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HCV the road to “elimination”: drugs and strategies

Disclosures

- Massimo Puoti
  - Advisory Committees or Review Panels: MSD, Gilead Sciences, Abbvie,
  - Speaking and Teaching: MSD, Gilead Sciences, Abbvie,

HCV the road to elimination: drugs and strategies

- Towards a pangenotypic universal treatment
  - Evolution of DAAs
  - Efficacy of pangenotypic regimens
  - Any exception for universal pangenotypic treatment?
- Towards HCV elimination
  - Simplification of HCV management: when and how
  - From microelimination to a search and destroy strategy

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Characteristics of 1st gen DAA

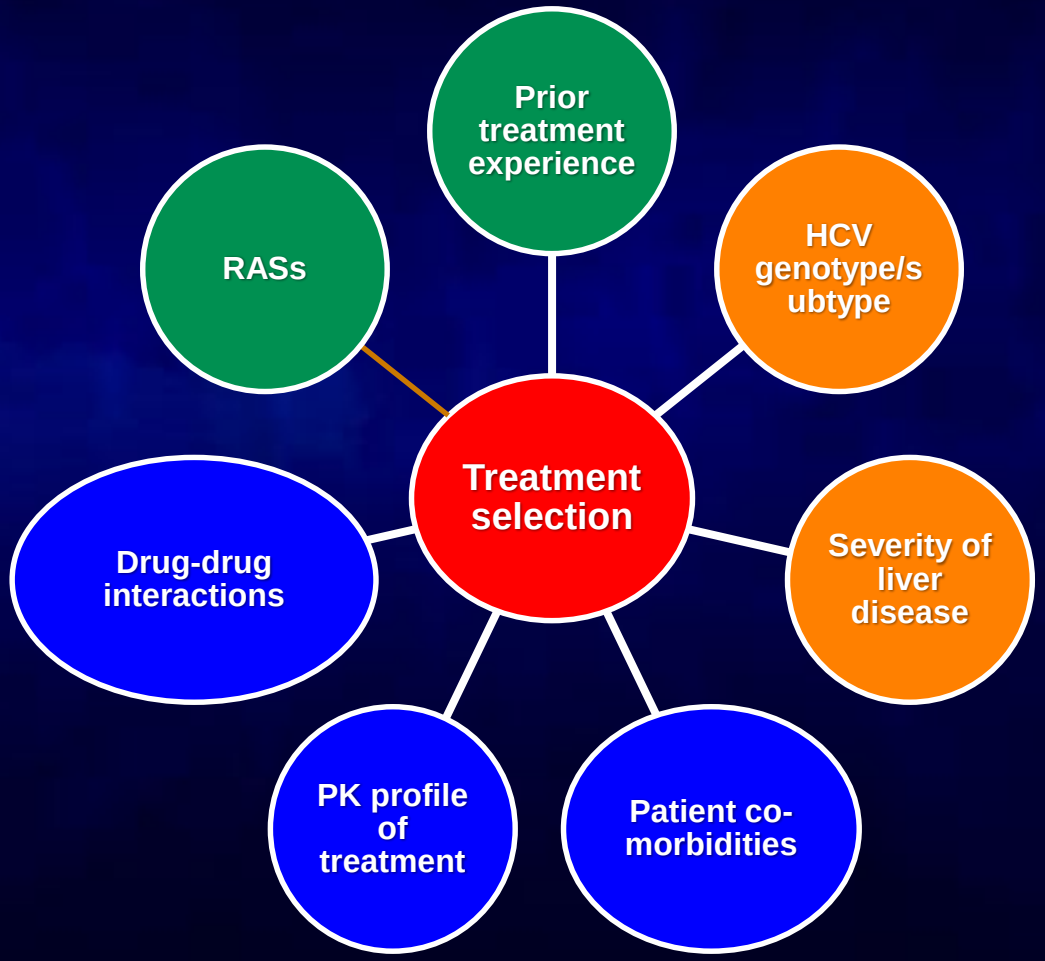
Drug class	NS3/NS4 Inhibitors (--- "previrs")	NS5A inhibitors (..."asvirs")	NS5B inhibitors (..."buvirs")	
	1st gen 2nd wave	1st gen	NN	NUC
Drugs	Paritaprevir/r Simeprevir	Ledipasvir, Ombitasvir Elbasvir **Daclatasvir**	Dasabuvir	**Sofosbuvir**
Antiviral Potency	🟠	🟢	🟠	🟢
Resistance profile	🔴	🔴	🔴	🟢
Pangenotypic efficacy	🔴	🔴 / 🟢	🔴	🟢

STRATEGY Combinations of DAA genotype specific to achieve potent antiviral effect, high barrier to resistance and broad genotypic spectrum

Modified from Shinazi Liv Int 2014

EASL The Home of Hepatology 2016

Characteristics that Inform Treatment Option Selection



Characteristics of 2nd gen DAA

Drug class	NS3/NS4 Inhibitors (--- "previrs")		NS5A inhibitors (..."asvirs")		NS5B inhibitors (..."buvirs")	
	1st gen 2nd wave	2nd gen	1st gen	2nd gen	NN	NUC
Drugs	Paritaprevir/r Simeprevir	**Grazoprevir, Glecaprevir Voxilaprevir**	Ledipasvir, Ombitasvir Elbasvir	**Velpatasvir Pibrentasvir**	Dasabuvir	**Sofosbuvir**
Antiviral Potency	🟠	🟢	🟢	🟢	🟠	🟢
Resistance profile	🔴	🟠	🔴	🟠	🔴	🟢
Pangeno-typic efficacy	🔴	🟢	🔴/🟢	🟢	🔴	🟢

STRATEGY Combinations of DAA to achieve potent antiviral effect, high barrier to resistance and broad genotypic spectrum → Development of FDC

Modified from Shinazi Liv Int 2014

PK and potential for Drug Drug Interactions of Anti HCV oral antivirals

	Excretion	Drug solubility with gastric Ph	Enzymes		Transporters	
			Substrates	Inhibition	Substrates	Inhibition
SOF	Renal Metabolite GS 33107	Minimal effect	CatA CES1 Hint1 Phosph UMP-CMP & NDP kinases	No	PgP BCRP	
VEL	Biliary	Important Decrease	CYP2B6 CYP2C8 CYP3A4	No	PgP BCRP OATP1B1 OATP1B3	PgP BCRP OATP1B1 OATP1B3
VOX	Biliary	Mild decrease	CYP1A2, CYP 2C8, CYP3A4	No	BCRP OATP1B1	BCRP, OATP1B1/3, BSEP
EBR	Biliary	No effect	CYP3A	No	PgP	PgP BCRP
GZR	Biliary	No effect	CYP3A4	CYP3A4	OATP1B1/3 PgP	BCRP
GLE	Biliary	Mild decrease	CYP3A4/5CYP2D6, 2C9, and 2C8.	CYP2C8, CYP2C9 CYP3A4. UGT1 UGT1A4	PgP BCRP	PgP BCRP OATP1B1/3B SEP
PIB	Biliary	No effect	None	None	PgP BCRP OATP1B1 OATP1B3	PgP BCRP OATP1B1 OATP1B3
PrOD	Biliary	No effect	CYP3A4 CYP2C8	CYP3A4 CYP2C8 UGT1A1 CYP2C19	PgP BCRP OATP1B1/3	OCT1 PgP BCRP OATP1B1/3

mild potential for DDI; moderate potential for DDI; high potential for DDI

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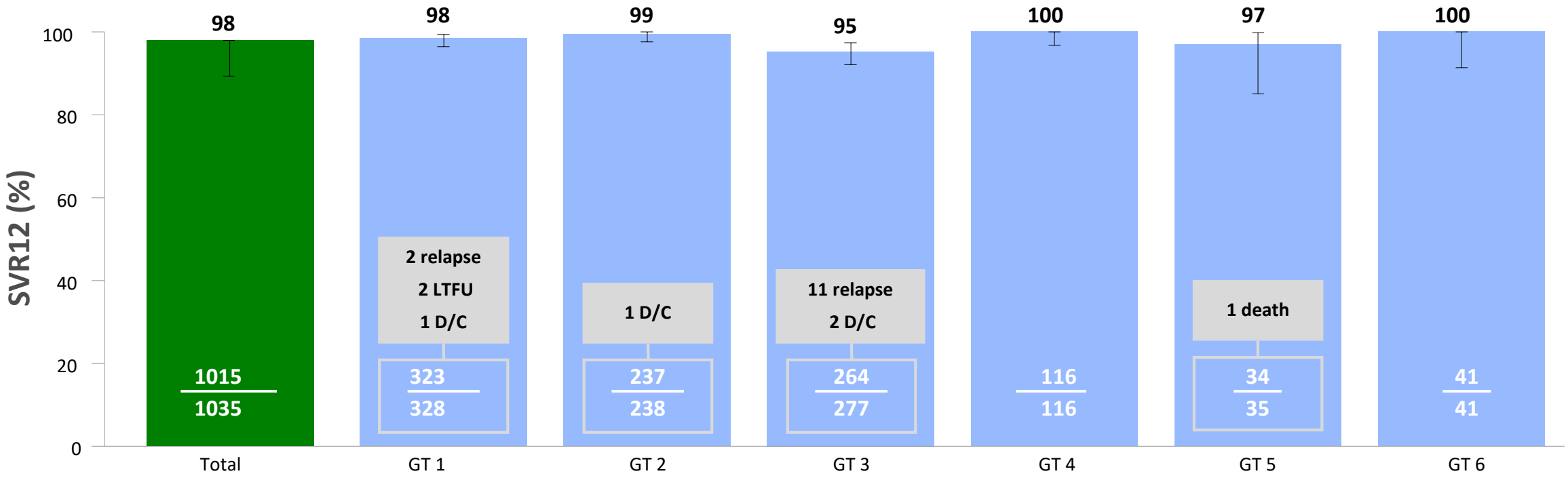
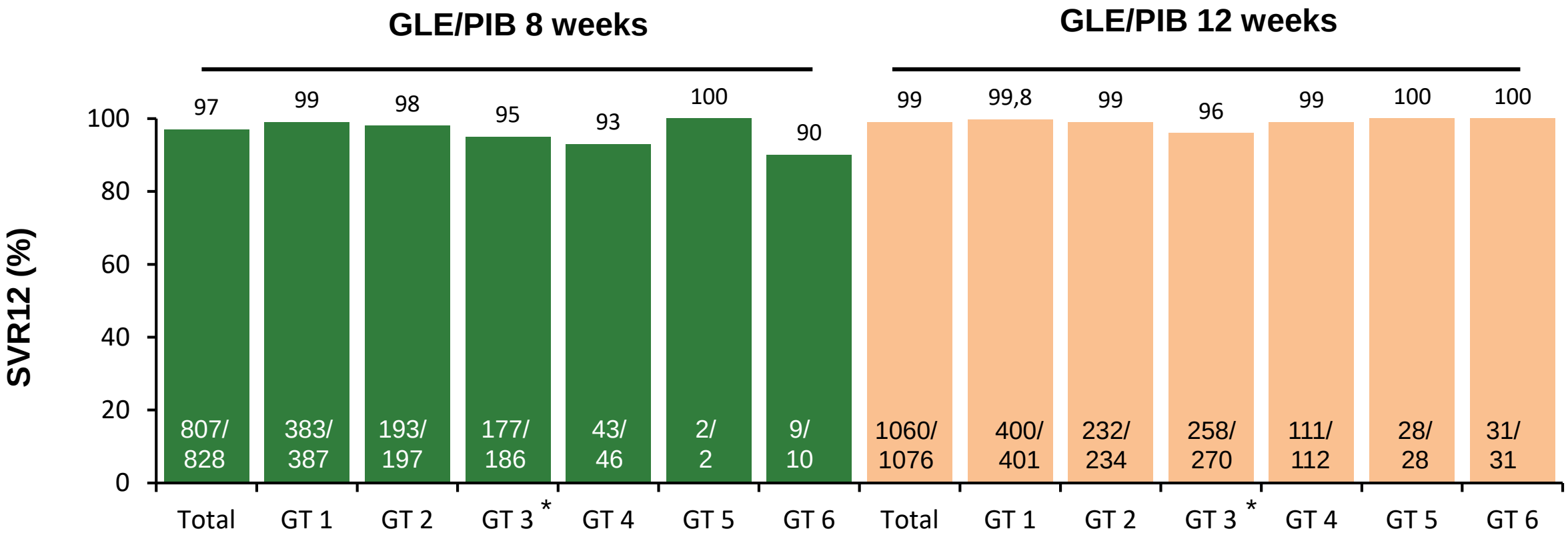
Sofosbuvir + Velpatasvir
Integrated Efficacy: SVR12



Agarwal, EASL 2016, Poster SAT-195

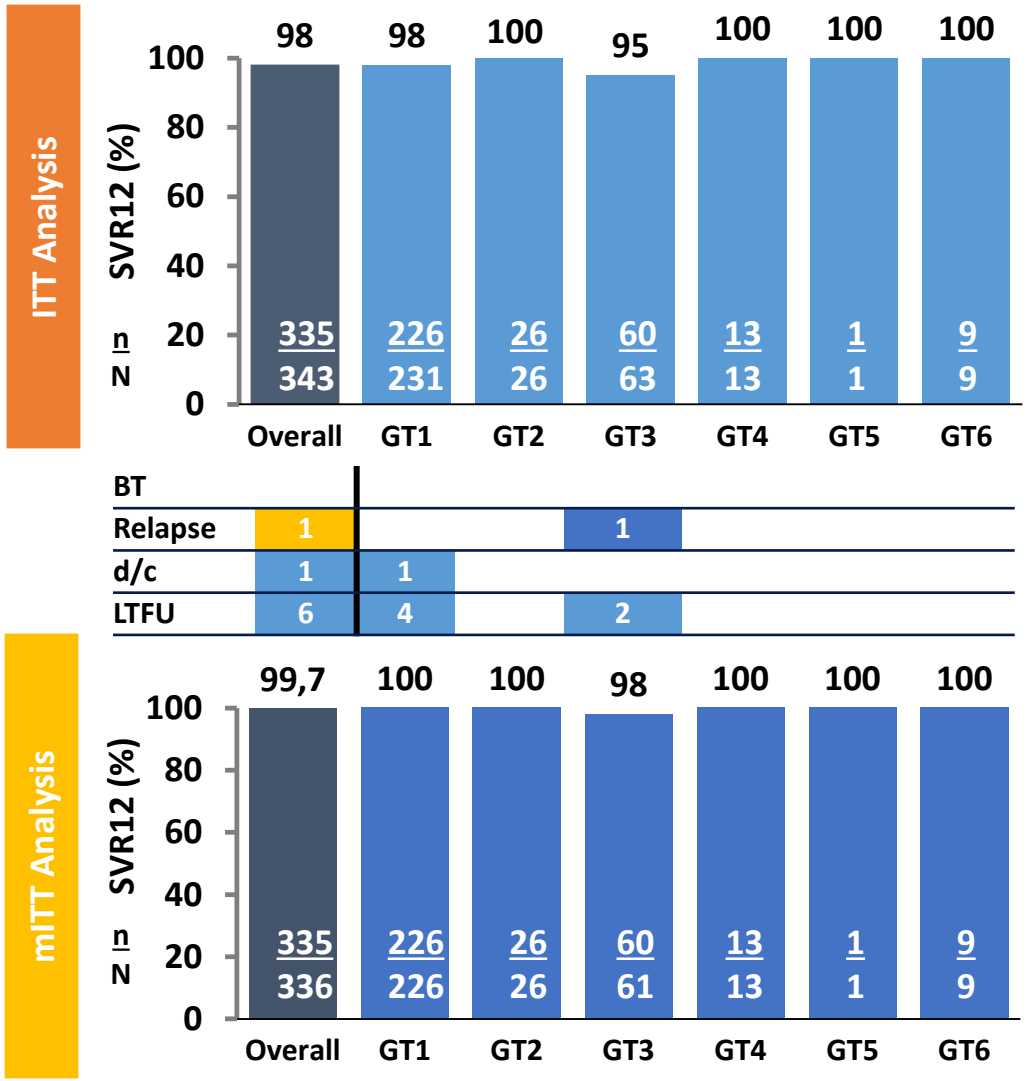
Integrated efficacy and tolerability of GLE/PIB for 8 or 12 weeks in GT 1–6 patients without cirrhosis (APRI < 1?)

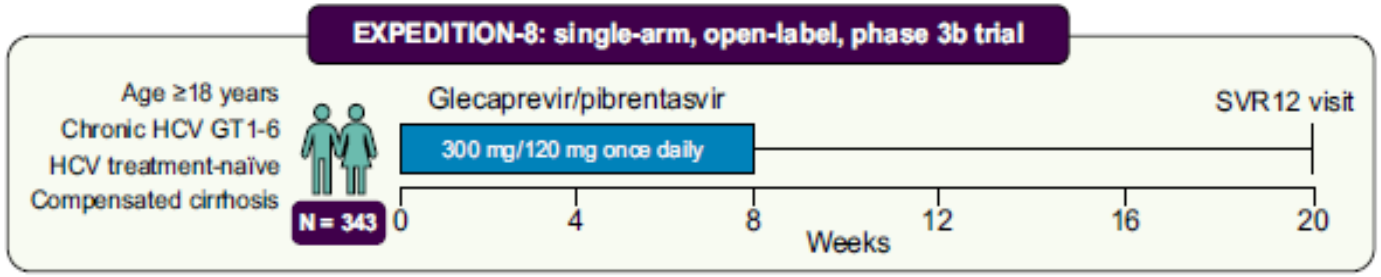


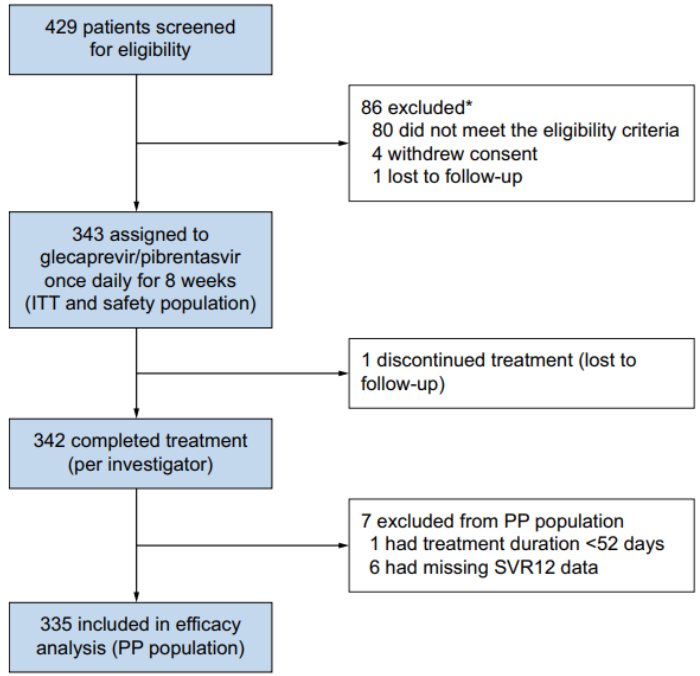
Puoti M, et al. ILC 2017; Poster #SAT-233

*GT 3 patients included in the analysis were TN only. GLE/PIB for 8 weeks or 16 weeks (not 12 weeks) is approved in the EU for the treatment of patients without cirrhosis depending on their genotype and prior treatment experience. Studies included: ENDURANCE-1, -2, -3, -4, EXPEDITION-4, SURVEYOR-1, -2. TE=IFN or SOF-based regimens (n=16); patients experienced with a DAA other than SOF were excluded. TE: treatment-experienced; TN: treatment-naïve

EXPEDITION-8 Full Results







No G/P-related liver-related toxicities or drug-induced liver injury were observed

Brown et al.DOI: https://doi.org/10.1016/j.jhep.2019.10.020

LDV/SOF for 8, 12, or 24 weeks in Dialysis Patients

Baseline Characteristics	LDV/SOF N=95
Mean age, years (SD)	61 (11)
Female, n (%)	39 (41)
TE, n (%)	21 (22)
Cirrhosis, %	20
GT, n (%) 1 2 4 5 6 Indeterminate	 68 (72) 21 (22) 2 (2) 1 (1) 2 (2) 1 (1)
Hemodialysis, n (%)	87 (92)
Peritoneal dialysis, n (%)	8 (8)
History of renal tx, n (%)	20 (21)

Overall Safety Analysis (ITT Population) Patients, n (%)	Overall N=95	LDV/SOF 8 Wk n=45	LDV/SOF 12 Wk n=31	LDV/SOF 24 Wk n=19
Any AE	78 (82)	31 (69)	30 (97)	17 (90)
Grade ≥3	11 (12)	3 (7)	1 (3)	7 (37)
SAE	12 (13)	4 (9)	2 (7)	6 (32)
Treatment-related SAE	0	0	0	0
AE leading to premature D/C of study drug	0	0	0	0
AE leading to interruption of study drug	3 (3)	0	0	3 (16)
Death	6 (6)	3 (7)	0	3 (16)
Any grade lab abnormalities	94	44	31	19
Grade 3	14 (15)	6 (14)	2 (7)	6 (32)
Grade 4	3 (3)	1 (2)	1 (3)	1 (5)

LDV/SOF was well tolerated

SVR12 was 94% (89/95, ITT)

No virological failures

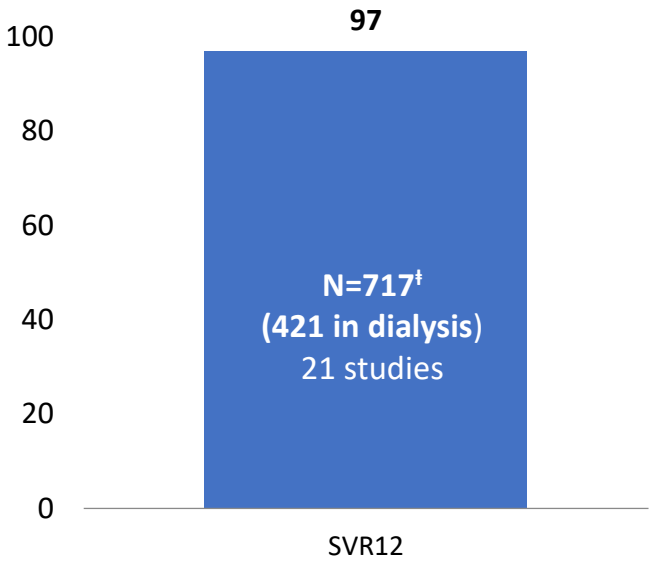
Hu, EASL, 2019, THU-144

*1 patient died of cardiac arrest, 1 patient died of intestinal ischemia, 2 patients died of sudden death, 1 patient died of pulmonary embolism, 1 patient's death was not classified

SOF-Based Regimens in HCV-Infected Patients with Stage 4–5 CKD

Systematic review and meta-analysis of 21 SOF-based studies treating HCV patients with Stage 4 or 5 CKD through August 2018

Efficacy Data of SOF-based regimens*



- Dialysis patients achieved 95.1% SVR12/24
- No SVR difference cirrhotic vs. non-cirrhotic patients
- Higher SVR rate of 99% in RBV-free regimens

Pooled Safety analysis (16 studies)

SAE rate	4.8%
Number of SAE events	15

- eGFR was generally stable during treatment
- 2 cases of discontinuation from hemodialysis due to eGFR improvement

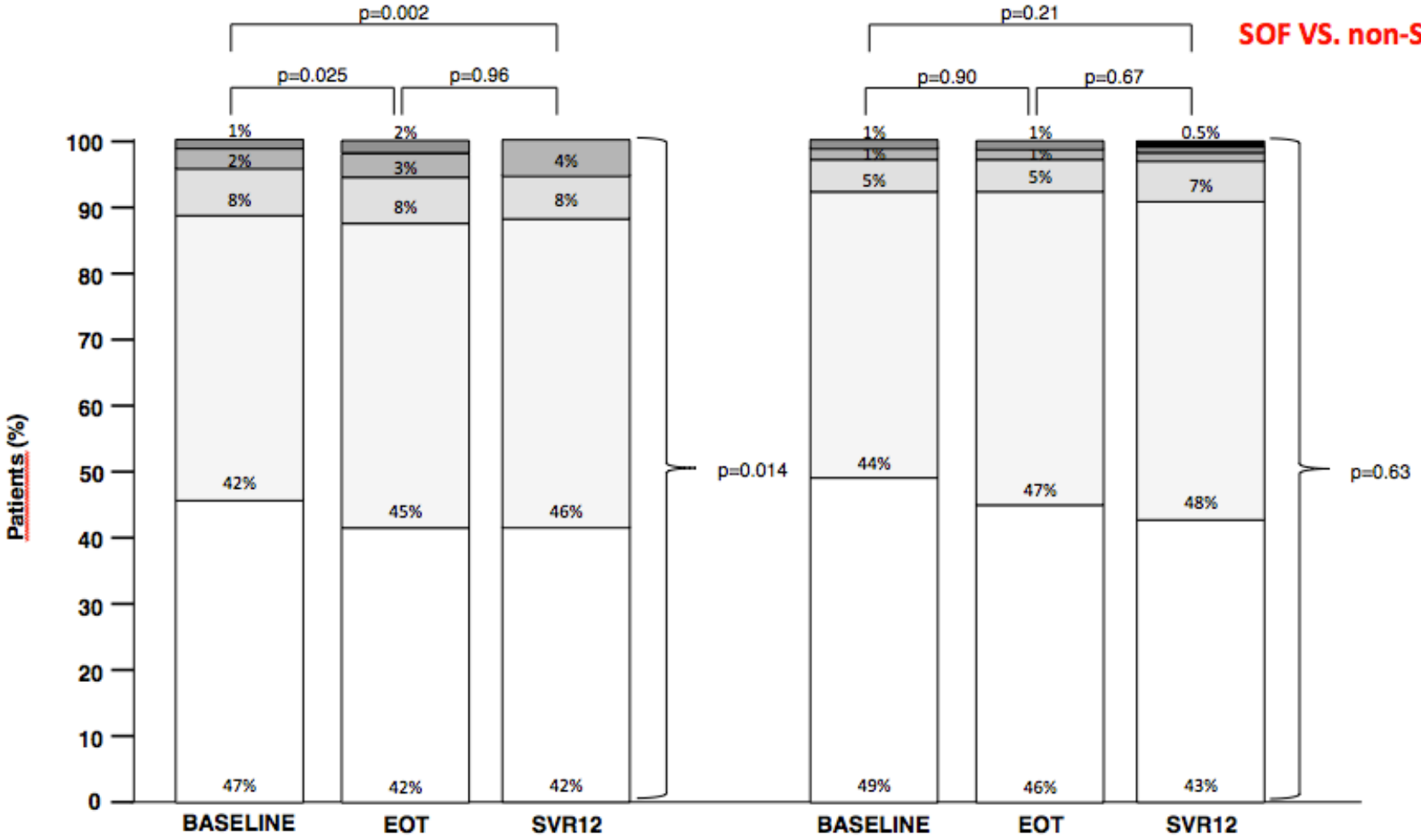
Study suggests SOF-based regimens may be used safely and effectively in HCV-infected patients with stage 4-5 CKD

*Regimens included LDV/SOF±RBV, SOF+DCV±RBV, SOF+SMV±RBV, SOF+RBV, SOF+PR with variable SOF-dosing: 400mg daily, 400mg/48h, 400mg three times a week

Li, EASL, 2019, THU-153. Li et al, Virology Journal, 2019; 16:34

RENAL SAFETY IN 3,264 HCV PATIENTS TREATED WITH DAA-BASED REGIMENS: RESULTS FROM A LARGE ITALIAN REAL-LIFE STUDY

- In patients with preserved baseline renal function, DAA treatment led to statistically significant eGFR decline that was not reverted upon drug discontinuation. This detrimental effect was not observed in those with moderate to severe kidney dysfunction.



D'Ambrosio R et al EASL 2019

Patients with Renal Impairment

Recommendation for Patients With CKD Stage[a] 1, 2, or 3

RECOMMENDED	RATING
No dose adjustment in direct-acting antivirals is required when using recommended regimens.[b]	I, A

[a] Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 mL/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR <15 mL/min)

[b] A dose adjustment in ribavirin may be required in patients with CKD stage 3; see package insert for details.

Recommended regimens listed by evidence level and alphabetically for:

Patients With CKD Stage[a] 4 or 5 (eGFR <30 mL/min or End-Stage Renal Disease)

RECOMMENDED	GENOTYPE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	1a, 1b, 4	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	1, 2, 3, 4, 5, 6	8 to 16 weeks[c]	I, A[c]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	1, 2, 3, 4, 5, 6	12 weeks	1,B[d]

[a] Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 ml/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR <15 mL/min)

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

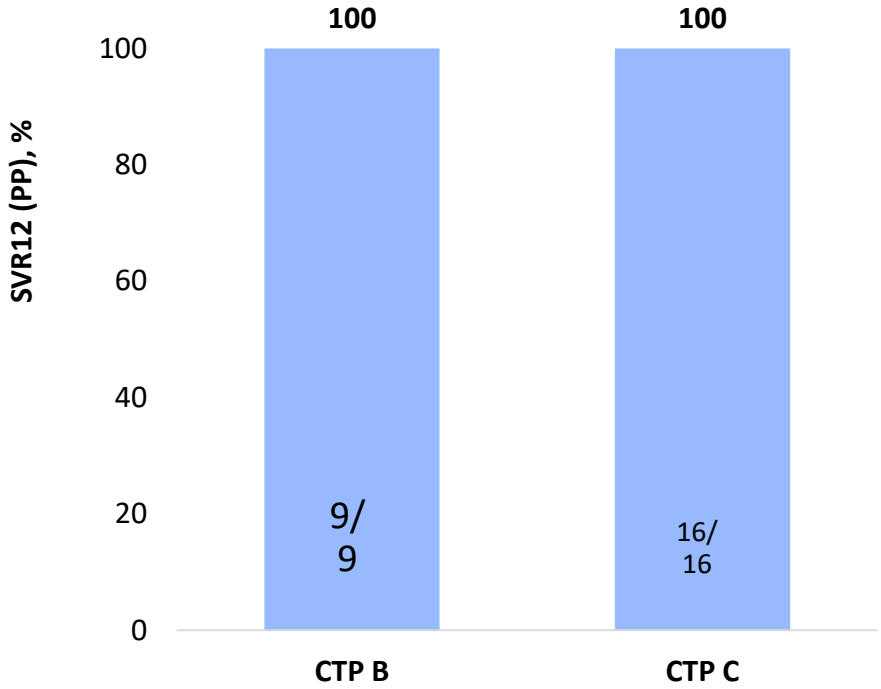
[c] Patients in this group should be treated as would patients without CKD. Duration of glecaprevir/pibrentasvir should be based on presence of cirrhosis and prior treatment experience (please refer to appropriate section). As such, strength of rating may be lower for certain subgroups.

[d] All patients with stage 5 CKD on chronic dialysis with the majority on hemodialysis

SOF/VEL+RBV for 12 Weeks in Patients with CTP-C Decompensated Cirrhosis

Phase 2, single-arm, open-label study in patients with any GT and CTP score of 10–12

Baseline Characteristics	N=32
Male, n (%)	26 (81)
Age, mean (range)	55 (39-77)
Genotype, n (%)	
1	18 (56)
2	5 (16)
3	7 (22)
undetermined	2 (6)
CTP class, n (%)	
B (7-9)	9 (28)
C (10-15)	23 (72)
MELD score, n (%)	
10-15	13 (41)
16-20	17 (53)
21-25	2 (6)
Mean $eGFR_{CG}$ mL/min (SD)	113 (41)

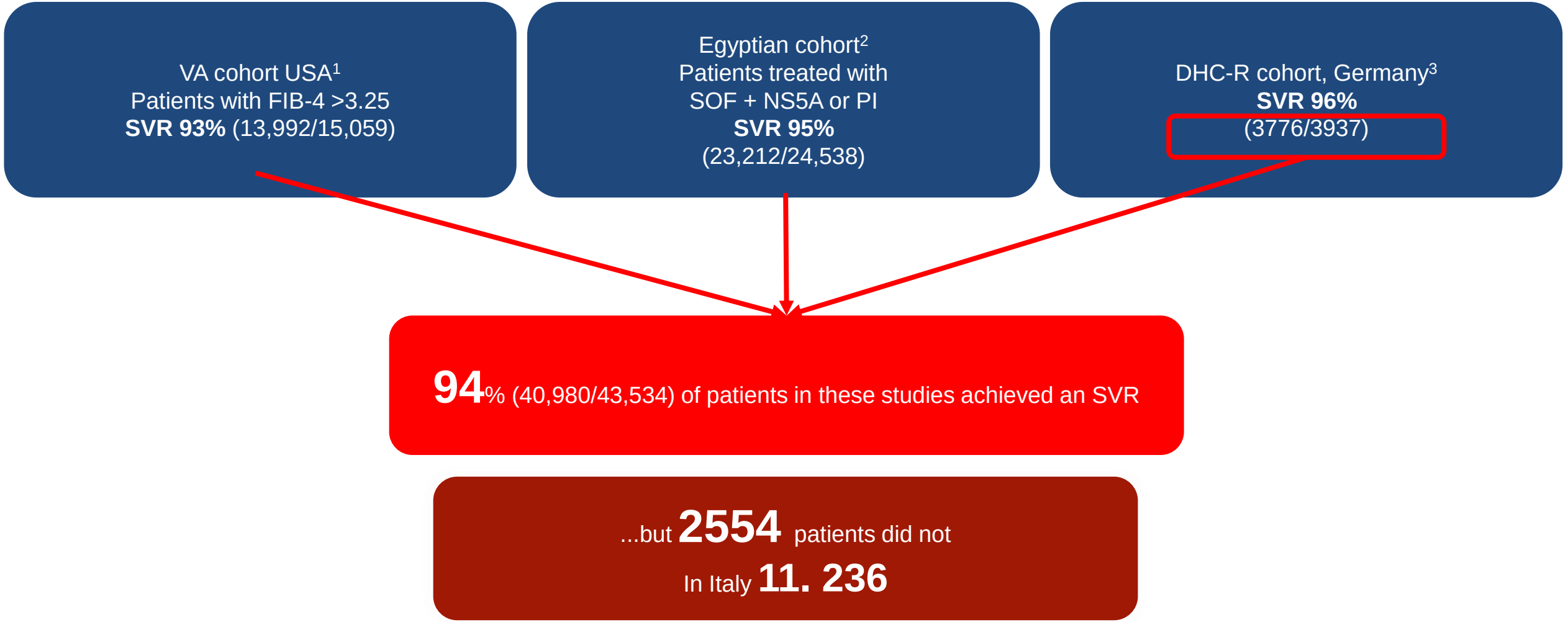


	N=32
Any AE	31 (97)
Grade 3-4 AE*	11 (34)
Serious AE*	17 (53)
AE leading to D/C to study drug	2 (6)
Death*≠	8 (25)

*unrelated to study drug
≠2 deaths prior to treatment

SVR was high in patients who completed treatment
SOF/VEL+RBV was well tolerated
CTP-C is associated with high mortality

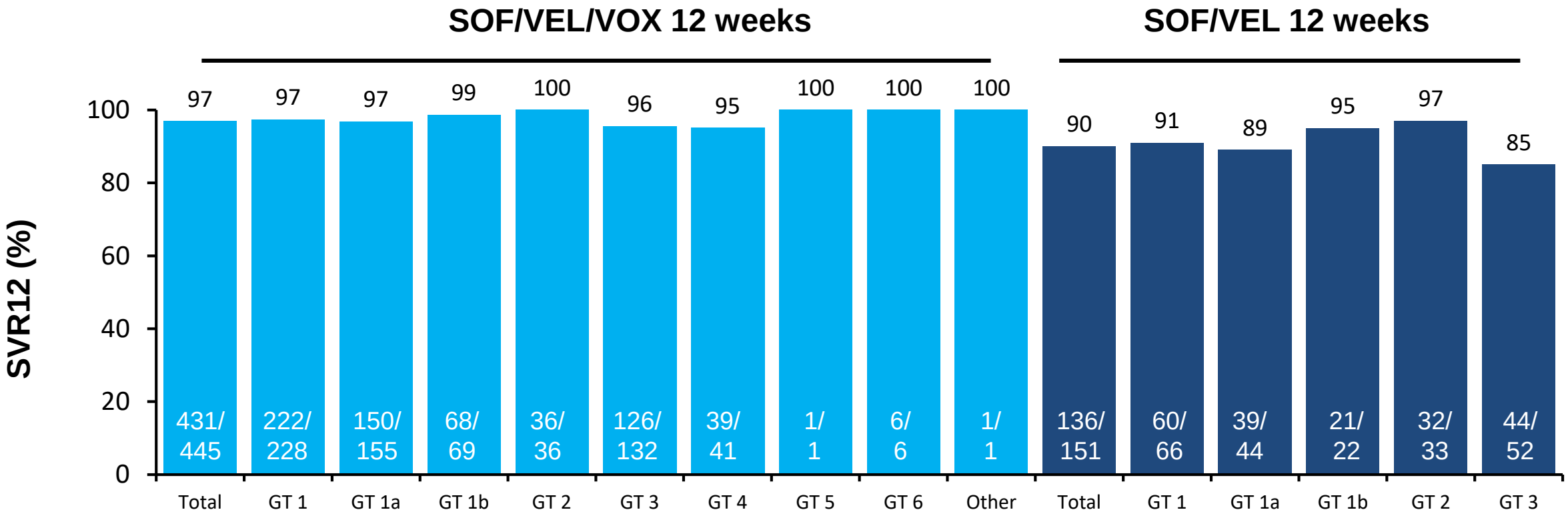
Patients who have experienced DAA treatment failure are a small but important HCV patient population



1. Backus LI, et al. Hepatology 2017;doi: 10.1002/hep.29408;
2. Gomaa A, et al. Hepat Med 2017;9:17–25;
3. Welzel TM, et al. ILC 2016; Poster #SAT-274

VA: Veterans Affairs; DHC-R: German Hepatitis C Registry

SOF/VEL/VOX for 12 weeks is effective in GT 1–6 DAA-experienced patients



Tolerability of SOF/VEL/VOX for 12 weeks

- SAEs were reported in 9 (2%) patients receiving SOF/VEL/VOX for 12 weeks, none were considered treatment-related
- 1 patient died 2 days after completing treatment from an illicit drug overdose

Bourliere M, et al. N Engl J Med 2017;376:2134–46

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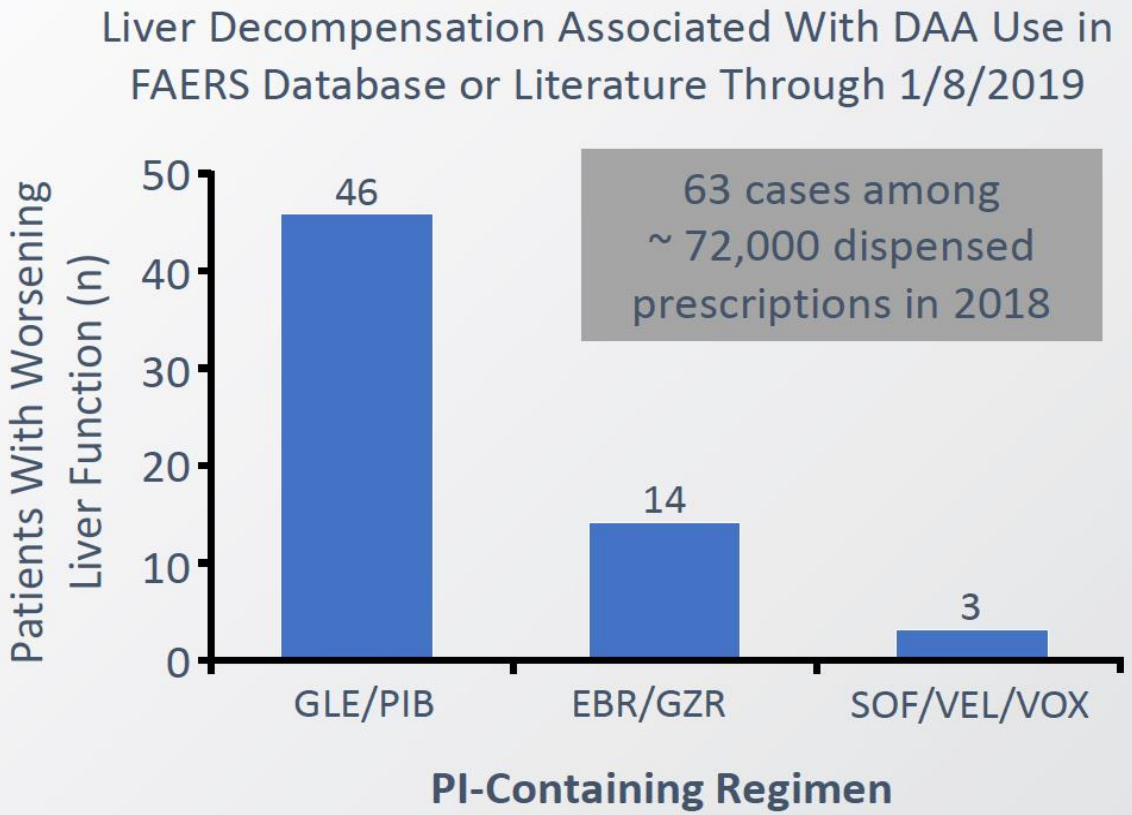
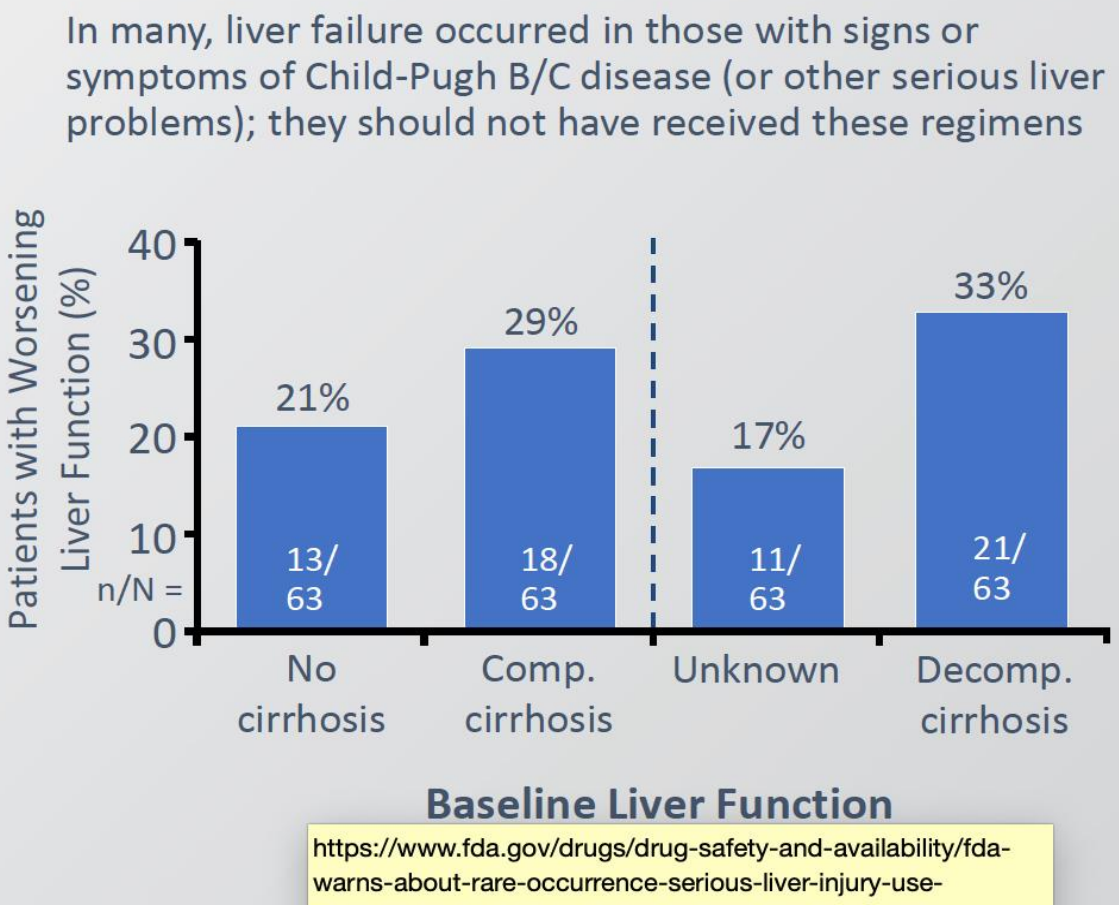
FDA Drug Safety communication: Rare but Serious Liver Injury With PI-Based Therapy in Advanced Liver Disease





https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and.

Treatment-Naive Genotype 1a With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:
Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	8 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a RASs at amino acid position 28, 30, 31, or 93 known to confer antiviral resistance. If 1 or more RASs are present, another recommended regimen should be used.
[c] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

Treatment-Naive Genotype 2 With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:
Treatment-Naive Genotype 2 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)[b]	8 weeks[c]	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

Treatment-Naive Genotype 1b With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:
Treatment-Naive Genotype 1b Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks[c]	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

Treatment-Naive Genotype 3 With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:
Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks[c]	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for patients without baseline NS5A RAS Y93H for velpatasvir	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for patients with baseline NS5A RAS Y93H for velpatasvir	12 weeks	IIa, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for patients with baseline NS5A RAS Y93H for velpatasvir	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

Treatment recommendations for TN or TE patients with CHC with HCV genotype 3 and compensated (Child–Pugh A) cirrhosis

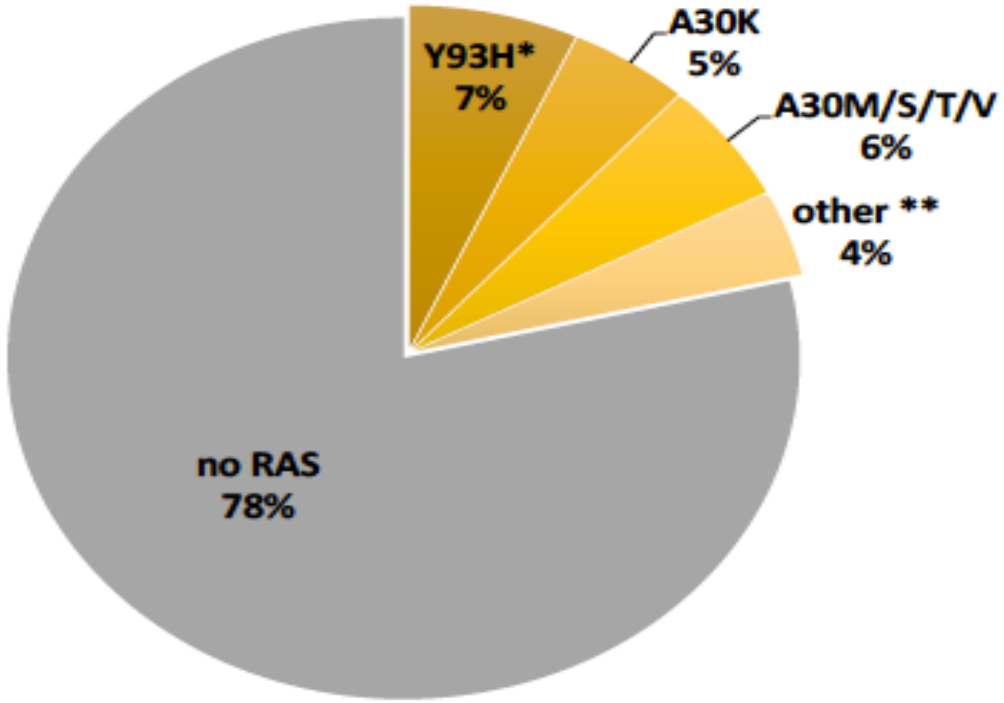
Patients infected with HCV genotype 3 with compensated cirrhosis				
Availability/ performance of HCV NS5A resistance testing	**Results of HCV NS5A resistance testing***	**SOF/VEL-based regimen**		**GLE/PIB-based regimen**
		SOF/VEL/VOX available and affordable	**SOF/VEL/VOX not available or affordable**	**GLE/PIB available**
Not available/ not performed	-	SOF/VEL/VOX for 12 weeks	SOF/VEL + RBV for 12 weeks	GLE/PIB for **12 (8 ?)** weeks in TN or 16 weeks in TE patients†
Available and performed	Presence of Y93H RAS at baseline	SOF/VEL/VOX for 12 weeks	SOF/VEL + RBV for 12 weeks	GLE/PIB for **12 (8?)** weeks in TN or 16 weeks in TE patients†
	No Y93H RAS at baseline	SOF/VEL for 12 weeks	SOF/VEL for 12 weeks	GLE/PIB for **12 (8?)** weeks in TN or 16 weeks in TE patients†

*The presence of the NS5A RAS Y93H at baseline is by population sequencing or >15% by deep sequencing;
†Data with 12 weeks of treatment with GLE/PIB in TE patients with cirrhosis are needed
EASL. J Hepatol 2018; doi: 10.1016/j.jhep.2018.11.004;
EASL CPG HCV. J Hepatol 2018;69:461–511.

NS5A and NS3 RAS in DAA-naïve GT-3a patients

SHARED HEP C HOPE

NS5A RAS
(N=351)



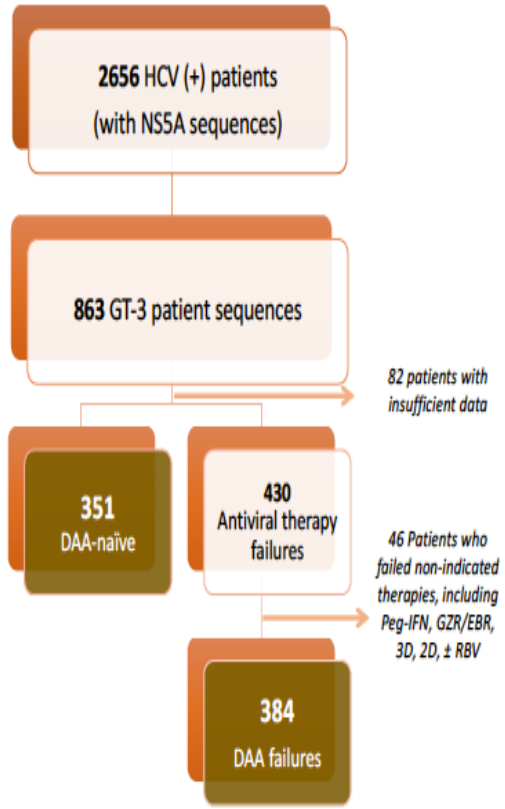
*including A30V/T + Y93H (n=2), P58T + Y93H (n=1)
**M28I/V (n=7), L31I (n=2), P58S/G/T (n=5)

SHARED
Surveillance of Hepatitis-C Antiviral Resistance, Epidemiology and MethoDologies

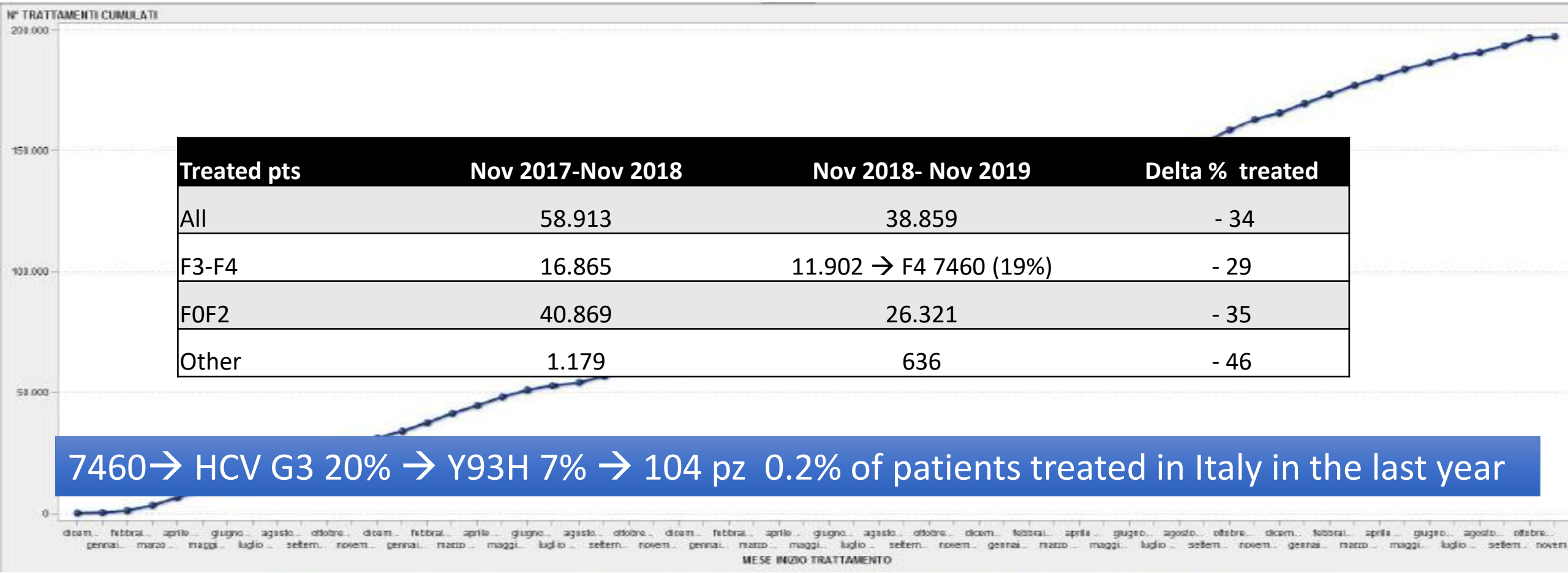
An international collaboration of viral sequences, treatment histories, and health outcomes related to the hepatitis C virus

HEP C HOPE

SHARED Participating Centers



Trend cumulativo dei trattamenti avviati



Treated pts	Nov 2017-Nov 2018	Nov 2018- Nov 2019	Delta % treated
All	58.913	38.859	- 34
F3-F4	16.865	11.902 → F4 7460 (19%)	- 29
F0F2	40.869	26.321	- 35
Other	1.179	636	- 46

7460→ HCV G3 20% → Y93H 7% → 104 pz 0.2% of patients treated in Italy in the last year

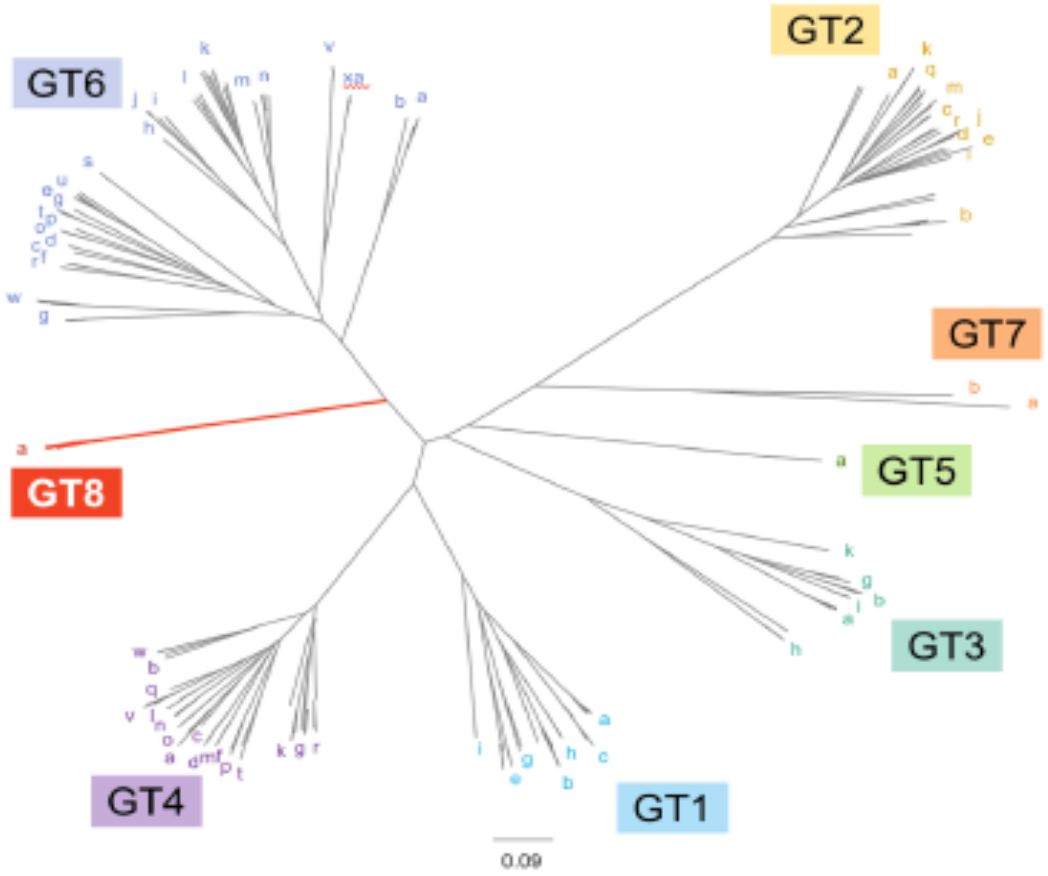
197.274 «avviati» sono i trattamenti (solo pazienti eleggibili)
con almeno una scheda di Dispensazione farmaco

HCV unusual subtypes

- HCV is a highly diverse virus
  - 8 genotypes
  - >100 subtypes

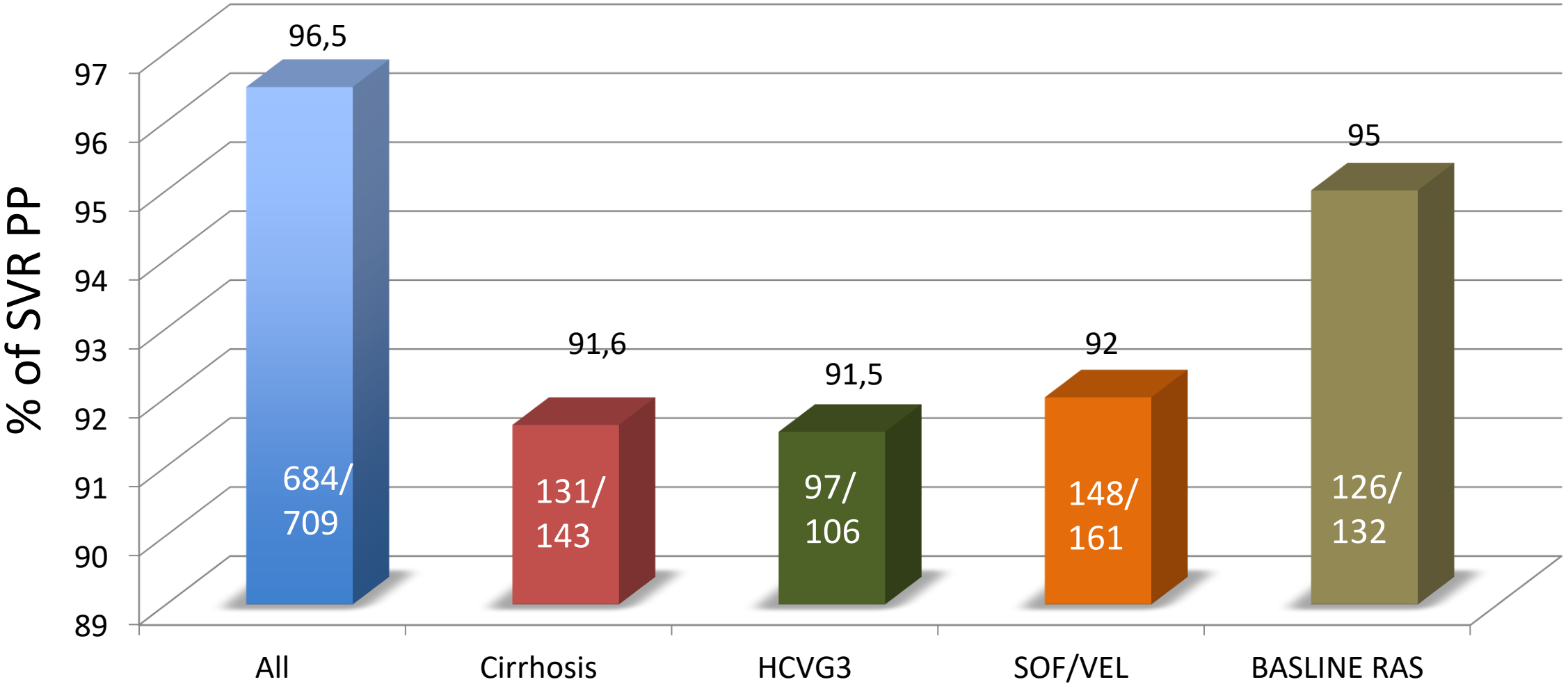
- "Unusual" subtypes
  - GT1 non 1a/b,
  - GT2 non 2a/b,
  - GT3 non 3a
  - GT4 non 4a/d
  - GT5, GT6, GT-7 and GT-8

- "Unusual" subtypes
  - Mostly originating from Africa and Asia
  - Multiple polymorphisms in NS5A
  - Lower SVR rates than "usual" subtypes



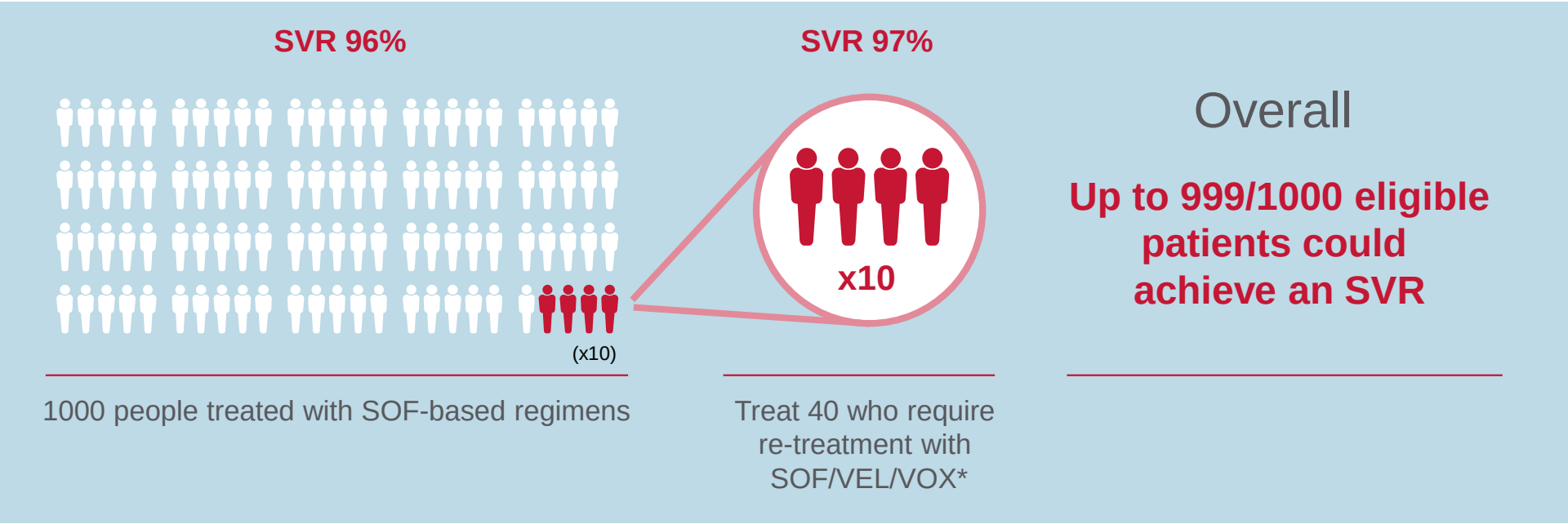
SM Borgia et al JID 2018; K Childs et al. J of Hepatol 2019; Wei et al. Lancet gastroenterol hepatol 2019; Gupta N et al. Lancet gastroenterol hepatol 2019

Real Life efficacy of SOF/VEL/VOX for DAA failures



deQuadros O & De Gasperi E & Flamm F & Krajden K and Zeuzem S AASLD 2019

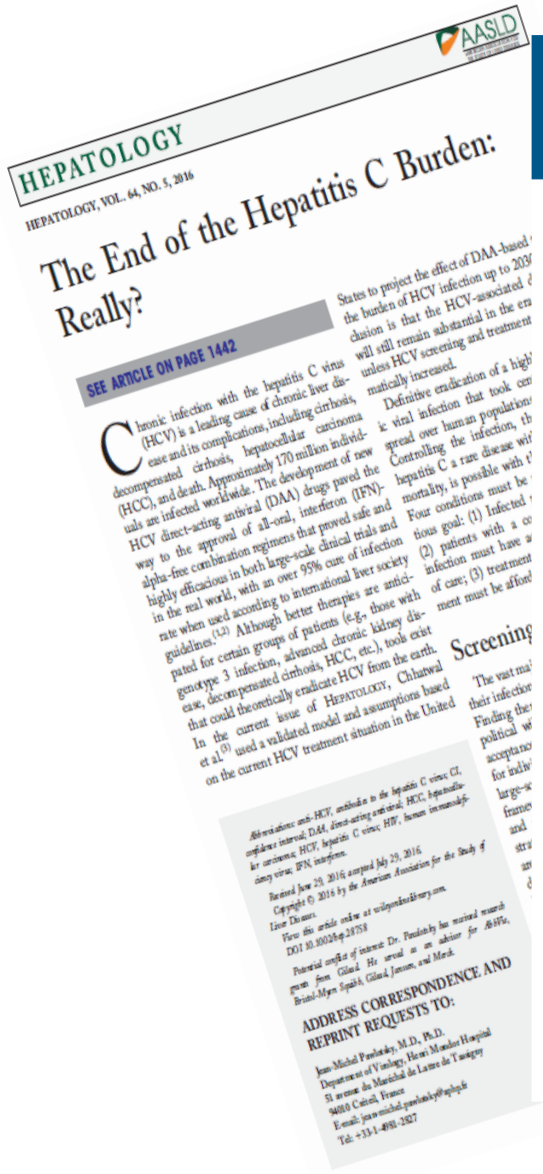
With an effective treatment and re-treatment strategy, the vast majority of patients could achieve an SVR



With the potential for an up to 99.9% SVR at the population level, elimination of HCV could become a reality!

Flamm S, et al. ILC 2017; Poster #SAT-279; Curry M, et al. ILC 2017; Oral #102; Terrault N, et al. Gastroenterology 2016;151:1131–40; Khalili M, et al. ILC 2017; Poster #SAT-222; Vermehren J, et al. ILC 2017; Poster #FRI-247; Welzel TM, et al. ILC 2016; Poster #SAT-274; Roberts S, et al. ILC 2017; Poster #SAT-280

*SOF/VEL/VOX is not recommended in patients with moderate or severe hepatic impairment (CTP B or CTP C). This is a concept slide based on a real-world SVR of 96% calculated from 9391 patients treated with LDV/SOF ± RBV and SOF/VEL ± RBV in the TRIO, HCV-TARGET and DHC-R cohorts. Re-treatment SVR of 97% with SOF/VEL/VOX is reported in the POLARIS-1–4 integrated analysis



HEPATOLOGY

HEPATOLOGY, VOL. 64, NO. 5, 2016

The End of the Hepatitis C Burden: Really?

SEE ARTICLE ON PAGE 1442

Chronic infection with the hepatitis C virus (HCV) is a leading cause of chronic liver disease and its complications, including cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), and death. Approximately 170 million individuals are infected worldwide. The development of new HCV direct-acting antiviral (DAA) drugs paved the way to the approval of all-oral, interferon (IFN)-alpha-free combination regimens that proved safe and highly efficacious in both large-scale clinical trials and in the real world, with an over 95% cure of infection rate when used according to international liver society guidelines.[1,2] Although better therapies are anticipated for certain groups of patients (e.g., those with genotype 3 infection, advanced chronic kidney disease, decompensated cirrhosis, HCC, etc.), tools exist that could theoretically eradicate HCV from the earth. In the current issue of HEPATOLOGY, Chhatwal et al.[3] used a validated model and assumptions based on the current HCV treatment situation in the United States to project the effect of DAA-based ... the burden of HCV infection up to 203... clusion is that the HCV-associated ... will still remain substantial in the era ... unless HCV screening and treatment ... matically increased.

Definitive eradication of a high... ic viral infection that took cen... spread over human population... Controlling the infection, th... hepatitis C a rare disease wit... mortality, is possible with t... Four conditions must be ... tious goal: (1) Infected ... (2) patients with a co... infection must have a ... of care; (3) treatment ... ment must be afford...

Screening

The vast ma... their infection... Finding ther... political w... acceptanc... for indiv... large-s... framew... and ... strat... an... d...

Abbreviations: anti-HCV, antibodies to the hepatitis C virus; CI, confidence interval; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon.

Received June 29, 2016; accepted July 29, 2016.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.28758

Potential conflict of interest: Dr. Pawlotsky has received research grants from Gilead. He served as an advisor for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.

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EDITORIALS

Hepatitis C Drugs: Is Next Generation the Last Generation?

See "High efficacy of ABT-493 and ABT-530 treatment in patients with HCV genotype 1 or 3 infection and compensated cirrhosis," by Gane E, Poordad F, Wang S, et al, on page 651.

Much has been written about the "hepatitis C virus (HCV) drug revolution." For an individual who started to work on the newly discovered HCV in 1990, at the time happy to describe rates of sustained virologic response (SVR) on the order of 6% with standard interferon (IFN)-α administered 3 times per week for 6 months,[1] the current HCV treatment landscape could look miraculous. It is simply the result of an enormous intellectual, scientific, and financial effort of the publicly funded academic and the industrial sectors to solve a major public health problem, building on the experience accumulated in the fight against the human immunodeficiency virus.

This unprecedented effort led to the approval of IFN-free treatment regimens based on combinations of direct-acting antiviral (DAA) drugs. Four classes of HCV DAAs are available in the United States and Europe, including inhibitors of the HCV RNA-dependent RNA polymerase (the nucleotide analog sofosbuvir and the non-nucleoside inhibitor dasabuvir), nonstructural 5A (NS5A) protein inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir, and velpatasvir), and inhibitors of the NS3-4A protease (simeprevir, paritaprevir, and grazoprevir). These drugs are available either as fixed-dose combinations, including sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) and grazoprevir/elbasvir, or as single agents that can be combined (sofosbuvir, daclatasvir, and simep... DAA combinations should be administered f... weeks, with or without weight-based rib... to baseline parameters, including the HCV ... type, the stage of fibrosis, prior HCV ... comorbidities, and co-administered med... tical use is guided by recommendations ... larly updated by the international liver ...

In phase II and III clinical tria... approved drug combinations, SVR ... achieved in most patient groups, w... effects. Real-world studies involvi... tients from various continents con... and the excellent safety and toler... approved HCV DAA combination... issues remained unsolved:

- The ideal treatment durat... ment can be shortened t...
- Many groups of patien... with ribavirin, a medic... to achieve high rates ...
- Treatment of genoty... cure genotype, wit... lower SVR rates th...
- The ideal timing ... patients with dec... awaiting liver tr...
- Whether pre-li... clinical benefi...

Review

CrossMark

EASL JOURNAL OF HEPATOLOGY

From non-A, non-B hepatitis to hepatitis C virus cure

Jean-Michel Pawlotsky[1,2,*], Jordan J. Feld[3], Stefan Zeuzem[4], Jay H. Hoofnagle[5]

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Review

Summary

The hepatitis C virus (HCV) was discovered in the late 1980s. Interferon (IFN)-α was proposed as an antiviral treatment for chronic hepatitis C at about the same time. Successive improvements in IFN-α-based therapy (dose finding, pegylation, addition of ribavirin) increased the rates of sustained virologic response, i.e. the rates of curing HCV infection. These rates were further improved by adding the first available direct-acting antiviral (DAA) drugs to the combination of pegylated IFN-α and ribavirin. An IFN-free era finally started in 2014, yielding rates of sustained virologic response over 90% in patients treated for 8 to 24 weeks with all-oral regimens. Major challenges however remain in implementation of these new treatment strategies, not only in low- to middle-income countries, but also in high-income countries where the price of these therapies is still prohibitive. Elimination of HCV infection through treatment in certain areas is possible but raises major public health issues.

Introduction

Twenty-five years after the discovery of the hepatitis C virus (HCV), new orally administered antiviral drug combinations yielding infection cure rates over 90% were approved in 2014–2015 in Europe, the US and other regions of the world. Some called it a "revolution". A revolution is defined by "a sudden, complete or marked change in something". This definition does not apply to what happened to the field of HCV therapy. Instead, a slow, progressive, successful succession of discoveries in which academic scientists, clinicians and commercial entities were collaboratively involved, led to the current situation (Fig. 1). It is the story of this adventure, from discovery to cure, that we are telling here.

To begin at the beginning

The era of discovery

In the 1960s and early 1970s, viral hepatitis was considered to represent two clinically and epidemiologically distinct diseases: infectious and serum hepatitis [1]. Infectious hepatitis, or hepatitis A, was marked by a short incubation period (1–3 weeks), fecal-oral transmission, a high degree of contagiousness and an acute self-limited illness that could be protracted and severe (and even fatal) but did not result in chronic hepatitis or cirrhosis. Serum hepatitis, or hepatitis B, in contrast was marked by a longer incubation period (1–3 months), parenteral or sexual transmission, a low degree of contagiousness, and an acute illness, that was usually self-limited but could be severe or fatal and could also result in chronic infection, chronic hepatitis and even cirrhosis. This duality was supported by human transmission studies [1] and by the discovery that the Australia antigen was a part and parcel of the hepatitis B virus (HBV) [2–4], considered at the time to be the sole cause of serum hepatitis. Development of sensitive tests for Australia antigen, later named the hepatitis B surface antigen (HBsAg), provided means of diagnosis and screening that could be applied to blood donations and prevention of post-transfusion hepatitis [5]. Application of donor screening for HBsAg, however, led to a decrease in post-transfusion hepatitis of only 25-50% [6]. The residual cases were considered to be due to hepatitis A or to hepatitis B that was not detected by the then-available serologic assays.

The discovery of the hepatitis A virus (HAV) was another landmark advance in hepatitis research and paved the way for development of serological assays for diagnosis and epidemiologic studies and ultimately for an HAV vaccine [7]. This discovery also showed that hepatitis A was not a cause of post-transfusion hepatitis; indeed, virtually none of the non-B cases of hepatitis from blood products could be linked to HAV [8]. The third form of viral hepatitis was appropriately termed "non-A, non-B" (NANB)

Keywords: Hepatitis; Discovery; Direct-acting antivirals; Interferon; Ribavirin.
Received 26 January 2015; accepted 4 February 2015

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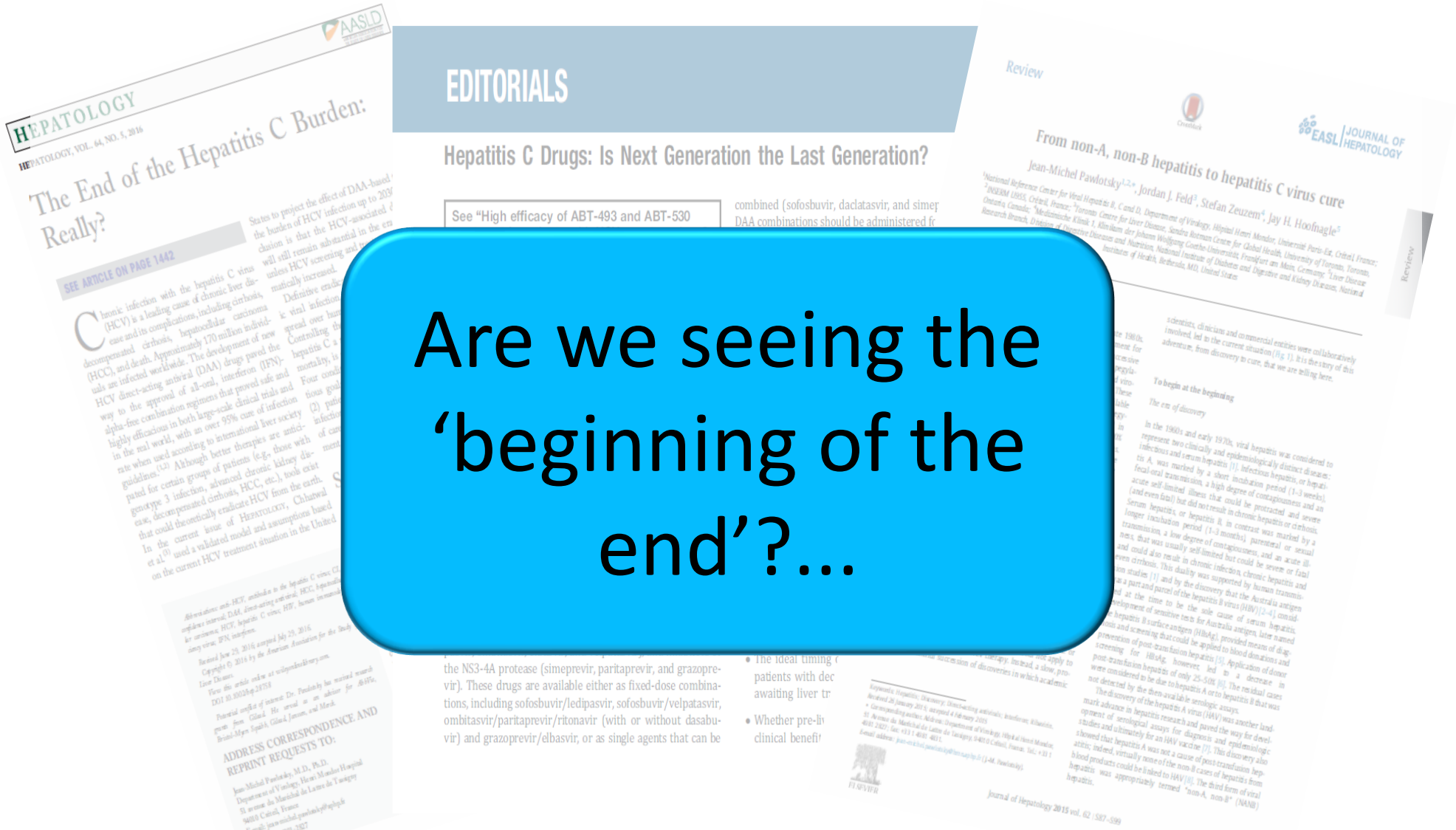
E-mail address: jean-michel.pawlotsky@inserm.fr (J.-M. Pawlotsky).


HEPATOLOGY
The End of the Hepatitis C Burden: Really?
EDITORIALS
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Review
From non-A, non-B hepatitis to hepatitis C virus cure
Are we seeing the 'beginning of the end'?...

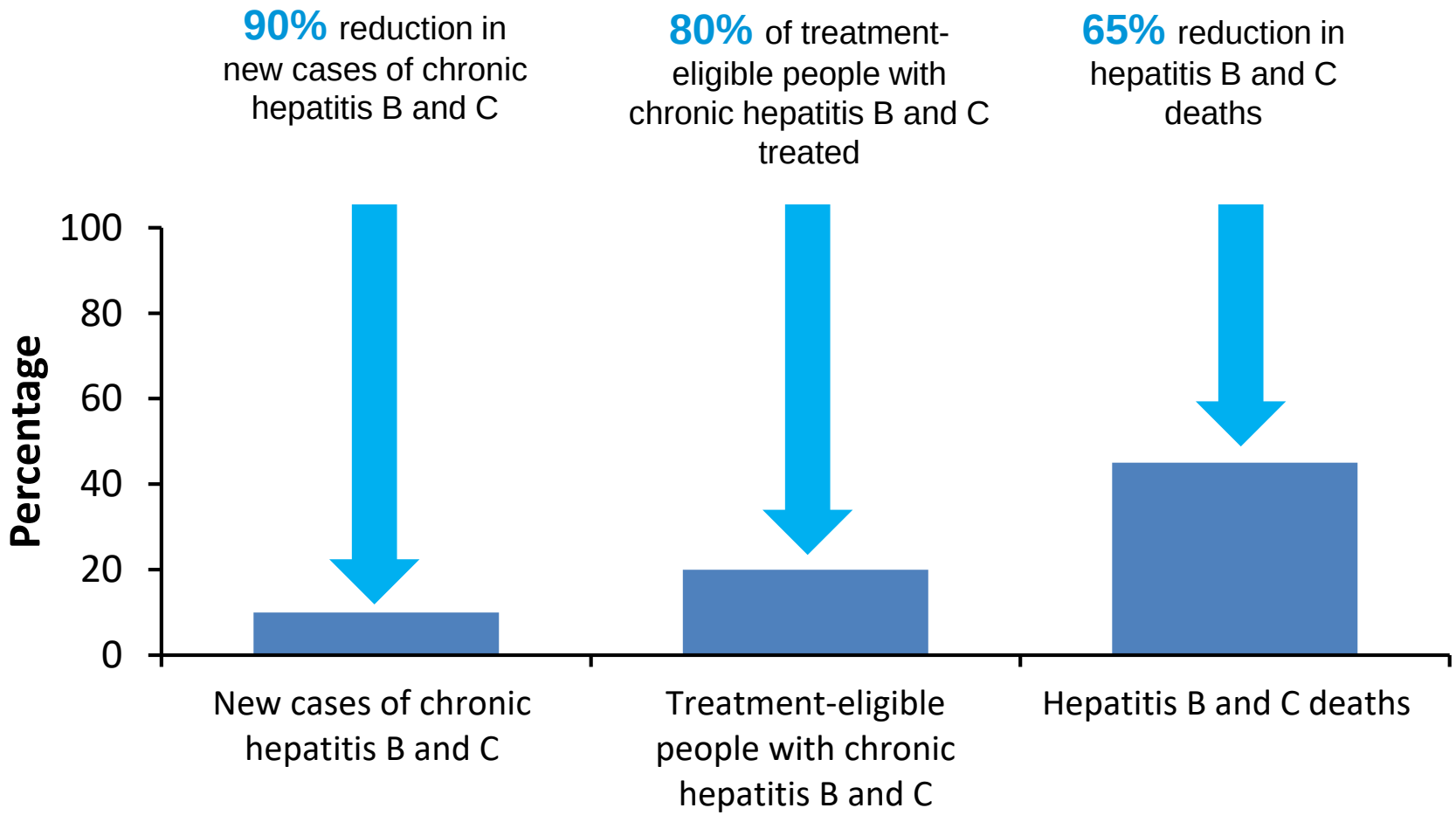
T.S. Eliot “ The Little gidding”

…..to make an end is to make a beginning. The end is where we start from….

HCV the road to elimination: drugs and strategies

- Towards a pangenotypic universal treatment
  - Evolution of DAAs
  - Efficacy of pangenotypic regimens
  - Any exception for universal pangenotypic treatment?
- Towards HCV elimination
  - Simplification of HCV management: when and how
  - From microelimination to a search and destroy strategy

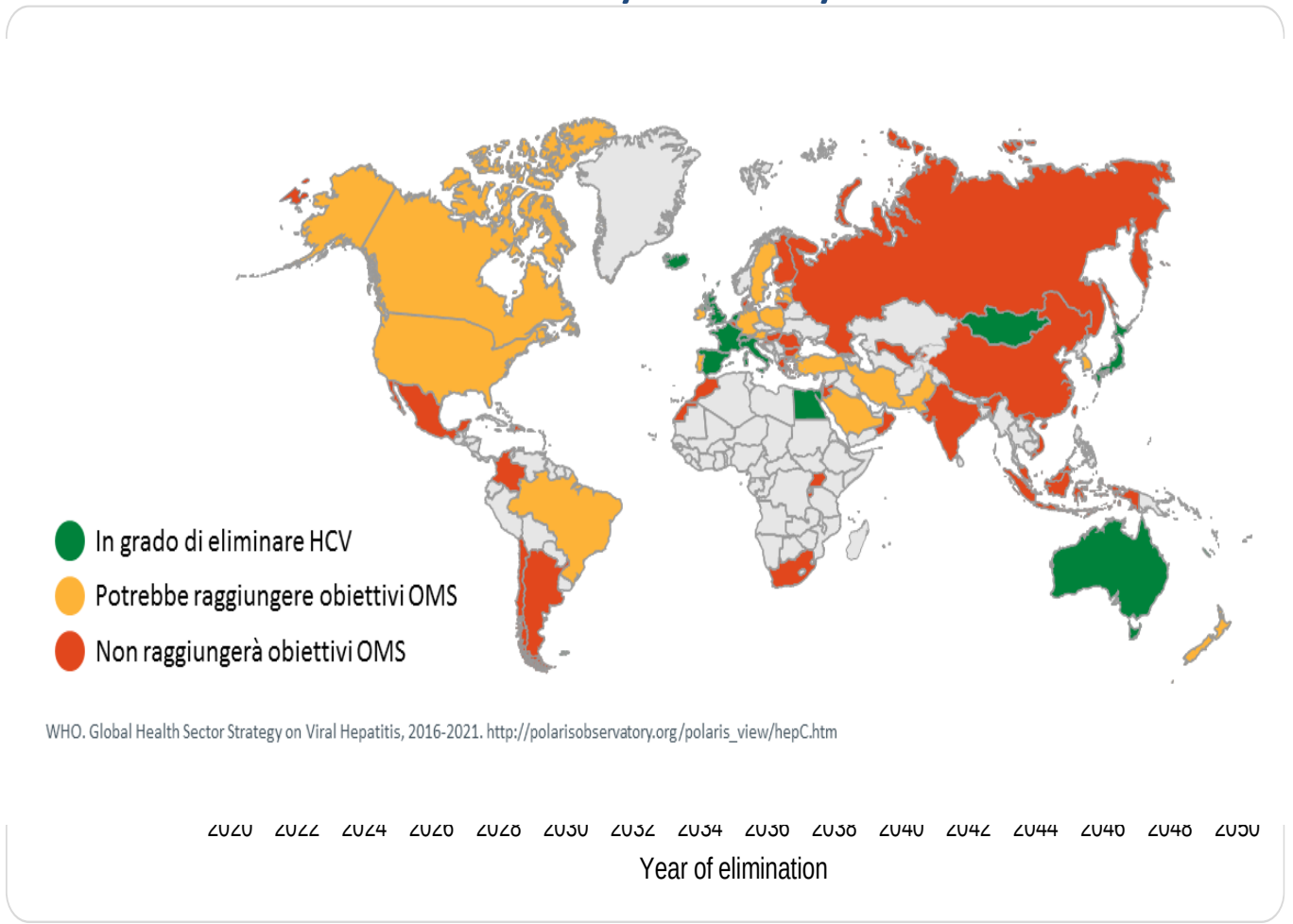
The global targets set by WHO to control viral hepatitis by 2030 are ambitious



WHO global health sector strategy on viral hepatitis. Available at: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1 (accessed December 2017)

WHO: World Health Organization

Only 20% of 45 high income countries are forecasted to reach the WHO elimination targets by 2030 and only 33% by 2050



Razavi H, Sanchez Y, Pangerl A, Cornberg M, Global timing of hepatitis C virus elimination: estimating the year countries will achieve theWorld Health Organization elimination targets, EASL poster SAT-290, 2019

HCV the road to elimination: drugs and strategies

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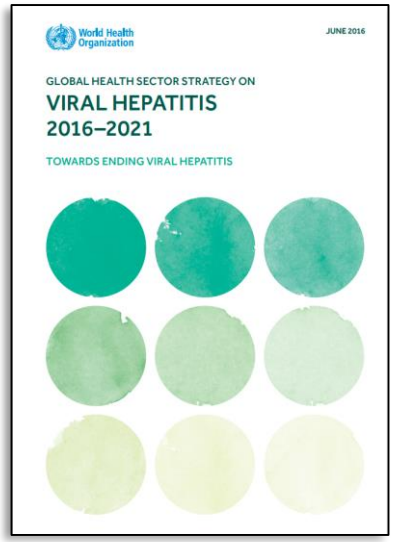
Global HCV elimination: the state of play

We have a global strategy to eliminate HCV



We have therapeutic tools

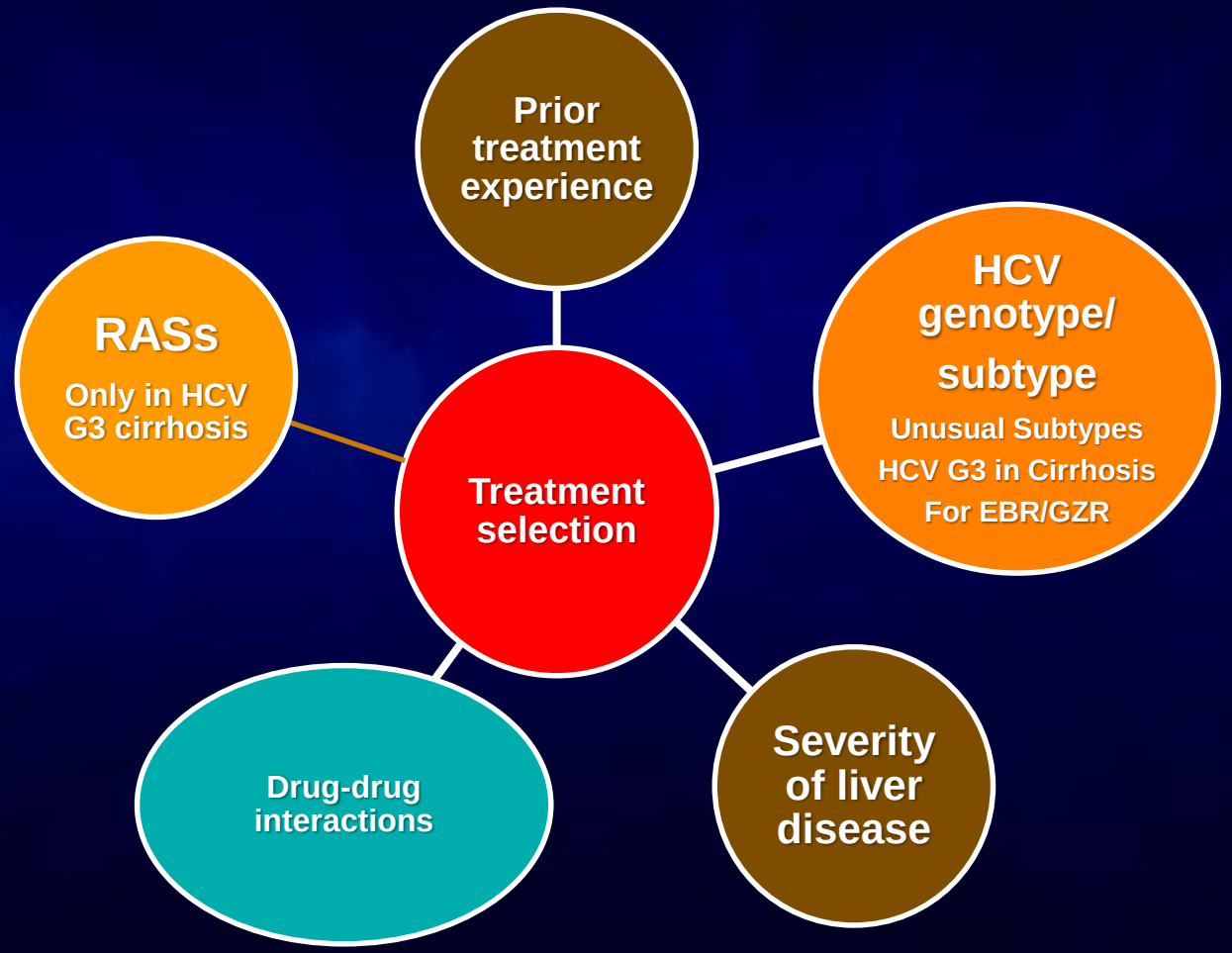
We have strong interest among many stakeholders in carrying it out

How do we go about implementing the strategy?

Lazarus J, et al. J Hepatol 2017;67:665–6

EASL The Home of Hepatology 2016

Characteristics that Inform Treatment Option Selection



HCV GUIDANCE: RECOMMENDATIONS FOR TESTING, MANAGING, AND TREATING HEPATITIS C

Simplified HCV Treatment* for Treatment-Naive Patients Without Cirrhosis

WHO IS ELIGIBLE FOR SIMPLIFIED TREATMENT

Patients with chronic hepatitis C who do not have cirrhosis and have not previously received hepatitis C treatment

↓

WHO IS *NOT* ELIGIBLE

Patients who have any of the following characteristics:

- Prior hepatitis C treatment
- Cirrhosis
- Prior liver transplant
- HIV or HBsAg positive
- End-stage renal disease (ie, eGFR <30 mL/min/m^2)
- Currently pregnant

PRETREATMENT ASSESSMENT*

- **Cirrhosis assessment**
  Liver biopsy is not required. The cutoffs of the following tests suggest cirrhosis. If any test suggests cirrhosis, treat the patient as having cirrhosis.
  - FIB-4 >3.25
  - APRI >2.0
  - Platelet count <150,000/mm^3
  - Fibroscan™ stiffness >12.5 kPa
- **Medication reconciliation**
  Record current medications, including over-the-counter drugs and herbal/dietary supplements.
- **Potential drug-drug interaction assessment**
  Drug-drug interactions can be assessed using the AASLD/IDSA guidance (https://www.hcvguidelines.org) or the University of Liverpool drug interaction checker. (https://www.hep-druginteractions.org/checker).
- **Education**
  Educate the patient about proper administration of medications, adherence, avoidance of alcohol, and prevention of reinfection.
- **Pretreatment laboratory testing**

  Within 6 months of initiating treatment
  - Complete blood count (CBC)
  - Hepatic function panel (ie, albumin, total protein, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels)
  - Calculated glomerular filtration rate (eGFR)

  Anytime prior to starting antiviral therapy
  - Quantitative HCV RNA (HCV viral load)
  - HIV antigen/antibody test
  - Hepatitis B surface antigen (HBsAg)

  Before initiating antiviral therapy
  - Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

HCV GUIDANCE: RECOMMENDATIONS FOR TESTING, MANAGING, AND TREATING HEPATITIS C

Simplified HCV Treatment* for Treatment-Naive Patients Without Cirrhosis

RECOMMENDED REGIMENS*

Glecaprevir (300 mg) / pibrentasvir (120 mg)
to be taken with food for a duration of 8 weeks

Sofosbuvir (400 mg) / velpatasvir (100 mg)
for a duration of 12 weeks

ON-TREATMENT MONITORING

- Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. Monitoring for hypoglycemia is recommended.
- Inform patients taking warfarin of the potential for changes in their anticoagulation status. Monitoring INR for subtherapeutic anticoagulation is recommended.
- No laboratory monitoring is required for other patients.
- An in-person or telehealth visit may be scheduled, if needed, for patient support, assessment of symptoms, and/or new medications.

POST-TREATMENT ASSESSMENT OF CURE (SVR)

- Monitoring patients taking diabetes medication for hypoglycemia is recommended.
- Monitoring INR for patients taking warfarin is recommended.
- Assessment of quantitative HCV RNA and hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization.
- Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.

FOLLOW-UP AFTER ACHIEVING VIROLOGIC CURE (SVR)

- No liver-related follow-up is recommended for noncirrhotic patients who achieve SVR.
- Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin.

FOLLOW-UP FOR PATIENTS WHO DO *NOT* ACHIEVE A VIROLOGIC CURE

- Assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and international normalized ratio (INR) is recommended.
- Patients in whom initial HCV treatment fails to achieve cure (SVR) can be retreated, often successfully. Consult the AASLD/IDSA guidance for recommendations regarding the evaluation of patients for retreatment and selection of an appropriate HCV antiviral regimen. (https://www.hcvguidelines.org)

* More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment, including the treatment of patients with cirrhosis, can be found at https://www.hcvguidelines.org. Updated: November 6, 2019

HCV the road to elimination: drugs and strategies

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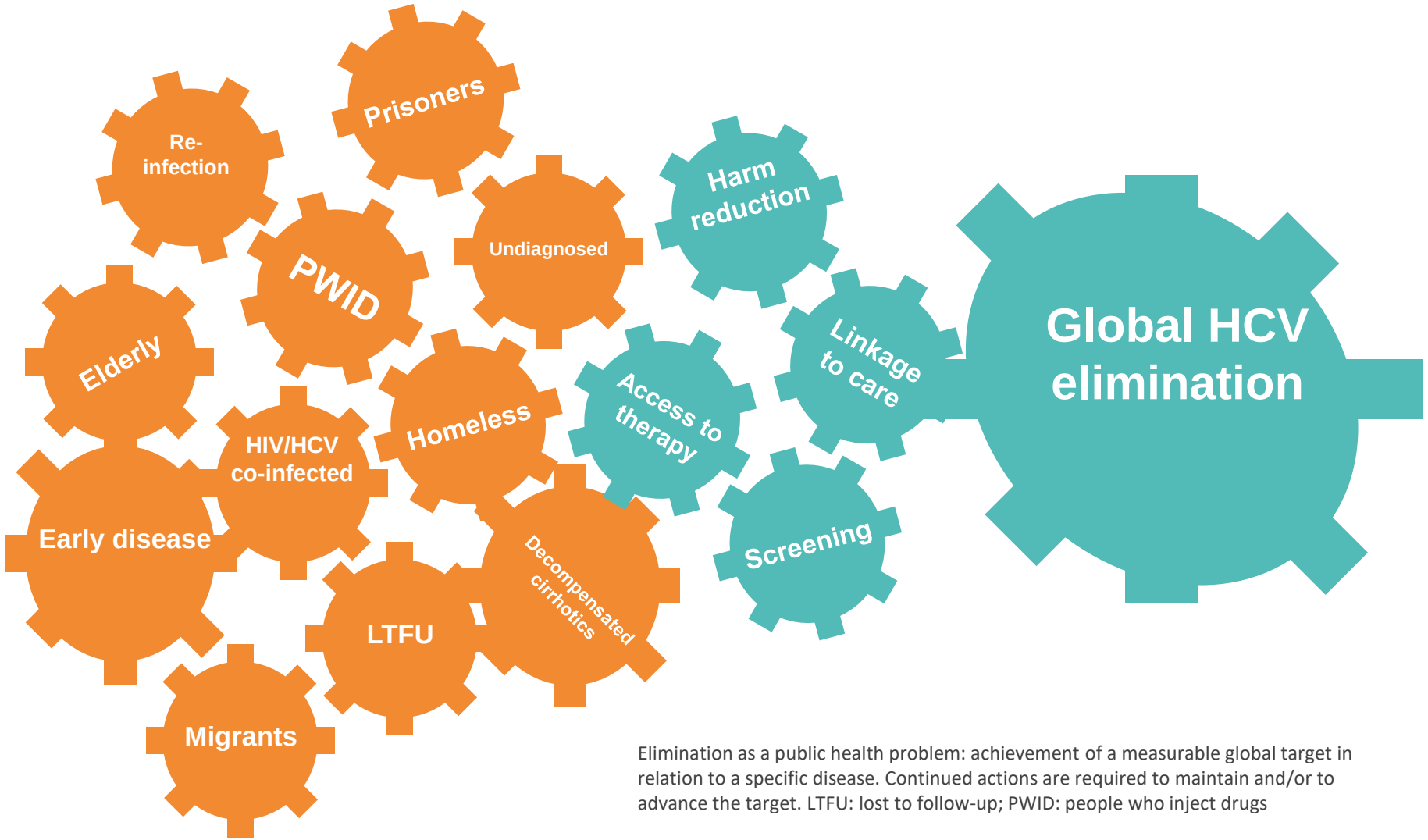
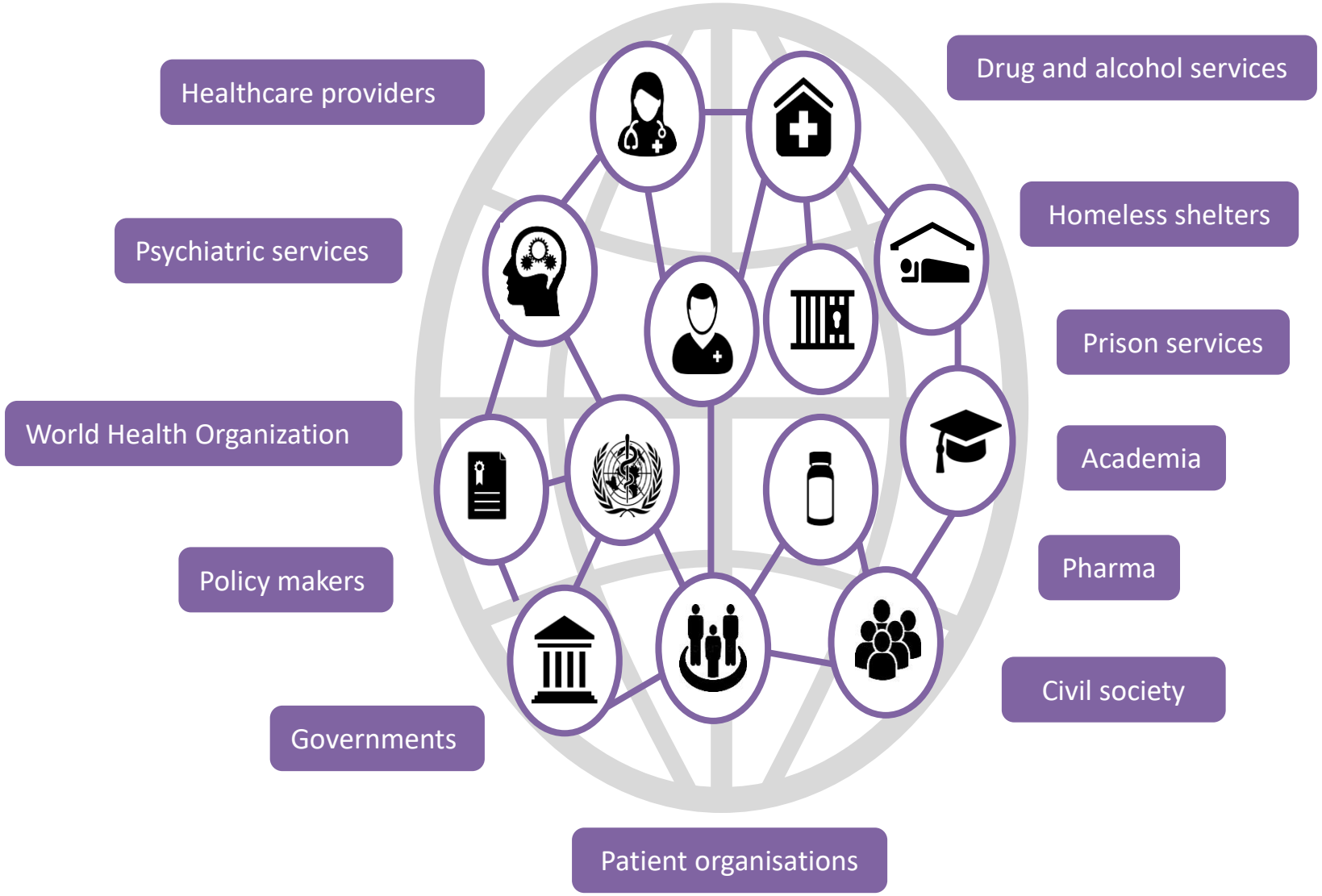
Global HCV elimination as a therapeutic goal can seem daunting… but 100 flowers may rise

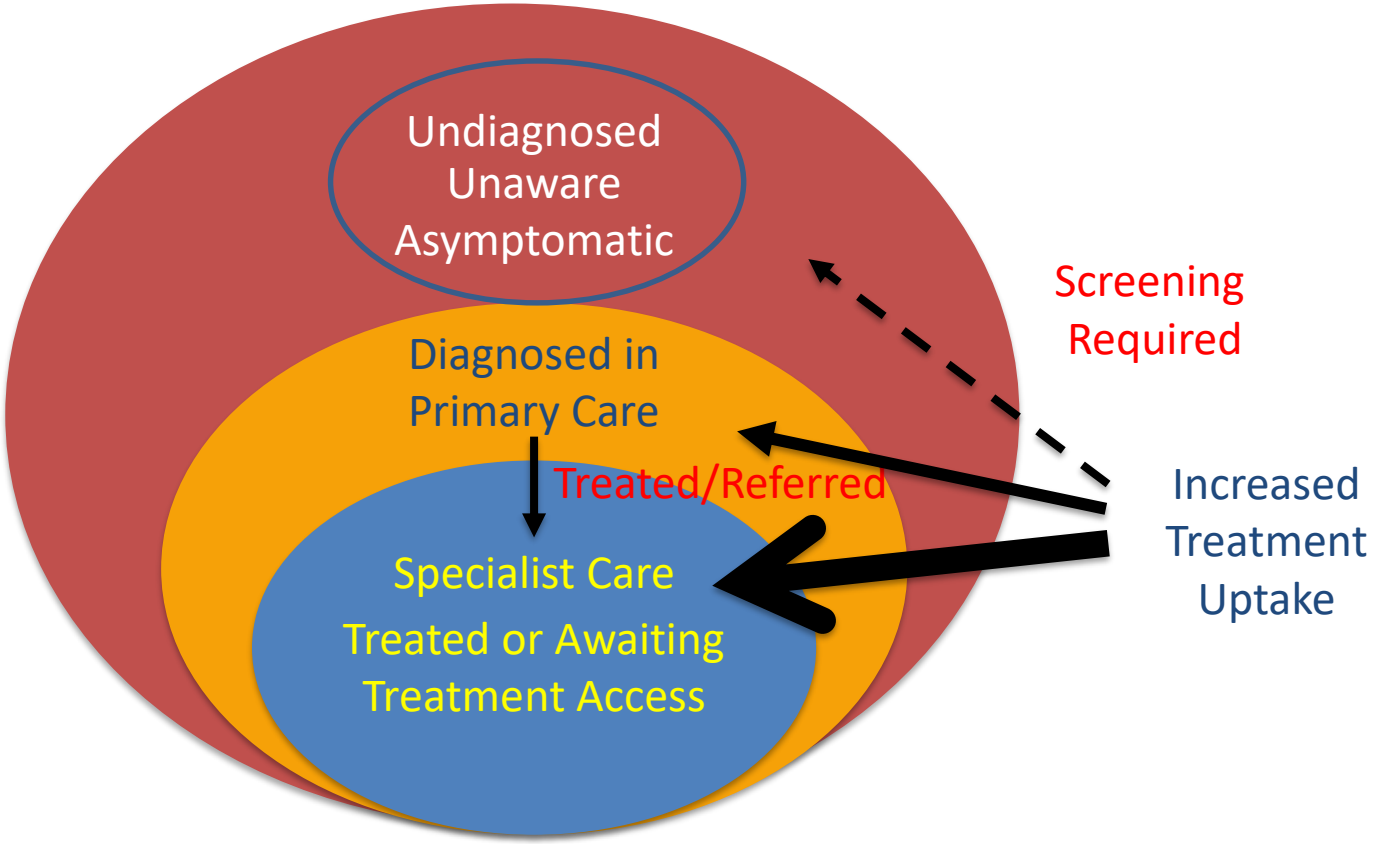


Elimination as a public health problem: achievement of a measurable global target in relation to a specific disease. Continued actions are required to maintain and/or to advance the target. LTFU: lost to follow-up; PWID: people who inject drugs

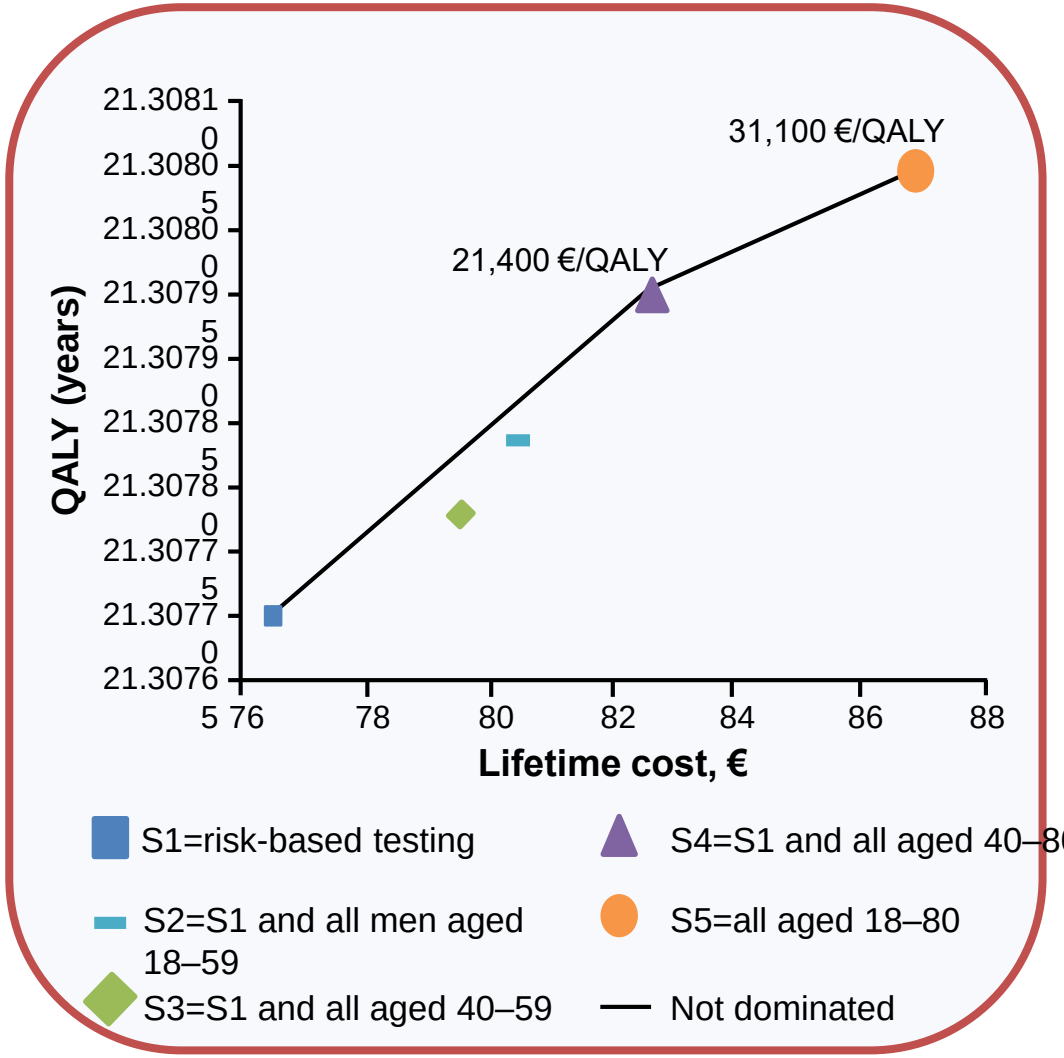
HCV elimination requires broad multi-stakeholder involvement

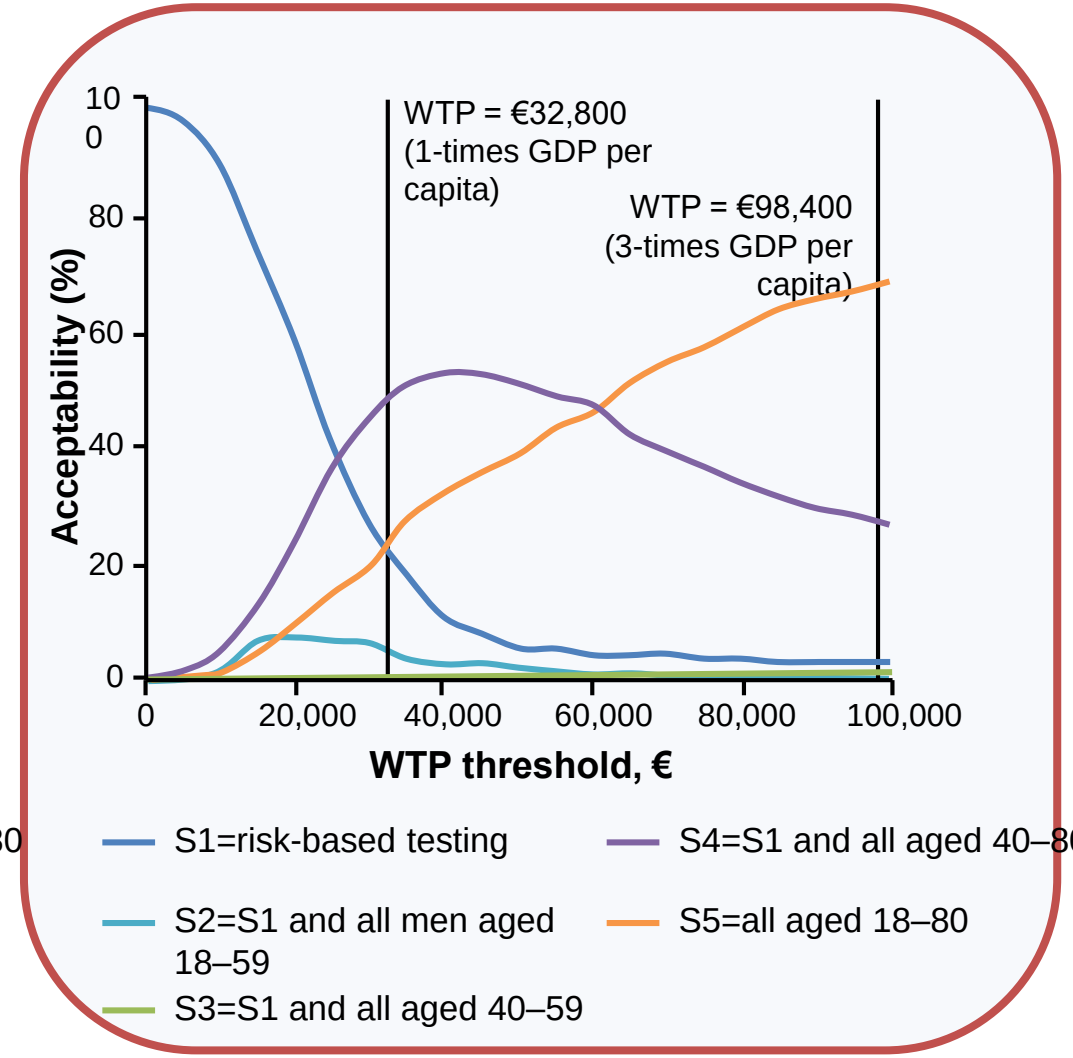


HCV Population



Universal screening is the most cost-effective strategy, at least in France





Deuffic-Burban S, et al. J Hepatol 2018;69:785–92

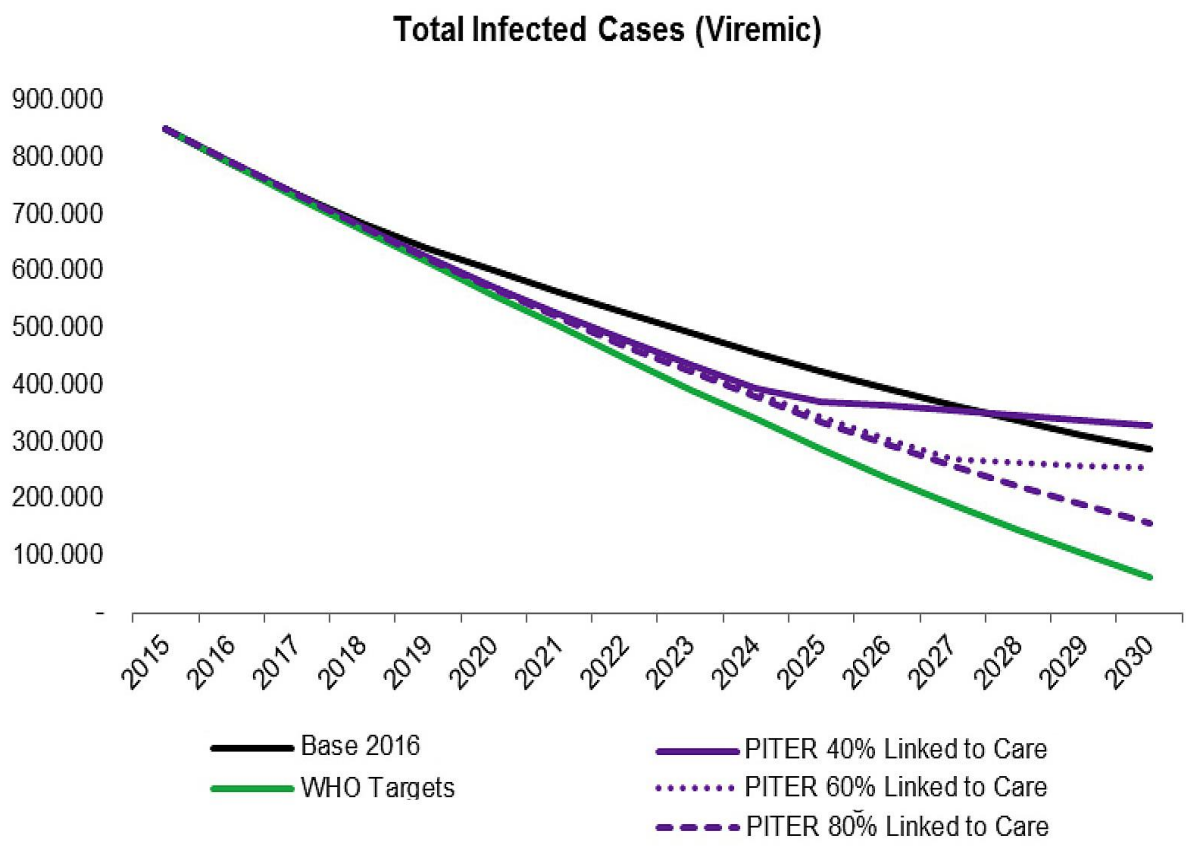
GDP: gross domestic product; QALY: quality-adjusted life years; S: scenario; WTP: willingness to pay

A modeling strategy to reach the WHO targets for HCV based on real life PITER and AIFA Registry data

Importance of Linkage to care

With an annual rate of treatment ≥ 35.000 patients the pool of treatment will be depleted between 2025-2028

Screening for birth cohort



Kondili L et al, Liver Int. 2018;38:2190-2198

Direct costs and health effects, by scenario, 2018–2031

Scenario		Cost (€ Millions), 2018–2031	QALYs Gained, 2018–2031	ICER Relative to Status Quo (€/QALY)	ICER relative to previous least costly scenario (€/QALY)
Status quo		5,463	–	–	
GHSS Targets	**Graduated Screening**	**5,974**	**144,000**	**3,552**	**3,552**
	Screening 1948-1977	6,081	142,000	4,349	*
	Screening 1958-1977	6,083	128,000	4,831	*
	Universal Screening	6,441	145,000	6,758	562,855

Values have been rounded, so ICERs may not be reproducible using table values

ICER — incremental cost-effectiveness ratio; QALY — quality-adjusted life year; GHSS — Global Health Sector Strategy

** Strongly dominated scenario (costlier and less effective than another scenario)*

HCV the road to elimination: drugs and strategies

- DAAs evolution allows a simplified «one size for all» management of HCV infection with two treatment options for 8 or 12 weeks and one retreatment option for failure of fisrt line treatment
- In advanced cirrhosis, HCV G3 cirrhosis and failures to first line options with complex RAS profile still require a tailored approach
- Simplified treatment options in non cirrhotic naive HCV infection (most of those to treat) may facilitate elimination of HCV
- Two strategies for HCV elimination:
  - 100 flowers microelimination projects are easy to plan and cover
  - However universal screening (all at the same time or graduated cohorts screening) is mandatory