs resulted in high SVR, despite ongoing drug use. Directly observed therapy was associated with greater adherence than SIT.

People who inject drugs (PWID) are at the heart of the hepatitis C virus (HCV) epidemic, and most HCV cases in the United States and other developed nations are related to illicit drug use (1). In the United States, cases of acute HCV infection increased annually from 2010 through 2015, rising more than 2.9-fold over this period, a growth driven predominantly by injection drug use (2). Hepatitis C virus results in up to 15 000 deaths annually and is the leading cause of cirrhosis and liver transplantation in the United States (3, 4). Outcomes of HCV treatment have improved substantially with the emergence of direct-acting antiviral (DAA) agents, which are associated with nearly 100% sustained virologic response (SVR) or HCV cure, defined as absence of detectable virus 12 weeks after therapy completion, convenient dosing, and few side effects (5). Sustained virologic response has been shown to improve quality of life (6–8) and to lengthen survival (9–11).

Despite the central role PWID occupy in the HCV epidemic, few are offered DAA treatment because of concerns regarding suboptimal adherence, cost, and medication resistance (12, 13). People who inject drugs face many adherence challenges, including mental illness, homelessness, lack of positive social support, poor adherence-related skills, low HCV-related knowledge, and poor access to and mistrust of the health care system (14–17). Yet, most PWID with HCV are willing to undergo treatment (18–21), and the simplicity of DAA therapy promises great advantages for achieving HCV cure. Despite these advances, optimal models of care that promote adherence and SVR for PWID have not been elucidated.

Opioid agonist therapy (OAT) programs are ideal settings in which to co-locate HCV therapy. Opioid agonist therapy is an effective strategy to reduce HCV risk behavior and active drug use (22, 23). Nationwide, more than 375 000 patients receive OAT in the form of methadone or buprenorphine from approximately 1500 opioid treatment programs (OTPs) (24), and conservative estimates suggest that more than 60% of PWID in OTPs have HCV infection (25). Several studies evaluating multidisciplinary models of care in drug-using and methadone-maintained patients in OTPs have demonstrated HCV treatment outcomes similar to those found in PWID who received interferon-based HCV therapy in large clinical trials (26, 27). However, limited DAA-era data on real-world outcomes among PWID in OAT programs suggest that SVR may be lower (85%) than has been observed in large clinical trials (28). Whether intensive models of care in the DAA era can improve outcomes among PWID in OAT programs is not yet known.

The goal of this randomized trial was to assess the effectiveness of 2 models of intensive onsite HCV care-directly observed therapy (DOT) and group treatment (GT)–compared with self-administered individual treatment (SIT) for promoting adherence, completing treatment, and achieving SVR. We hypothesized that rates of adherence, treatment completion, and SVR would be higher in the intensive intervention groups versus the control group. An additional goal was to examine the relationship between adherence and SVR, the relationship between drug use and adherence, and patient-level factors associated with both adherence and SVR.

Methods

Participants and Setting

Hepatitis C virus–infected PWID from 3 OAT programs in Bronx, New York, were enrolled beginning in October 2013, and participants were followed until April 2017. Potential participants were referred by clinicians if they were eligible for HCV treatment on the basis of guidelines from the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD/IDSA) (29). Eligibility was assessed by an oral screener and a confirmatory chart review. Eligible participants were aged 18 years or older, spoke English or Spanish, had HCV genotype 1, were psychiatrically stable, were willing to receive HCV therapy on site in their OAT program, were HCV treatment naive (or treatment experienced with interferon-based regimens after December 2014, when combination DAA treatment was available and interferon exposure no longer predicted response to therapy), were receiving OAT in person at the OTP medication window at least 3 times per week (once per week after June 2015), and could provide informed consent. Exclusion criteria included decompensated cirrhosis, inability to provide informed consent, pregnancy or breastfeeding, and hypersensitivity to HCV medication.

Study Design

This 3-group, multisite, unblinded trial randomly assigned participants to 1 of 3 models of care (DOT, GT, or SIT) in a 1:1:1 ratio in varying block sizes (3 to 6 blocks) via central, computer-generated randomization (Figure 1). We stratified randomization by IL28B

genotype (TC/TT vs. CC), HIV status, and stage of liver disease (cirrhosis vs. no cirrhosis, assessed by a combination of liver biopsy and noninvasive testing) (30).

Research visits were conducted at baseline, then every 4 weeks during the first 12 treatment weeks (treatment weeks 4, 8, and 12; at the end of treatment if it was not at treatment week 12; and 4, 12, and 24 weeks after treatment). All 3 models of care included co-located, onsite care at the OAT program, which consisted of HCV care and substance use treatment. Participants received the following HCV treatments according to AASLD/IDSA guidelines: telaprevir, pegylated interferon, and ribavirin (TVR/IFN/RBV); sofosbuvir, pegylated interferon, and ribavirin (SOF/IFN/RBV); sofosbuvir and ribavirin (SOF/RBV); or a combination DAA regimen of sofosbuvir and simeprevir (SOF/SMV) or sofosbuvir/ledipasvir (SOF/LDV).

Study Assessments

Participants answered surveys using audio computer-assisted self-interview technology at each research visit (31). The surveys assessed factors hypothesized to be associated with adherence, including unstable housing, employment, relationship status, psychiatric illness (Patient Health Questionnaire-9), and substance use (Addiction Severity Index) (32, 33).

Treatment completion was determined on the basis of chart review. We obtained results of HCV RNA tests through medical chart review or from blood draws at baseline and treatment weeks 4, 8, and 12 (or end of treatment if it was not treatment week 12) and post-treatment weeks 4, 12, and 24. We defined SVR as an HCV RNA level below the limit of quantitation 12 weeks after treatment completion, using COBAS TaqMan real-time reverse transcriptase polymerase chain reaction assay (Roche Diagnostics), version 1.0 (<43 IU/mL), or version 2.0 (<15 IU/mL) after October 2014. At each research visit, participants provided urine specimens, which were tested for amphetamines, benzodiazepines, cocaine, methadone, opioids, and oxycodone with the enzyme multiplied immunoassay technique.

Study Interventions and Control Condition

DOT—Because DOT with HCV medications was linked to OTP methadone visits, the number of directly observed oral doses varied according to the number of days the participant attended the OTP to obtain methadone. We considered this intervention to be “modified” DOT, because not all oral medication doses were observed. The nonobserved doses were packaged in electronic blister packs as take-home doses for self-administration on non-OTP pick-up days. For participants receiving interferon-based therapy, providers administered interferon doses in the OTP. Nurses at the OTP clinics notified clinicians of declined doses, assessed side effects, and referred participants to onsite clinicians as necessary.

GT—The GT model, described in detail elsewhere (34), was adapted from models of HCV peer-based support (35). New participants were first oriented to the group and met other patients and the treatment team (physician and physician assistant). The treatment team then presented an overview of the HCV epidemic and its impact on PWID; HCV natural history; and the risks, benefits, and efficacy of HCV treatment. Weekly GT meetings had the

following 5 components: a brief physical examination, psychosocial support from peers and providers, HCV education, side effect management, and a closing meditation on positive health. Six to 12 participants attended each group session, and group entry was rolling. Participants received interferon (for those receiving interferon-based therapy) and 7-day blister packs during GT.

SIT—Participants randomly assigned to SIT received all medications packaged in 7-day blister packs from an OTP clinic nurse and self-administered the medications at home. Patients receiving interferon were instructed on proper home administration. The provider administered the first interferon injection, and the participant administered the second injection under provider observation. Remaining doses were distributed in boxes containing 1 month's supply for self-administration at home.

Study Outcomes

The primary outcome was adherence, measured in all 3 groups by using electronic Med-ic blister packs (Information Mediary), which have a 99.6% event accuracy (time of dose removal correctly recorded within ± 2 minutes) (36). Adherence was computed by using daily and window timeframes (Table 1) (37). Adherence was defined as a continuous outcome, calculated as the percentage of expected blister-pack medication dispensed during 2-week intervals. Secondary outcomes included HCV treatment completion, SVR, and cost-effectiveness (will be addressed elsewhere in a forthcoming article).

Sample Size Determination

Our previous pilot DOT study observed that mean adherence in the DOT group was 87% (SD, 12%), compared with 77% (SD, 20%) in the SIT group (standardized effect size [or Cohen *d*], 0.6) (38). On the basis of these estimates, we calculated a sample size of 150 participants ($n = 50$ per group) and anticipated a 20% attrition rate, resulting in 40 participants per group. The power of the mixed-effects linear model for the repeatedly measured continuous adherence outcome with 6 postbaseline time points would therefore be greater than 90%, even if anticipated intraclass correlation was as high as 0.5.

Statistical Analysis

Participant characteristics and outcomes were reported in percentages or frequencies and compared among the 3 groups. To compare both daily and window adherence rates among groups, we applied mixed-effects linear models (SAS Proc Mixed [SAS Institute]) to account for within-participant longitudinal correlations by using a first-order autoregressive covariance structure. The fixed effects were group, time, and group-by-time interactions, in addition to site and the 3 stratifying variables. We then repeated these analyses for the subgroup of participants who received a combination DAA regimen (SOF/LDV or SOF/SIM). We conducted 2 post hoc comparisons according to our study protocol (DOT vs. SIT and GT vs. SIT) of the outcomes of adherence with Bonferroni-corrected *P* values.

To test the significance of differences in rates of treatment completion and SVR across the 3 study groups, we applied multivariable exact logistic regression models (SAS Proc Logistic), adjusting for site and the 3 stratifying variables. We repeated these analyses for the subgroup

of participants who received a combination DAA regimen (SOF/LDV or SOF/SIM). We conducted 2 post hoc comparisons of SVR and treatment completion (DOT vs. SIT and GT vs. SIT) with Bonferroni-corrected *P* values, according to our study protocol (30). The 95% CIs for differences in proportions were computed on the basis of the Wilson method, with a continuity correction.

In addition, we determined treatment completion and SVR (and Clopper–Pearson exact 95% CI) among all randomly assigned participants ($n = 158$). We used Fisher exact tests to compare outcomes among study groups, considering participants who did not initiate treatment ($n = 8$) as having not completed treatment or not achieving SVR (intention-to-treat analysis). Finally, we examined differences among groups in another secondary outcome, HCV viral load over time, using a generalized mixed-effects linear model (SAS Proc Glimmix) with the logit link to determine effect of group on the repeatedly measured outcome of detectable (vs. undetectable) viral load, adjusting for time, site, and the stratifying variables. We then conducted post hoc logistic regressions on detectable viral load status at each time point with the same adjusting variables but without the time effect.

To test associations between adherence and SVR 12 weeks after treatment completion, we applied multivariable logistic regression models, adjusting for the following potential confounding variables: age, sex, race, psychiatric illness, unstable housing, use of alcohol to intoxication, DAA regimen, site, and study group. In these models, adherence was an independent variable and SVR was the outcome. We determined the proportion (and Clopper–Pearson exact 95% CI) of participants achieving SVR in each group among all those who initiated treatment ($n = 150$).

To identify participant characteristics, including the stratifying variables that might be associated with adherence, we applied a series of mixed-effects models using the characteristics of interest as main effects and adjusting for study group and site. To identify participant characteristics associated with SVR, we conducted a series of exact logistic regressions, adjusting for group and site.

We used SAS, version 9.4, for all statistical analyses, and statistical significance was determined at $P < 0.050$.

Informed Consent

All participants provided written informed consent, and the study was conducted in accordance with Good Clinical Practice and the ethical principles that originated in the Declaration of Helsinki. The study was approved by the institutional review board of Albert Einstein College of Medicine.

Results

Between October 2013 and May 2016, a total of 190 patients were screened for study inclusion and 32 were excluded. Of 158 patients randomly assigned to a study group, 150 received the intervention as assigned (Figure 1). Participants had a mean age of 51 years (SD, 10.6). Most were male, Latino, and unemployed and had genotype 1a HCV (Table 2).

Most (65%) had used drugs in the previous 6 months, most commonly opioids (47%) or cocaine (47%), with 75% reporting ever injecting drugs. More than 75% of participants picked up methadone 4 to 6 times per week. Most participants (n = 115 [77%]) received combination DAA treatment (Table 2).

Adherence

Overall adherence estimated from mixed-effects models using the daily timeframe and considering all treated participants (n = 150) was 78% (95% CI, 75% to 81%). The daily timeframe adherence was significantly different across the 3 groups (P = 0.003) and was greater in the DOT (86% [CI, 80% to 92%]) than the SIT group (75% [CI, 70% to 81%]; difference, 11% [CI, 5% to 18%]; Bonferroni-corrected P = 0.001). However, no significant difference was observed between the GT (80% [CI, 74% to 86%]) and the SIT group (difference, 4.7% [CI, −2% to 11%]; Bonferroni-corrected P = 0.29). Estimated overall window timeframe adherence among all treated participants was 67% (CI, 64% to 70%). The window timeframe adherence was significantly different among the groups (P < 0.001) and greater in the DOT (81% [CI, 74% to 88%]) than the SIT group (65% [CI, 59% to 72%]; difference, 16% [CI, 8% to 23%]; Bonferroni-corrected P < 0.001); however, no significant difference was observed between the GT (66% [CI, 59% to 73%]) and the SIT group (difference, 1% [CI, −7% to 8%]; Bonferroni-corrected P = 1.00) (Figure 2). All these results were virtually unchanged in sensitivity analyses of the handling of missing adherence data, including application of a fully conditional specification imputation model (data not shown). In the subgroup of participants receiving combination DAA therapy, daily adherence was significantly different among the groups (P < 0.001) and greater in the DOT (91% [CI, 84% to 98%]) than the SIT group (76% [CI, 70% to 82%]; difference, 15% [CI, 8% to 22%]; Bonferroni-corrected P < 0.001); however, no significant difference was observed between the GT (83% [CI, 77% to 89%]) and the SIT group (difference, 7% [CI, 0.3% to 13%]; Bonferroni-corrected P = 0.080). In the window timeframe, adherence was significantly different among the groups (P < 0.001) and was greater in the DOT (91% [CI, 82% to 99%]) than the SIT group (68% [CI, 61% to 75%]; difference, 23% [CI, 15% to 31%]; Bonferroni-corrected P <0.001); however, no significant difference was observed between the GT (73% [CI, 66% to 80%]) and the SIT group (difference, 5% [CI, −3% to 13%]; Bonferroni-corrected P = 0.39) (Appendix Figure 1, available at Annals.org). Factors significantly associated with poor daily adherence were psychiatric illness at baseline (P = 0.048) and drinking alcohol to intoxication in the 30 days before baseline (P = 0.028). Drug use was not significantly associated with poor adherence (Figure 3, *top*) and was noted to be consistent throughout the study period (Figure 4).

Treatment Completion and SVR

Among all participants who initiated treatment (n = 150), overall completion was 97% (CI, 92% to 99%), with no significant difference among groups (P = 0.53): DOT, 98% (CI, 90% to 100%); GT, 98% (CI, 89% to 100%); SIT, 94% (CI, 84% to 99%); DOT versus SIT difference, 3.9% (CI, −7% to 15% [Bonferroni-corrected P = 1.00]); and GT versus SIT difference, 3.8% (CI, −8% to 15% [Bonferroni-corrected P = 1.00]). Overall SVR was 94% (CI, 89% to 97%), with no significant difference among groups (P = 0.152): DOT, 98% (CI, 90% to 100%); GT, 94% (CI, 83% to 99%); SIT, 90% (CI, 79% to 97%); DOT versus SIT

difference, 7.8% (CI, −4% to 20% [Bonferroni-corrected $P = 0.40$]); and GT versus SIT difference, 3.6% (CI, −10% to 17% [Bonferroni-corrected $P = 1.00$]). No participant characteristics were significantly associated with SVR (Figure 3, *bottom*). Among participants receiving combination DAA therapy, overall SVR was 95% (CI, 89% to 98%), with no significant difference among groups ($P = 0.056$): DOT, 100% (CI, 90% to 100%); GT, 95% (CI, 83% to 99%); and SIT, 90% (CI, 76% to 97%) (Appendix Table 1, available at Annals.org). With regard to the intention-to-treat analysis using all randomly assigned participants ($n = 158$), treatment completion was 92% (CI, 86% to 96%) overall, with no significant difference among groups ($P = 0.77$): DOT, 94% (CI, 84% to 99%); GT, 90% (CI, 79% to 97%); and SIT, 91% (CI, 79% to 97%). Overall SVR was 89% (CI, 83% to 94%), with no significant difference among groups ($P = 0.36$): DOT, 94% (CI, 84% to 99%); GT, 87% (CI, 74% to 94%); and SIT, 87% (CI, 75% to 95%).

The proportions of participants with detectable HCV viral loads longitudinally over the treatment and posttreatment periods were significantly different across the 3 groups ($P = 0.021$): DOT versus GT adjusted odds ratio (AOR), 0.15 (CI, 0.04 to 0.58 [$P = 0.006$]), and DOT versus SIT AOR, 0.24 (CI, 0.06 to 0.93 [$P = 0.039$]). At week 4 in particular, on the basis of the post hoc analysis, 14% of DOT participants had week 4 detectable HCV viral load, compared with 37% of GT participants (AOR, 0.32 [CI, 0.12 to 0.86]; $P = 0.025$) and 27% of SIT participants (AOR, 0.54 [CI, 0.19 to 1.52]; $P = 0.24$) (Appendix Figure 2, available at Annals.org).

Sustained virologic response, by treatment regimen and characteristics of the 9 treatment failures, including 2 deaths, is shown in Appendix Tables 2 and 3 (available at Annals.org).

Adherence, SVR, and Drug Use

Greater adherence was significantly associated with SVR, with the odds of SVR 1.81 times higher for each 10% increase in daily adherence (CI, 1.06 to 3.11 [$P = 0.030$]) and 1.71 times higher for each 10% increase in window adherence (CI, 1.04 to 2.82 [$P = 0.035$]).

Discussion

To our knowledge, the PREVAIL (Prevent Resistance Eliminate Virus and Improve Life) study is the first randomized trial to test intensive models for providing HCV care with DAAs to PWID receiving OAT. Although other studies have used self-reported medication adherence questionnaires and electronic diaries (39–41), the PREVAIL trial used electronic blister packs to monitor adherence to DAAs. Using electronic blister pack technology, we found that adherence was greater in the DOT than the SIT group. Using both daily and window timeframes, we demonstrated that increases in adherence were associated with an increased likelihood of SVR. Drinking alcohol to intoxication and psychiatric illness were associated with poor adherence, which suggests that additional adherence support may be warranted for PWID who use alcohol or have a psychiatric disorder and are receiving HCV treatment.

All 3 models had a high proportion of patients receiving OAT who completed treatment and achieved SVR, including those actively using drugs. The overall SVR rate was 94% (CI,

89% to 97%), which is similar to that of a large registration trial in patients with genotype 1 HCV treated with SOF/LDV, in which the SVR rate was 99% (CI, 96% to 100%) (42). This result is notable, because approximately one quarter of study participants received interferon- or ribavirin-based HCV therapies that are associated with lower SVR rates, particularly when combined with certain host and viral factors, including African American race, advanced liver fibrosis, IL28B genotype, and prior treatment experience (43–45). Moreover, registration trials of DAA therapies generally have excluded or minimized entry of patients who are either active PWID or receiving OAT. Our study provides evidence that similar SVR rates may be achieved in PWID receiving OAT.

Although a greater percentage of patients were cured (achieved SVR) in the more intensive models of care (DOT and GT), no statistically significant differences in SVR were found among groups, despite a significant difference in adherence among groups and adherence being predictive of SVR. The threshold for optimal adherence that predicts SVR is not known in the DAA era. We postulate that a larger trial is needed to determine definitively whether the models differ with respect to SVR. We did, however, see significant differences in rates of decline of HCV viral load, driven primarily by rates of viral clearance in the first 4 weeks of treatment. Rapid virologic response, or undetectable viral load at treatment week 4, was identified as a predictor of SVR in the interferon era (46), but the importance of this outcome may be limited in the DAA era (47). However, with therapy being shortened to 8 weeks or less (48) and emerging discussions about the reintroduction of response-guided therapy (49), adherence throughout the treatment period may become more influential, with the benefits of adherence associated with DOT becoming more pronounced.

Our data demonstrate that active drug use has no substantial effect on virologic outcomes in HCV treatment. This finding supports treating PWID receiving OAT, regardless of current drug use. Two recent clinical trials (phase 2 and phase 3) examining DAA therapy among PWID receiving and those not receiving OAT demonstrated similar findings. In a study by Dore and colleagues (41), 96% of patients reported greater than 95% adherence using electronic diaries, with an SVR of 92%. Grebely and colleagues (50) observed 94% daily adherence among patients using electronic blister packs, with an SVR of 94%. In our trial, daily adherence was 78%, with an SVR of 94%, suggesting that lower adherence may be tolerated without affecting SVR. Further studies are needed to assess the effect of adherence on SVR to determine the threshold at which SVR is affected.

This study has several limitations. First, it occurred during the transition from interferon- and ribavirin-based treatments to state-of-the-art combination DAA therapy. Because of the emergence of combination DAA regimens, all participants did not receive the same therapy; however, we observed no differences in HCV treatment among groups. Second, our results may not be generalizable to HCV-infected PWID not enrolled in OAT programs or to rural populations. However, the intensive models of care studied may be even more important in other settings where PWID are served, including syringe service programs, in which attention to adherence and social support may have an even greater impact. Another limitation is that psychiatric stability is no longer a criterion for treatment eligibility, as it was in the interferon era. However, in this study, treatment eligibility was determined by

providers, and nearly half of our participants were found to have psychiatric diagnoses; therefore, we do not believe this limits generalizability.

In conclusion, DOT in OAT settings was associated with greater adherence than self-administered treatment, and improved adherence was associated with SVR. All models of onsite HCV care resulted in high treatment completion and SVR rates despite ongoing drug use, thereby supporting treatment of PWID in the OAT setting.

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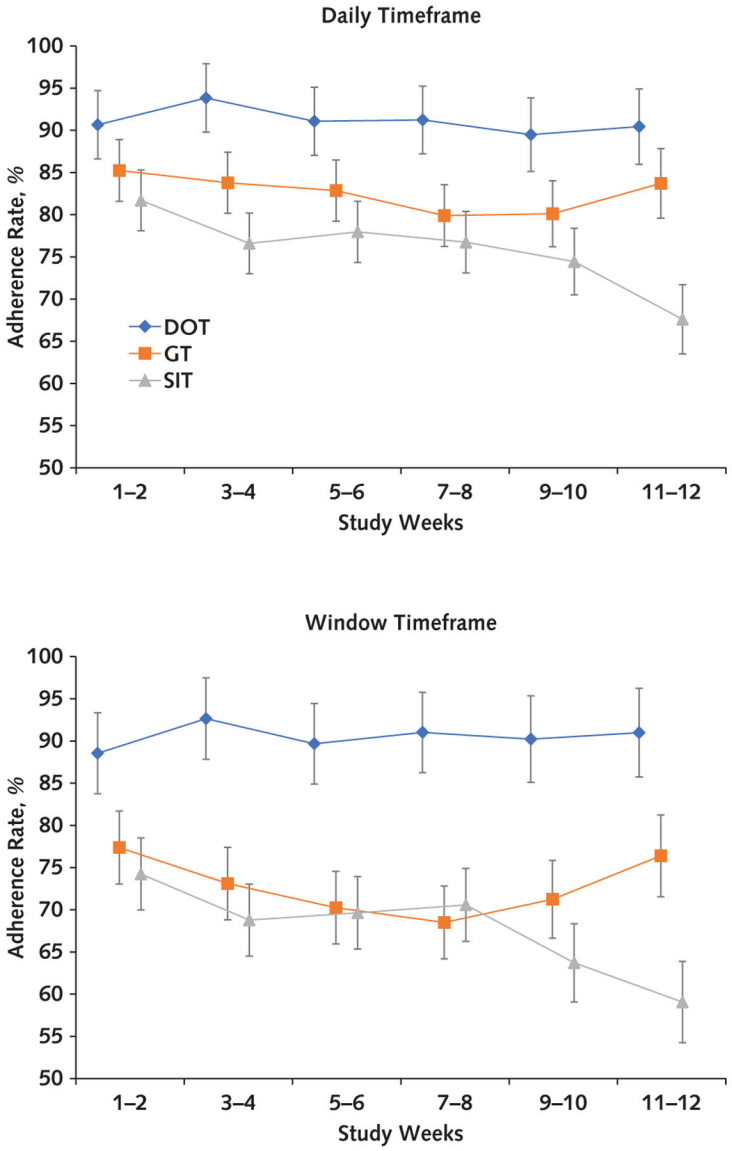
National Institute on Drug Abuse and Gilead Sciences.

Role of the Funding Source

This research was supported by the National Institute on Drug Abuse and Gilead Sciences. Gilead Sciences also provided study medication, SOF/LDV.

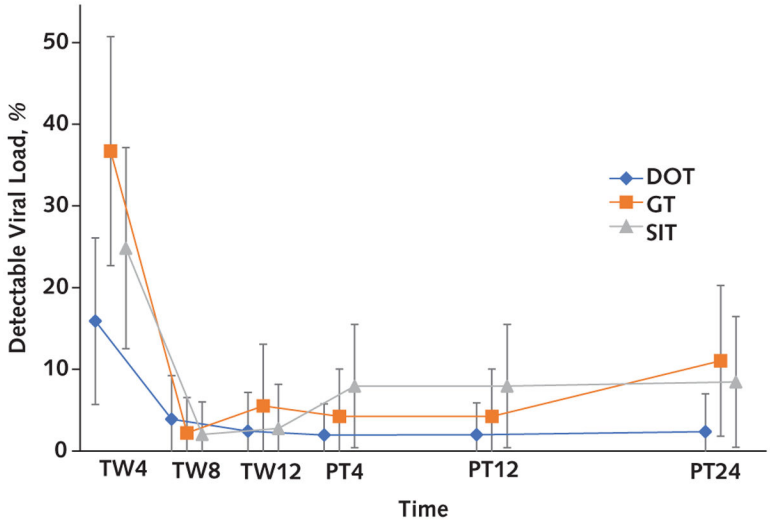
Appendix



Appendix Figure 1. Adherence rates among PREVAIL participants receiving combination DAA therapy.

Adherence rates and their error bars are model-based estimates; SEs were obtained from the mixed-effects linear models adjusting for site and the 3 stratifying variables. No missing data were observed for this analysis. Error bars represent ± SEs. DAA = direct-acting antiviral; DOT = directly observed therapy; GT = group treatment; PREVAIL = Prevent Resistance Eliminate Virus and Improve Life; SIT = self-administered individual treatment.

Appendix



Appendix Figure 2. Percentage of detectable HCV viral loads over time.
The overall percentages of longitudinal detectable HCV viral loads during and after treatment were significantly different across the 3 groups ($P = 0.021$). Error bars represent 95% CIs. DOT = directly observed therapy; GT = group treatment; HCV = hepatitis C virus; PT = posttreatment week; SIT = self-administered individual treatment; TW = treatment week.

Appendix

Appendix Table 1.

SVR, by Group, for Study Participants Overall and for Those Receiving a Combination DAA Regimen*

Group	Overall			Combination DAA Regimen		
	Patients, *n*	**SVR, *n (%)***	**SVR, 95% CI, %**	**Patients, *n***	**SVR, *n (%)***	**SVR, 95% CI, %**
Overall						
DOT	51	50 (98)	90 to 100	36	36 (100)	90 to 100
GT	48	45 (94)	83 to 99	40	38 (95)	83 to 99
SIT	51	46 (90)	79 to 97	39	35 (90)	76 to 97
Total	150	141 (94)	89 to 97	115	109 (95)	89 to 98
		Difference in SVR (95% CI), *percentage points*			**Difference in SVR (95% CI), *percentage points***	
Comparison						
DOT vs. GT	–	4 (–7 to 16)		–	5 (–8 to 18)	
DOT vs. SIT	–	8 (–4 to 20)		–	10 (–4 to 25)	
GT vs. SIT	–	4 (–10 to 17)		–	5 (–10 to 21)	

DAA = direct-acting antiviral; DOT = directly observed therapy; GT = group treatment; SIT = self-administered individual treatment; SVR = sustained virologic response.

[*] No significant differences in SVR were found across the 3 groups ($P = 0.152$) among all participants or among those receiving combination DAA treatment ($P = 0.056$), on the basis of multivariable exact logistic regression adjusting for site and the 3 stratifying variables. No missing data were observed for this analysis.

Appendix

Appendix Table 2.

SVR, by Treatment Regimen [*]

Regimen	Patients, *n*	SVR, *n (%)*	SVR, 95% CI, %
SOF/LDV	104	98 (94)	88–98
SOF/SMV	11	11 (100)	72–100
SOF/IFN/RBV	15	14 (93)	68–100
SOF/RBV	17	15 (88)	64–99
TVR/IFN/RBV	3	3 (100)	29–100
Total	150	141 (94)	89–97

IFN = pegylated interferon; LDV = ledipasvir; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; TVR = telaprevir.

[*] No significant differences in SVR were found among treatment regimens ($P = 0.69$). No missing data were observed for this analysis.

Appendix

Appendix Table 3.

Characteristics of Virologic Failure Cases

Case Number	Group	Psychiatric Diagnosis/HIV	HCVVL, *IU/mL*	Genotype 1a or 1b	Cirrhosis	Tx Naive	Tx Regimen	Weeks of Treatment Regimen Completed (n/N)	Drug 6 Months Before Tx	Drug During Tx	Daily Adherence, %	Viral and Clinical Outcomes
1	DOT	Bipolar disorder	213 832	1a	No	Yes	SOF/RBV	4/24	C/O/B	O	79	Week 4 VL: 233 110 IU/mL DOT 3×/wk, Tx discontinued at week 4
2	SIT	Depression	1 114 267	1b	Yes	Yes	SOF/RBV/IFN	8/12	O/B	None	No data	Week 4 VL: 93 692 IU/mL Week 8 VL: 3516IU/mL Tx discontinued because of side effects
3	SIT	Depression	188 936	1a	No	Yes	SOF/LDV	8/8	No	B	43	ETR, no SVR4 or SVR12
4	SIT	Depression	2 471 964	1a	No	Yes	SOF/LDV	8/8	C/O	C/O	31	ETR, no SVR4 or SVR12
5	GT	Depression	7 300 001	1a	No	Yes	SOF/LDV	12/12	C/O	C/O	38	No ETR UD at weeks 4 and 8
6	GT	None	12 143 424	1a	No	Yes	SOF/RBV	12/24	C/O	O	45	Week 4 VL: 43 IU/mL Week 8 VL: 585 602 IU/mL Incarcerated
7	SIT	None	15 961 170	1a	Yes	Yes	SOF/LDV	12/12	C/O	O	82	ETR, no SVR
8	GT	Depression HIV	19 508 733	1a	No	Yes	SOF/LDV	7/12	C/B	C/O	91	UD at week 4 Deceased: cardiac
9	SIT	Depression	621 760	1a	No	Yes	SOF/LDV	8/12	O/B	None	86	UD at week 8 Deceased: MVA

B = benzodiazepines; C = cocaine; DOT = directly observed therapy; ETR = end-of-treatment response; GT = group treatment; HCV = hepatitis C virus; IFN = pegylated interferon; LDV = ledipasvir; MVA = motor vehicle accident; O = opioids; RBV = ribavirin; SIT = self-administered individual treatment; SOF = sofosbuvir; SVR = sustained virologic response; SVR4 = SVR at week 4; SVR12 = SVR at week 12; Tx = treatment; UD = undetectable; VL = viral load.

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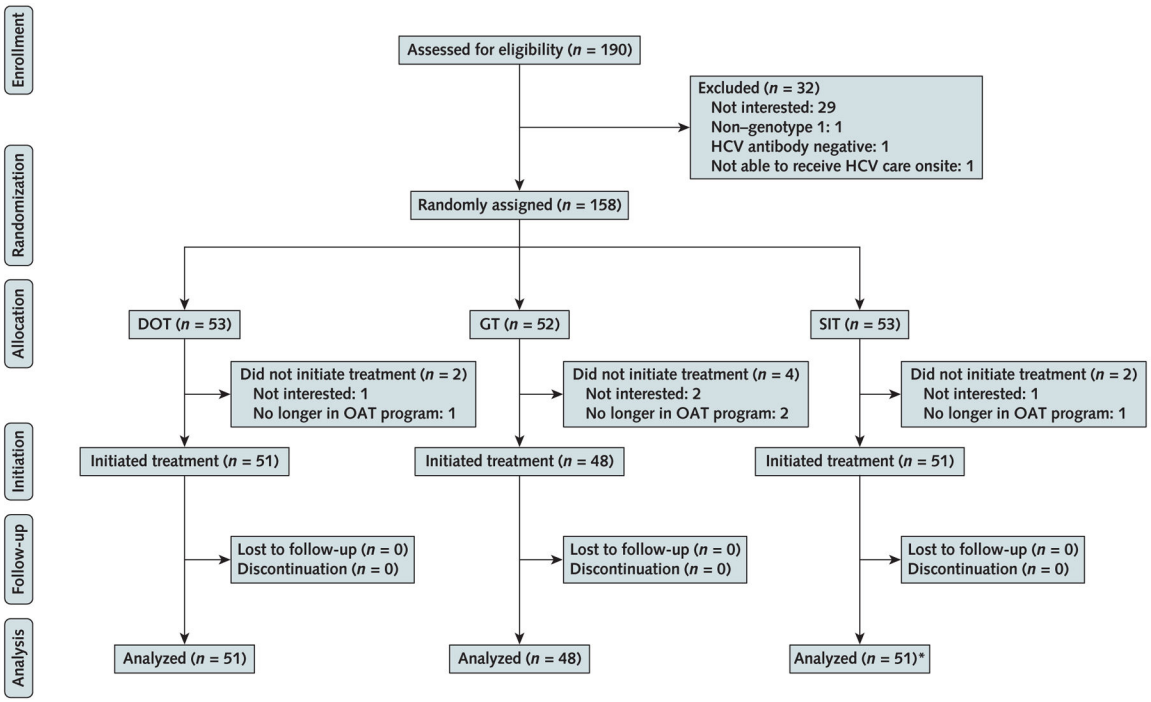

Figure 1. Flow diagram of PREVAIL study participants.

DOT = directly observed therapy; GT = group treatment; HCV = hepatitis C virus; OAT = opioid agonist therapy; PREVAIL = Prevent Resistance Eliminate Virus and Improve Life; SIT = self-administered individual treatment.

* Three SIT participants with no available blister pack adherence data were not included in the analysis of the primary adherence outcome.

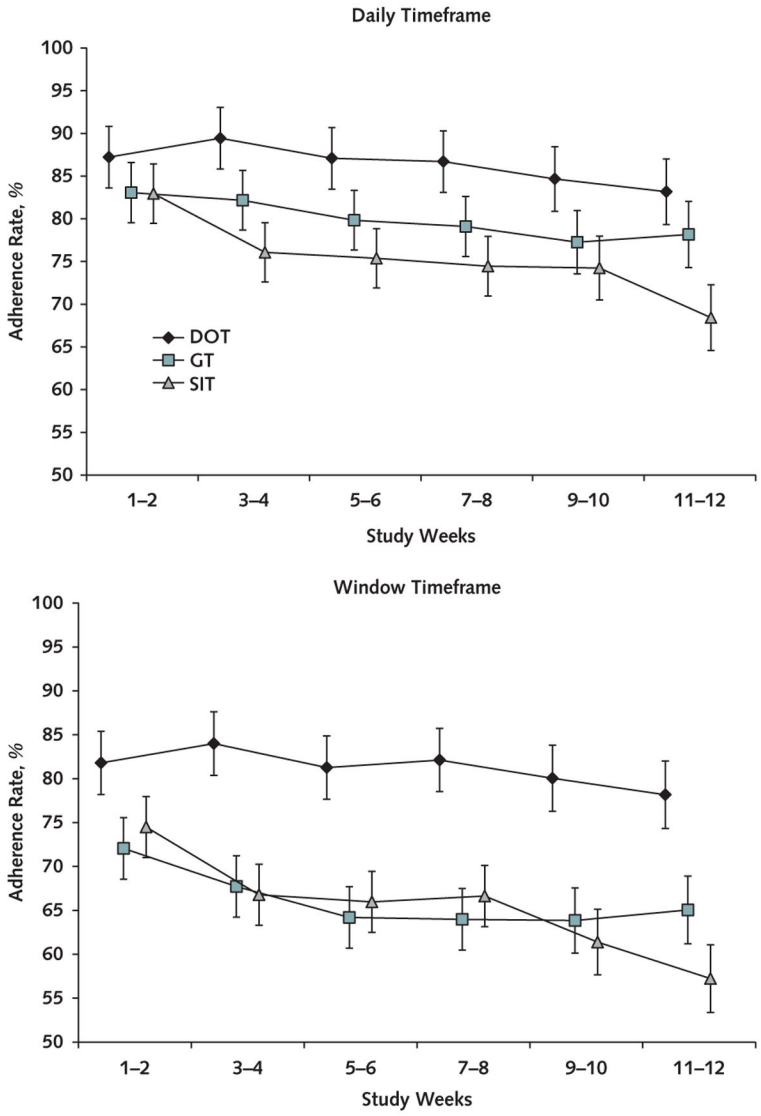

Figure 2. Adherence rates over time.

Adherence rates and their error bars are model-based estimates; SEs were obtained from the mixed-effects linear models adjusting for site and the 3 stratifying variables. Three SIT participants with no available blister pack adherence data were not included in this analysis. Error bars represent ± SEs. DOT = directly observed therapy; GT = group treatment; SIT = self-administered individual treatment.

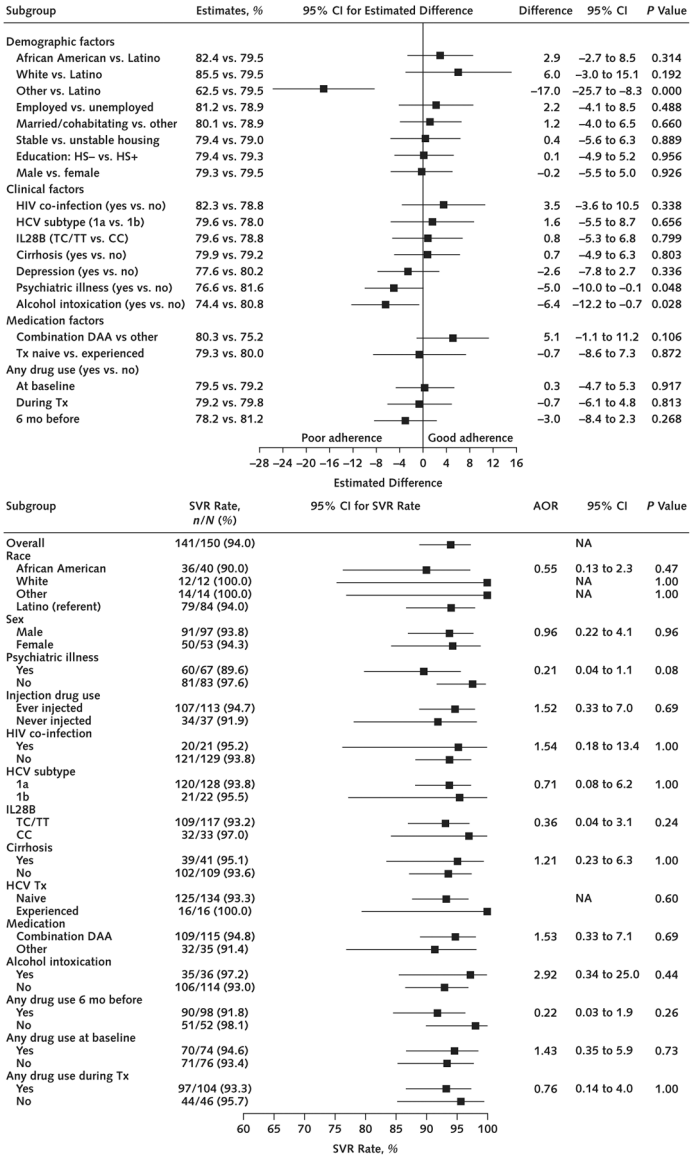

Figure 3. Forest plots comparing participant characteristics with daily adherence and SVR.

AOR = adjusted odds ratio; DAA = direct-acting antiviral; HCV = hepatitis C virus; HS = high school; NA = not available; SIT = self-administered individual treatment; SVR = sustained virologic response; Tx = treatment. **Top**. Participant characteristics and daily adherence. All statistics, including *P* values, are estimated from a mixed-effects model adjusting for site and the study groups. Three SIT participants with no available blister pack adherence data were not included in this analysis. **Bottom**. Participant characteristics and SVR. AORs and their 95% CIs and *P* values were obtained from exact multivariable logistic regressions adjusting for site and the study groups. No missing data were observed for this analysis.

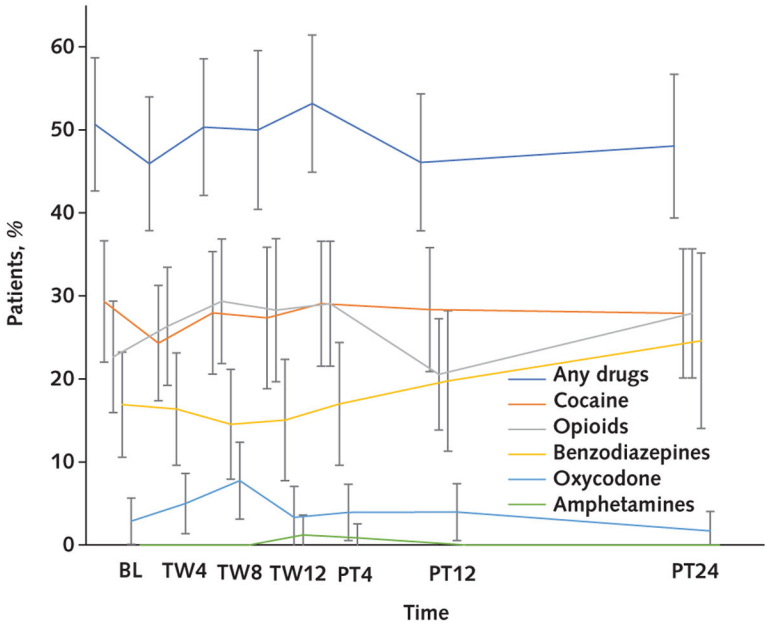

Figure 4. Urine toxicology testing over time.

Comparisons among substances at each time point were not conducted. Error bars represent 95% CIs. BL = baseline; PT = posttreatment week; TW = treatment week.

Table 1.

PREVAIL Study Primary and Secondary Outcomes

Adherence
Daily adherence: Participants received credit if doses were taken on the specified day.
Window adherence: Participants received credit if doses were taken within a window based on 25% of the dosing interval. For example, a participant scheduled to take once-daily medication at 10:00 a.m. received credit if the dose was taken between 4:00 a.m. and 4:00 p.m.
HCV treatment completion
Completion of ≥80% of the planned treatment course. For example, ≥10 wk of a 12-wk course, or ≥20 wk of a 24-wk course.
SVR
Undetectable HCV RNA at posttreatment week 12.

HCV = hepatitis C virus; PREVAIL = Prevent Resistance Eliminate Virus and Improve Life; SVR = sustained virologic response.

Table 2.

Baseline Characteristics of PREVAIL Study Participants [*]

Characteristic	DOT (*n* = 51)	GT (*n* = 48)	SIT (*n* = 51)	Total (*n* = 150)
Mean age (SD), *y*	51.4 (10)	51.2 (11)	51.0 (11)	51.2 (11)
Male	33 (65)	32 (67)	32 (63)	97 (65)
Race/ethnicity				
Latino	31 (61)	24 (50)	29 (57)	84 (56)
African American	13 (26)	13 (27)	14 (27)	40 (27)
White	4 (8)	5 (10)	3 (6)	12 (8)
Other	3 (6)	6 (13)	5 (10)	14 (9)
Homeless	9 (18)	10 (21)	15 (29)	34 (23)
Unemployed	43 (84)	38 (79)	41 (80)	122 (81)
Married (living with partner)	18 (35)	21 (44)	16 (31)	55 (37)
Urine drug screen (6 mo before baseline) [†]				
Any drug	34 (67)	34 (71)	30 (58)	98 (65)
Opioids	23 (45)	26 (54)	21 (41)	70 (47)
Cocaine	24 (47)	23 (48)	24 (47)	71 (47)
Benzodiazepines	15 (29)	15 (31)	13 (26)	43 (29)
Urine drug screen (at baseline)				
Any drug	26 (51)	23 (48)	25 (49)	74 (49)
Opioids/oxycodone	12 (24)	14 (29)	11 (22)	37 (25)
Cocaine	17 (33)	11 (23)	16 (31)	44 (29)
Benzodiazepines	9 (18)	4 (8)	10 (20)	23 (15)
Amphetamines	0 (0)	0 (0)	0 (0)	0 (0)
Self-reported drug use (30 d before baseline)				
Heroin	9 (18)	9 (19)	10 (20)	28 (19)
Other opioids/analgesics	10 (20)	8 (17)	15 (29)	33 (22)
Cocaine	12 (24)	12 (25)	12 (24)	36 (24)
Sedatives/hypnotics/tranquilizers	9 (18)	12 (25)	12 (24)	33 (22)
Amphetamines	3 (6)	0 (0)	1 (2)	4 (3)
Alcohol use to intoxication (30 d before baseline)	13 (26)	11 (23)	12 (24)	36 (24)

Characteristic	DOT (*n* = 51)	GT (*n* = 48)	SIT (*n* = 51)	Total (*n* = 150)
Injection drug use (ever)	38 (75)	40 (83)	35 (69)	113 (75)
Comorbid psychiatric conditions				
Any	20 (39)	22 (46)	25 (49)	67 (45)
Major depressive episode	11 (22)	15 (31)	12 (24)	38 (25)
Generalized anxiety disorder	8 (16)	10 (21)	10 (20)	28 (19)
Psychotic disorder	12 (24)	17 (35)	20 (39)	49 (33)
Current manic episode	1 (2)	6 (13)	4 (8)	11 (7)
Depression (PHQ-9)				
None or mild	33 (65)	33 (69)	31 (60)	97 (65)
Moderate or severe	18 (35)	15 (31)	20 (39)	53 (35)
HIV/HCV co-infection	6 (12)	6 (13)	9 (18)	21 (14)
HCV subtype				
1a	43 (84)	41 (85)	44 (86)	128 (85)
1b	8 (16)	7 (15)	7 (14)	22 (15)
IL28B CC	9 (18)	11 (23)	13 (25)	33 (22)
IL28B TC	26 (50)	26 (54)	27 (53)	79 (53)
IL28B TT	16 (31)	11 (23)	11 (22)	38 (25)
Cirrhosis	15 (29)	16 (33)	10 (20)	41 (27)
Treatment experienced	4 (8)	6 (13)	6 (12)	16 (11)
DAA regimen				
SOF/LDV	31 (61)	38 (79)	35 (69)	104 (69)
SOF/SMV	5 (10)	2 (4)	4 (8)	11 (7)
SOF/RBV	9 (18)	3 (6)	5 (10)	17 (11)
SOF/IFN/RBV	5 (10)	3 (6)	7 (14)	15 (10)
TVR/IFN/RBV	1 (2)	2 (4)	0 (0)	3 (2)
Opioid agonist therapy				
Methadone	51 (100)	47 (98)	49 (96)	147 (98)
Buprenorphine	0 (0)	1 (2)	2 (4)	3 (2)
Pick-up schedule				
1–3 per week	6 (12)	12 (25)	14 (28)	32 (21)
4–6 per week	45 (88)	36 (75)	37 (73)	118 (79)

DAA = direct-acting antiviral; DOT = directly observed therapy; GT = group treatment; HCV = hepatitis C virus; IFN = pegylated interferon; LDV = ledipasvir; PHQ-9 = Patient Health Questionnaire-9; PREVAIL = Prevent Resistance Eliminate Virus and Improve Life; RBV = ribavirin; SIT = self-administered individual treatment; SMV = simeprevir; SOF = sofosbuvir; TVR = telaprevir.

*No missing values wsere observed for any characteristics. Values are numbers (percentages) unless otherwise indicated.

†Oxycodone and amphetamine data were not obtained via chart review.