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TITLE PAGE

Adherence to sofosbuvir and velpatasvir among people with chronic HCV infection and recent injection drug use: the SIMPLIFY study

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Abstract

Background: This study investigated treatment adherence among people with recent injecting drug use in a study of sofosbuvir/velpatasvir therapy for HCV infection. **Methods**: SIMPLIFY is an international open-label, single-arm multicentre study that recruited participants with recent injecting drug use (previous six months) and chronic HCV genotype (G) 1-6 infection between March and October, 2016 in seven countries (19 sites). Participants received sofosbuvir/velpatasvir once-daily for 12 weeks administered in a one-week electronic blister pack (records the time and date of each dose) for 12 weeks. We evaluated non-adherence (<90% adherent) as measured by electronic blister-pack assessed using logistic regression and generalised estimating equations (continuous) with detailed analyses of dosing dynamics. **Results**: Among 103 participants, 97% (n=100) completed treatment. Median adherence to therapy was 94%. Overall, 32% (n=33) were considered non-adherent (<90% adherence). Adherence significantly decreased over the course of therapy. Recent stimulant injecting (cocaine and/or amphetamines) at treatment initiation and during treatment was independently associated with non-adherence. Inconsistent dose timing (standard deviation of daily dose timing of ≥240 minutes) was also independently associated with non-adherence to therapy. Factors associated with inconsistent dose timing included lower levels of education and recent stimulant injecting. SVR was similar among adherent and non-adherent populations (94% vs. 94%, *P*=0.944). **Conclusion**: This study demonstrated high adherence to once-daily sofosbuvir/velpatasvir therapy among a population of people with recent injecting drug use. Recent stimulant injecting prior to and during DAA therapy and inconsistent dose-timing during treatment was associated with non-adherence. However, there was no impact of non-adherence on response to therapy, suggesting that adherence is not a significant barrier to successful DAA therapy in people with recent injecting drug use.

Introduction

There is a significant burden of hepatitis C virus (HCV) infection among people who inject drugs (PWID) globally [1]. The World Health Organization has set a goal to eliminate HCV as a major global public health concern by 2030. Between 2015 and 2030, targets include reducing new infections by 80%, reducing HCV deaths by 65%, increasing HCV diagnoses from <20% to 90%, and increasing the number of eligible persons receiving treatment from <10% to 80% [2]. Given that 23% of new HCV infections occur among recent PWID globally [3], scale up of HCV therapy will be required among this population to achieve HCV elimination targets in many countries. While HCV therapy has been demonstrated to be safe and effective in PWID [4], some countries including certain states in the United States and a number of European countries continue to withhold HCV therapy from people with ongoing injecting drug use. These restrictions are implemented at the level of government policy for the reimbursement of HCV DAA therapies and are based in part on concerns of poor adherence to therapy [5-7].

Studies in the interferon era demonstrated that treatment completion and adherence among recent PWID is comparable to people without recent injecting drug use ~~[8, 9].~~[8, 9]. In the era of direct acting antiviral (DAA) therapy, studies have demonstrated that adherence to DAA therapy is high among people receiving opioid substitution therapy (OST) ~~[10-15].~~[10-15]. However, there are limited data on adherence to DAA therapy among people with recent injecting drug use [4]. Further data is needed to fully understand HCV treatment adherence in the DAA era among recent PWID, including the evaluation of daily dosing dynamics and factors associated with adherence among people with recent injecting drug use.

SIMPLIFY is an international multicentre, open-label phase 4 trial evaluating the efficacy and safety of a fixed-dose once-daily combination of sofosbuvir and velpatasvir for 12 weeks in

patients infected with HCV genotypes 1 through 4 with recent injecting drug use (in the last six months). ~~Overall, 96%~~The primary study analysis demonstrated that 96% of the population completed therapy, the median adherence was 94% and the proportion who achieved SVR was 94% [16].

The aims of this analysis from the SIMPLIFY study were to further evaluate adherence to HCV DAA therapy and associated factors among PWID, evaluate dosing dynamics including consistency of dose timing and the change in adherence over the course of therapy, and compare adherence as measured by self-report and electronic blister-pack.

Methods

Study design and participants

In this international, multicentre, open-label phase 4 trial, we enrolled participants from 19 sites, in Australia (seven sites), Canada (six sites), New Zealand (one site), Norway (one site), Switzerland (two sites), the UK (one site), and the USA (one site). We recruited people from three drug treatment clinics, 12 hospital clinics, a private practice, and three community clinics [17].

Participants had to be ≥18 years of age, have chronic HCV genotypes 1-6 (but no patients with genotype 5 or 6 were enrolled), be naïve to NS5A-based HCV therapy, and have recent injecting drug use (self-reported injecting drug use within six months of enrolment). Participants with HIV infection and/or decompensated liver disease were excluded. Full eligibility criteria are provided in the study protocol as previously published [16].

All participants gave written informed consent before study procedures started. The study protocol was approved by St Vincent's Hospital, Sydney Human Research Ethics Committee (primary study committee), and local ethics committees at all study sites, and was done according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. An independent data and safety monitoring board reviewed the progress of the study.

Procedures

Patients received a fixed-dose combination tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir, administered orally once daily for 12 weeks. Participants received all study drugs weekly in an electronic blister pack (Information Mediary Corporation, Ottawa, Canada) with an integrated sensor grid that recorded the time and date that each daily dose was punched out of the pack, thus allowing us to track medication adherence. Participants were instructed to maintain the

same daily dosing interval and if a dose was missed to take the dose as soon as possible on the same day. In cases of a missed day of treatment, participants were instructed not to double the next dose. Participants were given the equivalent of AUS$10 as an incentive to return the blister pack. Once the packs were returned, a specific reader was used to download data on adherence. In addition to blister-pack measurement, adherence was also measured by counting any pills remaining in the blister-pack when returned and through the completion of a self-reported adherence questionnaire every four weeks to record the number of missed doses in the last 28 days. and the patient-reported reasons for missed doses.

We assessed participants at screening, enrolment (baseline), weeks 2, 4, 8, and 12 (end) of therapy, and at weeks 16 (SVR4), 24 (SVR12), and 36 (SVR24) after the beginning of treatment. Participants also visited the study site weekly to receive their medication in the electronic blister pack. Study nurses and physicians provided services to reduce risk and harm (eg, access to sterile syringes, other injecting equipment, and opioid substitution therapy) as per standard of care in their country.

Participants completed a self-administered questionnaire on a tablet computer at enrolment, baseline (start of treatment), every fourth week during treatment, and at 12 weeks after completing treatment. Participants received the equivalent of AUS$20 for their time and expenses. The questionnaires collected information on demographics (age, sex, ethnicity, employment status, education level, and housing status), drug and alcohol use, injecting risk behaviours, drug treatment, and health utility. To assess alcohol consumption, we used the Alcohol Use Disorders Identification Test–Consumption, which is derived from the first three questions of the full test; scores of 3 or more (women) and 4 or more (men) indicate hazardous consumption or active alcohol use disorders.

Outcomes

The primary outcome of this analysis was treatment non-adherence, as measured by receiving <90% of doses to a maximum of one dose per day~~.~~ consistent with previous studies into medication adherence [18, 19]. A secondary endpoint analysed in this study was inconsistent dose timing, as measured by a standard deviation of daily dose timing of ≥240 minutes and ongoing daily adherence.

Daily adherence was measured by electronic blister-packs which recorded the date and time each dose of sofosbuvir/velpatasvir was removed. Each day was assigned 0 if no doses were removed from the blister-pack or was assigned 1 if at least one dose was removed from the blister-pack on an individual day of therapy. On days where more than one dose was removed, participants were assigned an adherence of 1 for the day.

Weekly adherence to sofosbuvir/velpatasvir was calculated as the number of doses removed from a blister-pack in a given treatment week (to a maximum of seven) divided by seven days.

Overall adherence was calculated by dividing the number of total doses removed from the blister-pack (to a maximum of one per day) by the total number of expected doses (84 doses). Among individuals in whom therapy was extended, adherence was calculated as the proportion of expected doses received in the first 84 days of therapy. In the case of a damaged blister-pack from which data could not be retrieved, clinical pill count data was used.

Self-reported overall adherence to sofosbuvir/velpatasvir therapy was calculated by subtracting the total number of missed doses reported by the participant in each four week period (three periods

over 84 days) from the total expected number of doses (n=84). The number of reported doses was then divided by the total expected number of doses (n=84).

Inconsistent dose timing was determined by calculating the standard deviation in daily dose timing in minutes. The standard deviation of dose timing for each participant was then stratified by <240 minutes and ≥240 minutes to represent consistent dose timing and inconsistent dose timing respectively.

Statistical Analyses

Daily blister-pack was assessed and the proportion of participants with overall adherence of <90% was calculated. Participants with <90% and ≥90% adherence were compared using Chi-square or Fisher's exact test, as appropriate.

Logistic regression was used to assess baseline predictors of <90% adherence (non-adherence) and dosing consistency. Factors hypothesised to be predictive of non-adherence and inconsistent dose timing were determined based on factors previously shown or hypothesised to be associated with adherence to HCV therapy. These predictors included age (stratified by median), sex, education, hazardous alcohol consumption at baseline, current OST at baseline, recent (past month) injecting drug use at baseline, recent heroin injecting at baseline, recent cocaine injecting at baseline, recent amphetamine injecting at baseline, recent stimulant (cocaine and/or amphetamine) injecting at baseline, and frequency of injecting drug use at baseline. Unadjusted logistic regression analyses were performed to estimate odds ratios (OR) and corresponding 95% confidence intervals (95% CI) to identify predictors of an overall adherence of <90% and inconsistent dose timing. All variables with $p<0.20$ in the unadjusted analyses were considered for multivariate logistic regression models using a backward stepwise approach and sequentially eliminated subject to the

result of a likelihood ratio test. Odds ratios and corresponding 95% confidence intervals were generated to identify on-treatment behavioural predictors of an overall adherence of <90%.

Logistic regression was also used to assess on-treatment behavioural factors associated with non-adherence. On-treatment behavioural factors hypothesised to be associated with non-adherence included hazardous alcohol consumption on treatment, OST on treatment, any injecting drug use on treatment, any heroin injecting on treatment, any cocaine injecting on treatment, any amphetamine injecting on treatment, any stimulant (cocaine and/or amphetamine) injecting on treatment, average dose timing on treatment, and consistency of dose timing on treatment. Unadjusted logistic regression analyses were performed to identify factors associated with an overall adherence of <90%. All variables with $p<0.20$ in the unadjusted analyses were considered for multivariate logistic regression models using a backward stepwise approach as above.

Generalised estimating equation (GEE) analyses were used to investigate the change in adherence over the course of therapy and the impact of on-treatment behavioural factors on treatment adherence. GEE methods were used to account for the correlated nature of repeated measurements among individual participants and to provide a detailed time-updated analysis of ongoing treatment adherence. The impact of time on treatment was assessed by including day of treatment as a factor in GEE analyses with the effect reported per study week. On-treatment behavioural factors hypothesised to be associated with non-adherence included hazardous alcohol consumption on treatment, OST on treatment, any injecting drug use on treatment, any heroin injecting on treatment, any cocaine injecting on treatment, any amphetamine injecting on treatment, any stimulant injecting on treatment, and treatment duration. GEE models were specified using a gaussian family function. ORs with corresponding 95% CIs and p-values were calculated. All

variables with $p<0.20$ in the unadjusted analyses were considered for multivariate logistic regression models using a backward stepwise approach as above.

Statistically significant differences were assessed at $p<0.05$; p values are two-sided. All analyses were performed using the statistical package Stata v14.1 (College Station, TX, United States).

Role of the funding source

The study (including study medications) was funded by a research grant from Gilead Sciences. The sponsor (The Kirby Institute, UNSW Sydney) designed the study, collected the data, managed study samples, monitored study conduct and performed the statistical analysis.

Results

Baseline characteristics

Overall, 103 participants were enrolled in the study and initiated HCV therapy. The baseline demographic and behavioural characteristics of the participants are shown in Table 1. The median age was 48 years, 72% were male, and 48% reported an education level of high school or greater.

Fifty-six percent of participants were receiving OST at baseline and 74% reported injecting drug use in the last month. Twelve percent of participants neither injected drugs in the last month nor were receiving OST at baseline. The drugs most commonly injected in the month prior to commencement of therapy were heroin (55%) and amphetamines (30%; Table 1).

Treatment completion, adherence, and dosing patterns

Overall, 97% (n=100) of participants completed treatment (Table 2). Reasons for not completing treatment were loss to follow-up (n=2) and death due to overdose (n=1).

The overall daily blister-pack adherence was 94% (IQR 88-98%; Table 2 and Figure 1). Adherence was higher when measured by weekly blister-pack adherence (98%, IQR 94-100%) and self-reported adherence (99%, IQR 98-100%; Table 2 and Figure 2). Patient reported reasons for non-adherence were available in 81 instances over the course of therapy and included "Forgot" (n=54, 67%), "Inaccessible at time of dose" (n=14, 17%), "Lost pill(s)" (n=7, 9%), and "Other" (n=6, 7%). There were five instances of a damaged blister-pack from which electronic adherence data could not be obtained. In all cases of damaged blister-packs, no pills remained in the returned blister-pack and therefore these days with missing adherence data were counted as doses received. One participant had no available blister-pack data due to being lost to follow-up before the return of the first blister-pack.

By daily blister-pack measurement, the majority of participants missed at least one daily dose with 88% missing at least one dose of scheduled therapy. The majority (54%) of participants missed between one and eight daily doses of sofosbuvir/velpatasvir therapy (Table 2) and 54% of participants missed no more than one consecutive day of therapy. Eleven participants had at least one episode of nonadherence for ≥7 consecutive days with one participant having two episodes of nonadherence for ≥7 consecutive days. These episodes of nonadherence of ≥7 days occurred in four participants (4%) in the first six weeks of therapy and in eight participants (8%) in the last 6 weeks of therapy. Individual examples of adherent and non-adherent participant's dosing patterns are shown in Figure 3a and 3b respectively.

Daily dose timing as collected by electronic blister-pack was tabulated to determine the average time of day during which participants took their dose (Table 2). The majority of participants, on average, took their daily dose in the morning or afternoon (5:00 AM–11:59 AM, 41%; 12:00 PM-4:59 PM~~; 82~~, 41%). Daily dose timing was inconsistent, with only 24% (24 of 102) of participants with available blister-pack data demonstrating a standard deviation in dose time of less than 120 minutes. Daily blister-pack adherence of ≥90% was reported in 100% (24 of 24), 77% (33 of 43), and 31% (11 of 35) of those with a standard deviation in dose time of less than 120 minutes, 120-240 minutes, and ≥240 minutes respectively.

Baseline predictors of overall blister-pack adherence

The proportion of participants with <90% blister-pack adherence stratified by key behavioural and demographic characteristics is shown in Table 3. In unadjusted logistic regression analyses, the only baseline factor that was associated with non-adherence to therapy was injecting stimulants (cocaine and/or amphetamines) in the last month at baseline (OR 2.77, P=0.019; Table 3).

On-treatment behavioural predictors of overall blister-pack adherence

The proportion of participants with <90% blister-pack adherence stratified by key on-treatment behavioural characteristics is shown in Table 4. In unadjusted logistic regression analyses, on-treatment behavioural factors that were associated with non-adherence to therapy included amphetamine injecting during treatment, stimulant injecting during treatment, and a standard deviation of dose timing of ≥240 minutes. In adjusted analyses, behavioural factors which were associated with non-adherence to therapy were stimulant injecting on treatment (adjusted odds ratio [aOR] 3.33, P=0.023), and a standard deviation of dose timing of ≥240 minutes (aOR 12.57, P<0.001; Table 4).

In GEE analyses past month stimulant injecting during treatment remained associated with daily nonadherence to therapy (aOR 2.13, P<0.001). Past month heroin injecting was also associated with daily nonadherence to therapy (aOR 1.78, P<0.001) in GEE analyses (Supplementary table 1).

Change in adherence over the course of therapy

Change in adherence over the course of therapy is illustrated in Figures 2 and 4. In GEE analyses, later study visit was associated with non-adherence to therapy (per week; aOR 1.08, P<0.001; Supplementary table 1).

Baseline predictors of inconsistent dose timing

The proportion of participants with blister-pack data with a standard deviation of dose timing of ≥240 minutes stratified by key behavioural and demographic characteristics is shown in Table 5.

In unadjusted analyses participants with less than high school education were more likely to take their dose at inconsistent times. In adjusted analyses, baseline factors which were associated with inconsistent dose timing were less than high school education (aOR 2.77, *P*=0.025) and recent stimulant injecting (aOR 2.43, *P*=0.048; Supplementary Table 2).

Impact of DAA adherence on sustained virologic response

There were no cases of virological failure or virological relapse among participants in this study [16]. There was no difference in SVR among those with sofosbuvir/velpatasvir adherence ≥90% (94%, 66 of 70) as compared to those with sofosbuvir/velpatasvir adherence of <90% (94%, 31 of 33, *P*=0.944). There was also no statistically significant difference in the proportion achieving SVR between those with (93%, 85 of 91) and without missed doses during therapy (100%, 12 of 12, *P*=0.359). However, compared to the proportion with SVR in those patients who received all 12 weeks of therapy (~~98~~97%, 97 of ~~99~~100), participants who did not complete therapy (0%, 0 of ~~4~~3) had a significantly lower likelihood of achieving SVR due to loss to follow-up or death (*P*<0.001). Of the 11 participants with at least one episode of nonadherence for ≥7 consecutive days, nine (82%) completed treatment and there were no cases of virological failure.

Discussion

This study investigated adherence to once-daily sofosbuvir/velpatasvir therapy for HCV infection among a cohort of people with recent injecting drug use. A high adherence to therapy was observed overall, but treatment adherence declined during therapy. Recent stimulant injecting at the time of treatment initiation was associated with non-adherence to therapy. During treatment, stimulant injecting and inconsistent dose timing were associated with non-adherence. Adherence did not impact response to therapy. These data demonstrate that adherence to HCV DAA therapy among PWID can occur concurrently with ongoing injecting drug use. However, recent stimulant injecting prior to and during therapy was associated with non-adherence to therapy.

The overall median adherence to sofosbuvir/velpatasvir was high at 94~~%.~~% as measured by electronic blister pack with higher adherence as measured by self-report, consistent with a recent study of HCV DAA therapy which monitored adherence using measured using medication event monitoring system (MEMS) caps [20]. However, 88% of participants missed at least one dose of therapy, with the majority only missing between one and eight doses. The adherence observed in this study is higher than adherence observed in studies of interferon-based therapies among PWID ~~[9, 18]~~[9, 21] and similar to what has been observed in previous studies of HCV DAA therapy among people receiving OST ~~[19-24].~~[20, 22-26]. This similarity was observed despite the strict definition of adherence used in this study based on data collection using an electronic blister-pack. It is likely that the weekly contact with healthcare providers and the use of a blister-pack for the administration of therapy may have assisted with improving adherence. However, despite imperfect daily adherence and the inconsistent adherence patterns observed, treatment completion and response to therapy was high with 96% of participants completing therapy and 94% of all participants achieving an SVR with no virological failures [16]. All treatment failures were due to treatment non-completion and post-treatment loss to follow-up. One hundred percent of

participants who completed treatment and attended their SVR12 visit achieved an SVR. There was no impact of non-adherence on SVR. Episodes of non-adherence of ≥7 consecutive days which occurred in 11 participants did not impact the proportion achieving SVR. These data suggests that once-daily sofosbuvir/velpatasvir is a robust regimen with some forgiveness in terms of the level of adherence required to achieve an SVR.

Recent stimulant injecting prior to and during treatment was associated with non-adherence to therapy. Although previous studies in the interferon era demonstrated that recent injecting drug use at baseline was not associated with reduced adherence to HCV therapy ~~[8, 9, 23, 25-32]~~[8, 9, 25, 27-34] or treatment completion ~~[9, 25, 27, 33]~~[9, 27, 29, 35], many of these studies were limited by small sample sizes, were conducted at a single centre, and were retrospective (without standardized collection of drug use data). More recent studies conducted in the DAA era have demonstrated an association between recent drug use and reduced adherence to HCV therapy in people with a history of injecting drug use ~~[22, 24].~~[20, 26]. This study of people with recent injecting drug use is consistent with these findings and provides novel data to demonstrate that the type of drug injected, specifically stimulants, may have an impact on adherence to DAA therapy among recent PWID. Although non-adherence did not impact SVR in this study, interventions to improve adherence may be needed in the context of shortened treatment where the impact of non-adherence may be amplified.

Very little is known about the dosing dynamics of HCV treatment among PWID. In this study, electronic blister-pack monitoring of therapy allowed for detailed analysis of dosing dynamics including episodes of nonadherence, dose timing and the consistency of dose timing. Analyses of episodes of nonadherence demonstrated that consecutive missed doses were common with 46% of participants having at least one episode of nonadherence longer than a single day and 11% of

participants missing at least seven consecutive days of therapy. The method of evaluating adherence to HCV therapy using an electronic blister pack is novel, providing considerable insight into adherence in this setting and may have applications in other settings (for HCV treatment and adherence to therapies for other conditions). Given the lack of virologic failure in this study it is apparent that these brief episodes of non-adherence did not impact SVR. Further, even among people with ≥7 consecutive missed doses, there were no cases of virological relapse or non-response. Further research is needed to fully understand the impact of missed doses of therapy (particularly extended periods of missed doses) on treatment outcomes and to determine the threshold at which SVR is hampered.

In logistic regression analyses participants with inconsistent dose timing were more likely to be non-adherent to therapy. Lower education levels and recent stimulant injecting were found to be associated with inconsistent dose timing. Similar to the analysis of factors associated with non-adherence, this finding suggests that interventions to enhance treatment adherence among participants with stimulant injecting may be needed. In particular, interventions which aid in consistent dose timing among this population could be beneficial. However, the improved adherence among the group with consistent dose timing may have been a result of unmeasured factors and therefore further research is needed to understand if interventions to improve consistency in dose timing could result in improved adherence.

The measurement of adherence by electronic blister-pack also allowed for a detailed investigation of the change in adherence over the course of therapy. Later time points during therapy were independently associated with reduced daily adherence, consistent with a recent study of inner-city patients in the United States which demonstrated a decrease in adherence to DAA therapy over the course of treatment ~~[22].~~[20]. Given the high potency of many modern DAA regimens,

there have been a number of recent studies investigating shortened HCV DAA therapy ~~[34-36].~~[36-38]. This finding of decreased treatment adherence over the course of therapy suggests that these efforts to shorten therapy could potentially result in increased overall treatment adherence among PWID.

This study had some limitations. Despite the robust measurement of treatment adherence using electronic blister-packs to record the date and time of doses, this measurement relied on the accurate usage of the device. In some instances, multiple pills were removed on one day followed by missed doses on subsequent days. By daily blister-pack adherence, this would have only counted as one dose given that dosing is meant to be daily. If the previously removed pill was taken on a subsequent day, this dose would not be recorded by the blister-pack. As a result, daily blister-pack adherence likely represents an underestimation of the true adherence to therapy. Conversely, weekly blister-pack adherence assumes that the patient took all pills removed in a given week when this may not be the case (e.g. multiple pills removed on the last day of the week before the blister-pack was retuned). As a result, weekly blister-pack adherence likely overestimates the true treatment adherence. Thus, true adherence probably exists somewhere between daily and weekly blister-pack measurements. Despite this, daily blister-pack measurement is a significantly more robust method for measuring adherence when compared to clinical pill count or self-report and provides interesting insights into the dosing dynamics of PWID. Although SIMPLIFY is an international study, these results cannot necessarily be generalised to the wider PWID population. Patients were treated at hospital-based HCV clinics, community-based drug treatment clinics, and community health centres experienced in HCV care in PWID. Furthermore, HIV-infected people were excluded from this study and the study population consisted of a high proportion of people on OST. As such, patients recruited into this study likely represent a somewhat selected population of PWID who are engaged with health

services and is not necessarily generalisable to treatment in other settings~~.~~ or among populations with a differing prevalence of OST. These results also cannot necessarily be generalised to other DAA regimens which may require more complex dosing or increased pill burden and may have a lower barrier to resistance. Lastly, treatment adherence is a highly complex phenomenon that may be influenced by a number of unmeasured factors including the effect of close monitoring of adherence, as was done in this trial. Further, although the incentive given for return of the blister pack was not directly tied to a participant's adherence, this incentive may have indirectly encouraged greater adherence to therapy. Despite these limitations this study represents a highly detailed and robust investigation of treatment adherence among a population of PWID with recent injecting drug use.

Despite intermittent and consecutive days of nonadherence, SVR remained high with no cases of virological failure or viral relapse, demonstrating that there is some forgiveness with a regimen of once- daily sofosbuvir/velpatasvir [16]. However, further research is needed to investigate the impact of adherence to HCV DAA therapies on response to therapy in larger, more diverse studies of recent PWID and with other HCV regimens. Taken together, these data support the inclusion of PWID in HCV treatment strategies, which will be essential for achieving HCV elimination targets in many countries.

Declaration of Interests

JG reports grants and personal fees from AbbVie, Cepheid, Gilead Sciences, and Merck. OD reports grants from Gilead Sciences during this study and grants from Gilead Sciences, Merck, and AbbVie. PB reports grants and personal fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck Sharp & Dohme. MH reports grants from Gilead Sciences, Bristol-Myers Squibb, and AbbVie. JBr reports consultant fees from Gilead Sciences and Merck. AHL reports grants and personal fees from Gilead Sciences and Merck. GVM reports grants and personal fees from Gilead Sciences and grants from AbbVie. JP reports personal fees from Janssen and Genetech. CC reports grants and personal fees from Gilead Sciences. JJF reports grants and personal fees from AbbVie, Merck, Gilead Sciences, and Janssen, personal fees from Contravir, and grants from Abbott. CF reports grants and non-financial support from Kirby Institute during this study and grants from Gilead Sciences, ViiV HealthCare, and Merck. GJD reports grants, personal fees, and non-financial support from AbbVie, Merck, Bristol-Myers Squibb, and Roche; grants and personal fees from Janssen; personal fees and non-financial support from Gilead Sciences; and personal fees from GlaxoSmithKline and Abbott Diagnostics. PR reports fees for educational talks from Gilead Sciences, Merck Sharp & Dohme, and AbbVie, and is on the advisory board for Merck Sharp & Dohme. BC reports grants, personal fees, and non-financial support from Gilead Sciences, Merck, and AbbVie. EG reports personal fees from being a Clinical Advisor for Gilead Sciences, Merck, Janssen, and AbbVie, and personal fees from Gilead Sciences Speaker Bureau and AbbVie Speaker Bureau. JFD reports grants and personal fees from Gilead, Merck Sharp & Dohme, Janssen, and AbbVie. All other authors declare no competing interests.

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Table 1: Participant baseline characteristics of all participants in the SIMPLIFY study

Characteristic, n (%)	**Overall (n=103)**
Age, median (25%, 75%)	48 (41, 53)
Male sex	74 (72)
High school or greater education	49 (48)
Any injecting drug use in the last month	
Heroin	57 (55)
Cocaine	13 (13)
Amphetamines	31 (30)
Any poly-drug injecting in the last month	40 (39)
Heroin and stimulant	15 (15)
Single drug injecting in the last month	
Only heroin	24 (23)
Only cocaine	3 (3)
Only amphetamines	10 (10)
Injecting drug use frequency in the last month	
Never	27 (26)
<daily	49 (48)
≥daily	27 (26)
Opioid substitution treatment (ever)	84 (82)
OST and recent injecting (past month) at baseline	
No OST, no recent injecting	12 (12)
No OST, recent injecting	33 (32)
OST, no recent injecting	15 (15)
OST, recent injecting	43 (42)
Study site distribution	
Australia/New Zealand	43 (42)
North America	40 (39)
Europe	20 (19)

Table 2: Treatment adherence and dosing patterns among all participants in the SIMPLIFY study

Variable	**Overall (n=103) n (%)**
Treatment completion	100 (97)
Missed doses of sofosbuvir/velpatasvir as measured by electronic blister-pack, n (%)	
No missed doses (100%)	12 (12)
1-4 missed doses (95-<100%)	36 (35)
5-8 missed doses (90-<95%)	20 (19)
9-17 missed doses (80-<90%)	17 (17)
≥18 missed doses (<80%)	18 (17)
Longest episode of non-adherence*	
1 day	44 (43)
2 days	19 (18)
3 days	3 (3)
4 days	9 (9)
5 days	2 (2)
6 days	3 (3)
≥7 days	11 (11)
Median on-treatment sofosbuvir/velpatasvir adherence percent	
Patient report	99 (98-100)
Blister-pack, weekly	98 (94-100)
Blister-pack, daily	94 (88-98)
Dose timing*	
Morning (5:00AM-11:59AM)	42 (41)
Afternoon (12:00PM-4:59PM)	42 (41)
Evening (5:00PM-12:00AM)	17 (17)
Night (12:00AM-4:59AM)	1 (1)
Consistency in dose timing (standard deviation in minutes)*	
<120	24 (24)
≥ 120-<240	43 (42)
≥ 240	35 (34)

*Among those with available blister-pack data (n=102)

Table 3: Unadjusted baseline factors associated with overall treatment adherence of <90% among all participants in the SIMPLIFY study (n=103).

	Sofosbuvir/velpatasvir adherence of ≥90% (%; n=70) [a]	**Sofosbuvir/velpatasvir adherence of <90% (%; n=33)** [a]	**OR (95% CI)**	***P***
Age (years)				
≤41	17 (61)	11 (39)	1.00	-
>41	53 (71)	22 (29)	0.64 (0.26-1.59)	0.337
Gender				
Female	23 (79)	6 (21)	1.00	-
Male	47 (64)	27 (36)	0.45 (0.16-1.25)	0.128
Education				
<High school	37 (70)	16 (30)	1.00	-
High school or greater	33 (66)	17 (34)	1.19 (0.52-2.73)	0.679
Hazardous alcohol consumption				
No	56 (66)	29 (34)	1.00	-
Yes	14 (78)	4 (22)	0.55 (0.17-1.83)	0.331
Current OST				
No	32 (71)	13 (29)	1.00	-
Yes	38 (66)	20 (34)	1.30 (0.56-3.01)	0.547
Injecting (last month)				
No	20 (74)	7 (26)	1.00	-
Yes	50 (66)	26 (34)	1.49 (0.56-3.97)	0.430
Frequency of injecting (last month)				
Never	20 (74)	7 (26)	1.00	-
Less than daily	31 (63)	18 (37)	1.66 (0.59-4.69)	0.339
Daily or greater	19 (70)	8 (30)	1.20 (0.36-3.97)	0.761
Heroin injecting (last month)				
No	33 (72)	13 (28)	1.00	-
Yes	37 (65)	20 (35)	1.37 (0.59-3.18)	0.461
Cocaine injecting (last month)				
No	64 (71)	26 (29)	1.00	-
Yes	6 (46)	7 (54)	2.87 (0.88-9.36)	0.080
Amphetamine injecting (last month)				
No	53 (74)	19 (26)	1.00	-
Yes	17 (55)	14 (45)	2.30 (0.95-5.54)	0.064
Stimulant injecting (last month)				
No	47 (77)	14 (23)	1.00	-
Yes	23 (55)	19 (45)	2.77 (1.18-6.50)	0.019

[a] Percentages represent row percentages

Table 4: Unadjusted and adjusted analysis of on-treatment factors associated with overall treatment adherence of <90% among all participants in the SIMPLIFY study (n=103).

	Sofosbuvir/velpatasvir adherence of ≥90% (%; n=70)[a]	**Sofosbuvir/velpatasvir adherence of <90% (%; n=33)[a]**	**OR (95% CI)**	***P***	**aOR (95% CI)**	***P***
Hazardous alcohol consumption while on treatment						
No	53 (65)	29 (35)	1.00	-	-	-
Yes	17 (81)	4 (19)	0.43 (0.13-1.40)	0.161	-	-
OST while on treatment						
No	33 (80)	8 (20)	1.00	-	-	-
Yes	37 (62)	23 (38)	2.56 (1.01-6.51)	0.048	-	-
Injecting while on treatment						
No	12 (67)	6 (33)	1.00	-	-	-
Yes	58 (70)	25 (30)	0.86 (0.29-2.55)	0.789	-	-
Heroin injecting while on treatment						
No	33 (75)	11 (25)	1.00	-	-	-
Yes	37 (65)	20 (35)	1.62 (0.68-3.88)	0.278	-	-
Cocaine injecting while on treatment						
No	62 (71)	25 (29)	1.00	-	-	-
Yes	8 (57)	6 (43)	1.86 (0.59-5.91)	0.293	-	-
Amphetamine injecting while on treatment						
No	51 (77)	15 (23)	1.00	-	-	-
Yes	19 (54)	16 (46)	2.86 (1.19-6.90)	0.019	-	-
Stimulant injecting while on treatment						
No	44 (80)	11 (20)	1.00	-	-	-
Yes	26 (57)	20 (43)	3.01 (1.27-7.14)	0.012	3.39 (1.19-9.67)	0.023
Dose timing (average)						
Morning (5:00AM-11:59AM)	31 (74)	11 (26)	1.00	-	-	-
Afternoon (12:00PM-4:59AM)	25 (60)	17 (40)	2.11 (0.84-5.30)	0.842	-	-
Evening (5:00PM-12:00AM)	13 (76)	4 (24)	0.87 (0.23-3.23)	0.832	-	-
Night (12:00AM-4:59AM)	1 (100)	0 (0)	*	*	-	-
Consistency in dose timing (standard deviation in minutes)						
<240	12 (34)	23 (66)	1.00	-	-	-
≥ 240	58 (87)	9 (13)	12.35 (4.59-33.24)	<0.001	12.44 (4.37-35.41)	<0.001

[a] Percentages represent row percentages; *Insufficient numbers for inclusion in logistic regression

Figure 1: Daily adherence to sofosbuvir/velpatasvir therapy as measured by weekly-administered electronic blister-packs. Rows represent individual participants and columns represent days of therapy. Green boxes represent a dose received, with light green boxes indicating a damaged blister-pack where clinical pill count data was used. Yellow boxes represent no dose received on that treatment day and white boxes represent early treatment discontinuation or death. Published with permission from [16].

Figure 2: Mean 4-weekly treatment adherence over time stratified by self-reported adherence (red), weekly assessed blister-pack adherence (blue), and daily assessed blister-pack adherence (yellow).

Figure 3: Examples of daily adherence to treatment among four adherent (>=90%) participants (a) and four nonadherent (<90%) participants (b). All patients achieved SVR.

Figure 4: Mean daily treatment adherence to sofosbuvir/velpatasvir therapy over the 84 day treatment course among all participants in the SIMPLIFY study.

Supplementary table 1: GEE analysis of factors associated with daily non-adherence to therapy as measured by electronic blister-pack among all participants in the SIMPLIFY study with available blister-pack data (n=102).

	Unadjusted OR	**95% CI**	**P**	**Adjusted OR**	**95% CI**	**P**
Hazardous alcohol consumption						
No	1.00	-	-	-	-	-
Yes	1.43	0.92-2.24	0.113	-	-	-
Current OST						
No	1.00	-	-	-	-	-
Yes	1.11	0.79-1.56	0.544	-	-	-
Injecting (last month)						
No	1.00	-	-	-	-	-
Yes	1.57	1.17-2.11	0.002	-	-	-
Frequency of injecting (last month)						
Never	1.00	-	-	-	-	-
Less than daily	1.56	1.16-2.10	0.003	-	-	-
Daily or greater	1.68	1.09-2.60	0.019	-	-	-
Heroin injecting (last month)						
No	1.00	-	-	-	-	-
Yes	1.44	1.10-1.89	0.008	1.78	1.34-2.35	<0.001
Cocaine injecting (last month)						
No	1.00	-	-	-	-	-
Yes	0.91	0.56-1.49	0.719	-	-	-
Amphetamine injecting (last month)						
No	1.00	-	-	-	-	-
Yes	1.97	1.48-2.62	<0.001	-	-	-
Cocaine or amphetamine injecting (last month)						
No	1.00	-	-	-	-	-
Yes	2.07	1.57-2.74	<0.001	2.13	1.62-2.81	<0.001
Time since treatment initiation						
Per week	1.07	1.05-1.10	<0.001	1.08	1.06-1.11	<0.001

Supplementary table 2: Unadjusted and adjusted analysis of baseline factors associated with a standard deviation of dose timing of ≥240 minutes among all participants in the SIMPLIFY study with available blister-pack data (n=102).

	Standard deviation of dose timing of <240 minutes (%; n=67) [a]	**Standard deviation of dose timing of ≥240 minutes (%; n=35) [a]**	**OR (95% CI)**	***P***	**aOR (95% CI)**	***P***
Age (years)						
≤41	14 (52)	13 (48)	1.00	-	-	-
>41	53 (71)	22 (29)	0.45 (0.18-1.10)	0.081	-	-
Gender						
Female	49 (67)	24 (33)	1.00	-	-	-
Male	18 (62)	11 (38)	1.25 (0.51-3.05)	0.628	-	-
Education						
High school or greater	37 (76)	12 (24)	1.00	-	-	-
<High school	30 (57)	23 (43)	2.36 (1.01-5.52)	0.047	2.77 (1.14-6.72)	0.025
Hazardous alcohol consumption						
No	54 (64)	30 (36)	1.00	-	-	-
Yes	13 (72)	5 (28)	0.69 (0.23-2.13)	0.521	-	-
Current OST						
No	33 (73)	12 (27)	1.00	-	-	-
Yes	34 (60)	23 (40)	1.86 (0.80-4.34)	0.151	-	-
Injecting (last month)						
No	16 (59)	11 (41)	1.00	-	-	-
Yes	51 (68)	24 (32)	0.68 (0.28-1.70)	0.413	-	-
Frequency of injecting (last month)						
Never	16 (59)	11 (41)	1.00	-	-	-
Less than daily	34 (71)	14 (29)	0.6 (0.22-1.61)	0.309	-	-
Daily or greater	17 (63)	10 (37)	0.86 (0.29-2.56)	0.78	-	-
Heroin injecting (last month)						
No	30 (65)	16 (35)	1.00	-	-	-
Yes	37 (66)	19 (34)	0.96 (0.42-2.19)	0.928	-	-
Cocaine injecting (last month)						
No	59 (66)	30 (34)	1.00	-	-	-
Yes	8 (62)	5 (38)	1.23 (0.37-4.08)	0.736	-	-
Amphetamine injecting (last month)						
No	51 (71)	21 (29)	1.00	-	-	-
Yes	16 (53)	14 (47)	2.13 (0.88-5.12)	0.093	-	-
Stimulant injecting (last month)						
No	44 (72)	17 (28)	1.00	-	-	-
Yes	23 (56)	18 (44)	2.03 (0.88-4.66)	0.097	2.43 (1.01-5.85)	0.048

[a] Percentages represent row percentages

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Figure 1

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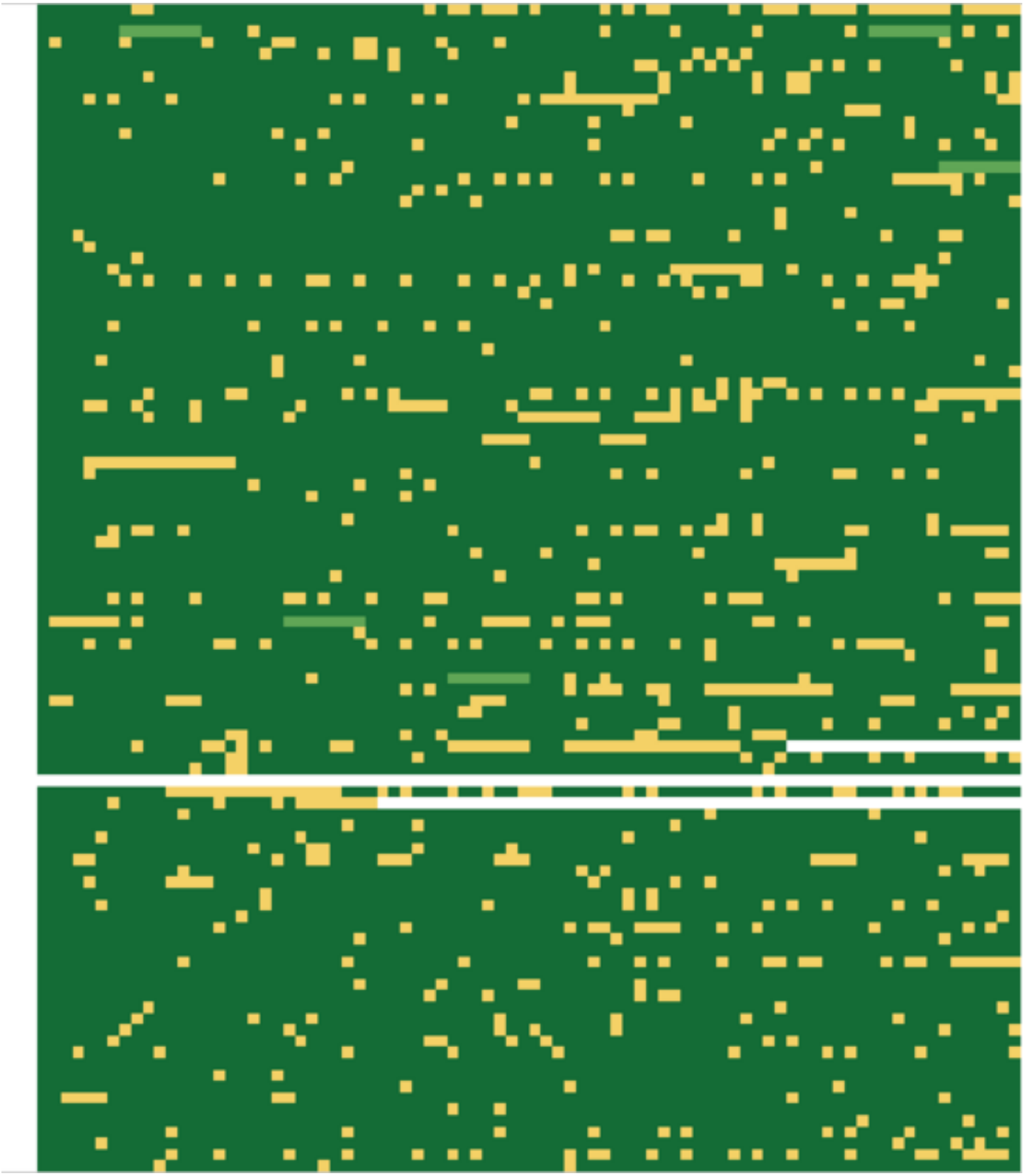

Figure 2

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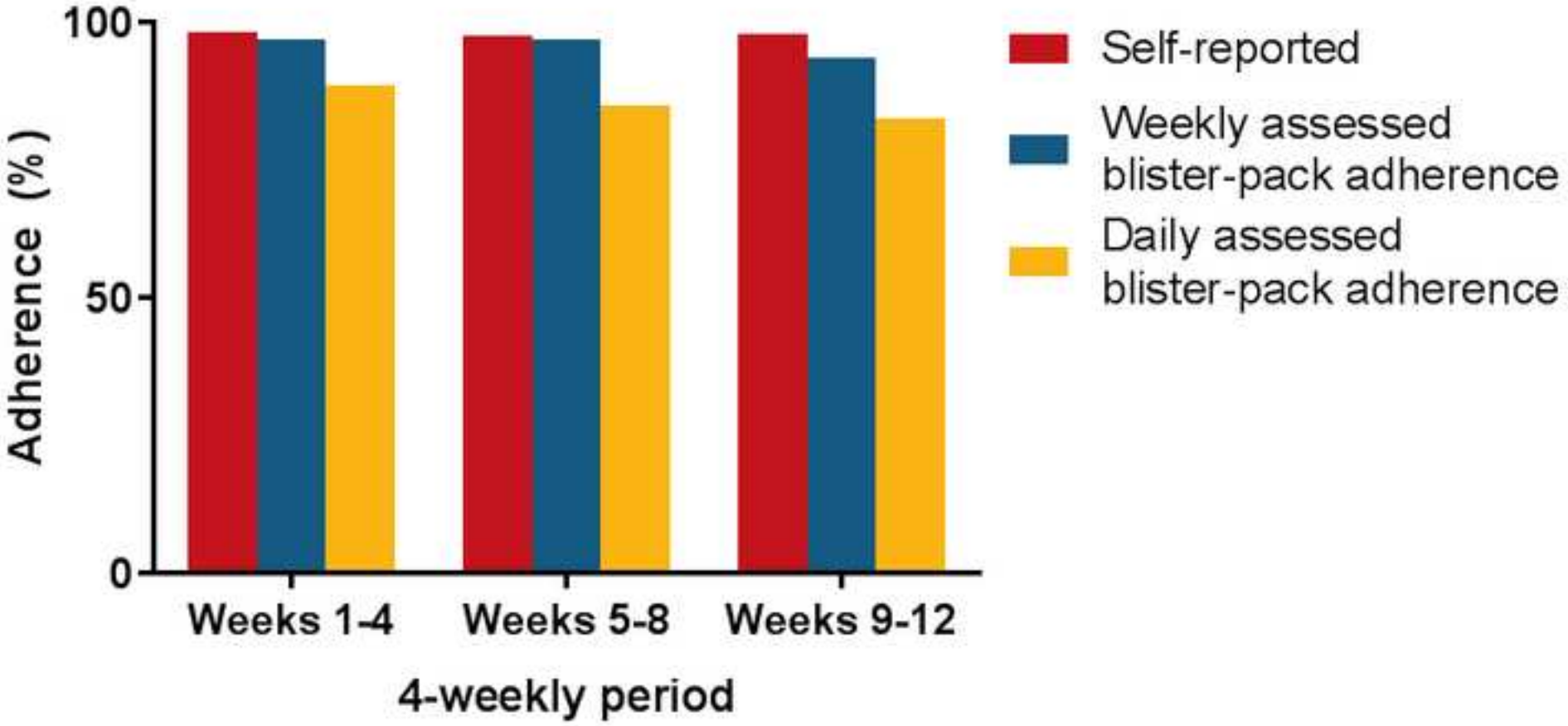

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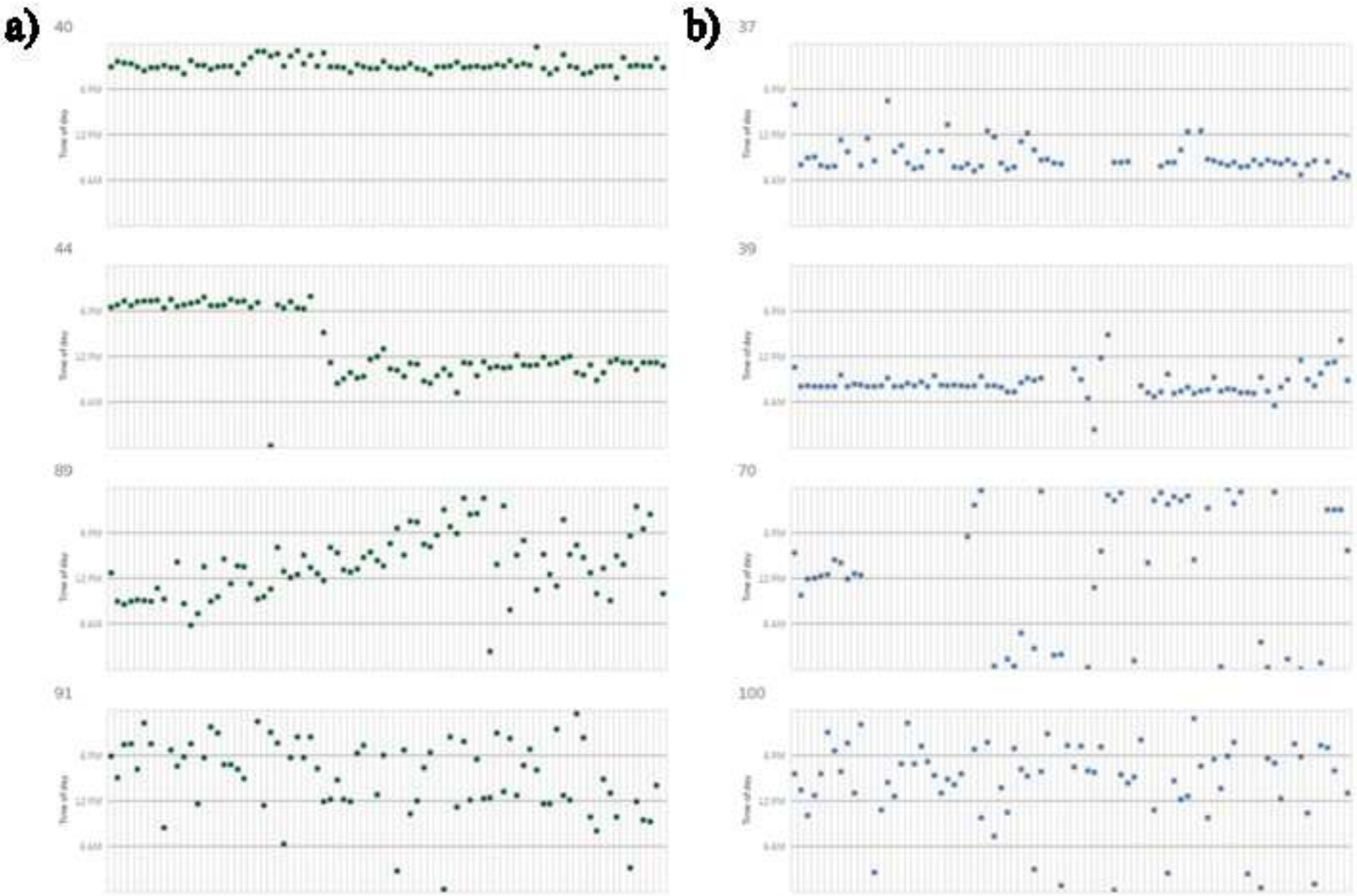

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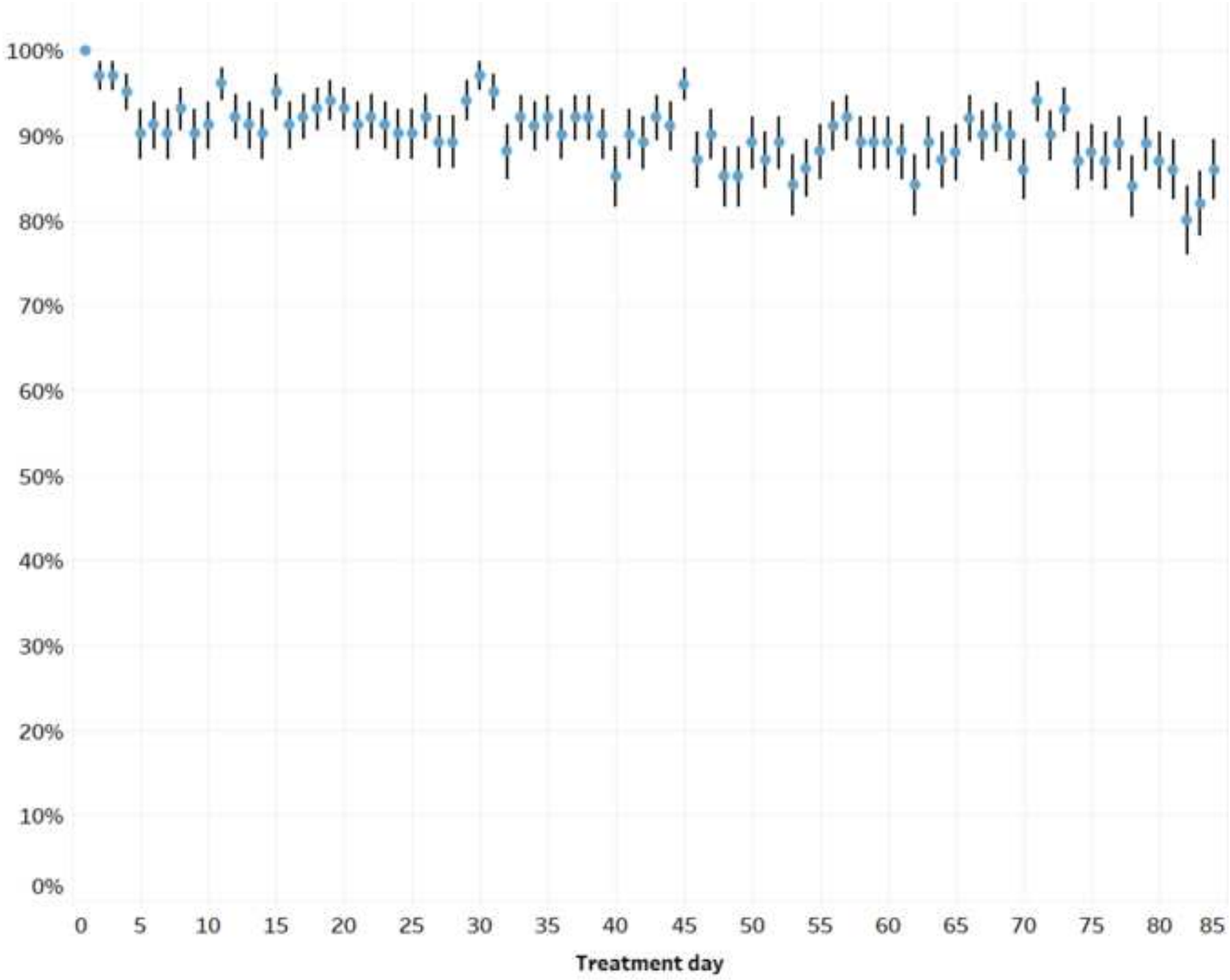

Declaration of Interests

JG reports grants and personal fees from AbbVie, Cepheid, Gilead Sciences, and Merck. OD reports grants from Gilead Sciences during this study and grants from Gilead Sciences, Merck, and AbbVie. PB reports grants and personal fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck Sharp & Dohme. MH reports grants from Gilead Sciences, Bristol-Myers Squibb, and AbbVie. JBr reports consultant fees from Gilead Sciences and Merck. AHL reports grants and personal fees from Gilead Sciences and Merck. GVM reports grants and personal fees from Gilead Sciences and grants from AbbVie. JP reports personal fees from Janssen and Genetech. CC reports grants and personal fees from Gilead Sciences. JJF reports grants and personal fees from AbbVie, Merck, Gilead Sciences, and Janssen, personal fees from Contravir, and grants from Abbott. CF reports grants and non-financial support from Kirby Institute during this study and grants from Gilead Sciences, ViiV HealthCare, and Merck. GJD reports grants, personal fees, and non-financial support from AbbVie, Merck, Bristol-Myers Squibb, and Roche; grants and personal fees from Janssen; personal fees and non-financial support from Gilead Sciences; and personal fees from GlaxoSmithKline and Abbott Diagnostics. PR reports fees for educational talks from Gilead Sciences, Merck Sharp & Dohme, and AbbVie, and is on the advisory board for Merck Sharp & Dohme. BC reports grants, personal fees, and non-financial support from Gilead Sciences, Merck, and AbbVie. EG reports personal fees from being a Clinical Advisor for Gilead Sciences, Merck, Janssen, and AbbVie, and personal fees from Gilead Sciences Speaker Bureau and AbbVie Speaker Bureau. JFD reports grants and personal fees from Gilead, Merck Sharp & Dohme, Janssen, and AbbVie. All other authors declare no competing interests.

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Contributors

JG, GJD, PB, PM, JBr, OD, AD, and SQ designed the study. JG and GD were the principal investigators. TLA was responsible for the laboratory work. EBC, JG, JA, and GJD led the study analyses. All authors contributed to the implementation, conduct, data interpretation, and writing and review of this work