Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

Massimo Puoti
Marco Merli
Infectious Diseases Dept
ASST GRANDE OSPEDALE
METROPOLITANO NIGUARDA
MILANO

HCV: dove siamo
le ultime evidenze dai congressi internazionali

Convegno Internazionale
GIORNATE INFETTIVOLOGICHE "LUIGI SACCO" 2019
MILANO, 28-29 MAGGIO 2019
OSPEDALE LUIGI SACCO POLO UNIVERSITARIO – ASST FATEBENEFRATELLI SACCO
AULA MAGNA POLO LITA

Le ultime evidenze dei congressi

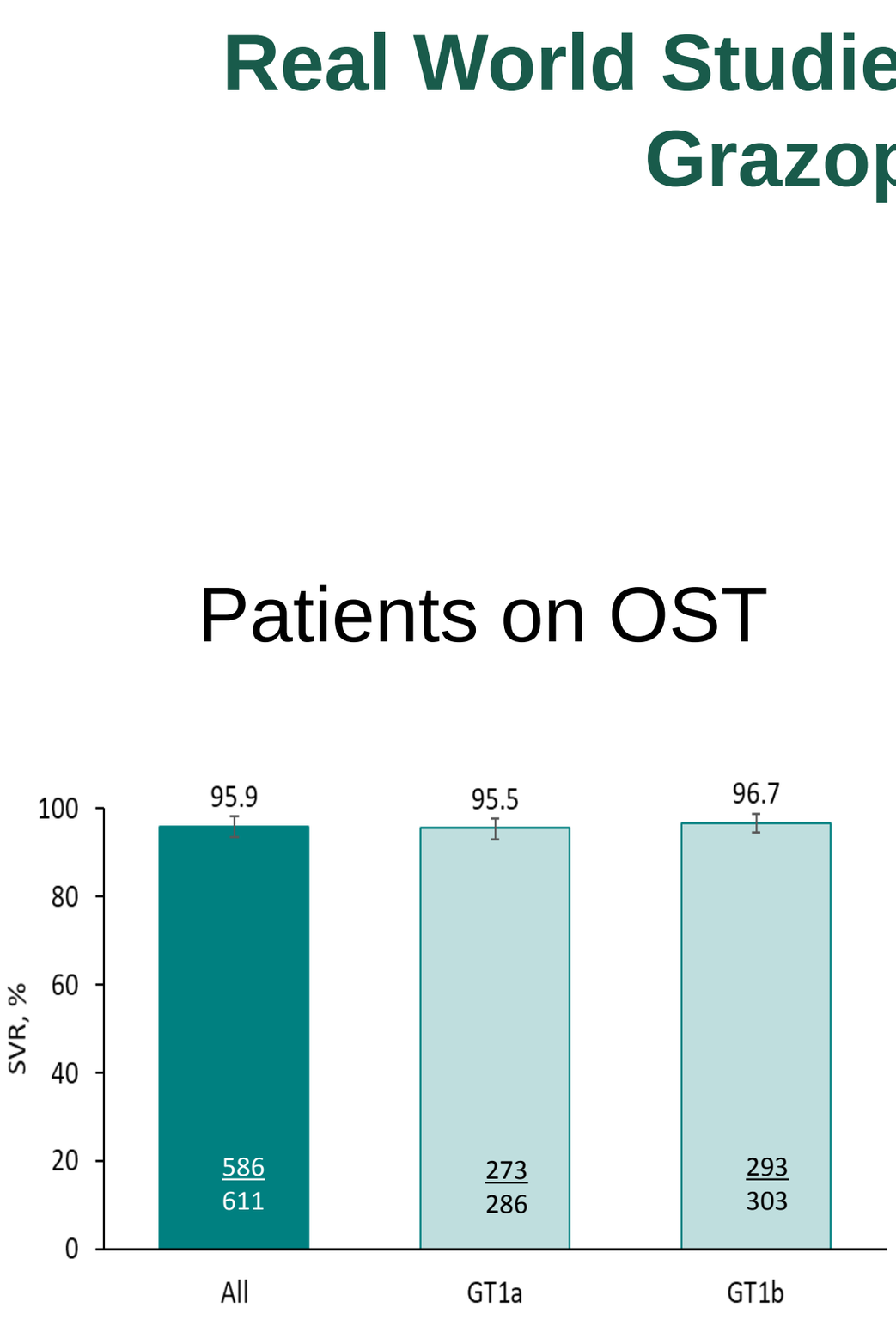
- Dati Real life
- Due opzioni nella pratica clinica
- Ottimizzazione: meglio meno visite ?
- Off label: corto è bello ?
- Eterogeneità virale: ha un ruolo nell’epoca della taglia unica pangenotipica

Le ultime evidenze dei congressi

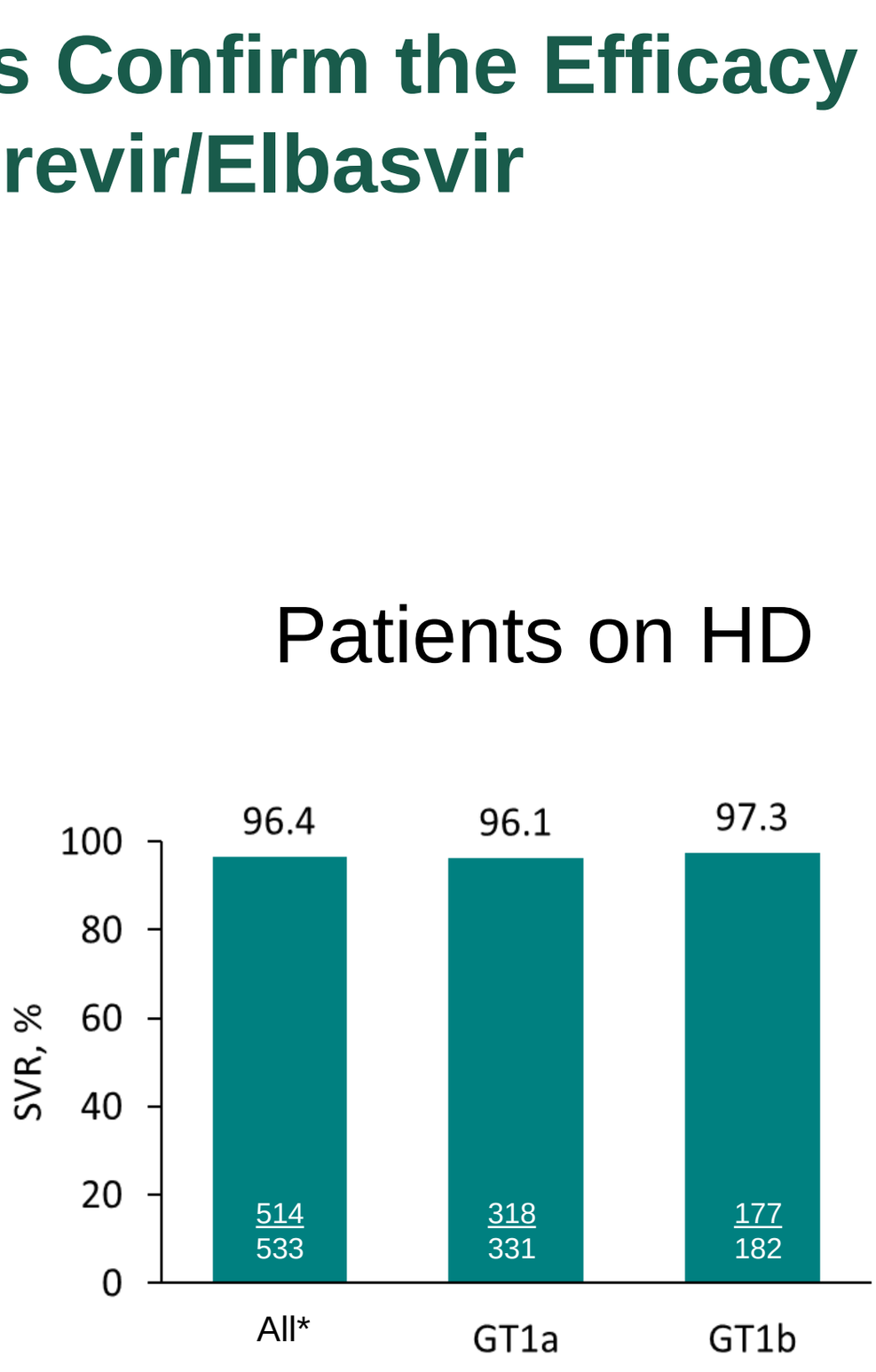
- Dati Real life
- Due opzioni nella pratica clinica
- Ottimizzazione: meglio meno visite ?
- Off label: corto è bello ?
- Eterogeneità virale: ha un ruolo nell’epoca della taglia unica pangenotipica

Real World Studies Confirm the Efficacy of Grazoprevir/Elbasvir

Patients on OST



Patients on HD



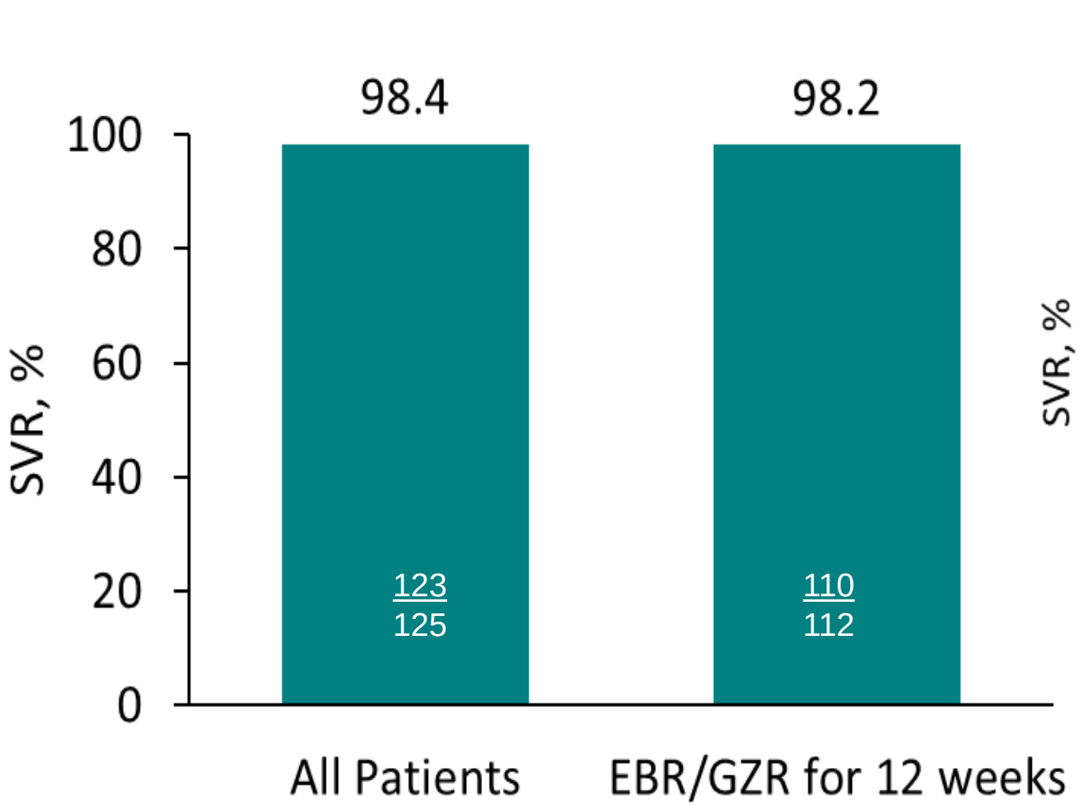
*Includes 9 patients with HCV GT1a/1b mixed infection and 11 patients with unknown HCV GT1 subtype

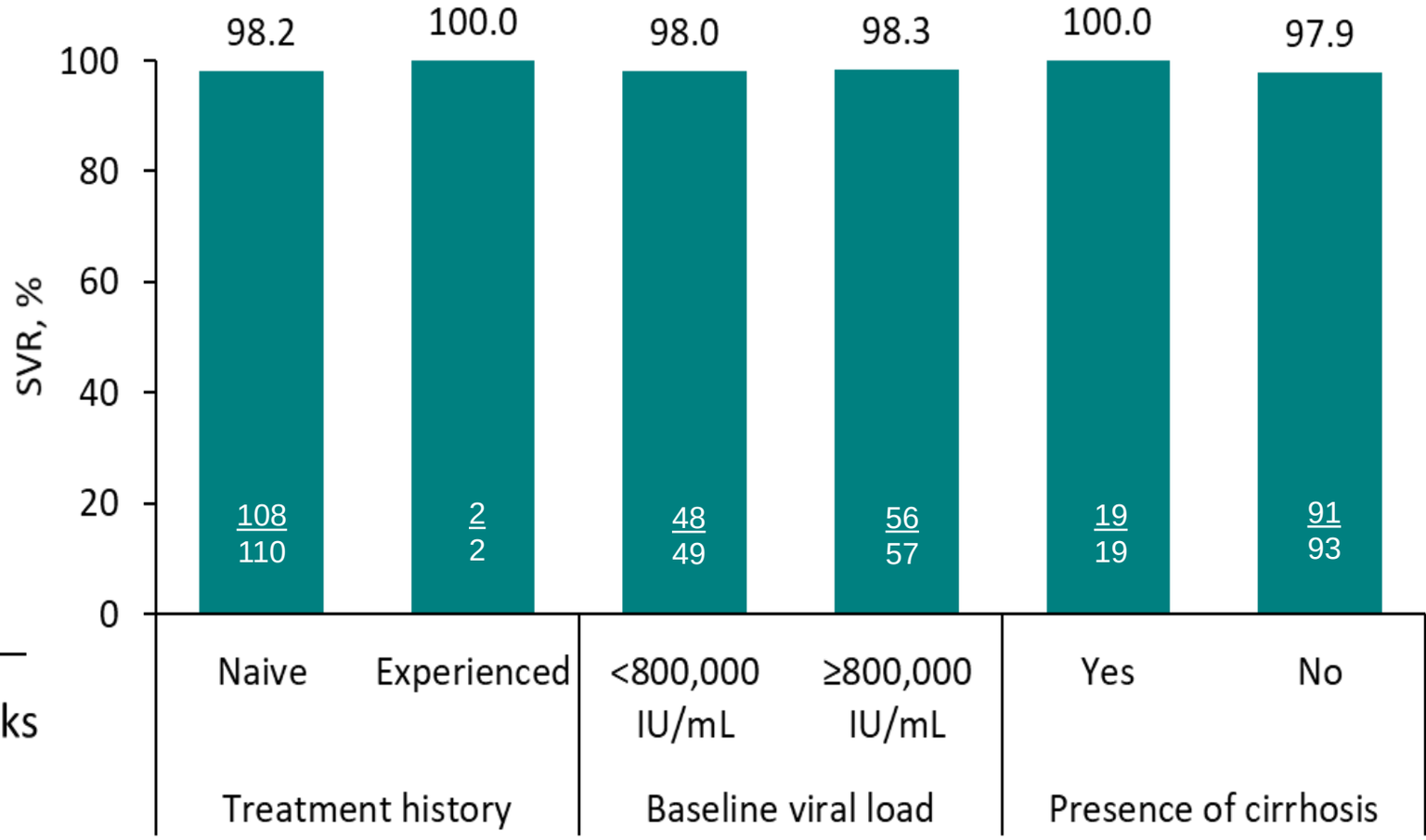
Kramer JR et al. Effectiveness of Elbasvir/Grazoprevir in Patients with Hepatitis C virus Genotype 1 Infection Who Receive Opioid Agonist Therapy: Treatment Utilization and the Impact of Concomitant Psychiatric Medications. EASL 2019

A. Puempatom. Effectiveness of elbasvir/grazoprevir in patients with hepatitis C virus genotype 1 infection receiving dialysis. EASL 2019

Real World Studies Confirm the Efficacy of Grazoprevir/Elbasvir

HCV genotype 4



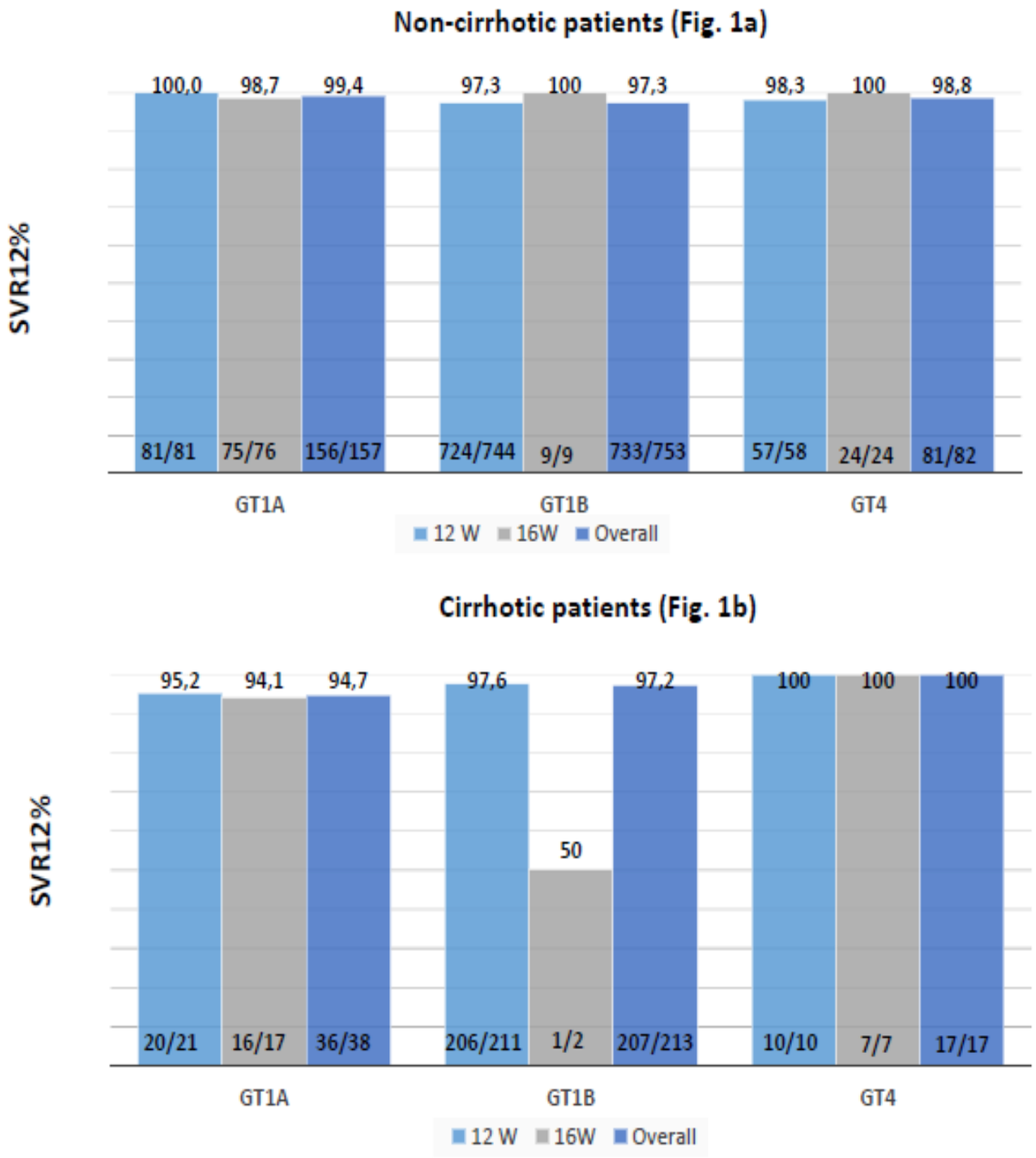


Kramer JR et al. Real-world effectiveness of elbasvir/grazoprevir in patients with hepatitis C virus genotype 4 infection: results from a Veterans Affairs population. EASL 2019

Real World Studies Confirm the Efficacy of Grazoprevir/Elbasvir in Italy

Univariate analysis of SVR12 according clinical and virological features

SVR12 Population n=1260	SVR12	95% CL	P-value
Gender			
Female	97.4%	96-98.4	ns
Male	97.8%	96-98.6	
Genotype			
G1a	98.5%	95.7-99.5	
G1b	97.4%	96.2-99.2	ns
G4	99%	94.7-99.8	
HIV-coinfection			
Present	100%	95.9-100	ns
Absent	97.5%	96.4-98.2	
Treatment duration			
12W	97.5%	96.5-98.2	ns
16W	98.6%	94.9-99.6	
CKD stage			
Stage 1	98%	96.4-98.9	
Stage 2	97.5%	95.4-98.6	
Stage 3	93.9%	88.4-96.9	ns
Stage 4	100%	70-100	
Stage 5	100%	70-100	
Cirrhosis stage			
F4	97.1%	94.5-98.4	ns
F<4	97.7%	96.7-98.5	

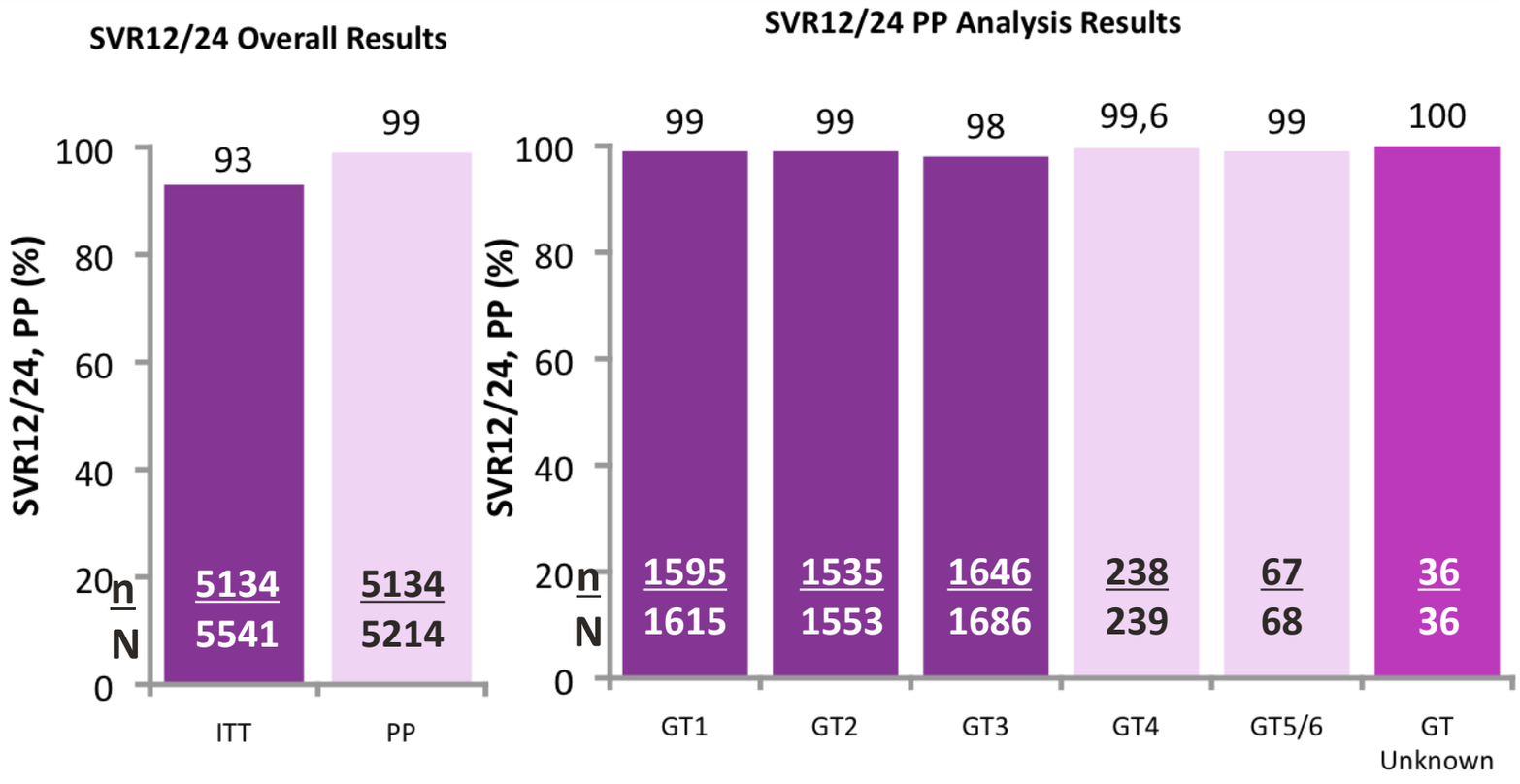


Gambato M. et al. Real world effectiveness and utilization patterns of Elbasvir/Grazoprevir for treatment of HCV G1 G4 infected patients in Italy

GS-03 Mangia: Global RWE of SOF/VEL as a Simple, Effective Regimen for the Treatment of Chronic HCV: Integrated Analysis of 12 Clinical Practice Cohorts

Real-world effectiveness study of SOF/VEL for 12 weeks as a treatment in a large heterogeneous population in the US, Canada, Germany, France, Spain, Italy and Greece (N = 5541)

Baseline Characteristics	ITT N = 5340*
Mean age, years	54
Caucasian/White race, n (%)	3511 (73)
HIV/HCV co-infection, n (%)	196 (4)
Former or ongoing IV drug use, n (%)	706 (13)
PPI use at baseline, n (%)	287 (5)
Treatment experienced,† n (%)	660 (12)
Compensated cirrhosis, n (%)	1108 (21)
Fibrosis, % F0-F2/F3/F4/Unknown	54/13/21/12
HCV GT, % 1/2/3/4–6	30/30/33/



In a PP analysis, SVR12/24 rates were >96% across all patient subgroups

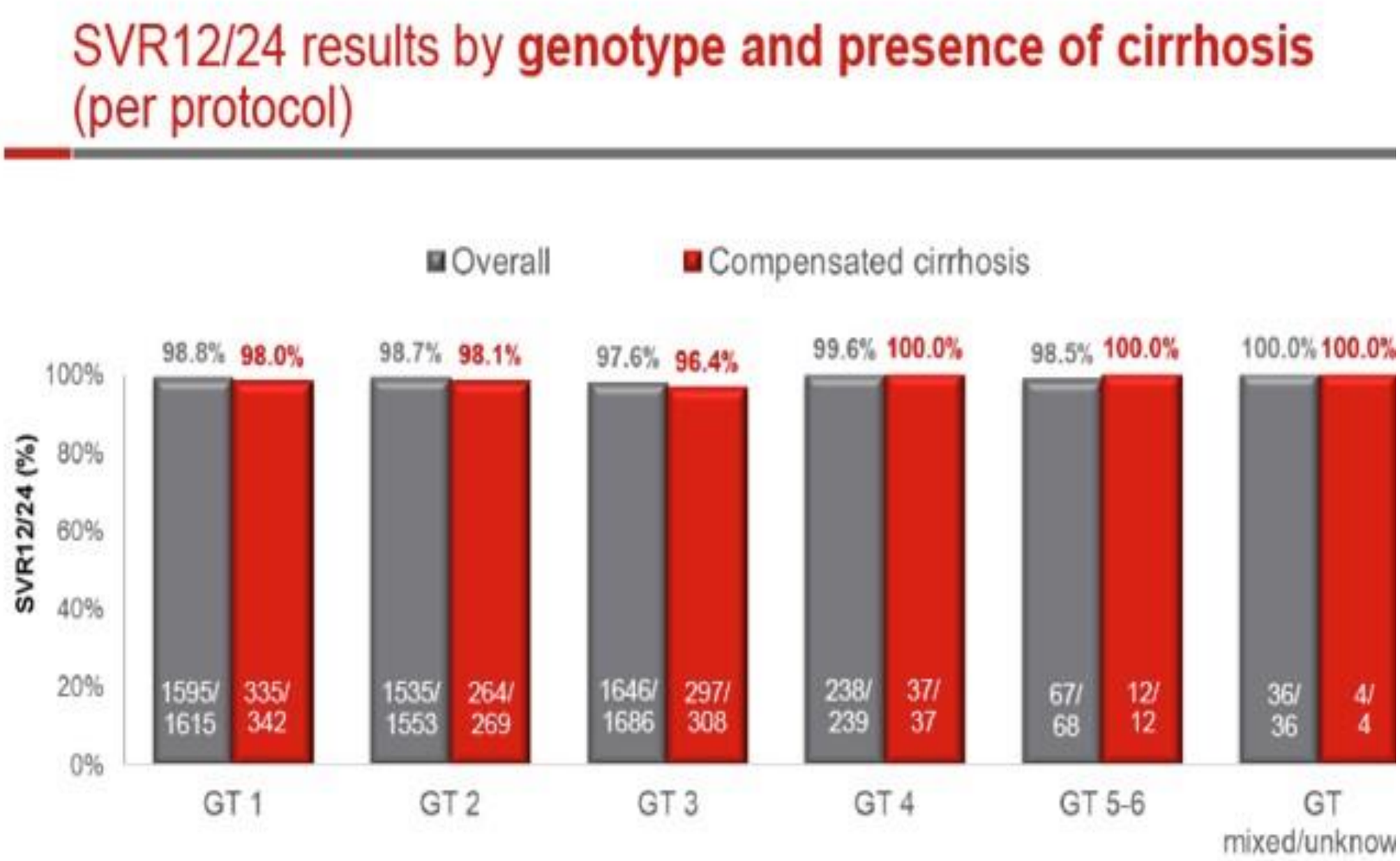
407 (7.3%) patients did not achieve SVR12/24
- 327 (5.9%) overall non-virologic failure rate
- 80 (1.4%) overall virologic failure rate

12 weeks of SOF/VEL is highly effective in a large, diverse population regardless of GT, fibrosis stage, treatment history† or patient characteristics

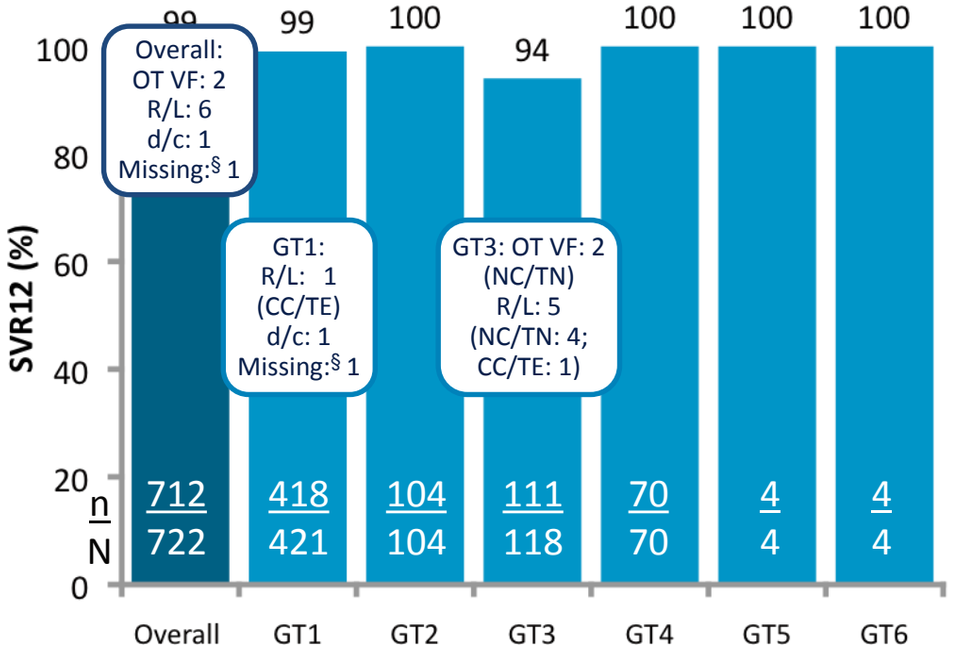
*Total number of patients varies across characteristics due to missing data; †Treatment experience with pegIFN + RBV ± PI.
BT, breakthrough; d/c, discontinuation; GT, genotype; ITT, intention to treat; LTFU, lost to follow-up;
PI, protease inhibitor; PPI, protein pump inhibitor; PP, per protocol.

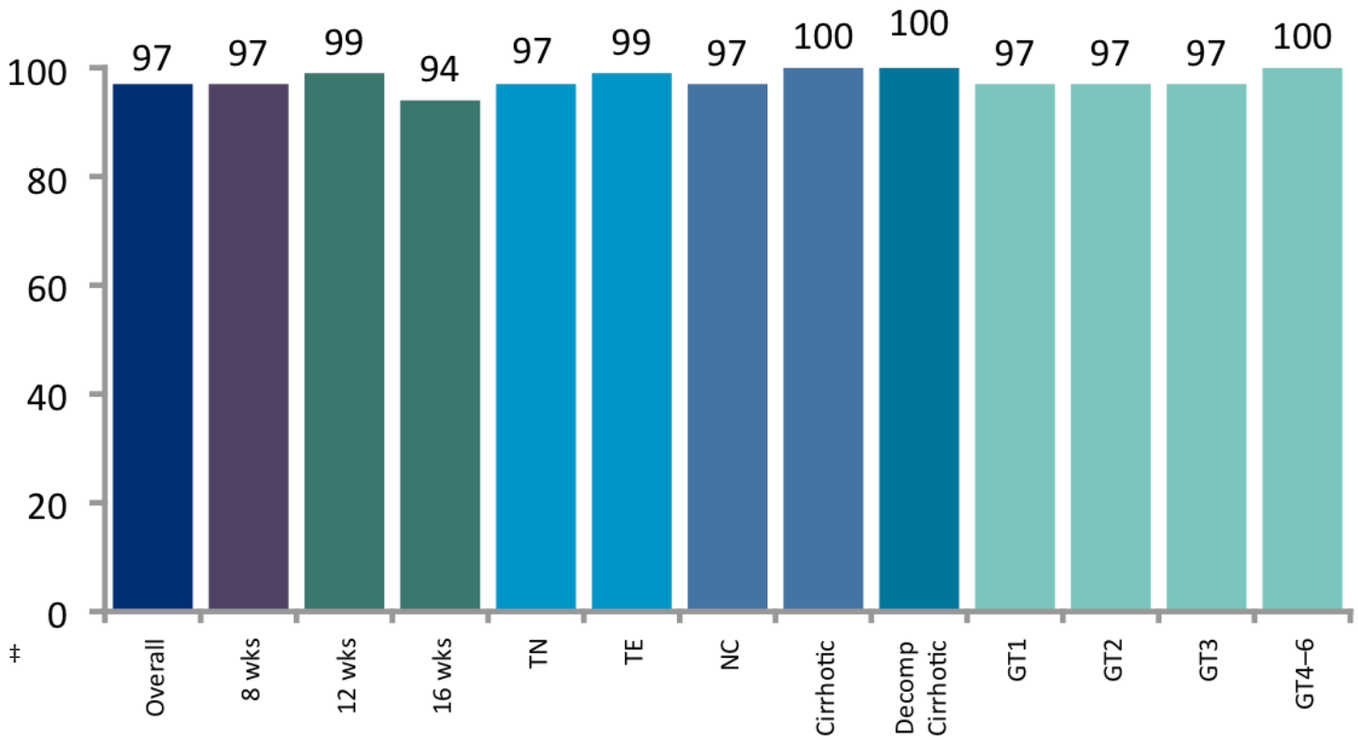
Mangia A, et al. EASL 2019; oral presentation (GS-03).

Real World Studies Confirm the Efficacy of Sofosbuvir/Velpatasvir



Real World Studies Confirm the Efficacy of Glecaprevir/Pibrentasvir





Pooled analysis to evaluate the real-world effectiveness and safety of G/P in HCV-infected TN or TE* patients ± CC in PMOS in Austria, Belgium, France, Greece, Israel, Italy, Poland, and Switzerland (N = 1276)

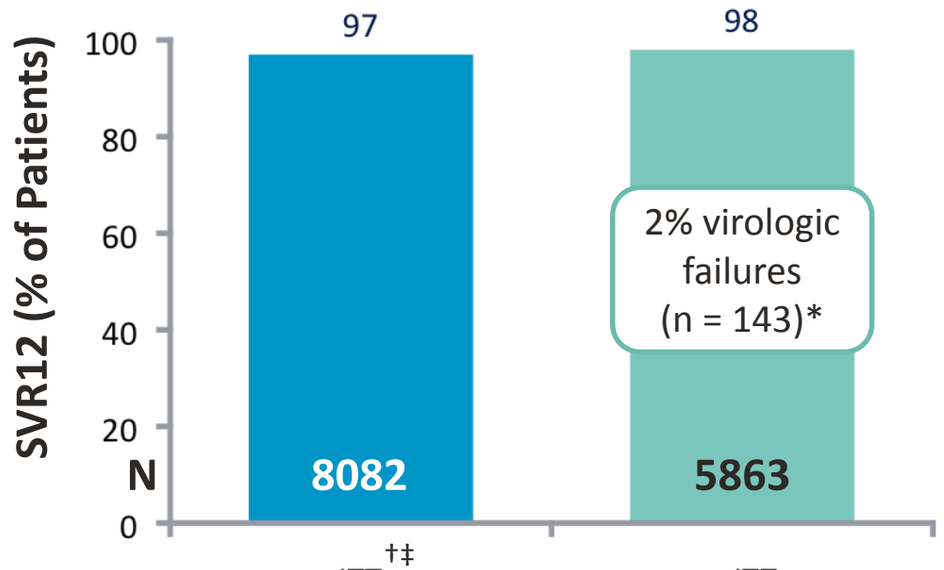
Real-world safety and efficacy analysis of HCV GT1–6-infected, TN/TE patients with or without compensated cirrhosis enrolled in HCV-TARGET and treated with 8-, 12-, or 16-weeks' G/P (N = 726) prior to 1 September 2018

Lampertico P, *et al. EASL* 2019; poster presentation (THU-151).

Sterling R, *et al*. EASL 2019; poster presentation (THU-181).

Real World Studies Confirm the Efficacy of Glecaprevir/Pibrentasvir

Cohort	Country	N
Austrian Real Life Cohort	Austria	116
Japan Registry	Japan	798
England NHS Registry	UK	773
German Registry	Germany	1242
Italian NAVIGATORE	Italy	723
Scottish HCV	Scotland	354
Spanish HepaC Cohort	Spain	1581
Trio	US	1131
VA Registry	US	1940
Japan Tamori	Japan	280
Japan Uemura	Japan	131
Kaiser Permanente	US	50
Italian MISTRAL	Italy	1177
Global G/P PMOS	Global	755
DAA-exp (Osawa)	Japan	30
DAA-exp (Akuta)	Japan	20

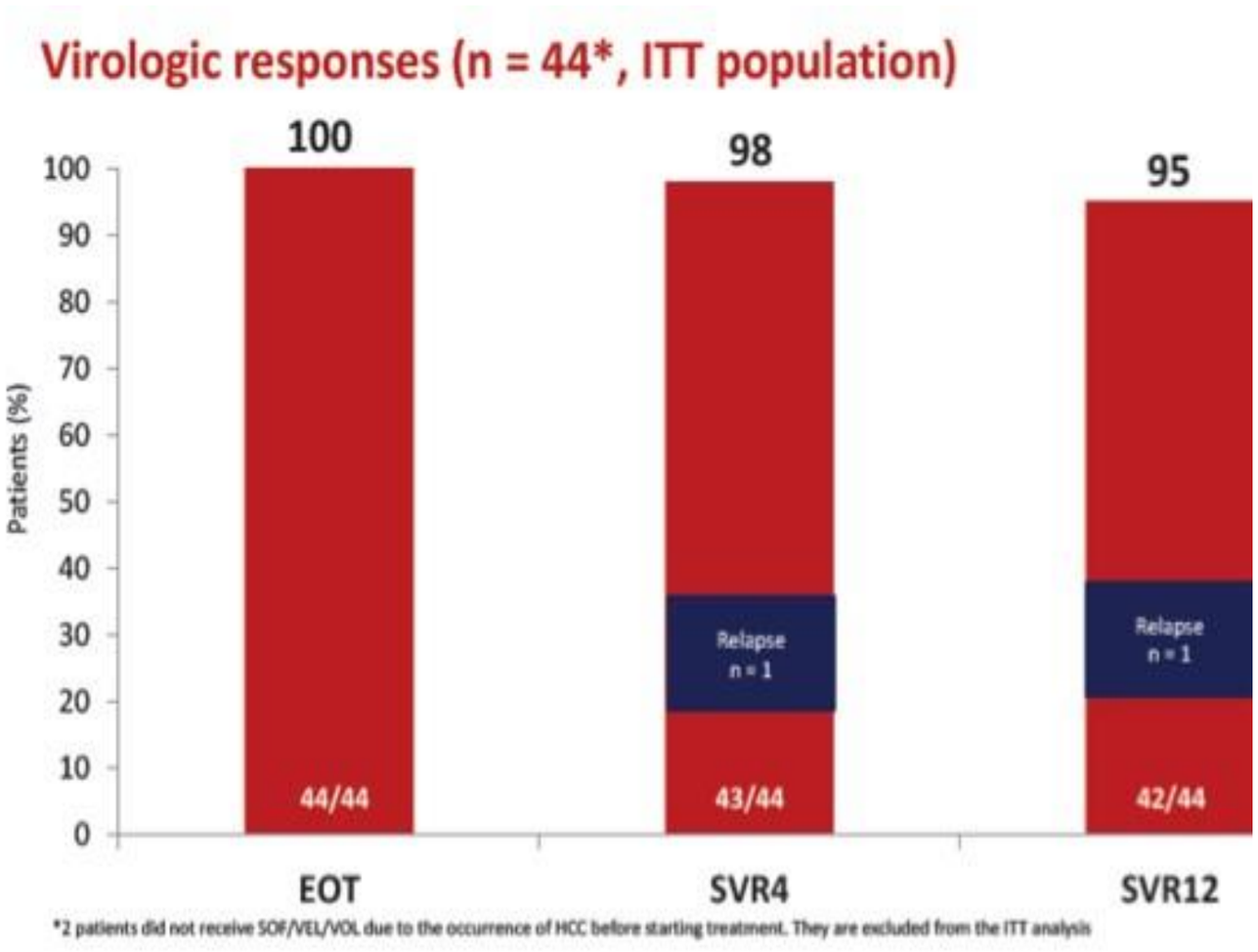


Safety	% (n/N)	Cohorts, N §
Any AE	13 (725/5685)	6
AEs leading to d/c	0.5 (24/4508)	5
Most common AEs		
Pruritus	5 (126/2698)	3
Fatigue	4 (146/3305)	4
Headache	3 (102/3759)	4

Cornberg M, *et al.* EASL 2019; oral presentation (PS-184).

Real World Studies Confirm the Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir

French Cohort



*2 patients did not receive SOF/VEL/VOL due to the occurrence of HCC before starting treatment. They are excluded from the ITT analysis

German Cohort

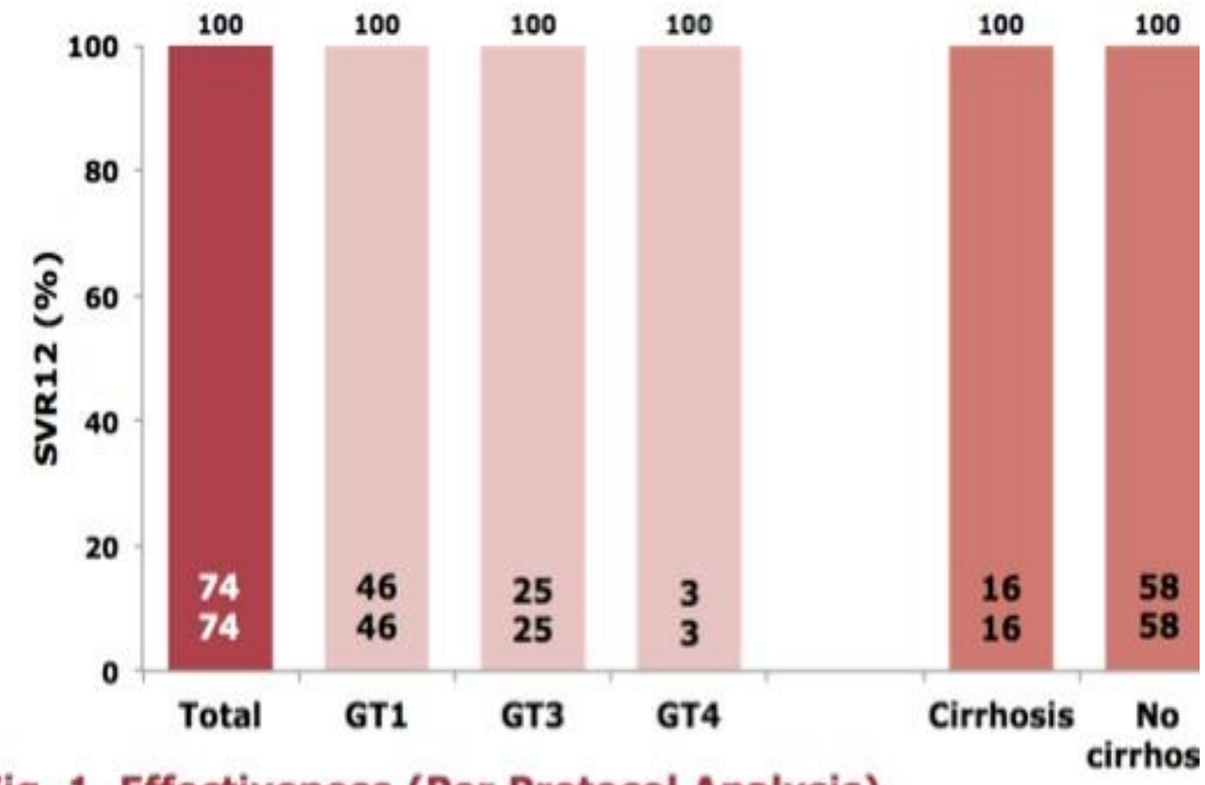
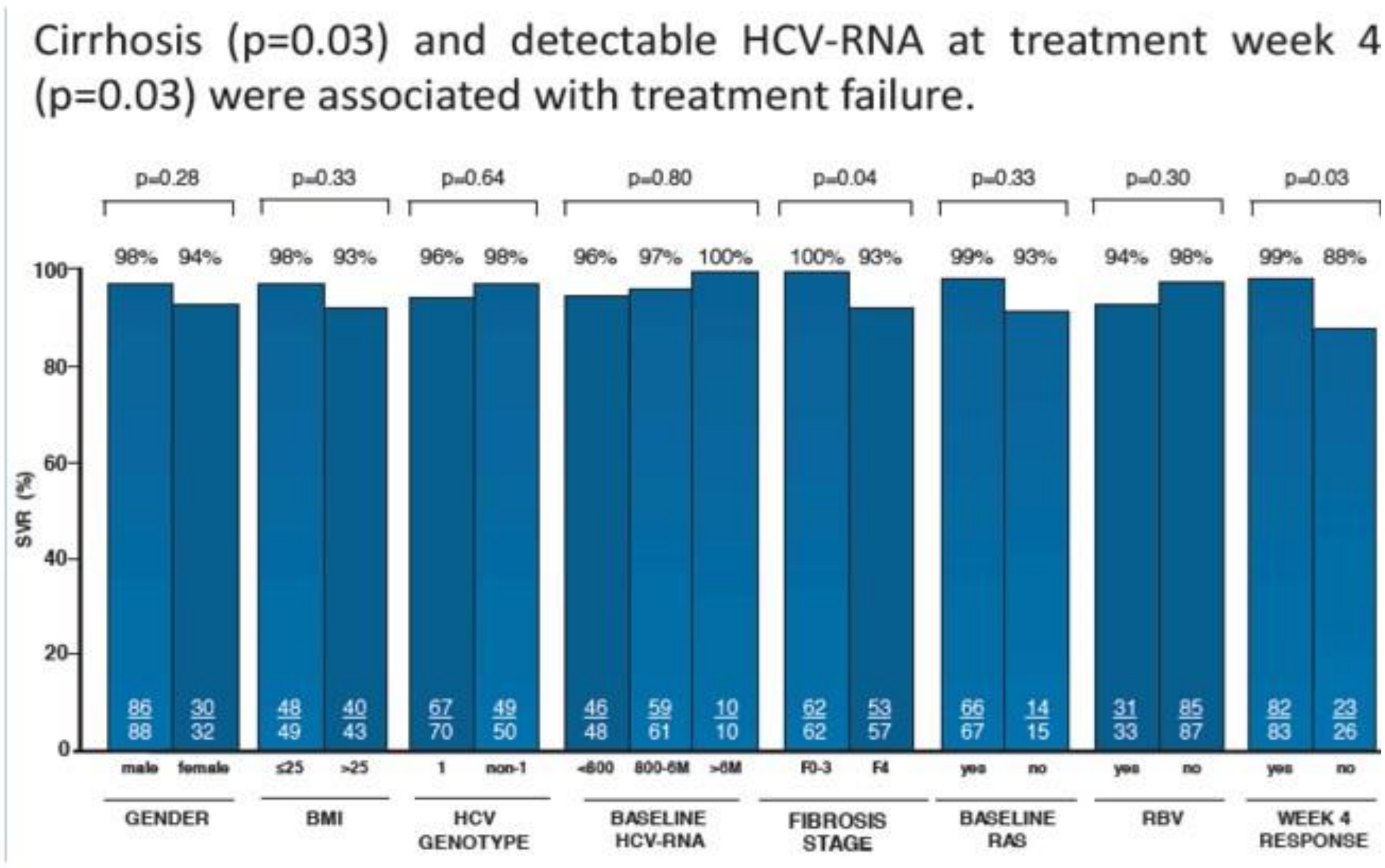


Fig. 1. Effectiveness (Per Protocol Analysis)

Real World Studies Confirm the Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir



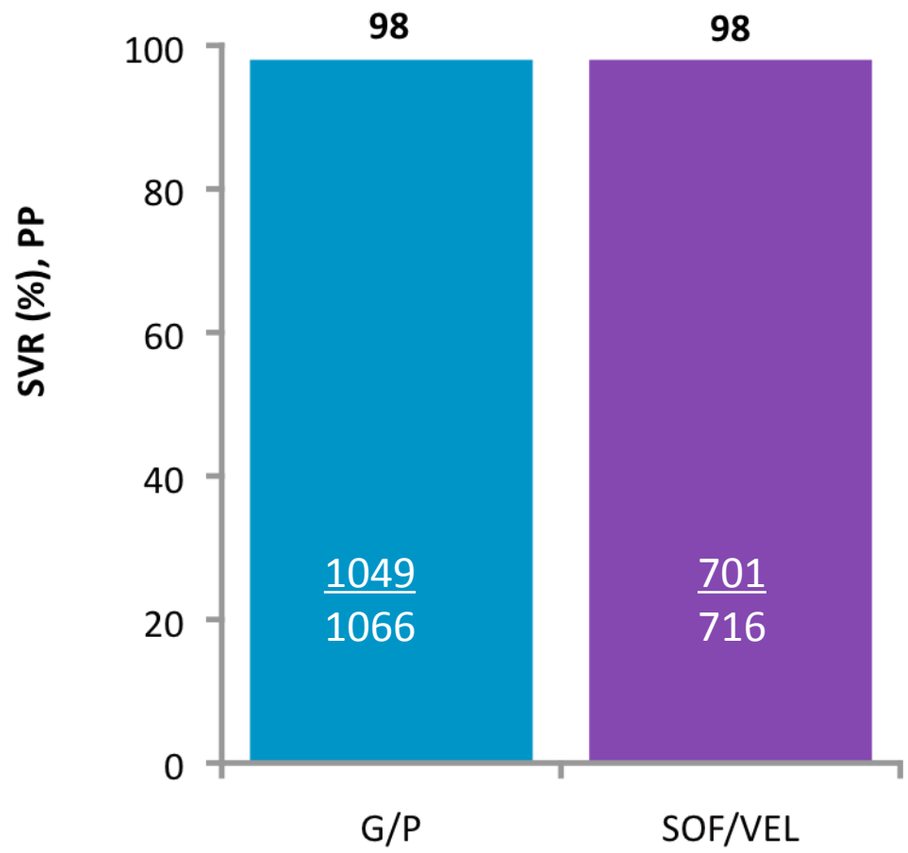
Degasperi E *et al.* EASL 2019;

Le ultime evidenze dei congressi

- Dati Real life
- Due opzioni nella pratica clinica
- Ottimizzazione: meglio meno visite ?
- Off label: corto è bello ?
- Eterogeneità virale: ha un ruolo nell’epoca della taglia unica pangenotipica

Curry: Clinical Practice Experience with Pan-genotypic Therapies G/P and SOF/VEL; Data from the TRIO Network

Baseline Characteristics, n (%)	G/P N = 1131	SOF/VEL N = 777
Actual duration		
< 8 weeks	10 (1)	25 (3)
8 weeks	844 (75)	15 (2)
12 weeks	237 (21)	733 (94)
> 12 weeks	40 (4)	4 (1)
HCV genotype		
1	805 (71)	170 (22)
2	167 (15)	315 (41)
3	133 (12)	262 (34)
4–6	26 (2)	30 (4)
CKD Stage 1–3, n (%)	336 (30)	287 (37)
CKD Stage 4–5, n (%)	74 (7)	10 (1)
Fibrosis		
No cirrhosis/no score	144 (13)	115 (15)
0–2 (no to moderate)	665 (59)	352 (45)
3 (severe)	140 (12)	101 (13)
4 (cirrhosis)	182 (16)	209 (27)



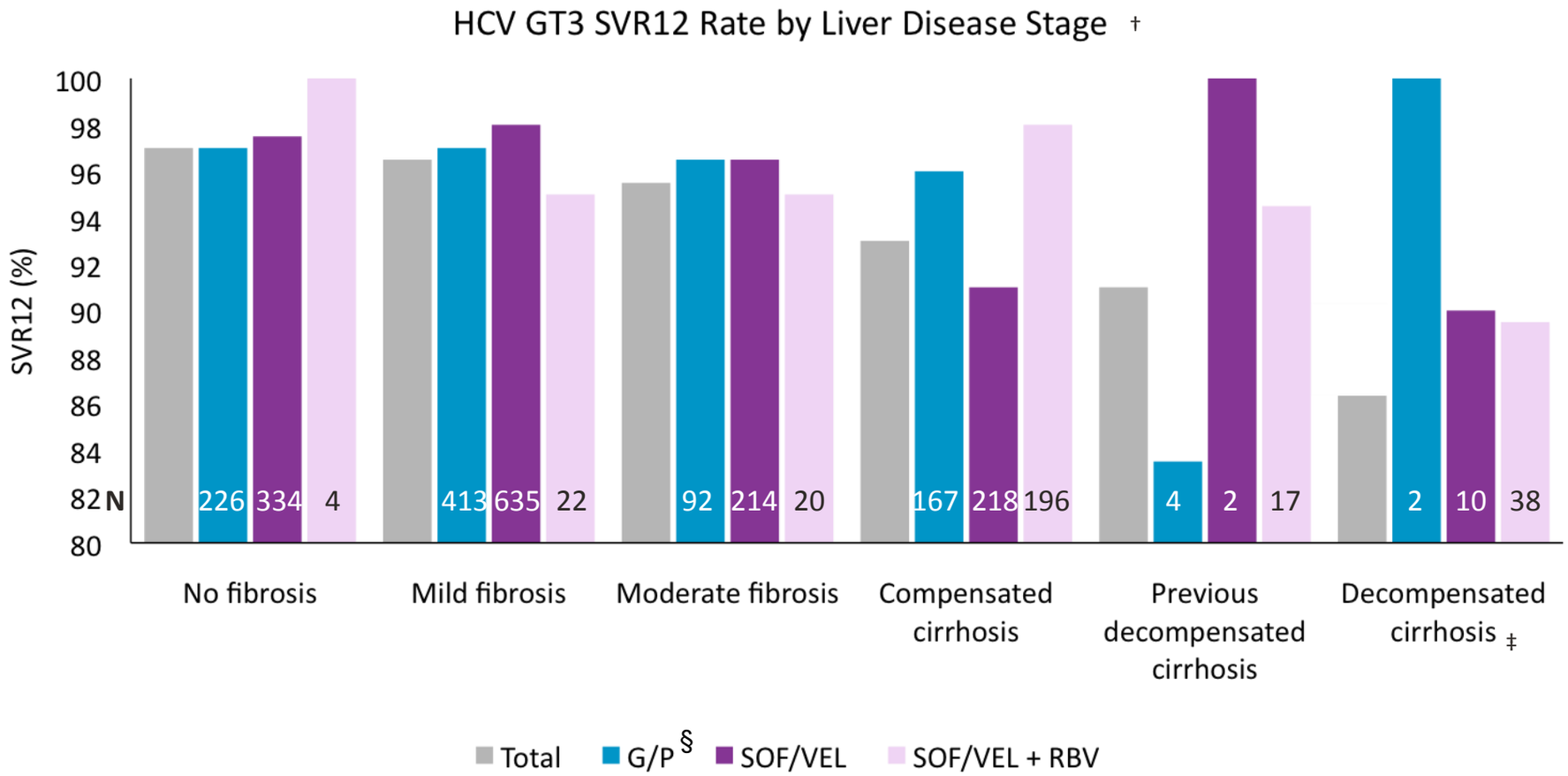
VF in the G/P group was associated with TE, cirrhosis, and VL>6MM (GT3)
For SOF-VEL, VF was associated with +RBV

CK

Curry M, *et al.* EASL 2019; poster presentation (THU-127).

LB-07 Drysdale: Effectiveness of Therapy in 16,756 DAA Treated People in England: High Response Rates in GT3 HCV Infection Regardless of Degree of Fibrosis, But RBV Improves Response in Cirrhosis

Meta-analysis of the England Hepatitis C Treatment Registry to determine the effects of liver disease stage on patient outcomes when using different DAA regimens to treat HCV GT3 (N=16,756*)



Overall PP SVR12 rate was 96% in all GTs

In patients with HCV GT3 SVR12 rate was 95%

High SVR rates with 12 weeks of G/P were achieved in patients with GT3 and compensated cirrhosis

8 weeks of G/P and 12 weeks of SOF/VEL in patients with HCV GT3 and moderate fibrosis have similar efficacy. Addition of RBV to SOF/VEL significantly increases efficacy in patients with HCV GT3 and compensated cirrhosis

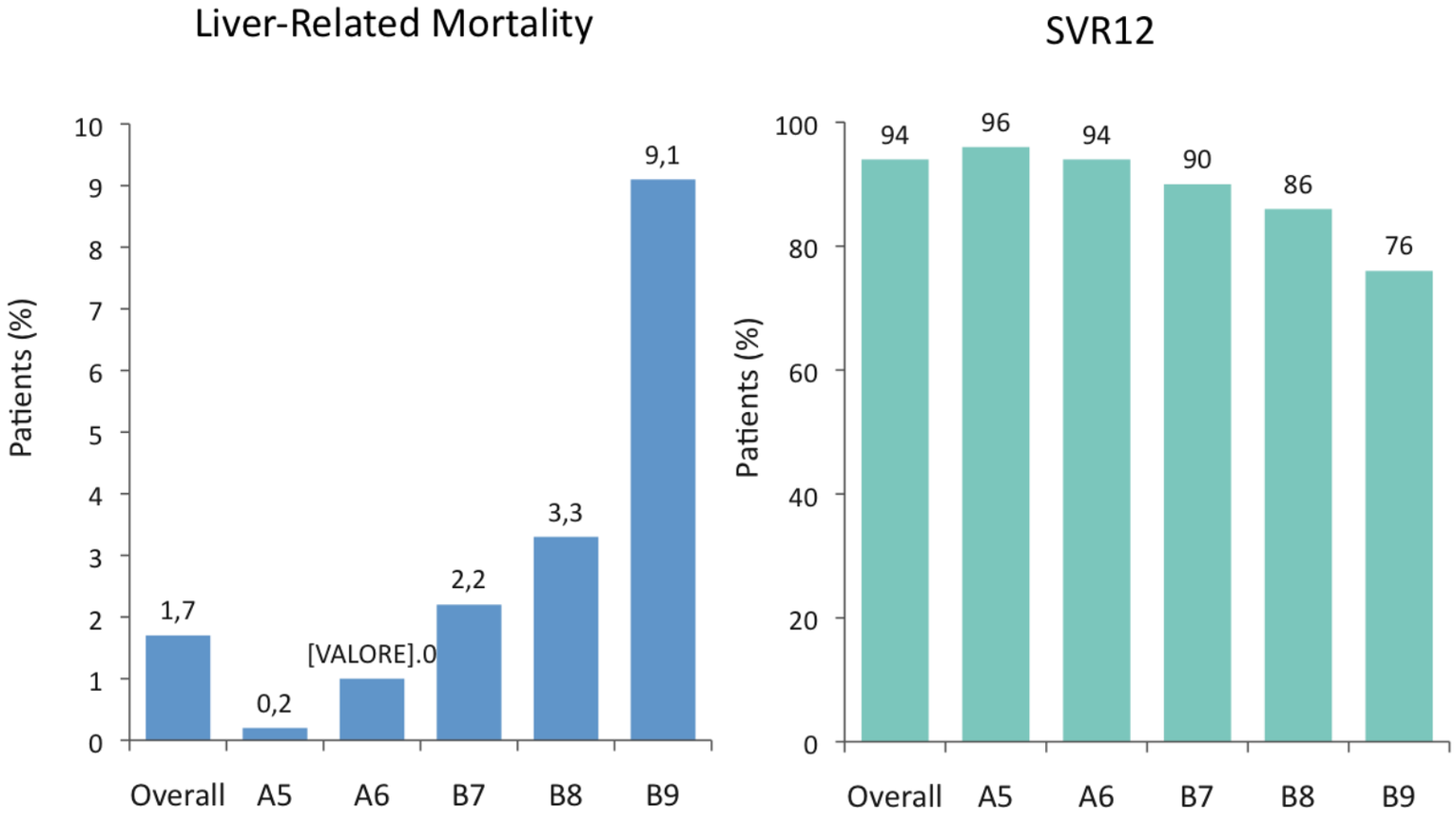
*Patients who received a valid treatment; †Graphical data has been estimated from the provided source presentation but no exact numbers are available; ‡ G/P is contraindicated in patients with severe hepatic impairment (Child-Pugh C); § Treatment durations with G/P were 8 weeks in patients with no fibrosis, mild fibrosis or moderate fibrosis and 12 weeks in patients with compensated cirrhosis, past decompensated cirrhosis or decompensated cirrhosis; Treatment durations were 12 weeks with SOF/VEL ± RBV for all stages of liver disease.

Drysdale K, *et al.* EASL 2019; oral presentation (LB-07).

G/P has not been approved in mainland China. G/P is not recommended in patients with moderate hepatic impairment (Child-Pugh B); and is contraindicated in patients with severe hepatic impairment (Child-Pugh C)

SAT-262, Paolo Russo: Long-Term Liver Function Outcome and Related Risk Factors in HCV Cirrhotic Patients Treated with DAA Therapy: Results from the Navigatore Platform in Veneto-Italy

Long-term, real-world, prospective study to determine liver function outcome and related risk factors in HCV cirrhotic patients initiating DAAs in Veneto-Italy between Dec 2014 and Sep 2017 (N = 3959)



- Predictors of CP improvement at both PTW12 and PTW48 were **baseline INR < 1.5** (OR = 0.25/0.18), **albumin > 3.5 g/dL** (OR = 0.05/0.04) and **bilirubin < 2.5 µmol/L** (OR = 0.23/0.11) (*P* = 0.0001 for all)
- Predictors of CP worsening at PTW12 and PTW48 were **PLT > 100 x 10^3/mL** (OR =0.56, *P* = 0.004) and **bilirubin < 2.5 µmol/L** (OR = 0.11, *P* = 0.0001)
- Complication of cirrhosis before DAA treatment is a risk factor for early CP worsening, and it must be taken into consideration before starting therapy

Most of the cirrhotic patients in the cohort were Child-Pugh A and remained stable after DAA therapy

CP, Child-Pugh; EOT, end of treatment; INR, international normalized ratio; PLT, platelet; PTW, per treatment week.

Paolo Russo F, *et al.* EASL 2019; poster presentation (SAT-262).

THU-128, D'Ambrosio: Renal Safety in 3264 HCV Patients Treated with DAA-Based Regimens: Results from a Large Italian Real-Life Study

Retrospective analysis of changes in renal function from baseline to EOT and 12 weeks post SVR for patients treated with DAAs between Dec 2014 and Nov 2017* in the Italian NAVIGATORE-Lombardia cohort (N = 3264)

Baseline Characteristics	N = 3264
Male, n (%)	2116 (65)
Cirrhosis, n (%)	2208 (67)
HCV GT1, n (%)	1989 (61)
Diabetic, n/N (%)	437/2744 (16)
Median eGFR, mL/min/1.73 m^2, n (range)	88 (9–264)
CKD stage 4–5, n (%)	23 (0.7)
Treatment regimen, n (%): SOF-containing	2568 (79)

CKD Stage	1	2	3a	3b	4/5
Decline in eGFR during Tx	Yes (P < 0.0001)	Yes (P = 0.0002)	–	–	–
Improvement in eGFR	–	–	Yes (P = <	Yes (P =	Yes (P = 0.024)

Changes in eGFR remained stable at SVR

Predictors of Worsening CKD at EOT:
Age > 75 years (P = 0.05)
Preserved BL renal function (P < 0.0001)
Diabetes (P = 0.04)

Predictors of Worsening CKD at SVR:
Age > 75 years (P = 0.005)
Preserved BL renal function (P < 0.0001)
Arterial hypertension (P = 0.0006)
On-treatment renal worsening (P < 0.0001)

DAA treatment (primarily SOF- and RBV-based) led to a statistically significant decline in eGFR in patients with preserved baseline renal function that did not improve upon discontinuation of DAA therapy

D'Ambrosio R, *et al.* EASL 2019; poster presentation (THU-128).

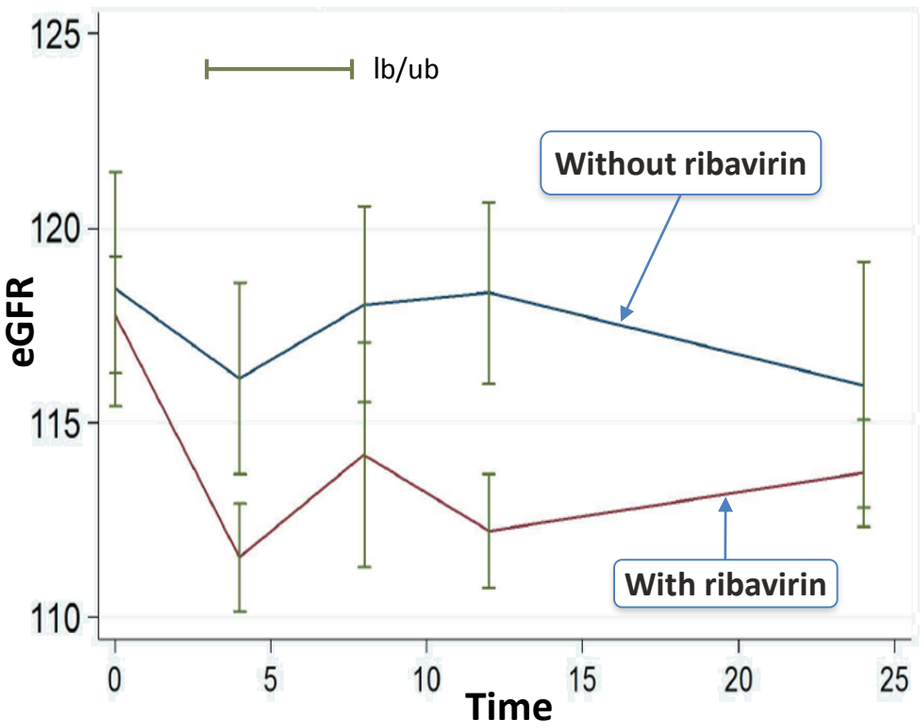
* Patients with available kidney function tests at baseline, EOT, and 12 weeks post treatment (SVR).
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EOT, end of treatment; Tx, treatment.

SAT-218, Fouad: Impact of SOF-based Therapy on Renal Function Indices in Chronic Hepatitis C Patients who Achieved SVR

Evaluation of the changes in renal function indices during and after SOF-based therapy in chronic HCV patients who achieved SVR (N = 1004*)

Baseline Characteristics	N = 1004
Mean age, years (SD)	53 (10)
Male, %	56
Diabetes, %	25
Hypertension, %	20
Cirrhosis, %	40
Stage of renal function, %	75
S1	22
S2	3
S3	
Type of HCV treatment, %	12
DCV + SOF	33
DCV + SOF + RBV	3
LDV/SOF	3
LDV/SOF + RBV	34
SOF + RBV	15
SMV + SOF	

Changes in eGFR by RBV use



Median eGFR

	Baseline	EOT	SVR12
All patients	112.1	108.1 (P = 0.0003)	109.7 (P = 0.0002)
+ RBV	111.9	106.4 (P < 0.0001)	109.8 (P = 0.0001)
- RBV	No significant change		

- Remained unchanged in 15%
- Worsened at EOT vs baseline in 47%

SOF-based therapy is associated with decreased eGFR among HCV patients who receive RBV. Renal function should be monitored during and after SOF-based therapy which includes RBV

* Patients who didn't achieve SVR, had HIV or HBV, decompensated cirrhosis, transplant recipients and patients with eGFR < 30 ml/min/1.73m2 before antiviral therapy were excluded
eGFR, estimated glomerular filtration rate; EOT, end of treatment.

Fouad R, *et al*. EASL 2019; poster presentation (SAT-218).

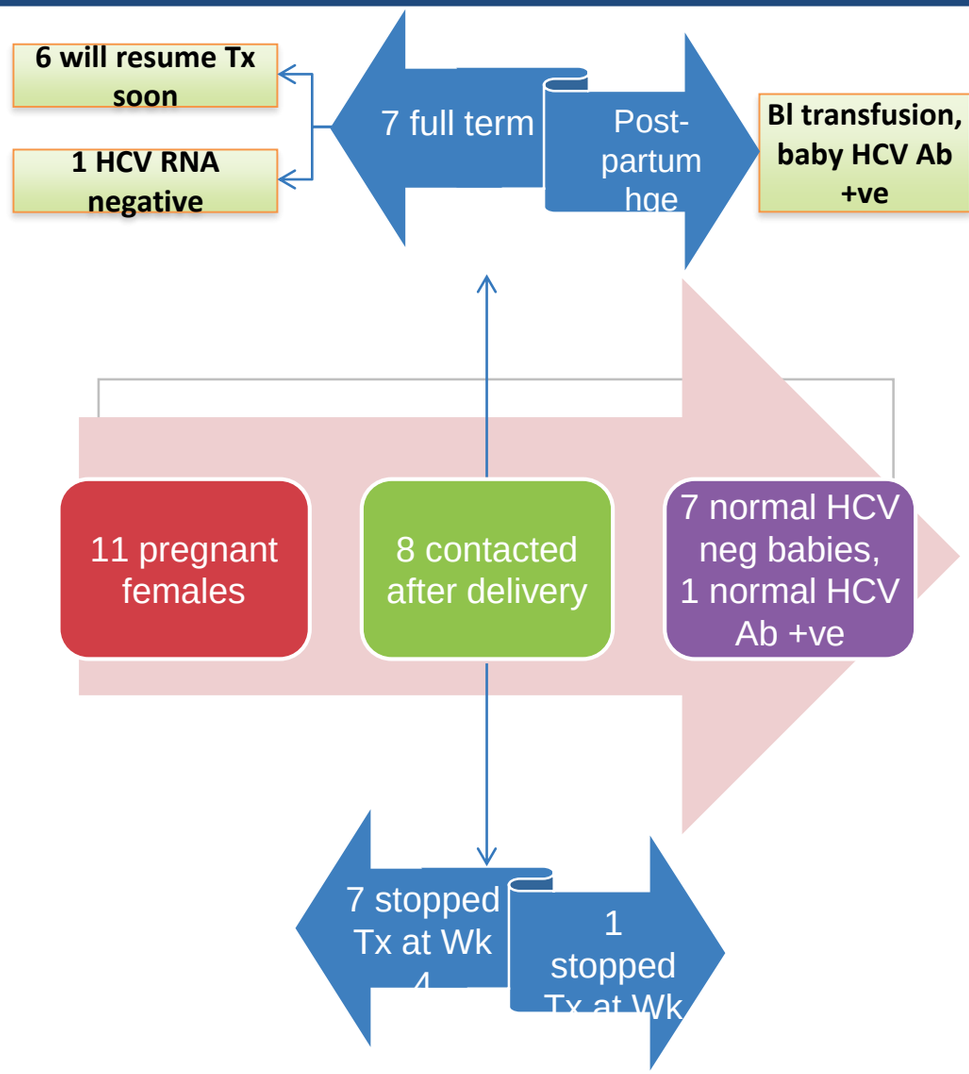
THU-137, El-Sayed: DAA Therapy in Women of Child Bearing Age: Accidental Conception During Therapy and Pregnancy Outcome

Retrospective study of the pregnancy outcome of women with chronic HCV who became pregnant during DAA therapy (N = 11) through the Egyptian national program for control of viral hepatitis

58,059 women were retrospectively assessed

- 93% treatment-naive
- 11% cirrhotic
- 81% treated with DCV + SOF (97% SVR)
- 11 became pregnant during therapy*

Baseline Characteristics	N = 11*
Age years, mean ± SD	29 ± 6
ALT IU/L, mean ± SD	49 ± 26
AST IU/L, mean ± SD	45 ± 23
HCV RNA IU/L, median (range)	441,500 (10,000 – 6,390,000)
Fib-4, mean ± SD	0.8 ± 0.3



Infants tested for HCV antibodies at 18 months old:

- n=7 negative
- n=1 positive with low viremia

- n=7 full-term non-interventional deliveries of normal weight newborns with no congenital abnormalities
- n=1 reported postpartum hemorrhage and received blood transfusion

Report of healthy infants with no congenital abnormalities despite accidental pregnancy during treatment with DCV + SOF. More data on the safety of DAAs during pregnancy is required to prevent the need to discontinue DAAs during pregnancy

* Discontinued treatment for accidental pregnancy, n=3 were not able to be contacted, all treated with DCV + SOF for 12 weeks. n=7 discontinued at Week 4, n=1 discontinued at Week 8 (HCV-RNA negative and maintained SVR). Hge, hemorrhage; Tx, treatment.

El-Sayed M H, *et al*. EASL 2019; poster presentation (THU-137).

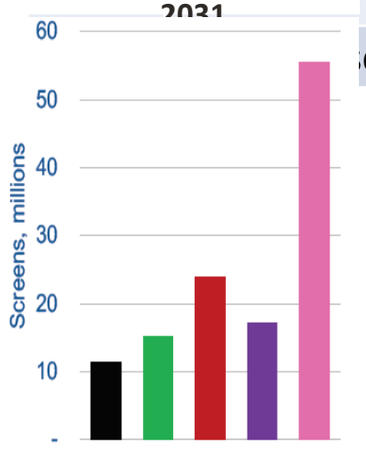
Le ultime evidenze dei congressi

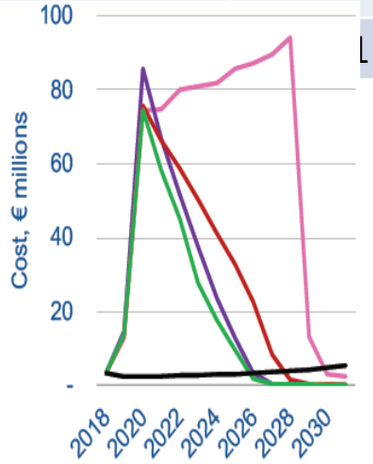
- Dati Real life
- Due opzioni nella pratica clinica
- Ottimizzazione: meglio meno visite ?
- Off label: corto è bello ?
- Eterogeneità virale: ha un ruolo nell’epoca della taglia unica pangenotipica

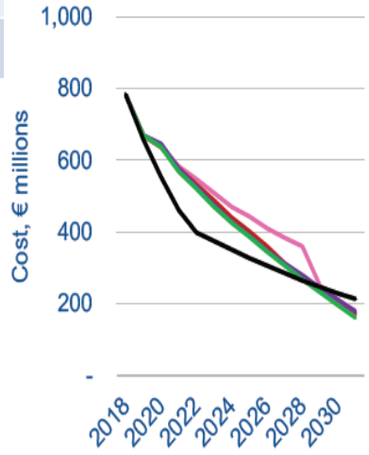
THU-397, Gamkrelidze: Screening Strategies for HCV Elimination in Italy

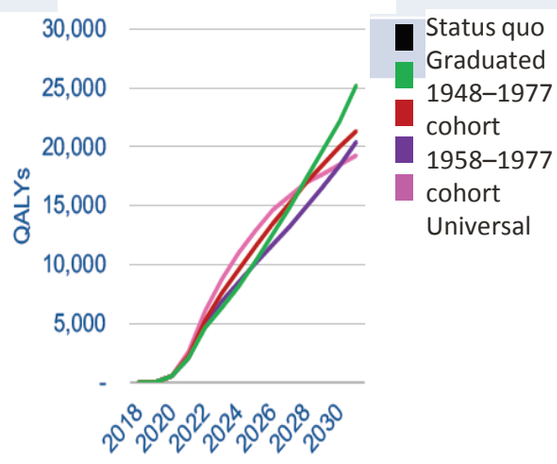
Modelling study assessing elimination scenarios under four screening strategies to determine if birth cohort-based screening would be cost effective in Italy between 2018–2031

Scenario		Cost (€ millions), 2018–2031	QALYs gained relative to status quo, 2018–31	ICER relative to status quo (€/QALY)	ICER relative to prior least costly scenario (€/QALY)	Reduction in HCV cases, 2018–31 (%)
Status quo		5463	–	–	–	–
GHSS target	Graduated screening[†]	5974	143,929	3552	3552	89.3
	Screening 1948–77 birth cohort	6081	142,244	4349	*	89.0
	Cumulative HCV antibody screens, 2018–2031	1958	Screening costs, annual	31	QALYs gained relative to status quo, annual	89.7









- Graduated screening was the least costly scenario
- Relative to the status quo, graduated screening yielded the lowest ICER of €3552 per QALY
- Screening of the 1958–77 birth cohort showed the biggest reduction in HCV-infected cases by 2031

Graduated screening was the most cost-effective and showed the second largest reduction in HCV disease burden by 2031. This strategy should be considered to aid Italy's efforts in achieving HCV elimination goals

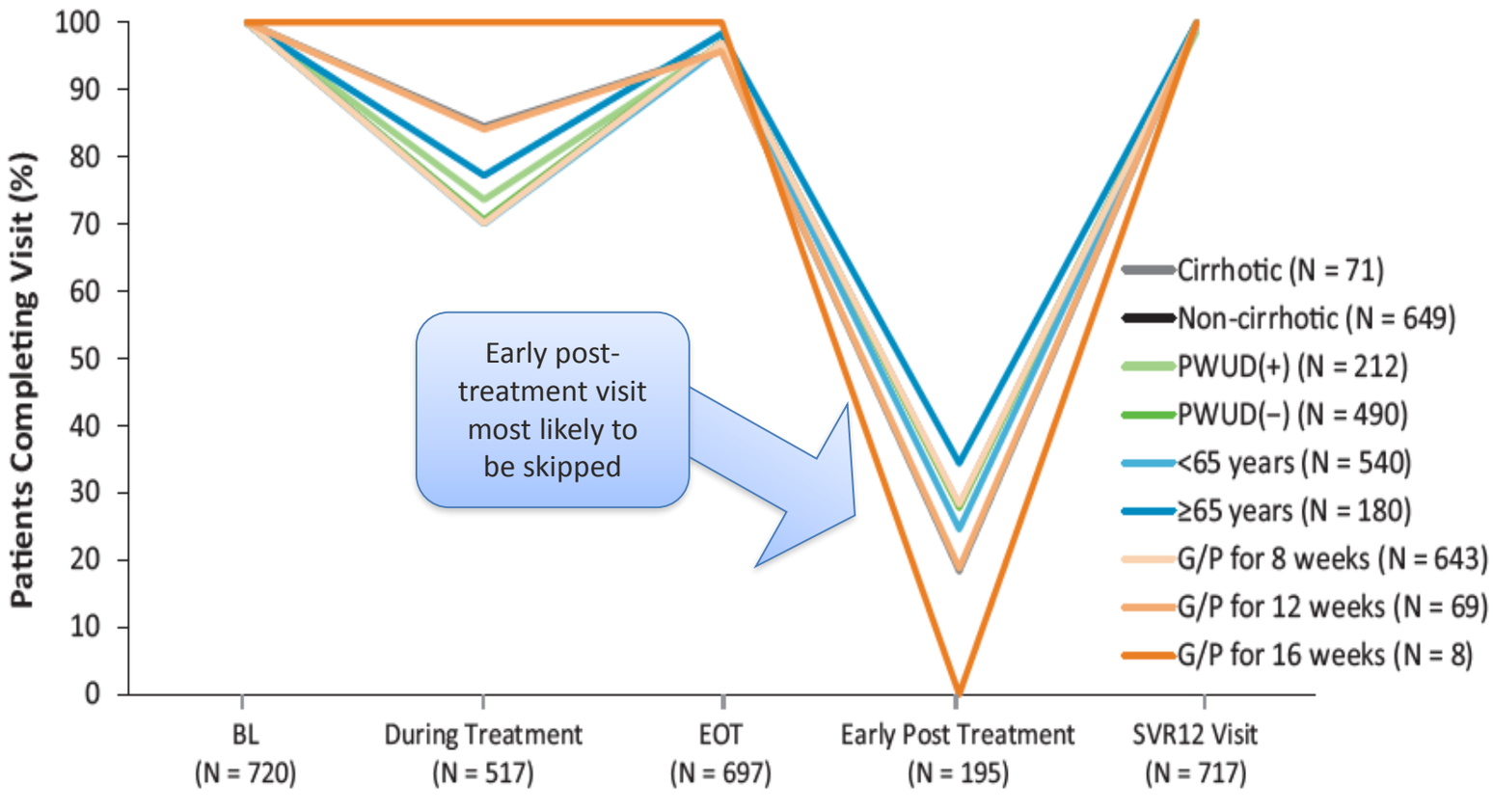
[†] Beginning with 1968–87 birth cohort in 2020, followed by 1948–67 cohort from 2030; * Strongly dominated scenario (costlier and less effective than graduated).
GHSS, Global Health Sector Strategy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Gamkrelidze I, *et al*. EASL 2019; poster presentation (THU-397).

What is the Optimal Treatment Monitoring Schedule?

A pooled analysis of patients treated with G/P from PMOS in 6 different countries (Austria, Belgium, France, Israel, Italy, and Switzerland) assessed the impact of treatment on real-world HCRU and HRQoL (N = 720)

Figure 1. Percentage of Patients Attending Each Visit by Subgroup of Interest



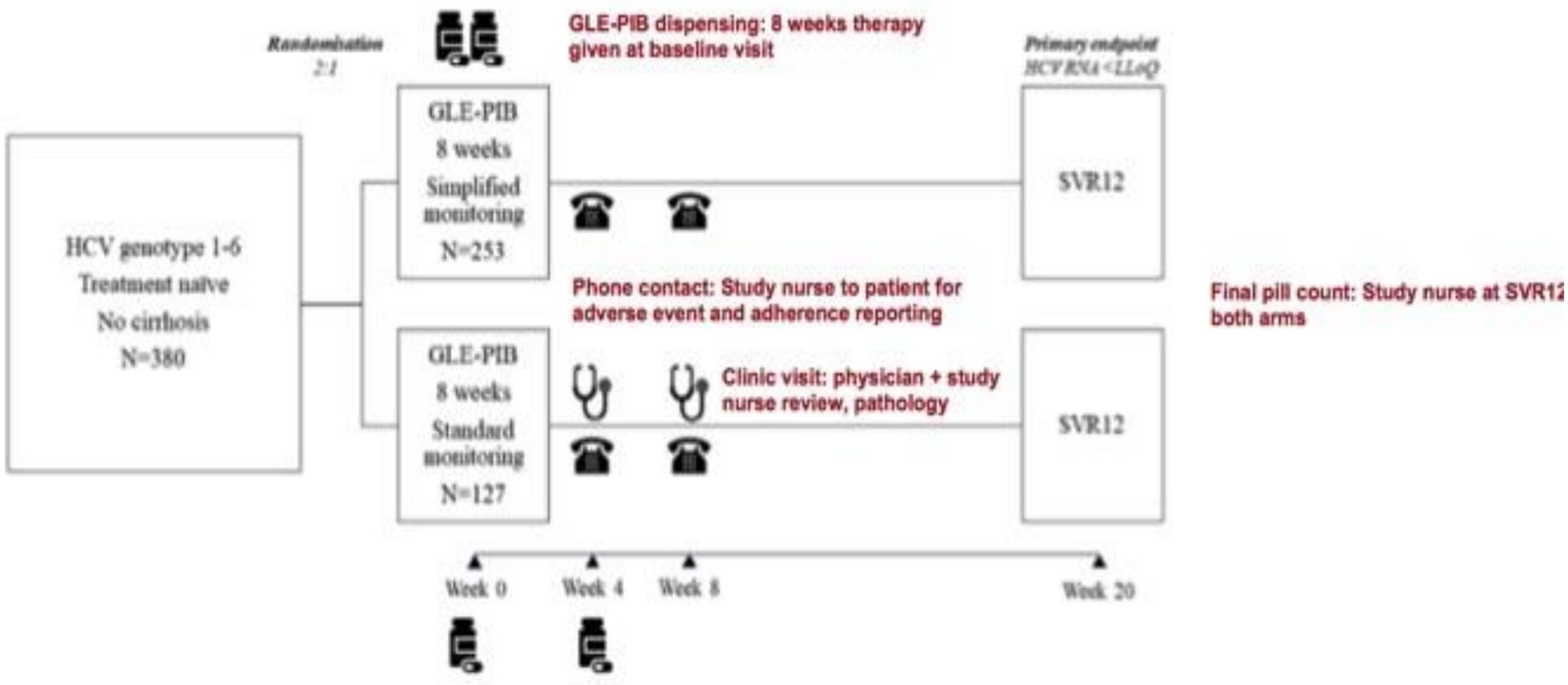
BL, baseline; EOT, end of treatment; G/P, glecaprevir/pibrentasvir; PWUD, person who uses drugs; SVR12, sustained virologic response at post-treatment Week 12.

Overall SVR12 rate was 98.9 (712/720)

Aghemo A, *et al.* EASL 2019; poster presentation (THU-112).

What is the Optimal Treatment Monitoring Schedule?
The SMART-C Trial

Study design



GLE-PIB = glecaprevir-pibrentasvir; SVR12 = sustained virological response 12 weeks post-treatment; LLoQ = lower limit of quantification

Study endpoints and statistics

Dore G *et al.* EASL 2019

What is the Optimal Treatment Monitoring Schedule?
The SMART-C Trial

Study endpoints and statistics

- **Primary endpoint: SVR12 (HCV RNA <LLoQ, central lab) on ITT population**

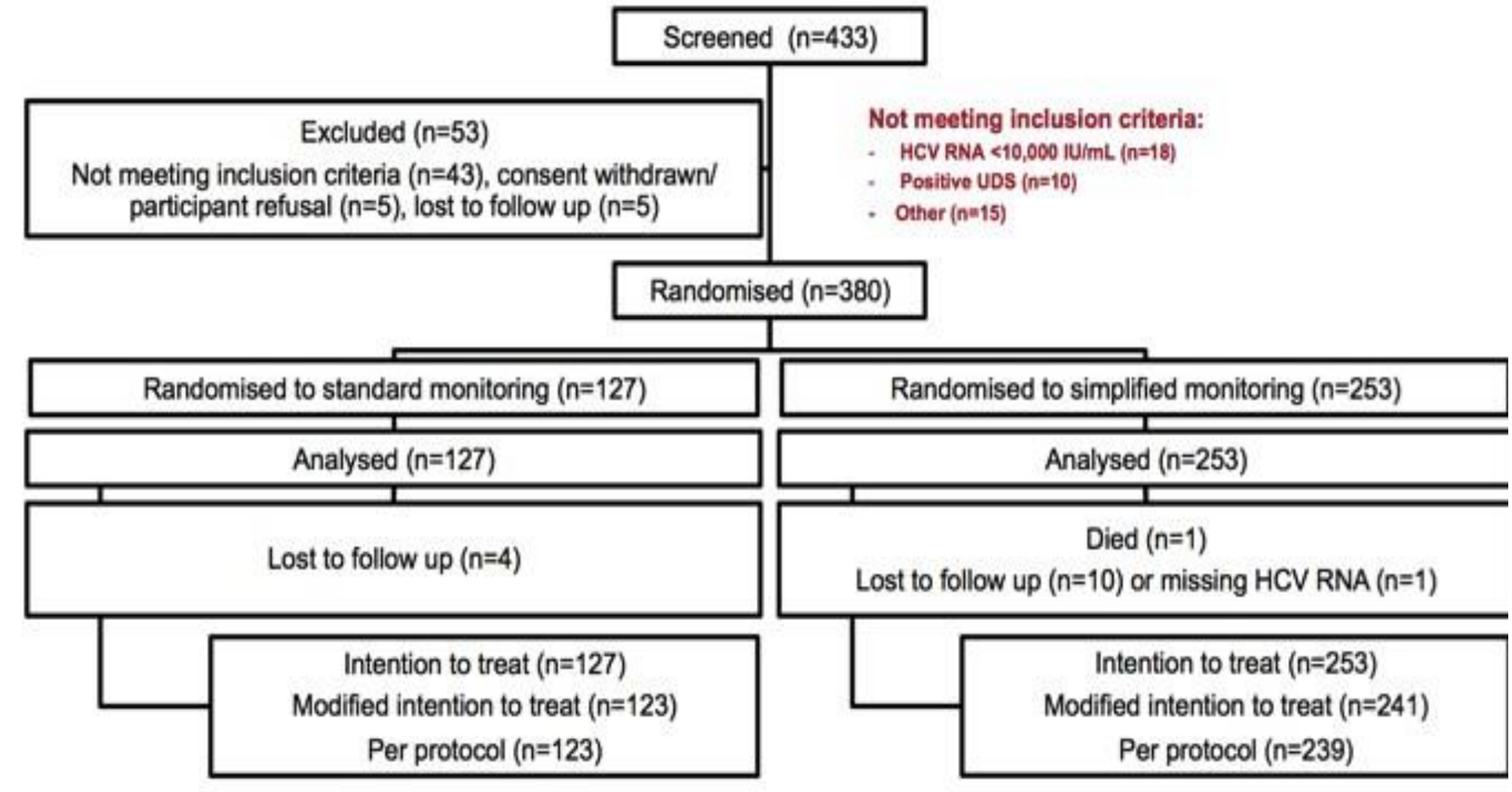
- Secondary endpoints:
  - SVR12 on modified ITT (excluded those without SVR12 follow-up) population
  - SVR12 on PP (completed treatment and SVR12 attended follow-up) population
  - Treatment adherence (>95/95 = treatment adherent)
  - Premature discontinuation and treatment completion
  - Adverse events, including serious adverse events

- Sample size and non-inferiority:
  - **375 planned for enrolment**, based on expected SVR12 of 96% and 80% power to determine non-inferiority
  - **Non-inferiority margin 6%** (lower 95% confidence bound for difference between arms greater than -6%)

Dore G *et al.* EASL 2019

What is the Optimal Treatment Monitoring Schedule?
The SMART-C Trial

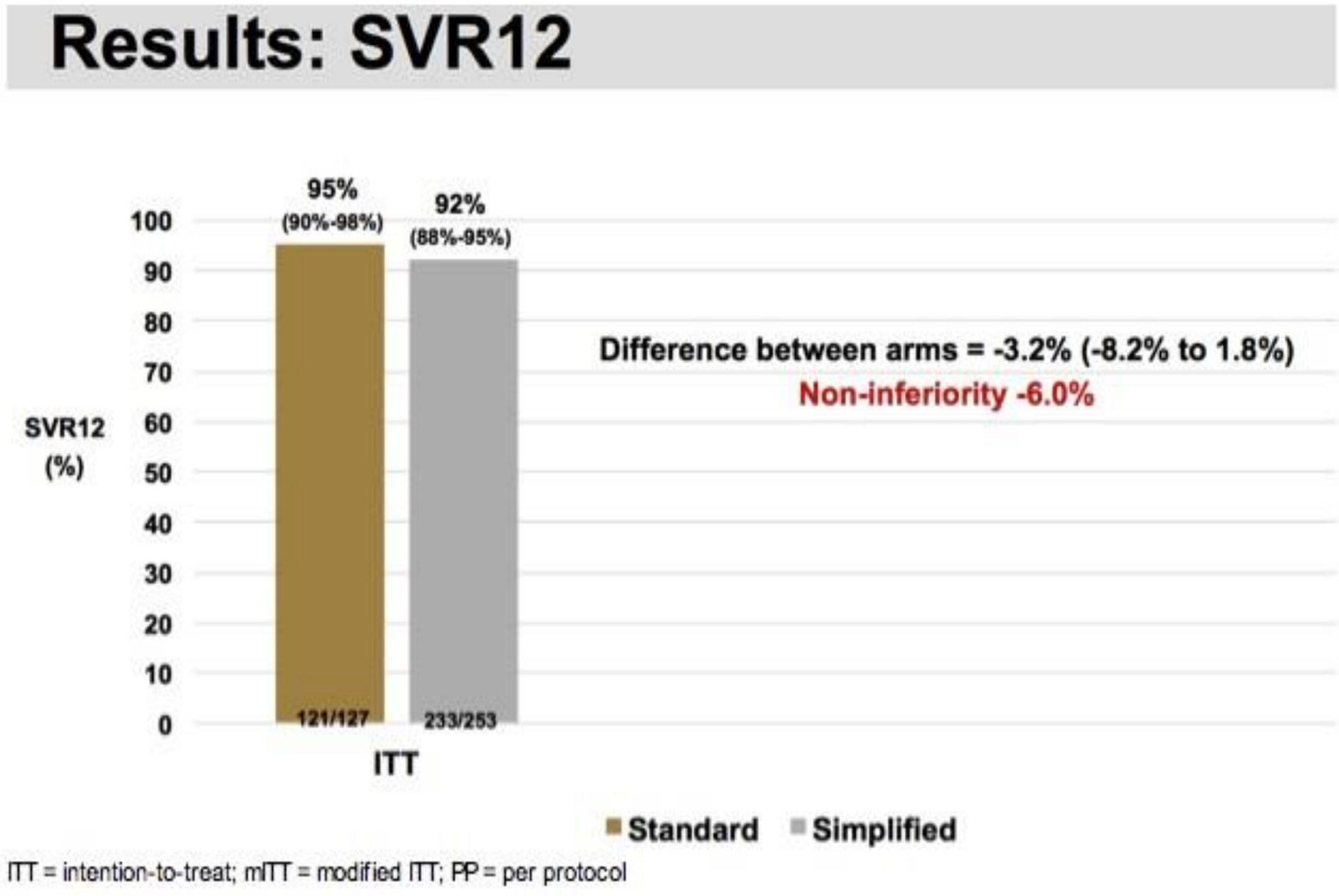
Results: participant disposition



UDS = urinary drug screen

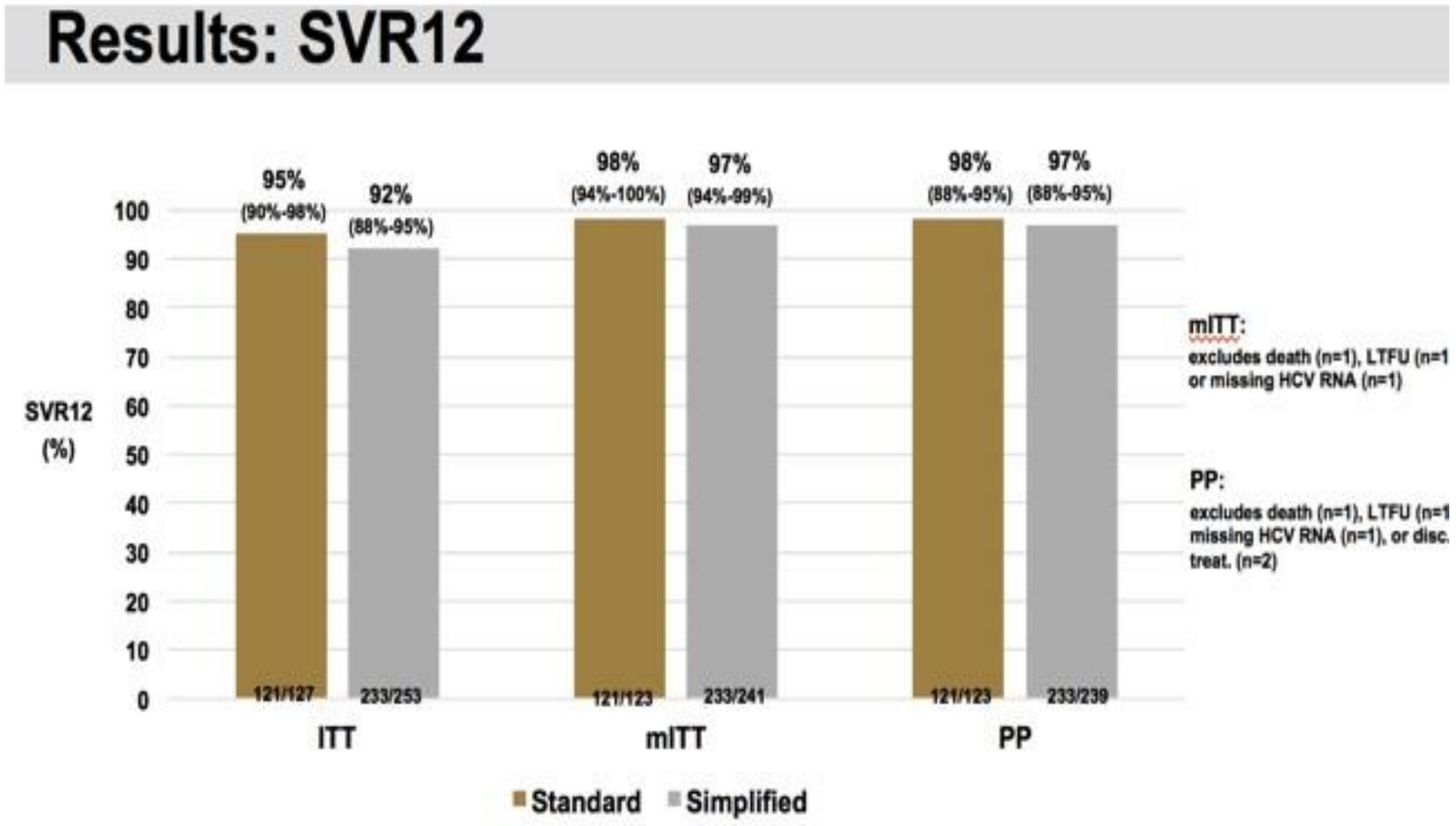
Dore G *et al.* EASL 2019

What is the Optimal Treatment Monitoring Schedule?
The SMART-C Trial



Dore G *et al.* EASL 2019

What is the Optimal Treatment Monitoring Schedule?
The SMART-C Trial



ITT = intention-to-treat; mITT = modified ITT; PP = per protocol; LTFU = lost to follow up

Dore G *et al.* EASL 2019

What is the Optimal Treatment Monitoring Schedule?
The SMART-C Trial

Results: treatment failure

	Standard (n=127)	Simplified (n=253)	Total (n=380)
Virological failure	2 (1.6%)	6 (2.4%)	8 (2.1%)
- On treatment	0	6	
- Post treatment	2		
Failure for other reasons			
- Death	0	1* (0.4%)	1 (0.3%)
- Discontinuation	0	2** (0.8%)	2 (0.5%)
- LTFU / missing HCV RNA	4 (3.1%)	11 (4.3%)	15 (3.9%)

*Death: Lung adenocarcinoma after post-treatment week 4; **Discontinuations: both in week 1

LTFU = loss to follow up

Dore G *et al.* EASL 2019

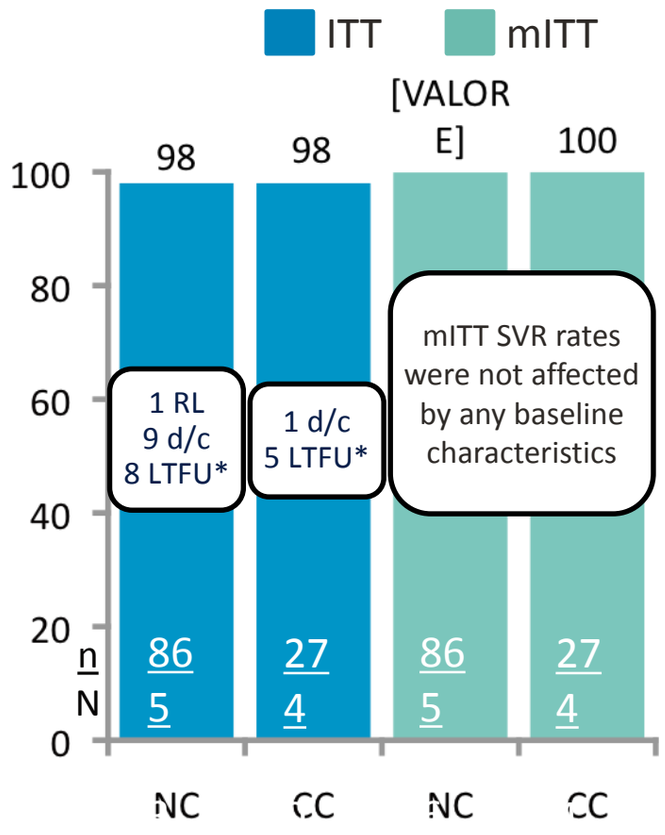
Le ultime evidenze dei congressi

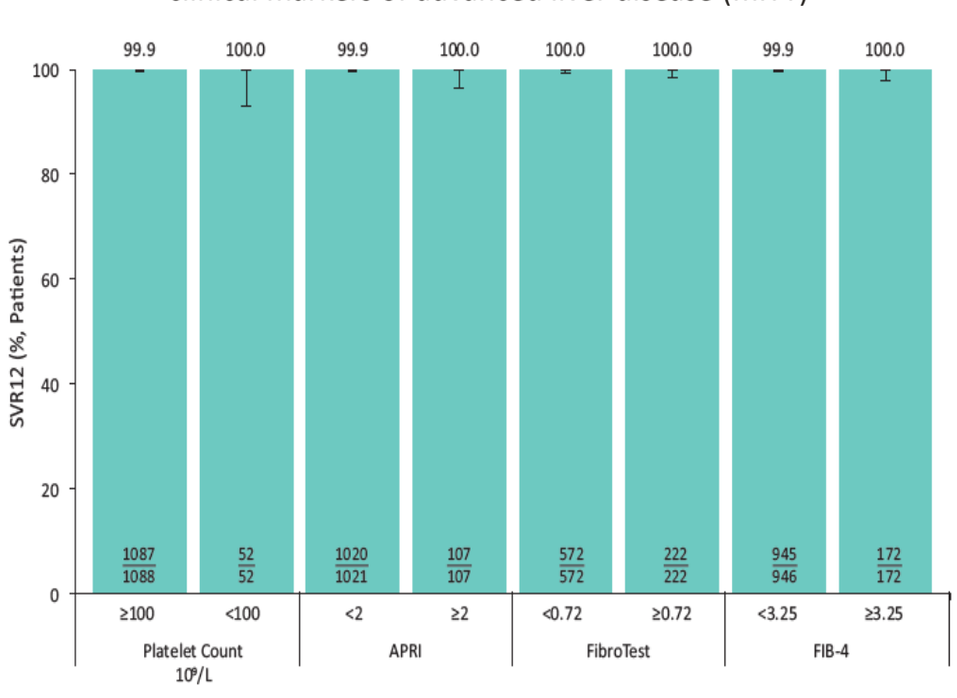
- Dati Real life
- Due opzioni nella pratica clinica
- Ottimizzazione: meglio meno visite ?
- Off label: corto è bello ?
- Eterogeneità virale: ha un ruolo nell’epoca della taglia unica pangenotipica

Efficacy & Safety of G/P Treatment for 8 Weeks in Treatment-Naive Patients with Chronic HCV Infection ± Compensated Cirrhosis: Analysis of Data Pooled from Phase 2 & 3 Studies

A pooled analysis of pre- and post-approval studies evaluating the efficacy and safety of 8 weeks' G/P in TN patients with chronic HCV GT1, 2, or 4–6 infection without cirrhosis or with compensated cirrhosis (N = 1163)

Baseline Characteristics	NC (N = 883)	CC (N = 280)
Male, n (%)	460 (52)	168 (60)
White race, n (%)	697 (79)	223 (80)
Median age, years	53	60
HCV GT, n (%) 1 2 4 5/6	 504 (57) 234 (27) 62 (7) 19 (2)/64 (7)	 231 (83) 26 (9) 13 (5) 1 (< 1)/9 (3)
Fibrosis stage, n/N (%) F0–F1 F2 F3 F4	 577/880 (66) 42/880 (5) 66/880 (8) 0	 0 0 0 280/280 (100)
History of IDU, n/N (%)	323/882 (37)	72/280 (26)





G/P for 8 weeks was highly efficacious and well tolerated in TN patients with chronic HCV GT1, 2, or 4–6 infection, regardless of cirrhosis status and baseline characteristics

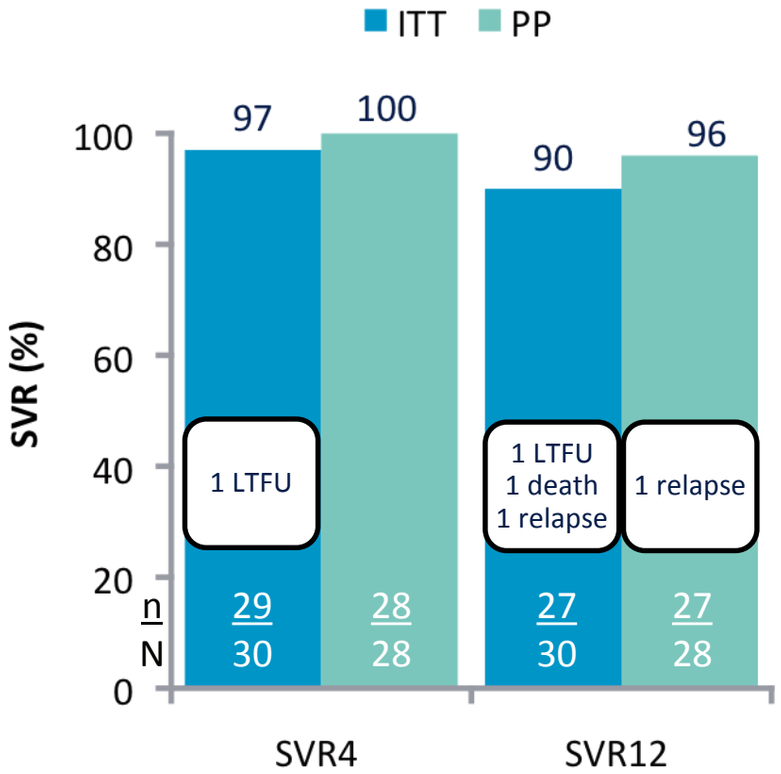
* Some patients were missing data because studies were ongoing.
CC, compensated cirrhosis; d/c, discontinuation; IDU, injection drug use; ITT, intention-to-treat; LTFU, lost to follow-up; mITT, modified ITT; NC, non-cirrhotic; RL, relapse; TN, treatment-naive.

Zuckerman E, *et al.* EASL 2019; poster presentation (THU-198).

Shortened Duration Pan-genotypic Therapy with G/P for 6 Weeks among People with Acute and Recent HCV Infection

Open-label study to assess the efficacy of G/P for 6 weeks in patients with acute and recent HCV infection* in Australia, New Zealand, and England (N = 30)

Baseline Characteristics, n (%)	ITT population (N = 30)
Male	30 (100)
MSM	26 (87)
HIV/HCV co-infection	23 (77)
History of IDU	14 (47)
HCV re-infection	4 (13)
HCV GT	
1	24 (80)
2	1 (3)
3	2 (7)
4	3 (10)



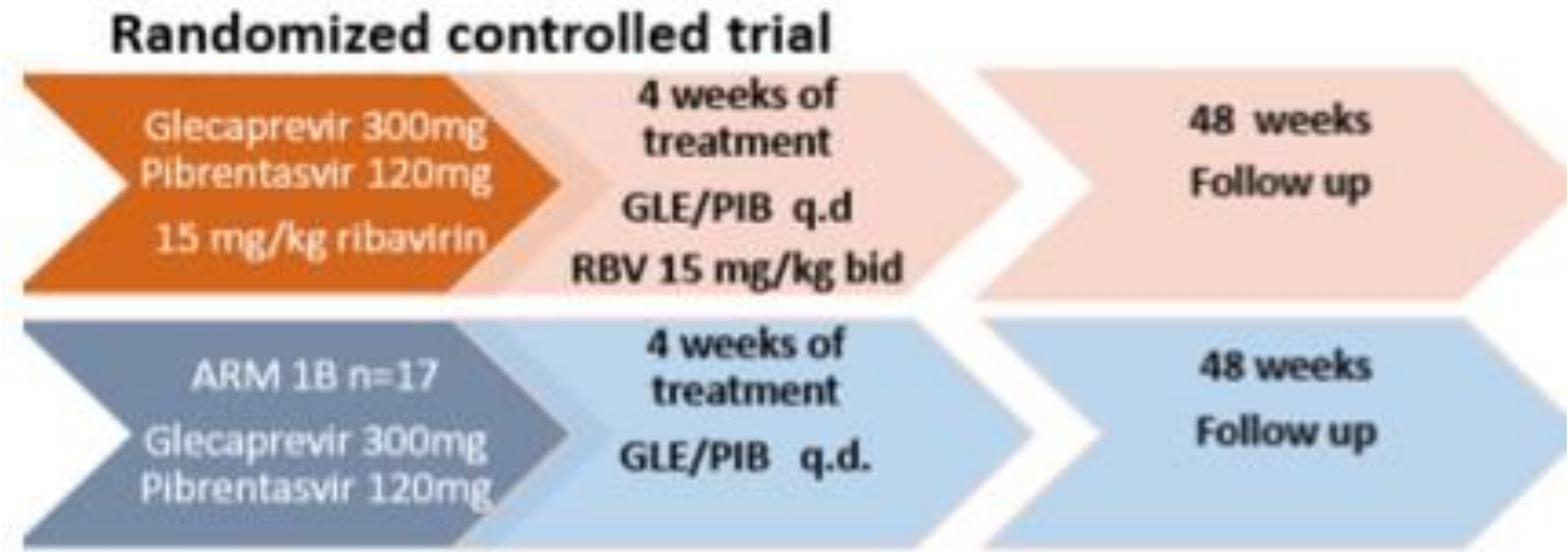
- 1 patient with acute GT1a HCV had virologic failure, confirmed as relapse on sequencing
- Patient had baseline HCV RNA level of ~8 $\log_{10}$ IU/mL

There was one treatment-emergent SAE† and no treatment-related SAEs

* Recent infection defined as HCV infection of < 12 months' duration with a first positive anti-HCV antibody and/or HCV RNA within 6 months of enrollment and either acute clinical hepatitis within the past 12 months (jaundice or ALT > 10 × upper limit of normal) or documented anti-HCV antibody seroconversion within 18 months;

Martinello M, *et al.* EASL 2019; poster presentation (THU-157).

Ultra Short Treatment with G/P. Is it Possible?



Main inclusion criteria

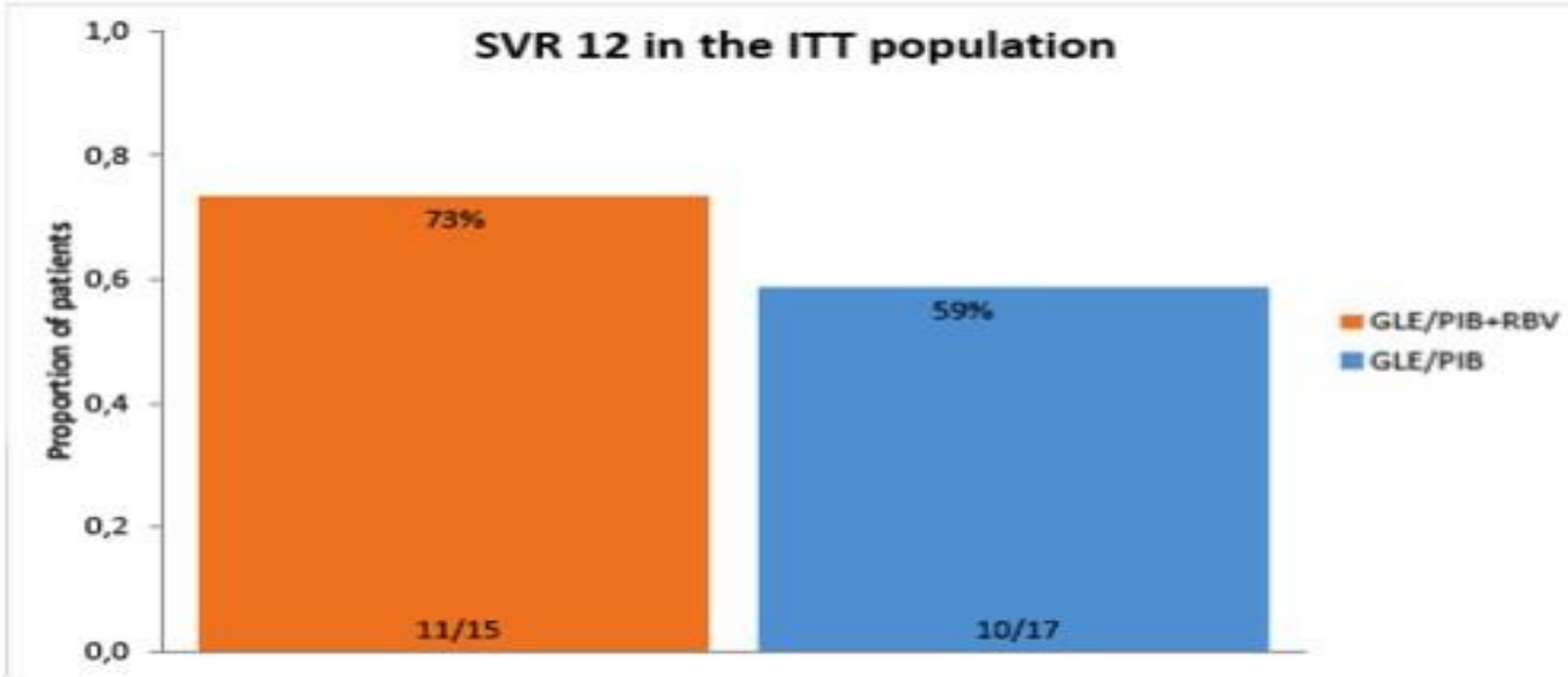
- Chronic hepatitis C of all genotypes
- Age 18-49
- Fibroscan <8 kPa or Liver biopsy with F0 or F1 (Metavir score)
- Naive to all hepatitis C treatment
- Negative test for anti-HIV and HBsAg

Main exclusion criteria

- Hemoglobin <7.0 mmol/l
- Any clinical or laboratory suspicion of cirrhosis
- Contraindication to treatment with study drugs

Madsen LW et al, EASL 2019

Ultra Short Treatment with G/P. Is it Possible?



RESULTS - CONTINUED

Viral recurrence

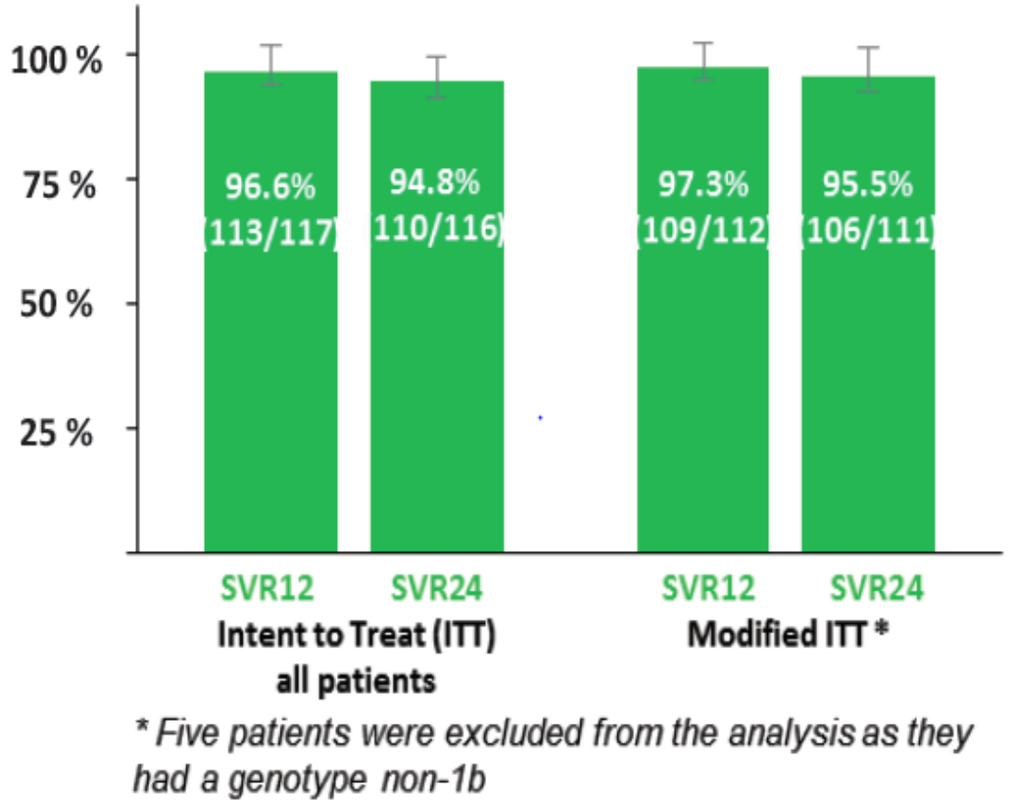
- Viral recurrence was observed in 11 individuals.
- 91% (10/11) with viral recurrence were INFL3 non CC (not significant, p=0.12).

- Madsen LW et al, EASL 2019

Elbasvir Grazoprevir in HCV G1b F0-F2 Study Results

Twelve weeks after EOT (SVR12) 97.3% (109/112) of patients had HCV RNA<LLOQ.
Overall, 3 patients relapsed at week 12 and 2 other patients at week 24 post-treatment despite reaching SVR12.
SVR24 results was 95.5% (106/111), one patient is lost to follow-up.

No adverse event grade III or IV was observed. The main adverse events with a frequency higher than 10% were asthenia (28%), headache (23%) and digestive disorders (13%).



** Five patients were excluded from the analysis as they had a genotype non-1b*

Characteristics of the 5 relapsers

	BMI Kg/m2	ALT ULN	Viral load IU/mL	Fibrosis Score	Date of relapse	RAS at baseline	RAS at relapse
Patient 1	31.4	1.6	14.000.000	6.4 kPa (F0-F1)	FU 12	Y93H[a]	Y93H[a]
Patient 2	25.5	0.7	16.437.573	5.1 kPa (F0-F1)	FU 4	L31M[a] Y93H[a]	L31M[a] Y93H[a]
Patient 3	22.5	1.25	8.250.000	4.9 kPa (F0-F1)	FU 12	Y93H[a]	L31M[a] Y93H[a]
Patient 4	28.3	0.9	1 819 701	6.3 kPa (F0-F1)	FU 24	Y93H[a]	Y93H[a] L31F[a]
Patient 5	20.3	0.5	5 736 800	4.3 kPa (F0-F1)	FU 24	Y56F[b] Y93H[a]	Y56F[b] R155W[b] L31V[a] Y93H[a]

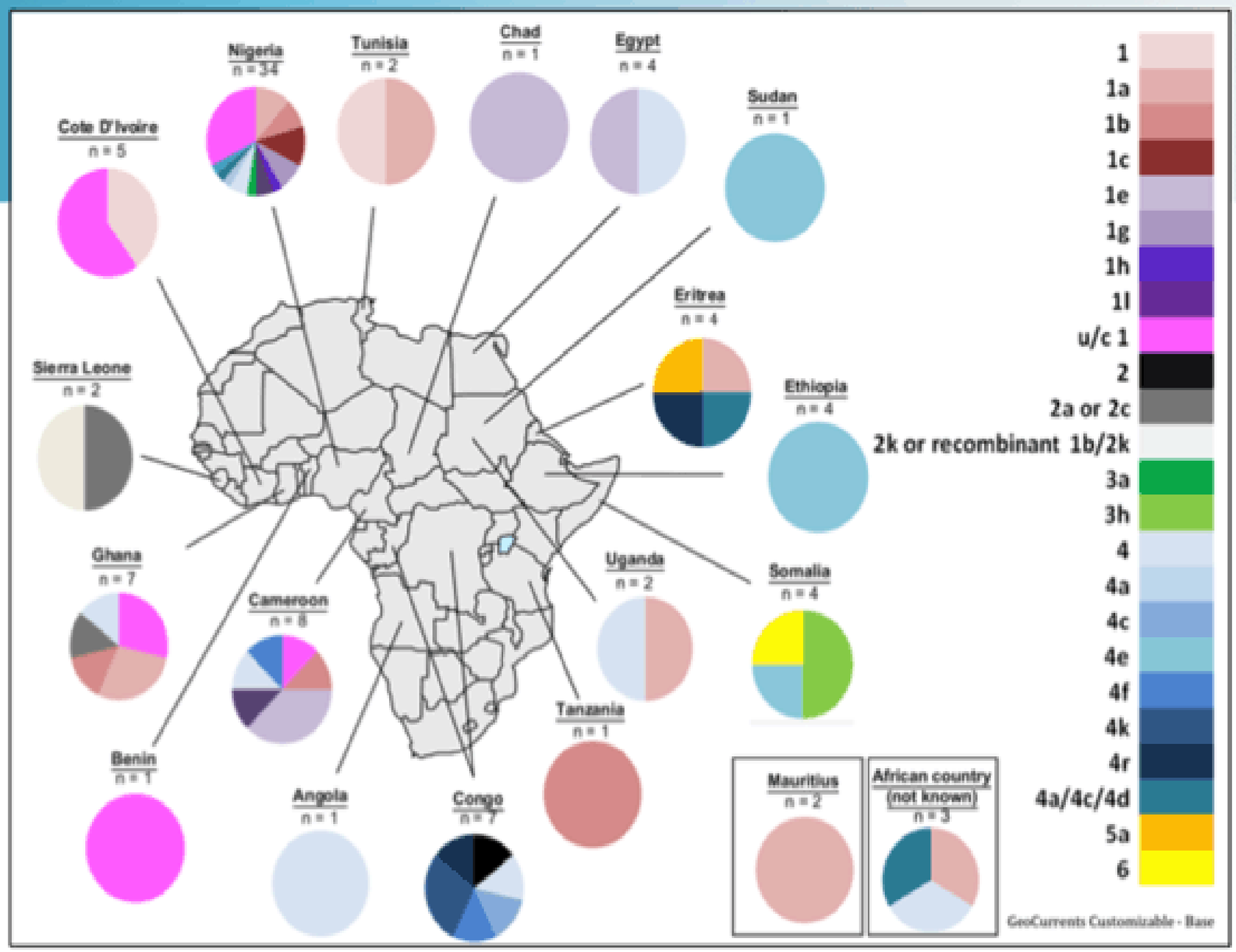
[a] NS5A RAS [b] NS3 RAS

Abergel A. et al. A Phase 3, Global, Multicenter, Open-Label Study to Investigate the Efficacy of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve, HCV GT1b-Infected Patients, with non-severe fibrosis : STREAGER

Le ultime evidenze dei congressi

- Dati Real life
- Due opzioni nella pratica clinica
- Ottimizzazione: meglio meno visite ?
- Off label: corto è bello ?
- Eterogeneità virale: ha un ruolo nell’epoca della taglia unica pangenotipica

47/91 African patients (52%) were infected by distinct subtypes

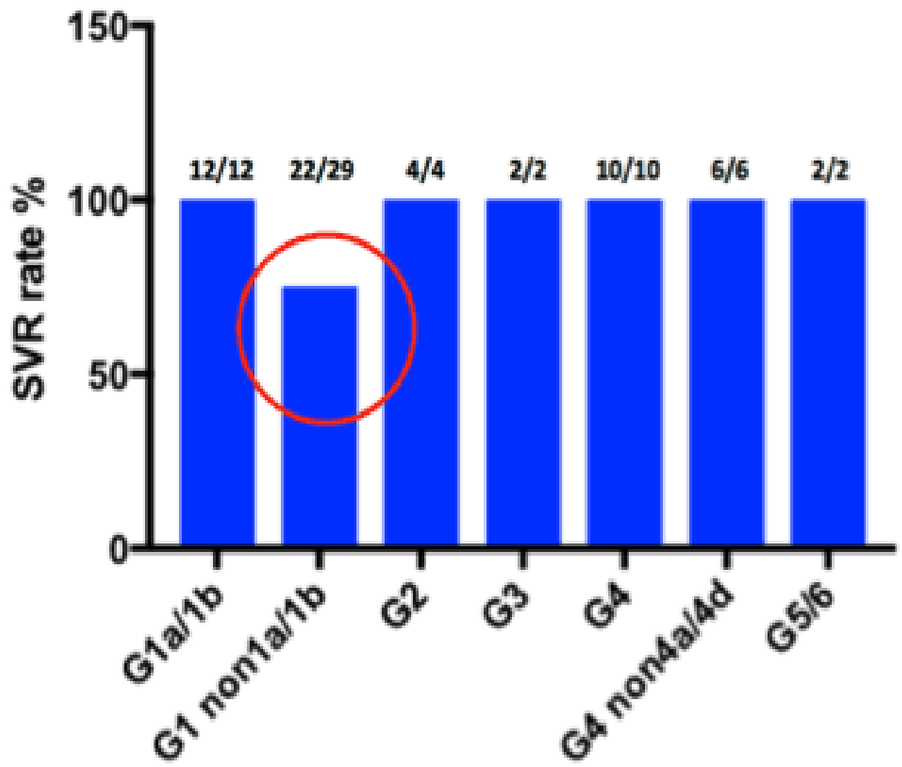


Geographical distribution of patients in the cohort and their HCV genotypes

Childs K et al., EASL 2019

There was a lower SVR rate in those with distinct subtypes of G1

Overall SVR rate of 75% in Distinct G1 Subtypes



In univariate analysis, distinct genotype 1 and use of NS5A based regimen were associated with failure to achieve SVR

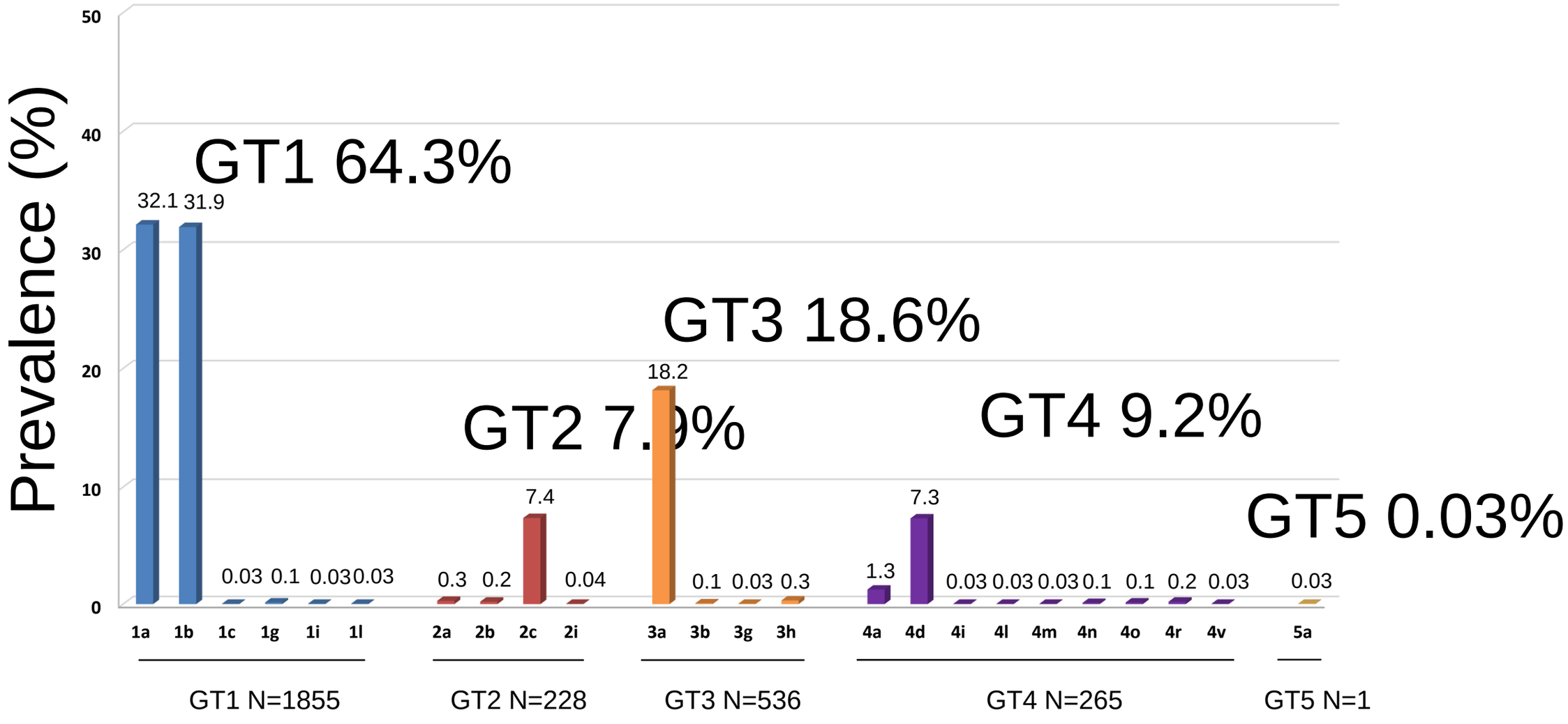
Childs K et al. EAS

In distinct African subtypes, there was a high prevalence of NS5A polymorphisms at baseline

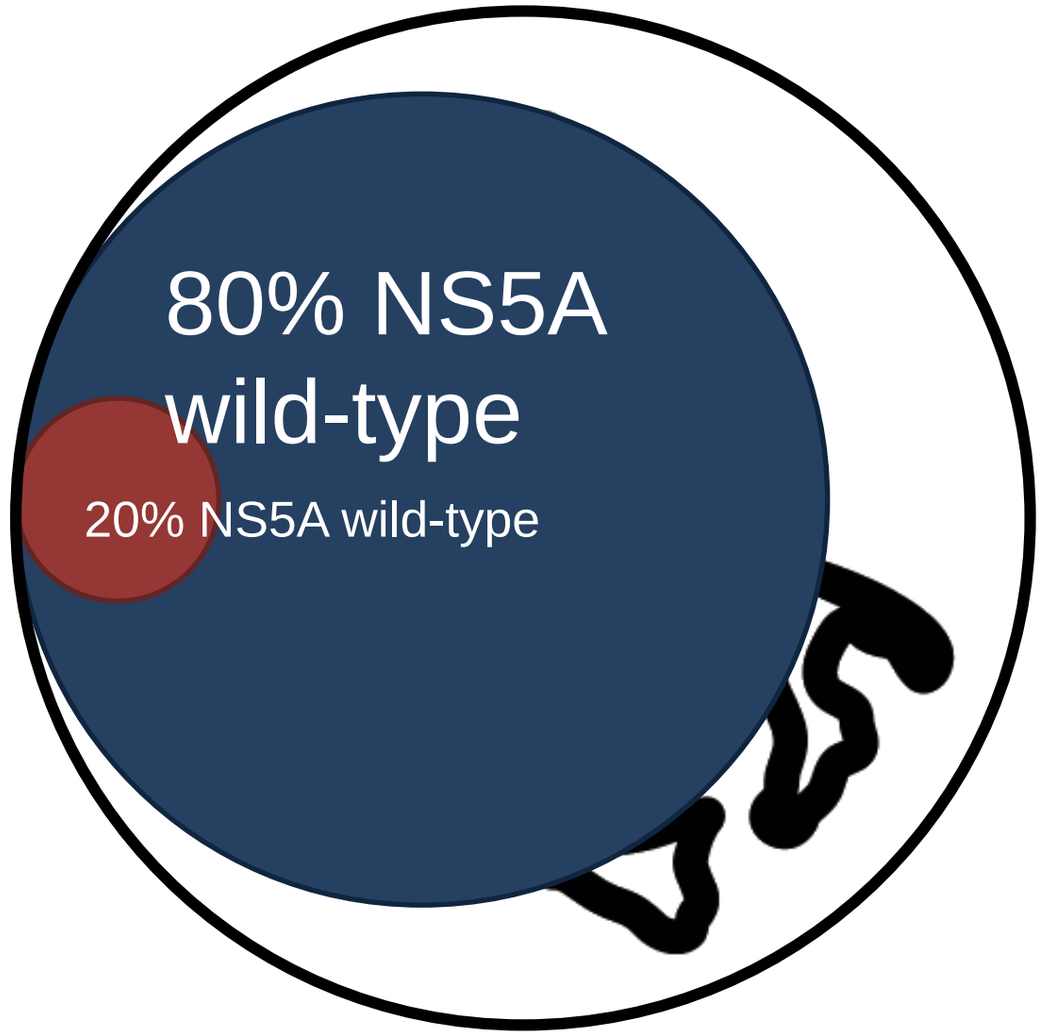
		NS5A											
	Subtype	K24	K26	M28	P29	Q30	L31	P32	S38	H58	Q62	A92	Y93
Relapser	1L	G	K	M	P	Q	M	P	S	P	Q	A	Y
Relapser	u/c 1	K	K	M	P	Q	M	P	S	P	E	A	Y
Relapser	u/c 1	K	K	L	P	Q	L	P	S	P	D	A	Y
Relapser	u/c 1	K	K	S	P	L	L	P	S	P	P	A	Y
Relapser	1L	G	K	M	P	R	M	P	S	P	Q	A	Y
Relapser	1L	S	K	M	P	Q	M	P	S	P	Q	A	Y
SVR	1L	G	K	M	P	Q	L	P	S	P	Q	A	Y
SVR	u/c 1	K	K	M	P	Q	M	P	S	P	D	A	Y
SVR	u/c 1	K	K	M	P	Q	L	P	S	P	D	A	Y
SVR	u/c 1	Q	K	M	P	Q	L	P	S	P	K	A	H
SVR	u/c 1	K	K	M	P	Q	L	P	S	P	D	A	Y
SVR	u/c 1	Q	K	L	P	R	L	P	S	P	Q	A	Y
SVR	u/c 1	K	K	M	P	Q	L	P	S	P	Q	A	Y
SVR	u/c 1	Q	K	L	P	L	M	P	S	P	K	A	Y
SVR	u/c 1	K	K	L	P	L	M	P	S	P	Q	A	Y
SVR	u/c 1	K	K	M	P	Q	L	P	S	H	E	A	Y
SVR	1e	Q	K	L	P	R	M	P	S	P	Q	T	Y
SVR	u/c 1	K	K	V	P	Q	L	P	S	P	D	A	Y
SVR	u/c 1	K	K	V	P	T	L	P	S	P	Q	A	N
SVR	1g	R	K	L	P	Q	L	P	S	P	Q	A	F
SVR	u/c 1	S	K	M	P	Q	L	P	S	S	Q	A	Y
SVR	u/c 1	K	K	M	P	Q	L	P	A	P	D	A	Y

Childs K et al., EA

HCV genotypes/subtypes distribution within the Italian Resistance Database VIRONET C (N=2885 patients with an available sample amplified)



Last update: May 6, 2019



Natural NS5A RASs prevalence in **NS5A-naive** patients in Italy:

20%[1]

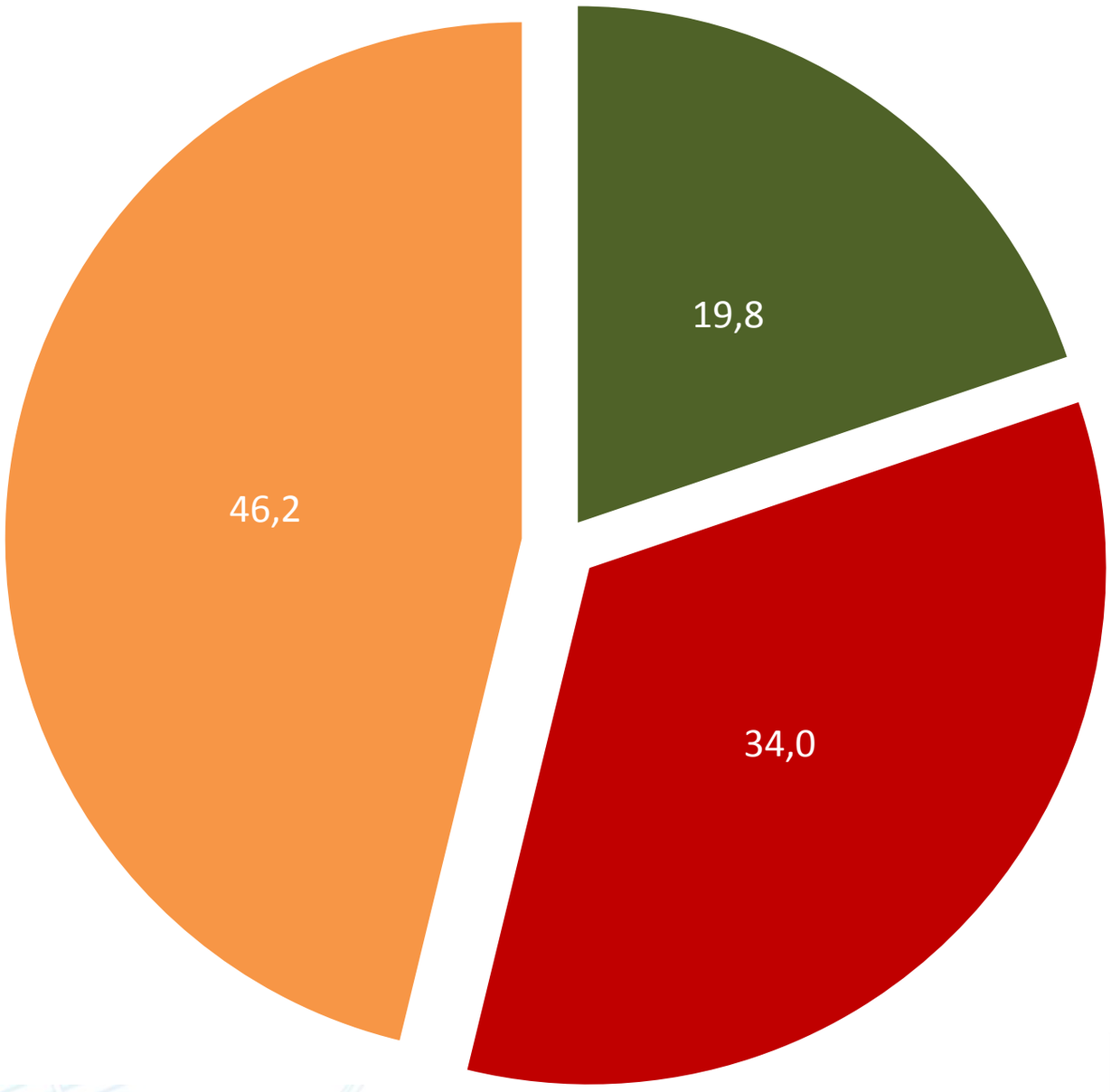
NS5A RASs prevalence in **NS5A-experienced** patients in Italy:

80-92%[2-4]

[1]Bertoli A et al., Sci Rep. 2018 Jun 12;8(1):8988; [2]Ceccherini Silberstein F. et al., Hepatology. 2016 Mar;63(3):1058-9; [3]Di Maio V.C. et al., EASL 2019; [4]Degasperi E. et al., EASL 2019

What to expect in a DAA failing patient, when considering retreatment

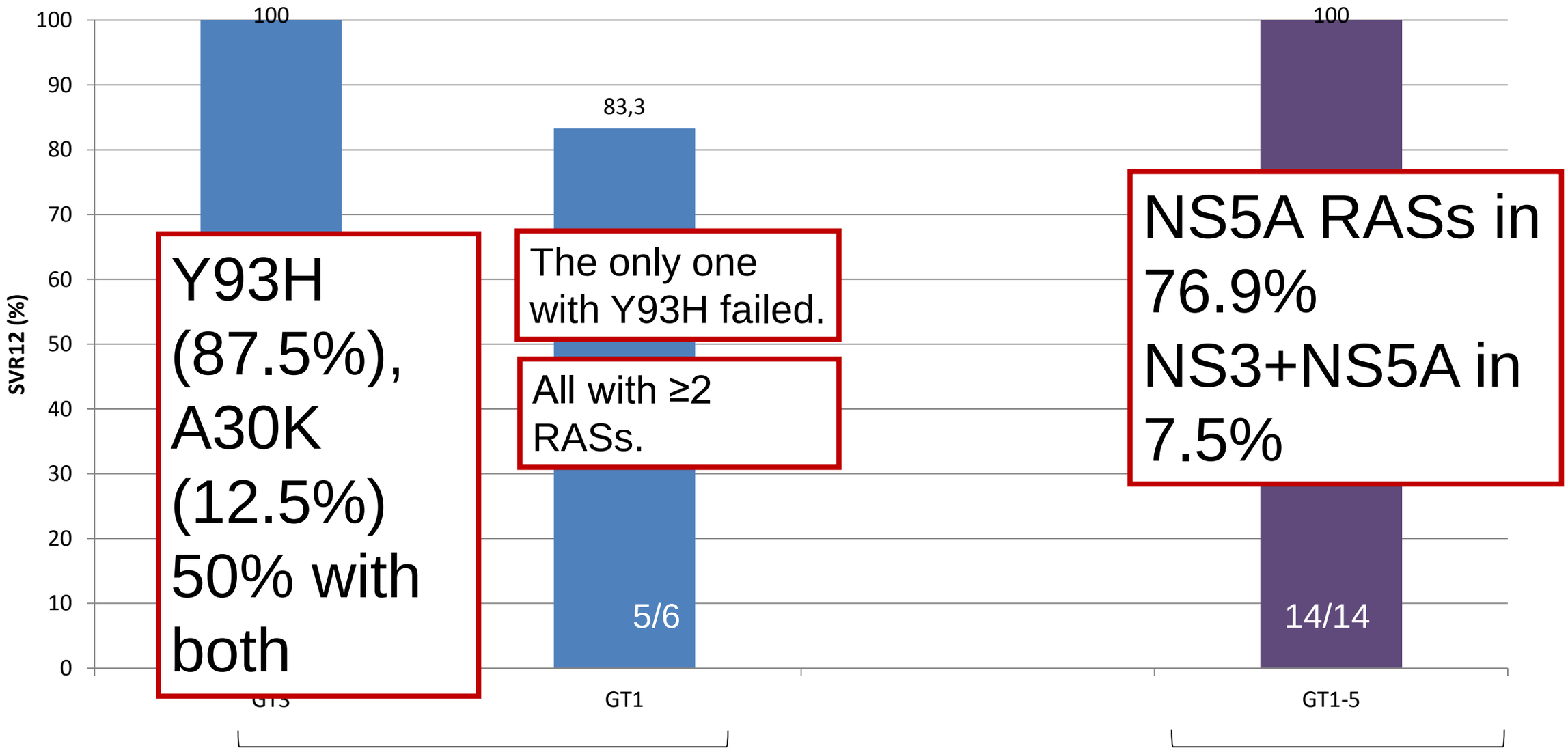
Within the Italian VIRONET-C, a total of 444 patients who failed a NS5A inhibitor-containing regimen recommended by the 2016 or 2018 EASL guidelines, and with a valid resistance test at failure, were analyzed.



EASL The Home of Hepatology | THE INTERNATIONAL LIVER CONGRESS™ APRIL 10 - 14, VIENNA, AUSTRIA 2019

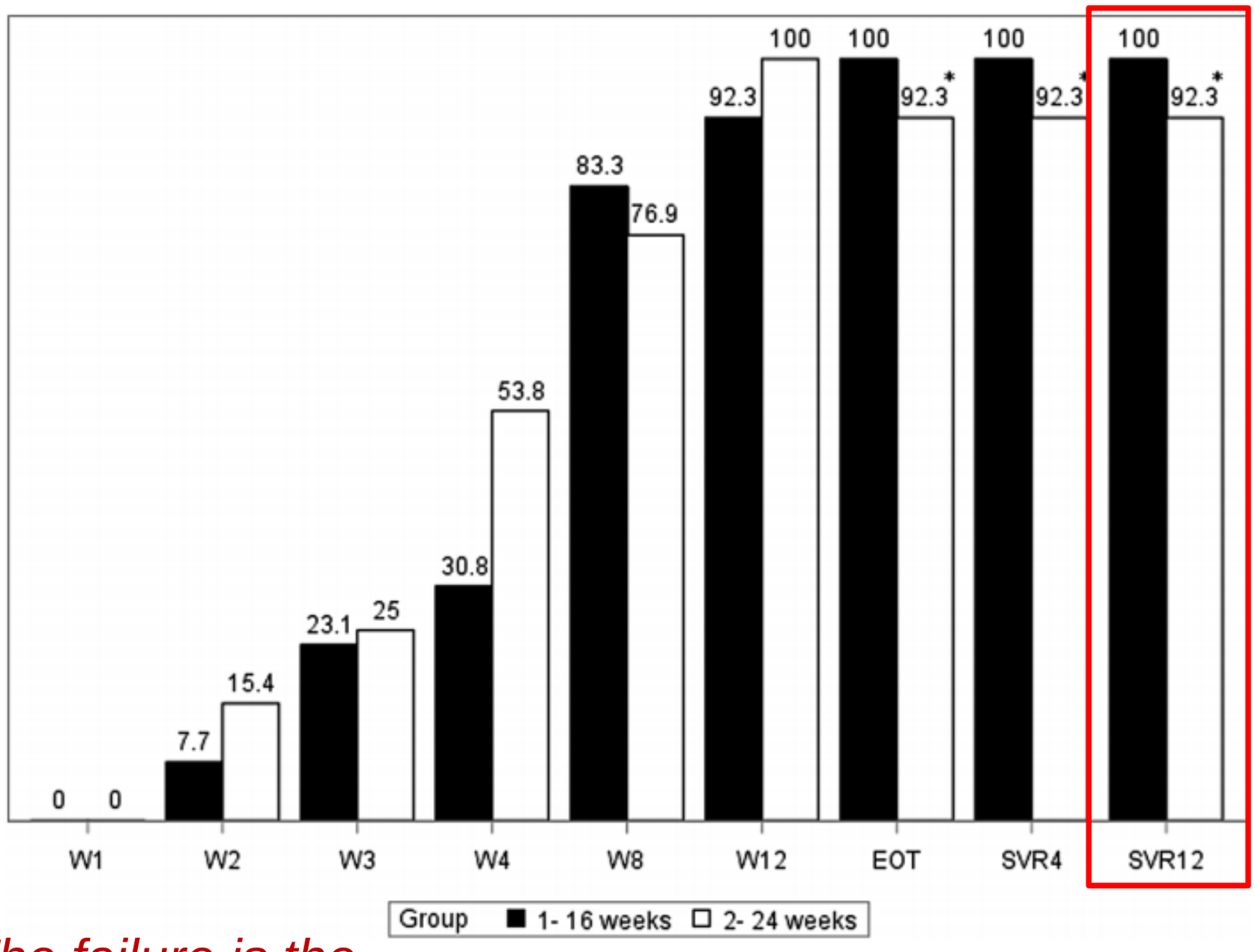
Di M C. et al., EASL 2019

Sofosbuvir + Glecaprevir/Pibrentasvir in patients with difficult to treat HCV infection. Clinical trial and real-life



[1]Wyles D, et al. EASL 2018 [Abstract PS-040]; [2]Ledinghen V.D. et al., EASL 2018, [Abstract THU-291]

Retreatment with Grazoprevir/Elbasvir + Sofosbuvir led to very high SVR rates in GT1 and GT4 patients: ANRS HC34 REVENGE



- 26 patients underwent 16 or 24 weeks of treatment, always with ribavirin.
- 50% with cirrhosis.
- 92% with NS5A RASs, most commonly Y93H.

**The failure is the deceased patient.*

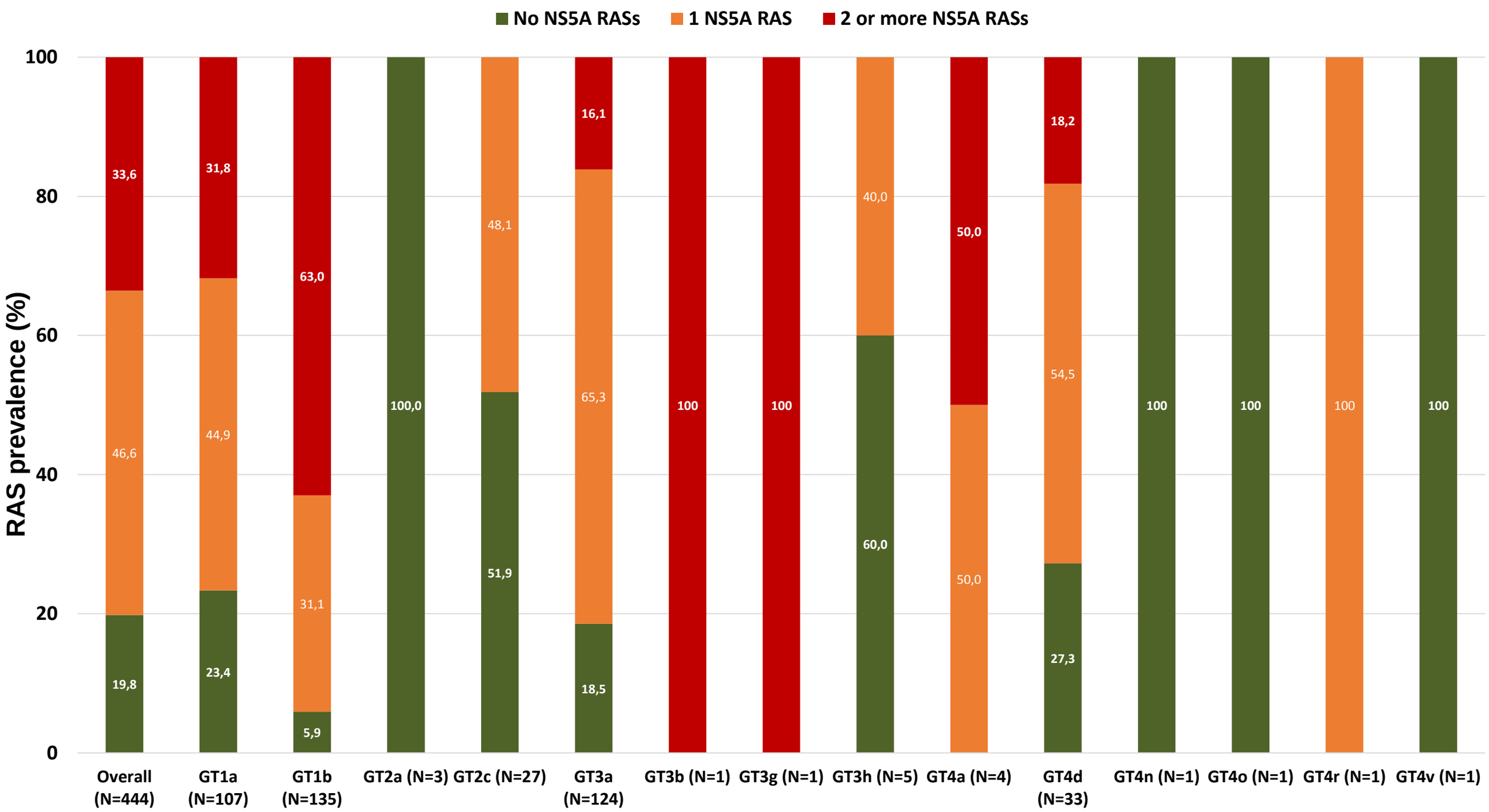
de Lédinghen et al., Clin Inf Dis 2018

Within the Italian VIRONET-C, a total of 444 patients who failed a NS5A inhibitor-containing regimen recommended by the 2016 or 2018 European Association for the Study of the Liver (EASL) guidelines, and with a valid resistance test at failure, were analyzed.

DAA regimen	HCV genotype/subtype														Total
	1a	1b	2a	2c	3a	3b	3g	3h	4a	4d	4n	4o	4r	4v	
DCV+SOF ±RBV	8	5		7	86	1		2		3		1			113
2D ±RBV	1									3	1				5
LDV/SOF ±RBV	36	67			4				4	21				1	133
3D ±RBV	38	32		3	12			3							88
EBR/GZR ±RBV	5	27								5					37
GLE/PIB	7	1	1	11	9					1					30
SOF/VEL ±RBV	12	3	2	6	13		1						1		38
Total	107	135	3	27	124	1	1	5	4	33	1	1	1	1	444

Di Maio V.C. et al., EASL 2019

Complex NS5A RASs patterns were common across HCV-genotypes and subtypes …



Di Maio V.C. et al., EASL 2019

Within VIRONET-C, 125 NS5A-experienced patients were retreated with a second generation DAA regimen

	Males, N(%)	90 (72.0)
	Age (years), Median (IQR)	57 (50-64)
HCV geno/subtype	1a	34 (27.2)
	1b	42 (33.6)
	2a/c	8 (6.4)
	3a/b/g	29 (23.2)
	4a/d/n/o	12 (9.6)
	HCC, N (%)	7 (5.6)
	HIV coinfection, N (%)	10 (9.9)
	Cirrhotic patients, N (%)	61 (49.6)
	IFN experienced[a], N (%)	35 (47.3)
Prior DAA experience	DCV+SOF ±RBV	27 (21.6)
	2D	1 (0.8)
	SOF/LDV ±RBV	36 (28.8)
	3D ±RBV	26 (20.8)
	EBR/GZR ±RBV	20 (16.0)
	SOF/VEL ±RBV	8 (6.4)
	GLE/PIB	7 (5.6)

[a]3 patients had previously failed a treatment with telaprevir or boceprevir

2D, paritaprevir/ritonavir, ombitasvir; 3D, paritaprevir/ritonavir, ombitasvir and dasabuvir; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; IQR, interquartile range

Di Maio V.C. et al., EASL 2019

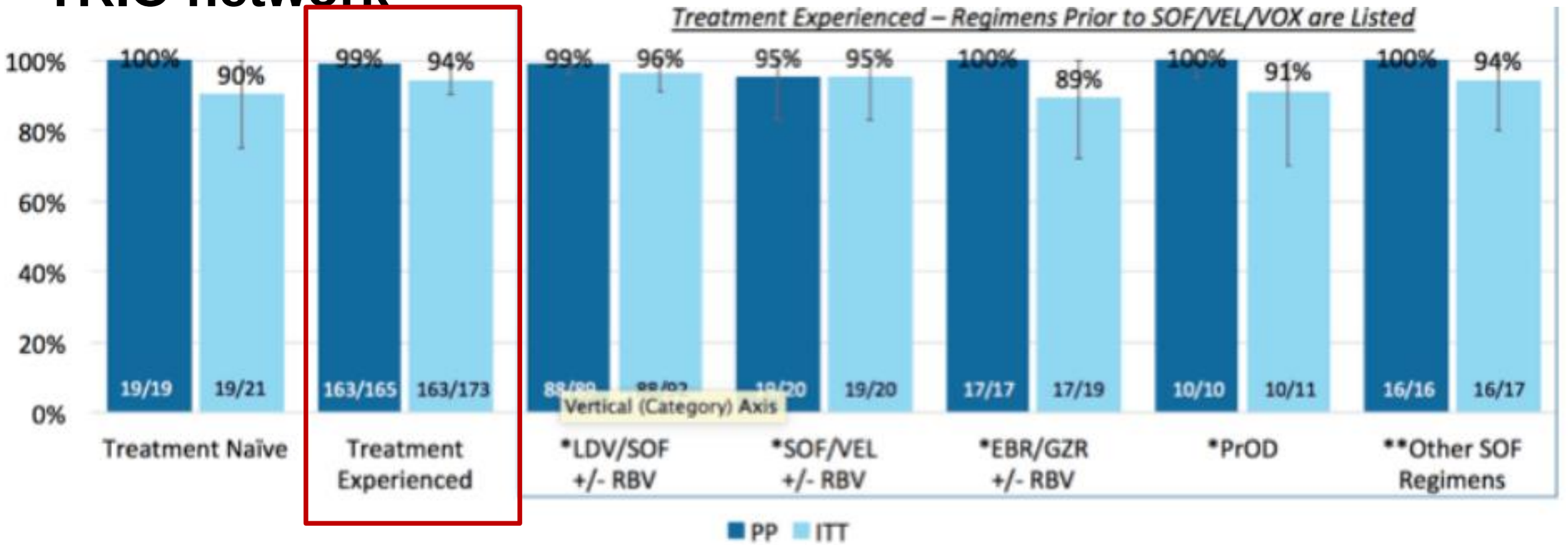
Within VIRONET-C, 125 NS5A-experienced patients were retreated with a second generation DAA regimen

DAA regimen		Ribavirin association, N(%)	HCV genotype, N(%)					SVR_{12}*, N(%)
			1a	1b	2	3	4	
SOF/VEL/VOX	*12 weeks, N=84*	14 (16.7)	23 (27.4)	28 (33.3)	6 (7.1)	17 (20.2)	10 (11.9)	45 (90.0)
SOF/VEL	*12 weeks, N=7*	1 (14.3)	3 (42.9)	1 (14.3)	2 (28.6)	-	1 (14.3)	5 (71.4)
	16 weeks, N=1	-	-	-	-	1 (100)	-	1 (100)
	24 weeks, N=22	14 (63.6)	4 (18.2)	8 (36.4)	-	9 (40.9)	1 (4.5)	15 (78.9)
GLE/PIB	*8 weeks, N=1*	-	-	1 (100)	-	-	-	1 (100)
	12 weeks, N=5	1 (20.0)	1 (20.0)	3 (60.0)	-	1 (20.0)	-	5 (100)
	16 weeks, N=1	-	-	-	-	1 (100)	-	1 (100)
GRZ/EBV+SOF	*12 weeks, N=1*	1 (100)	1 (100)	-	-	-	-	1 (100)
	24 weeks, N=2	2 (100)	1 (50.0)	1 (50.0)	-	-	-	
GRZ/EBV	*24 weeks, N=1*	1 (100)	1 (100)	-	-	-	-	1 (100)
Overall	N=125	30 (24.0)	26.8	34.1	4.9	29.3	4.9	75 (79.8)

* Currently available for 94 patients

Modified from Di Maio V.C. et al., EASL 2019

Effectiveness of the salvage therapy sofosbuvir/velpatasvir/ voxilaprevir (SOF/VEL/VOX) in chronic hepatitis C; clinical practice experience from the TRIO network



Bacon B. et al., EASL 2019

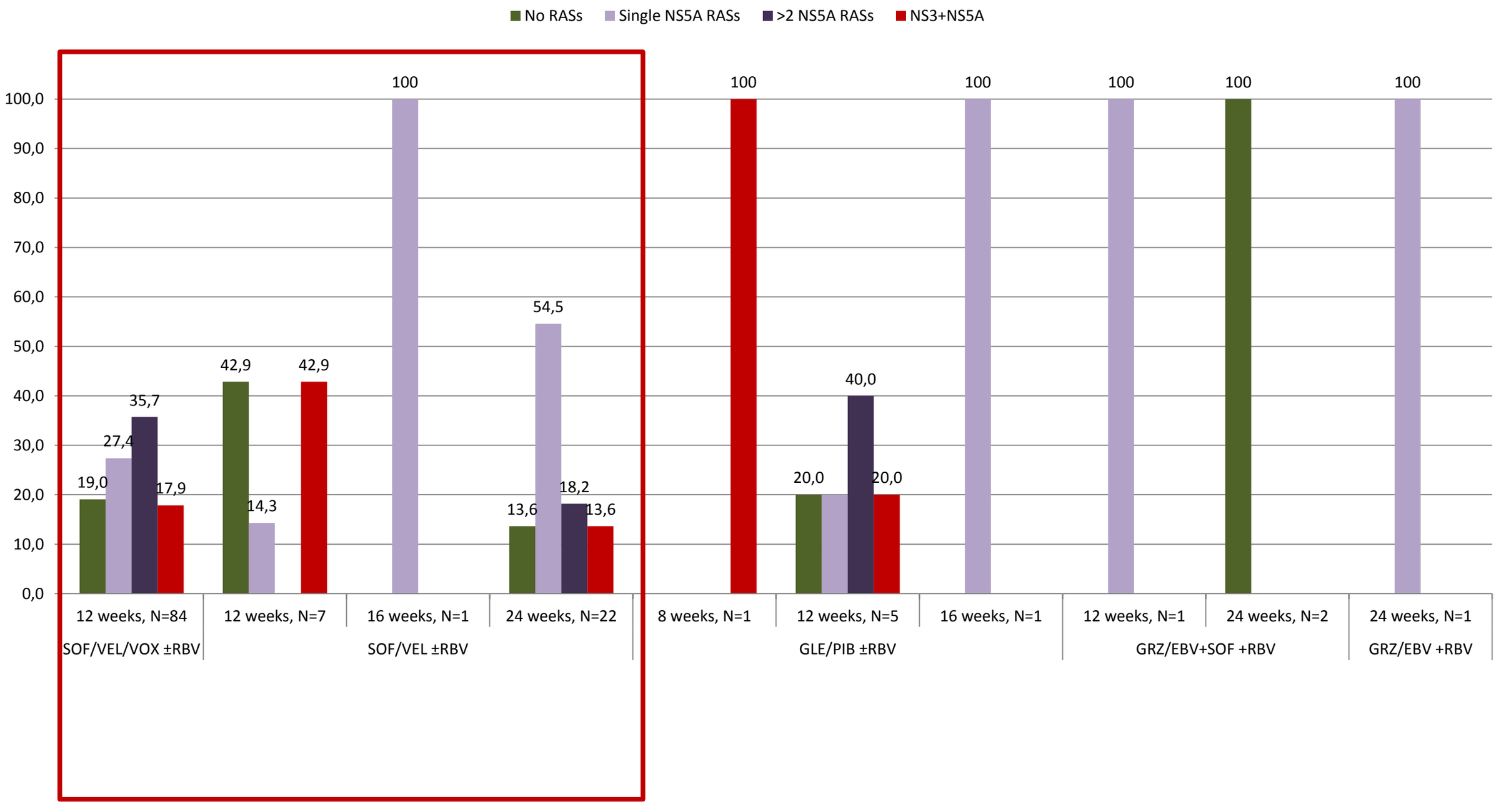
Within VIRONET-C, 125 NS5A-experienced patients were retreated with a second generation DAA regimen

DAA regimen		Ribavirin association, N(%)	HCV genotype, N(%)					SVR_{12}*, N(%)
			1a	1b	2	3	4	
SOF/VEL/VOX	*12 weeks, N=84*	14 (16.7)	23 (27.4)	28 (33.3)	6 (7.1)	17 (20.2)	10 (11.9)	45 (90.0)
SOF/VEL	*12 weeks, N=7*	1 (14.3)	3 (42.9)	1 (14.3)	2 (28.6)	-	1 (14.3)	5 (71.4)
	16 weeks, N=1	-	-	-	-	1 (100)	-	1 (100)
	24 weeks, N=22	14 (63.6)	4 (18.2)	8 (36.4)	-	9 (40.9)	1 (4.5)	15 (78.9)
GLE/PIB	*8 weeks, N=1*	-	-	1 (100)	-	-	-	1 (100)
	12 weeks, N=5	1 (20.0)	1 (20.0)	3 (60.0)	-	1 (20.0)	-	5 (100)
	16 weeks, N=1	-	-	-	-	1 (100)	-	1 (100)
GRZ/EBV+SOF	*12 weeks, N=1*	1 (100)	1 (100)	-	-	-	-	1 (100)
	24 weeks, N=2	2 (100)	1 (50.0)	1 (50.0)	-	-	-	
GRZ/EBV	*24 weeks, N=1*	1 (100)	1 (100)	-	-	-	-	1 (100)
Overall	N=125	30 (24.0)	26.8	34.1	4.9	29.3	4.9	75 (79.8)

* Currently available for 94 patients

Modified from Di Maio V.C. et al., EASL 2019

RAS profile at baseline of retreatment



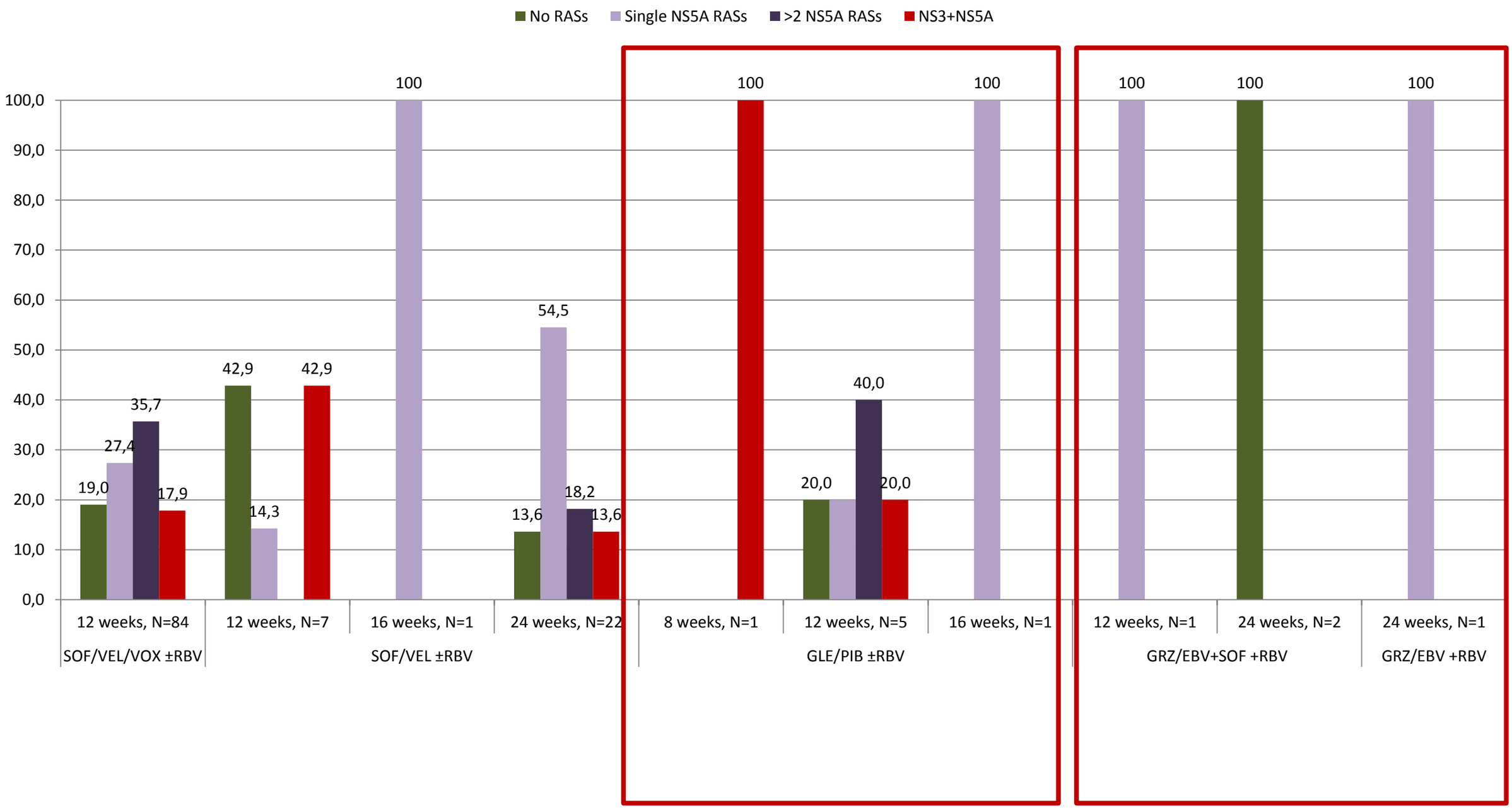
Modified from Di Maio V.C. et al., EASL 2019

11 patients failed retreatment:
5 with SOF/VEL/VOX and 6 with VEL+SOF+/-RBV

ID/Paziente	Cirrhosis	HCV genotype	Previous DAA regimen	NS3 resistance		NS5A resistance	
				Baseline	Failure	Baseline	Failure
SOF/VEL/VOX for 12 weeks							
3806	yes	1b	3D	-	n.a.	-	n.a.
663	yes	4d	LDV/SOF	D168V	n.a.	M31V+Y93H	n.a.
3817	yes	1a	LDV/SOF	-	n.a.	Q30R+L31M	n.a.
6971	yes	1a	LDV/SOF	Q80K	n.a.	-	n.a.
10125	no	1a	VEL/SOF	Q80K	n.a.	-	n.a.
VEL/SOF for 12 weeks							
2649	no	1b	3D	Y56H+D168V	n.a.	Y93H	n.a.
4827	no	2c	DCV+SOF	-	n.a.	-	n.a.
VEL/SOF plus RBV for 24 weeks							
933	yes	1a	LDV/SOF	Q80K	Q80K	Q30K+A92T+Y93H	Q30K+**L31M**+A92T+Y93H
1641	yes	1a	LDV/SOF	-	-	L31M	L31V
2669	yes	1b	LDV/SOF	-	n.a.	L31I+Y93H	n.a.
3767	yes	3a	DCV+SOF	-	-	Y93H	Y93H

Di Maio V.C. et al., EASL 2019

RAS profile at baseline of retreatment



Modified from Di Maio V.C. et al., EASL 2019

Within VIRONET-C, 125 NS5A-experienced patients were retreated with a second generation DAA regimen

DAA regimen		Ribavirin association, N(%)	HCV genotype, N(%)					SVR_{12}*, N(%)
			1a	1b	2	3	4	
SOF/VEL/VOX	*12 weeks, N=84*	14 (16.7)	23 (27.4)	28 (33.3)	6 (7.1)	17 (20.2)	10 (11.9)	45 (90.0)
	12 weeks, N=7	1 (14.3)	3 (42.9)	1 (14.3)	2 (28.6)	-	1 (14.3)	5 (71.4)
SOF/VEL	*16 weeks, N=1*	-	-	-	-	1 (100)	-	1 (100)
	24 weeks, N=22	14 (63.6)	4 (18.2)	8 (36.4)	-	9 (40.9)	1 (4.5)	15 (78.9)
	8 weeks, N=1	-	-	1 (100)	-	-	-	1 (100)
GLE/PIB	*12 weeks, N=5*	1 (20.0)	1 (20.0)	3 (60.0)	-	1 (20.0)	-	5 (100)
	16 weeks, N=1	-	-	-	-	1 (100)	-	1 (100)
GRZ/EBV+SOF	*12 weeks, N=1*	1 (100)	1 (100)	-	-	-	-	1 (100)
	24 weeks, N=2	2 (100)	1 (50.0)	1 (50.0)	-	-	-	
GRZ/EBV	*24 weeks, N=1*	1 (100)	1 (100)	-	-	-	-	1 (100)
Overall	N=125	30 (24.0)	26.8	34.1	4.9	29.3	4.9	75 (79.8)

* Currently available for 94 patients

Modified from Di Maio V.C. et al., EASL 2019

EASL Recommendations

Retreatment of DAA failures

- Retreatment strategy depends on initial regimen

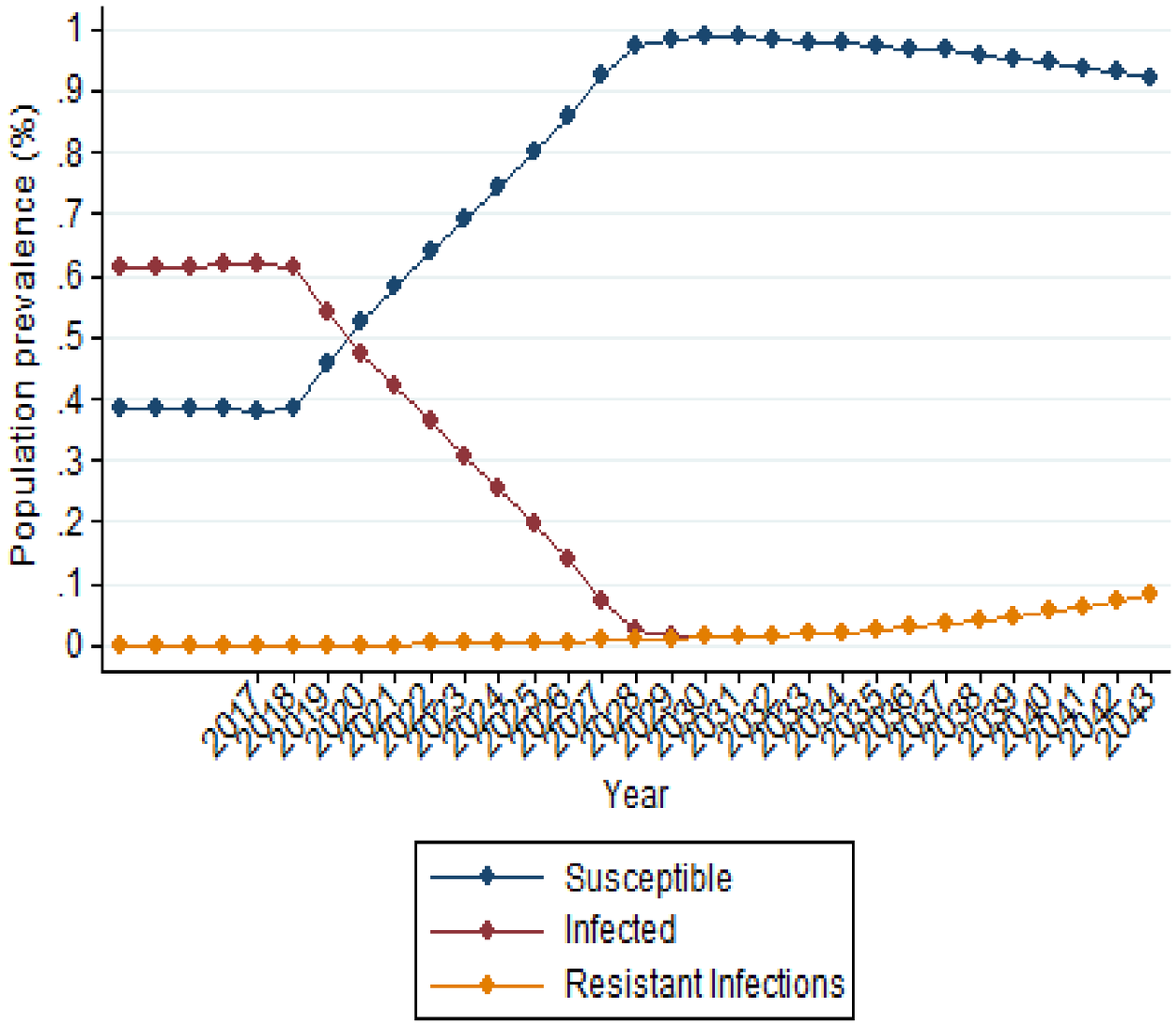
Recommendations	Grade of evidence	
After failure of PEG-IFNα + RBV, SOF + PEG-IFNα/RBV or SOF + RBV • Retreat according to recommendations for TE patients, by HCV genotype	A	1
HCV resistance testing after failure of any DAA-based regimen (excluding regimens with SOF as the only DAA) is a useful guide to retreatment	B	2
After failure of DAA (PI and/or NS5A inhibitor)-containing regimen		
• First-line retreatment – SOF/VEL/VOX for 12 weeks (without cirrhosis/with compensated cirrhosis) – SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis)	A B	1 2
• Patients with predictors of poor response, SOF + GLE/PIB for 12 weeks: – Advanced liver disease – Multiple courses of DAA-based treatment – Complex NS5A RAS profile	B	2
• Very difficult-to-cure patients:† SOF/VEL/VOX + RBV or SOF + GLE/PIB + RBV for 12 weeks or for 16 or 24 weeks	C	2

*Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance;
†Patients with NS5A RASs who failed twice to achieve SVR after a combination regimen including a PI and/or an NS5A inhibitor
EASL CPG HCV. J Hepatol 2018;69:461–511.

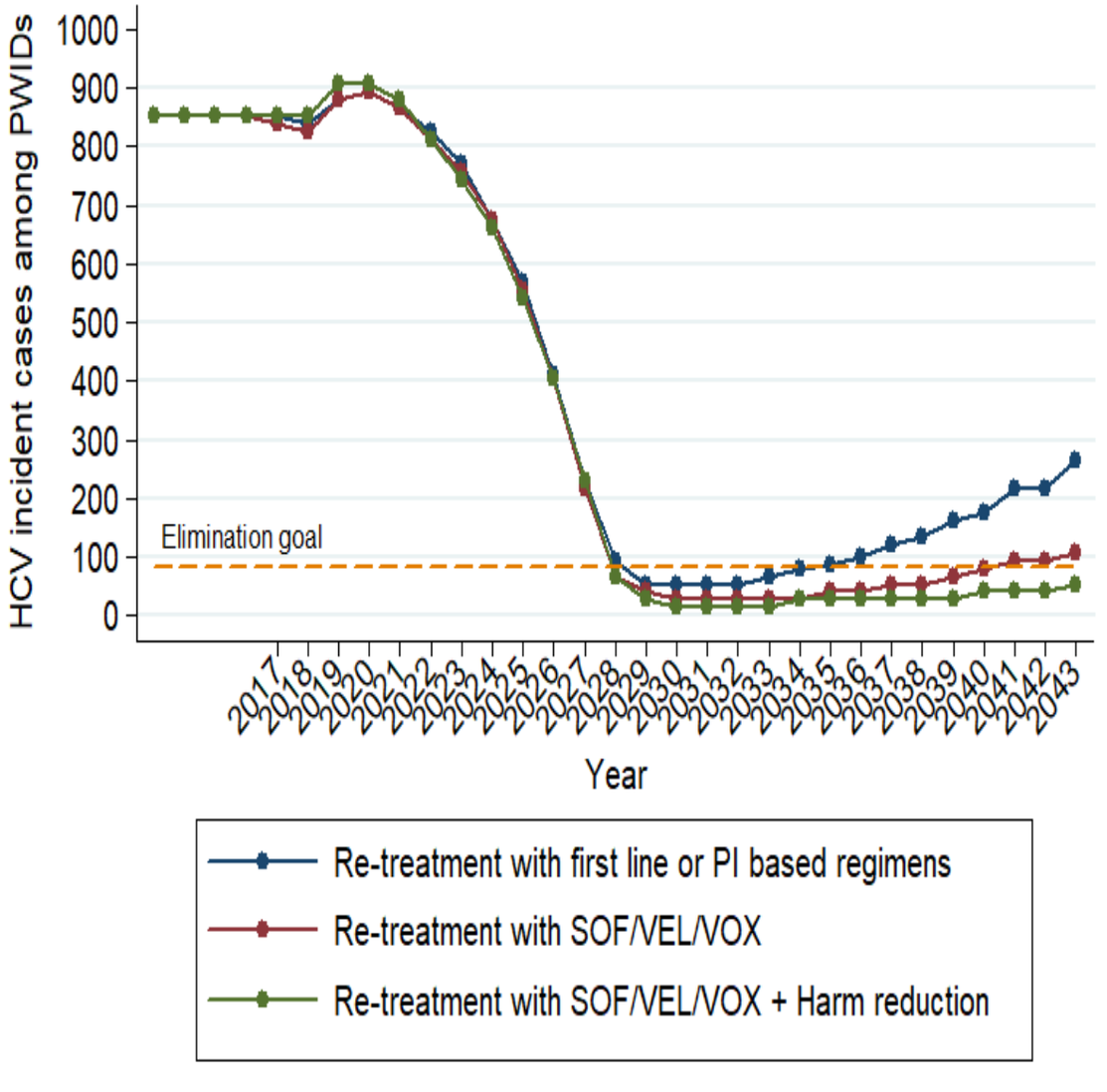
Is There a Risk for Multi-Resistant HCV Spread?

60% CHC prevalence

CHC Prevalence



HCV Incident cases



Gkountas I et al, EASL 2019

In nosocomial HCV transmission-clusters, the NS5A-RAS Y93H was often transmitted and distributed differently within the same transmission-clusters, independently by the IL-28-polymorphism

Cluster HCV	Pt	HCV Infection	HCV-RNA (UI/ml)	IL 28	RAS					Others Mutations			
					NS3 Sanger	NS5B Sanger	NS5A Sanger	NS5A NGS	FREQ. NGS	NS3 Sanger	NS5A Sanger	NS5A NGS	NS5B Sanger
CT1	Pt1	Acute	3.270	TC	None	None	Y93H	Y93H	99.7%	V48I, V51A, A66G, T72I, P86Q, K87A, V132I, F147S, V170I, S174T (5-180aa)	K6R, S17T, K26R, L34V, L37F, K78R, R123QR, V164AE, V174T, Q176M (1-184aa)	K6R, S17T, K26R, L34V, L37F, K78R, V164E, V174T, Q176M, P206K, S207A, H208T, I209C, A211T (1-211 aa)	T181N, S210A, C213S (153-337aa)
	Pt2	Chronic	2.820.000	CC	None	None	Y93H	Y93HY	97.8%	V48I, V51A, A66G, T72I, P86Q, K87A, V132I, F147LS, V170I, S174T (1-180aa)	K6R, S175T, K26R, L34V, L37F, G49EG, K78R, V164A, V174T, Q176M (1-211aa)	K6R, V8IV, S17ST, K26KR, L34V, L37FL, G49EG, I63IL, K78R, 98CS, N105NS, R108KR, A114AS, N137NS, V138MV, A146AT, V164AE, V174T, Q176MT (1-213aa)	S19NS, M57L, K81R, Q90K, R98K, N110NS, V116I, N117KN, K124E, Q127L, T181N, S210A, C213RS, S231NS, T377S, C451H, A513S, R531K (1-540aa)
CT2	Pt3	Chronic	2.340.000	CT	S122N	None	Y93HY	Y93HY	32.9%	S7A, V48I, Y56F, A66G, P86Q, K87S, V132I, F147S, A150V (2-180aa)	S3T, K6R, S17T, L34V, K44R, Q54H, T56IT, T64A, H85R, T122V, M133MV, V138LV, R157QR, V164A, V174T (1-213aa)	S3T, K6R, S17T, L34V, K44R, D50DE, I52DINV, Q54H, T56IT, T64A, H85R, A92AT, T122AV, V124GV, M133MV, V138LV, R157QR, V164A, V174T (1-213aa)	M57L, V85IV, Q90K, Q127L, N206K, K209A, A252AV, T377S, A513S, T520I, K523MR (1-548aa)
	Pt4	Acute	2.090	TC	S122N	None	None	None	None	V48I, Y56F, A66G, P86Q, K87S, V132I, F147S, V170I (15-180aa)	S3T, K6R, S17T, L34V, K44R, Q54H, T64A, H85R, T122V, V138I, R157Q, V164A, V174T (1-187aa)	S3T, K6R, S17T, L34V, K44R, Q54H, T64A, H85R, T122V, V124GV, V138L, R157Q, V164A, V174T (1-213aa)	N206K, K209A, A252V, T377S, I424V, M426T, A513S, T520I, K523R (151-538aa)
	Pt5	Acute	165	CC	S122N	None	None	None	None	V48I, Y56F, A66G, P86Q, K87S, V132I, F147S, V170I (15-180aa)	S3T, K6R, S17T, L34V, K44R, Q54H, T64A, H85R, T122V, V138I, R157Q, V164A, V174T, C190CG (1-196aa)	S3T, K6R, V15AV, S17T, P32PS, L34V, K44R, Q54H, A61AV, T64A, T83MT, H85R, T122MV, V124GV, G132AG, V138L, R157Q, V164A, V174T, L199I (1-213aa)	N206K, K209A, A252V, R254KR, E258EQ, T377S, A513S, T520I, K523R, S549G, V552A (151-562aa)
CT3	Pt6	Chronic	1.800.000	TC	None	None	None	None	None	S7A, C16CW, V48I, S61A, A66G, P86Q, K87AS, F147S (1-180aa)	K6R, S17T, L34V, L37F, T56I, K78R, T79A, V164A, V174T, L183V, S201ST, M202MR, T213AT (1-213 aa)	K6R, S17AT, L34V, L37FL, Y43FY, Q54HQ, T56IT, I63FL, K78R, T79A, T83MT, N105NS, R108KR, V164AT, V174T, L183V, A197AT, T213AT (1-212aa)	A15S, M57L, Q90K, N117R, R120N, Q127L, T130N, F162Y, G198K, N206NS, C213S, R254K, T377S, V405I, Q464E, V499T, A513S, R531K, S549G (1-565a aa)
	Pt7	Chronic	577.000	CC	None	None	Y93H	Y93H	99.65%	S7A, V48I, V51A, S61A, A66G, T72I, P86Q, K87A, S122G, F147S, V170I (1-181aa)	K6R, S17T, L34V, L37F, K44R, G49EG, Q54H, K78R, H85N, V138I, V164A, V174T, Q176L, L183V (1-194 aa)	K6R, S17T, L34V, F36FL, L37F, K44R, G49EG, Q54H, T56IT, T64AT, V75AV, K78R, H85NS, V124GV, F127FS, V138I, K139KR, V164A, V174T, Q176L, Q181HQ, L183V (1-JU5aa)	A15S, M57L, Q90K, V116I, N117R, R120N, Q127L, T130N, V147IV, F162Y, S189PS, G198GR, C213S, R254K, T377S, V405IV, A421V, I424V, T427P, Q464E, V499T, A513S, T520MT, Q544R, S549G, L564V, S565P (1-569aa)
	Pt9	Chronic	94.600	CC	None	None	None	None	None	S7A, L14F, V48I, V51A, S61A, A66G, P86Q, K87A, F147S, S174A (1-180aa)	K6R, S17T, L34V, L37F, Q54H, V75A, K78R, T83M, Y161H, V164A, V174T (1-185aa)	K6R, I12IL, S17T, K26KR, L34V, P35LP, L37F, Q54H, V75A, K78R, C80CR, T83M, H85CHRY, A92AS, T99AT, P102LP, R108KR, V124GV, Y161H, V164A, V174T, A197AT, P206K, S207A, H208T, I209C, A211T (1-211aa)	A15S, M57L, Q90K, N110S, V116I, N117R, R120N, Q127L, F162Y, K270R, T312S, L314S, V315A, A333AV, S335N, T377S, V405I, K441Q, Q464E, V499T, A513S, K535R, S549G (1-568aa)
CT4	Pt8	Chronic	219.000	TC	None	None	R30Q L31M Y93H	R30Q L31M Y93H	98.8% 98.8% 99.1%	V48I, A66G, P86Q, K87A, F147S, A150V, I153V (1-180aa)	K6R, S17T, L34V, L37F, Q54H, K78R, , R123Q, V124I, M133V, V164A, E171Q, V174T, Q176L, T204TP (1-210aa)	K6R, S17T, L34V, L37F, Q54H, N69NT, K78R, T95MT, R108KR, R123Q, V124I, M133MV, K139KR, V164A, E171Q, V174T, Q176L, A197T, L199V (1-213aa)	A39S, M57L, R65Q, Q90K, K106KR, S113G, Q127L, E131N, I134L, F162Y, S231N, I262V, T377S, A513S, R531K (1-568aa)
	Pt10	Acute	163	CC	None	None	R30Q L31M Y93H.	R30Q L31M Y93H	99.4% 99.4% 97.6%	V48I, A66G, P86Q, K87A, F147S, A150V, I153V (16-180aa)	K6R, S17T, L34V, L37F, Q54H, K78R,, R123Q, V124I, M133V, V164A, E171Q, V174T, Q176LQ (1-177aa)	K6R, S17T, L23LP,, L34V, L37F, Q54H, K78R, R123Q, V124I, M133V, G155EG, V164A, E171Q, V174T, Q176L, A197T, L199V (1-205aa)	F162Y, S231N, I262V, T377S, T403AT, A513S, R531K (153-550aa)

Bellocchi et al Cells in revision 2019

Le ultime evidenze dei congressi

- Real life = trial registrativi
- Due opzioni pangenotipiche nella pratica clinica coporono pazienti differenti
- Screening universale in Italia→ è più sostenibile se graduale per coorti succesive
- Ottimizzazione: meglio meno visite ma non biosgna sagerare
- Off label: corto è bello ma se l'immunità innata funziona
- Eterogeneità virale: ha sicuramente un ruolo nell'epoca della taglia unica pangenotipica
  - Per pazienti da aree esotiche
  - Per il ritrattamento
  - Per evitare possibili epidemie di HCV XDR o PDR