High Rates of Sustained Virological Response in People Who Inject Drugs Treated with All-Oral Direct Acting Antiviral Regimens

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Background

- The majority of existing and new cases of HCV in the USA occur among people who inject drugs (PWID)
- HCV incidence and prevalence can be reduced if treatment is targeted to those most likely to transmit virus
- However, PWID are frequently excluded from DAA trials, and PWID often do not have access to treatment – (C-EDGE CO-STAR was an important exception)
- Real-world DAA data in PWID are urgently needed

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Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States

Ann Intern Med. 2015;163(3):215-223. doi:10.7326/M15-0406

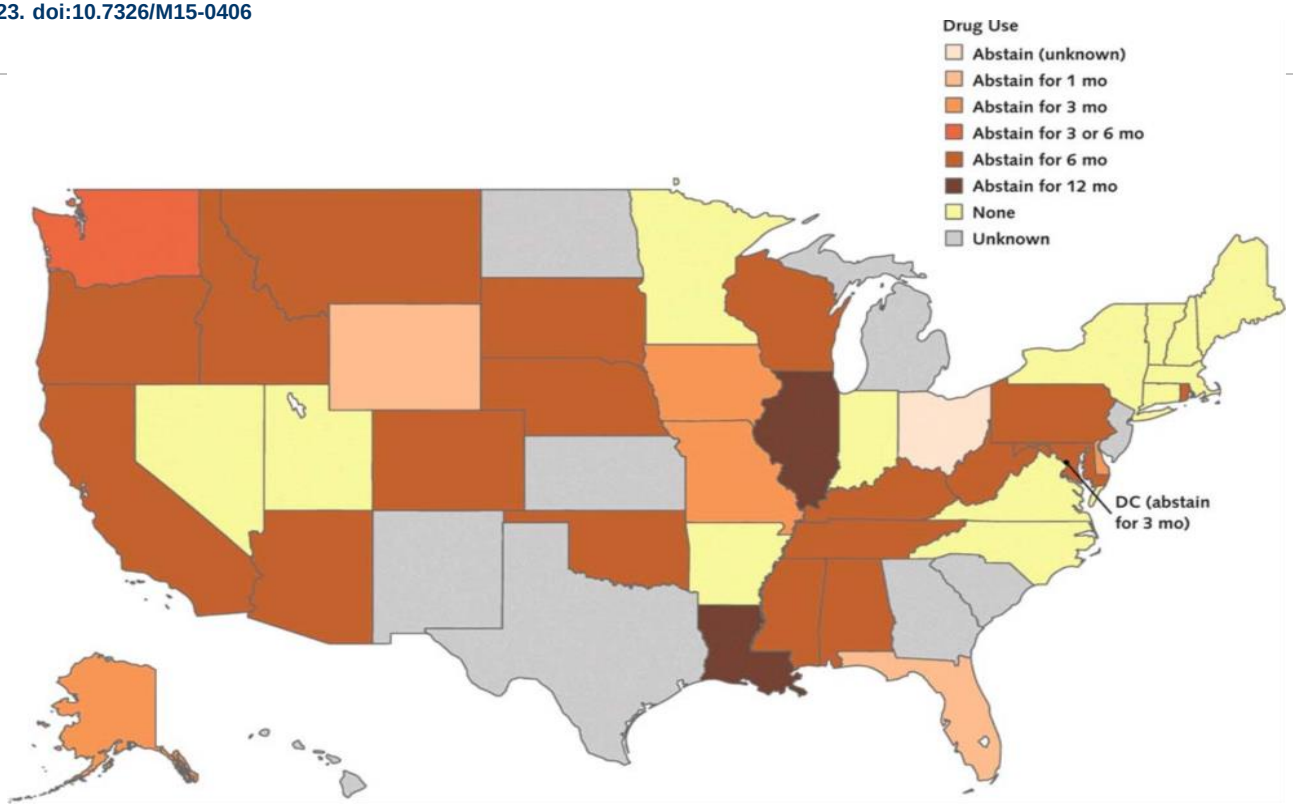

Figure Legend:

Medicaid reimbursement criteria for sofosbuvir based on the required period of abstinence from drug and alcohol use.

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Specific Aims of the RISE-2 Study

- To determine rates of adherence and SVR in a cohort of PWID initiating treatment on-site at an opiate agonist treatment program with sofosbuvir-based regimens
    - Hypothesis: SVR will be equivalent to registration trials
- To determine if active drug use (prior to or during antiviral treatment) is associated with both adherence and SVR
    - Hypothesis: Active drug use will be associated with decreased adherence but not with SVR

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Clinic Locations

Methods: Overview

- RISE II - single-arm prospective trial (n=61)
- Patients received DAA regimen according to AASLD/IDSA guidelines (G1/4): sofosbuvir/ledipasvir or sofosbuvir/simeprevir for 8-24 weeks
- Adherence monitored by weekly electronic blister packs (compensated $10 for each pack)
  - Weekly time-frame
  - **Daily time-frame**
  - Window daily time frame
  - Duration and timing of treatment interruptions
- Adherence monitored monthly by self-report using visual analogue scale (VAS): 0-100%
- Urine toxicologies obtained through chart review

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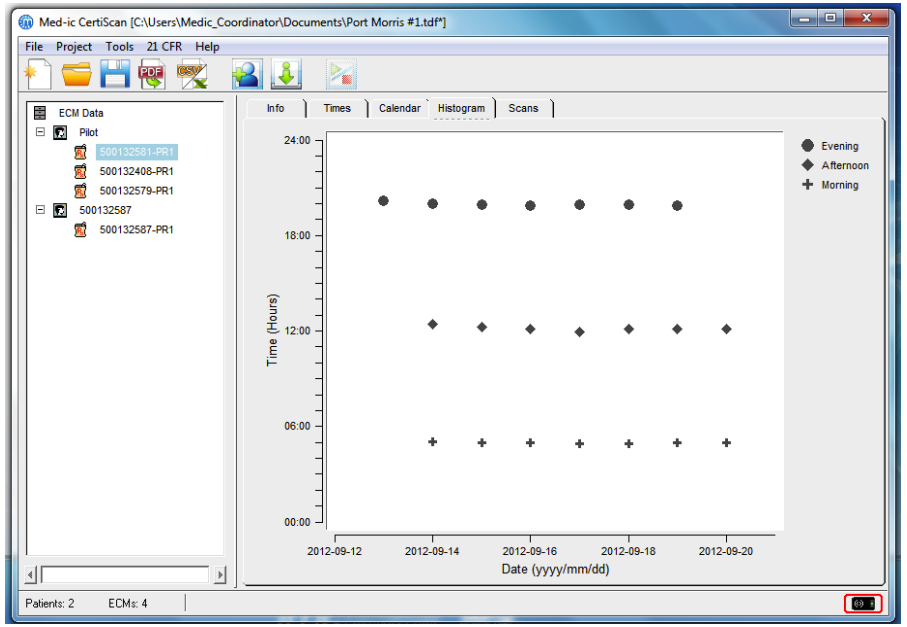
Electronic Blister Packs



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Adherence Definitions

- **Weekly time-frame adherence**: subject receives credit if medication is popped out of the weekly blister pack on any day and time
  - 0 – 7 doses credited each week
  - Patient adherence is reported at 100% if 7 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 - 1 doses credited each day
  - Adherence is reported at 100% if 1 dose 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 6 hours of assigned time each day
- **Treatment interruptions**: characterize consecutive days of non-adherence and timing of treatment interruption (e.g. month 1, 2 or 3)

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Baseline Characteristics (n=61)

Characteristic	N(%) or Mean +/- SD
Age (years)	53.0 +/-13.3
Race/Ethnicity:	
Latino	40 (65.6)
African American	11 (18.0)
Caucasian	7 (11.5)
Other	3 (4.9)
Gender:	
Male	38 (62.3)
Female	23 (37.7)
Insurance:	
Medicaid	57 (93.4)
Medicare	4 (6.6)
Uninsured	0 (0)
HIV	
HIV -	52 (85.3)
HIV +	9 (14.8)
CD4 for HIV + patients: Mean (+/- SD)	501 (+/-243)
HIV viral load (for HIV + patients)	
Detectable	1/14 (7.1)
Undetectable	13/14 (92.8)
Psychiatric comorbidities:	
Any	45 (73.7)
Depression	38 (62.3)
Anxiety	24 (39.3)
Bipolar disorder	6 (9.8)
Psychotic disorder	3 (4.9)
Medical comorbidities	
Any	52 (85.3)
Hypertension	35 (57.4)
Diabetes	13 (21.3)
Asthma/COPD	15 (24.6)

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Baseline Characteristics (n=61)

Characteristic	N(%) or Mean +/- SD
Drug use in 6 months prior based on urine toxicology*	
Any drug	34/58 (58.6)
Other opiates	24/58 (41.4)
Cocaine	18/58 (31.0)
Benzodiazepines	20/58 (34.5)
Injection drug use	
Yes	58 (95.1)
No	3 (4.9)
Opiate agonist treatment	
Methadone	58/61 (95.1)
None	3/61 (4.92)
Methadone weekly pick up schedule	
1-2	23/58 (39.6)
3-4	13/58 (22.4)
5-6	22/58 (37.9)
Current Tobacco	
Yes	47 (77.1)
No	14 (22.9)
Current Alcohol	
No	52 (85.3)
Any use	3 (4.9)
Abuse/dependence	6 (9.8)

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Baseline Characteristics (n=61)

Characteristic	N(%)
HCV Genotype	
1	59/61 (96.7)
4	2/61 (3.28)
Prior Treatment	
Treatment Naive	45/61 (73.1)
Treatment Experienced	16/61 (26.2)
Cirrhosis*	
Cirrhosis	20/61 (32.8)
No cirrhosis	41/61 (67.2)
DAA Regimen	
Simeprevir + Sofosbuvir	15/61 (24.6)
Ledipasvir + Sofosbuvir	46/61 (75.4)
Treatment Duration (weeks)	
8	5 (13.1)
12	50 82.0)
24	6 (9.8)
Models of Care	
Individual	33 (54.1)
Group	15 (24.6)
DOT	13 (21.3)

*Cirrhosis defined by APRI≥2 or Fibrosure≥0.75

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Results: Drug Use Before and During Treatment

Drug use	N (%)
Drug use in 6 months prior to treatment initiation	
Any drug	34/58 (59)
Other opiates	24/58 (41)
Cocaine	18/58 (31)
Benzodiazepines	20/58 (34)
Drug use during treatment	
Any drug	34/58 (59)
Other opiates	23/58 (40)
Cocaine	14/58 (24)
Benzodiazepines	13/58 (22)

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Results: Adherence

Time Frame	N	Mean	SD	Min	Max
Visual Analogue Scale	61	98.4	2.04	92.5	100.0
Weekly time frame	61	90.2	11.3	48.8	100.0
Daily time Frame	**61**	**73.4**	**16.4**	**26.8**	**96.5**
Window daily time frame	61	63.4	21.6	9.5	96.5

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Overall Daily Time Frame Adherence Per Model of Care (p=0.60)

Arm	N	Mean	SD
DOT	13	77.0	11.6
Group	15	70.7	16.2
Individual	33	73.2	18.1

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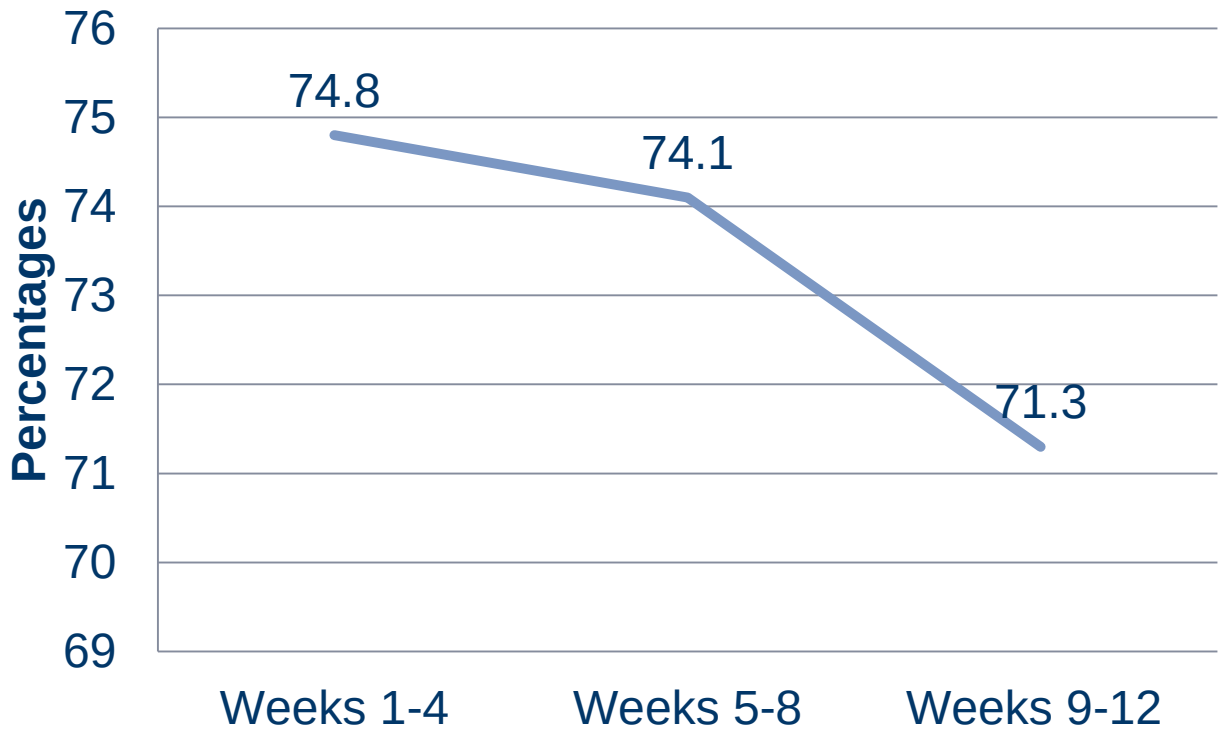
Daily Time Frame Adherence



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Characteristics of Patients Adherent (≥ 80%) by Daily Time Frame

Patient characteristics	N	%	P
Cirrhosis			
No	12/41	29.3%	0.008
Yes	13/20	65.0%	
HIV status			
Negative	18/47	38.3%	0.435
Positive	7/14	50.0%	
Depression			
No	11/23	47.8%	0.398
Yes	14/38	36.8%	
Any drug use 6M			
No	13/23	56.5%	0.033
Yes	10/35	28.6%	
Frequent Drug Use 6M			
No	21/45	46.7%	0.042
Yes	2/13	15.4%	
Any Drug Use during tx			
No	13/24	54.2%	0.058
Yes	10/34	29.4%	
Frequent Drug Use during tx			
No	21/45	46.7%	0.042
Yes	2/13	15.4%	

Frequent drug use ≥ 50% positive urine toxicologies

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Multivariate analysis: Effect on Adherence Rates, Adjusting for HIV Status, Depression and Cirrhosis

Drug	OR	95% CI	P-value
Any drug 6M	0.28	(0.08,1.02)	0.054
Any drug tx	0.27	(0.08, 0.93)	0.039
Frequent drug use tx	0.24	(0.04,1.33)	0.103
Frequent drug 6M	0.23	(0.04,1.28)	0.093

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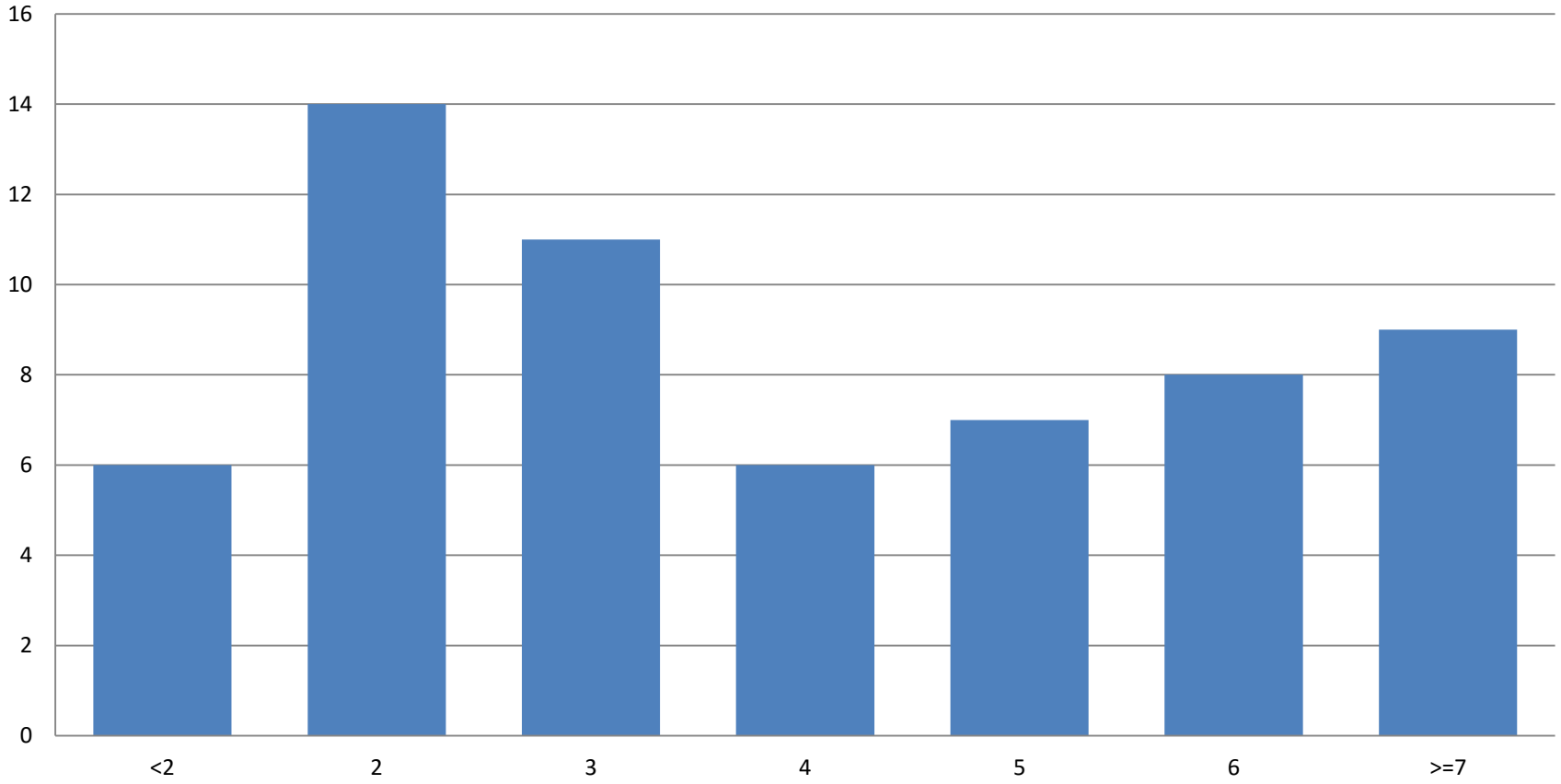
Distribution of longest consecutive missing days



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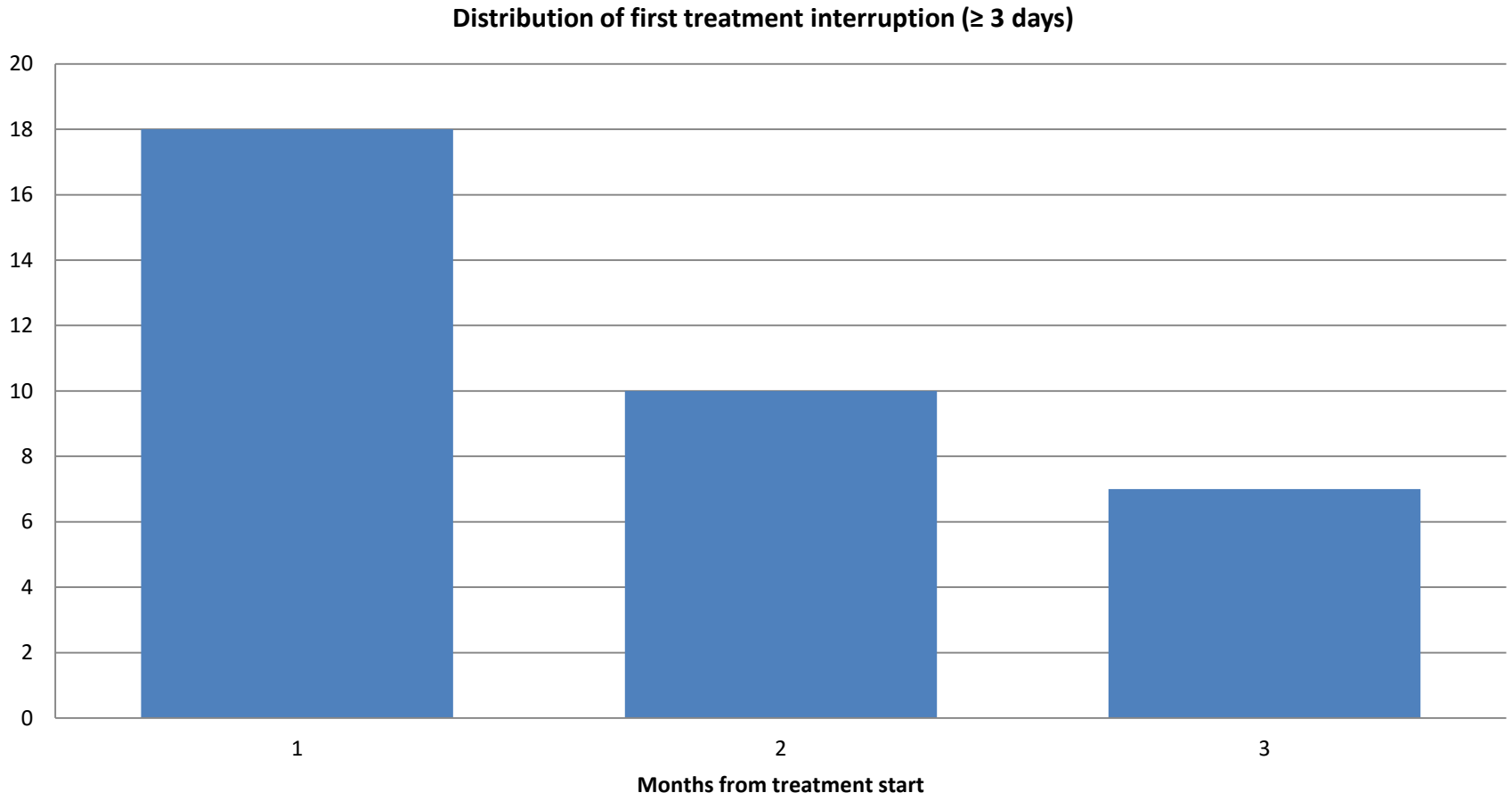
Distribution of first treatment interruption (≥ 3 days)
20
18
16
14
12
10
8
6
4
2
0
1
2
3
Months from treatment start

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Results: SVR 12 Outcomes

SVR 12	N	%
Yes	60	98.4
No	1*	1.6

*1 patient achieved SVR4 but was lost to follow-up

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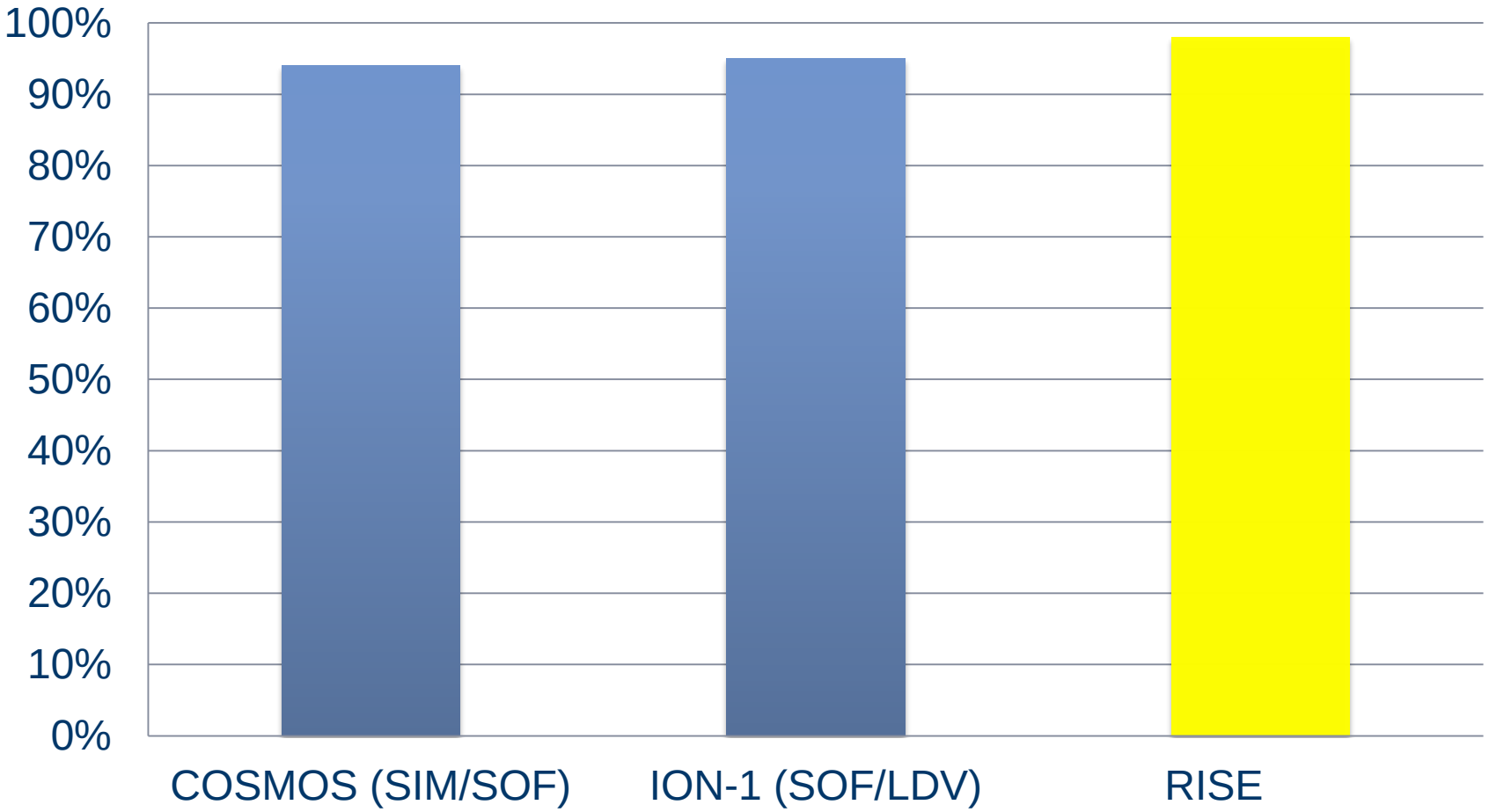
Comparison to Registration Trials



Lawitz, et al., 2014; Jensen et al., 2016

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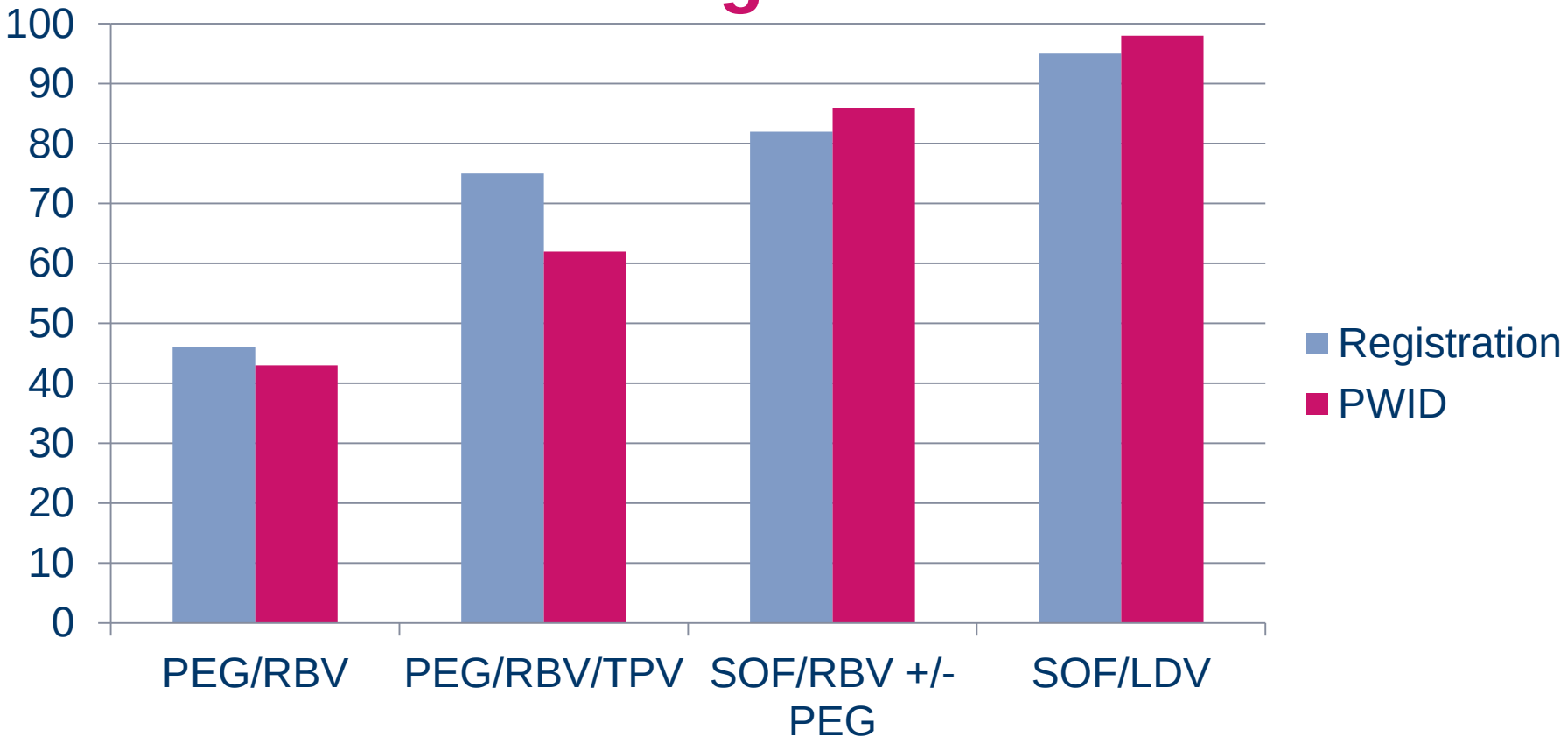
Genotype 1 – PWID Treatment Outcomes Similar to Registration Trials



Fried, 2002; Litwin, 2008; Jacobson, 2011; Osinusi, 2013; Kowdley, 2013; Afdhal, 2014; Litwin, 2015; Litwin, INHSU 2015/2016

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Limitations

- Single treatment program study – three sites
- Modest sample size
- Urine toxicology results
  - Chart review of clinical data
  - did not take into account prescriptions (other opiates and benzodiazepines)
- Limited data on route of drug use

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Conclusions

- Rates of SVR are high in people who inject drugs initiating sofosbuvir-based regimens within an on-site HCV treatment program
- Drug use during treatment was associated with decreased adherence
- Unable to determine association between adherence and SVR
- Reluctance to treat PWID due to concerns about concurrent drug use is unwarranted
- Increased treatment of PWID with HCV within opiate agonist treatment centers may significantly curtail the HCV epidemic

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Acknowledgments

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