Efficacy and safety of sofosbuvir/velpatasvir in people with chronic hepatitis C virus infection and recent injecting drug use: The SIMPLIFY study

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Protocol Steering Committee – Gregory Dore (Chair, UNSW Sydney, Sydney, Australia), Philip Bruggmann (Arud Centres for Addiction Medicine, Zurich, Switzerland), Jason Grebely (UNSW Sydney, Sydney, Australia), Philippa Marks (UNSW Sydney, Sydney, Australia), Julie Bruneau (Centre Hospitalier de l'Université de Montréal, Canada), Tracy Swan (Médecins Sans Frontières, New York, United States), Olav Dalgard (Akershus University Hospital, Oslo, Norway), Jude Byrne (Australian Injecting & Illicit Drug Users League), Melanie Lacalamita (Poliklinik für Infektiologie, Inselspital, Bern, Switzerland) and Adrian Dunlop (Newcastle Pharmacotherapy Service, Newcastle, Australia).

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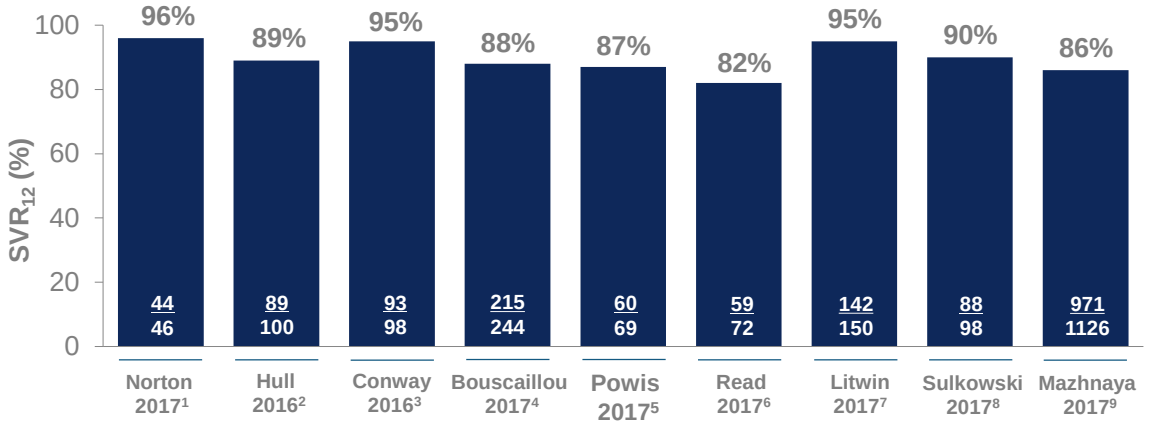
Background/rationale

- DAA therapy is effective in people receiving OST[1-7] and people with a history of injecting drug use (including current/former people who inject)[7-16]
- Ongoing concern from some clinicians regarding DAA efficacy and risk of HCV reinfection among recent PWID
- In some settings in the US[17-18] and Europe (Marshall, FRI Session O)[19], DAA reimbursement restrictions are in place for recent PWID
- Recent PWID excluded from most HCV phase II/III protocols
- There are little data on DAA outcomes among recent PWID

1) Grebely J, ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017 (FRI-236). 2) Grebely CID 2016. 3) Grebely CID 2016. 4) Grebely J, ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017 (FRI-235). 5) Zeuzem, S. Ann Intern Med 2015. 6) Dore, GJ Ann Intern Med 2016. 7) Grebely, Hajarizadeh, and Dore Nature Rev Gastro Hepatology 2017. 8) Norton B, et al. Int J Drug Policy In Press 2017; 9) Hull M, et al. INHSU 2016. 10) Conway AASLD 2016. 11) Bouscaillou EASL 2017. 12) Powis J. Int J Drug Policy 2017. 13) Read P. Int J Drug Policy 2017; 14) Litwin AL, et al. ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017; 15) Sulkowski M, et al. ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017. 16) Mazhnaya Int J Drug Policy In Press 2017. 17) Barua Ann Int Med 2017. 18) Ooka Am J Gastroenterol. 2017. 19) Marshall, AD et al. INHSU 2017, New York, United States, Sept 6-8, 2017.

SVR12 among former/recent PWID



1) Norton B, et al. Int J Drug Pol 2017. 2) Hull M, et al. INHSU 2016. 3) Conway AASLD 2016. 4) Bouscaillou EASL 2017. 5) Powis J. Int J Drug Policy 2017. 6) Read P. Int J Drug Policy 2017; 7) Litwin AL, et al. ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017; 8) Sulkowski M, et al. ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017. 16) Mazhnaya Int J Drug Policy In Press 2017.

Study Design

- Investigator-initiated, Kirby/UNSW sponsored, international open-label trial
- 19 sites, 7 countries
- Study recruitment conducted through a network of drug and alcohol clinics (n=1), hospital clinics (n=12), and community clinics (n=2)
- Participants enrolled between April 2016 and October 2016

Study design and participant eligibility

- DAA treatment-naïve patients with GT1-6 chronic HCV infection (F0-4)
- People with recent injecting drug use (past six months)
- Participants with HIV and decompensated liver disease excluded
- Electronic blister packs to monitor adherence

Study endpoints and statistical analysis

- SVR12 was the primary efficacy endpoint (intent-to-treat)
  - HCV RNA levels measured on local testing
  - Central testing with the Abbott RealTime HCV Viral Load assay (Abbott Molecular, lower limit of quantification of 12 IU/mL) is underway
- Adherence
  - Measured using an electronic blister-pack
  - Calculated by dividing the number of total doses received during therapy by the total expected number of doses
- Participants completed a self-administered questionnaire to collect information on demographics, drug and alcohol use, and injecting risk behaviours
- Detailed information on adverse events

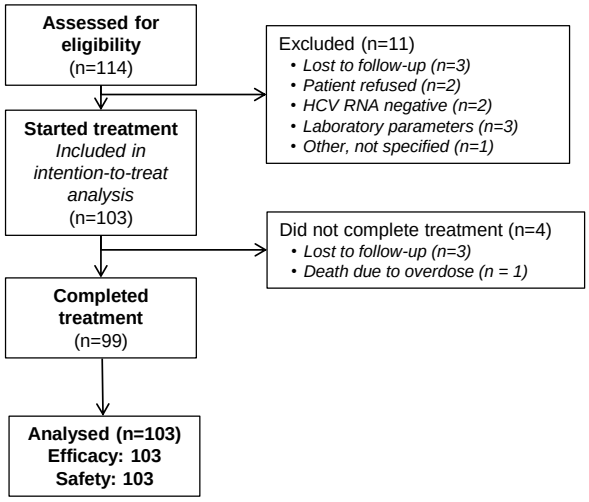
Participant characteristics

Characteristic	SOF/VEL (12 weeks) N = 103
Female, n (%)	29 (28%)
Age, median years (25%, 75%)	48 (41, 53)
Any injecting drug use (last 30 days), n (%)	76 (74%)
Heroin	57 (55%)
Methamphetamines	31 (30%)
Other opioids	22 (21%)
Cocaine	13 (13%)
≥Daily injecting drug use (last 30 days), n (%)	27 (26%)
Current opioid substitution therapy, n (%)	
Methadone	45 (44%)
Buprenorphine ± naloxone	16 (16%)

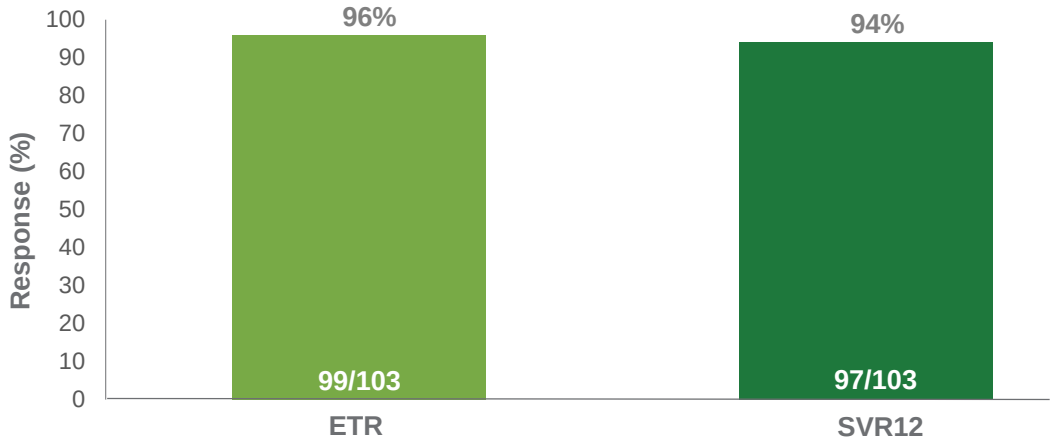
Participant characteristics

Characteristic	SOF/VEL (12 weeks) N = 103
HCV genotype, n (%)	
1	36 (35%)
2	5 (5%)
3	60 (58%)
4	2 (2%)
Fibrosis stage (METAVIR), n (%)	
F0-F1	59 (62%)
F2-F3	27 (28%)
F4	9 (9%)
Study site distribution, n (%)	
Canada/US	40 (39%)
Europe	20 (19%)
Australasia	43 (42%)

Participant disposition

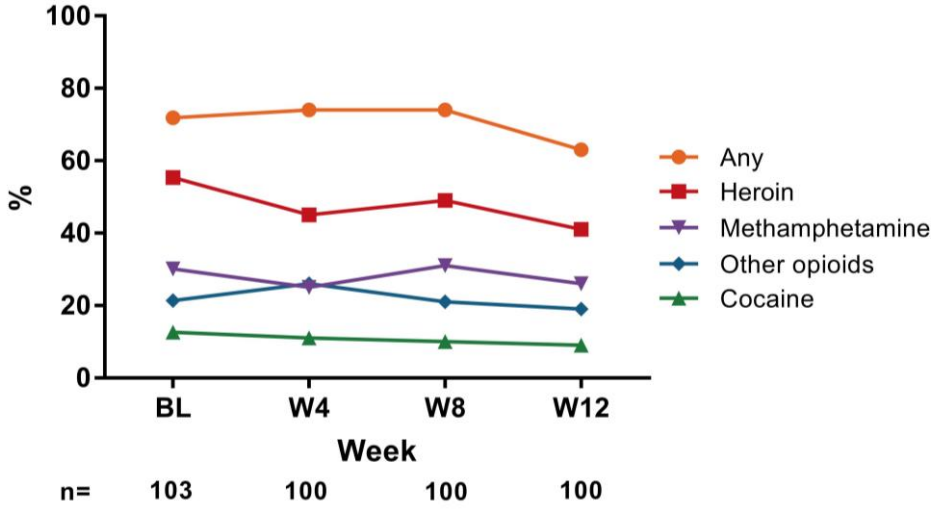


SVR12: Intent-to-treat



- 3 people lost to follow-up between ETR and SVR12 (no virological failure or viral relapse)
- 1 case of reinfection (1a-1a, % nucleotide: NS5A, 10.1%; NS5B, 4.6%, Core-E2, 12.0%)

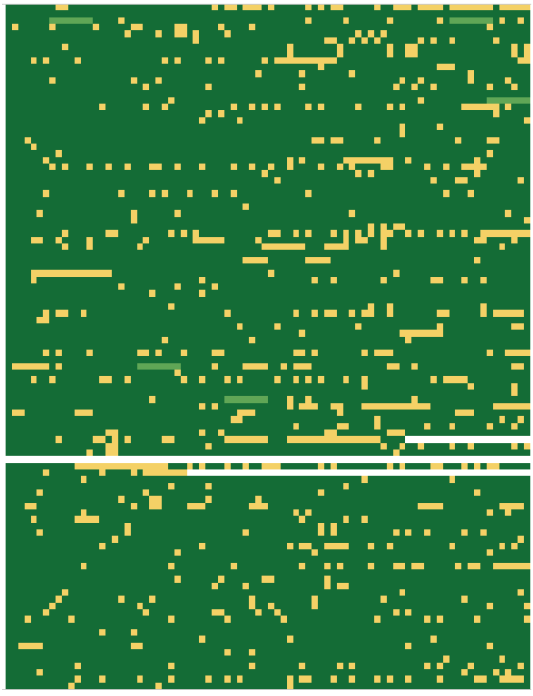
Drug use during therapy

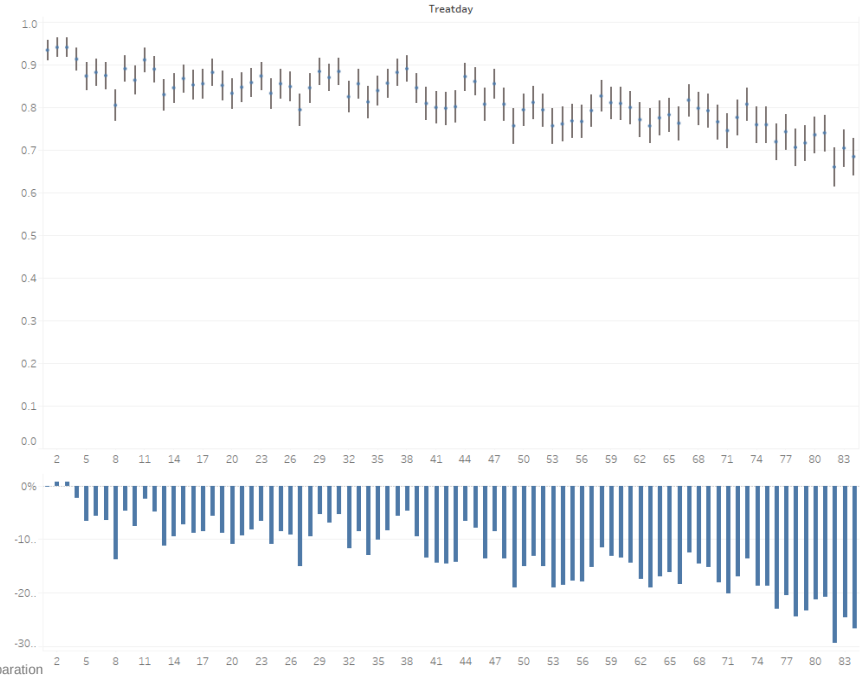


Impact of drug use and OST on SVR12

- No difference in SVR12 among people with (95%) and without recent injecting drug use (past month) at baseline (93%, P=0.683)
- No difference in SVR12 among people with (96%) and without recent ≥daily injecting drug use (past month) at baseline (93%, P=0.584)
- No difference in SVR12 among people receiving (93%) and not receiving OST at baseline (96%, P=0.598)

- Median adherence: 94%
- Mean adherence: 89%





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Discontinuations and adverse events

Characteristic	SOF/VEL (12 weeks) N = 103
AE leading to treatment discontinuation of, n (%)	1 (1%)
Serious adverse event, n (%)	7 (7%)
Any adverse event, n (%)	80 (78%)
Common adverse events, n (%)	
Fatigue	23 (11%)
Headache	19 (9%)
Nausea	13 (6%)
Insomnia	9 (4%)
Arthralgia	6 (3%)

HCV reinfection

- One case of HCV reinfection over 38 person-years follow-up for a reinfection rate of 2.7 cases per 100-person-years (95% CI, 0.1-13.8)
- 55 year old male - smoking cocaine and injecting morphine 2-3 times most days in the last month at baseline, but reported using sterile injecting equipment for all injections
- HCV genotype 1a prior to initiating therapy, was negative at ETR, and had recurrent viraemia with HCV genotype 1a at SVR12
- During treatment - ongoing injecting morphine (frequency of >3 times per day) at the end of treatment, but reported using sterile injecting equipment for all injections
- Sequencing and phylogenetic analysis was consistent with reinfection with HCV genotype 1a (nucleotide divergence NS5A, 10.1%; NS5B, 4.6%; Core-E2, 12.0%).

Summary and conclusions

- Among recent PWID (past six months) with chronic HCV genotypes 1-4 treated with sofosbuvir and velpatasvir, SVR12 was 94%
- There was no impact of injecting drug use or OST at treatment initiation
  - Analyses are underway to evaluate the impact of on-treatment drug use
- There were no cases of virological failure or viral relapse, but one case of HCV reinfection was observed
- These data provide support for DAA HCV treatment among recent PWID
- Further studies are needed in people with more recent injecting and people with HCV/HIV co-infection

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