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Adherence and 007-TP DBS Levels in Active Drug Users with HCV: The INCLUD Trial

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National Institute on Drug Abuse

Background

- Injection and non-injection drug use is prevalent among individuals with HCV,[1] but access to HCV treatment lags behind in this population.[2,3]
- Recent studies have reported high but variable adherence to different DAA regimens in people who inject drugs[4-7] and former users on opioid substitution therapy.[8,9] However, objective adherence data and assessments of risk factors for poor adherence in active drug users are limited.
- The triphosphate anabolite of sofosbuvir (SOF), GS-3310007 (007-TP, also known as GS-461203) has a half-life of ~120 hours in red blood cells (RBC),[10,11] and may serve as a pharmacologic adherence measure. Additional data are needed on factors that influence 007-TP levels in RBC, as measured in dried blood spots (DBS).
- Here, we report key findings that address some of these knowledge gaps from the Antiviral Pharmacology and Adherence in Drugs Users Study (INCLUD) (NCT02573376), which is an open-label study to characterize adherence to and the pharmacology of ledipasvir/sofosbuvir (LDV/SOF, Harvoni®, Gilead Sciences, Inc.) in persons with HCV and active drug use.

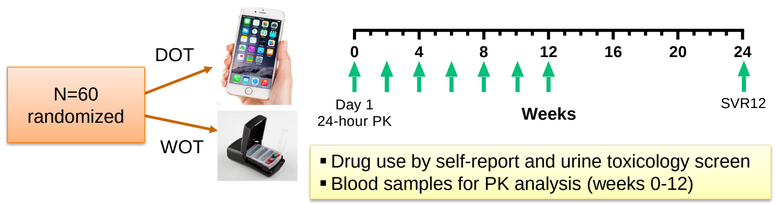
Objectives

- To describe treatment outcomes, objective adherence data, and predictors of adherence and 007-TP levels in DBS among active drug and/or alcohol users receiving LDV/SOF for HCV treatment

Methods

- Persons with HIV/HCV or HCV mono-infection and self-reported drug use within 30 days of screening were eligible for the study.
- Participants were randomized to video-based directly observed therapy (DOT, emocha Mobile Health, Inc.; Baltimore, MD) or wireless pillboxes (WOT, Wisepill Technologies®; Capetown, South Africa), and had study visits every two weeks (**see Figure 1**).

Figure 1. Study Design



- Drug use by self-report and urine toxicology screen
- Blood samples for PK analysis (weeks 0-12)

- 007-TP concentrations in DBS were quantified from a 7mm punch size using LC/MS-MS methods.
- Conditional logistic regression models examined risk factors for ≥1 missed dose between visits (i.e., adh2wk ≥100% vs. <100%) and mixed models identified predictors of ln-transformed 007-TP in DBS. Select covariates were screened (p≤0.2), followed by backward selection (p≤0.1).

Results

Table 1. Baseline Demographics

Characteristic	WOT (N=31)	DOT (N=29)	Total (N=60)
Sex, N(%)			
Male	24 (77%)	23 (79%)	47 (78%)
Female	7 (23%)	6 (21%)	13 (22%)
Race, N(%)			
White	21 (68%)	23 (79%)	43 (72%)
Black	7 (23%)	6 (21%)	13 (22%)
Native American / Alaska Native	3 (10%)	0 (0%)	3 (5%)
Hispanic or Latino, N(%)	7 (23%)	7 (24%)	14 (23%)
Age (yrs), 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/1.73m^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 (3%)	3 (5%)
Transient Elastography Score, median (range)	8 (4, 57)	8 (4, 71)	8 (4, 71)
Cirrhosis Present, N(%)	8 (26%)	7 (24%)	15 (25%)
HIV-infected, N(%)	24 (77%)	23 (79%)	47 (78%)
IVDU, N(%)	9 (29%)	9 (31%)	18 (30%)

Figure 2. Alcohol & Drug Use During Treatment

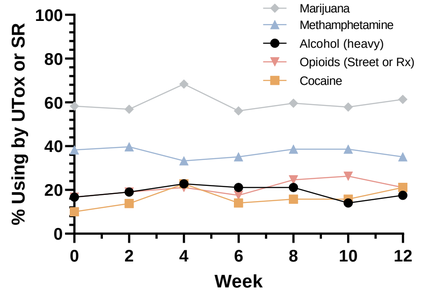


Table 2. 007-TP in DBS by Adherence

Adherence	0-49%	50-79%	80-108%
# Person-visits	13	30	181
Geomean (fmol/punch)	218	495	665
%lnCV	20.1%	9.7%	6.3%

Table 3. SVR12 Results (ITT and As-Treated)

	WOT	DOT	Total
Intention to Treat (ITT)[a]			
N per group	31	29	60
Achieved SVR12, n(%)	26 (84%)	26 (90%)	52 (87%)
As-treated[b]			
N per group	28	27	55
Achieved SVR12, n(%)	26 (93%)	26 (96%)	52 (95%)

[a]ITT includes all persons that enrolled and received ≥1 LDV/SOF dose
[b]As-treated includes all persons that enrolled, received ≥1 LDV/SOF dose, and have SVR12 results available (excludes 2 removals for noncompliance, 3 LTFU)

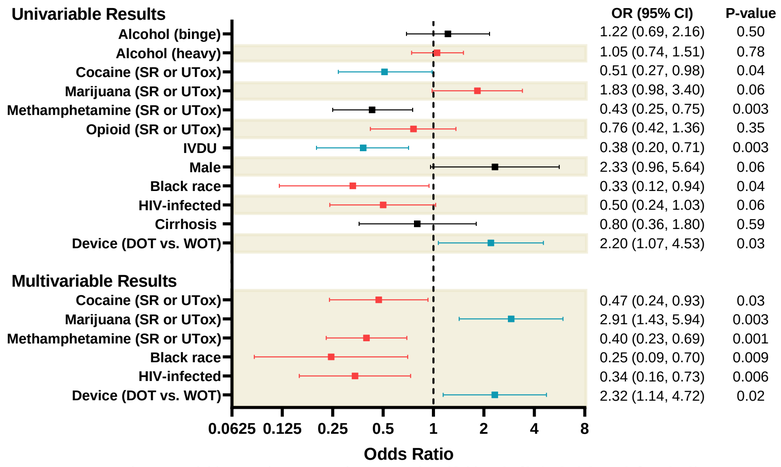
Three confirmed failures:
1 relapse (confirmed) ● 2 reinfections (1 likely, 1 suspected)

Table 4. Between Visit[a] and Total[b] Adherence

Group	WOT (n=31)	DOT (n=29)	Total (n=60)
Between Visit Adherence[a]	93 (79, 100) 7 - 100	100 (91, 100) 0 - 107	100 (86, 100) 0 – 107
Total Adherence[b]	89 (80, 99) 1-100	98 (92, 100) 2 – 101	96 (83, 99) 1 – 101
As-Treated	**Not Cured (n=3)**		**Cured (n=52)**
Total Adherence[b]	90 (90, 91) 89-92		97 (84, 100) 30 - 101

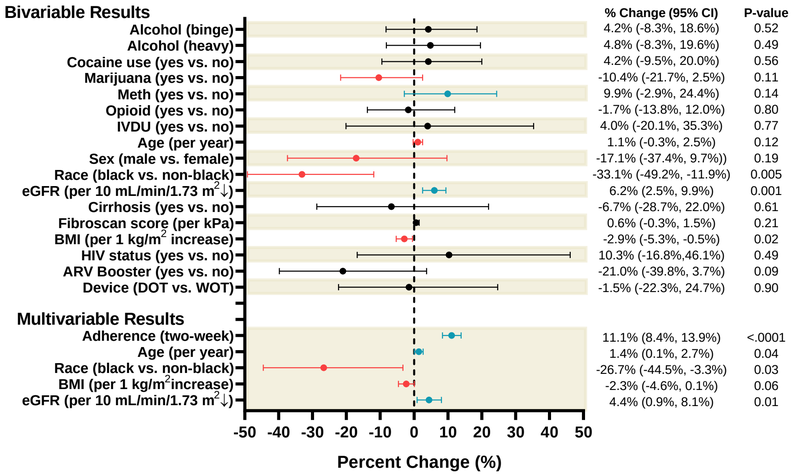
Calculated as # doses taken divided by [a]# days between visits (n=343 observations) or [b]# doses taken; data presented as median (IQR), range

Figure 3. Factors associated with odds of ≥100% two-week adherence (Weeks 2-12)



Note: age as a continuous variable was also screened as a covariate (Odds 1.01 [95% CI 0.97, 1.05]; p=0.58).

Figure 4. Factors associated with 007-TP levels in DBS (Weeks 4-10)



Acknowledgements & References

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Conclusions

- Active drug users with HCV had good but variable LDV/SOF adherence using technology-based methods.
- Cocaine use, methamphetamine use, black race, and HIV infection were associated with lower odds of 100% adherence, whereas marijuana use and video-based DOT were associated with higher odds.
- 007-TP in DBS increased with adherence, older age, and lower eGFR. 007-TP DBS levels were lower in blacks and decreased as BMI increased.
- SVR12 rates were high despite variable adherence, demonstrating substantial PK forgiveness.
- These findings support efforts to expand HCV treatment to active drug users.

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