X Workshop Nazionale
Innovazione e Ricerca per la Pratica Clinica

Terapie Innovative delle epatiti croniche virali

Il paziente fallito: prospettive terapeutiche

Maurizia Rossana Brunetto

Medicina Interna – Dipartimento di Medicina Clinica e Sperimentale -Università di Pisa
UO Epatologia - Azienda Ospedaliero Universitaria Pisana

HCV infection management

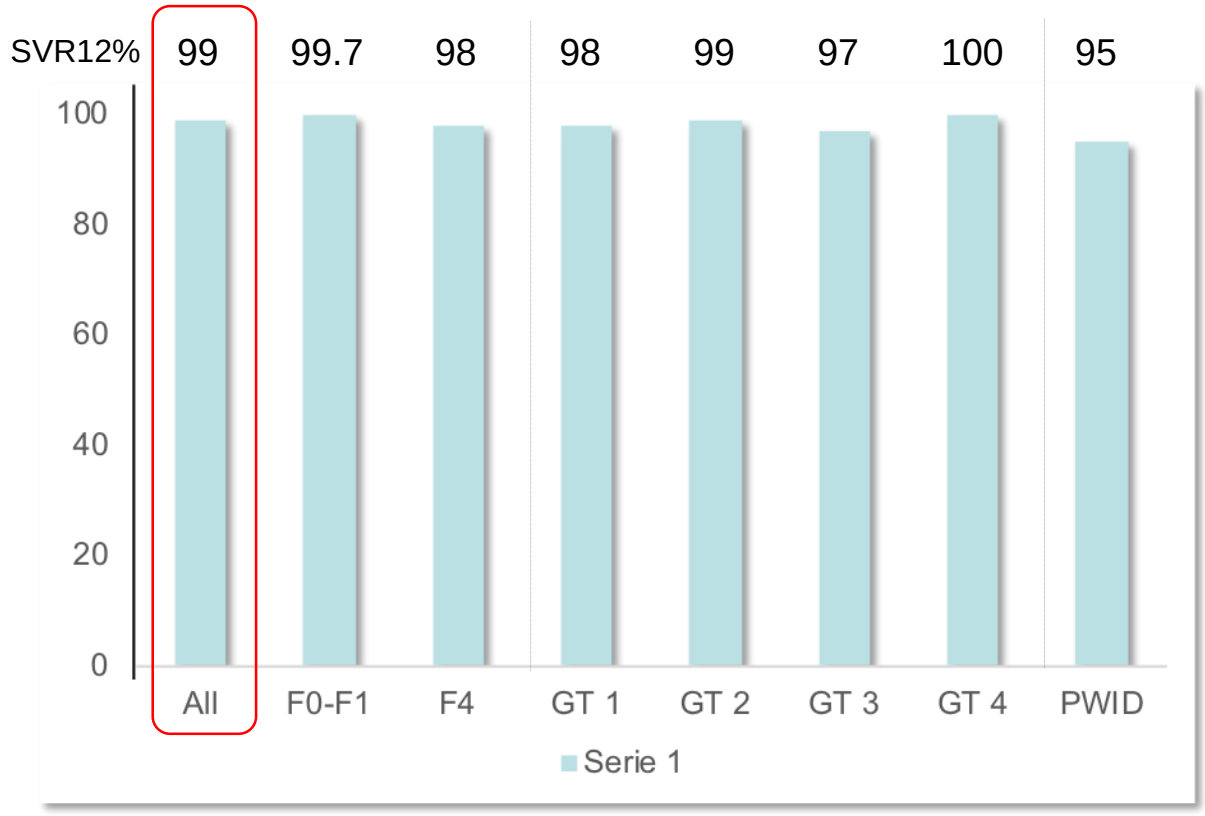
……. are we at the happy end?

Tempi moderni, 1936

Real World Data:
SVR12 rates higher than 99% after SOF/VEL in patients with F0-F1 fibrosis stage

- 1492 patients treated fro 12 weeks from June 2017 and May 2018 in Puglia
- 1319 (92.4%) reached week 12 post-treatment
- 96.6% of 1319 did not receive RBV

SVR12 was:
- 92.7% in RBV +
- 98.7% in RBV –



Mangia A et al , Ploos One 2019

UO Epatologia – AOUP

Valutazione della efficacia (SVR-12) **-** Trattamenti avviati al 10/01/2020

	Trattamenti	**Valutabili x SVR**	**%**	**SVR-12**	**%**	**Fallimenti**	%
Totale	**2134**	1998	93.6%	1964	**98,35%**	33	**1,65%**

	Cirrosi + F3	**F0-F1-F2**	**CRIO e Linfomi**	**IRC / trap. Fegato e altri organi**
Pz valutati	1002	910	55	28
Fallimenti	20	11	1	1
%	**2.00%**	**1.21%**	**1.82%**	**3.57%**

Treatment outcome

Treatment failure

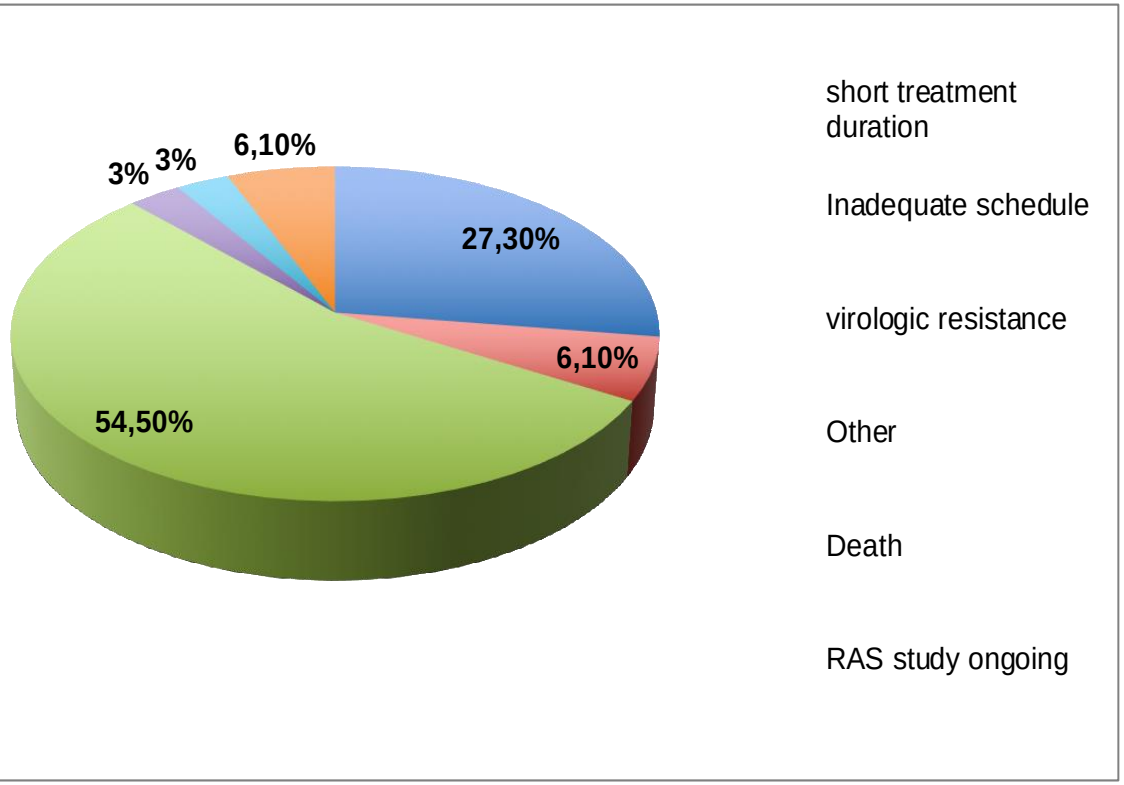
Inadequate Treatment schedule

- Type of drugs' combination → genotype
- Treatment duration → genotype, disease stage, patient's complexity
- Adherence

Viral resistance

UO Epatologia – AOUP

Reasons for treatment failure



33.4% of the failures associated with inadequate treatment schedule

Possible actions to improve treatment management

Failures with inadequate or not completed (n.10) treatment schedules or without RAS (n.1)

N	Età	Sesso	Gen.	Pregressa Terapia P/R	Fibroscan	Ipertensione portale		Criterio AIFA	Inizio terapia	wks	Schedula	**Ragioni fallimento**	NS3	NS5A	NS5B	Re-Trattamento	SVR12
1	76,5	F	1b	NO	16	No		1	01-apr-15	12	SIM+SOF+RBV	Short duration				**NO (NHL)**	
2	57,9	M	1a	NO	75	No		1	09-giu-15	24	DCV+SOF	Short duration				**NO (HCC)**	
3	57,6	M	4	Partial Respond	75	F1		5	13-lug-15	24	LDV+SOF	RAS: no	wt	wt	wt	VOX+VEL+SOF	YES
4	73,5	M	1b	NO	14,3	No		1	25-feb-16	12	3D+RBV	Short duration				LDV+SOF 24W	YES
5	83,6	M	1b	NO	7,8	No		3	06-apr-16	24	LDV+SOF	Death				NO (Death)	
6	69,6	M	1b	NO		No		1	22-giu-16	24	LDV+SOF	Short duration				**NO (renal failure)**	
7	55,2	F	1a	NO	13,3	No		1	26-ott-16	12	SOF+RBV	Inadeguate schedule	wt	wt	wt	NO (D.O.)	
8	45,8	M	3	NO	10,1	No		4	07-nov-16	12	DCV+SOF	Short duration				VEL+SOF 12W	YES
9	42,5	M	1a	NO	3,8	No		8	07-ago-17	12	VEL+SOF	Short duration	wt	L31M	wt	VOX+VEL+SOF	YES
10	50,7	M	1a	NO	5,6	No		8	26-mar-18	12	GRZ+EBV	Inadeguate schedule	wt	M28A, Q30R	wt	VOX+VEL+SOF	YES
11	48,2	M	2	NO	6,6	No		10	23-apr-18	12	GP	Short duration				VOX+VEL+SOF	ongoing
12	79,7	F	1b	NO	21,8	No		1	17-set-18	1,4	GP	Short duration				GRZ+EBV 12W	ongoing
13	40,1	F		NO	6,3	No		8	19-dic-18	8	GP	Short duration				**No (Pregnancy)**	

UO Epatologia – AOUP

Reasons for short treatment duration

	Patients						Adverse Events detailed:
Treatment NOT completed	10	0,48%	due to	**Adverse Events**	**6**		
				HCC (sorafenib start)	1		Renal insuff: 2, Pruritus: 2, Iperbilirub. 1, Headache 1.
				NHL(disease progression)	1		
				Carceration	1		
				Pregnancy	1		

UO Epatologia – AOUP

RAS and treatment FAILURE

			Re-Treatment				NO
RAS/SP* Regions	**Failures**	% of Tot	FU12 available	SVR	%	Ongoing	Re-Treatm.
NS3	**2**	7,7%	**1**	1	100%	1	0
NS5A	**7**	26,9%	**6**	6	100%	2	0
NS5B	**0**	0,0%	**-**	-	-	-	-
NS3+NS5A	**12**	46,2%	**4**	4	100%	3	3
NS3+NS5A+NS5B	**2**	7,7%	**2**	2	100%	0	0
NS3+NS5B	**0**	0,0%	**-**	-	-	-	-
NS5A+NS5B	**2**	7,7%	**1**	1	100%	0	1
None	**2**	3,8%	**1**	1	100%	0	1
Tot. n. of Failures analysed	**27**	100,0%	**15**	15		6	6
% of Total Failures	81,8%						

34.6% RAS on single Target
53.9% RAS on **2 Targets**
7.7% RAS on 3 Targets

Failures with RAS

N	Age (y)	Gender	Genot	Pregressa Terapia P/R	Fibroscan	Ipertensione portale		Criterio AIFA	Start Date	weeks	Schedula	**Ragioni fallimento**	**NS3**	**NS5A**	**NS5B**	RE-TREATMNET	SVR12
1	68,8	F	1b	Partial Responder	12	Gastropatia congestizia		1	08-apr-15	12	SIM+SOF+RBV	RAS: NS5A e NS5B (?)	wt	L31M, Y93Y/H	C445F	VEL+SOF 12W	YES
2	51,8	M	1a	Non responder	39,1	F1		1	14-apr-15	12	SIM+SOF+RBV	RAS: NS3 e NS5A	N174S, D168V	M28V, 32S	wt	LDV+SOF 24W	YES
3	74,8	M	1b	Non responder	34,3	Gastropatia congestizia		1	08-mag-15	12	SIM+SOF+RBV	RAS: NS3	168A	wt	wt	VEL+SOF 12W	YES
4	68,1	F	1b	NO	75	F1		1	10-ago-15	24	LDV+SOF	RAS: NS5A e NS5B (?)	na	Y93H	559G	NO (Child C)	
5	80,4	M	1b	NO	12,3	F1		1	27-giu-16	24	LDV+SOF	RAS: NS3 e NS5A	S122T	R30HQ, Y93H	wt	**VOX+VEL+SOF**	YES
6	79,4	F	1b	NO	41	NO		1	20-ott-16	24	LDV+SOF	RAS: NS3 e NS5A	D168I	L28M, Y93H	wt	NO (Child C)	
7	66,8	F	4	NO	26,7	No		1	13-apr-17	12	LDV+SOF+RBV	RAS: NS5A	wt	I28M, R30S	wt	**VOX+VEL+SOF**	YES
8	53,9	M	1a	NO	22,8	Gastropatia congestizia		1	31-lug-17	12	VEL+SOF	RAS: NS5A	wt	Q30H, Y93R/H	wt	**VOX+VEL+SOF**	YES
9	82,0	M	1b	NO	na	na		1	07-set-17	12	GRZ+EBV	RAS: NS3 e NS5A	Y56H	Y93H	wt	NO (Child C)	
10	52,2	F	2c	NO	7,7	No		8	27-set-17	12	VEL+SOF	RAS: NS5A	D168G (sp)	F28C, R30K(sp)	wt	**VOX+VEL+SOF**	YES
11	52,2	M	3	NO	4,8	No		8	09-feb-18	12	VEL+SOF	RAS: NS3 e NS5A	A156P	A30K, Y93H	wt	**VOX+VEL+SOF+RBV**	ongoing
12	40,4	M	1a	NO	9,4	No		7	12-mar-18	12	VEL+SOF	RAS: NS3 e NS5A	D168T	Q30Q/K	wt	**VOX+VEL+SOF**	YES
13	80,3	F	1b	NO	14,9			1	16-mag-18	12	GRZ+EBV	RAS: NS3 e NS5A	V170I	L28M, Y93H	S556G	**VOX+VEL+SOF**	YES
14	53,0	M	3	NO	21,9			1	12-set-18	12	GP	RAS: sequencing ongoing				NO (D.O.)	
15	72,5	M	2	NO	5			8	26-ott-18	8	GP	RAS: NS5A	wt	F28C	wt	**VOX+VEL+SOF**	YES
16	73,4	M	1b	NO	9,4			7	03-dic-18	12	GRZ+EBV	RAS: NS3 e NS5A	S122N	L28M, Y93H	Y448N(sp)	**VOX+VEL+SOF**	YES
17	63,1	F	1b	NO	6,3			7	14-gen-19	12	GRZ+EBV	RAS: NS3 e NS5A	Y56H, D168A	L28M, Y93H	wt	tbd	
18	67,1	F	1b	NO	6,9	No		8	06-feb-19	12	GRZ+EBV	RAS: NS5A	S174T(sp)	L28M, Y93H	wt	**VOX+VEL+SOF**	ongoing
19	45,2	M	3	NO	73			1	23-apr-19	12	VEL+SOF	RAS: NS5A	wt	Y93H, A62S(sp)	wt	**VOX+VEL+SOF**	ongoing
20	46,7	M	3	NO	5,1			7	12-giu-19	12	VEL+SOF	RAS: sequencing ongoing				tbd	

Re-treatment of patients with previous DAAs failure

- **21** patients with previuous DAAs failure re-started treatment at 10.1.2020
- Treatment schedules were:

Ledipasvir+Sofosbuvir	**2**
Velpatasvir + Sofosbuvir	**3**
Velpatasvir + Voxilaprevir – Sofosbuvir	**15**
Grazoprevir+ Elbasvir	**1**

- SVR12 available for 16 → all responders

Italian real life experience of resistance guided retreatment in HCV infected patients who previously failed a NS5A inhibitor containing regimen

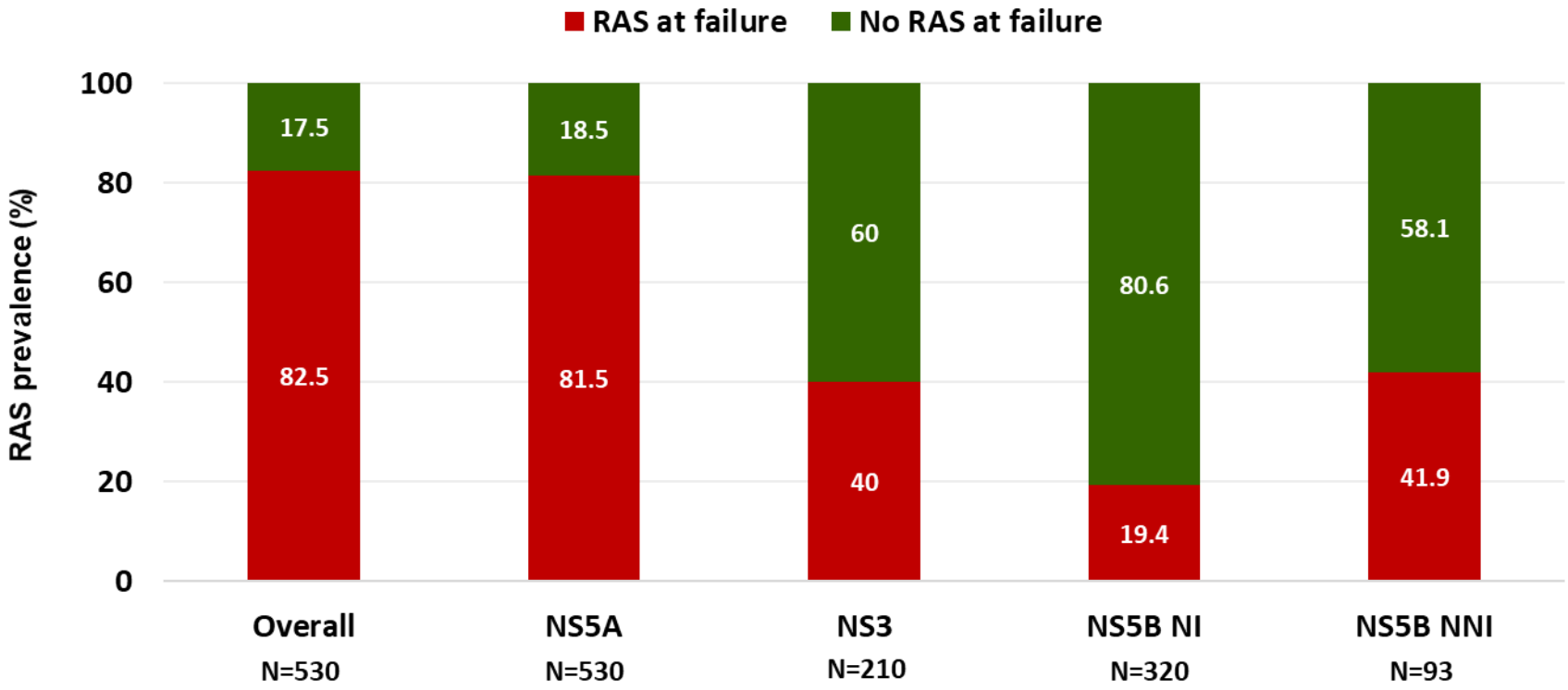
V.C. Di Maio, M. Aragri, C. Masetti, S. Paolucci, B. Bruzzone, E. Degasperi, S. Barbaliscia, T. Pollicino, C. Minichini, V. Calvaruso, M. Rendina, V. Cento, E. Teti, V. Micheli, V. Ghisetti, E. Polilli, V. Pace Palitti, S. Landonio, I. Lenci, S. Francioso, L. Donnarumma, L.A. Nicolini, A. Bertoli, M. Starace, C. Pasquazzi, A.P. Callegaro, F. Morisco, G. Cenderello, S. Marenco, R. Gulminetti, S. Novati, A. Scuteri, P. Andreone, S. Galli, A. Ciancio, V. Sangiovanni, N. Cuomo, A. Raddi, G. Morsica, H. Hasson, V. Borghi, I. Maida, M. Brunetto, P. Colombatto, R. Cozzolongo, A. De Santis, M. Lichtner, S. Babudieri, E. Biliotti, G. Taliani, T. Santantonio, M. Di Stefano, C. Paternoster, R. Ganga, M. Puoti, G. Rizzardini, A. Pellicelli, E. Milano, C. Mastroianni, A. Licata, F. Di Lorenzo, A. Giorgini, L. Sighinolfi, C. Dentone, A. Lleo, B. Rossetti, I. Beretta, P. Lampertico, G. Parruti, N. Coppola, G. Raimondo, M. Zazzi, M. Andreoni, M. Angelico, C.F. Perno, A. Craxì, **F. Ceccherini-Silberstein**[#]

[#]on behalf of HCV Virology Italian Resistance Network (Vironet C)

530 failures following 7 different NS5A inhibitor containing regimens were studied

17.5% (93/530) of DAA failing patients did not show RAS at failure

RAS prevalence was found in all genes tested: **NS5A** very frequent (**81.5%**), **NS3** frequent (**40.0%**), **NS5B** less common (**41.9%** NNI and **19.4%** NI)



RAS, resistance associated substitutions; NNI Non-Nucleoside Inhibitor; NI, Nucleotide inhibitor

36.8% (195/530) NS5A failing patients showed RASs on ≥2 DAA-targets at failure

136 patients with retreatment after a NS5A inhibitor containing regimen failure

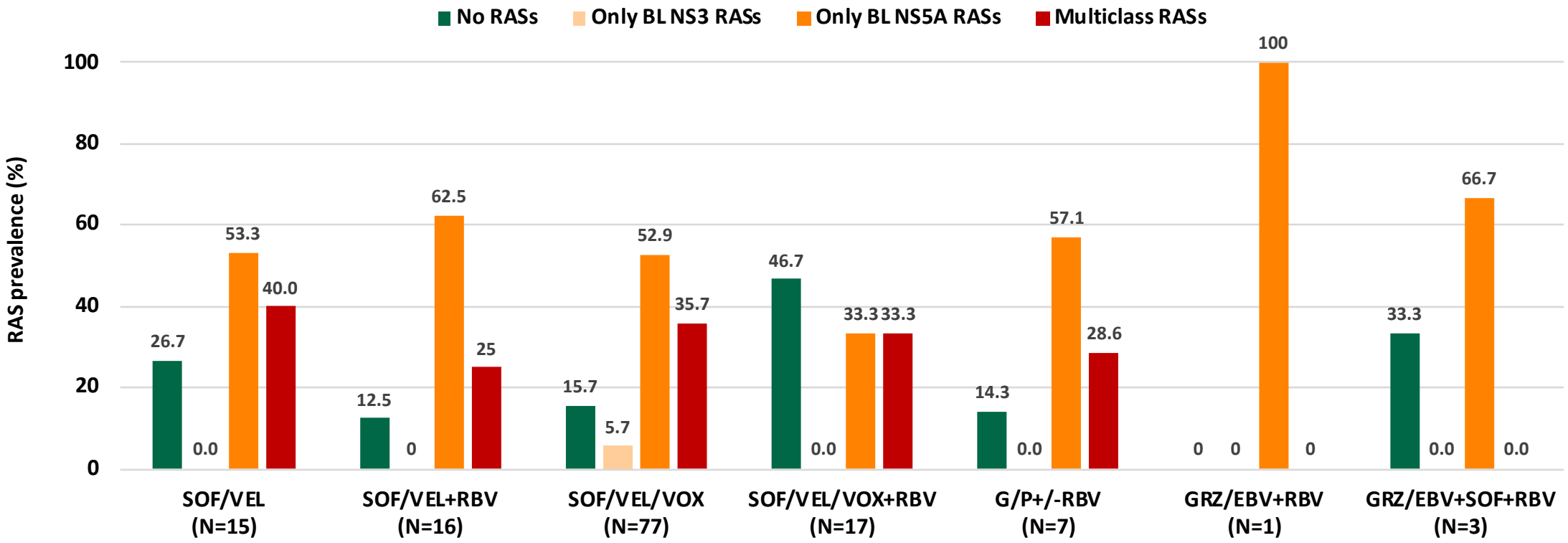
	Patients, N	136
	Males, N(%)	98 (72.0)
	Age (years), Median (IQR)	58 (50-65)
HCV geno/subtype	**1a**	**35 (25.7)**
	1b	**44 (32.5)**
	2a/c	13 (9.5)
	3a/b/g	**31 (22.8)**
	4a/d/n/o	13 (9.5)
	HCC, N (%)*	7 (6.8)
	HIV coinfection, N (%)*	12 (10.7)
	Cirrhosis, N (%)*	**61 (45.2)**
	IFN experience, N (%)*	35 (48.6)
Prior DAA experience	**2D**	1 (0.7)
	3D+/-RBV	28 (20.6)
	GRZ/EBV	19 (14.0)
	G/P	14 (10.3)
	SOF/LDV+/-RBV	37 (27.2)
	DCV+SOF+/-RBV	27 (19.8)
	SOF/VEL+/-RBV	10 (7.4)
	Baseline HCV-RNA (logIU/ml), Median (IQR)	6.0 (5.6-6.4)

2D, paritaprevir/ritonavir, ombitasvir; 3D, paritaprevir/ritonavir, ombitasvir and dasabuvir; DAA, direct-acting antiviral;
HCC, hepatocellular carcinoma; IQR, interquartile range; IU, international units; *values were calculated according to the information available

Overall, **at baseline** of retreatment 108/136 (**79.4%**) patients showed **at least 1 HCV RAS**

No RASs: in 28/136 failures (**20.6%**)

- At least 1 NS5A RAS: in 105/136 failures (77.2%)
- At least 1 NS3 RAS: in 31/136 failures (22.8%)
- At least 1 NS5B RAS: in 37/136 failures (27.2%)
- **Multiple class RASs: in 48/136 failures (35.3%)**



SOF/VEL sofosbuvir/velpatasvir; RBV, ribavirin; VOX, voxilaprevir; G/P, glecaprevir/pibrentasvir; GRZ/EBV, grazoprevir/elbasvir

56/136 (**41.2%**) **patients** were fully **susceptible** to the **retreatment** regimen chosen

Patients with complex resistance profile (N=16) where retreated with a combination of 3 DAAs +/- RBV

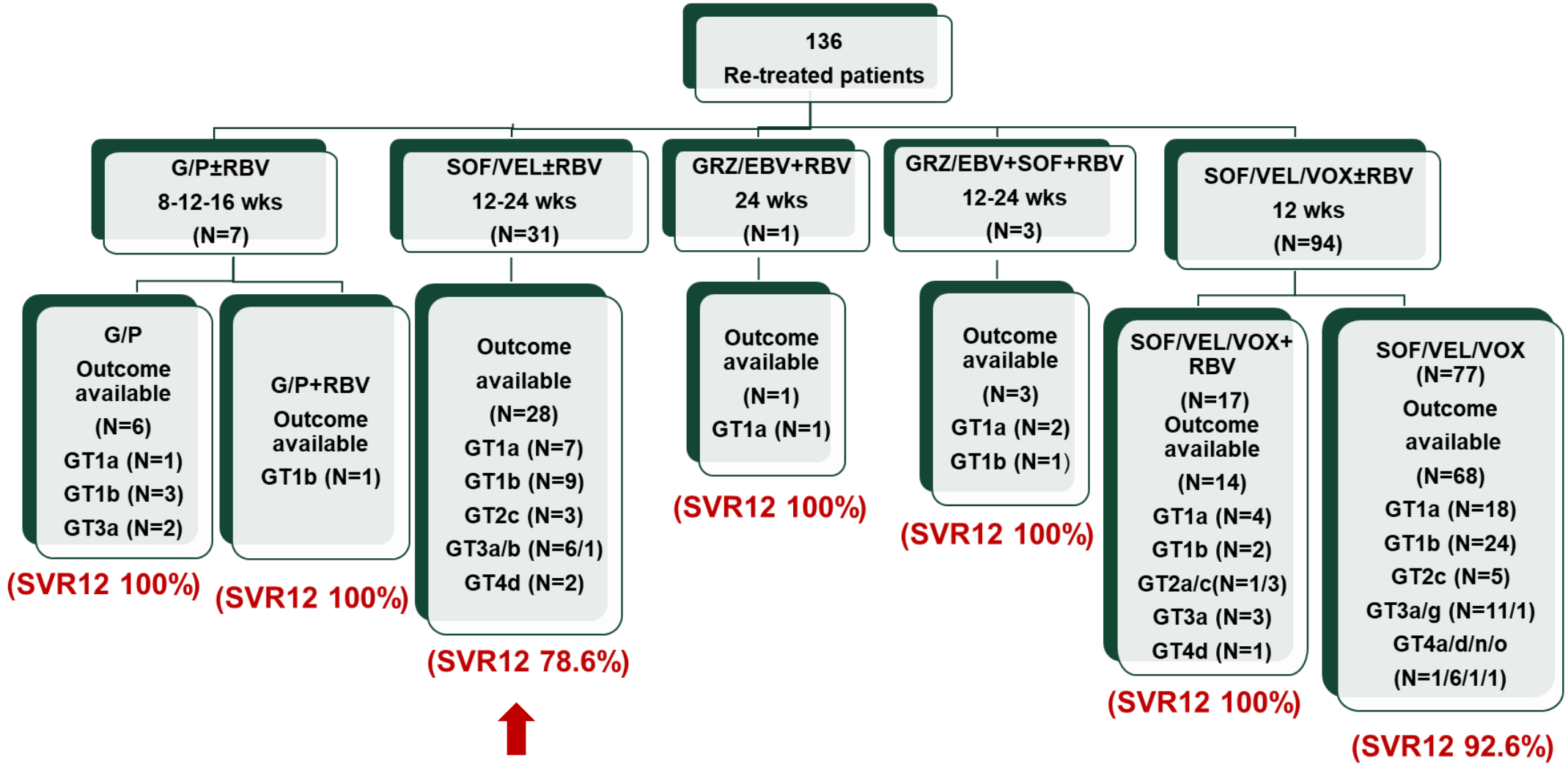
Retreatment regimen	Level of Resistance according to resistance test	HCV genotype/subtype											TOT
		1a	1b	2a	2c	3a	3b	3g	4a	4d	4n	4o	
G/P±RBV (N=7)	Full susceptibility		4/4 (100)			2/2 (100)							**6/7 (85.7)**
	Reduced susceptibility	1/1 (100)											1/7 (14.3)
	1 DAA resistant												
	≥2 DAA resistant												
GRZ/EBV+RBV (N=1)	Full susceptibility												
	Reduced susceptibility												
	1 DAA resistant	1/1 (100)											1/1 (100)
	≥2 DAA resistant												
GRZ/EBV+SOF+RBV (N=3)	Full susceptibility	1/2 (50.0)	1/1 (100)										**2/3 (66.7)**
	Reduced susceptibility	1/2 (50.0)											1/3 (33.3)
	1 DAA resistant												
	≥2 DAA resistant												
SOF/VEL/VOX±RBV (N=94)	Full susceptibility	10/24 (41.7)	7/30 (23.3)	1/1 (100)	9/9 (100)	2/18 (11.1)			1/1(100)	6/8 (75.0)	1/1(100)	1/1(100)	**38/94 (40.5)**
	Reduced susceptibility	5/24 (20.8)				2/18 (11.1)		1/1 (100)					8/94 (8.5)
	1 DAA resistant	6/24 (25.0)	11/30 (36.7)			14/18 (77.8)				1/8 (12.5)			32/94 (34.0)
	≥2 DAA resistant	3/24 (12.5)	12/30 (40.0)							1/8 (12.5)			16/94 (17.0)
VEL/SOF±RBV (N=31)	Full susceptibility	1/7 (14.3)	2/9 (22.2)		3/3 (100)	2/9 (22.2)				2/2 (100)			**10/31 (32.3)**
	Reduced susceptibility	5/7 (71.4)	7/9 (77.8)										12/31 (38.7)
	1 DAA resistant	1/7 (14.3)				7/9 (77.8)	1 (100)						9/31 (29.0)
	≥2 DAA resistant												

Sorbo MC et al, 2018; Geno2pheno: https://hcv.geno2pheno.org/

No RASs: 20.6% At least one NS5A RAS: 77.2% Multiple class RASs: 35.3%

Overall **SVR12** in 110/121 (**90.9%**) patients completing post retreatment follow-up

- **86%** (48/56) SVR in **cirrhotic** patients
- **different SVR** according to **GT**: **85% GT1a**, 92% GT1b, 92% GT2, 95% GT3, 91% GT4



SOF/VEL/VOX Retreatment: previous DAA combination treatments and HCV genotype

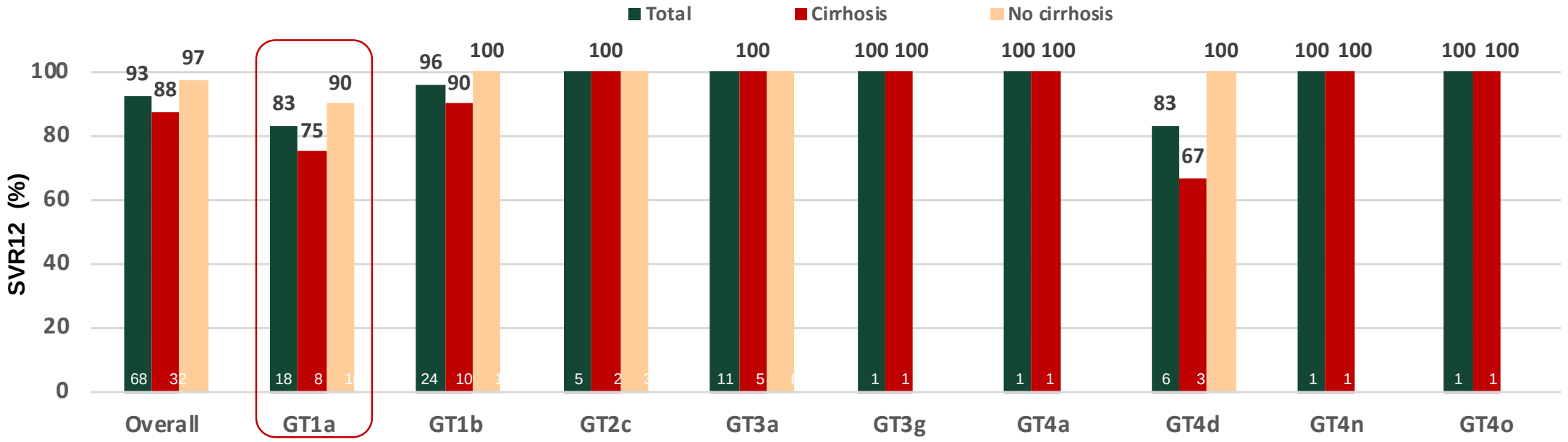
SOF/VEL/VOX +RBV 12 weeks (14 pts): SVR12 100%

Previous DAA regimen	Overall (N=14)	GT1a (N=4)	GT1b (N=2)	GT2a (N=1)	GT2c (N=3)	GT3a (N=3)	GT4d (N=1)
3D	2 (14.3)	1 (25.0)	1 (50.0)				
DCV+SOF+RBV	1 (7.1)					1 (33.3)	
G/P	5 (35.7)	1 (25.0)		1 (100)	3 (100)		
GRZ/EBV	1 (7.1)		1 (50.0)				
SOF/LDV	3 (21.4)	1 (25.0)				1 (33.3)	1 (100)
SOF/LDV+RBV	1 (7.1)	1 (25.0)					
SOF/VEL+RBV	1 (7.1)					1 (33.3)	

SOF/VEL/VOX 12 weeks (68 pts): SVR 12 92.6%

Previous DAA regimen	Overall (N=68)	GT1a (N=18)	GT1b (N=24)	GT2c (N=5)	GT3a (N=11)	GT3g (N=1)	GT4a (N=1)	GT4d (N=6)	GT4n (N=1)	GT4o (N=1)
2D	1 (1.5)								1 (100)	
3D	8 (11.8)	5 (27.8)	3 (12.5)							
3D+RBV	5 (7.4)	4 (22.2)	1 (4.2)							
DCV+SOF	7 (10.3)		1 (4.2)	1 (20.0)	4 (36.4)					1 (100)
DCV+SOF+RBV	3 (4.4)			1 (20.0)	2 (18.2)					
G/P	6 (8.8)	1 (5.6)		3 (60.0)	2 (18.2)					
GRZ/EBV	14 (20.6)	3 (16.7)	10 (41.7)					1 (16.7)		
SOF/LDV	16 (23.5)	3 (16.7)	8 (33.3)				1 (100)	4 (66.7)		
SOF/LDV+RBV	1 (1.5)							1 (16.7)		
SOF/VEL	7 (10.3)	2 (11.1)	1 (4.2)		3 (27.3)	1 (100)				

SVR12 was 88% (28/32) in **cirrhotic** patients **vs 97%** (35/36) in **non-cirrhotic** patients **(p = 0.17)**



11/121 patients failed retreatment: 5 with SOF/VEL/VOX and 6 with SOF/VEL±RBV

72.7 % were cirrhotic – 63.6 % showed BL NS5A RASs - 18.2 % showed no BL RASs

ID	Gender	Cirrhosis	GT	Regimen failed	RASs at failure (Baseline of re-treatment)			Retreatment	Week	Outcome	RASs at failure of re-treatment		
					NS3	NS5A	NS5B				NS3	NS5A	NS5B
933*	M	Yes	1a	LDV/SOF+RBV	Q80K	Q30K/Q+A92A/T+ Y93H/Y	WT	SOF/VEL+RBV	24	relapser	Q80K	Q30K+ **L31L/M+** A92A/T+ Y93H/Y	WT
1641	M	Yes	1a	LDV/SOF	WT	L31M	WT	SOF/VEL+RBV	24	non responder	WT	**L31V**	WT
2649	F	No	1b	3D	Y56H+ D168V	Y93H	L159F+ C316N	SOF/VEL	12	relapser	n.a.	n.a.	n.a.
2669	M	Yes	1b	LDV/SOF+RBV	WT	L31I+ Y93H	L159F+ C316N	SOF/VEL+RBV	24	relapser	n.a.	n.a.	n.a.
1111	M	No	2c	DCV+SOF	WT	WT	WT	SOF/VEL	12	non responder	n.a.	n.a.	n.a.
3767**	M	Yes	3a	DCV+SOF	WT	Y93H	WT	SOF/VEL+RBV	24	relapser	WT	Y93H	WT
341	F	Yes	1b	3D+RBV	WT	WT	WT	SOF/VEL/VOX	12	non responder	WT	WT	WT
352	M	Yes	1a	LDV/SOF	WT	Q30R+ L31M	WT	SOF/VEL/VOX	12	relapser	WT	Q30R+ L31M	WT
4004	F	Yes	1a	LDV/SOF	Q80K	WT	WT	SOF/VEL/VOX	12	relapser	Q80K	WT	WT
663	M	Yes	4d	LDV/SOF+RBV	D168V	M31V+ Y93H	WT	SOF/VEL/VOX	12	relapser	D168V+ **A156S**	M31V+ Y93H	WT
4009	M	No	1a	SOF/VEL	Q80K	WT	WT	SOF/VEL/VOX	12	relapser	Q80K	WT	WT

W, weeks; WT, wild type; n.a., not available *This patient was then re-treated with 3D+SOF+RBV for 12 weeks and achieved SVR

**This patient was then re-treated with SOF/VEL/VOX+RBV for 12 weeks and achieved SVR

11/121 patients failed retreatment: 5 with SOF/VEL/VOX and 6 with SOF/VEL±RBV

72.7 % were cirrhotic – 63.6 % showed BL NS5A RASs - 18.2 % showed no BL RASs

ID	Gender	Cirrhosis	GT	Regimen failed	RASs at failure (Baseline of re-treatment)			Retreatment	Week	Outcome	RASs at failure of re-treatment		
					NS3	NS5A	NS5B				NS3	NS5A	NS5B
933*	M	Yes	1a	LDV/SOF+RBV	Q80K	Q30K/Q+A92A/T+ Y93H/Y	WT	SOF/VEL+RBV	24	relapser	Q80K	Q30K+ **L31L/M+** A92A/T+ Y93H/Y	WT
1641	M	Yes	1a	LDV/SOF	WT	L31M	WT	SOF/VEL+RBV	24	non responder	WT	**L31V**	WT
2649	F	No	1b	3D	Y56H+ D168V	Y93H	L159F+ C316N	SOF/VEL	12	relapser	n.a.	n.a.	n.a.
2669	M	Yes	1b	LDV/SOF+RBV	WT	L31I+ Y93H	L159F+ C316N	SOF/VEL+RBV	24	relapser	n.a.	n.a.	n.a.
1111	M	No	2c	DCV+SOF	WT	WT	WT	SOF/VEL	12	non responder	n.a.	n.a.	n.a.
3767**	M	Yes	3a	DCV+SOF	WT	Y93H	WT	SOF/VEL+RBV	24	relapser	WT	Y93H	WT
341	F	Yes	1b	3D+RBV	WT	WT	WT	SOF/VEL/VOX	12	non responder	WT	WT	WT
352	M	Yes	1a	LDV/SOF	WT	Q30R+ L31M	WT	SOF/VEL/VOX	12	relapser	WT	Q30R+ L31M	WT
4004	F	Yes	1a	LDV/SOF	Q80K	WT	WT	SOF/VEL/VOX	12	relapser	Q80K	WT	WT
663	M	Yes	4d	LDV/SOF+RBV	D168V	M31V+ Y93H	WT	SOF/VEL/VOX	12	relapser	D168V+ **A156S**	M31V+ Y93H	WT
4009	M	No	1a	SOF/VEL	Q80K	WT	WT	SOF/VEL/VOX	12	relapser	Q80K	WT	WT

W, weeks; WT, wild type; n.a., not available *This patient was then re-treated with 3D+SOF+RBV for 12 weeks and achieved SVR

**This patient was then re-treated with SOF/VEL/VOX+RBV for 12 weeks and achieved SVR

12 or 16 w.of G/P ± RBV in GT-1 patients with failure to NS5A+SOF± RBV

Virologic Failures – On-treatment virologic failure (n=6)

Arm	Prior Tx & days since exp	Response	NS3 RAS		NS5A RAS	
			Baseline	Failure	Baseline	Failure
No cirr G/P 12 wk	LDV/SOF 470	BT	none	R155W+A156G	Q30N+Y93H	M28T+Q30N+Y93H
No cirr G/P 12 wk	LDV/SOF 711	BT	none	A156V (21%)	Q30R+L31M	Q30R+L31M+H58D
No cirr G/P 16 wk	LDV/SOF 210	BT	none	A156V (90%) A156V+D168E (10%)	Q30R+L31M+H58D	Q30R+L31M+H58D
Cirr, G/P+ RBV 12 wk	LDV/SOF 425	BT	none	A156V	M28T+Q30R (28%) Q30R (14%)	M28T+Q30R+H58D
Cirr, G/P+ RBV 12 wk	LDV/SOF 580	BT	none	R155W+A156G	Q30H+L31M+Y93H	Q30H+L31M+Y93H
Cirr, G/P+ RBV 12 wk	LDV/SOF 684	BT	none	none	L31M	L31M+P32-del

All RAS are >95% abundance unless specified; "+" = RAS linkage; RED = Treatment Emerging RAS
Cirr, cirrhosis; REL, relapse; Tx, treatment; exp, exposure

The complexity of viral quasispecies increases with retreatment

Virologic Failures – Relapse (n=7) or re-infection(n=1)

Arm	Prior Tx & days since exp	Response	NS3 RAS		NS5A RAS	
			Baseline	Failure	Baseline	Failure
No cirr G/P 12 wk	LDV/SOF 936	REL	none	none	Y93N	L31M+Y93N
No cirr G/P 12 wk	VEL/SOF 284	REL	none	none	Q30H+Y93H	Q30H+L31V+Y93H (60%) Q30N+Y93H (40%)
No cirr G/P 12 wk	LDV/SOF 788	REL	none	S122G*	none	none
No cirr G/P 12 wk	LDV/SOF 861	REL	R155K	R155K	Q30E	Q30E+H58D
No cirr G/P 16 wk	DCV/SOF 180	REL	none	A156T (3%)	M28V+Q30R+L31V	M28A+Q30R+L31V
No cirr G/P 16 wk	LDV/SOF 958	REL	none	none	M28T+Q30R	M28S+Q30R
Cirr G/P16 wk	LDV/SOF 912	REL	none	A156V (4%)	Y93N	H58D+Y93N
No cirr G/P 12 wk	LDV/SOF 325	Reinfection	none	none	none	none

Cirr, cirrhosis; REL, relapse; Tx, treatment; exp, exposure; *no change with S122G in EC50 for glecaprevir
All RAS are >95% abundance unless specified; "+" = RAS linkage; RED = Treatment Emerging RAS

Sulkowski MS et al AASLD 2018

11/121 patients failed retreatment: 5 with SOF/VEL/VOX and 6 with SOF/VEL±RBV

72.7 % were cirrhotic – 63.6 % showed BL NS5A RASs - 18.2 % showed no BL RASs

ID	Gender	Cirrhosis	GT	Regimen failed	RASs at failure (Baseline of re-treatment)			Retreatment	Week	Outcome	RASs at failure of re-treatment		
					NS3	NS5A	NS5B				NS3	NS5A	NS5B
933*	M	Yes	1a	LDV/SOF+RBV	Q80K	Q30K/Q+A92A/T+ Y93H/Y	WT	SOF/VEL+RBV	24	relapser	Q80K	Q30K+ **L31L/M+** A92A/T+ Y93H/Y	WT
1641	M	Yes	1a	LDV/SOF	WT	L31M	WT	SOF/VEL+RBV	24	non responder	WT	**L31V**	WT
2649	F	No	1b	3D	Y56H+ D168V	Y93H	L159F+ C316N	SOF/VEL	12	relapser	n.a.	n.a.	n.a.
2669	M	Yes	1b	LDV/SOF+RBV	WT	L31I+ Y93H	L159F+ C316N	SOF/VEL+RBV	24	relapser	n.a.	n.a.	n.a.
1111	**M**	**No**	**2c**	**DCV+SOF**	**WT**	**WT**	**WT**	**SOF/VEL**	**12**	**non responder**	**n.a.**	**n.a.**	**n.a.**
3767**	M	Yes	3a	DCV+SOF	WT	Y93H	WT	SOF/VEL+RBV	24	relapser	WT	Y93H	WT
341	**F**	**Yes**	**1b**	**3D+RBV**	**WT**	**WT**	**WT**	**SOF/VEL/VOX**	**12**	**non responder**	**WT**	**WT**	**WT**
352	M	Yes	1a	LDV/SOF	WT	Q30R+ L31M	WT	SOF/VEL/VOX	12	relapser	WT	Q30R+ L31M	WT
4004	F	Yes	1a	LDV/SOF	Q80K	WT	WT	SOF/VEL/VOX	12	relapser	Q80K	WT	WT
663	M	Yes	4d	LDV/SOF+RBV	D168V	M31V+ Y93H	WT	SOF/VEL/VOX	12	relapser	D168V+ **A156S**	M31V+ Y93H	WT
4009	M	No	1a	SOF/VEL	Q80K	WT	WT	SOF/VEL/VOX	12	relapser	Q80K	WT	WT

W, weeks; WT, wild type; n.a., not available *This patient was then re-treated with 3D+SOF+RBV for 12 weeks and achieved SVR

**This patient was then re-treated with SOF/VEL/VOX+RBV for 12 weeks and achieved SVR

Conclusions

- In this Italian real-life experience, NS5A-RASs were frequently detected in NS5A-failing patients, and multiclass-resistance was about 30%.
- The type and resistance level varied according to regimen and HCV-genotype/subtype.
- Overall, after resistance test guided retreatment SVR was >90%, with the exception of the sofosbuvir/velpatasvir retreatment.
- Our results show how the HCV genotypic resistance test after treatment failure can help to optimize the retreatment strategy.

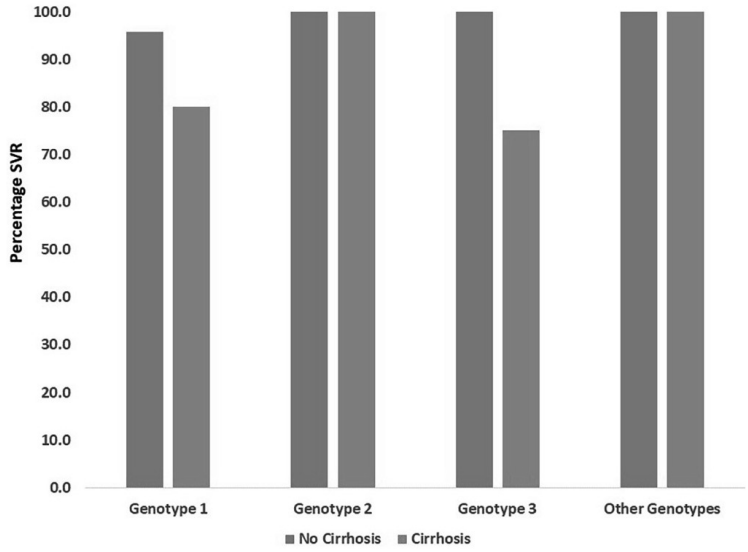
Real-World Effectiveness of SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR as a Hepatitis C Virus Infection Salvage Treatment

Mel Krajden et al University of British Columbia

- The effectiveness of SOF/VEL/VOX in treating treatment experienced patients with HCV genotype 1 (GT1) to genotype 6 (GT6) infection was studied in **146 Canadian patients**.
- Overall, 120 people treated with SOF/VEL/VOX and 26 with S/V/V + RBV
- **58.9%** were **GT1**, **26% GT3 and 9.6% GT2**
- 41.1% of patients had received sofosbuvir/ledpisavir, 15.8% sofosbuvir+ ribavirin and 11.64% sofosbuvir/velpatasvir. **52.7%** of pts received a **previous NS5A** containing regimen

- The **overall SVR** with SOF/VEL/VOX treatment was **95%** (139/146).
- SVR for **GT1**, **GT2** and **GT3** was **93.0%, 100%,** and **97.4%**, respectively.
- SVR for patients with **cirrhosis 83.3%** vs 97.5% in non cirrhotics P=0.003.
- **SVR** was also **lower** for those with diagnosed problematic **alcohol use** (88.9% vs 97.3%, *P*=0.04).
- SVR rates were lower among those with cirrhosis than those without cirrhosis in NS5B polymerase inhibitor (81.8% vs 96.5%), NS5A inhibitors (78.9% vs 96.1%) and those without cirrhosis in NS3/4A protease inhibitors (88.2%) experienced patients.

- **Conclusion:** In this real-world cohort of patients with virological failure after prior DAA treatments, retreatment with SOF/VEL/VOX results in SVR rates of more than 90% across all genotypes; however, underlying cirrhosis and diagnosed problematic alcohol use reduces, cure rates by about 10% to 15%.



Patients with cirrhosis infected by Gt 1 and 3 or previously treated with NS5A containing regimens with cirrhosis showed a lower SVR rate

Safety and Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir -Based Regimens for the Treatment of HCV Genotype 1-6: Results of the HCV-Target Cohort

Stefan Zeuzem et al,University Hospital Frankfurt, and USA

- We report real-world safety and efficacy of SOF/VEL/VOX in HCV-TARGET participants [academic (n=45) and community medical centers (n=19) in North America (n=60) and Europe (n=4)].

- **128 patients** were treated with SOF/VEL/VOX+/-RBV of whom 99.2% were treatment experienced and **94%** were **NS5A experienced**

- Amongst the patients with available SVR data, **overall SVR12 is 90.8%** (GT1 92.1%, GT2 100%, **GT3 85.7%**).
- SVR12 in Per Protocol population (patients with virological outcome excluding those who discontinued early for non-virological reasons) overall is **93%** and **92% in NS5A experienced** patients.

- SOF/VEL/VOX-based regimens in this real-world cohort show overall high efficacy (91% SVR, 93% Per Protocol SVR). SOF/VEL/VOX has been used exclusively in treatment experienced patients with predominantly GT1 followed by GT3 infected patients. **Nine of 10 patients experiencing treatment failure to date were GT1a or 3a**. Safety and virologic results for all 128 patients will be presented.

Table 1: Patient characteristics

	SOF/VEL/VOX+/- RBV	
All	128	100.0%
Male	101	79%
Black	32	25%
Co-administered with RBV	14	11%
GT1	91	71%
GT3	30	23%
GT2/Other	5/2	4%/2%
Cirrhosis	48	38%
Prior history of hepatic decompensation	14	11%
Treatment experienced	127	99%
NS5A Prior failure	120	94%
Patients with On-treatment Adverse Event(s)	62	48%
Patients with SAEs (none treatment related)	4	3%
Disposition		
Started treatment	128	100%
Completed full treatment	117	91%
Discontinued prematurely	5	4%
Lost to follow up	6	4%
OUTCOMES		
Virological outcome available	109	85%
SVR12 (excludes lost to FU)	99/109	91%
SVR12 Per Protocol (excludes early discont. For non-virological reasons)	98/106	93%
Overall SVR12 in NS5A failures (Per protocol population)	90/98	92%
Relapse; Non-response	7; 3	6%; 3%

Real-Life Effectiveness and Safety of Sofosbuvir/Velpatasvir/Voxilaprevir for Chronic Hepatitis C Patients With Prior DAA Failure: Final Results of the Navigatore Network

Elisabetta Degasperi et al., Policlinico Milano

- All consecutive HCV patients receiving SOF/VEL/VOX between May-October 2018 in 27 centers in Northern Italy were enrolled.

- **179 patients** were included: Fibrosis stage was F0-F2 in 32%, F3 in 21%, **F4 in 44%.**
- HCV genotype was 1 in 58% (1b 33%, 1a 24%, 1nc 1%), 2 in 10%, 3 in 23% and 4 in 9%;
- **82% of patients carried resistance** associated substitutions (RAS) in the NS3, NS5A or NS5B regions.
- Patients received SOF/VEL/VOX for 12 weeks, RBV was added in 22% of treatment schedules.

- Undetectable HCV-RNA was achieved by 74% of patients at week 4 and by 99% at week 12.
- Overall, **98% patients** achieved the **SVR4** and **96%** the **SVR12**;
- **Cirrhosis** (p=0.005) and **detectable HCV-RNA at treatment week 4** (p=0.04) were associated with **treatment failure**.

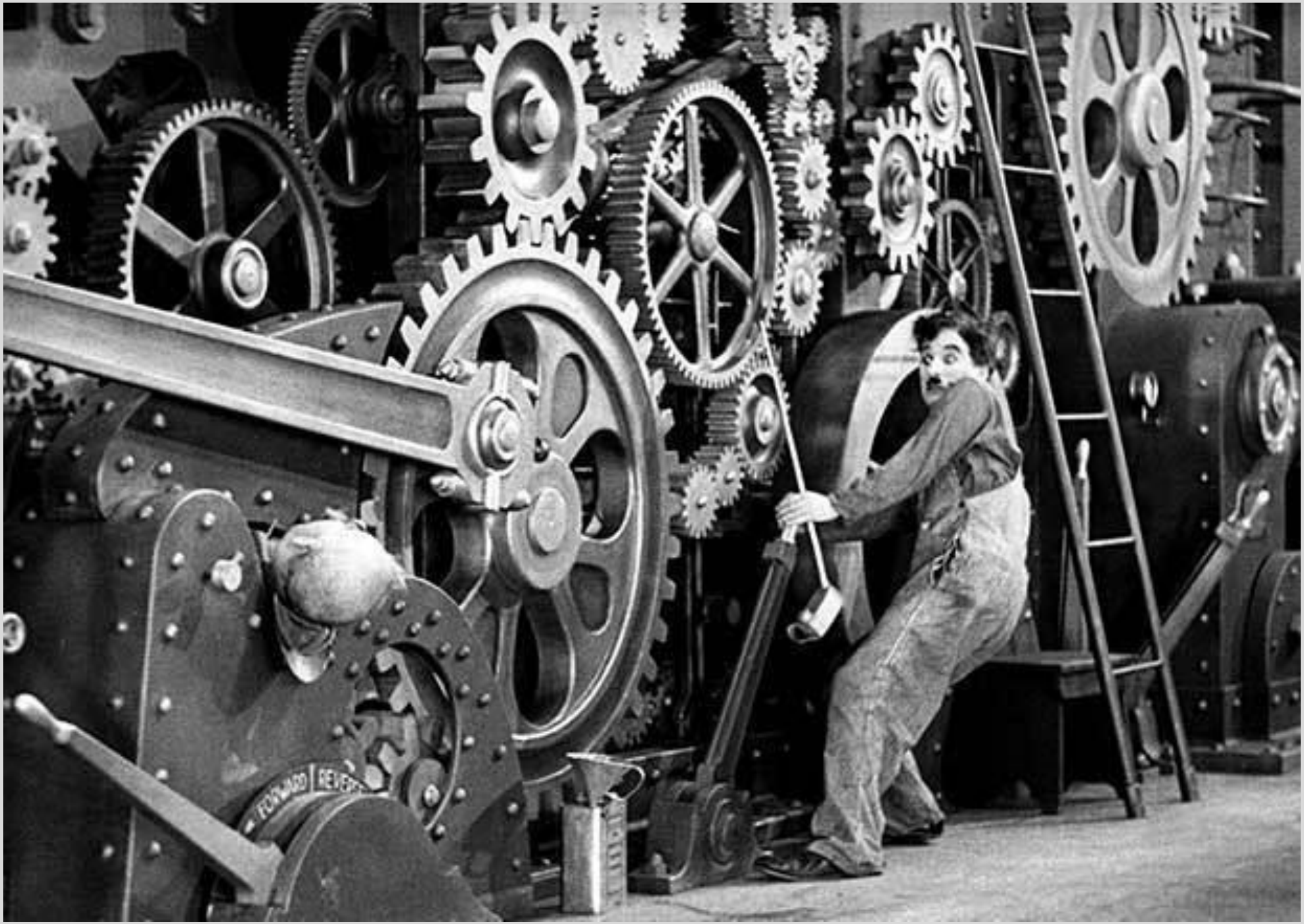
JOURNAL
OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2018☆

European Association for the Study of the Liver*

Recommendations

- Patients who failed after pegylated IFN-α and ribavirin, pegylated IFN-α, ribavirin and sofosbuvir, or sofosbuvir and ribavirin combination treatment must be retreated according to the above recommendations for "treatment-experienced" patients, by HCV genotype (**A1**).
- HCV resistance testing prior to retreatment in patients who failed after any of the DAA-containing treatment regimens is useful to guide retreatment by probabilities of response, according to the resistance profile observed in the context of a multidisciplinary team including experienced treaters and virologists (**B2**).
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen should be retreated with the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks, ideally in the context of a multidisciplinary team including experienced treaters and virologists (**A1**).
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen and have predictors of lower response (advanced liver disease, multiple courses of DAA-based treatment, complex NS5A RAS profile) can be retreated with the combination of sofosbuvir plus the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks, based on an individual decision in the context of a multidisciplinary team including experienced treaters and virologists (**B2**).
- In very difficult-to-cure patients (patients with NS5A RASs who failed twice to achieve SVR after a combination regimen including a protease and/or an NS5A inhibitor), the triple combination of sofosbuvir, velpatasvir and voxilaprevir, or the triple combination of sofosbuvir, glecaprevir and pibrentasvir can be administered for 12 weeks with weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) and/or treatment duration can be prolonged to 16 to 24 weeks, based on an individual decision in the context of a multidisciplinary team including experienced treaters and virologists (**C2**).
- Patients with decompensated (Child-Pugh B or C) cirrhosis who failed after a DAA (protease inhibitor and/or NS5A inhibitor)-containing regimen have a contraindication for the use of protease inhibitors, and should therefore be retreated with the fixed-dose combination of sofosbuvir and velpatasvir with weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks, based on an individual decision in the context of a multidisciplinary team including experienced treaters and virologists (**B2**).


FORWARD

Hepatology Unit
University Hospital of Pisa, Italy

Barbara Coco
Piero Colombatto
Filippo Oliveri
Veronica Romagnoli
Antonio Salvati
Gabriele Ricco
Lidia Surace
Patriza Bleve

Antonella Cristofani
Simonetta Ferretti (part-time)
Simona Giannetti
Teresa Crisponi
Barbara Zucchelli
Raffaele Apuzzo

Nurses

Medical Doctors

Administrative Personel

Arianna Del Chicca

Bio-Physics

Luigi Civitano
Ranieri Bizzarri

Biologists

Daniela Cavallone
Francesco Moriconi

INNOVATIVE MODEL OF PERSONALIZED CARE

Ferruccio Bonino
UPMC Institute for Health
Chianciano