High Rates of Sustained Virological Response in People Who Inject Drugs Treated With Sofosbuvir-Based Regimens

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Background

- The majority of existing and new cases of HCV occur among people who inject drugs.
- Many people who inject drugs (including those maintained on opiate agonist treatment) are denied potentially life-saving HCV treatment because of ongoing drug use.
- Treatment of patients with sofosbuvir (SOF) – based regimens is associated with high rates of SVR in genotypes 1 – 4 patients in registration trials.
- However, these trials excluded people who are actively injecting drugs.

Background

- Prior treatments in on-site HCV treatment setting were associated with high rates of SVR in genotype 1 patients (Litwin et al, 2009; Litwin et al, 2012; Litwin et al, 2015)
  - Pegylated IFN and RBV: 43% (n=86)
  - Telaprevir/boceprevir with pegylated IFN and RBV: 62% (n=50)

- Little data exist describing clinical outcomes for people who inject drugs initiating sofosbuvir-based regimens in real-world settings.

Specific Aims

- To determine rates of adherence and SVR in a cohort (n=60) of people who inject drugs initiating treatment on-site at an opiate agonist treatment program with sofosbuvir-based regimens.
  - Hypothesis: SVR will be equivalent to registration trials
- To determine adherence over time in people who inject drugs initiating 24 week IFN-free regimen
  - Hypothesis: Adherence will decrease over time
- To determine if active drug use (prior to or during antiviral treatment) is associated with SVR
  - Hypothesis: Active drug use will not be associated with SVR

Methods: Overview

- Prospective single-arm trial (n=60)
  - Gilead Sciences supported this study through IIS and provided study drug
- Subjects (G1, 2, 3, and 4) initiating on-site treatment with sofosbuvir and ribavirin with or without pegylated interferon between January, 2014 and March, 2015
  - On-site HCV providers determined the regimen
  - Genotype 1 patients received sofosbuvir and ribavirin if IFN ineligible or unwilling
- Subjects and providers selected the model of on-site care:
  - Individual: subjects given 4 weekly blister packs each month and seen by provider monthly
  - Group: subjects seen once weekly in 60 minute group and dispensed weekly blister pack
  - Directly observed treatment: subjects provided AM dose on days seen in clinic and receive weekly blister pack for take-home doses
- Adherence measured by electronic monitors and self-report
  - weekly by electronic blister packs (compensated $10 for each pack up to $240 for 24 weeks)
  - monthly by self-report using visual analog scale (VAS): 0 – 100%
- Urine toxicologies obtained through chart review

Clinic Locations

Eligibility Criteria

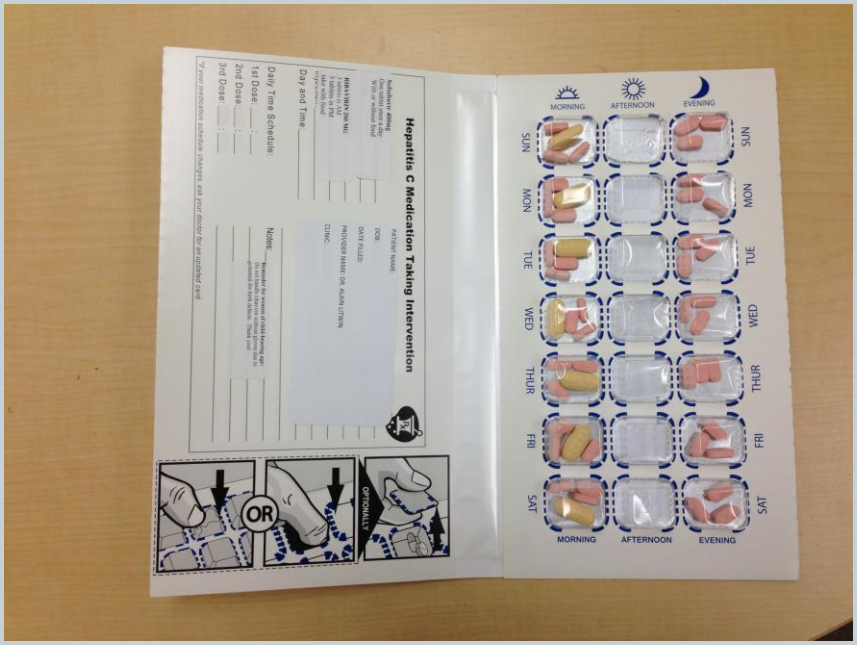
Inclusion Criteria

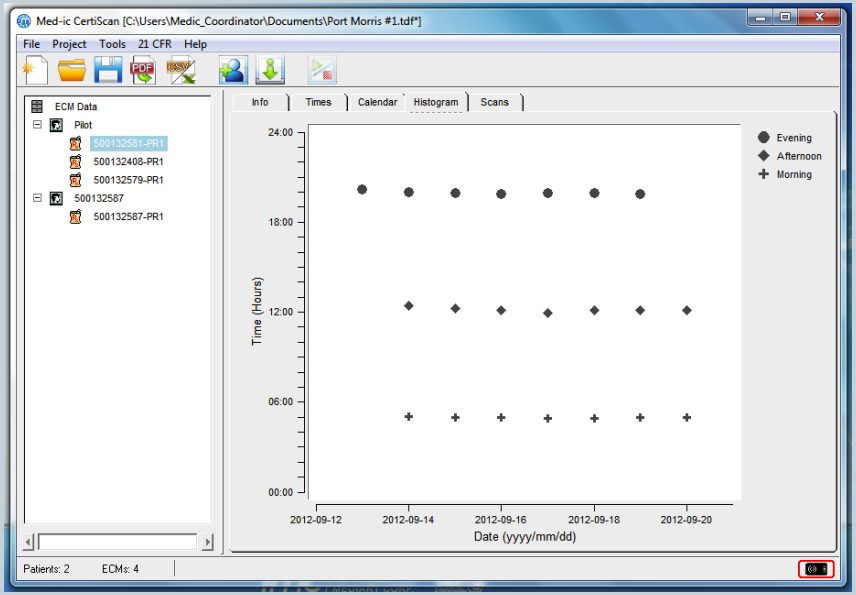
- HCV-infected (HCV viral load about the limit of quantification)
- Health care provider decision to treat patient with sofosbuvir, ribavirin +/- pegylated interferon alfa-2a as per 2014 AASLD/IDSA guidelines
- Willing to receive treatment on-site at opiate agonist treatment program
- Age 18 or older
- Able to provide informed consent
- English or Spanish-speaking

Exclusion Criteria

- Known hypersensitivity to sofosbuvir, ribavirin, or interferon
- Pregnant or breast-feeding

Electronic Blister Packs

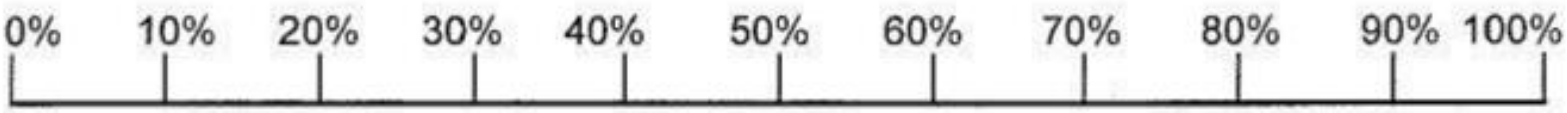




Adherence Definitions

- **Weekly time-frame adherence**: subject receives credit if medication is popped out of the weekly blister pack on any day and time within the week
  - 0 – 14 doses credited each week
  - Patient adherence is reported at 100% if 14 doses popped out at the same time
  - Adherence rates ≥ 100% adjusted to 100%
- **Daily time-frame adherence**: subjects receive credit only if medication is popped out of blister pack within the correct day
  - 0 - 2 doses credited each day
  - Adherence is reported at 100% if 2 doses popped out within 24 hour period
  - Adherence rates ≥ 100% adjusted to 100%
- **Window daily time-frame adherence**: subject receive credit if medication is taken within 3 hours of assigned time each day

Visual Analogue Scale (VAS)



Study Flow Diagram

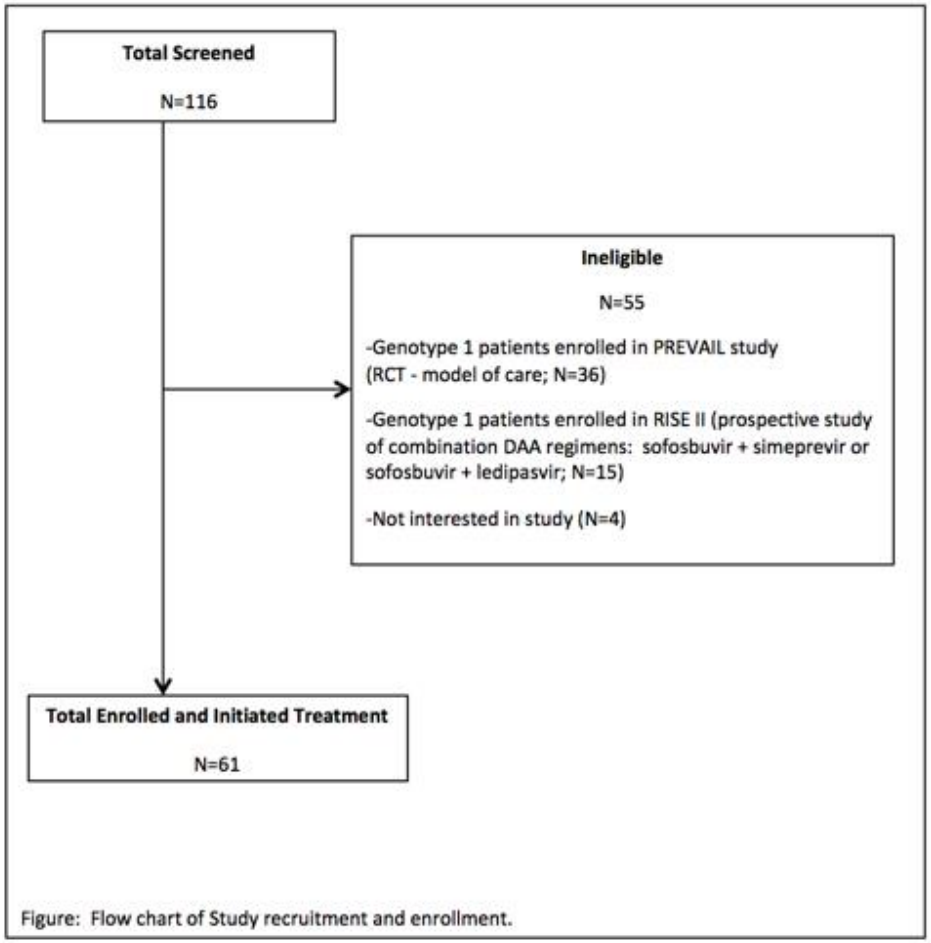


Figure: Flow chart of Study recruitment and enrollment.

Baseline Characteristics (n=61)

Characteristic	N (%) or Mean +/- SD
Age (mean +/- SD)	53.6 +/- 9.4
Race/ethnicity:	
Hispanic	34 (56)
African American	16 (26)
Caucasian	11 (18)
Gender:	
Male	38 (62)
Female	23 (38)
Insurance:	
Medicaid	58 (95)
Medicare	2 (3)
Uninsured	1 (2)

Baseline Characteristics (n=61)

Characteristic	N (%) or Mean +/- SD
BMI (mean +/- SD)	31.2 +/- 6.2
Current psychiatric comorbidities:	
Any	44 (72)
Depression	39 (64)
Anxiety	23 (38)
Bipolar disorder	11 (18)
Psychotic disorder	4 (7)
Medical comorbidities:	
Any	54 (89)
Hypertension	23 (38)
Diabetes	12 (20)
Asthma/COPD	11 (18)
HIV	10 (16)

Baseline Characteristics (n=61)

Characteristic		N (%)
Cirrhosis (biopsy or FibroSure)		14 (23)
IL28B (n=59):	CC CT or TT	13 / 59 (22) 46 / 59 (78)
Genotype:	1 2 3 4	21 (34) 17 (28) 21 (36) 1 (2)
Prior treatment:	Naive Prior relapser Partial responder Non-responder Unknown response	41 (67) 7 (11) 5 (8) 4 (7) 4 (7)

Drug Use Characteristics (n=61)

Characteristic		N (%)
Injection drug use		58 (95)
Opiate agonist treatment:	Methadone Buprenorphine None	54 (88) 4 (7) 3 (5)
Methadone weekly PUS (n=55):	1 - 3 4 – 6	24 of 54 (44) 30 of 54 (56)
Drug use (within 6 months): (n=57)	Any Opiates Cocaine Benzos	37 of 57 (65) 29 of 57 (51) 12 of 57 (21) 9 of 57 (16)
Drug use (during treatment): (n=54)	Any Opiates Cocaine Benzos	31 of 54 (57) 19 of 54 (35) 13 of 54 (24) 13 of 54 (24)

Treatment Characteristics (n=61)

Characteristic		N (%)
Regimen		
G1 (SOF/RBV/PEG)		7 (11)
G1 (SOF/RBV)		14 (23)
G2 (SOF/RBV)		17 (28)
G3 (SOF/RBV/PEG)		1 (1)
G3 (SOF/RBV)		21 (34)
G4 (SOF/RBV)		1 (1)
Treatment Duration		
12 weeks		24 (39)
24 weeks*		37 (61)
Model of Care:	Individual	32 (52)
	Group	20 (33)
	DOT	9 (15)

Virologic Outcomes (n=61)

Virologic Outcome	N (%)
Overall ETR	58 (95)
Overall SVR12	49 (80)
Genotype 1 (n=21)	18 of 21 (86)
G1 (SOF/RBV/PEG; n=7)	7 of 7 (100)
G1 (SOF/RBV; n=15)	11 of 14 (79)
Genotypes 2 and 3 (n=39)	31 of 39 (79)
G2 (SOF/RBV; n=17)	13 of 17 (76)
G3 (SOF/RBV/PEG; n=1)	1 of 1 (100)
G3 (SOF/RBV; n=21)	17 of 21 (81)
Genotype 4	0 of 1 (0)
G4 (SOF/RBV; n=1)	0 of 1 (0)

Overall SVR - Similar to Registration Trials

Genotype	Regimen	Studies	SVR	# Subjects	Expected # SVR (%)	Actual # SVR (%)
1	SOF/RBV/ PEG	NEUTRINO	90%	7	6.3 (90%)	7 (100%)
1	SOF/RBV	PHOTON-1	76%	14	10.6 (76%)	11 (79%)
2	SOF/RBV	POSITRON	93%	17	15.8 (93%)	13 (76%)
3	SOF/RBV/ PEG	BOSON	95%	1	0.95 (95%)	1 (100%)
3	SOF/RBV	VALENCE	84%	21	17.6 (84%)	17 (81%)
4	SOF/RBV	Ruane, 2014; Doss, 2015; Molina, 2015	90%	1	0.90 (90%)	0 (0%)
Total				61	52 (85%)	**49 (80%)** 95% CI (70%-90%)

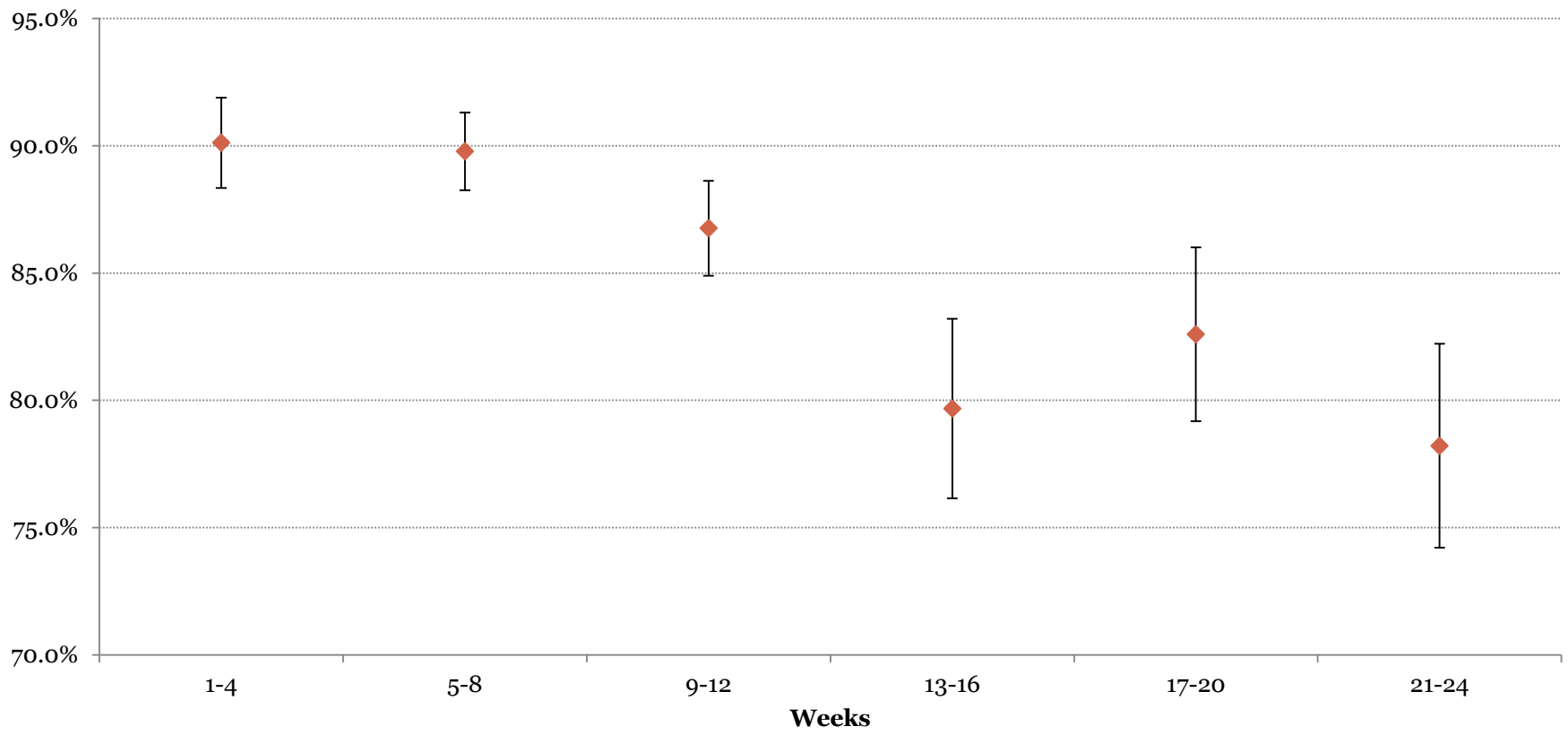
Other Outcomes (n=61)

Outcome	N (%)
Stopped treatment 1st 12 weeks	1 (2)
<80% of planned treatment duration	3 (5)
Erythropoietin	7 (11)

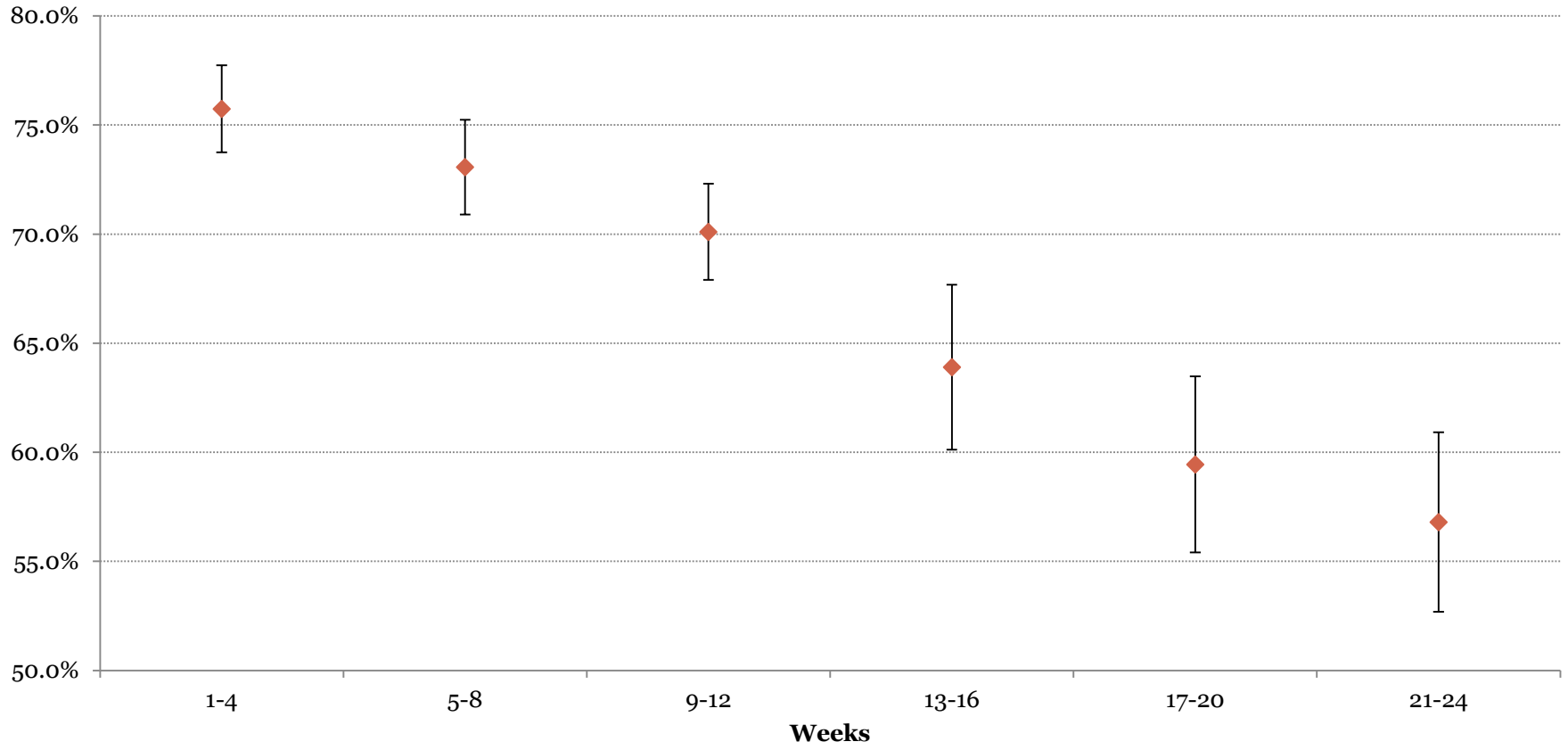
Adherence by Electronic Blister Packs

		Weekly Time-Frame Adherence		Daily Time-Frame Adherence		Window Daily Time-Frame Adherence	
Weeks	N	Mean	SD	Mean	SD	Mean	SD
1-4	61	90.1%	13.8%	75.7%	15.6%	59.6%	17.6%
5-8	61	89.8%	11.9%	73.1%	16.9%	52.6%	19.5%
9-12	61	86.8%	14.5%	70.1%	17.2%	49.8%	19.1%
13-16	37	79.7%	21.5%	63.9%	23.0%	44.4%	21.8%
17-20	36	82.6%	20.5%	59.4%	24.2%	39.7%	18.4%
21-24	35	78.2%	23.7%	56.8%	24.3%	36.7%	18.1%

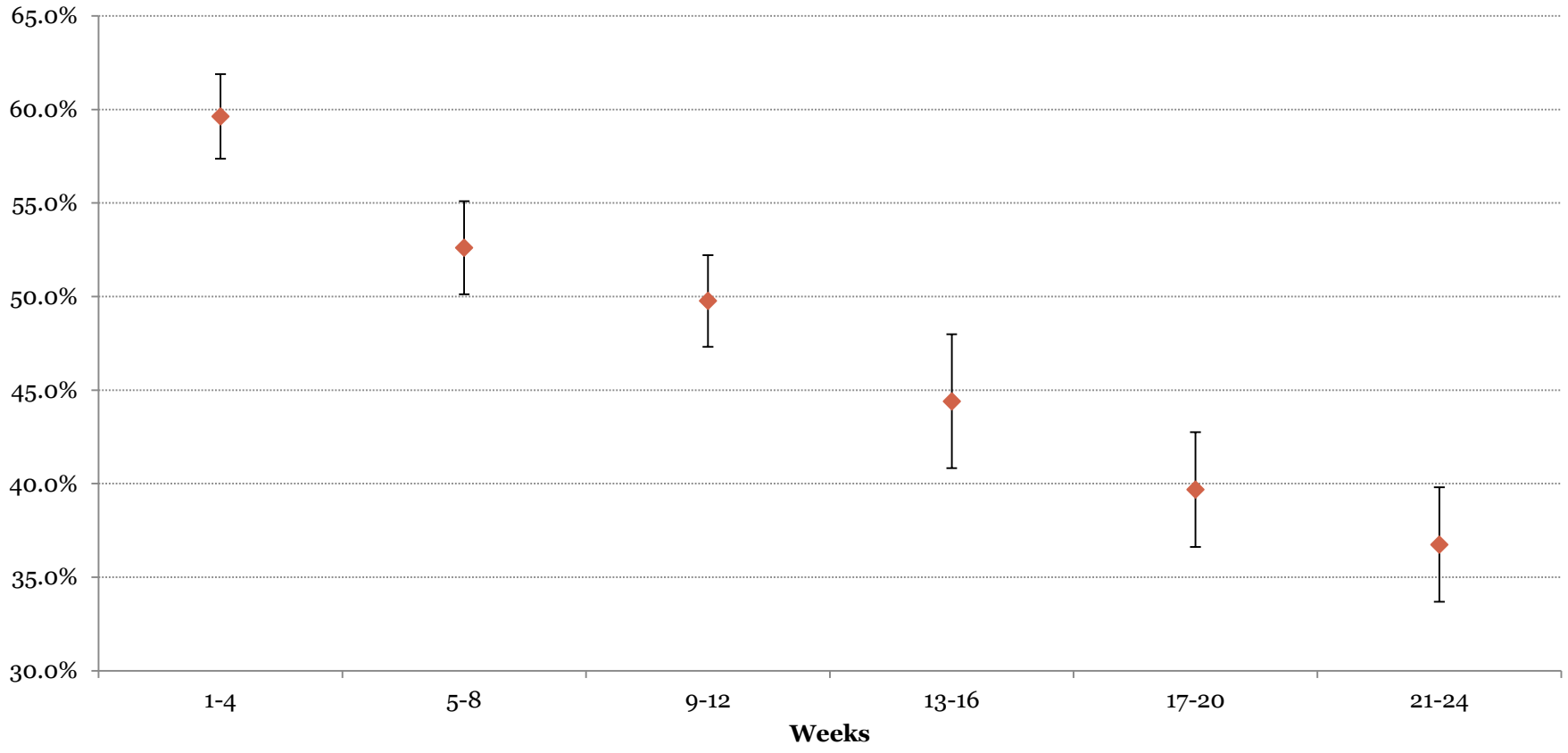
Weekly Time-Frame Adherence Decreased Over Time (90% over 1st 4 weeks; 87% over 1st 12 weeks)



Daily Time-Frame Adherence Decreased Over Time (76% over 1st 4 weeks; 70% over 1st 12 weeks)



Window Daily Time-Frame Adherence Decreased Over Time (60% over 1st 4 weeks; 51% over 1st 12 weeks)



High Adherence by Visual Analogue Scale (97% over 1st 4 weeks; 96% over 1st 12 weeks)

Visual analog scale scores over the study period

Week	N	Mean	SD
4	61	96.8	5.2
8	59	96.0	6.4
12	59	95.0	8.7
16	36	93.0	11.6
20	33	94.7	8.9
24	32	95.2	8.7

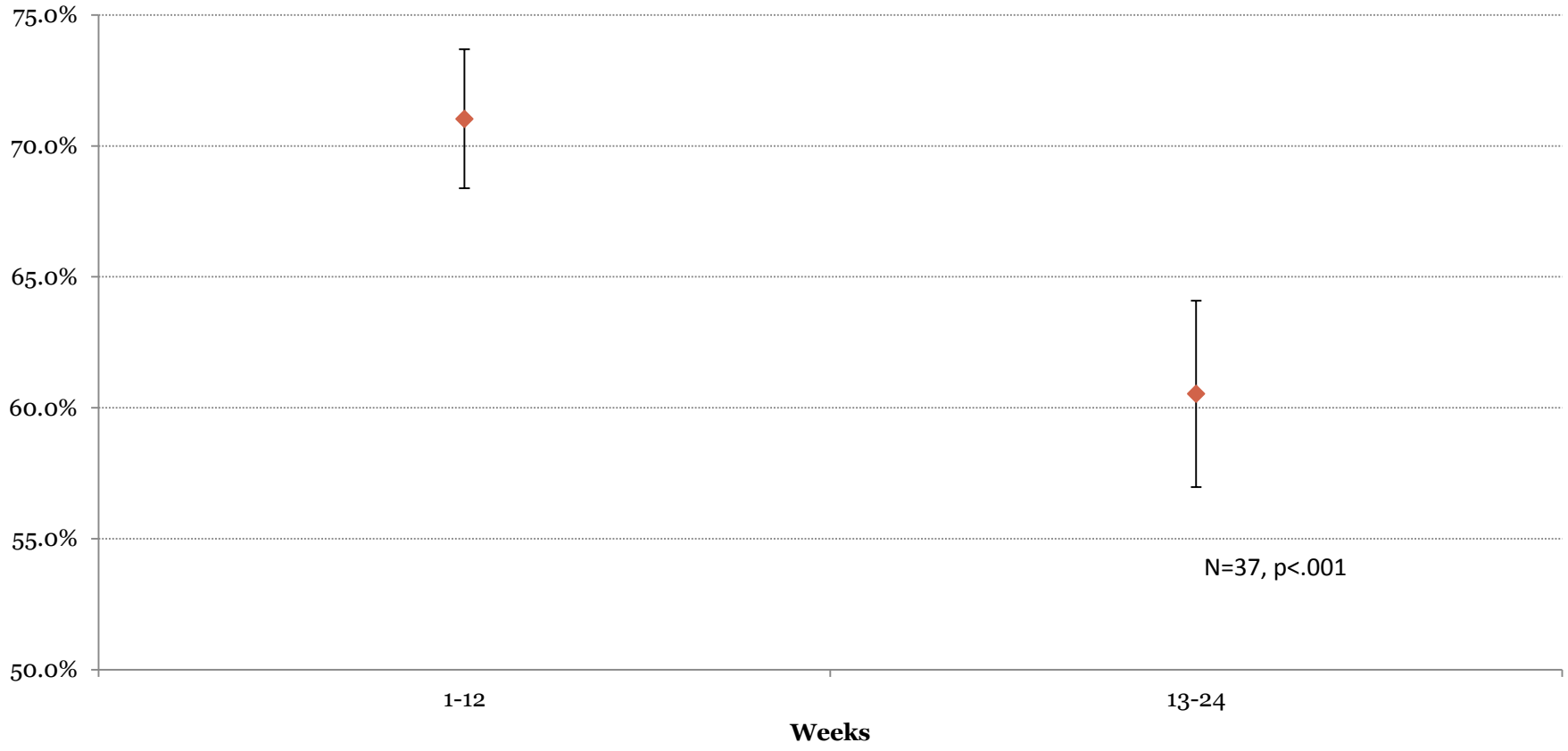
Note: No significant differences in VAS scores over time; p=0.53 (repeated-measure ANOVA).

Adherence significantly decreased between 1st 12 weeks and 2nd 12 weeks of treatment

		Weeks 1-12		Weeks 13-24		
Adherence	N	Mean	SD	Mean	SD	p
Weekly Time-Frame	37	88.4%	13.0%	80.4%	18.2%	<.001
Daily Time-Frame	37	71.0%	16.1%	60.5%	21.6%	<.001
Window Daily Time-Frame	37	51.3%	16.6%	40.1%	17.7%	<.001

Note: p-value's are based on paired t-tests.

Daily Time-Frame Adherence (n=37) Decreased from 71% (weeks 1-12) to 61% (week 13-24)



Comparison of Patient Characteristics with SVR

Characteristics	N(%)	SVR(N=61)	OR for SVR
Genotype			
1/4	22 (36)	18/22 (82)	1.54 (0.33, 7.26)
2	17 (28)	13/17 (76)	Ref
3	22 (36)	18/22 (82)	1.23 (0.26, 5.90)
IL28B*			
CC	13 (22)	9/13 (69)	Ref
TC or TT	46 (78)	38/46 (83)	2.11 (0.52, 8.59)
Cirrhosis			
No	47 (77)	37/47 (79)	Ref
Yes	14 (23)	12/14 (86)	1.62 (0.31, 8.46)
Depression			
No	24 (39)	18/24 (75)	Ref
Yes	37 (61)	31/37 (84)	1.72 (0.48, 6.14)
Prior Treatment*			
Naïve or prior relapse	48 (84)	38/48 (79)	Ref
Partial or Non-responder	9 (16)	8/9 (89)	2.11 (0.24, 18.86)
Recent Drug Use in the past 6 months*			
Yes	37 (65)	29/37 (78)	Ref
No	20 (35)	16/20 (80)	1.10 (0.29, 4.24)
Active Drug Use during Treatment*			
No	23 (43)	17/23 (74)	Ref
Yes	31 (57)	25/31 (81)	1.47 (0.41, 5.33)
Daily Time-Frame Adherence			
< 80%	45 (74)	35/45 (78)	Ref
≥ 80%	16 (26)	14/16 (88)	2.00 (0.39, 10.31)

* Missing data present

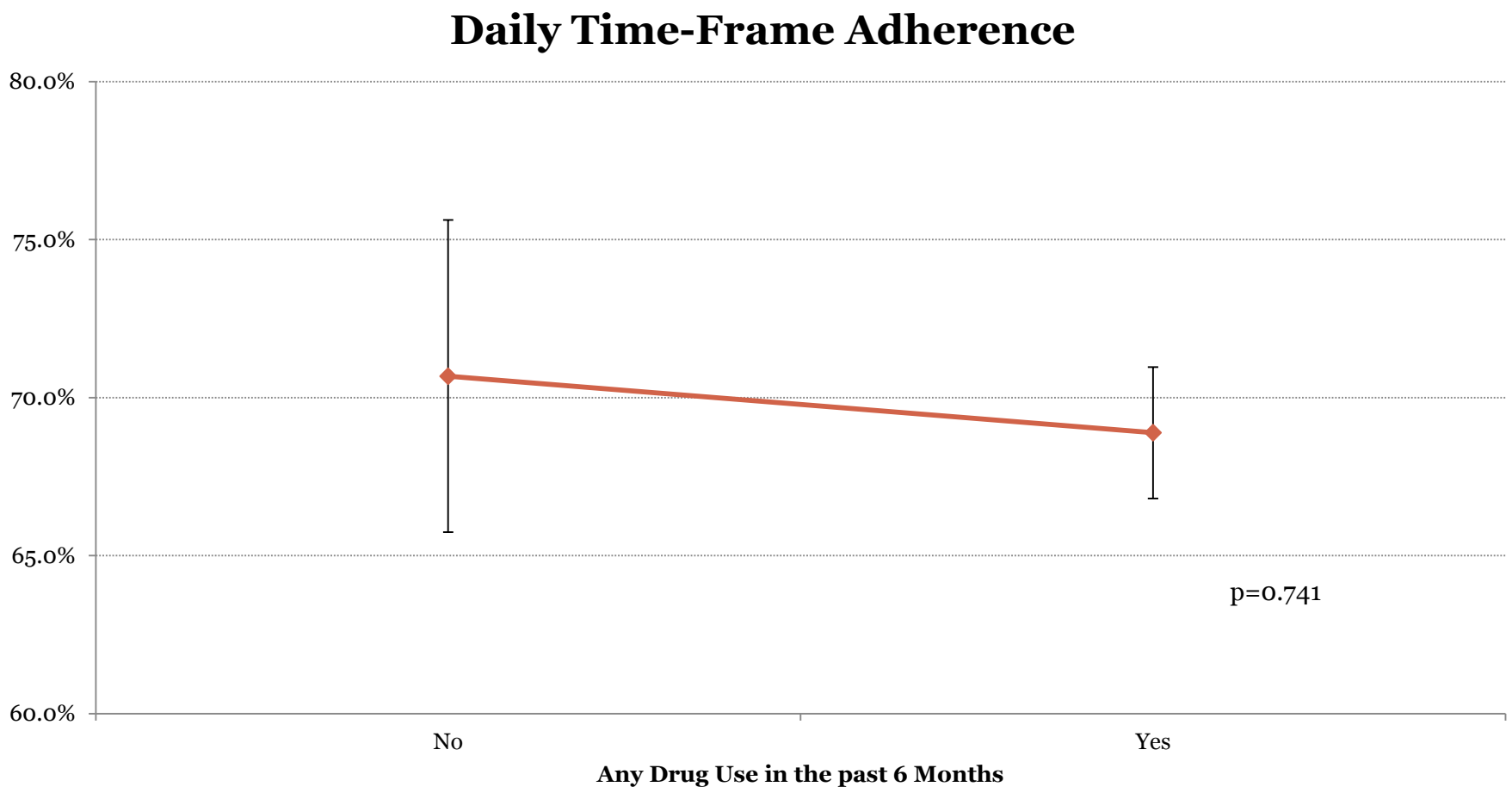
Multivariate Analysis: Drug use and adherence not associated with SVR

Effect of Drug use and daily time-frame adherence on the SVR outcome adjusting for patient clinical characteristics

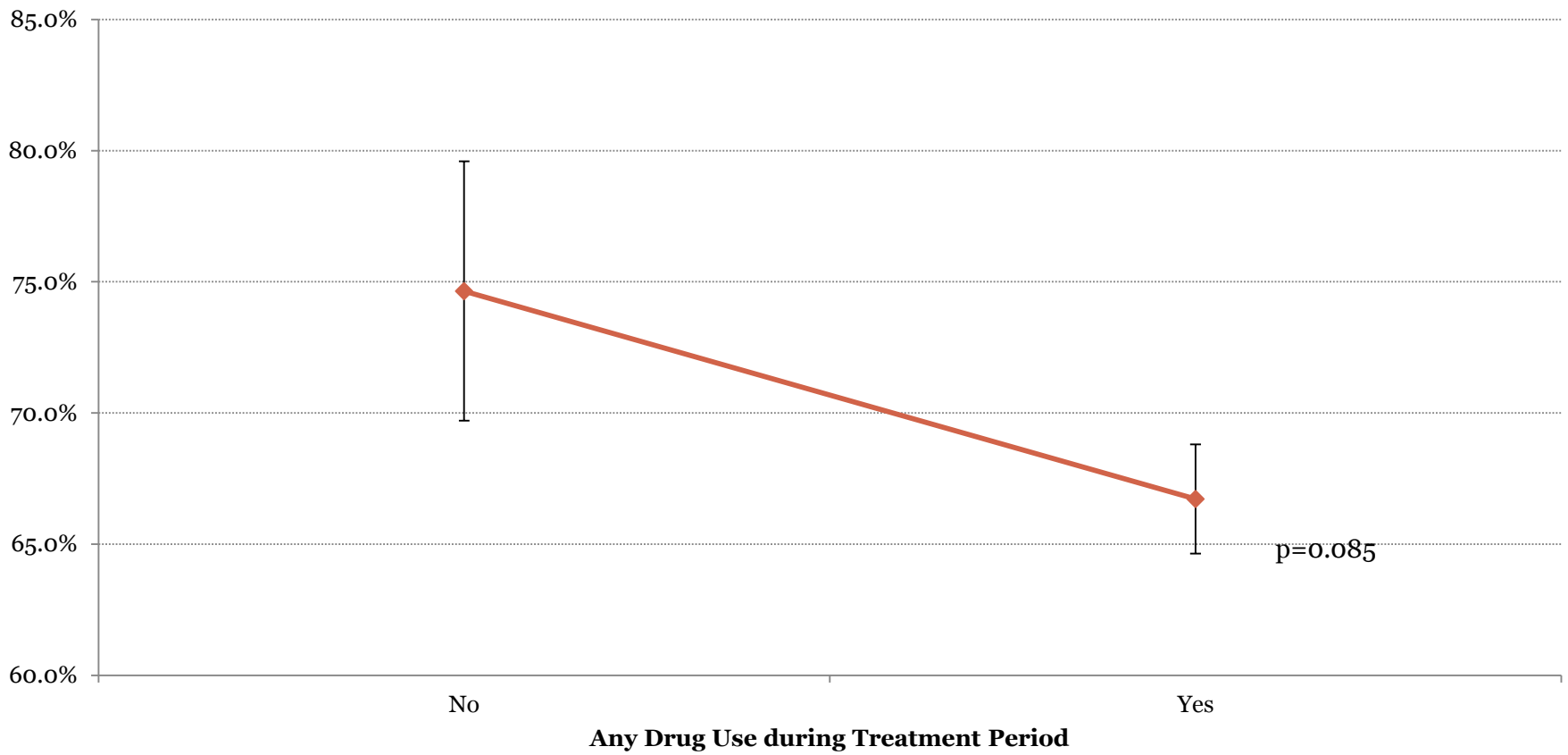
Predictor	OR	95%CI	p-value*
Any drug use (6 months)	0.83	(0.18, 3.74)	0.803
Any drug use during tx	0.79	(0.15, 4.06)	0.773
Adherence>=80%	1.82	(0.30, 10.92)	0.511

* P-values are obtained based on multivariable logistic regressions on SVR with the following adjusting variables: Genotype, IL28B, Cirrhosis, Depression, and Response to prior treatment

Adherence same regardless of drug use prior to treatment



Adherence decreased with drug use during treatment, but not significant



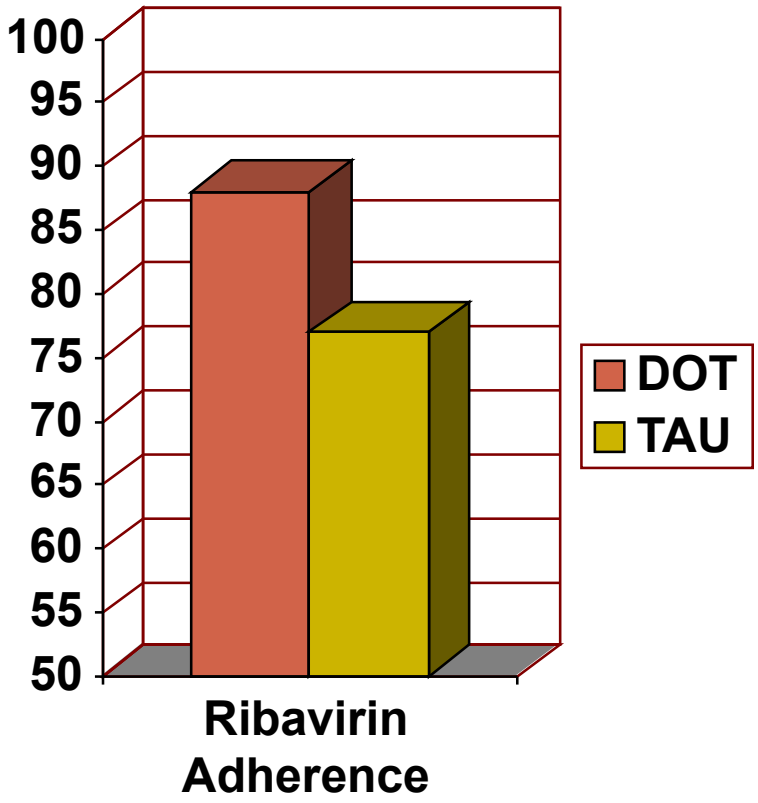
No significant differences in adherence among models of care

		Weekly Time-Frame Adherence		Daily Time-Frame Adherence		Window Daily Time-Frame Adherence	
Arm	N	Mean	SD	Mean	SD	Mean	SD
DOT	9	84.2%	8.4%	63.1%	14.9%	51.7%	15.7%
Group	20	87.3%	17.7%	69.6%	17.9%	53.9%	19.7%
Individual	32	86.8%	9.9%	72.2%	15.0%	48.8%	16.1%
Total	61	86.6%	12.7%	70.0%	16.0%	50.9%	17.2%

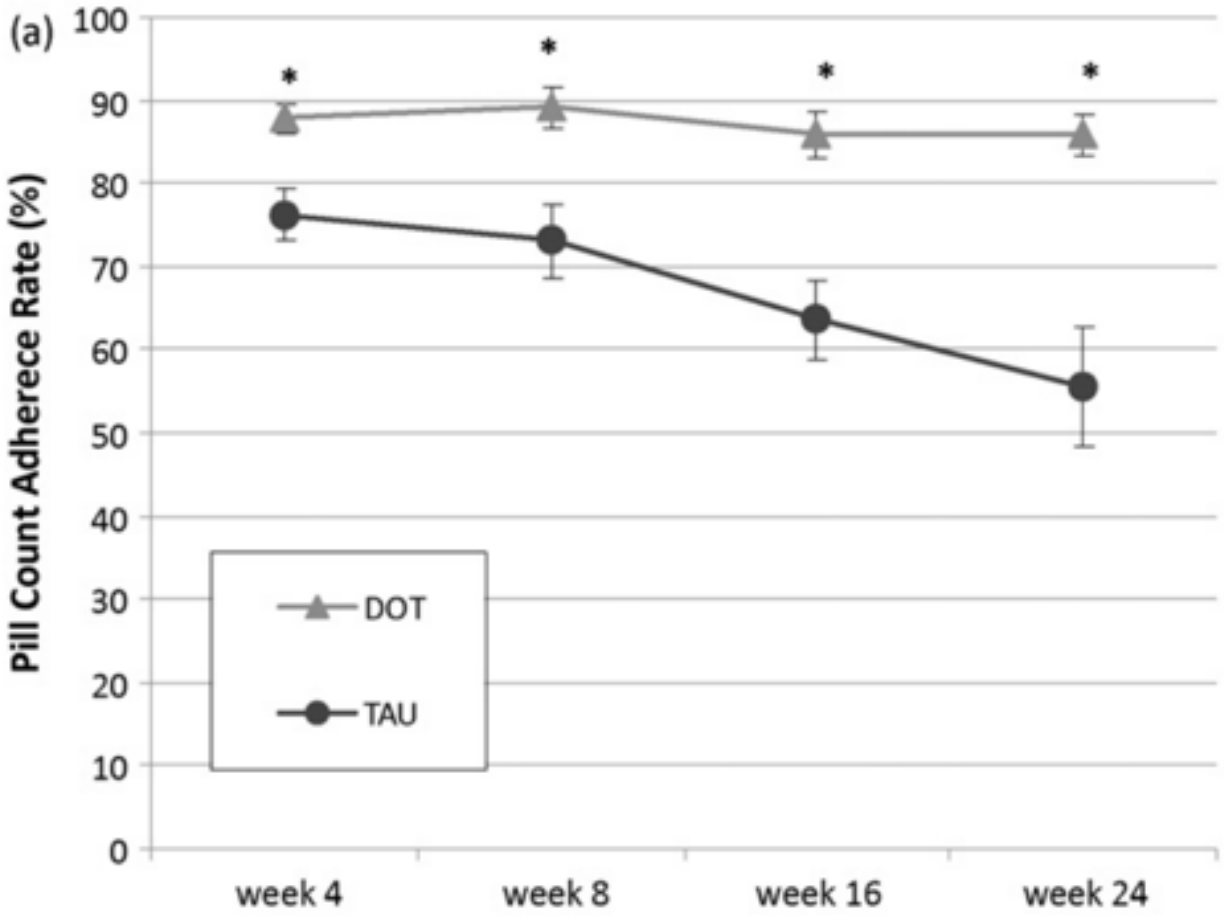
Note: No significant differences in any types of adherence rates based on ANOVA test; $p = 0.82$, 0.33, and 0.58, respectively.

HCV DOT RCT trial reveals similar rates of adherence (Litwin et al)

- Mixed effects linear model
  - Study arm, time, and interaction of study arm and time
- Over 24 weeks, pill count adherence higher for DOT than TAU subjects
- 88% DOT vs. **77% TAU** (p =0.02)



HIV DOT study reveals similar rates of adherence (Berg, Litwin, et al)



Limitations

- Single treatment program study – three sites
- Modest sample size
- Urine toxicology results
  - Chart review of clinical data
  - did not take into account prescriptions (opiates for pain or benzodiazepines for anxiety)
- No data on route of drug use during treatment

Conclusions

- Rates of SVR are high in people who inject drugs initiating sofosbuvir-based regimens within an on-site HCV treatment program
- Adherence (measured by electronic blister packs) is suboptimal but in this small study adherence was not associated with SVR
- Adherence significantly decreases over 24 week period suggesting shorter courses of treatment (≤ 12 weeks) important in people who inject drugs
- No association between active drug use (either prior or during treatment) and SVR
- Using weekly blister packs (for take-home doses) to administer modified DOT may be suboptimal (may not be as good as individually packaged daily take-home doses)

Real-world clinical trials vs. registration trials

- Adherence in this real-world trial is lower than seen in registration trials even with similar populations
  - Registration trials likely more selective (e.g. 80% adherence to pre-enrollment visits)
  - Registration trial infrastructure is a robust intervention (frequent visits. aggressive case management, and smaller sample sizes at each site)
  - Adherence by electronic patient diary higher than electronic monitors but also serves as an adherence intervention as patients reminded if doses are missed

Ongoing Studies

- RISE II: Prospective study of adherence and SVR in genotype 1 patients treated with once-daily combination DAA regimens (n=60; enrollment is complete)
  - Simeprevir + sofosbuvir OR fixed dose sofosbuvir + ledipasvir (n=60)
  - Compare adherence in twice daily versus once daily regimens AND two pills once daily versus one pill once daily
- PREVAIL: Randomized controlled trial of genotype 1 patients (n=150; >100 enrolled)
  - Individual
  - Group
  - DOT

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