Il trattamento farmacologico dei consumatori di sostanze con HCV

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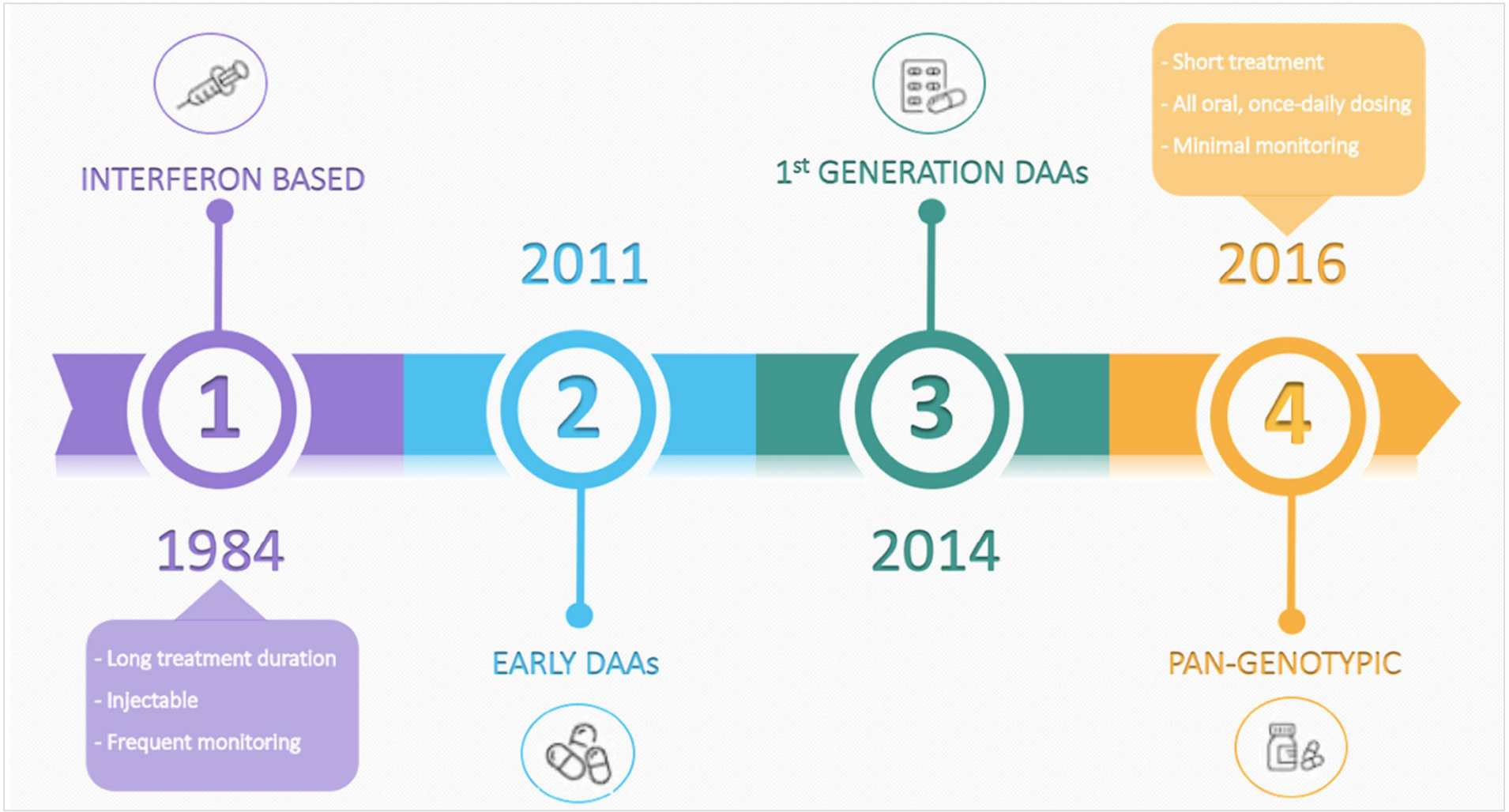
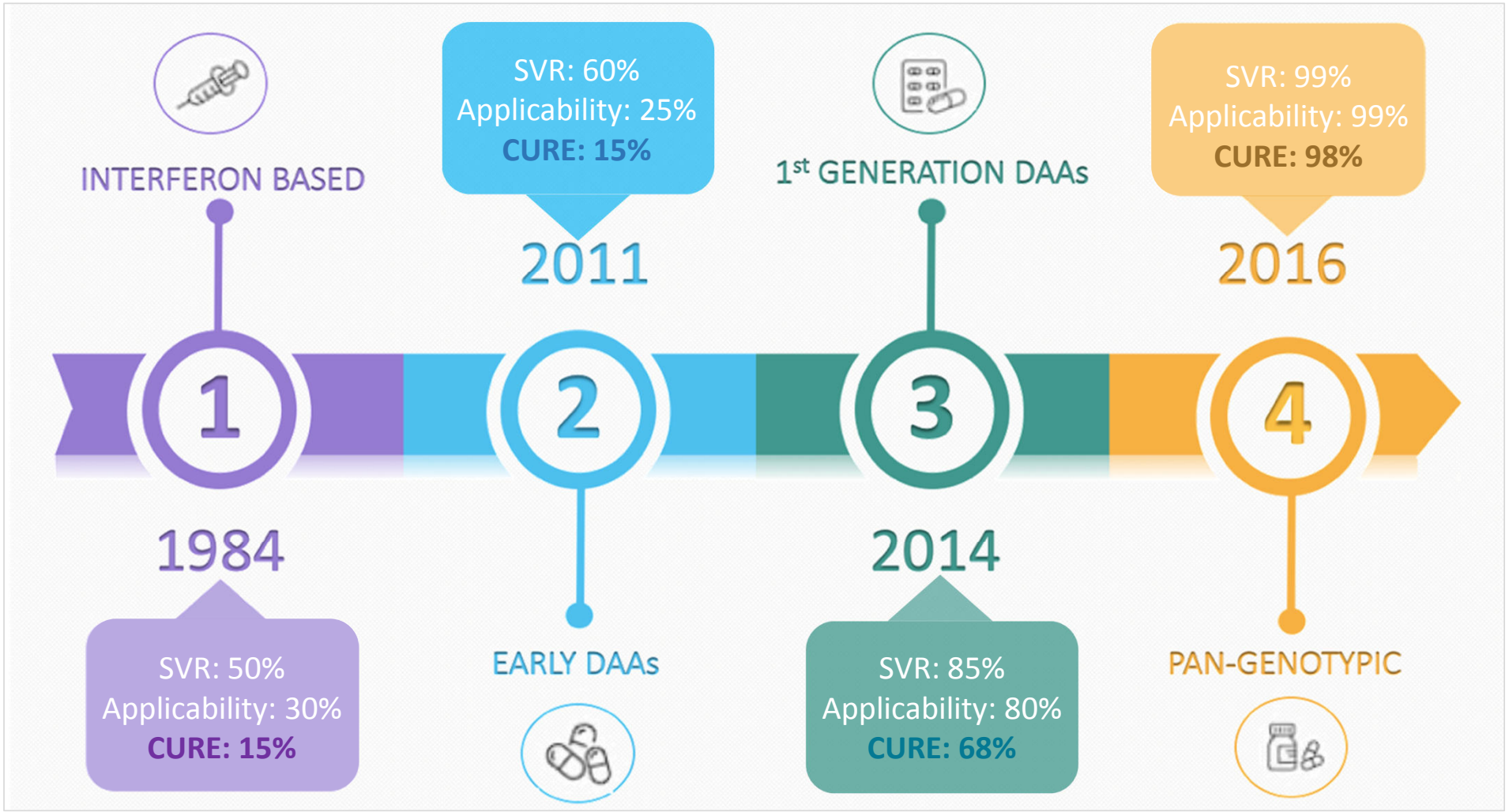
HCV cure timeline



1. Pawlotsky JM, et al J. Hepatol 2016
2. Manns M, et al Nat Rev Dis Primers 2017

HCV cure timeline



1. Pawlotsky JM, et al J. Hepatol 2016
2. Manns M, et al Nat Rev Dis Primers 2017

HCV treatment guidelines prioritize the treatment of PWID

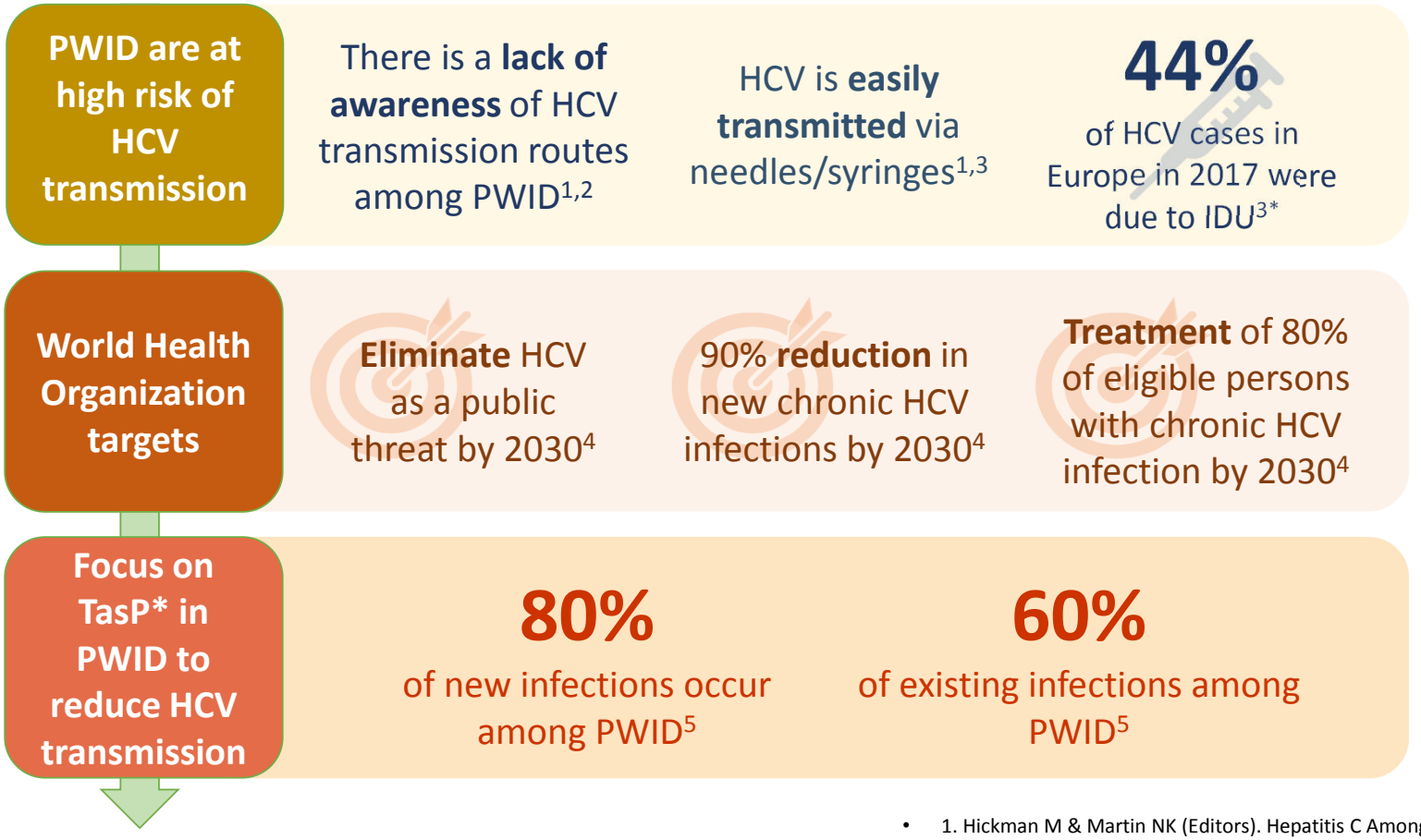
EASL[1]	AASLD[2]	WHO[3]
Screening: *"PWIDs should be routinely and voluntarily tested for anti-HCV antibodies and HCV RNA. PWIDs who are HCV RNA-negative should be tested for HCV RNA annually and following any high-risk injecting episode (A1)"*	Screening: *"Annual HCV testing is recommended for PWID with no prior testing, or past negative testing and subsequent injection drug use. Depending on the level of risk, more frequent testing may be indicated (Class IIA, Level C)"*	Screening: *All PWID should be offered screening for HCV as an integral component of a comprehensive package of harm reduction interventions*
"Treatment must be considered without delay in individuals at risk of transmitting HCV (PWID) (A1)"	*"Active or recent drug use or a concern for reinfection is **not** a contraindication to HCV treatment (Class IIA, Level B)"*	*PWID can be referred to appropriate care packages that include treatment and address other medical and/or psychological issues*

All guidelines recommend regular HCV testing for PWID and if HCV positive, PWIDs should start HCV therapy

1. European Association for the Study of the Liver. *J Hepatol* 2018; **69:**461–511;
2. AASLD Management of Unique and Key Populations with HCV infection 2018. Available at: https://www.hcvguidelines.org/unique-populations/pwid (accessed June 2019);
3. WHO Guidelines for the Care and Treatment of Persons with Chronic Hepatitis C Infection 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1 (accessed June 2019).

PWID, people who inject drugs.

It is critical to treat PWID to prevent the spread of HCV



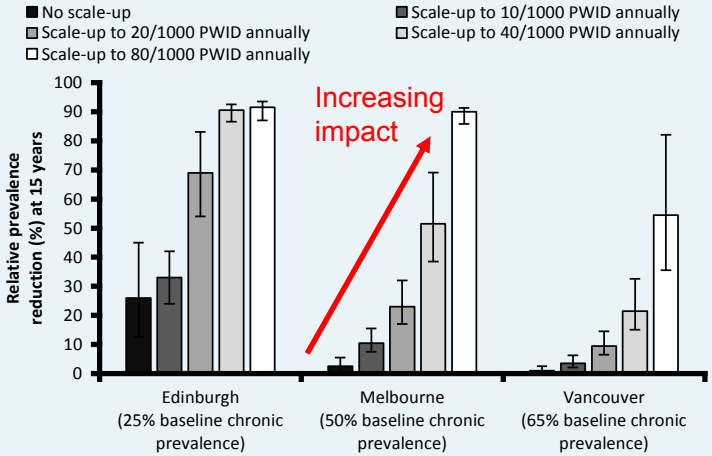
- * Cases with a known transmission route (26%).
- IDU, injection drug use; PWID, people who inject drugs;
- TasP, treatment as prevention.

- 1. Hickman M & Martin NK (Editors). Hepatitis C Among Drug Users in Europe: Epidemiology, Treatment and Prevention, Insights 23, 2016. Luxembourg: EMCDDA, Publications Office of the European Union; 2. Eckhardt B, *et al. PLoS One* 2017; **12:**e0177341; 3. ECDC Annual Epidemiological Report 2017. Available at: https://ecdc.europa.eu/en/publications-data/hepatitis-c-annual-epidemiological-report-2017 (accessed June 2019); 4. WHO Global Health Sector Strategy on Viral Hepatitis 2016–2021. Available at: http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/ (accessed June 2019); 5.Grebely J, *et al*. *Antiviral Res* 2014; **104:**62–72.

TasP is an important tool to reduce HCV transmission among PWID

Current levels of HCV treatment will have a negligible or modest impact on HCV prevalence among PWID

Scaling up antiviral treatment could result in substantial decreases in HCV prevalence in PWID



Modelling shows that a TasP approach and scaling up antiviral treatment nationally, can impact populations at high-risk of HCV infection such as PWID

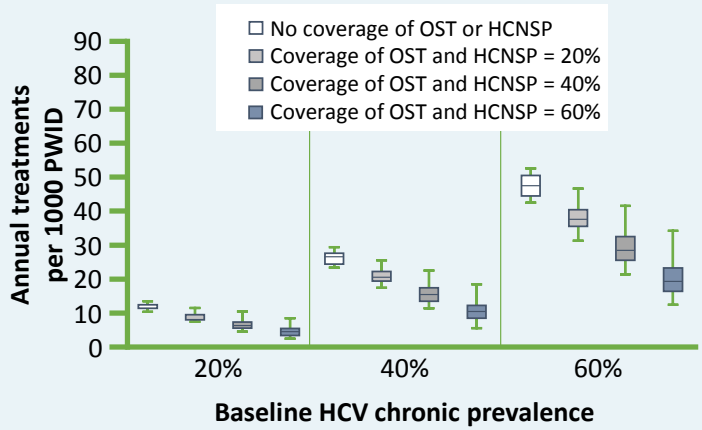
- Bars indicate the mean relative prevalence reductions, with whiskers representing the 95% credibility intervals for the simulations.
- PWID, people who inject drugs.

Martin NK, *et al*. *Hepatol* 2013; **58**:1598–1609.

Harm reduction and HCV treatment

Strategies that combine harm reduction tactics with IFN-free DAAs have been shown to reduce the number of treatment required to half HCV prevalence in 10 years

Modelling antiviral treatment with different levels of OST and NSP coverage (0%, 20%, 40% and 60%) for 3 baseline chronic HCV prevalence settings (20%, 40% and 60%)

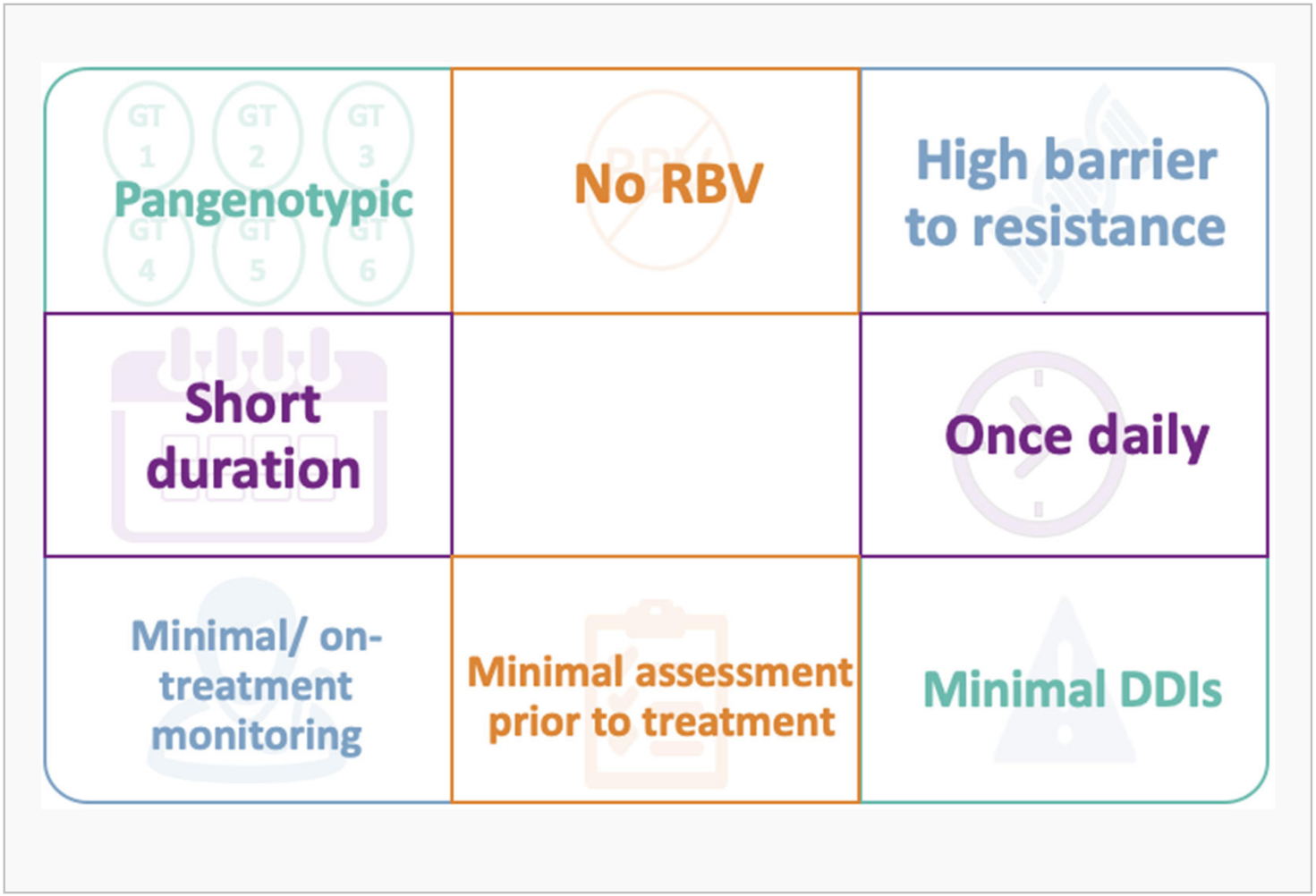


Treating PWID with IFN-free DAAs required ~30% fewer treatments than with pegIFN + RBV to halve HCV prevalence in 10 years

- DAA, direct antiviral agents; HCNCP, high-coverage needle and syringe programs; IFN, interferon; NSP, needle/syringe program; OST, opioid substitution therapy; pegIFN, pegylated interferon; RBV, ribavirin.

Martin NK, *et al*. *Clin Infect Dis* 2013; **57**:S39–S45.

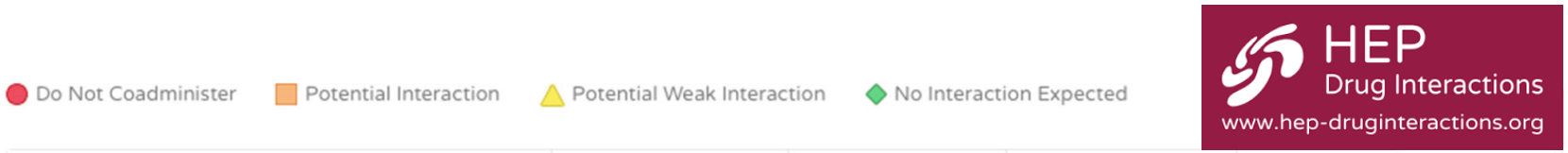
What are the attributes of an ideal HCV treatment regimen for PWID



Dore GJ, *et al. Clin Infect Dis* 2015; **60**:1829–36; WHO Guidelines for the Screening, Care and Treatment of Persons with Chronic HCV Infection, 2016.

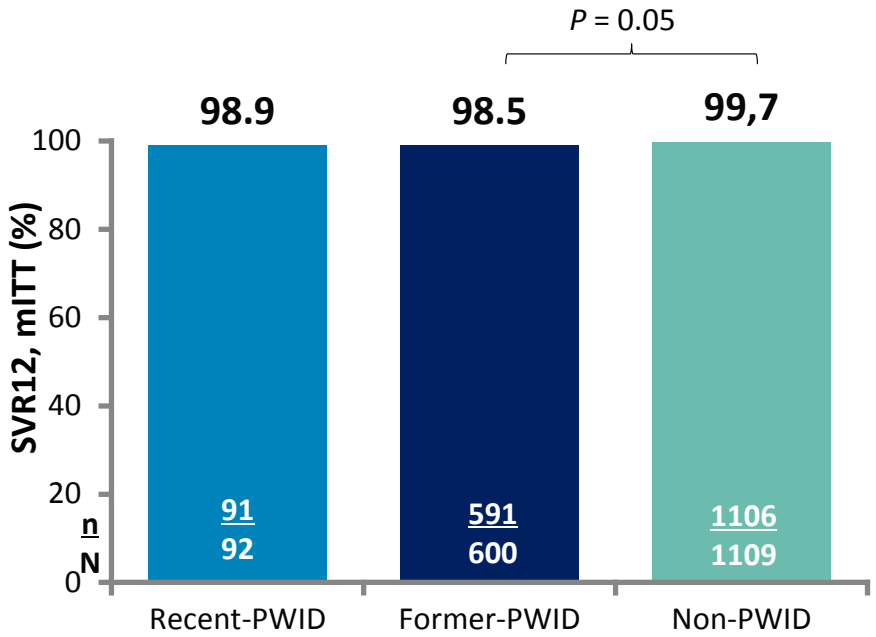
Available at: http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1 (accessed January 2018); Maviret SmPC.

Largely no clinically significant Drug–Drug Interactions between DAAs and OST or illicit/recreational drugs



	EBR/GZR	GLP/PIB	SOF/VEL	SOF/VEL/VOX
Acamprosate	◆	◆	◆	◆
Amphetamine	◆	◆	◆	◆
Buprenorphine	◆	◆	▲	▲
Cannabis	◆	◆	◆	◆
Cocaine	◆	◆	◆	◆
Diazepam	◆	◆	◆	◆
Ecstasy (MDMA)	◆	◆	◆	◆
Fentanyl	■	■	◆	◆
GHB (Gamma-hydroxybutyrate)	■	■	◆	◆
LSD (Lysergic acid diethylamide)	◆	◆	◆	◆
Mephedrone	◆	◆	◆	◆
Methadone	◆	◆	◆	◆
Methamphetamine	◆	◆	◆	◆
Naltrexone	◆	◆	◆	◆
Oxycodone	■	■	◆	◆

G/P for 8 Weeks Achieved High SVR12 Rates in Patients with HCV GT1–6 Infection and Recent Drug Use*



High treatment adherence‡ and completion (≥96%) regardless of drug use status

% (n/N)	Recent-PWID	Former-PWID	Non-PWID
Adherence	**96%** (75/78)	**99%** (524/528)	**99%** (1019/1030)
Completion	**97%** (95/98)	**98%** (599/610)	**99%** (1099/1111

Overall SVR rate in recent-PWUD (98.9%) is not significantly different from non-PWUD (99.7%)

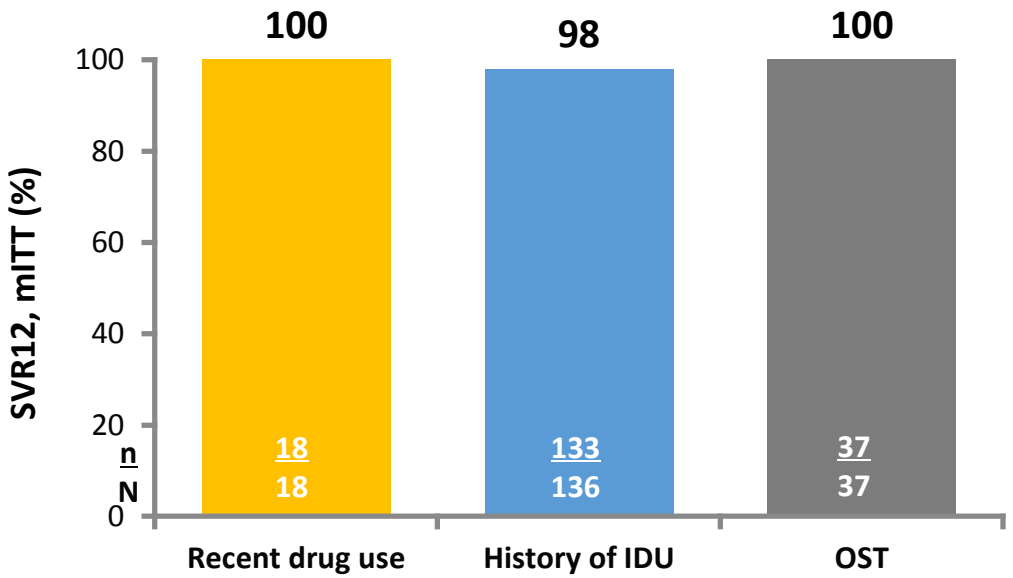
- * PWID, reported injection drug use ≤ 12 months prior to screening and/or a positive urine drug screen for cocaine, amphetamines, phencyclidine, propoxyphene, heroin, or other unprescribed opiates at baseline.
- † mITT, modified intent-to-treat (excludes non-virologic failures).
- ‡ Treatment adherence was considered ≥90% compliance based on pill counts; adherence data was not available for all patients. N = total number of patients in a given intention-to-treat subgroup; n = number of patients with treatment adherence or completion.
- mITT, modified intent to treat, PWID, people who inject drugs.

Foster GR, *et al*. *Drug Alcohol Depend* 2019; **194:**487–494.

G/P for 8 Weeks Achieved High SVR Rates in Non-cirrhotic HCV GT3-infected Patients with a History of or Recent Drug Use*

Baseline characteristics of patients (N=208†)

Characteristic	n (%)
HCV GT3	206 (99)
History of IDU	141 (68)
Recent drug use‡	20 (16)
OST	38 (18)



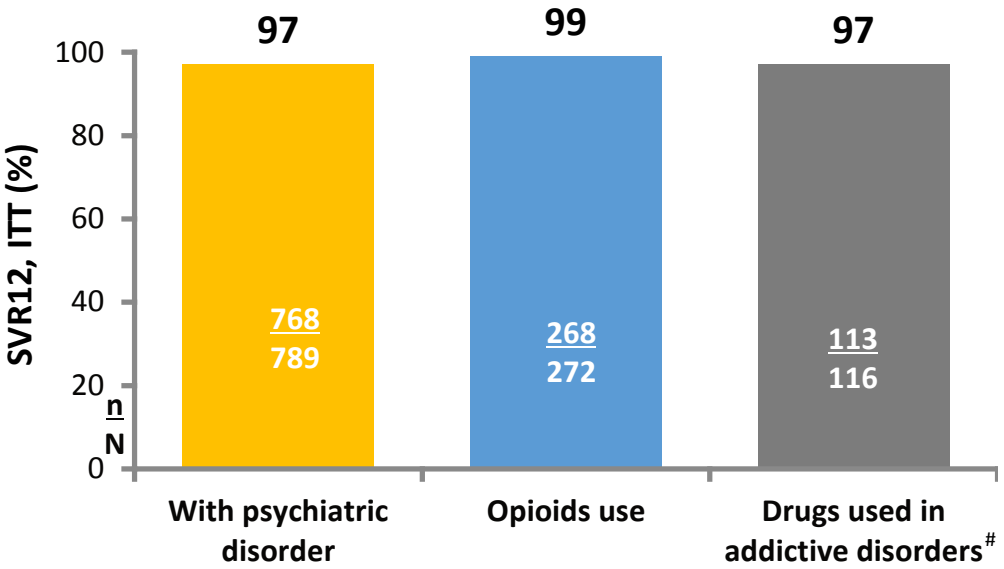
G/P achieved high efficacy in TN patients with HCV GT3 infection

- * <12 months prior to screening; † Pooled analysis from 7 Phase 2/3 trials; ‡ recent drug use data was not captured for patients enrolled in SURVEYOR-2.
- IDU, injection drug use; mITT, modified intent-to-treat (excludes non-virologic failures); NC, non-cirrhotic; OST, opioid substitution therapy; TN, treatment-naive.

Flamm S, *et al. J Viral Hepat* 2019; **26:**337–349.

G/P for 8, 12 or 16 Weeks achieved high SVR rates in patients with psychiatric disorders and history of injection drug use

Baseline characteristics of patients (N=789)	
Characteristic	**n (%)**
Depression*	506 (64)
History of IDU†	439 (56)
Opioids use‡	272 (34)
Drugs used in substance use disorders§	116 (15)



- Pooled analysis from 10 Phase 2/3 trials
- * History of psychiatric disorder in ≥5% of patients; † Includes all patients who previously injected drugs regardless of how recent the patient injected drugs; ‡ Concomitant CNS drug use in ≥10% of patients, grouped by Anatomical Therapeutic Chemical Classification System; § Includes the following drugs: methadone, buprenorphine (with or without naloxone), nicotine, diamorphine, levomethodone, disulfiram, naltrexone, varenicline, acamprosate, and naloxone; # 77% (89/116) had ≥80% treatment compliance.
- CNS, central nervous system; IDU, injection drug use; ITT, intent-to-treat.

G/P achieved high efficacy in patients with psychiatric disorders and/or taking drugs for addictive disorders

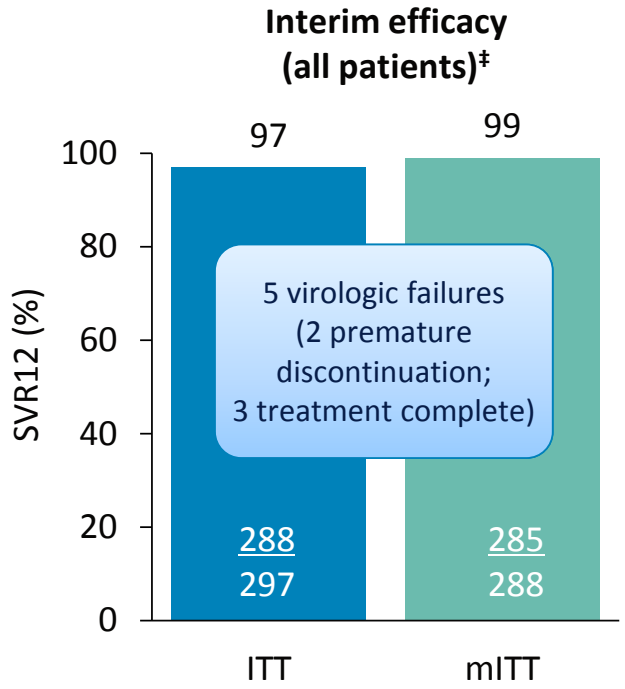
Back D, *et al*. *J Viral Hepatol* 2019

G/P was effective in a real world cohort with high rates of Opiate Replacement Therapy and drug use

Retrospective real-world cohort analysis of 354 HCV-infected patients commencing treatment with G/P in treatment centers in Glasgow, Scotland, prior to 1st May, 2018 (data from the Scottish Hepatitis C database)

REAL LIFE

Baseline characteristic	N=354
HCV genotype, n (%)	
GT1	125 (35.3)
GT2	38 (10)
GT3	187 (52.8)
Other	4 (1.1)
Self-reported drug use, n (%)*	
None	83 (42.1)
Any drug	114 (57.9)
Any IVDU	17 (8.6)
Positive urine DOA screen, n (%)†	83 (68.6)
Engaged in addiction care, n (%)	212 (59.9)
On ORT, n (%)	206 (58.2)
ORT as DOT, n/N (%)	164/206 (79.6)
Metavir score, n (%) F3	22 (6.2)
Metavir score, n (%) F4	33 (9.3)
Prior treatment experience, n (%)	12 (3.4)



*Data available for 197 patients; † Any positive. Includes 21 patients with no self-reported drug use or no available self-reported drug use data. DOA screens available for 121 patients; ‡ Treatment length not specified; DOA, drugs of abuse; DOT, department of transportation; ITT, intention-to-treat; IVDU, intravenous drug use; Mitt, modified intention-to-treat; ORT, opioid replacement therapy.

Boyle A, *et al. Hepatology* 2018; **68**(Suppl 1):368A–369A (poster presentation, 619)

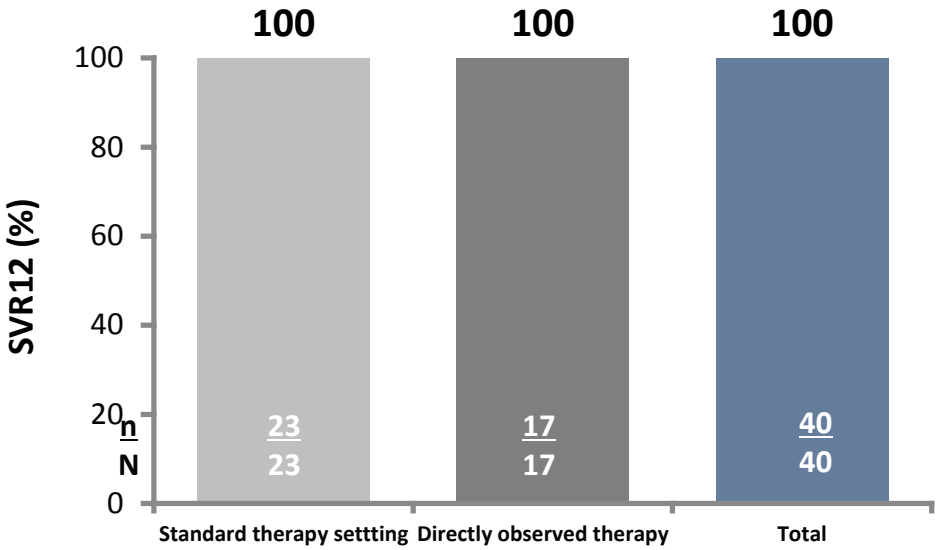
G/P was highly effective in an Austrian Real-World Cohort of PWID patients with ongoing intravenous drug use

In an open-label cohort study, HCV-infected patients with and without compensated cirrhosis started G/P treatment in an Austrian center between Sep 2017 and May 2018 – as of June 2018, 40 patients had achieved SVR

REAL LIFE

Baseline characteristics of patients

Characteristic, n (%)	Standard setting of therapy* (n=57)	Directly observed therapy† (n=59)	Total (n=116)
8-week treatment	46 (81)	44 (75)	90 (78)
12-week treatment	8 (14)	13 (22)	21 (18)
16-week treatment	3 (5)	2 (3)	5 (4)
OST	10 (18)	59 (100)	69 (59)
Ongoing IVDU	0	45 (76)	45 (39)



G/P achieved high efficacy in a real-life setting including PWID patients with ongoing intravenous drug use

- *Patients without OST and patients on stable OST with good compliance were treated at the outpatient clinic of Wilhelminenspital, and received packages of G/P for self-administration at home on a monthly basis.
- † Includes patients with 'borderline compliance', receiving antiviral treatment together with OST under direct observation of a pharmacist, physician or nurse at a pharmacy or at the Ambulatorium Suchthilfe Wien. Only during weekends drugs were usually given to the patient for self-administration at home.
- IVDU, intravenous drug use; OST, opioid substitution therapy, PWID, people who inject drugs.

Gschwantler M, *et al. Z Gastroenterol* 2018; 56:e45.

G/P achieved high SVR rates in PWID with ongoing intravenous drug use in a Scottish Real-World setting

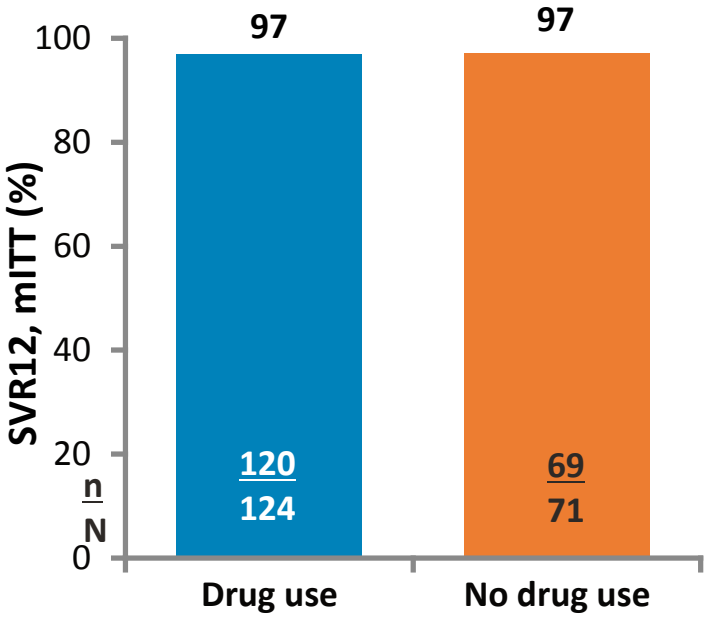
Analysis of self reported drug use and uptake of injecting equipment* 3 months pre- and post-treatment with G/P in HCV-infected patients using the Scottish HCV database prior to 1 May 2018 (N = 354)

REAL LIFE

Baseline Characteristics (N = 354):
71% male (n = 250); 53% GT3 (n = 187);
9% cirrhotic (n = 33); 63% on OST (n = 222)

Drug Use, n/N (%)	Pre-Tx	Post-Tx	*P*-value
Self-reported drug use	114/197 (58)	117/193 (61)	0.58
Self-reported IDU	17/197 (9)	28/193 (15)	0.07
Any evidence of drug use†	135/201 (67)	142/201 (71)	0.45
IEP transactions (all) Needle only	46/144 (32) 32/46 (70)	53/144 (37) 50/53 (94)	0.38 0.001

- Self-reported drug use was stable pre- and post-Tx
- There was a trend toward increased self-reported IDU and a numerical increase in patients accessing IEP post-Tx
- More patients accessed needles only and fewer accessed foil ± needles post-Tx



- *Patients attending specialist addictions clinics (not primary care OST clinics)
- were linked with local IEP database by identifiers based on name/date of birth;
- †Self-reported or toxicology.
- IDU, injection drug use; IEP, injecting equipment provision; OST, opioid substitution therapy;
- PWID, people who use drugs, Tx, treatment.

- Ritchie T, *et al*. *J Hepatol* 2019; **70:**e504–e505 (poster presentation, FRI-251).

SIMPLIFY

Efficacy and Safety of SOF/VEL for 12 Weeks in People with HCV GT 1-6 and Recent Injecting Drug Use

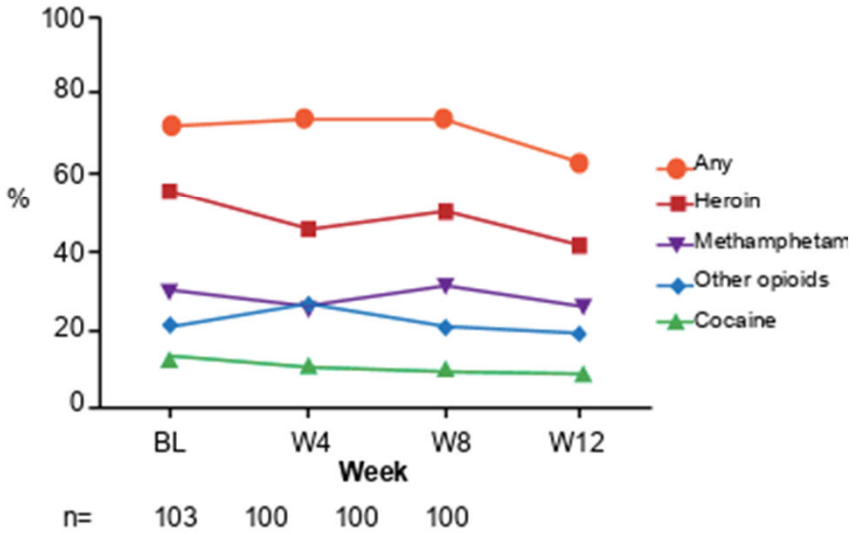
International Phase 4, open-label study of 103 patients

Baseline Demographics

	SOF/VEL (12 weeks) n=103
Age <40 years	25 (24%)
Female sex	29 (28%)
HCV genotype 1 / 2 / 3 /4	36 (35) / 5 (5) 60 (58) / 2 (2)
Fibrosis stage (METAVIR) F0-F1 / F2-F3 / F4	59 (62) / 27 (28) 9 (9)
Injecting drug use (in the last month)	
Heroin	57 (55%)
Methamphetamines	31 (30%)
Other opioids	22 (21%)
Cocaine	13 (13%)
≥Daily injecting drug use (in last month)	27 (26%)
Current OST, n (%)	
Methadone	45 (44%)
Buprenorphine ± naloxone	16 (16%)

Included patients with recent injection drug use (last 6 months) and compensated liver disease

Drug Use During Therapy



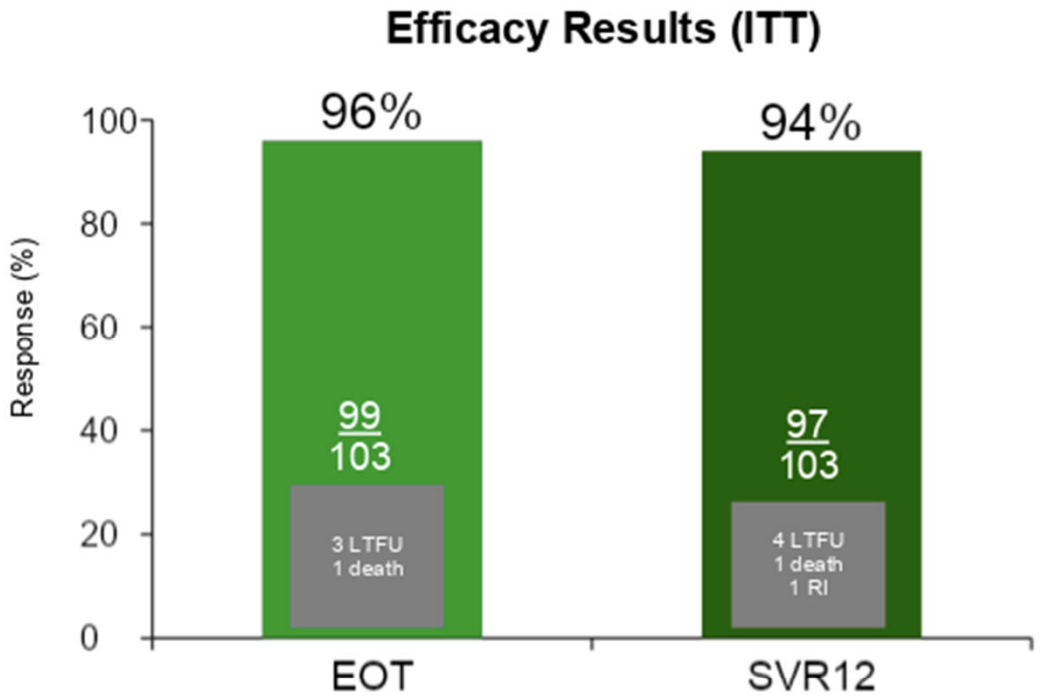
Adherence to HCV therapy

- Median: 94%
- Mean: 89%

The majority of patients continued drug use throughout HCV therapy

SIMPLIFY

Efficacy and Safety of SOF/VEL for 12 Weeks in People with HCV GT 1-6 and Recent Injecting Drug Use



LTFU: loss to follow-up; RI: re-infection
n=4 did not complete treatment (3 LTFU, 1 overdose death)
n=6 did not have an SVR12 (4 LTFU, 1 overdose death, 1 reinfection)

SOF/VEL for 12 weeks in patients with recent injecting drug use led to high SVR12 rates despite ongoing drug use

Grebely J, INHSU 2017, Oral_THU-1040

ANCHOR

SVR in PWID despite imperfect medication (SOF/VEL) adherence

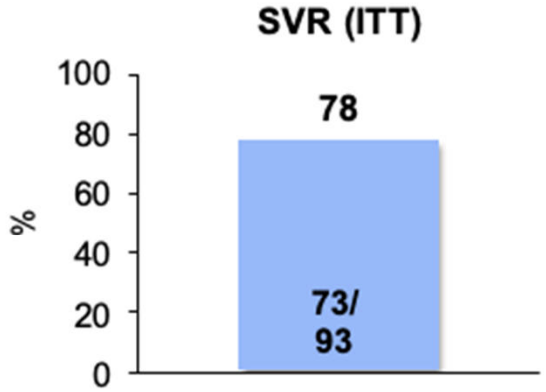
Real-world study of adherence to SOF/VEL in 100 patients with chronic HCV and an opioid use disorder

Baseline Characteristics

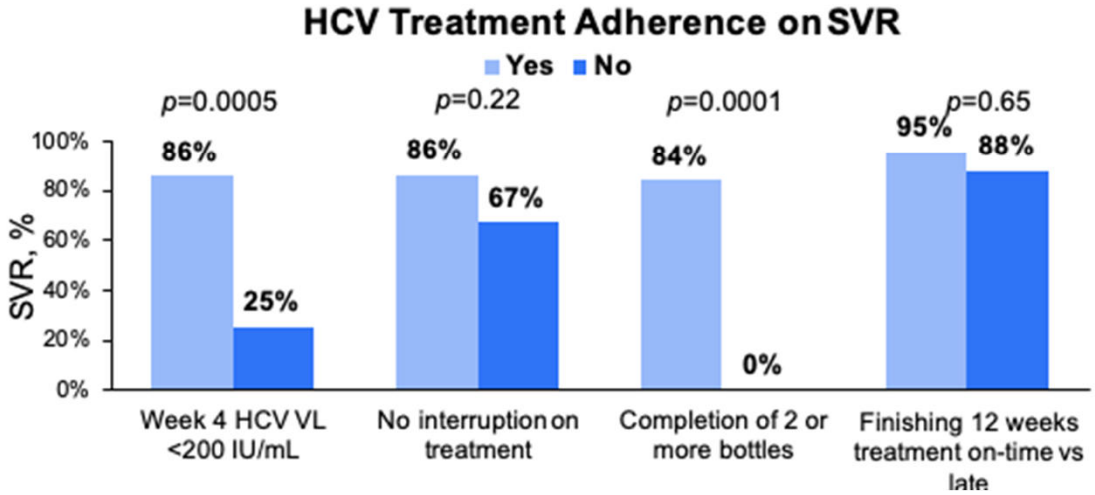
	n=100
Median age, years	57 (53-62)
Male, %	76
Black, %	93
Cirrhosis, %	33
Unstably housed, %	51
Prior incarceration, %	92
No income source or government benefits only, %	92
≥Daily IVDU, %	58
Medication assisted treatment, %	33

PWID achieve high rates of SVR, even with imperfect adherence

Kattakuzhy, AASLD2018, 18



- 10% VF
- 9% LTFU
- 3% died
- Baseline demographics, including drug use frequency, housing and medication assisted treatment status, are not associated with decreased SVR rates

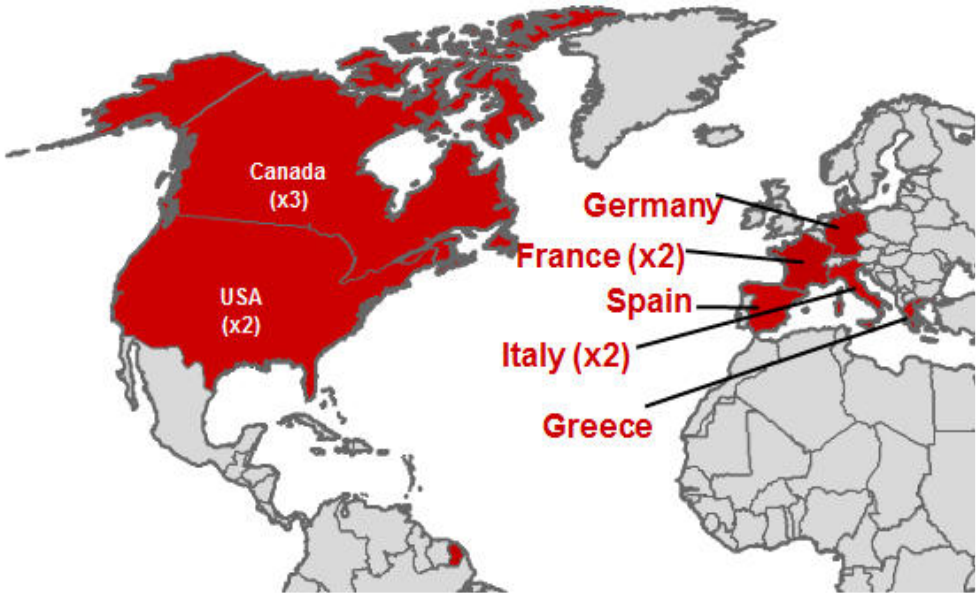


Global Real World Evidence of SOF/VEL for 12 Weeks

5541 patients were included, without use of RBV §

- Real world analysis of 12 clinical practice cohorts from 7 countries

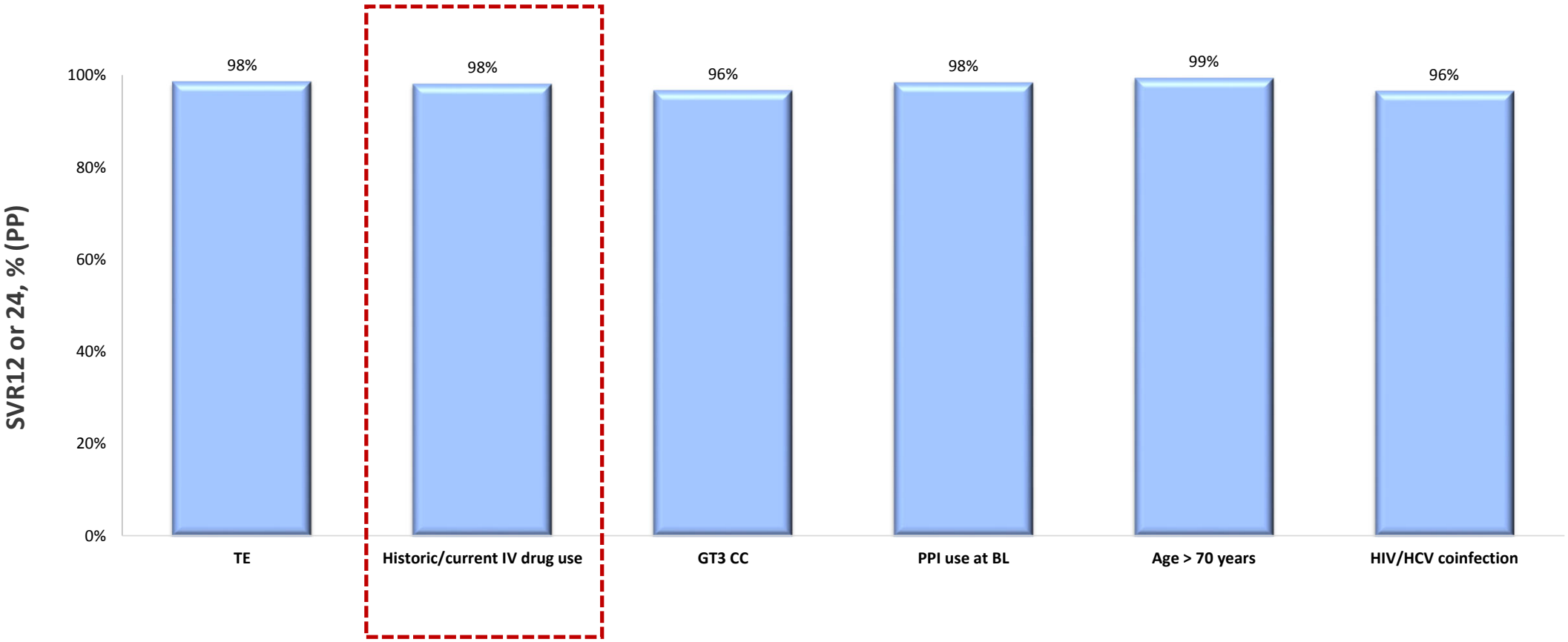
Baseline Characteristics	N=5340 (%)
Age – mean (SD)	54 (13%)
Male	2822 (53%)
Genotype, % **1**/ **2**/ **3**/ 4/ 5/ 6/ unknown	**30/ 30/ 33**/ 5/ 1/ 1
Fibrosis, % F0-F2/ **F3**/ **F4**/ unknown	54/ **13/ 21**/ 12
HIV/HCV coinfection	196 (4%)
Former or ongoing IVDU	706 (13%)
PPI use at Baseline	287 (5%)
TE (pegIFN + RBV ± PI)	660 (12%)



§Total number of patients varies across the characteristics, due to missing data
* Data from 1 cohort were not included in the ITT characteristics analysis due to missing data

Mangia, EASL, 2019, GS-03

SOF/VEL for 12 Weeks: SVR by Subpopulations



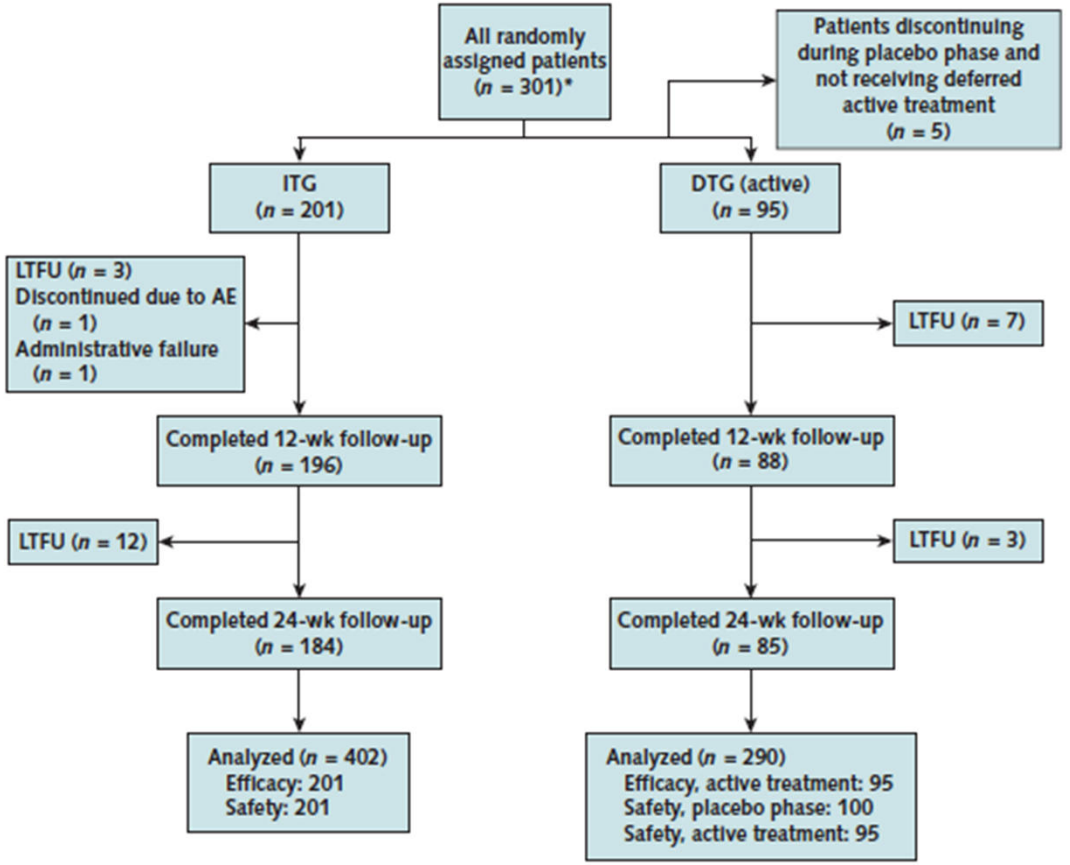
High SVR in the largest real-world cohort of diverse patients

Mangia, EASL, 2019, GS-03

C–EDGE CO-STAR

Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy

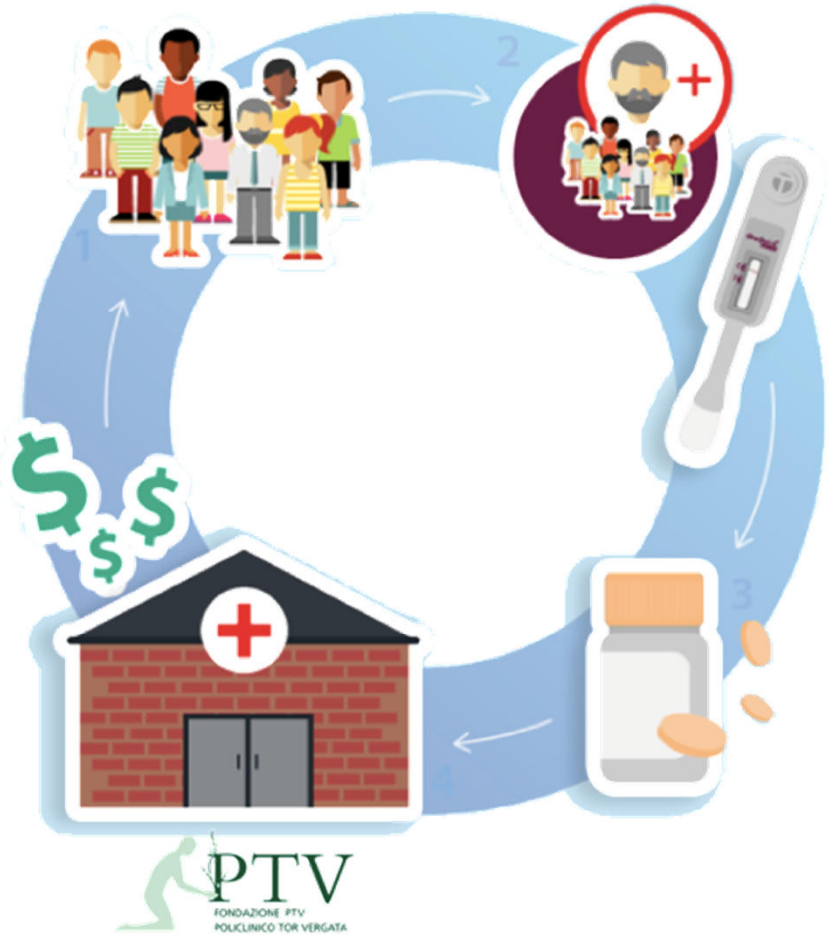
- Pts in OAT (80% methadone, 20% buprenorphine)
- At least 80% adherent to visits for OAT
- HCV Genotypes 1, 4 and 6

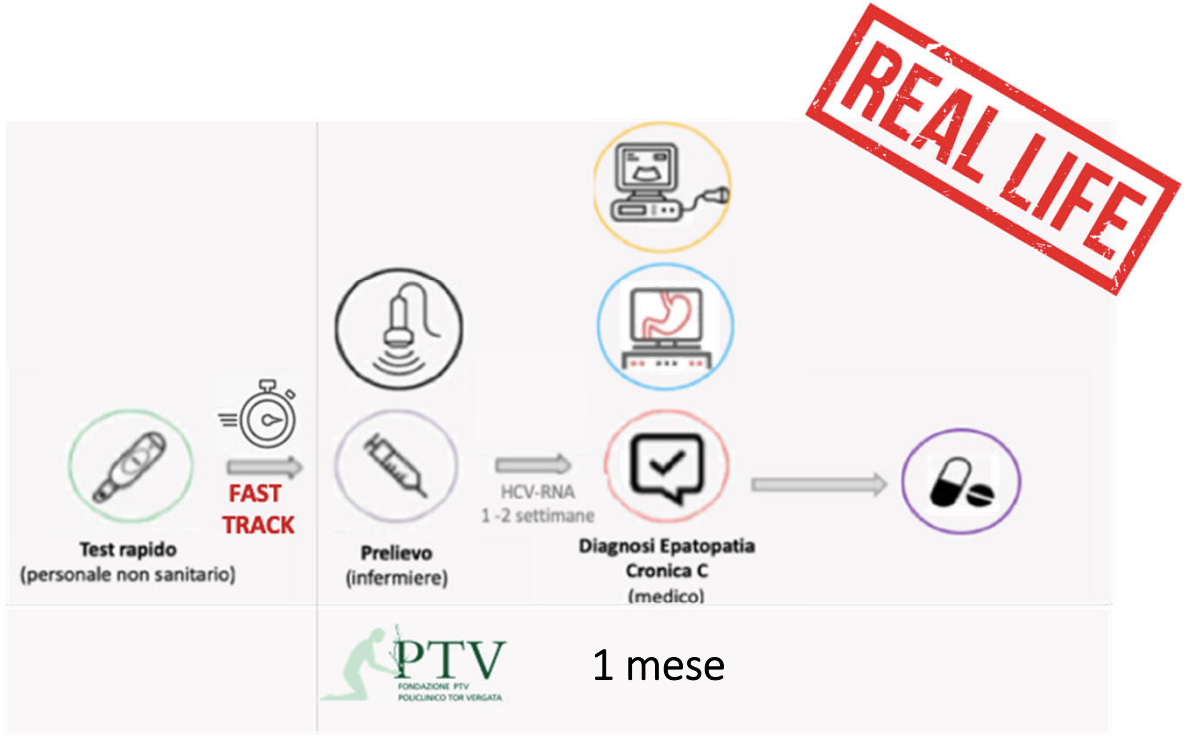


- **SVR_{12} ITT = 91.5 % (184/201)**
- **18 HCV RNA+ at FU24 (6 reinfections, 12 relapse)**

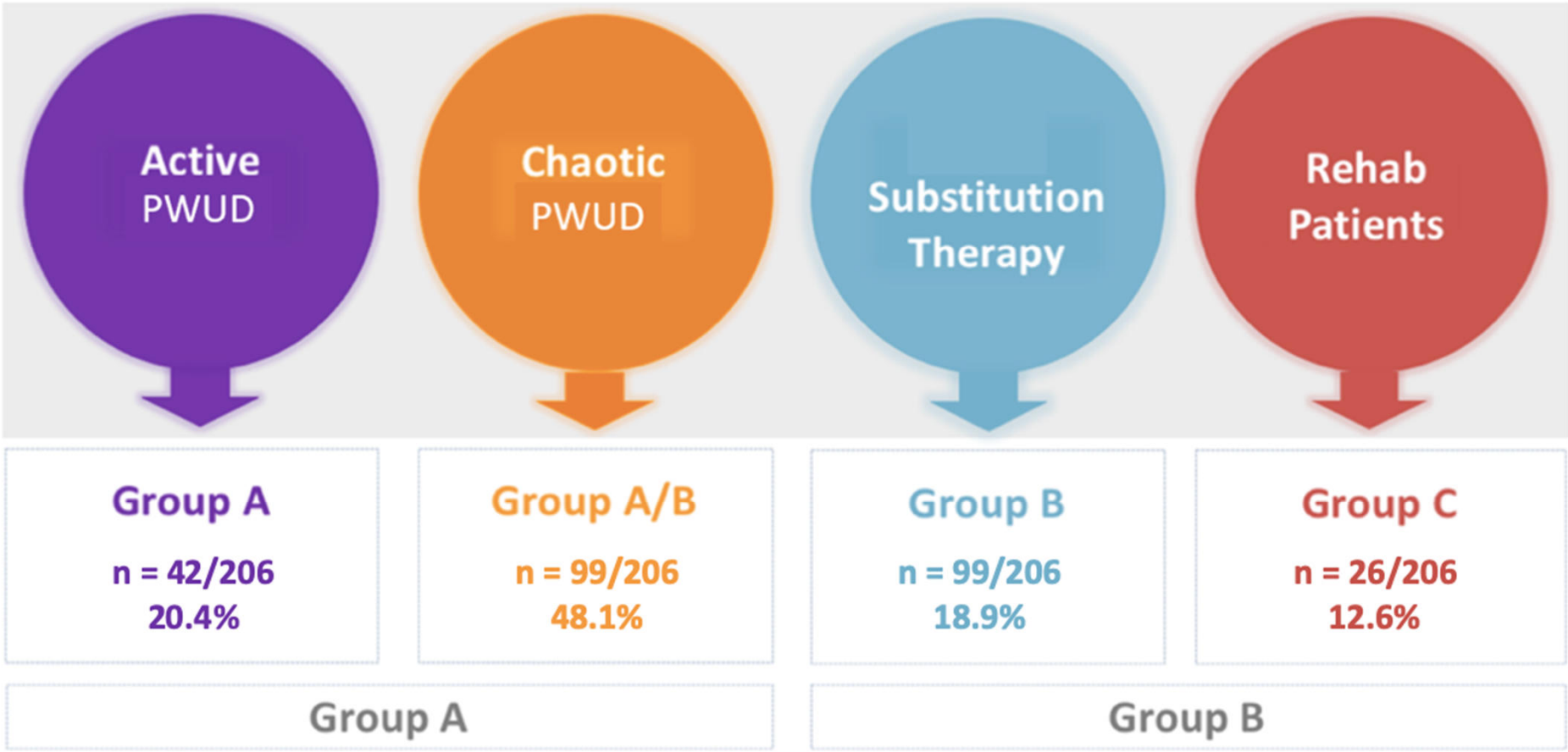
Dore GJ, Altice F, Litwin AH, et al Ann Intern Med. 2016;165:625–634.

Policlinico Tor Vergata – Malattie Infettive





206 PWUD

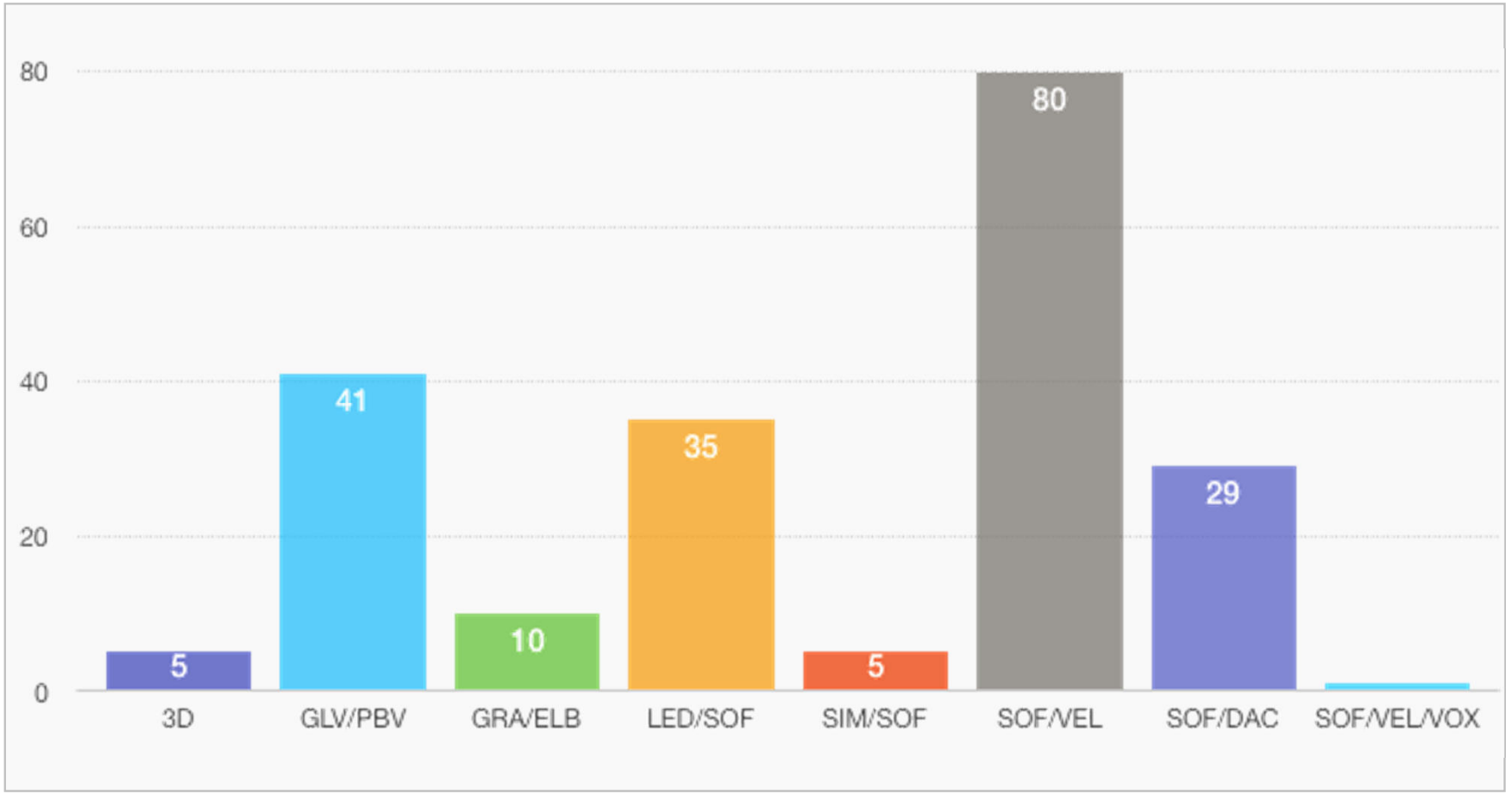

Active PWUD
Chaotic PWUD
Substitution Therapy
Rehab Patients
Group A
n = 42/206
20.4%
Group A/B
n = 99/206
48.1%
Group B
n = 99/206
18.9%
Group C
n = 26/206
12.6%
Group A
Group B

PWUD characteristics

Study Population	n. 206
Age, median	49 (42-54)
Sex ratio, M/F (%M)	181/25 (87.9%)
Duration of IDU, years, median (IQR)	29 (23-35,5)
Injection drug use	191 (92.7%)
Snorting/os drug use	122 (59.2%)
Substance	
Heroin	186 (90.3%)
Cocaine	86 (41.7%)
Alcohol	80 (38.8%)
Other	30 (14.6%)
Multidrug users	124 (60.2%)
Patients in Substitution Therapy	138 (66.7%)
Methadone	126 (61.2%)
Buprenorphine	15 (7.3%)
Work, Yes/No (N%)	74 (35.9%)
Detection	12 (5.8%)
Psychiatric Comorbidity	71 (34.5%)

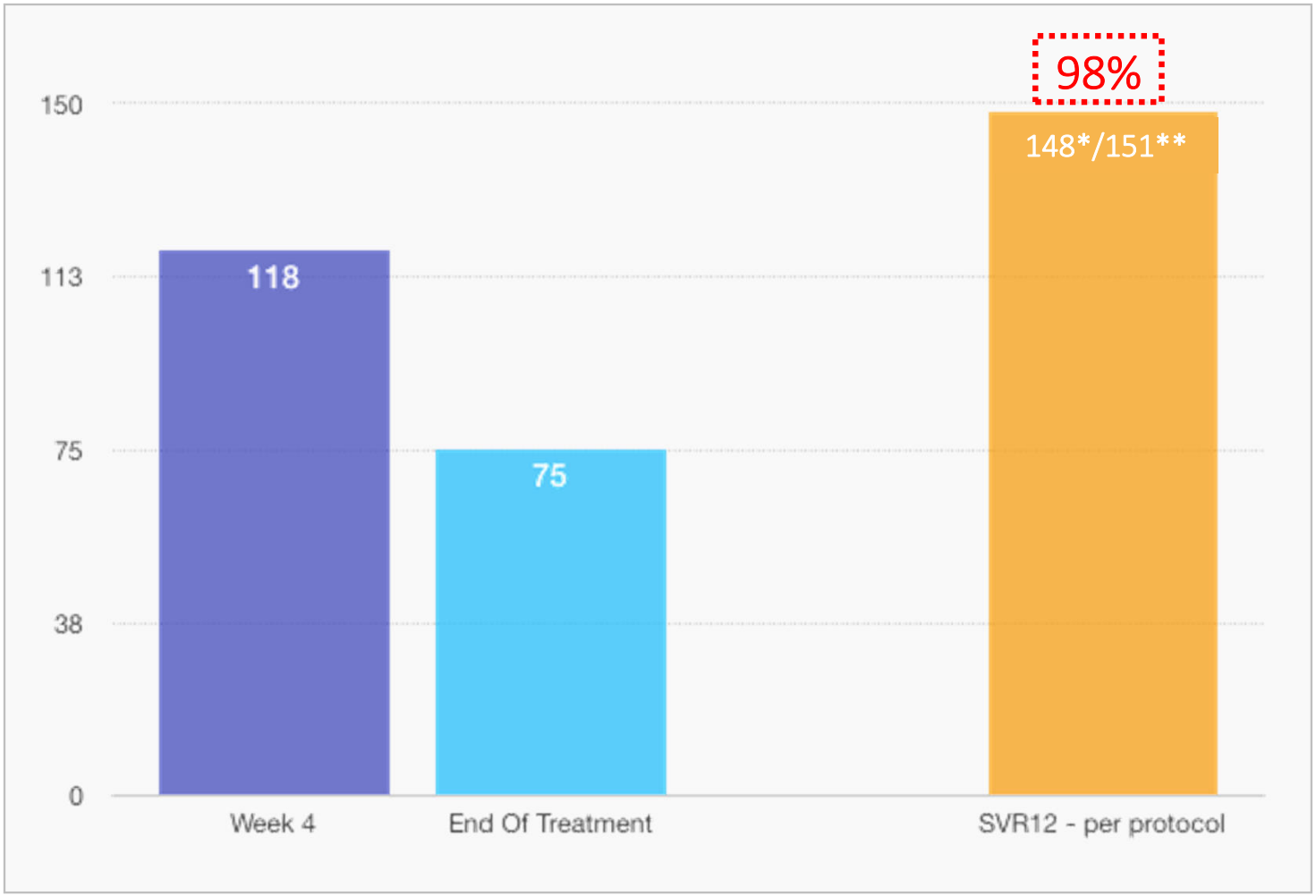
Study Population	n. 206
Duration of HCV infection, years, median (IQR)	22 (8-27)
HCV-Genotype	
Gt 1a	101 (49%)
Gt 1b	5 (2.4%)
Gt 3a	72 (35,2%)
Gt 4	23 (11.2%)
Mixed Gt 1a/3a	3 (1.4%)
HCV-RNA PCR, UI/mL	629943 (145545-2165815)
Resistance Associated-Substitutions	58 (29.1%)
NS3	45/58
NS5A	18/58
HIV-coinfection	15 (7.3%)
HBV-positive serology	97 (47.1%)
Latent tuberculosis	23 (11.2%)
METAVIR score	
Fibrosis F0-F2	89 (43.2%)
Fibrosis F3-F4	117 (56.8%)
FIB-4	1,48 (0,9-3,8)

DAAs regimens



Duration therapy	
8 weeks	36
12 weeks	135
16 weeks	5
24 weeks	30
Riba Y/N	28/178

Week of undetectability and SVR12 rates



*3 pts stopped DAAs at W4: SVR12!

**52 Lost to Follow-Up
↳ 3 pts died before EOT

*** 3 Relapser

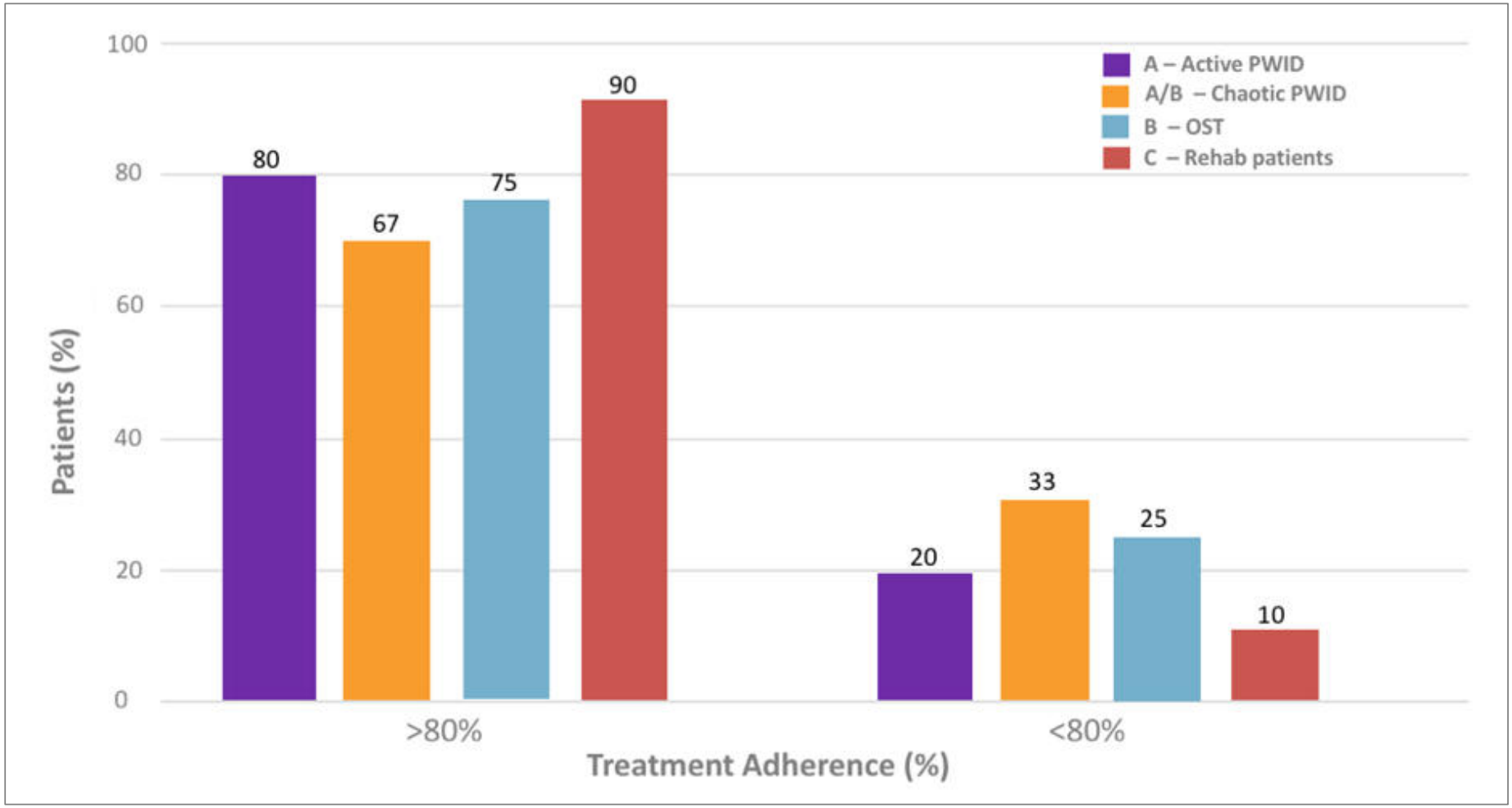
**** 4 Reinfections

«Lost to Follow up» Patients Have Equivalent Sustained Viral Response rates to Patients attending their Scheduled SVR12 Visit.»
Boyle A; *Oral Presentation, INHSU, Lisbon 19-21 September 2018*

Detectable HCV-RNA after DAAs: patient's analysis

	Genotipo	Fibrosi	HIV	DAAs	Risposta	Motivo
C. F.	3a	F0-F1	✓	SOF/VEL	REINFEZIONE	Condivisione Paraphernalia
D. E.	1a	F0-F1	✓	SOF/VEL	REINFEZIONE	Condivisione Paraphernalia
C. M.	1a	F4	✓	LED/SOF	REINFEZIONE	Condivisione Paraphernalia
N. R.	3a	F4	X	SOF/VEL	RELAPSER	?
P. S.	1a	F4	X	SOF/VEL	RELAPSER	?
P. A.	1a	F2	X	GL/PBV	REINFEZIONE	Condivisione Paraphernalia
S. F.	1a	F2	✓	SOF/VEL	RELAPSER	Scarsa aderenza

Adherence


100
80
60
40
20
0
Patients (%)
80
67
75
90
20
33
25
10
A – Active PWID
A/B – Chaotic PWID
B – OST
C – Rehab patients
>80%
<80%
Treatment Adherence (%)