Optimal Hepatitis C Treatment Adherence Patterns and Sustained Virologic Response. among People Who Inject Drugs: The HERO Study

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Daily adherence of participants (y-axis) across treatment days (x-axis): Darker and lighter green areas represent adherent and non-adherent days, respectively, among participants with SVR; black and white areas represent adherent and non-adherent days, respectively, among participants with no SVR indicated by markers in the right margin.

SVR rates across total adherent day intervals

Daily adherence rates between SVR and no SVR
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Abstract

Background: Direct-acting antivirals (DAA) are highly effective for treating hepatitis C virus (HCV) infection even among people who inject drugs (PWID). Yet, little is known about patients' adherence patterns and association with sustained virologic response (SVR) rates. We aimed to summarize various adherence patterns and determine their associations with SVR.

Methods: Electronic blister packs were used to measure daily adherence to once-a-day sofosbuvir/velpatasvir during the 12-week treatment period among active PWIDs. Blister pack data were available for 496 participants who initiated DAA, and had ascertained SVR status. Adherence was summarized in multiple patterns, such as total adherent days, consecutive missed days, and early discontinuations. Thresholds for adherence patterns associated with >90% SVR rates were also determined.

Results: The overall SVR rate was 92.7% with median 75% adherence rate. All adherence patterns indicating greater adherence were significantly associated with achieving SVR. Participant groups with 42/84 (50%) or more adherent days, or less than 26 consecutive missed days achieved >90% SVR rate. When adherence was stratified by <50% versus ≥50%, only among those with <50% adherence, greater total adherent days during 9-12 weeks, and no early discontinuation were significantly associated with higher SVR rate. Participants with first month discontinuation and ≥2 weeks of treatment interruption had low SVR rates, 25% and 85%, respectively. However, greater adherent days were significantly associated with SVR (aOR = 1.10 (1.04, 1.16), p<.001) even among participant with ≥14 consecutive missed days.

Conclusions: Although suboptimal adherence can still result high SVR rates among PWID population, encouraging patients to take as much medication as possible, with fewer than 2
weeks consecutive missed days, and without early discontinuation, was found to be important for achieving SVR.

**Impact and implications**

PWID can be cured of HCV with >90% chance even with as low as 50% adherence to DAAs, but early discontinuations and long treatment interruptions can significantly reduce the likelihood of achieving cure. Clinicians should encourage PWID living with HCV to adhere daily to DAAs as consistently as possible, but if any days are interrupted, to continue and complete treatment. These results from the HERO study are important for patients living with HCV, clinicians, experts writing clinical guidelines, and payers.
Introduction

Hepatitis C virus (HCV) infection, affecting approximately 3 million persons in the United States (US), leads to liver disease and can progress to cirrhosis and death.[1, 2] HCV is the leading cause of death among all infectious diseases including HIV and the 60 other reportable infectious diseases in the US combined.[3] It is also a significant health burden world-wide[4, 5] accounting for 58 million people living with chronic HCV as of 2019.[6] People who inject drugs (PWID) are particularly vulnerable to HCV infection[7-9] with 15.6 million PWID living with HCV globally.[10] Although 20 per 100,000 persons were newly infected with HCV in year 2020 globally in the general population, 8 per 100 persons (or 8,000 per 100,000) were newly infected among PWID.[11] HCV is a blood borne pathogen; transmission often occurs due to injection behaviors such as sharing needles or drug-using equipment. In the US, HCV infection incidence tripled between 2009 and 2018 due to the ongoing opioid crisis.[12] Global HCV treatment efforts have been deterred during the COVID-19 pandemic era[13] despite the global and national priority to treat PWID for HCV in order to reduce transmission and overall prevalence, improve individual health, reach elimination by 2030, and combat this public health threat as set out by the World Health Organization.[14-17]

Although there is currently no effective vaccine for HCV prevention,[18] all oral 8-12 week direct-acting antiviral (DAA) medications[19-21] have high rates of HCV cure, i.e., sustained virologic response (SVR),[22-24] with few side effects,[25, 26] which lead to a decrease in poor liver outcomes, reduced mortality and halted transmission. [27-29] DAAs are also proven effective among PWID,[30, 31] and thus HCV treatment programs often adopt co-located care models at opioid treatment programs (OTPs)[32-34] or at community health centers (CHCs) to facilitate treatment access.[35, 36]. Adequate adherence to DAAs, which can be more challenging for some PWID and others to achieve, is a key element for achieving SVR among
PWID[37, 38] although adherence requirements apply to all populations living with HCV. However, there is little known about the associations between various adherence patterns (including the number of missed days or early discontinuations) and SVR, or about optimal adherence thresholds associated with high SVR rates.[39] Given that actively injecting drugs may interfere with adhering to medications,[40] it is unknown as to how specific types of adherence patterns are associated with SVR among those with suboptimal adherence rates.

The Hepatitis C Real Option (HERO) [41, 42] US nationwide pragmatic randomized trial compared two intensive HCV care models, modified Directly Observed Therapy (mDOT)[43] and Patient Navigation (PN)[44], both of which intended to optimize adherence to DAA medications in OTP and CHC settings among active PWID who injected drugs within 90 days of enrollment. The HERO study used electronic blister packs to objectively measure day-by-day adherence. We aimed to: 1) summarize the individual participant level day-to-day adherence in a variety of adherence patterns including, e.g., total adherent days, consecutive missed/non-adherent days, and early discontinuations; 2) determine association between adherence patterns and SVR, overall and stratified by adherence levels (<50% or ≥ 50%), and also by duration on medication in days (84 days or <84 days); and 3) identify optimal cutoff points of adherence patterns associated with 90% or greater SVR rates.

Methods

Study Design and Settings

The detailed study design and settings of the HERO Study (ClinicalTrials.gov, NCT02824640) have been reported previously.[41] Briefly, the HERO Study was a pragmatic randomized clinical trial designed and aimed to test effectiveness of two care models, mDOT and PN, on a variety of HCV treatment outcomes. The study was conducted across eight U.S.
cities in 8 OTPs and 15 CHCs located in geographically diverse regions across USA including both east (Boston MA, Providence RI, New York NY, Baltimore MD) and west (San Francisco CA, Seattle WA) coasts in addition to Midwest (Morgantown WV) and Southwest (Albuquerque NM) regions.

Participants were randomized to PN or mDOT in a 1:1 ratio stratified by three factors: city, OTP versus CHC, and stage of liver disease (cirrhosis/FIB-4 ≥3.25 vs no cirrhosis). mDOT was delivered at both settings and considered a modified version of DOT as not all self-administered doses were directly observed or witnessed. The PN model was developed by the New York City Department of Health and Mental Hygiene (NYC DOHMH).[45] Patient navigators were trained by the NYC DOHMH and followed a protocol. The study was approved by the institutional review board of all participating institutions. All participants provided written informed consent, and all clinical investigations were carried out according to the principles of the Declaration of Helsinki.

Participants

Adults aged 18–70 years with current HCV infection and active substance injection within 90 days of screening were enrolled. Those participants receiving methadone maintenance were required to attend the program ≥5 times per week so as to be able to meet mDOT requirements. Eligible participants were required to have: 1) aspartate transaminase, alanine transaminase, and platelet evaluations within 12 months prior to randomization; 2) ability to provide written informed consent; and 3) fluency in English or Spanish. Ineligible participants were those who had previous treatment with a DAA agent for HCV infection, or who were pregnant, breastfeeding, or had a diagnosis of hepatocellular carcinoma. A total of 755
individuals were randomized, 623 initiated DAA treatment between September 2016 and August 2018, and the last follow-up was completed in November 2021.

Medication Dispensation and Daily Time Frame Adherence

All participants received Sofosbuvir(400mg)/Velpatasvir(100mg)(Epclusa) oral medications as a fixed-dose combination pill once daily for 12 weeks, or 84 days (contributed by Gilead Sciences). All treatments were packaged in electronic blister packs with an integrated sensor that recorded the time and date when each dose was removed. All participants received a 1-week supply of medication in single blister packs; the exception was that PN participants in OTP clinics received a 2-week supply.

Daily time frame (DTF) adherence was determined based on whether opening times of blisters on a blister pack were recorded between 12:00 am to 11:59 pm. Specifically, a binary DTF adherence measure for a given treatment day interval was defined as 0 for no openings, and as 1 for one or more openings. Undetermined DTF adherence on missing treatment dates due to lost or unreturned blister packs were treated as a missed day (i.e., DTF adherence = 0).

Adherence Patterns

Based on the DTF adherence, we defined a priori a variety of variables that portray adherence patterns from diverse perspectives that summarized day-by-day adherent or missed days over the 84 treatment days into single measures. First, we computed total adherent days (TAD) as the number of DTF adherent days during the 84 prescribed treatment days, ranging from 0 to 84 (0-84). The TAD was further broken down in each of the following intervals: TAD 1-4 weeks (0-28), TAD 5-8 weeks (0-28), and TAD 9-12 weeks (0-28). (Maximum) consecutive adherent days (0-84) and (maximum) consecutive missed days (0-84) were also computed. Duration on medication (in days), ranging from 0 to 84, were computed as the number of days
between the first and the last DTF adherent days determined strictly based on blister pack record, regardless of whether or not missed days are recorded in between. We also computed, percent total adherent days over 84 days; percent adherent days over total number of treatment days; and percent medication days over 84 days. Lastly, we also defined first month discontinuation for those who did not take any medication after the first 4 weeks, and second month discontinuation for those who did not take any medication after the first 8 weeks excluding the first month discontinuation. Computations of these pattern variables are illustrated in Supplementary Figure S1.

**Outcome**

SVR was defined as undetectable HCV RNA level below the limit of quantitation (≤15 IU/mL) based on HCV viremia from clinical chart review or by study blood draws between 70 and 365 days after the end of DAA treatment.

**Analytic Samples**

We considered two analytic samples: per-protocol (PP) and modified intentions-to-treat (mITT) sample, the primary and secondary/sensitivity analytic samples, respectively. The PP sample included a total of N=496 participants, whose SVR status was definitively ascertained based on viremia data from bloodwork, excluding crossovers during treatment period. The PP sample is a subset of the mITT sample that included a total of N=593 participants for whom data from at least one blister pack were available among those who initiated HCV treatment (N=623), i.e., no blister pack data from 30 participants (4.8%) out of 623 were available. In the mITT sample, participants with undeterminable SVR status due to no available bloodwork within the time interval was assumed to not have achieved SVR. The group of participants in the mITT
sample who do not belong to the PP sample is referred to herein as non-PP sample (N=97).

(Supplementary Figure S2)

Statistical Analysis

Descriptive statistics were computed in terms of median and IQR (Q1, Q3) for continuous variables, and frequency and percentage (%). 95% confidence intervals (95%CI) for the binary outcomes are computed based on the Clopper-Pearson exact method. Baseline characteristics and adherence pattern variables were compared between PP and non-PP sample among the mITT sample using Chi-square/Fisher exact and Wilcoxon rank sum test. To test significance of associations of adherence pattern variables with the binary SVR outcome, we applied multivariable logistic regression models, each of which included all of the following covariates for each pair of a predictor and an outcome: city, study arm, clinic setting, age, employment, injection times a day, weeks since last injection, number of days injected in the past 3 months, urine drug screen (UDS) amphetamine, UDS methamphetamine, UDS Opiate, and UDS Oxycodone. These covariates consist of study design parameters and factors associated with adherence [42].

The effect sizes of associations were quantified in terms of adjusted odds-ratio (aOR) per unit/day changes or between groups/categories along with its 95%CI estimated from the applied multivariable logistic regression models in addition to crude unadjusted ORs. This analysis was also conducted stratified by total adherence rates (<50% or ≥ 50%), this stratification dichotomization point being determined by ROC analysis (Supplementary Figure S3). The estimation of effects of consecutive missed days (<7, 7-13, and ≥14 days) on SVR treatment was further stratified by week intervals (1-4, 5-8, and 9-12 weeks) and duration on medication (84 and <84 days). We also estimated optimal cutoff points, or threshold levels, of the adherence
pattern variables associated with 90% or greater SVR, achievement of which is often clinically considered successful treatment. [22, 46]. To this end, we calculated SVR rates across individual or cumulative intervals in increment of 7 days in terms of total adherent days, consecutive missed adherent days, and duration on medication. However, we did not stratify any analysis by study arms as the HERO study did not show a significant difference in SVR rates between the two arms.[42] All statistical analyses were conducted using SAS v9.4 (SAS Inc., Cary, NC, USA). Statistical significance was declared if a two-sided p-value is <.05.

Results

Baseline Characteristics, Adherence Patterns and SVR Rate

Descriptive statistics are provided in Table 1. In the PP sample, the majority were males (72.6%), White (63.6%) non-Hispanic ethnicity (77.2%), and the median (IQR) age was 42.6 (35.3, 53.7) years. Approximately half had stable housing (51.7%), and less than half had available transportation (42.3%) and were employed (35.6%). In the PP sample, the median (IQR) total adherent days was 63 (48.0, 73.0), or 75.0% (57.1, 86.9%) per 84 days. The total adherent days declined as treatment weeks passed: weeks 1-4 (23 (18, 26)), 5-8 (22 (15, 26)) and 9-12 (20 (13, 25)). Median consecutive missed days was 6 (2, 14) days, and median consecutive adherent day was 16.0 (9, 27) days. See Supplementary Table S1 for means and standard deviations. The first- and second-month discontinuation rates were 0.8% and 4.0%, respectively, in the PP sample, and 3.4% and 6.1% in mITT sample. (Table 1). Although distributions of baseline demographic and clinical characteristic and all pattern variables are comparable between the mITT and PP samples (Table 1), the non-PP sample was significantly younger, more White participants, more marginally housed, less treated in OTP, more times injecting drugs a day, and worse in all adherence patterns compared to the non-PP sample (Table 1). In
addition, compared to those included in this study (N=593), the excluded participants without blister pack data (N=30) from participants who initiated DAA medication (N=623) are less likely to have stable housing and be treated in OTP (Supplementary Table S2).

The observed SVR rates were 460/496 (92.7%, 95%CI = (90.5%, 95.0%)) and 461/593 (77.4%, (74.2%, 81.0%)) for the PP and mITT samples, respectively, despite overall median adherence rates of 75% and 70% respectively. (Table 1). Figure 1 depicts DTF adherence over 84 treatment days in the PP sample and the Supplementary Figure S4 in the mITT sample, showing that participants with no SVR had smaller number of adherent days especially at the later stage of the treatment period.

Daily Adherence Rates between Participants with and without SVR

Figure 2 depicts the day-by-day adherence rates between participants who did and did not achieve SVR in the PP sample. The adherence rates declined for both groups (SVR and no SVR) as the treatment days passed, but the velocity of the decline was greater for those who did not achieve SVR (0.2% vs. 0.4% decline per day, p<.001). Nonetheless, the rate of adherence for each individual treatment day was higher for those who achieved SVR than those who did not. Supplementary Figure S5 depicts the day-by-day adherence rates in the mITT sample and again nearly identical findings are observed where the difference in decline per day was also significant (0.2% vs. 0.5%, p<.001).

Total Adherent Days and SVR

Greater total adherent days were significantly associated with SVR in overall (aOR =1.07, 95%CI = (1.04, 1.10)), and also in all treatment months in the PP sample (Table 2). Almost identical results in terms of crude and adjusted ORs were obtained in the mITT sample (Table 2). When further stratified between <50% and ≥50% adherence rates (Supplementary
Table S3), among participants with <50% adherence rate in the PP sample, total adherent days during 9-12 weeks were significantly associated with SVR (aOR=1.15 (1.01, 1.30)). In the mITT sample with <50% adherence, total adherent days (aOR=1.09 (1.04, 1.15)), total adherent days during 5-8 weeks (aOR = 1.12 (1.03, 1.21)), total adherent days during 9-12 weeks (aOR = 1.12 (1.04, 1.22) were significantly associated with SVR (Supplementary Table S3). But total adherent days were not significantly associated with SVR among those with ≥ 50% adherence rate in the PP or mITT sample, overall or in any treatment month (Supplementary Table S3).

SVR rates increased with increments in total adherent days in the range of <42 days (or <50% adherence rate) but the increase in SVR rates was marginal in the range of ≥50% adherence rate in both the PP and mITT samples (Figure 3(A)). That is, in the PP sample, participants in all individual intervals with ≥42 (except 56-62 with 89.7%) total adherent days achieved >90% SVR (Figure 3(A)), but participants in any individual intervals of total adherent days <42 did not (Figure 3(A)). In the mITT sample, >90% of participants across all intervals of total adherent days of 70 or more achieved SVR (Figure 3(A)) but <50% of participants achieved SVR across all intervals with <35 total adherent days (Figure 3(A)). With respect to minimum threshold or lower bound for >90% SVR rate, >90% of participants in the PP sample with greater than any lower bounds total adherent achieved SVR (Figure 4(A)), whereas >90% SVR rate was achieved among the group of participants with ≥ 63 total adherent days in the mITT sample (Figure 4(A)). All of these results are summarized in Supplementary Table S4 along with subgroups that achieved >95% SVR rate.

Consecutive Missed Days, Treatment Interruptions and SVR

Longer consecutive missed days were significantly inversely associated with SVR in the PP sample (aOR=0.93 (0.91, 0.96)), and also in the mITT sample (aOR=0.94 (0.92, 0.95)). In
particular, the SVR rate among participants with greater than 14 (consecutive) missed days was significantly less than those with < 7 missed days (85.25% vs. 96.9%, aOR = 0.19 (0.07, 0.55)) in the PP sample. (Table 3). The SVR rate was also significantly less for participants with greater than 14 missed days vs. < 7 missed days in the mITT sample, (58.9% vs. 89.2%, aOR = 0.22 (0.13, 0.39). (Table 3) When stratified by treatment months, compared to those with <7 missed days, participants with greater than 14 missed days had significantly lower SVR in every treatment month in the mITT sample, and so were in the PP sample except for the first month. (Table 3). The results for the mITT sample hold regardless of treatment durations between 84 and <84 duration on medication (Supplementary Table S5). Even in the PP sample, ≥14 missed days were significantly associated with low SVR depending on treatment months and treatment durations (Supplementary Table S5).

Although adherence consecutive missed days were not significantly associates with those with ≥50% adherence rate in the PP or mITT sample, it was significantly inversely associated with SVR among those with <50% adherence in the mITT sample (aOR = 0.97 (0.96, 0.99)) but not in the PP sample (Supplementary Table S3). Notably, however, greater total adherent days were still significantly associated with SVR even among participants with ≥7 (aOR = 1.08 (1.04, 1.13)), and with ≥14 consecutive missed days (aOR = 1.10 (1.04, 1.16)) in the PP sample, and also in the mITT sample: aOR = 1.07 (1.05, 1.10), and aOR = 1.09 (1.06, 1.12), respectively.

In the PP sample, >90 % participants were accounted for in all individual intervals with <28 consecutive missed days (Figure 3(B)). Although <50% of participant achieved SVR in no individual intervals of total adherent days or missed days in the PP sample but in all intervals with ≥42 missed days in the mITT sample (Figure 3(B)). No lower bound for consecutive missed days (Figure 4(B)) was determined for >90% SVR in either the PP or mITT sample, but
<50% SVR rate was observed among the group of participants with \( \geq 56 \) and \( \geq 21 \) consecutive missed doses in the PP and mITT samples (Figure 4(C)). All of these results are also summarized in Supplementary Table S4.

Duration on Medication and SVR

Longer durations on medication were significantly associated with SVR both in the PP (aOR=1.06, (1.03, 1.09)) and mITT (aOR=1.06, (1.04, 1.09)) (Table 2). When stratified by between <50% and \( \geq 50% \) adherence rates, longer durations were significantly associated with SVR (aOR=1.03, (1.01, 1.06)) only among participants with <50% adherence rate in the mITT sample (Supplementary Table S3). In the PP sample, SVR rates increased with increment of treatment durations only before <56 duration on medication in days since >90% of participants in all individual intervals with \( \geq 56 \) (except 63-69 with 89.3%) duration on medication in days achieved SVR (Figure 3(C)). In the mITT sample, however, SVR rates increased with increment of duration on medication over the entire days. (Figure 3(C)), and <50% of participant achieved SVR in across intervals of <35 duration on medications in days. (Figure 3(C)). In the PP sample, >90% of participants with duration on medication greater than any lower bounds of achieved SVR (Figure 4(C)) but in the mITT sample, no lower bound for duration on medication was determined for >90% SVR (Figure 4(C)). All of these results are also summarized in Supplementary Table S4.

Early Discontinuations and SVR

Compared to participants who did not discontinue early, those who discontinued in the first or second month had significantly lower SVR rates in the PP sample: 94.7% vs 25.0%, aOR = 0.02 (<.01, 0.19)), and 94.7% vs 60.0%, aOR = 0.09, (0.03, 0.29), respectively (Table 3).
Similar results were observed in the mITT sample: (83.2% vs 10.0%, aOR = 0.01 (<.01, 0.10)) and (83.2% vs 33.3%, aOR = 0.12, (0.06, 0.28)), respectively (Table 3).

Other Patterns and SVR

Associations of consecutive adherent days, percent total adherent days and percent duration on medications in days are presented in Table 2. Individual intervals and lower bounds of the consecutive adherent days that have >90% SVR rate are summarized in Supplementary Table S4.

Discussion

In a large geographically diverse sample of PWID, we found that improved adherence to various patterns of DAA self-administration were all significantly associated with achieving SVR, regardless of the PP or mITT sample. Greater total adherent days, longer duration on medication, longer consecutive adherent days, and shorter consecutive missed days are important patterns that could ensure successful SVR and should be emphasized in patient adherence conversations. These findings extend prior findings on electronic blister pack adherences and SVR from the PREVAIL trial [43, 47] and the SIMPLIFY trial. [37, 46, 48] Although these studies focused on PWID, the HERO study recruited significantly more participants, which is likely the largest sample size to date of active PWID injected within 3 months of enrollment. For example, in the SIMPLIFY phase II study (n=103) there were only 6 participants who did not achieve SVR, and median adherence to therapy was 94%. Even though PREVAIL (n=150) had only 9 participants who did not achieve SVR, the HERO results were consistent with the results from PREVAIL where overall daily adherence was 78%. In PREVAIL, participants who achieved at least 50% adherence had an overall SVR rate of 99%, with each 5% adherence interval >50% achieving at least 90% adherence. The HERO confirmed these results with a much larger sample size (n=496)
with median adherence of 75% and included 36 participants who did not achieve SVR in the PP sample. Additional findings are as follows. First, participants with early or premature discontinuation of medication, indicated by first- and second-month discontinuation, were less likely to achieve SVR. Second, participants who missed more than 14 consecutive adherent days had a significantly smaller chance of achieving SVR compared to those who missed seven or fewer consecutive days regardless of when it occurred during the entire treatment period, or 1st, 2nd, or 3rd months of treatment.

We also found that overall daily adherence was low and declined over time for the entire population, despite high SVR rates. In the PP sample median adherence was 70% and overall SVR was 92.7%, and in the mITT sample, median adherence was 66% and overall SVR was 77.8%. Furthermore, many people missed multiple consecutive adherent days, with the median consecutively missed days at approximately 1 week for both the samples. Longer consecutive missed daily days are shown to have significant negative effect on achieving SVR again replicating the PREVAIL study result.[47] Although it appears that many participants missed days without a significant effect on SVR, participants with greater than 14 consecutive missed days had significantly lower SVR rates compared to those with fewer than 7 consecutive missed days, irrespective of mITT or PP sample. More specifically, those who have treatment interruptions of ≥14 days have significantly lower rates of SVR even in the subset of patients who had 84 days duration on medication removing the possibility that those with ≥14 days of treatment interruption were just ones who discontinued treatment prematurely. Nevertheless, participants in the PP sample who missed between 14 and 28 consecutive days achieved at least 90% SVR, and even participants who missed more than 56 consecutive days achieved at least 50% SVR. These findings do not support the AASLD/IDSA HCV Clinical Guidelines[49] for
patients who have received at least 28 days of therapy, which call for stopping DAA therapy for those who: 1) miss between 8 and 20 consecutive days and have a positive HCV viral load (>25 IU/ml); 2) miss between 8 and 20 consecutive days and do not obtain HCV viral load; or 3) miss at least 21 consecutive days. A simpler approach may include restarting DAAs without rechecking HCV viral load regardless of the length of treatment interruption and continuing to encourage adherence and treatment completion. On the other hand, all HERO participants initiated treatment with 12 weeks of Sofosbuvir and Velpatasvir, so finding are not generalizable to patients treated with the 8-week regimen of Glecaprevir and Pibrentasvir.

It is worthy to note that greater total adherent days were significantly associated with SVR only among the subgroup of participants with <50% adherence rate. Furthermore, greater adherence, shorter consecutive missed days and no early discontinuation altogether matter even at the low ends of the adherence. It follows that patients struggling with medication adherence for any reasons should be encouraged to adhere as many days as possible avoiding early terminations or longer interruptions, also supported by European observational studies showing that higher adherence level was associated with a high rate of SVR. [50, 51] When taken together, it is therefore important in real practice to monitor and support adherence. As the use of electronic blister pack is unlikely in most clinic settings where DAAs are prescribed, self-report instruments such as visual analog scales serve as a viable option to measure adherence during the treatment,[52] along with implementing support elements such as phone calls by staff to check in and discuss adherence and trouble shoot problems, assistance with refills to avoid missed days, helping patients program daily alarms and addressing and assisting with storage of DAAs for patients with unstable housing, common among our participants.
Although it is an open question as to which sample between the primary PP and the secondary mITT samples would provide more relevant and reliable findings, both uncover insights relevant to clinicians and patients. The PP sample minimizes misclassification as SVR was ascertained in all patients except that reinfections may have been misclassified as failures. On the other hand, although the extent of failed SVR among those who did not return for SVR labs are largely unknown, the mITT sample where a significant minority do not return for SVR ascertainment reflects real-world situations more than the PP sample. The current convention is that those not having SVR checked are assumed to have not achieved SVR. Regardless, the findings are fairly comparable and consistent in general between the PP and mITT samples supporting the validity of the overall findings from both PP and mITT samples.

The HERO study, a pragmatic randomized trial, has many strengths pertinent to the present analysis including, but not limited to, diverse study settings across the US, large sample size, and rigorous measures of outcomes and adherence. Nevertheless, the following limitations for the present study should be noted. First, no single electronic blistered pack data were available from 30 participants (4.8%) out of 623 who started treatment after randomization. Although specific reasons are unknown (these might include possible diversions and lost or unreturned packs), the missing rate is tolerable with little effect on the mITT analysis results. However, compared to those included in this study (N=593), the excluded participants without blister pack data (N=162) from all randomized participants (N=755) are less likely to have stable housing and be treated in OTP, and more likely to inject more times a day (Supplementary Table S6). Undeterminable SVR was assumed to be failed SVR, that is, a conservative worst-case scenario imputation, and thus the mITT analysis is somewhat limited in that those lost to follow-up were considered not to have achieved SVR, which may have been misclassified for a
subset of participants. Although there might be cases where the treatment day was extended beyond 84 days likely without blister pack adherence data, the current analysis is strictly confined to the 84 days for which the blister pack data were available. Therefore, it is unknown whether people who took pills over a longer time period are more or less likely to achieve SVR than people with similar adherence in a shorter amount of time. Lastly, the finding that 50% adherence would be sufficient to achieve SVR rate >90% might be due to a composite of correlates of SVR relating to patient characteristics, disease stages, and less risky behaviors.

In conclusion, low adherence to DAA during a 12-week treatment regimen among PWIDs is common. However, patients with suboptimal adherence as low as 50% are able to achieve high SVR rate >90%. For patients with poor adherence (i.e., <50%), greater adherence is still important for increasing likelihood of achieving SVR. In addition, treatment interruptions of at least 2 weeks and early discontinuations are associated with lower SVR rates. Interventions targeting improved adherence could be most useful to offer to those who demonstrate poor adherence early on in treatment. In sum, greater total adherent days, longer consecutive adherent days, and shorter consecutive missed days all can ensure 90% or higher SVR rate, and a lower threshold of missed days does not make a difference. Encouraging and supporting patients to take as much medication, with less than 2 weeks consecutive misses, and without early discontinuation, defined as discontinuation in the first and/or second month, is important for achieving HCV cure.
References


HERO RESEARCH GROUP

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Figure Legends:

**Figure 1:** Observed daily adherence heatmap from the PP sample: x-axis represents treatment days; y-axis represents individual participants sorted by total adherent days in a descending manner from top to bottom; darker green and lighter green areas represent adherent days and missed days, respectively, among participants with successful SVR; black and white areas represent adherent days and missed days, respectively, among participants with failed SVR; and participants with failed SVR are indicated with the ‘-’ markers in the right-side margin.

**Figure 2:** Comparisons of day-by-day adherence rates over the treatment days, 1 to 84, between participants in the PP sample who did and did not achieve SVR. The lines represent the fitted regression lines of adherence rates on the treatment days along with their corresponding estimated regression equations.

**Figure 3:** SVR rates across individual intervals defined in terms of: (A) total adherent days; (B) consecutive missed days; and (C) duration on medication in days. The whiskers represent the size of standard errors (se), the two numbers in the first x-axis for each interval represent sample sizes for each interval in the PP and mITT samples, and the second axis labels represent the intervals of values which represent subgroups with values falling into those intervals.

**Figure 4:** SVR rates across cumulative intervals in terms of: (A) total adherent days; (B) consecutive missed days; and (C) duration on medication in days. The whiskers represent the size of standard errors (se), the two numbers in the first x-axis for each interval represent sample sizes for each interval in the PP and mITT samples, and the second axis labels represent the minimum threshold, or lower bound, values of the intervals which represent subgroups with values greater or equal to the thresholds.
Table 1: Baseline Demographic and Clinical Characteristics, Adherence Pattern Variable, and SVR: Comparisons between PP and non-PP samples

<table>
<thead>
<tr>
<th>Variables</th>
<th>mITT sample (N=593)</th>
<th>PP sample (N=496)</th>
<th>Non-PP sample (N=97)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>41.8 (34.2, 52.6)</td>
<td>42.6 (35.3, 53.7)</td>
<td>38.0 (32.2, 47.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Male</td>
<td>424/593 (71.5%)</td>
<td>360/496 (72.6%)</td>
<td>64/97 (66.0%)</td>
<td>.188</td>
</tr>
<tr>
<td>White/Caucasian Race</td>
<td>375/571 (65.7%)</td>
<td>304/478 (63.6%)</td>
<td>71/93 (76.3%)</td>
<td>.018</td>
</tr>
<tr>
<td>Latino/Hispanic Ethnicity</td>
<td>129/593 (21.8%)</td>
<td>113/496 (22.8%)</td>
<td>16/97 (16.5%)</td>
<td>.170</td>
</tr>
<tr>
<td>Married/Cohabitation</td>
<td>71/592 (12.0%)</td>
<td>57/495 (11.5%)</td>
<td>14/97 (14.4%)</td>
<td>.419</td>
</tr>
<tr>
<td>Less than High School</td>
<td>138/592 (23.3%)</td>
<td>117/495 (23.6%)</td>
<td>21/97 (21.6%)</td>
<td>.672</td>
</tr>
<tr>
<td>Stable Housing (Own/Rent)</td>
<td>290/592 (49.0%)</td>
<td>256/495 (51.7%)</td>
<td>34/97 (35.1%)</td>
<td>.003</td>
</tr>
<tr>
<td>Transportation Availability</td>
<td>252/591 (42.6%)</td>
<td>209/494 (42.3%)</td>
<td>43/97 (44.3%)</td>
<td>.713</td>
</tr>
<tr>
<td>Employed</td>
<td>213/591 (36.0%)</td>
<td>176/494 (35.6%)</td>
<td>37/97 (38.1%)</td>
<td>.637</td>
</tr>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid Treatment Program</td>
<td>265/593 (44.7%)</td>
<td>231/496 (46.6%)</td>
<td>34/97 (35.1%)</td>
<td>.037</td>
</tr>
<tr>
<td>&gt;2 times injecting drugs a day</td>
<td>256/561 (45.6%)</td>
<td>203/470 (43.2%)</td>
<td>53/91 (58.2%)</td>
<td>.008</td>
</tr>
<tr>
<td>&lt; 5 weeks since last drug injection</td>
<td>446/593 (75.2%)</td>
<td>368/496 (74.2%)</td>
<td>78/97 (80.4%)</td>
<td>.195</td>
</tr>
<tr>
<td>≥ 30 days of injection in the past 3 months</td>
<td>269/559 (48.1%)</td>
<td>222/468 (47.4%)</td>
<td>47/91 (51.7%)</td>
<td>.462</td>
</tr>
<tr>
<td>Urine drug screen Amphetamine positive</td>
<td>154/569 (27.1%)</td>
<td>131/475 (27.6%)</td>
<td>23/94 (24.5%)</td>
<td>.535</td>
</tr>
<tr>
<td>Urine drug screen Methamphetamine positive</td>
<td>177/569 (31.1%)</td>
<td>148/475 (31.2%)</td>
<td>29/94 (30.9%)</td>
<td>.953</td>
</tr>
<tr>
<td>Urine drug screen Opiate positive</td>
<td>288/569 (50.6%)</td>
<td>238/475 (50.1%)</td>
<td>50/94 (53.2%)</td>
<td>.585</td>
</tr>
<tr>
<td>Urine drug screen Oxycodone positive</td>
<td>148/569 (26.0%)</td>
<td>127/475 (26.7%)</td>
<td>21/94 (22.3%)</td>
<td>.375</td>
</tr>
<tr>
<td><strong>Adherence Pattern Variables</strong></td>
<td>N=593</td>
<td>N=496</td>
<td>N=97</td>
<td></td>
</tr>
<tr>
<td>Total adherent days (TAD)</td>
<td>59.0 (43.0, 71.0)</td>
<td>63.0 (48.0, 73.0)</td>
<td>35.0 (20.0, 58.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TAD week 1-4</td>
<td>23.0 (17.0, 26.0)</td>
<td>23.0 (18.0, 26.0)</td>
<td>19.0 (12.0, 24.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TAD week 5-8</td>
<td>21.0 (13.0, 25.0)</td>
<td>22.0 (15.0, 26.0)</td>
<td>12.0 (2.0, 21.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TAD week 9-12</td>
<td>19.0 (10.0, 24.0)</td>
<td>20.0 (13.0, 25.0)</td>
<td>7.0 (0.0, 18.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Consecutive adherent days</td>
<td>14.0 (8.0, 26.0)</td>
<td>16.0 (9.0, 27.0)</td>
<td>10.0 (6.0, 17.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Consecutive missed days</td>
<td>7.0 (2.0, 17.0)</td>
<td>6.0 (2.0, 14.0)</td>
<td>23.0 (7.0, 42.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Consecutive missed days &lt; 7</td>
<td>277 (46.7%)</td>
<td>255 (52.4%)</td>
<td>22 (22.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------</td>
<td>------------</td>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>Consecutive missed days 7-13</td>
<td>109 (18.4%)</td>
<td>99 (20.0%)</td>
<td>10 (10.3%)</td>
<td>.025</td>
</tr>
<tr>
<td>Consecutive missed days ≥14</td>
<td>207 (34.9%)</td>
<td>142 (28.6%)</td>
<td>65 (67.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration on medication in days</td>
<td>83.0 (70.0, 84.0)</td>
<td>83.0 (77.0, 84.0)</td>
<td>67.0 (41.0, 83.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Percent total adherent days over 84 days</td>
<td>70.2 (51.2, 84.5)</td>
<td>75.0 (57.1, 86.9)</td>
<td>41.7 (23.8, 69.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Percent total adherent days over duration on medication in days</td>
<td>78.0 (63.0, 89.2)</td>
<td>78.3 (65.1, 89.3)</td>
<td>72.6 (52.8, 86.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Percent duration on medication in days over 84 days</td>
<td>98.8 (83.3, 100.0)</td>
<td>98.8 (91.7, 100.0)</td>
<td>79.8 (48.8, 98.8)</td>
<td>.005</td>
</tr>
<tr>
<td>Treatment Discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fist Month Discontinuation</td>
<td>20 (3.4%)</td>
<td>4 (0.8%)</td>
<td>16 (16.5%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Second Month Discontinuation</td>
<td>36 (6.1%)</td>
<td>20 (4.0%)</td>
<td>16 (16.5%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neither</td>
<td>537 (90.6%)</td>
<td>472 (95.2%)</td>
<td>65 (67.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Sustained Virologic Response (SVR) Rate</strong></td>
<td>461 (77.7%)</td>
<td>460 (92.7%)</td>
<td>1 (1.0%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Comparisons between PP and Non-PP sample using Chis-square/Fisher exact or Wilcoxon rank sum tests.*
Table 2: Association of Adherence Pattern Variables with SVR

<table>
<thead>
<tr>
<th>Adherence Pattern Variables</th>
<th>PP sample</th>
<th></th>
<th>mITT sample</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR (95% CI)</td>
<td>p</td>
<td>Adjusted OR (95% CI)*</td>
<td>p</td>
</tr>
<tr>
<td>Total adherent day (TAD)</td>
<td>1.06 (1.04, 1.08)</td>
<td>&lt;.001</td>
<td>1.07 (1.04, 1.10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TAD week 1-4</td>
<td>1.08 (1.04, 1.13)</td>
<td>&lt;.001</td>
<td>1.08 (1.02, 1.14)</td>
<td>.005</td>
</tr>
<tr>
<td>TAD week 5-8</td>
<td>1.13 (1.08, 1.17)</td>
<td>&lt;.001</td>
<td>1.14 (1.08, 1.20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TAD week 9-12</td>
<td>1.12 (1.08, 1.17)</td>
<td>&lt;.001</td>
<td>1.13 (1.07, 1.18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Consecutive adherent days</td>
<td>1.07 (1.02, 1.11)</td>
<td>.002</td>
<td>1.08 (1.03, 1.13)</td>
<td>.002</td>
</tr>
<tr>
<td>Consecutive missed days</td>
<td>0.94 (0.92, 0.96)</td>
<td>&lt;.001</td>
<td>0.93 (0.91, 0.96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Consecutive missed days &lt; 7</td>
<td>ref</td>
<td></td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Consecutive missed days 7-13</td>
<td>0.43 (0.15, 1.21)</td>
<td>.108</td>
<td>0.49 (0.14, 1.67)</td>
<td>.249</td>
</tr>
<tr>
<td>Consecutive missed days &gt;=14</td>
<td>0.19 (0.08, 0.43)</td>
<td>&lt;.001</td>
<td>0.19 (0.07, 0.55)</td>
<td>.002</td>
</tr>
<tr>
<td>Duration on medication in days</td>
<td>1.06 (1.04, 1.08)</td>
<td>&lt;.001</td>
<td>1.06 (1.03, 1.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Percent total adherent days over 84 days</td>
<td>1.05 (1.04, 1.07)</td>
<td>&lt;.001</td>
<td>1.06 (1.04, 1.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Percent total adherent days over duration on medication in days</td>
<td>1.04 (1.02, 1.06)</td>
<td>&lt;.001</td>
<td>1.04 (1.01, 1.06)</td>
<td>.002</td>
</tr>
<tr>
<td>Percent duration on medication in days over 84 days</td>
<td>1.05 (1.03, 1.07)</td>
<td>&lt;.001</td>
<td>1.05 (1.03, 1.07)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment Discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Month Discontinuation</td>
<td>0.02 (&lt;.01, 0.19)</td>
<td>&lt;.001</td>
<td>0.02 (&lt;.01, 0.29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Second Month Discontinuation**</td>
<td>0.08 (0.03, 0.22)</td>
<td>&lt;.001</td>
<td>0.09 (0.03, 0.29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neither</td>
<td>ref</td>
<td></td>
<td>ref</td>
<td></td>
</tr>
</tbody>
</table>
Neither

*Adjusted for city, study arm, clinic setting, age, employment, injection times a day, weeks since last injection, number of days injected past 3 mo, urine drug screen (UDS) amphetamine, UDS methamphetamine, UDS Opiate, and UDS Oxycodone. Note: Significant estimates with two-sided p-values < .005 are denoted with **boldface**, and the two-sided p-values were calculated based on Wald t-tests for testing significance of regression coefficients of logistic regression models.
### Table 3: Effect of Early Treatment Discontinuation and Missed Dose on SVR by Treatment Months

<table>
<thead>
<tr>
<th>PP sample</th>
<th>Consecutive Missed Days</th>
<th>Effects</th>
<th>7-13</th>
<th>14 or more</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time frame</td>
<td>Rate, n/N (%)</td>
<td>&lt; 7</td>
<td>7-13</td>
<td>14 or more</td>
<td></td>
</tr>
<tr>
<td>Week 1-4/</td>
<td>365/388 (94.1%)</td>
<td>57/64 (89.1%)</td>
<td>38/44 (86.4%)</td>
<td>.084</td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>Crude OR</td>
<td>Ref</td>
<td>0.51 (0.21, 1.25)</td>
<td>0.40 (0.15, 1.04)</td>
<td>.093</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>Ref</td>
<td>1.08 (0.36, 3.22)</td>
<td>0.43 (0.14, 1.32)</td>
<td>.299</td>
<td></td>
</tr>
<tr>
<td>Week 5-8/</td>
<td>366/383 (95.6%)</td>
<td>56/65 (86.2%)</td>
<td>38/48 (79.1%)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Month 2</td>
<td>Crude OR</td>
<td>Ref</td>
<td><strong>0.29 (0.12, 0.68)</strong></td>
<td><strong>0.18 (0.08, 0.41)</strong></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>Ref</td>
<td><strong>0.33 (0.12, 0.94)</strong></td>
<td><strong>0.16 (0.06, 0.45)</strong></td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Week 9-12/</td>
<td>334/348 (96.0%)</td>
<td>70/76 (92.1%)</td>
<td>56/72 (77.8%)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>Crude OR</td>
<td>Ref</td>
<td>0.49 (0.18, 1.32)</td>
<td>0.15 (0.07, 0.32)</td>
<td>.093</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>Ref</td>
<td>0.69 (0.22, 2.13)</td>
<td>0.16 (0.06, 0.41)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Week 1-12/All</td>
<td>247/255 (96.9%)</td>
<td>92/99 (92.9%)</td>
<td>121/142 (85.2%)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>mITT sample</td>
<td>Consecutive Missed Days</td>
<td>Effects</td>
<td>7-13</td>
<td>14 or more</td>
<td>p**</td>
</tr>
<tr>
<td>Time frame</td>
<td>Rate, n/N (%)</td>
<td>&lt; 7</td>
<td>7-13</td>
<td>14 or more</td>
<td></td>
</tr>
<tr>
<td>Week 1-4/</td>
<td>366/447 (81.9%)</td>
<td>57/78 (73.1%)</td>
<td>38/68 (55.9%)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>Crude OR</td>
<td>Ref</td>
<td>0.60 (0.35, 1.05)</td>
<td><strong>0.28 (0.16, 0.48)</strong></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>Ref</td>
<td>0.94 (0.46, 1.85)</td>
<td><strong>0.36 (0.19, 0.69)</strong></td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Week 5-8/</td>
<td>366/424 (86.3%)</td>
<td>56/82 (68.3%)</td>
<td>39/87 (44.8%)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Month 2</td>
<td>Crude OR</td>
<td>Ref</td>
<td><strong>0.34 (0.20, 0.59)</strong></td>
<td><strong>0.13 (0.08, 0.21)</strong></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>Ref</td>
<td><strong>0.43 (0.22, 0.80)</strong></td>
<td><strong>0.12 (0.07, 0.23)</strong></td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Week 9-12/</td>
<td>334/381 (87.7%)</td>
<td>70/86 (81.4%)</td>
<td>57/126 (45.2%)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>Crude OR</td>
<td>Ref</td>
<td>0.61 (0.33, 1.15)</td>
<td><strong>0.12 (0.07, 0.19)</strong></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>Ref</td>
<td>0.76 (0.38, 1.53)</td>
<td><strong>0.16 (0.09, 0.28)</strong></td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Week 1-12/All</td>
<td>247/277 (89.2%)</td>
<td>92/109 (84.4%)</td>
<td>122/207 (58.9%)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

### Discontinuation Month

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effects</th>
<th>Time frame</th>
<th>Rate, n/N (%)</th>
<th>Neither</th>
<th>First Month</th>
<th>Second Month</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Crude OR</td>
<td>447/472 (94.7%)</td>
<td>1/4 (25.0%)</td>
<td>12/20 (60.0%)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>Ref</td>
<td>0.02 (&lt;.01, 0.19)</td>
<td>0.08 (0.03, 0.29)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td>Adjusted OR*</td>
<td>Ref</td>
<td>0.02 (&lt;.01, 0.29)</td>
<td>0.09 (0.03, 0.29)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### mITT sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effects</th>
<th>Time frame</th>
<th>Rate, n/N (%)</th>
<th>Neither</th>
<th>First Month</th>
<th>Second Month</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Crude OR</td>
<td>447/537 (83.2%)</td>
<td>2/20 (10.0%)</td>
<td>12/36 (33.3%)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>Ref</td>
<td>0.02 (&lt;.01, 0.10)</td>
<td>0.10 (0.05, 0.21)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td>Adjusted OR*</td>
<td>Ref</td>
<td>0.01 (&lt;.01, 0.10)</td>
<td>0.12 (0.06, 0.28)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted OR*</td>
<td>Ref</td>
<td>0.02 (&lt;.01, 0.29)</td>
<td>0.09 (0.03, 0.29)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for city, study arm, clinic setting, age, employment, injection times a day, weeks since last injection, number of days injected past 3mo, urine drug screen (UDS) amphetamine, UDS methamphetamine, UDS Opiate, and UDS Oxycodone.
**Chi-square or Wald test p-value for testing equality of effects of missed day categories on SVR**

Note: Significant estimates with two-sided p-values <.005 are denoted with **boldface**, and the two-sided p-values were calculated based on Wald t-tests for testing significance of regression coefficients of logistic regression models.
Figure Legends

**Figure 1:** Observed daily adherence heatmap from the PP sample. The x-axis represents treatment days whereas the y-axis represents individual participants sorted by total adherent days in a descending manner from top to bottom. The darker green and lighter green areas represent adherent days and missed days, respectively, among participants with successful SVR. The black and white areas represent adherent days and missed days, respectively, among participants with failed SVR. Participants with failed SVR are indicated with the ‘-’ markers in the right-side margin.

**Figure 2:** Comparisons of day-by-day adherence rates over the treatment days, 1 to 84, between participants in the PP sample who did and did not achieve SVR. The lines represent the fitted regression lines of adherence rates on the treatment days along with their corresponding estimated regression equations.

**Figure 3:** SVR rates across individual intervals defined in terms of: (A) total adherent days; (B) consecutive missed days; and (C) days on medication. The whiskers represent the size of standard errors (se), the two numbers in the first x-axis for each interval represent sample sizes for each interval in the PP and mITT samples, and the second axis labels represent the intervals of values which represent subgroups with values falling into those intervals.

**Figure 4:** SVR rates across cumulative intervals in terms of: (A) total adherent days; (B) consecutive missed days; and (C) days on medication. The whiskers represent the size of standard errors (se). The two numbers in the first x-axis for each interval represent sample sizes for each interval in the PP and mITT samples. The second axis labels represent the minimum threshold, or lower bound, values of the intervals which represent subgroups with values greater or equal to the thresholds.
Figure 1
Figure 2

The graph shows the daily adherence rates over treatment days, with two distinct lines representing SVR Achieved (blue) and SVR Failed (orange) cases. The equations for the linear fits are:

- SVR Achieved: $y = -0.0019x + 0.7955$
- SVR Failed: $y = -0.0043x + 0.6615$

The graph includes a percentage scale from 0% to 100% on the y-axis, and a sequence of numbers from 1 to 83 on the x-axis, representing treatment days.
Figure 3
Figure 4
Highlights

- The recent US nationwide HERO RCT study randomized 755 PWIDs living with HCV.
- Electronic blister packs measured day-by-day adherence to 12-week DAA regimen.
- Greater adherence is associated with SVR among those with <50% adherence rate.
- Treatment interruption and early discontinuation are associated with lower SVR.
- High SVR (>90%) can be achieved even with adherence as low as 50%.