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MAJOR ARTICLE

Adherence to Direct-Acting Antiviral Therapy in People Actively Using Drugs and Alcohol: The INCLUD Study

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Background. Hepatitis C virus treatment in persons who use drugs (PWUD) is often withheld due to adherence and reinfection concerns. In this study, we report treatment outcomes, technology-based adherence data, and adherence predictors in PWUD and/or alcohol.

Methods. INCLUD was a prospective, open-label study of ledipasvir/sofosbuvir for 12 weeks in PWUD aged 18–70 years. Participants were randomized to wireless (wirelessly observed therapy) or video-based directly observed therapy (vDOT). Drug use was assessed every 2 weeks. Sustained virologic response (SVR) was examined by intention-to-treat and as-treated. Factors associated with missing ≥1 dose(s) between visits were examined using generalized linear models.

Results. Sixty participants received ≥1 ledipasvir/sofosbuvir dose (47 human immunodeficiency virus [HIV]/hepatitis C virus [HCV], 13 HCV only; 78% male; 22% black; 25% cirrhotic). Substance use occurred at 94% of person-visits: 60% marijuana, 56% alcohol, 37% methamphetamine, 22% opioids, 17% cocaine, and 20% injection drug use. The SVR by intention-to-treat was 86.7% (52 of 60) and as-treated was 94.5% (52 of 55). Confirmed failures included 1 relapse, 1 reinfection, and 1 unknown (suspected reinfection). Median total adherence was 96% (interquartile range [IQR], 85%–100%; range, 30%–101%), and between-visit adherence was 100% (IQR, 86%–100%; range, 0%–107%). The odds of missing ≥1 dose between visits increased with HIV coinfection (2.94; 95% confidence interval [CI], 1.37–6.32; $P = .006$), black race (4.09; 95% CI, 1.42–11.74; $P = .009$), methamphetamine use (2.51; 95% CI, 1.44–4.37; $P = .0.001$), and cocaine use (2.12; 95% CI, 1.08–4.18; $P = .03$) and decreased with marijuana use (0.34; 95% CI, 0.17–0.70; $P = .003$) and vDOT (0.43; 95% CI, 0.21–0.87; $P = .02$).

Conclusions. Persons who use drugs achieved high SVR rates with high, but variable, ledipasvir/sofosbuvir adherence using technology-based methods. These findings support efforts to expand HCV treatment in PWUD.

Keywords. active drug use; alcohol; hepatitis C; HIV; ledipasvir/sofosbuvir.

Direct-acting antiviral (DAA) therapies have transformed hepatitis C virus (HCV) treatment. However, costs and insurance coverage continue to limit treatment uptake [1, 2], especially in persons who use drugs (PWUD) where adherence and reinfection are of concern [3]. Injection drug use (IDU) is the most common mode of HCV transmission, and incidence rates have been increasing largely due to the opioid epidemic [4]. Thus, withholding HCV therapy from PWUD is not compatible with efforts to reduce HCV prevalence and transmission [5] and ultimately eradicate HCV [6].

Several studies have examined DAA adherence and efficacy in persons who inject drugs (PWID) [7–12] and/or receive opioid agonist therapy (OAT) [13–18]. High but variable DAA adherence and sustained virologic response (SVR) rates between 82% and 100% were demonstrated, providing support for efforts to expand treatment to these populations. However, many of these studies examined factors associated with adherence in PWID given higher HCV prevalence and reinfection risk in this population [19, 20], but alcohol and drug use by noninjection routes may also affect DAA adherence and ultimately SVR [21, 22]. Human immunodeficiency virus (HIV) status is another important factor given the overlap with HCV coinfection [23], limited treatment uptake [24], and potential for drug-drug interactions with antiretroviral regimens. Studies in PWUD have primarily used self-report [12, 13, 21] or electronic [7, 8, 15, 18, 22] adherence monitoring approaches. Therefore, studies using technology-based adherence monitoring in PWUD are needed to identify adherence patterns,

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assess risk factors for poor adherence, and evaluate DAA treatment efficacy.

Ledipasvir/sofosbuvir is a fixed-dose DAA combination tablet that is taken once daily, is available as an authorized generic [25], and has a low potential for drug-drug interactions with antiretroviral medications and drugs of abuse [26], collective factors of which may facilitate treatment uptake in PWUD with HCV and HIV/HCV coinfection. In this study, we report findings from the "INtensive monitoring of hCv antiviraL adherence in persons Using Drugs (INCLUD)" study, which was an open-label study to characterize adherence to, and the pharmacology of, ledipasvir/sofosbuvir in persons actively using drugs and alcohol with HCV and HIV/HCV coinfection. The objectives of this study were to describe treatment outcomes, assess ledipasvir/sofosbuvir adherence using technology-based adherence monitoring approaches, and identify factors associated with imperfect medication adherence.

METHODS

Study Population

Participants between 18 and 70 years of age with active HCV infection (genotype 1, 4, 5, or 6), with or without concomitant HIV infection, and self-reported drug and/or alcohol use within 30 days of screening were eligible to participate. Key exclusion criteria included the following: estimated glomerular filtration rate (eGFR) < 30 mL/min per 1.73 m^2; receipt of prior HCV treatment with radiographic, histologic, or clinical evidence of cirrhosis; decompensated liver disease; medications not recommended per the ledipasvir/sofosbuvir package insert; chronic hepatitis B infection; unwillingness to use contraception, active pregnancy, or intent to become pregnant during the study; or medical conditions that may interfere with study participation or outcomes, in the opinion of investigators.

Patient Consent Statement

All participants provided written informed consent, and all study procedures were conducted in accordance with the ethical standards of the Colorado Multiple Institutional Review Board (15-0809) and the Declaration of Helsinki (1964, amended most recently in 2008) of the World Medical Association.

Study Design

INCLUD was a prospective, open-label study conducted in the greater Denver area (ClinicalTrials.gov: NCT02573376). Study visits occurred at the University of Colorado-Anschutz Medical Campus or the Denver Health and Hospital Authority system. After consent and confirmation of eligibility, participants were randomized to wireless pillboxes (wirelessly observed therapy [WOT] Wisepill RT2000; Wisepill Technologies, Capetown, South Africa) or video-based directly observed therapy ([vDOT] miDOT; emocha Mobile Health, Baltimore, MD) for adherence monitoring throughout treatment. Randomization was stratified by IDU and cirrhosis status. On study day 1, participants received their first dose of ledipasvir/sofosbuvir and underwent a 24-hour intensive pharmacokinetic assessment. A second observed dose was taken the following morning while participants were instructed on their adherence monitoring technology.

Study visits took place biweekly through week 12 of treatment and comprised study medication dispensation (~14-day supplies), assessment of drug use by self-report and urine toxicology screen (UScreen Drugs of Abuse, US Diagnostics, Inc., Huntsville, AL), and convenience blood samples for pharmacokinetic analysis. Pharmacology results will be reported separately. Participants were compensated $20 per visit and received additional compensation for engaging in their assigned adherence monitoring approach ($5 per video for those randomized to vDOT, $5 per week for exchanging the pill container for those randomized to WOT). SVR was assessed ~12 weeks after treatment completion. Participants who failed to achieve SVR had stored samples from baseline and the SVR visit sent for genotyping and NS5a resistance testing to assess relapse versus reinfection (ARUP Laboratories, Salt Lake City, UT). Safety laboratory assessments were performed at study weeks 4, 8, and 12, and adverse events (AEs) were monitored throughout the study. The AEs were graded according to the Division of AIDS AE Table v2.0 [27]. Participants had follow-up visits through 24 months to assess drug use and reinfection.

Sample Size Justification

The primary outcome was the SVR rate by WOT and vDOT. Assuming an SVR rate of 99% for the vDOT group based on prior studies [28, 29], a sample size of 30 participants per group achieved 80% power to detect a difference from a WOT SVR rate of 79% with a significance level of 0.05 using a 2-sided Z test with pooled variance.

Statistical Analyses

Baseline demographics and drug use during treatment were summarized using descriptive statistics. Adherence within each study arm was calculated using 3 separate strategies based on the number of pillbox openings or video-recorded ingestions divided by (1) the number of tablets dispensed (total adherence), (2) the first 84 days of treatment (84-day adherence), and (3) the number of days between visits (between-visit adherence). The SVR rates were examined in both the intent-to-treat ([ITT] all enrolled participants that received at least one dose) and as-treated populations (all enrolled participants that received at least 1 dose of ledipasvir/sofosbuvir and had SVR results available). Factors associated with between-visit adherence <100% (ie, missing 1 or more doses between visits) were examined among participants who enrolled and completed treatment using generalized linear models to account for repeated measures. Heavy alcohol use was defined as 8 or more

drinks per week for women and 15 or more drinks per week for men [28]. Opioid use was defined as (1) self-reported street (ie, heroin) or prescription opioid use in doses or ways other than prescribed or (2) a positive urine result for morphine, oxycodone, or methadone. Predictors of interest were screened on a univariable basis, and predictors with $P \leq .20$ were then included in a backward selection model where variables with $P < .10$ were retained.

RESULTS

Study Population

A total of 73 participants were screened, 61 were enrolled, and 60 were randomized and received at least 1 dose of ledipasvir/sofosbuvir. The single participant who enrolled but did not receive any study drug was diagnosed with pneumonia on the day-1 visit before drug administration and was referred for medical care then subsequently lost to follow up (LTFU). Forty-seven participants had HIV coinfection and were receiving antiretroviral therapy. Baseline demographics are summarized in Table 1, and participant flow in the context of the study design is shown in Figure 1.

Drug Use During Treatment

Drug use during treatment is summarized in Figure 2a and b. Ninety-four percent of the 343 person-visits during weeks 2–12 of treatment were positive for current drug use by either self-report or urine toxicology screen. Polysubstance use was common, as shown in Figure 2c and d. Marijuana use was most commonly reported during treatment (60% of person-visits), followed by methamphetamine (37%), opioids (22%), and cocaine (17%). Injection drug use was reported in 20% of person-visits during treatment, the majority of which reported injecting methamphetamine (72%). Injection of heroin or cocaine was reported at 24% and 4% of person-visits, respectively. Alcohol use was reported at 56% of person-visits, with 19% consisting of heavy alcohol use over the previous 2 weeks. The mean (standard deviation) number of self-reported daily drinks was 1 (3) and ranged from 0 to 17 drinks per day.

Hepatitis C Virus Cure Rates

By ITT, 52 of 60 participants achieved SVR (86.7%; 95% CI, 75.4%–94.1%). There was no significant difference in ITT SVR rates between WOT and vDOT (26 of 31, 83.9% [95% CI, 66.6%–94.6%] versus 26 of 29, 89.7% [95% CI, 72.6%–97.9%], respectively; $P = .71$) (Figure 1). Of the 8 who did not achieve SVR, 3 were confirmed failures (1 relapse, 1 reinfection [likely], and 1 unknown [suspected reinfection]), 2 participants were removed early due to noncompliance with study requirements, and 3 were LTFU. Two participants that were LTFU had HCV ribonucleic acid (RNA) results of 0 copies/mL at weeks 4, 8, and 12. The third had a result of 15 copies/mL at week 4 followed by 0 copies/mL at weeks 8 and 12. The single relapse case was confirmed by the presence of the same NS5a mutations at baseline and the SVR visit. His total adherence was 101%, he was cirrhotic (transient elastography [TE] score 71 kPa), and he had ongoing heavy alcohol consumption. The likely reinfection case had a history of IDU, was noncirrhotic (TE score 5.0 kPa), was previously treated with 5 weeks of sofosbuvir/daclatasvir but had no NS5a mutations identified at baseline or the SVR visit, and was genotype 1a at both assessments. His total adherence was 89%. The third virologic failure was a suspected reinfection. This participant was genotype 1b at entry, noncirrhotic (TE score 7.0 kPa), had undetectable HCV RNA throughout treatment, but denied IDU. His total adherence was 92%. No additional sample was available for genotyping and the patient was LTFU after the SVR visit. In the as-treated population (ie,

Table 1. Baseline Demographics

Characteristic	WOT (N = 31)	vDOT (N = 29)	Total (N = 60)
Sex at birth, N (%)			
Male	24 (77%)	23 (79%)	47 (78%)
Female	7 (23%)	6 (21%)	13 (22%)
Male-to-female transgender, N (%)	1 (3%)	1 (3%)	2 (3%)
Race, N (%)			
White	21 (68%)	22 (76%)	43 (72%)
Black	7 (23%)	6 (21%)	13 (22%)
Native American/Alaska Native	3 (10%)	0 (0%)	3 (5%)
Unknown/Not Reported	0 (0%)	1 (3%)	1 (2%)
Hispanic or Latino, N (%)	7 (23%)	7 (24%)	14 (23%)
Age (years), median (IQR)	50 (46–55)	51 (46–56)	51 (46–55)
Weight (kg), median (IQR)	71 (64–84)	71 (63–80)	71 (63–84)
BMI (kg/m^2), median (IQR)	24 (22–28)	24 (22–26)	24 (22–27)
eGFR (mL/min per 1.73 m^2), median (IQR)	90 (74–104)	91 (72–104)	91 (73–104)
HCV Genotype, N (%)			
1	3 (10%)	2 (7%)	5 (8%)
1a	18 (58%)	21 (72%)	39 (65%)
1b	8 (26%)	5 (17%)	13 (22%)
4/4a	2 (6%)	1 (4%)	3 (5%)
Treatment-naive[a], N (%)	30 (97%)	29 (100%)	59 (98%)
TE score, median (range)	8 (4–57)	8 (4–71)	8 (4–71)
Cirrhosis present, N (%)	8 (26%)	7 (24%)	15 (25%)
IDU, N (%)	9 (29%)	9 (31%)	18 (30%)
HIV coinfection, N (%)	24 (77%)	23 (79%)	47 (78%)
Antiretroviral medications[b], N (%)			
NRTI	23 (96%)	23 (100%)	46 (98%)
INSTI	17 (71%)	17 (74%)	34 (72%)
Boosted PI	10 (42%)	7 (30%)	17 (36%)
NNRTI	1 (4%)	2 (9%)	3 (6%)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; INSTI, integrase inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; PI, protease inhibitor; TE, transient elastography; vDOT, video-based directly observed therapy; WOT, wirelessly observed therapy.

[a]One person in the WOT group was previously treated with 5 weeks of sofosbuvir-daclatasvir.

[b]Numbers and percentages reflect those with HIV coinfection only; participants may fall into multiple antiretroviral (ARV) categories; of the 47 participants on ARV medications, 41 subjects were on 2 different ARV classes, 5 participants were on 3 ARV classes, and 1 participant was on 4 different ARV classes (NRTI, INSTI, boosted PI, and maraviroc).

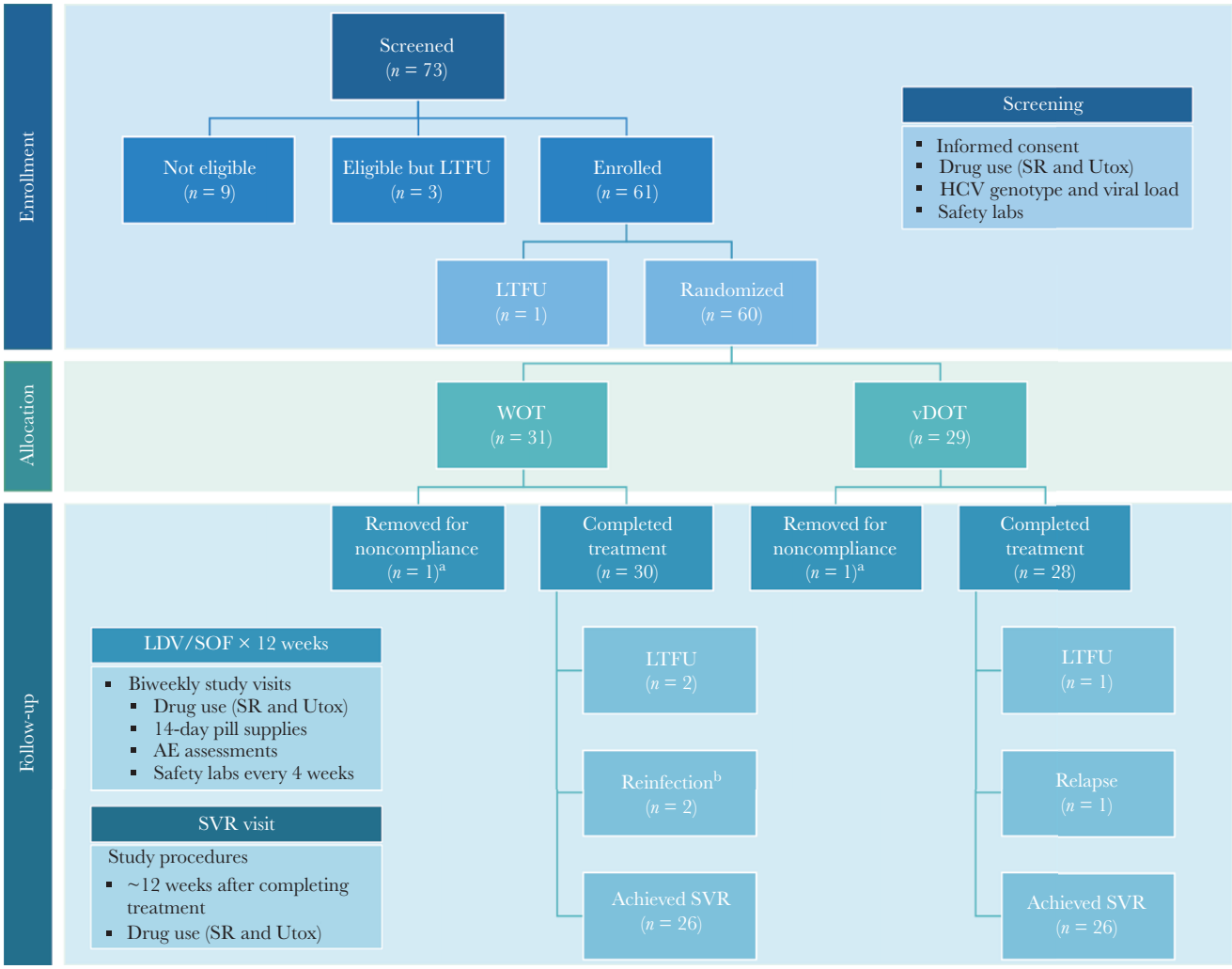

Figure 1. Study design and participant flow. [a]Noncompliance with predefined study requirements including respectful interactions with study personnel and clinic staff and following instructions. [b]One reinfection was considered likely, the other was suspected. HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; LTFU, lost to follow-up; SR, self-report; SVR, sustained virologic response; Utox, urine toxicology screen; vDOT, video-based directly observed therapy; WOT, wirelessly observed therapy.

those with SVR results available 12 weeks after treatment completion), 52 of 55 (94.5%; 95% CI, 84.8%–98.9%) were cured.

Adherence

Median total adherence was 96% (IQR, 83%–99%; range, 1%–101%) overall by ITT. The WOT and vDOT groups did not significantly differ by total (P = .08) or 84-day adherence (P = .09). Of the 58 who completed treatment (Figure 1 and Table 2), 10% completed all 84 doses within 84 days in the WOT group, compared with 21% in the vDOT group (P = .28). The majority of between-visit adherence rates were ≥75% for both groups. Median total adherence among those that achieved SVR was 96% (IQR, 84%–100%; range, 30%–101%). When comparing WOT versus vDOT among those that achieved cure, median total adherence was 89% (IQR, 81%–99%; range, 49%–100%) and 98% (IQR, 93%–100%; range, 30%–101%), respectively (P = .10). Median total adherence was 90% (IQR, 46%–94%; range, 1%–101%) in the failures by ITT and 92% (IQR, 90%–96%; range, 89%–101%) in the 3 confirmed failures.

Risk Factors for Poor Adherence

In univariable models, methamphetamine, cocaine, IDU, black race, and HIV infection were associated with higher odds of missing 1 or more doses between study visits (Figure 3), whereas marijuana use, male sex at birth, and vDOT were associated with lower odds. In the final multivariable model, factors associated with higher odds of missing doses between visits included cocaine use, methamphetamine use, black race, and HIV infection, whereas marijuana use and vDOT were associated with lower odds.

Safety Results

The AEs deemed possibly or related to study medication were mild or moderate in severity (n = 55). The most common

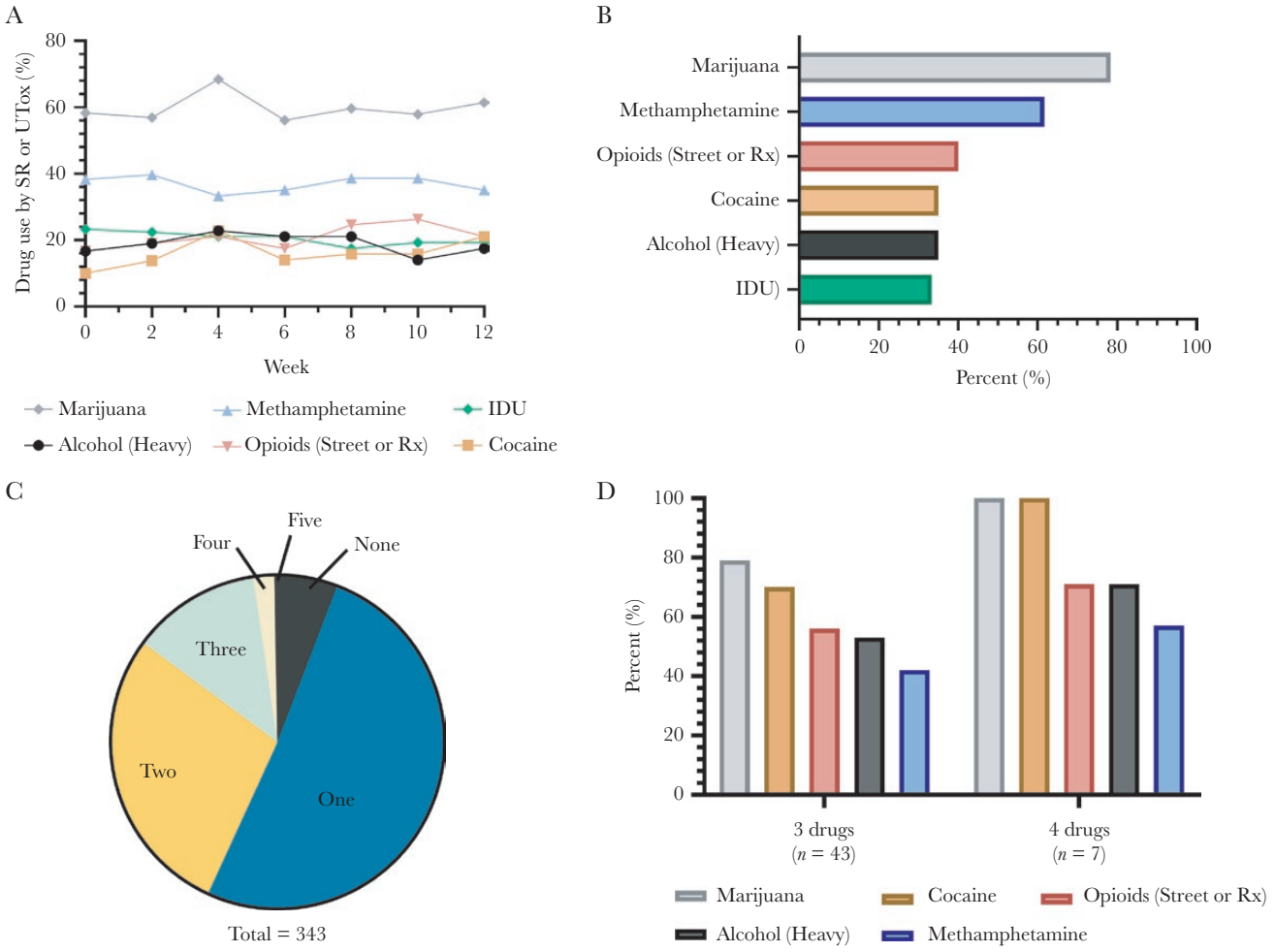

Figure 2. Drug use by urine toxicology screen or self-report throughout the 12-week treatment duration (a), percentage of participants reporting any drug use during treatment (b), number of substances (alcohol or drugs) used per person-visit (c), and breakdown of drug/alcohol use when 3 or 4 substances were used (d). IDU, injection drug use; Utox, urine toxicology screen; SR, self-report.

(≥10%) AEs included fatigue (12.1%), diarrhea (17.2%), headache (12.1%), and other gastrointestinal issues (10.3%). One participant discontinued study medication due to nausea/vomiting at treatment week 11 but still achieved SVR. Grade ≥3 laboratory abnormalities included one grade 3 decrease in hemoglobin and 8 participants with grade 3 eGFRs based on absolute values (30–60 mL/min per 1.73 m^2), all of whom were grade 2 at study entry. Six serious AEs occurred during treatment, none of which were related to study drug. No deaths occurred during treatment, but 2 deaths occurred during posttreatment follow-up (due to decompensated cirrhosis and heroin overdose).

DISCUSSION

This study quantified adherence to ledipasvir/sofosbuvir among PWUD and alcohol using wireless and video-based adherence monitoring. Despite the heavy use of drugs and alcohol in our population, median total adherence was 96% (IQR, 83%–99%). Factors associated with higher odds of missed doses between study visits included use of methamphetamine, cocaine, concomitant HIV, and black race, whereas factors associated with lower odds included use of vDOT and marijuana. The SVR rates were 84.6% by ITT and 94.5% in the as-treated population. These findings, taken together, illustrate ledipasvir/sofosbuvir forgiveness in a real-world cohort based on technology-based adherence data and offer support for the implementation of DAA therapy in a population often excluded from HCV treatment.

Our study used a vDOT smart phone application (miDOT) and wireless pillboxes (Wisepill) to monitor adherence, and median adherence rates of 98% and 90%, respectively, were measured with these platforms. The vDOT was associated with lower odds of missing doses between visits in comparison to WOT, although SVR rates did not differ between groups. Adherence monitoring approaches in other studies in PWUD have predominantly focused on participant self-report [12, 21] or other

Table 2. Total, 84-Day, and Between-Visit Adherence by WOT, vDOT, and Overall Among Participants Who Completed Treatment[a]

Adherence Measure	WOT	vDOT	Overall
Participants per group	30	28	58
Total Adherence			
Median (IQR)	90 (81–99)	98 (94–100)	96 (85–100)
Range	49–100	30–101	30–101
Adherence During First 84 Days			
Median (IQR)	89 (81–99)	96 (91–99)	95 (82–99)
Range	49–100	30–100	30–100
Observations per Group	180	163	343
Adherence Between Visits			
Median (IQR)	93 (79–100)	100 (91–100)	100 (86–100)
Range	7–100	0–107	0–107
Between Visit Adherence by Person-Visit, n (%)			
0 to ≤25%	3 (2%)	3 (2%)	6 (2%)
>25 to ≤50%	12 (7%)	4 (2%)	16 (5%)
>50 to ≤75%	26 (14%)	11 (7%)	37 (11%)
>75 to ≤108%	139 (77%)	145 (89%)	284 (83%)

Abbreviations: IQR, interquartile range; vDOT, video-based directly observed therapy; WOT, wirelessly observed therapy.

[a]Two participants were removed from the study for noncompliance with study procedures (1 in the WOT group equating to 1% total and 84-day day adherence, and 1 in the vDOT group equating to 2% total and 84-day adherence).

subjective monitoring techniques such as medication diaries [13], pill counts [10, 12, 14], and refill histories [14]. However, self-reported DAA adherence has been discrepant with electronic adherence monitoring, with average self-reported estimates of 98% and higher in comparison to electronic methods (73%–97%) [7, 18, 22]. Electronic blister packs [7, 15, 18] and MEMS caps [22] showed similar adherence rates to the Wisepill device used in our study. Mean adherence rates for these previous studies ranged from 73% to 97% [7, 15, 18, 22]. However, electronic approaches do not witness actual medication ingestion, and "pocket dosing" from a separate supply can also occur. Ingestible sensor systems in persons with HCV demonstrated mean adherence rates of 93%–97% [29, 30], but large-scale overencapsulation of medication tablets may be challenging to implement. Modified DOT strategies comprising in-person DOT during OAT clinic visits and either self-administered tablets [31] or electronic monitoring [15, 32] outside of clinic have been detailed, with mean adherence rates of 86%–95%. In-person DOT may be burdensome to coordinate outside of OAT clinic settings. The vDOT could bridge this gap where more objective adherence monitoring approaches are desired in persons where adherence is of concern. In line with this, artificial intelligence-based mobile adherence monitoring platforms have also been piloted [33], including a study in 17 PWID that showed mean DAA adherence rates of 91% [34]. Collectively, several adherence monitoring tools have been used with success in PWUD, and our findings provide support for vDOT and WOT as additional tools that can be used in this population.

Almost all person-visits during ledipasvir/sofosbuvir treatment were positive for drug or alcohol use by self-report and urine toxicology screen. A unique aspect of our study was the inclusion of persons actively using drugs by injection and noninjection routes. Although IDU is a known risk factor for HCV transmission, noninjection drug and alcohol use are also very common, and these may present challenges to ensuring medication adherence, treatment completion [21, 22], and potentially contribute to reinfection depending on drug administration route and other behaviors [35]. Stimulant injection has been identified as a risk factor for poor DAA adherence [7, 9]. However, the majority of methamphetamine

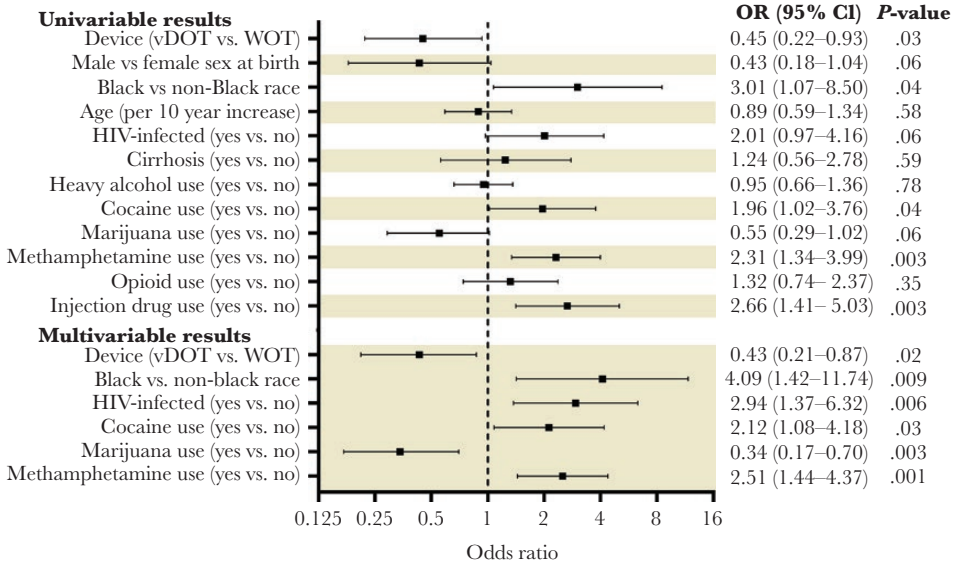

Figure 3. Demographic and drug use factors associated with odds of missing 1 or more doses (ie, <100% adherence) between study visits. CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; vDOT, video-based directly observed therapy; WOT, wirelessly observed therapy.

and cocaine users in our study did not inject these substances, demonstrating that use by other routes is still a barrier to adherence. Hazardous alcohol use was previously identified as a risk factor for poor DAA adherence [21, 22], but it was not identified in our study. However, alcohol use was based on self-report in our study, and more objective measures of alcohol intake (eg, phosphatidylethanol) may reveal different findings. The finding of lower odds of missing doses among marijuana users was surprising and in contrast to prior studies [22], but this finding is likely due to decreased use of other illicit substances at person-visits where marijuana use was detected, notably, methamphetamine, rather than a beneficial effect conferred by marijuana itself. More in-depth assessments of adherence patterns in this population, such as gaps in dosing, time on treatment, and whether certain drugs or alcohol use are associated with certain adherence patterns, warrant further investigation.

Demographic factors associated with higher odds of missing doses between visits included black race and HIV coinfection. Black race has previously been identified as a risk factor for nonadherence [29, 36, 37] and lower SVR rates in some DAA studies [29, 38–40], although available evidence suggests adherence is now markedly higher with DAAs than older HCV treatment regimens [41]. Human immunodeficiency virus coinfection has generally been associated with similar adherence and SVR rates in comparison to HCV-monoinfected populations to date [42, 43]. The majority of black participants in our study also had HIV coinfection, and used cocaine and marijuana more often than non-blacks and methamphetamine and IDU less often. Further investigation of socioeconomic barriers, comorbidities, ART adherence, and pill burden may reveal insight into underlying sources of imperfect adherence in these populations.

SVR was achieved over a range of adherence values from 30% to 101% in our study population, suggesting substantial forgiveness of ledipasvir/sofosbuvir therapy. Cure rates in our study were comparable to previous studies in PWID and those receiving OAT (82%–100%) [7–10, 13–18], providing further support for treatment expansion to PWUD and alcohol. Three confirmed failures occurred, 2 of which were possible or likely reinfections. Three participants were LTFU, with several attempts made for outreach. The challenges of losing patients to follow-up has previously been identified as a barrier to determining DAA treatment success [44]. Given the high SVR rates in our study, limited sample size, and treatment failure for reasons outside of adherence, further analyses to explore the impact of demographic factors, drug use, and adherence on achieving SVR were not pursued.

There are limitations to this study. Although adherence was high with WOT, pillbox opening does not necessarily equate to medication ingestion, and thus it is not as objective as vDOT. Participants may have taken pills separately from opening the Wisepill device, or they may have opened the device without taking any pills. However, this overestimation of adherence would support even greater ledipasvir/sofosbuvir forgiveness. Alternative definitions of nonadherence may have also yielded different conclusions. Multiple adherence thresholds between 80% and 95% and risk factors for nonadherence have been examined in HCV treatment studies with DAAs [7–9, 13]. A consistent definition of nonadherence with DAAs has not been established to date. Further investigations into adherence patterns and DAA forgiveness specific to individual first-line regimens for HCV treatment are warranted. The adherence and efficacy rates in our study may have been influenced by the frequent study interactions and compensation schedules. Payment was based on successful video submissions or exchange of pill boxes at study visits. Whether these adherence and efficacy rates hold in a setting where visits and adherence monitoring may occur less frequently, if at all, or whether vDOT is an approach that would be preferred to ensure treatment success in PWUD on a larger scale should be assessed further. A recent study evaluated whether cash incentives or peer-mentors would impact DAA treatment uptake in HIV/HCV-coinfected patients and found no differences in adherence between these groups [12]. Larger pooled analyses of DAA studies have not identified marked differences between clinical trials and real-world settings [45], and high cure rates in PWID have been detailed in settings outside of clinical trials [18, 46], which is also encouraging towards the applicability of our findings to real-world settings.

CONCLUSIONS

In conclusion, persons with HCV or HIV/HCV and active drug or alcohol use demonstrated variable but high adherence to ledipasvir/sofosbuvir. The SVR rates were high by ITT and as-treated analyses. Although overall adherence and SVR rates were high, risk factors for missed doses between study visits were identified, notably, the use of methamphetamine, cocaine, black race, and having HIV. These factors may be important to probe further in larger studies to ensure the successful treatment of HCV in persons actively using drugs. Our findings support expanding DAA treatment to PWUD to eradicate HCV and the use of technology-based measures to facilitate treatment uptake in this population.

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