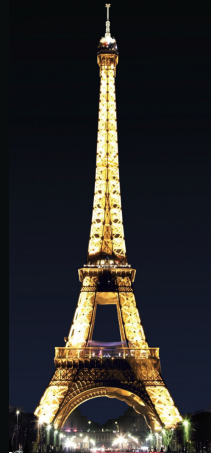
2015 8th Paris Hepatitis Conference

12 & 13 January 2015



Treatment of hepatitis C today and tomorrow

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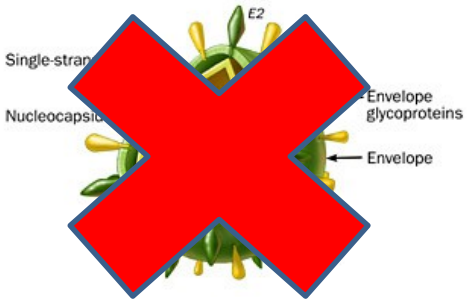
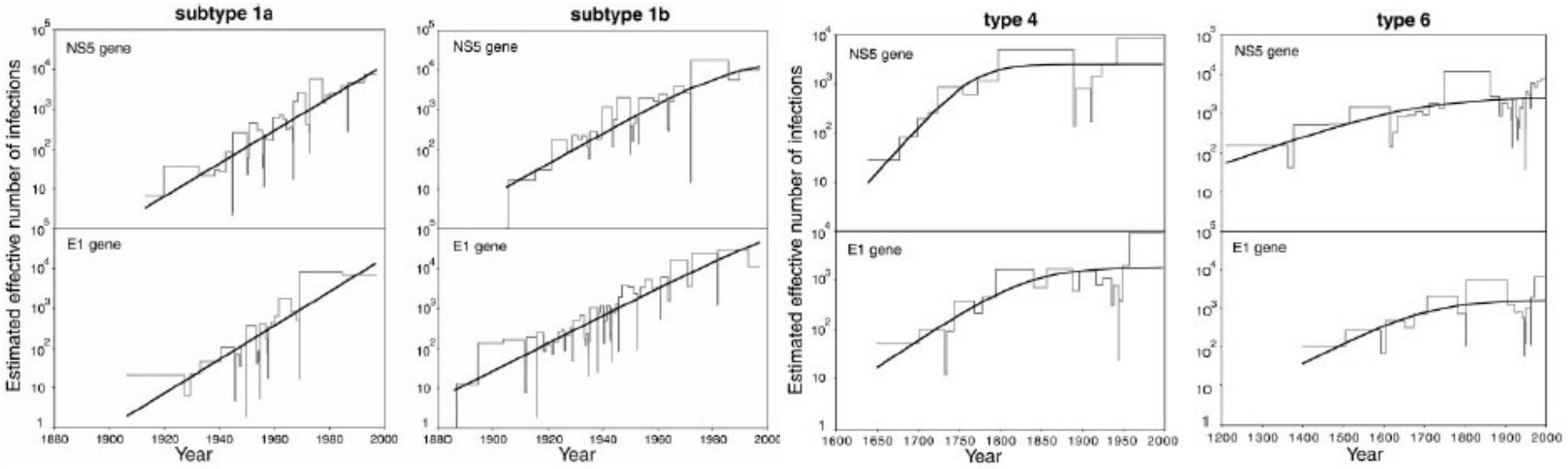
Ad Board and grants: Abbvie, Achillion, Bristol-Myers Squibb, Gilead, Janssen, Merck, Novartis, Roche

Speaker: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, Novartis, Roche

Flaviviridae could be as ancient as the differentiation of primate species (35 million years)

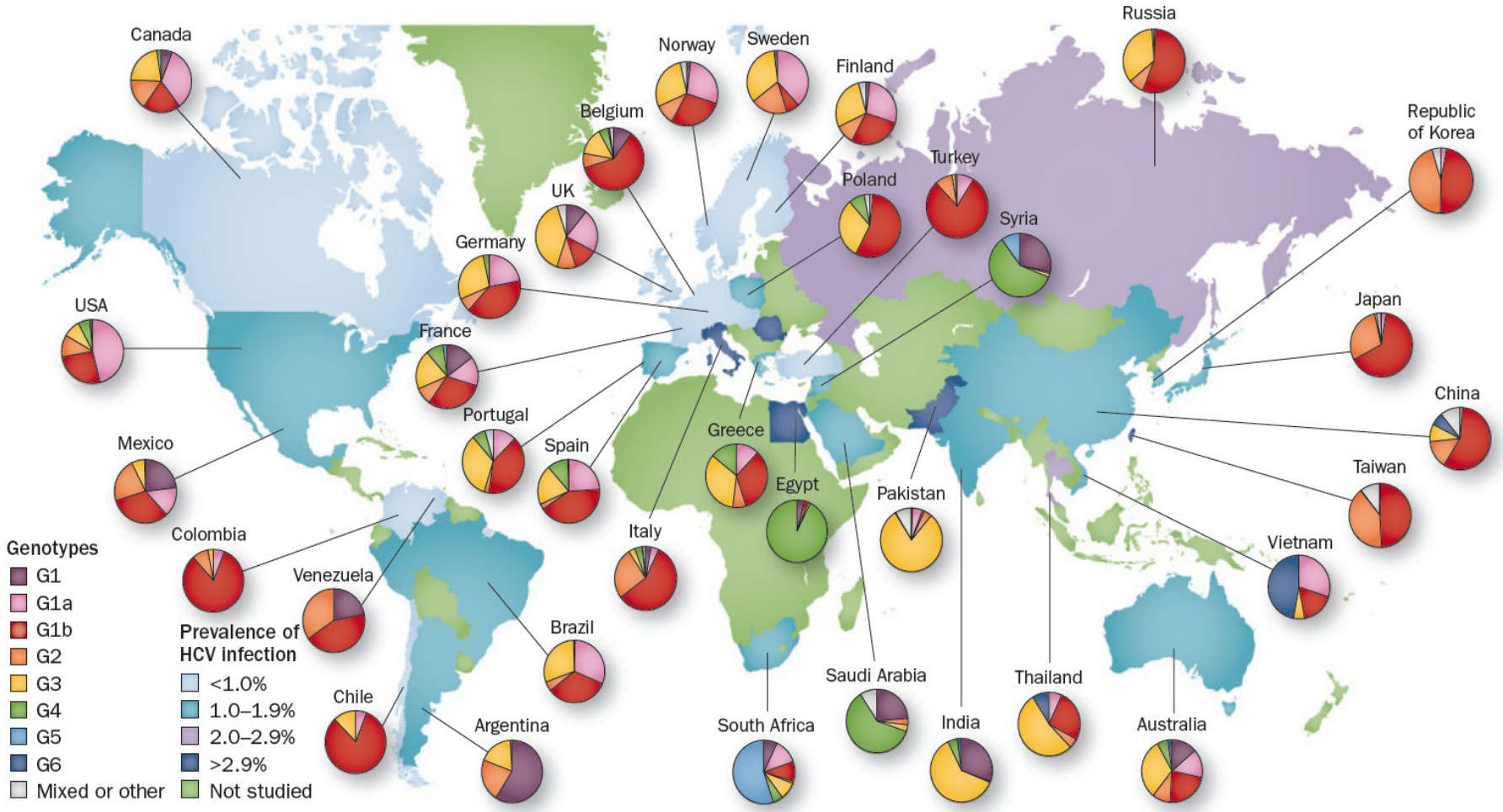
- HCV has coevolved with human populations migrating out of Africa within the past 100,000 to 150,000 years
- Current HCV genotypes appeared over the last 2,000 years
- Genotypes 6 and 4 originated 700 years and 350 years ago
- Subtypes 1a and 1b arose less than 100 years ago





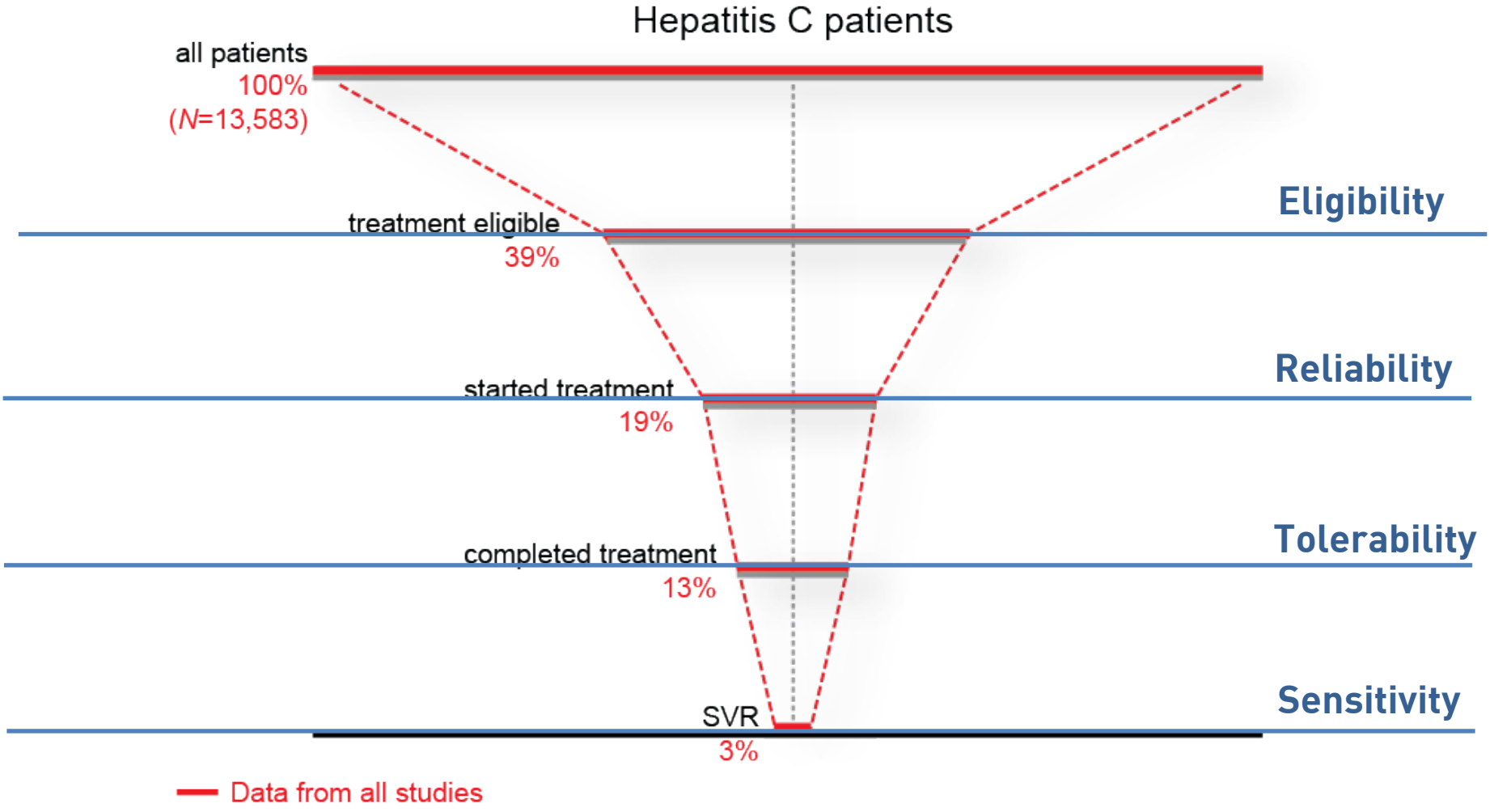
Pybus et al Science 2001

HCV infects →185 million people worldwide



HAJARIZADEH *et al.* Nat Rev Gastroenterol Hepatol 2013;10:553-562
NEGRO and ALBERTI. Liver Int 2011;31 Suppl 2:1-3
HANAFIAH *et al.* Hepatology 2013;57:1333-1342

Treated/cured patients represent only a small proportion of those diagnosed



North CS, et al. Gen Hosp Psych 2013;35:122–8.

DAAs currently approved

2013

Sofosbuvir

Nucleotide polymerase inh
All Gts (±3)

Simeprevir

Daclatasvir

Triple therapy with PEG IFN and ribavirin

SOF and ribavirin, no IFN

Off-label combination of two DAAs ± ribavirin

- Short therapy (8-12 wks), cirrhotics may need 24 wks
- →90% SVR
- Few pills, no IFN
- No RBV, but not for all pts
- Not all regimens suitable for decompensated pts

2014

Gt 1-(4)

Das

Nor
Polyr

Paritaprevir/R

Protease inh./ Ritonavir

Ombitasvir

NS5A inh.

Fixed dose combination of three DAAs ± ribavirin

Ledipasvir

NS5A inh

Sofosbuvir

Nucleotide polymerase inh.

Fixed dose combination of two DAAs ± ribavirin.

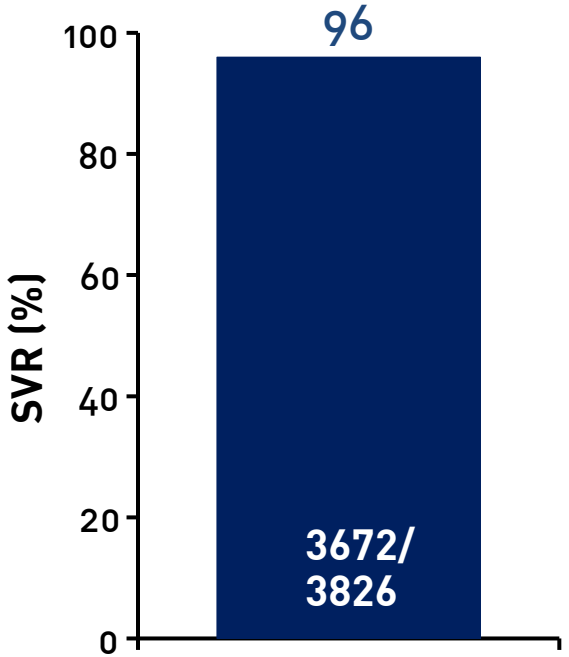
Large body of evidence shows IFN-free therapy new combinations are highly effective in GT 1

Summary of 8 N Engl J Med studies on IFN-free therapy in GT 1 published in 2014

Trial	Regimen
ION-1	LDV/SOF ± RBV
ION-2	LDV/SOF ± RBV
ION-	LDV/SOF ± RBV
SA	
SA	
PE	
PE	
TU	

PERFECTOVIR ?

© J. Feld



Short, well-tolerated treatment regimens 8–24 weeks
Included treatment-naïve and -experienced patients and cirrhotics

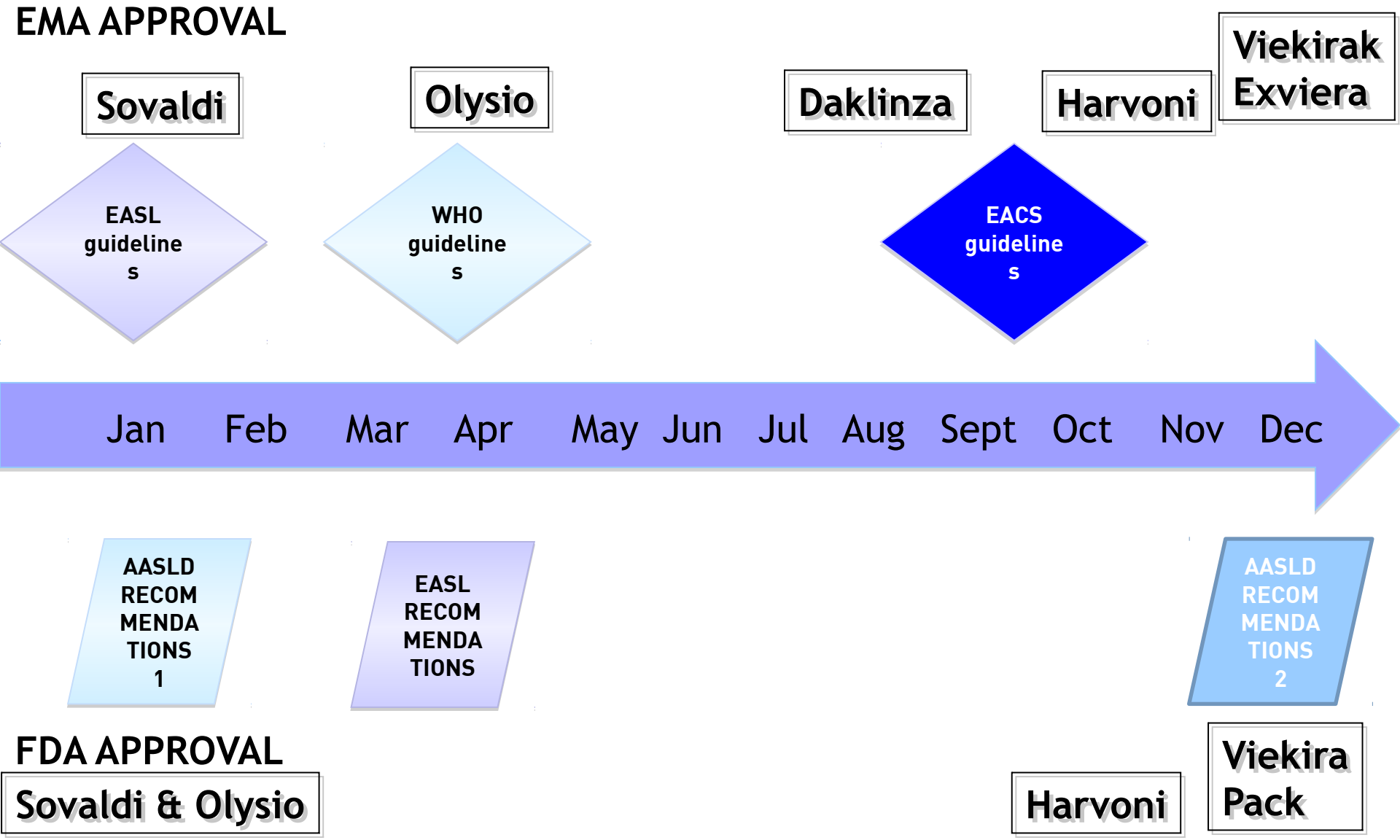
NB: Summary of 8 heterogeneous Phase 3 studies

LDV, PAR/r, OMB and DAS are investigational agents and not approved for use in HCV by the EMA/FDA

Liang J, Ghany MG. N Engl J Med 2013;368:1943-51

DAS: dasabuvir; LDV: ledipasvir; OMB: ombitasvir; PAR: paritaprevir; r: ritonavir

2014: HCV guidelines, recommendations & anti HCV drugs approval by International agencies



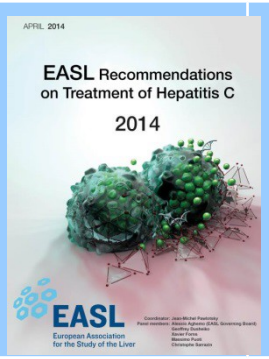
WHOM TO TREAT: EASL AND AASLD-IDSA RECOMMENDATIONS

		AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES AASLD IDSA Infectious Diseases Society of America Collaborating Partner IAS–USA International Antiviral Society–USA
Indications to treatment	**All treatment-naïve and -experienced** patients *with compensated disease due to HCV* **should be considered for therapy (A1)**	Treatment is **recommended for patients with chronic HCV infection** (IA)

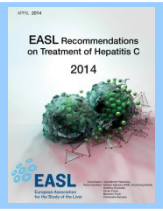
WHOM TO TREAT:
EASL AND AASLD-IDSA RECOMMENDATIONS

Clinical setting		
Compensated Cirrhosis	Strongly recommended (A1)	Highest priority (IA)
Decompensated cirrhosis not on the transplant list	On clinical trial or expanded access program or within experienced centres (B1)	treated by physicians with experience in treating HCV in conjunction with a liver transplantation center

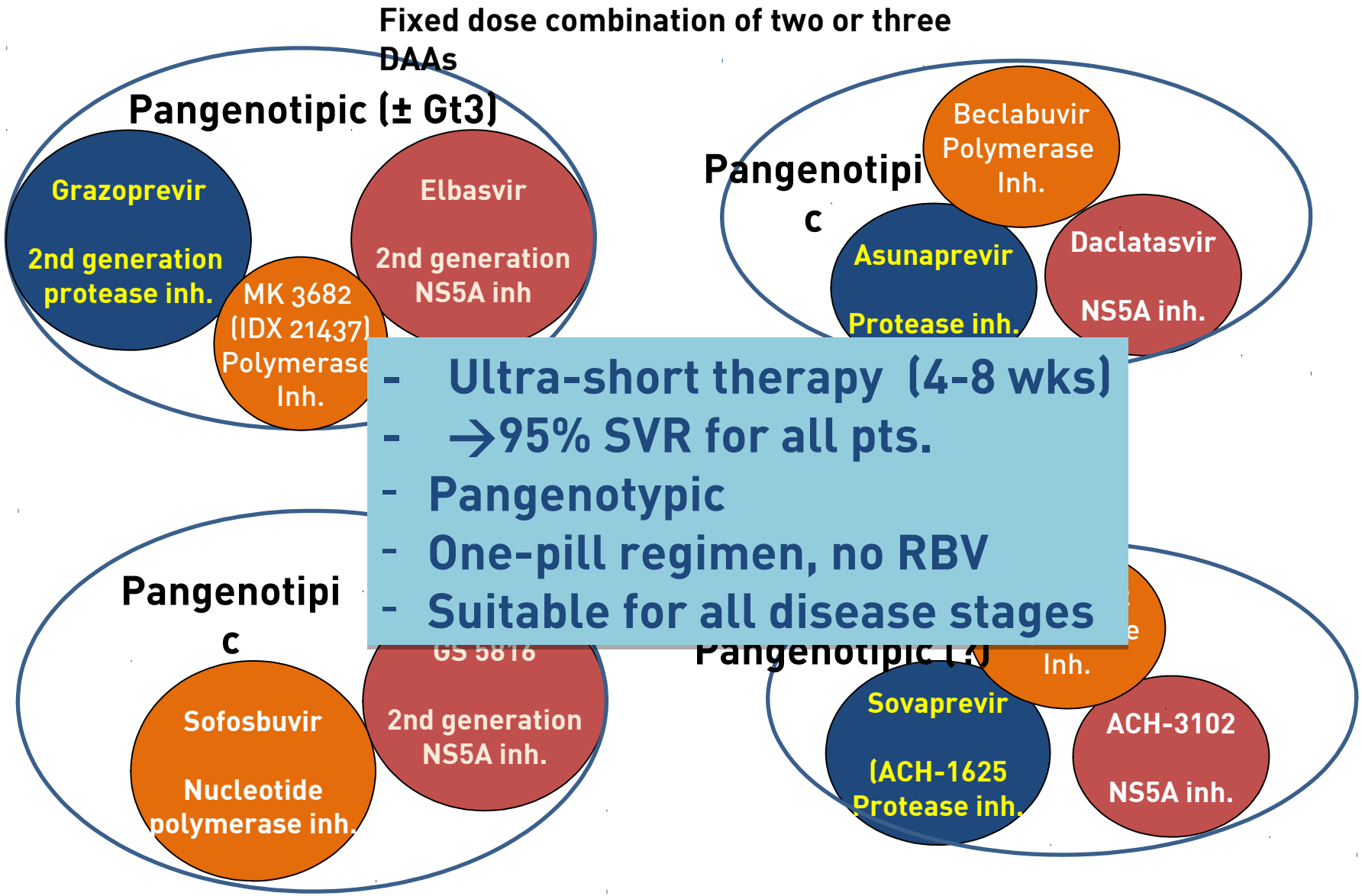
WHOM TO TREAT: EASL AND AASLD-IDSA RECOMMENDATIONS

Clinical setting		
F3	Strongly recommended (A1)	Highest priority (IA)
F2	Justified (A2)	High priority (IB)
F0-F1	Indication for and timing of therapy can be Individualized (B1)	Individual decision (IB)

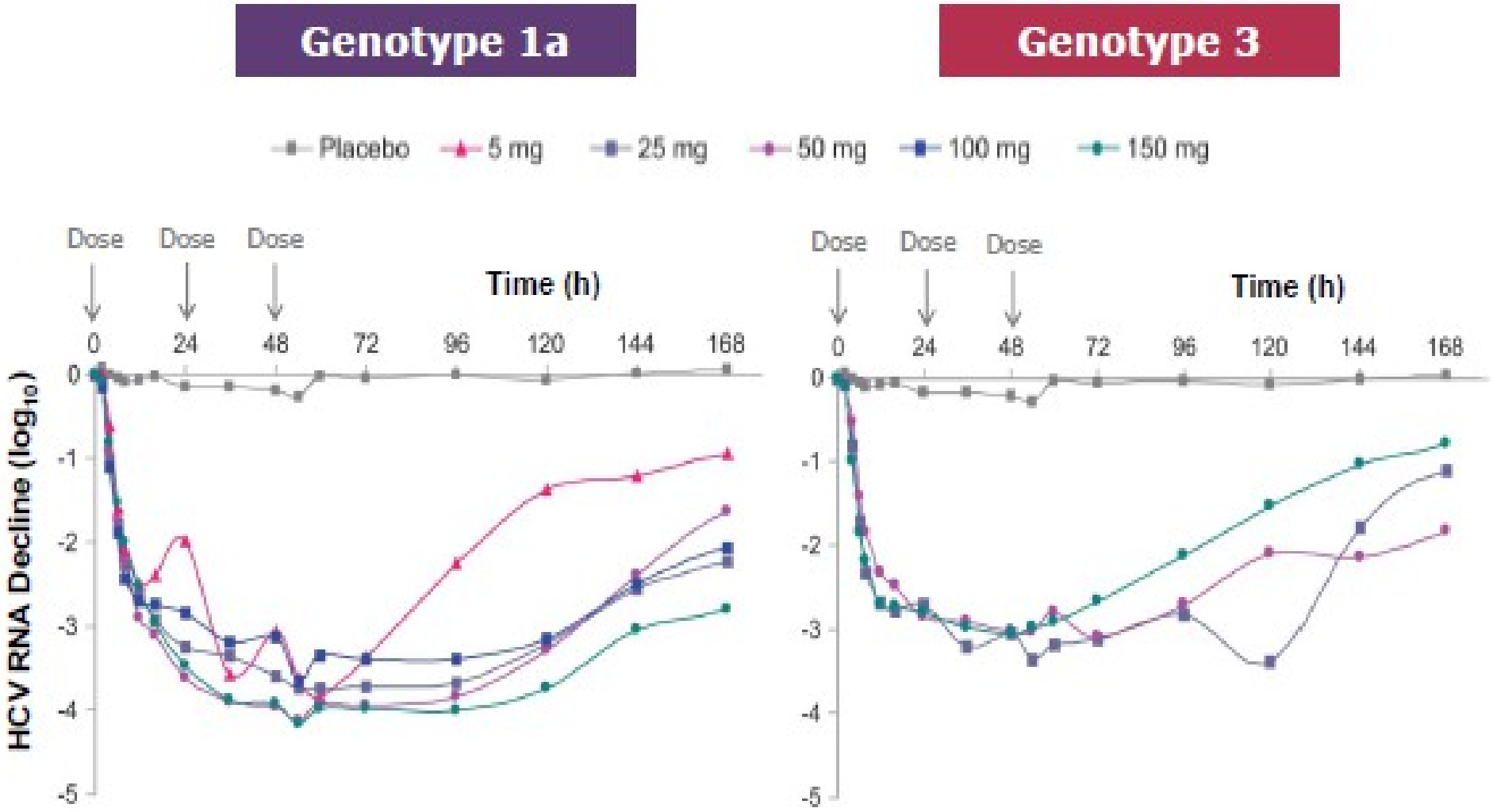
RECOMMENDATIONS
HCV related extrahepatic diseases & comorbidities

Clinical setting		AASLD / IDSA / IAS-USA
Cryoglobulinemia with vasculitis	Treatment should be prioritized (A1)	Highest priority (IB)
HCV related immune complex Nephropathy		Highest priority (IIaB)
Solid Organ Transplant Recipients	No specific priority (A2) considered for individual decision	Highest priority (IB)
Haemodialysis	Should be considered (B1)	Consider treatment prioritization In order to yield transmission reduction benefits (IIaC)
HIV	No specific priority (A1) considered for individual decision	High priority based on available resources(IB)

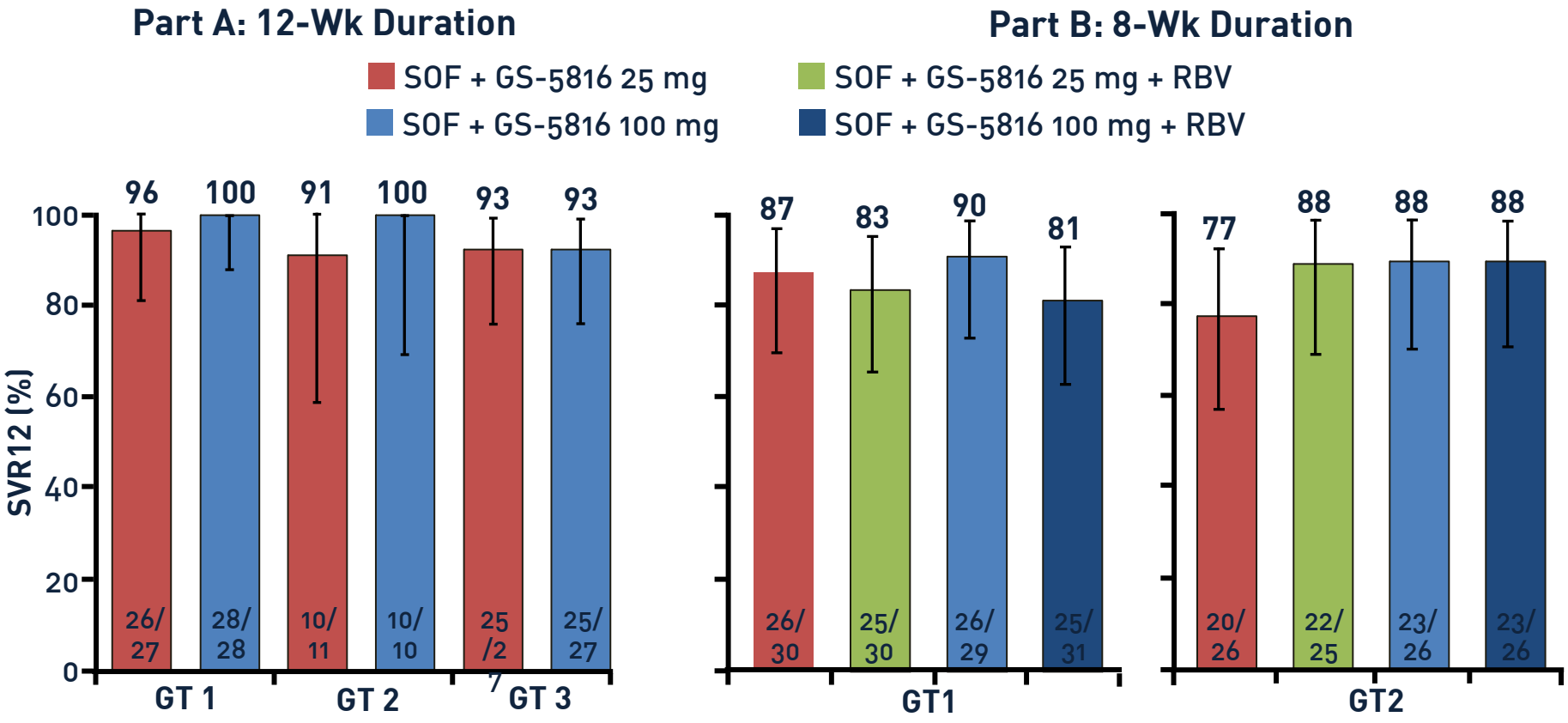
DAA combos reaching the clinic by 2016-7



GS-5816 Phase 1: Median Viral Decline

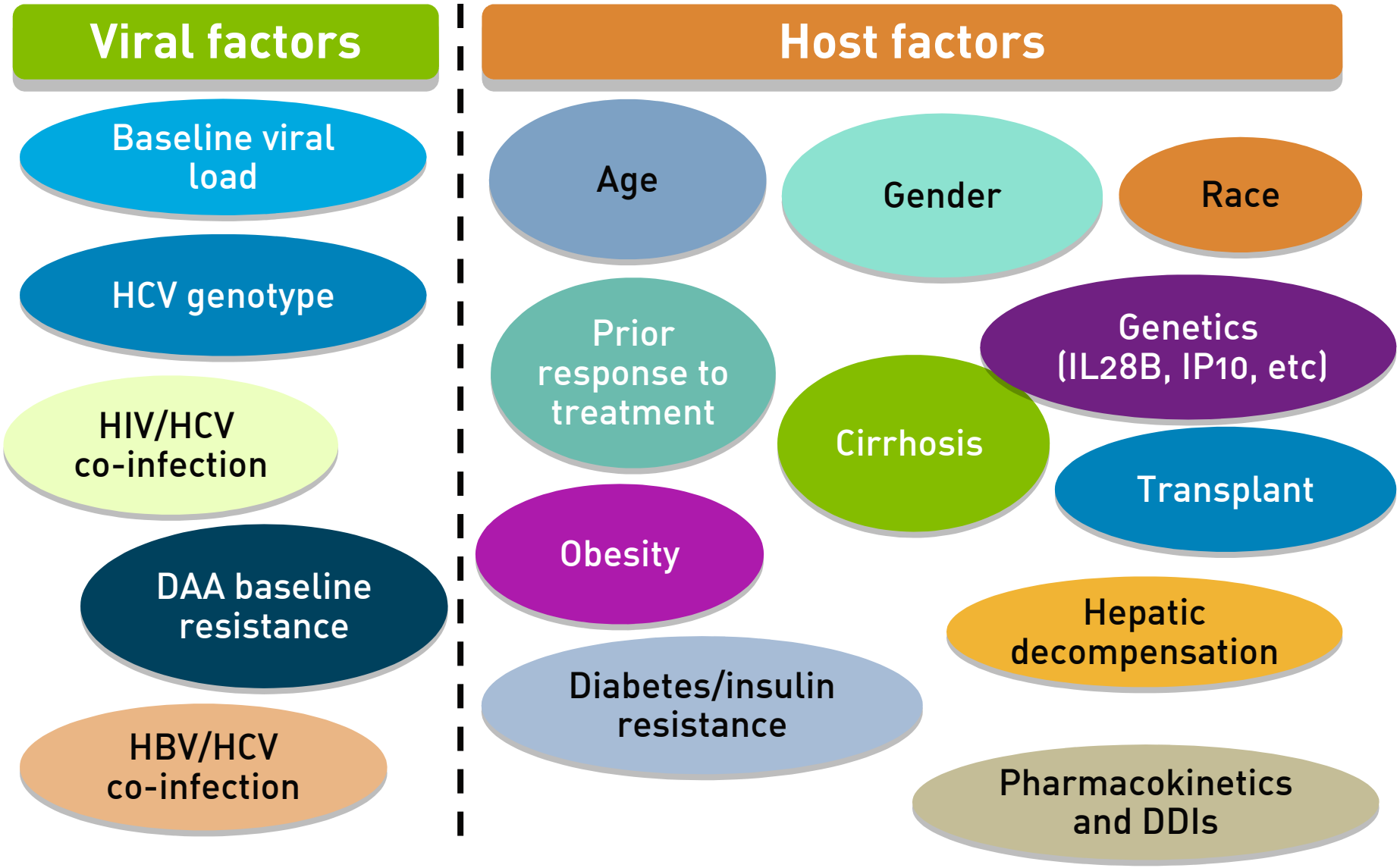


SVR rates with 12 and 8-wk regimens in Gt 1, 2, 3



Tran TT, et al. AASLD 2014. Abstract 80.

Factors impacting response to HCV treatment: before 2015



Factors impacting response to HCV treatment: after 2015

Viral factors

- HCV genotype
- Post-treatment DAA RAVs

Host factors

Can baseline HCV RNA inform decision to treat with LDV/SOF for 8 or 12 weeks?

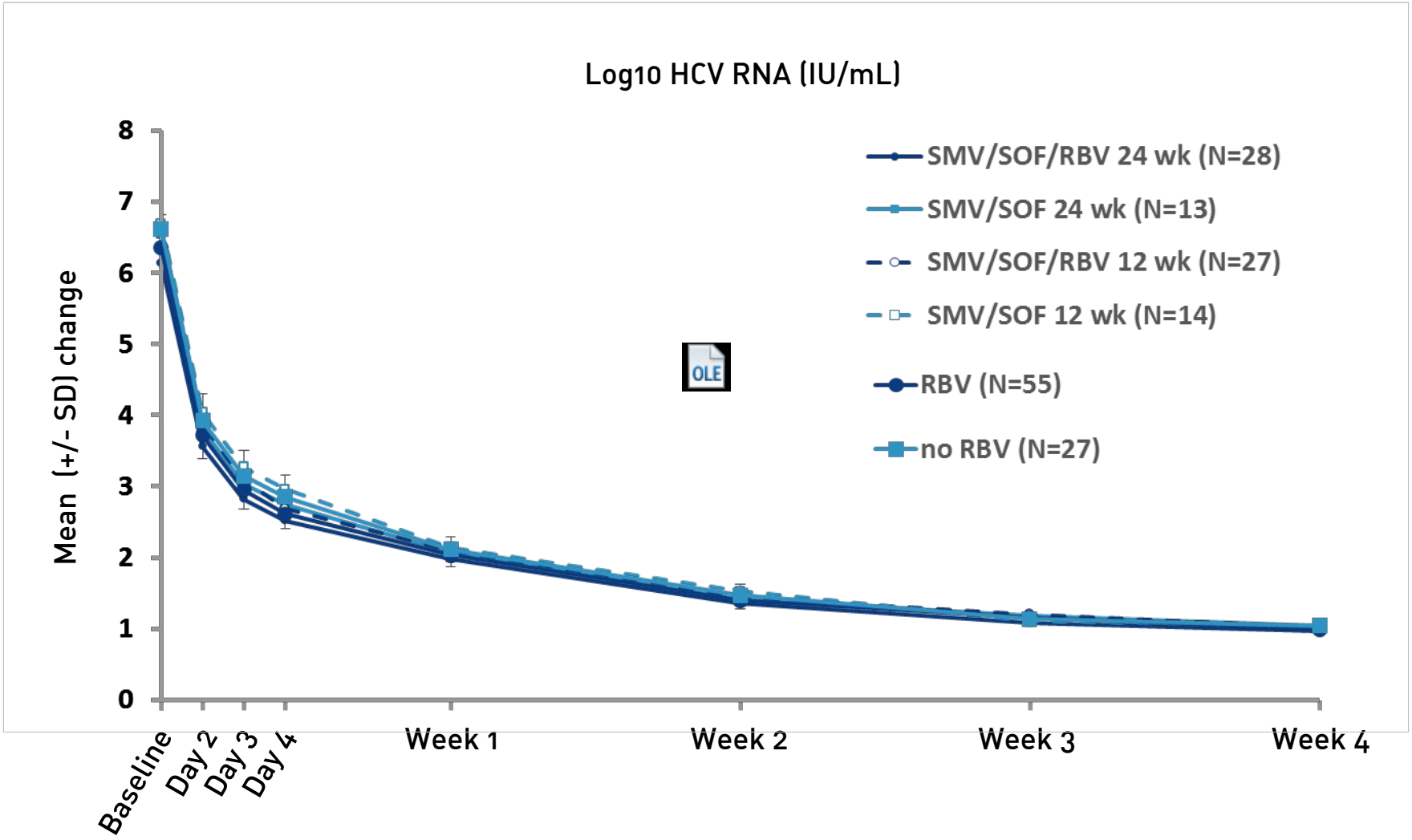
- Similar SVR rates for 8 and 12 weeks of therapy in ION-3
- If baseline HCV RNA ↘6 million IU/mL, treatment for 12 weeks can reduce chance of relapse

	LDV/SOF 8 weeks	LDV/SOF 12 weeks
SVR rate similar with 8 or 12 weeks		
	94% (202/215)	96% (208/216)
Relapse rate according to baseline HCV RNA		
HCV RNA ↓6 million IU/mL	2% (2/121)	2% (2/128)
HCV RNA ↘6 million IU/mL	10% (9/92)	1% (1/83)

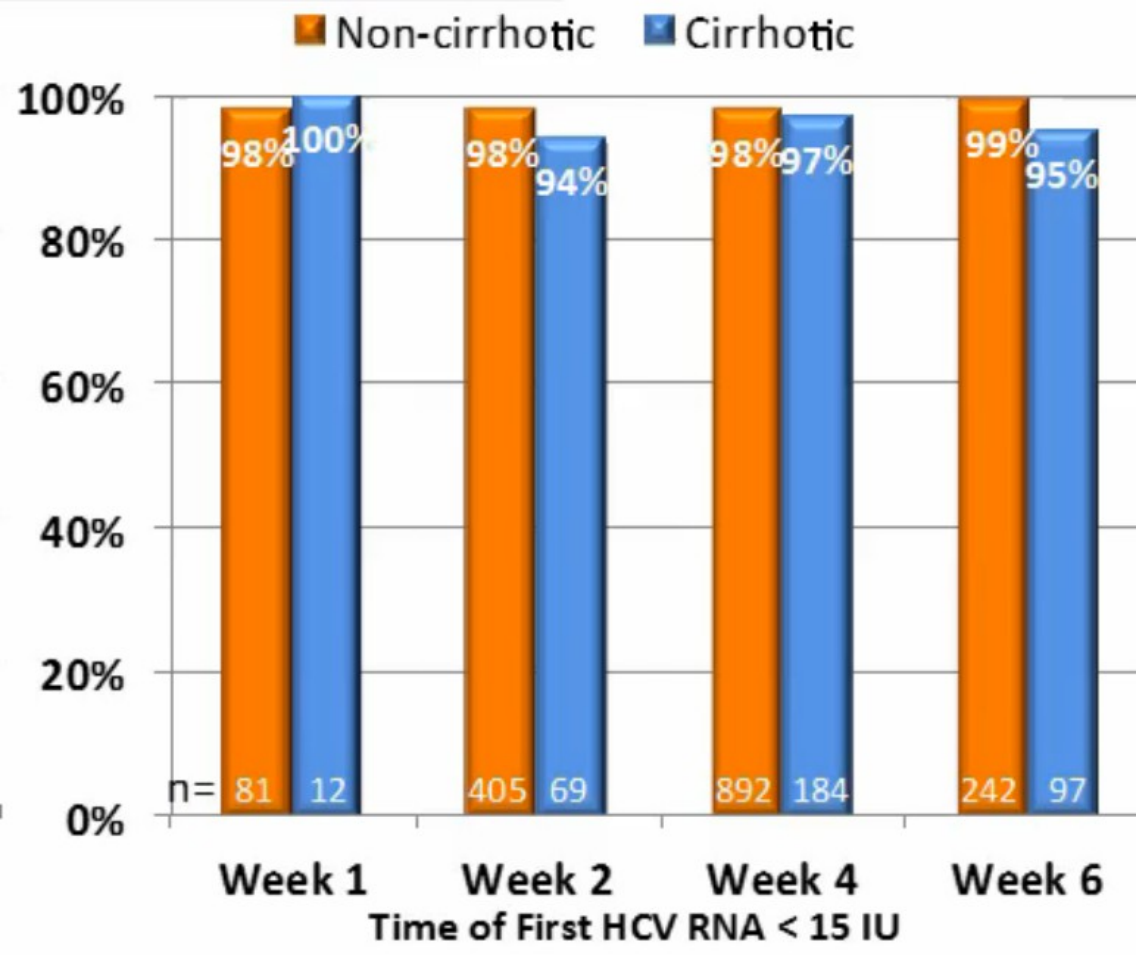
HCV-TARGET: 78% (253/323) of GT 1, non-cirrhotic, treatment-naïve had a baseline HCV RNA ←6 million IU/mL

- Gilead Sciences Europe Ltd. HARVONI▼(ledipasvir/sofosbuvir) Summary of Product Characteristics. November 2014; Jensen D, et al. AASLD 2014; Oral #45.

COSMOS Cohort 2: On-treatment HCV RNA over time



Time to Viral Suppression is not related to Achievement of SVR12 in GT1 treated with ABT-450/r/Ombitasvir+Dasabuvir +/- RBV

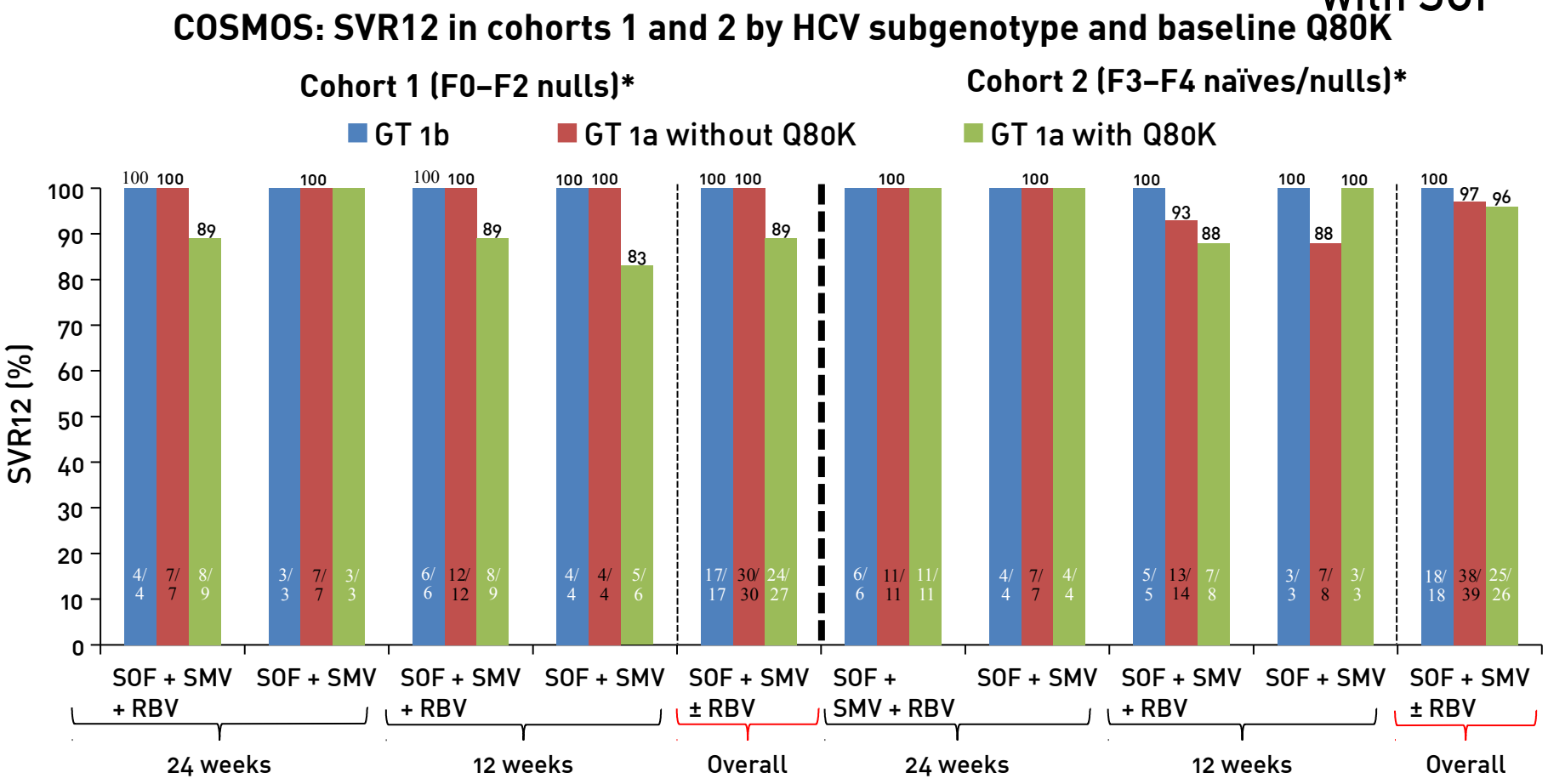


- Pooled analysis of 6 phase III Trials
- Aim: To evaluate the predictive value of time of first occurrence of HCV-RNA TND and SVR12
- Longer time to suppression associated with higher baseline HCV-RNA, older age, GT1a and cirrhosis

Sulkowsky M. Abst 1950 AASLD 2014

Is the Q80K mutation relevant for patients on SOF + SMV?

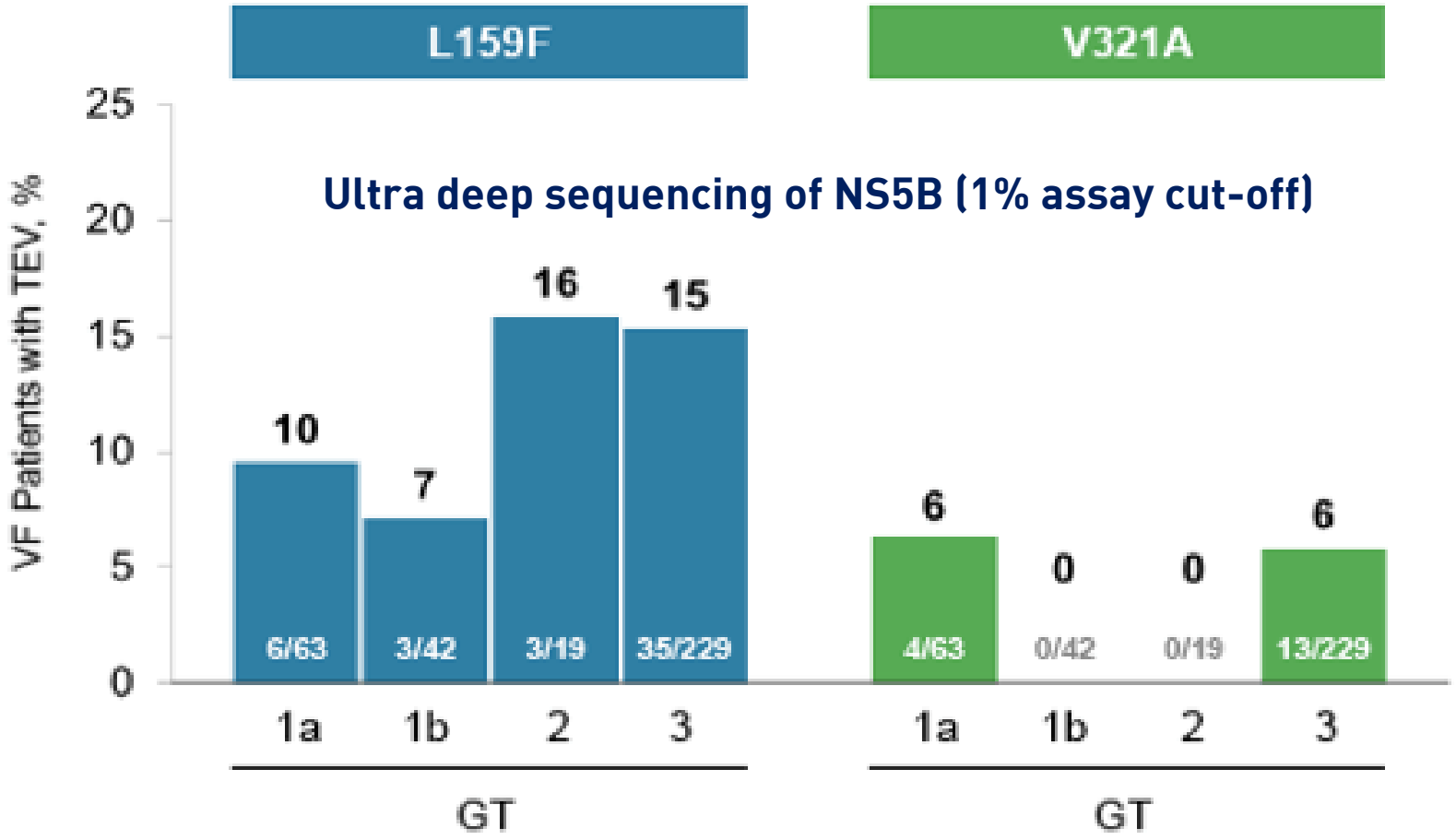
Limited data but little apparent effect of Q80K for SMV in combination with SOF



Lawitz E, et al. Lancet 2014;384:1756–65

*Excluding patients who discontinued for non-virological reasons

L159F and V321A emergence in 408 virological failures from 8 SOF and 5 LDV/SOF trials



VF, virologic failure; TEV, treatment-emergent variant.

Svarovskaia ES et al., AASLD 2014

Baseline L159F and V321A in SOF and LDV/SOF Studies by Deep Sequencing Analysis

	GT	Patients at Baseline: With Sequence Data, n	L159F, n	L159F and VF (n/N)
SOF + RBV Pretransplant	1-4	60	4 (All GT1b)	4/4
SOF + RBV Phase 3	1a	128	0	
	1b	33	2	1/2
	2	402	0	
	3	699	0	
SOF + RBV + PEG Phase 3	1a	224	0	
	1b	65	4	1/4
Total SOF		**1611**	**10 (0.6%)**	**6/10**
LDV/SOF Phase 2/3	1a	1150	1	0/1
	1b	320	22	0/22
Total LDV/SOF		**1470**	**23 (1.6%)**	**0/23**

- V321A was not detected at baseline in any patient

Svarovskaia ES et al., AASLD

Pooled Analysis of Resistance in Patients Treated with Ombitasvir/ABT-450/r and Dasabuvir with or without Ribavirin in Phase 2 and 3

- Over 2500 patients treated with 3D regimens
- Overall virological failure rate was low (2.9%), almost exclusively GT 1a
- All 74 virological failures (20 VBT and 54 relapsers) were studied
- Population sequencing used to evaluate RAVs at baseline and at virological failure

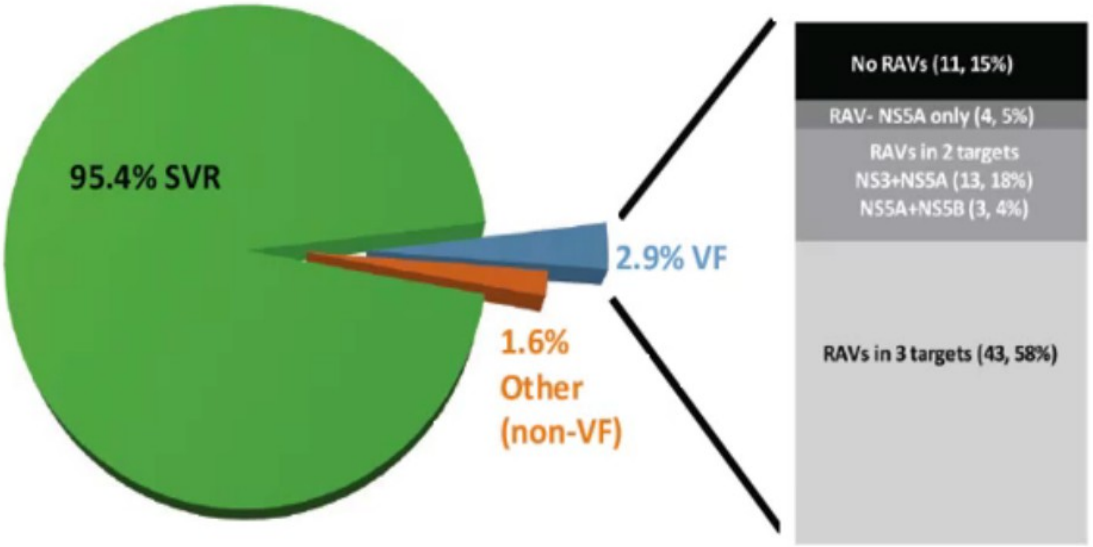
Baseline RAVs did not impact SVR

GT1a	Baseline Variant	Number of Patients Achieving SVR24 n/N, %[a] With Variant	Without Variant	*P* value
NS3	Q80K	78/89, 87.6	122/130, 93.8	.140
	D168A	0/1, 0	200/218, 91.7	.087
NS5A	M28T/V	12/14, 85.7	192/209, 91.9	.339
	Q30R	3/3, 100	201/220, 91.4	1.000
	L31V	1/1, 100	203/222, 91.4	1.000
	Y93C/N/H	4/5, 80	200/218, 91.7	.362
NS5B	S556G	7/7, 100	220/239, 92.1	1.000
	C316Y	1/2, 50	226/244, 92.6	.149

[a]Patients not achieving SVR24 due to non-virologic reasons, eg, early discontinuations, missing SVR24 data etc., were excluded from this analysis.

Distribution of RAVs in Virological Failure

- No RAVs = 15%
- NS3/NS5A RAVs = 18%
- NS5A/NS5B RAVs = 4%
- RAVs in 3 targets = 58%



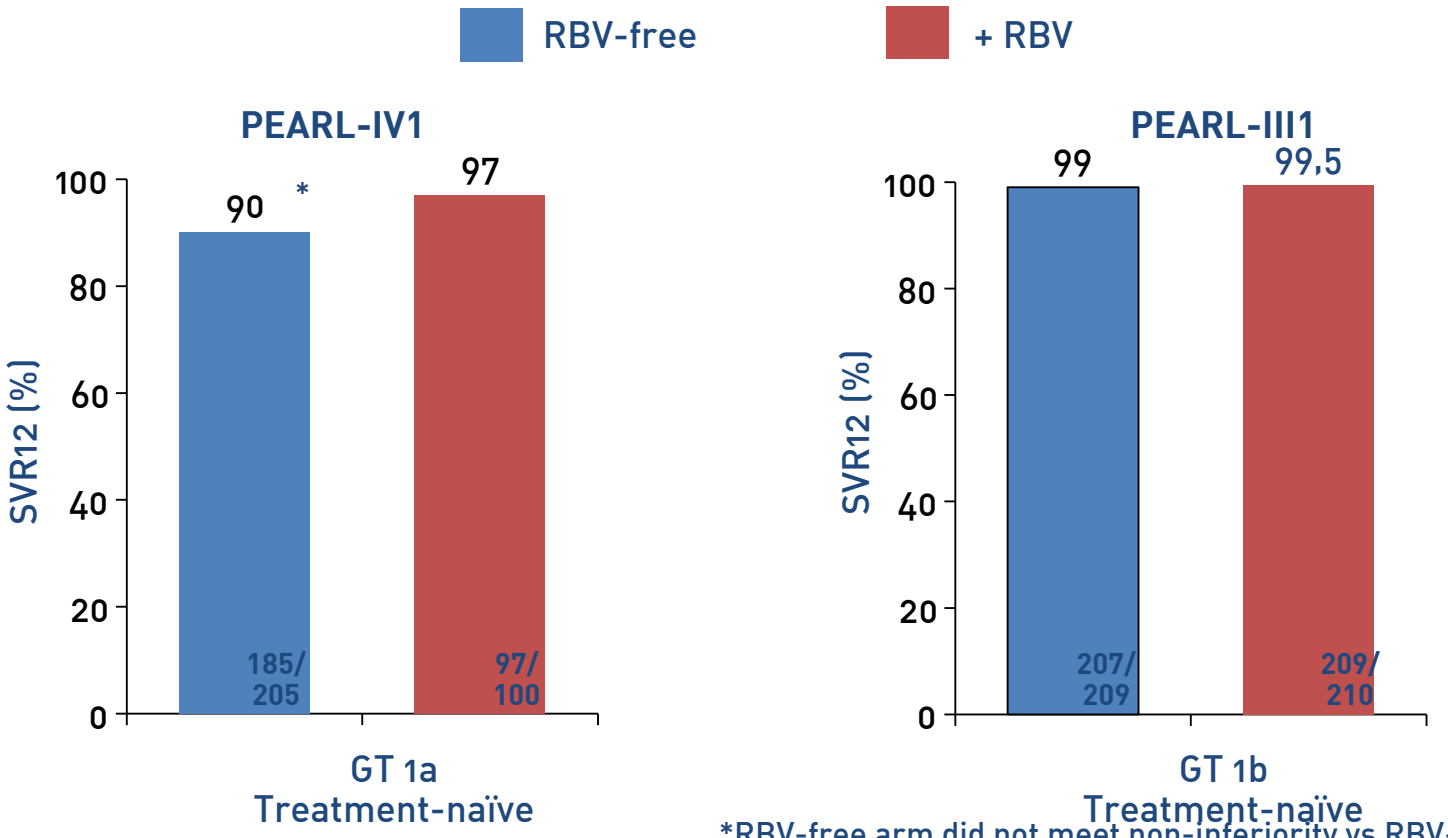
Krishnan, Abst 1936

Is Gt 1 subtype still relevant?

	LDV/SOF 8 weeks	LDV/SOF 12 weeks
SVR rate overall	94% (202/215)	95% (206/216)
SVR according to subtype		
GT 1a	93% (159/171)	95% (163/172)
GT 1b	98% (42/43)	98% (43/44)

Kowdley KV, et al. N Engl J Med 2014;370:1879–88.

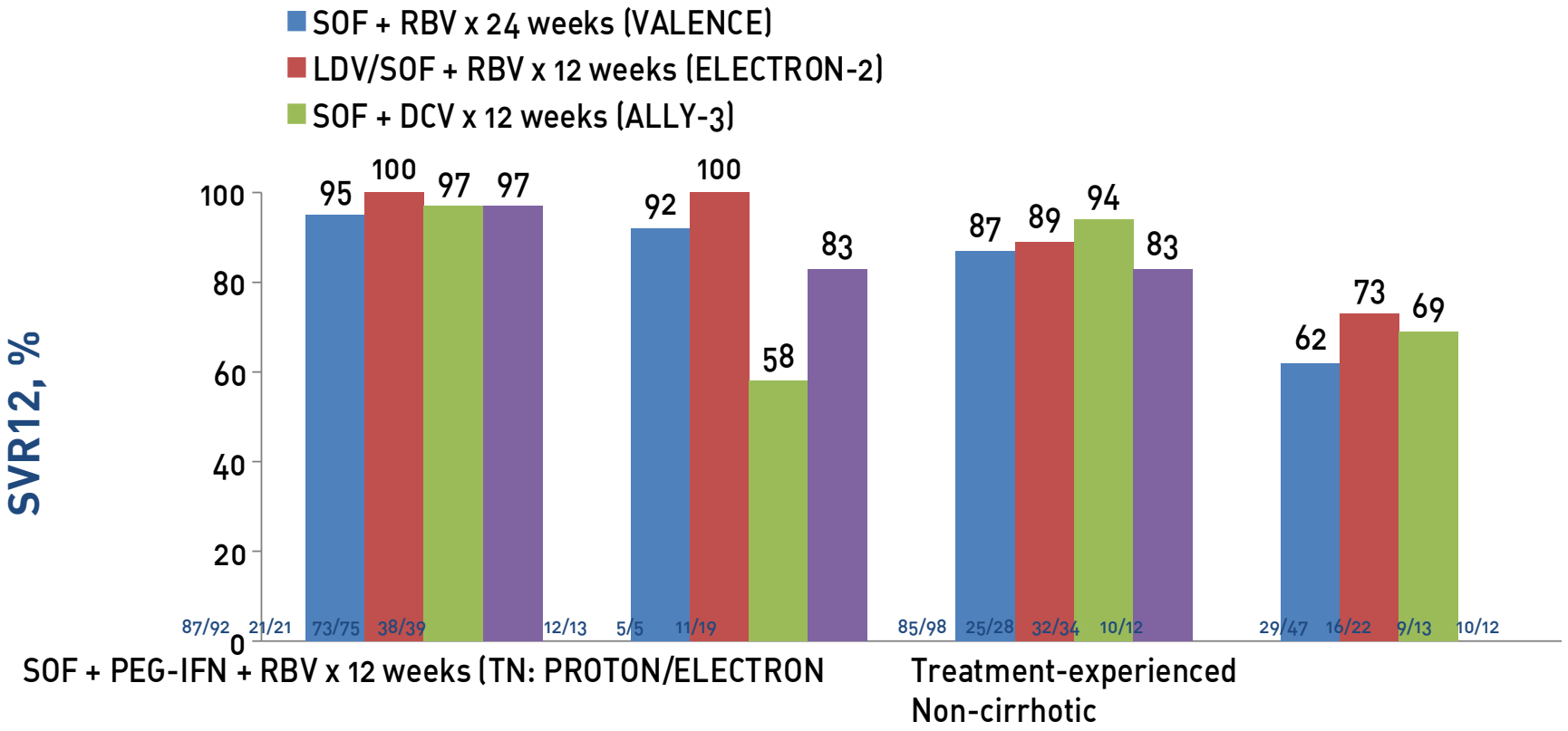
Is Gt 1 subtype still relevant?



Ferenci P, et al. N Engl J Med 2014;370:1983–92.

*RBV-free arm did not meet non-inferiority vs RBV-containing arm; Ombitasvir, paritaprevir, RTV + dasabuvir are not approved for use in HCV by the EMA; EMA: European Medicines Agency; RTV: ritonavir

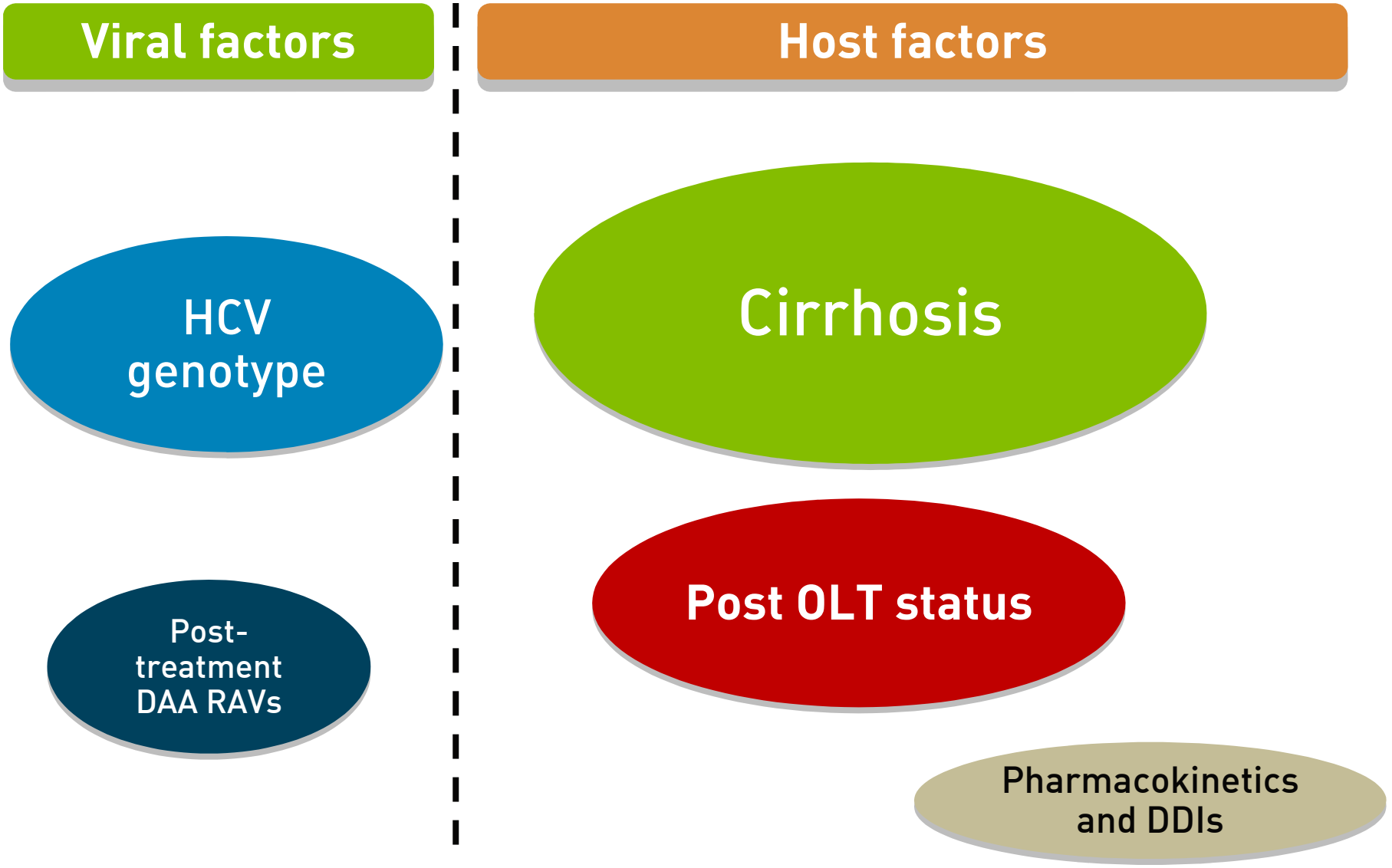
HCV Gt 3: still a difficult genotype



LDV/SOF + RBV for 12 weeks and SOF + DCV for 12 weeks
are not EMA-recommended treatment regimens for GT 3

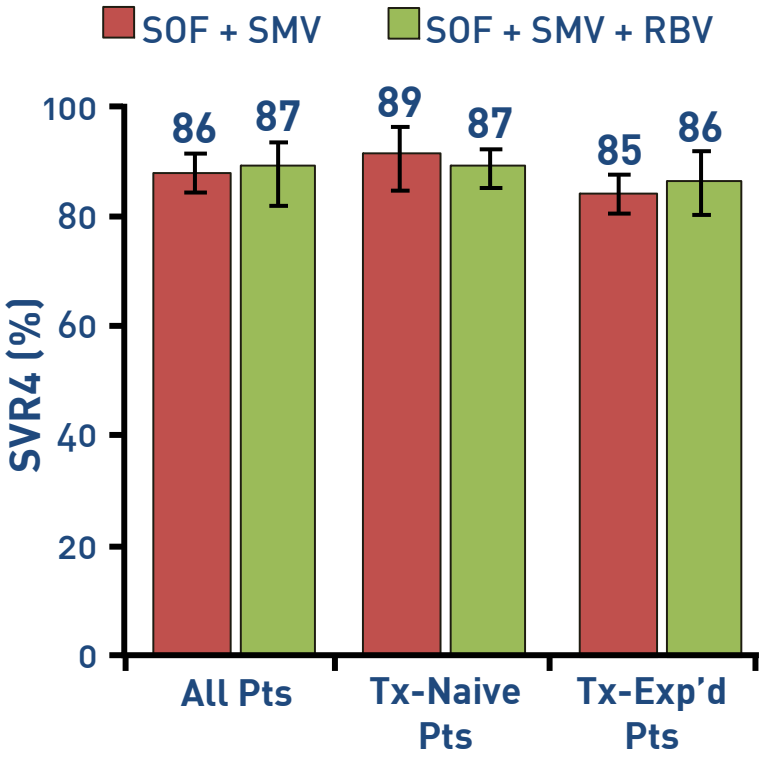
Zeuzem S, et al. N Engl J Med 2014;370:1604-14; Gane E, et al. EASL 2014; Oral #6; Gane E et al. NEJM 2013;368:34–44; Lawitz E et al. Lancet Infect Dis 2013;13:401–408; Gane E et al. AASLD 2014, Poster #LB-11; Lawitz E et al. AASLD 2013, Oral #LB-4; Nelson M et al. AASLD 2014, Oral #LB-3.

Factors impacting response to HCV treatment: after 2015

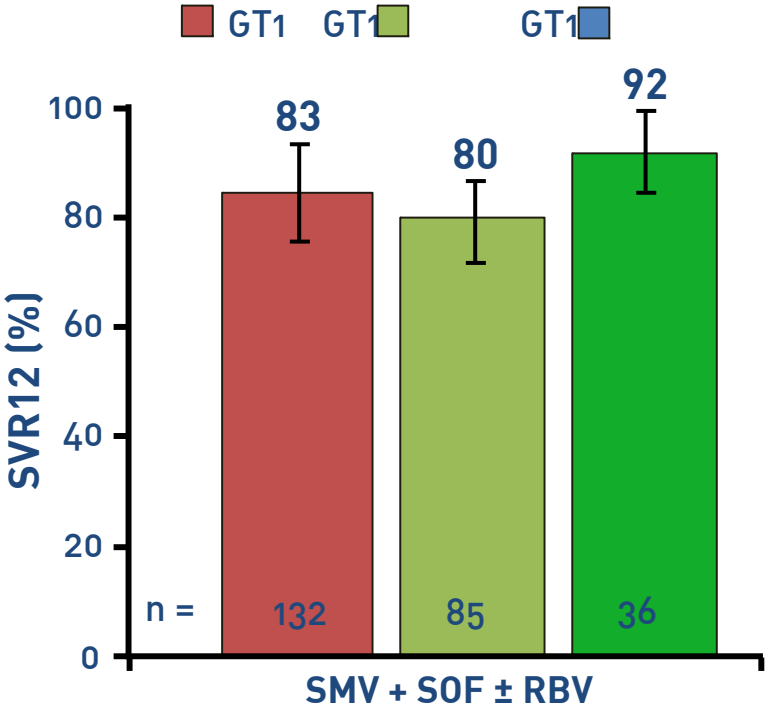


Efficacy of SOF + SMV ± RBV in real-world settings

HCV-TARGET: Prospective Observational Cohort Study: Adjusted SVR4 in GT1 HCV Pts[1]

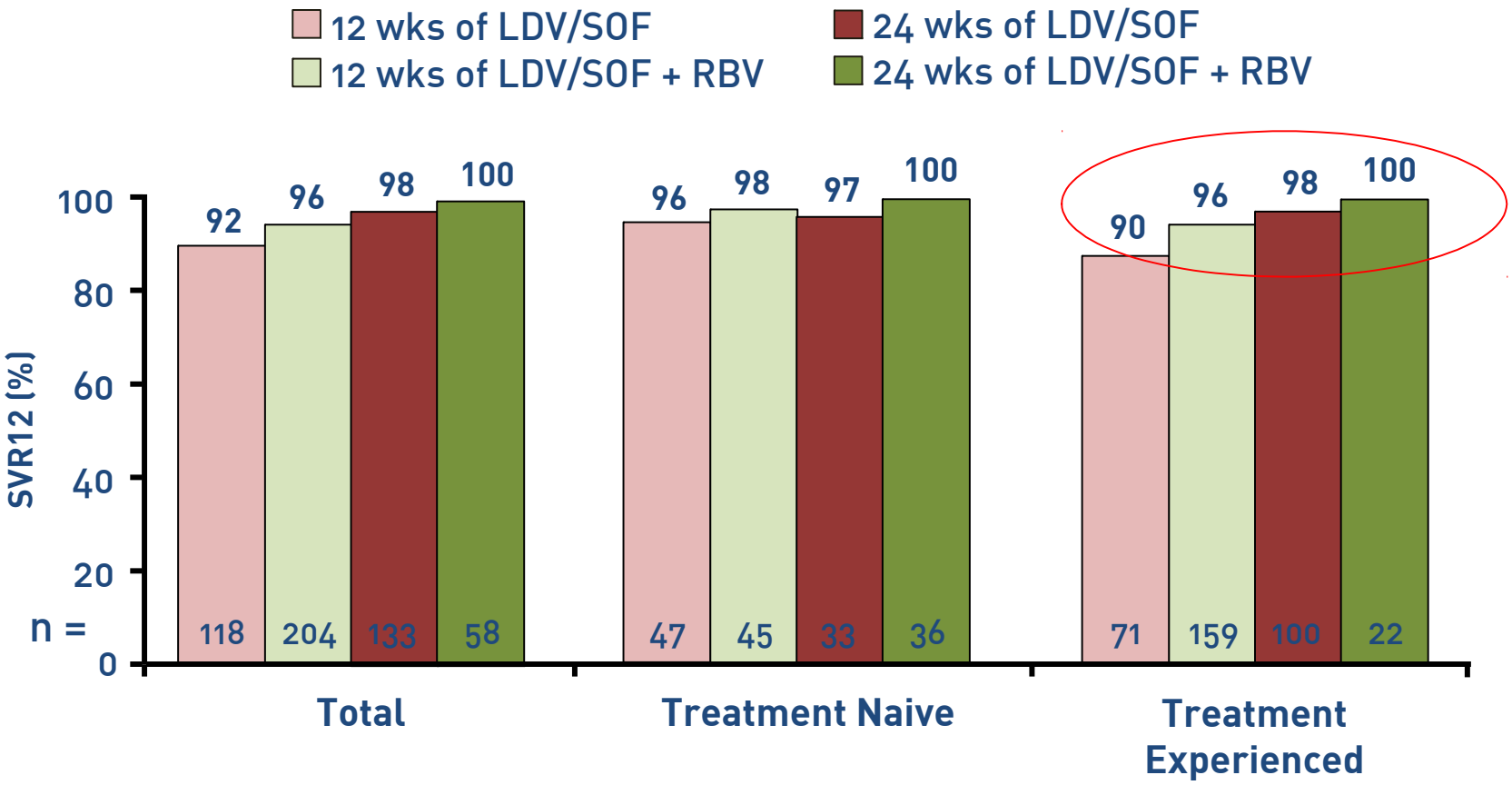


TRIO: Prospective Observational Cohort Study: SVR12 in Tx-Naive GT1 HCV Pts[2]



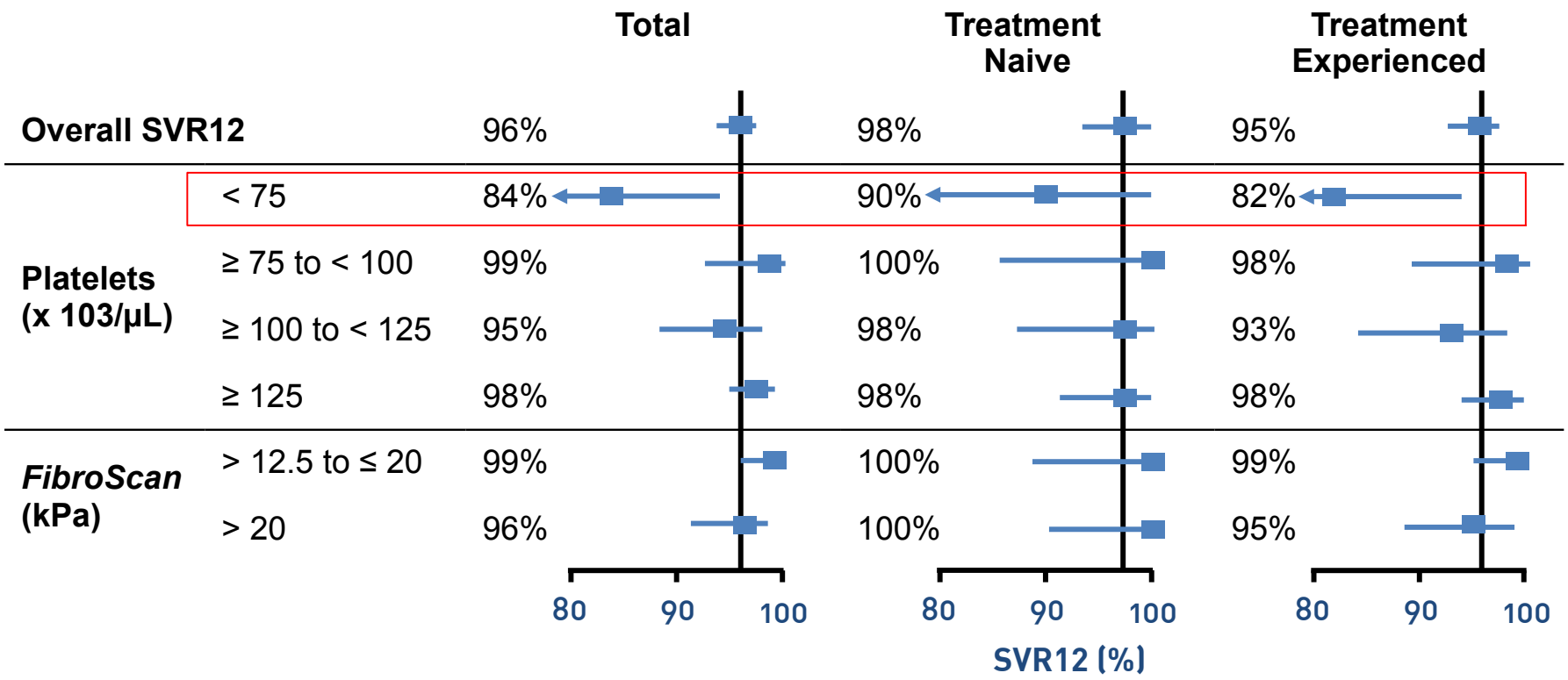
1. Jensen DM, et al. AASLD 2014. Abstract 45. 2. Dieterich D, et al. AASLD 2014. Abstract 46.

LDV/SOF efficacy in compensated Gt1 cirrhosis



Bourlière M, et al. AASLD 2014. Abstract 82.

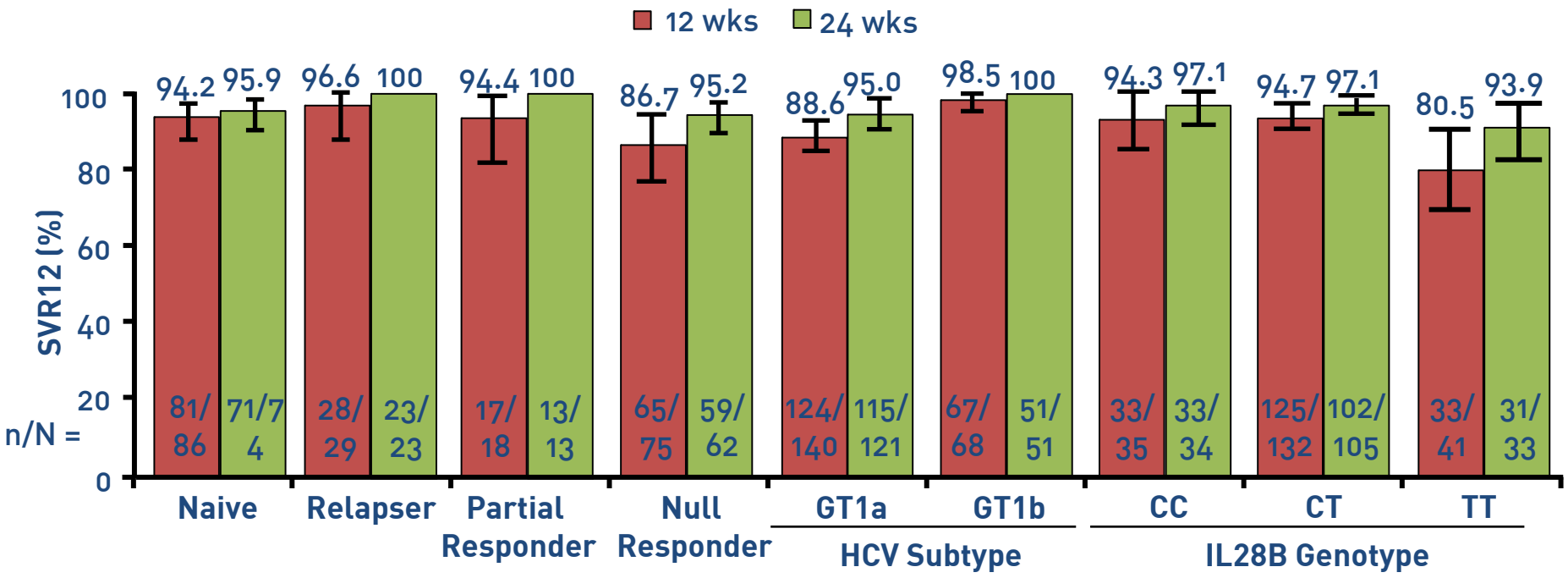
SVR12 rates with LDV/SOF ± RBV by stage of cirrhosis



- SVR12 rates lower among pts determined to have cirrhosis using *FibroTest* + APRI (89%) and among pts with a platelet count ↓ 75,000 cells/mm3 (84%)

Bourlière M, et al. AASLD 2014. Abstract 82.

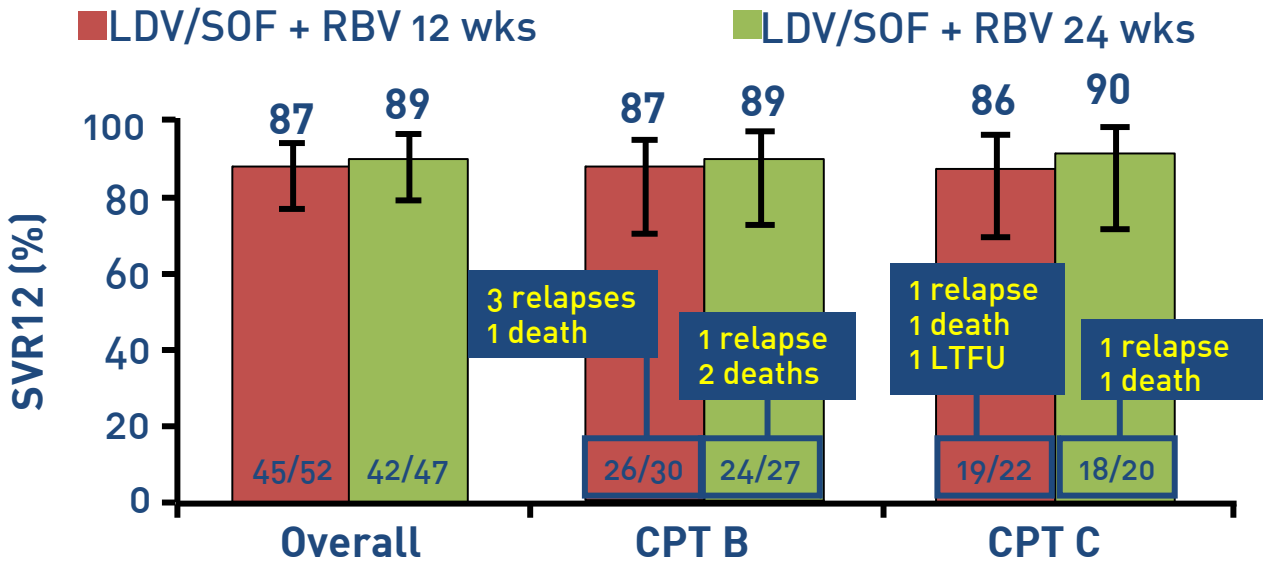
SVR12 with PTV/RTV/OMV + DSV + RBV in Gt1 compensated cirrhosis



Factor	*P* Value
IL28B TT genotype	.021
Previous null response to pegIFN/RBV	.038
GT1a HCV	.046

Fried MW, et al. AASLD 2014. Abstract 81.

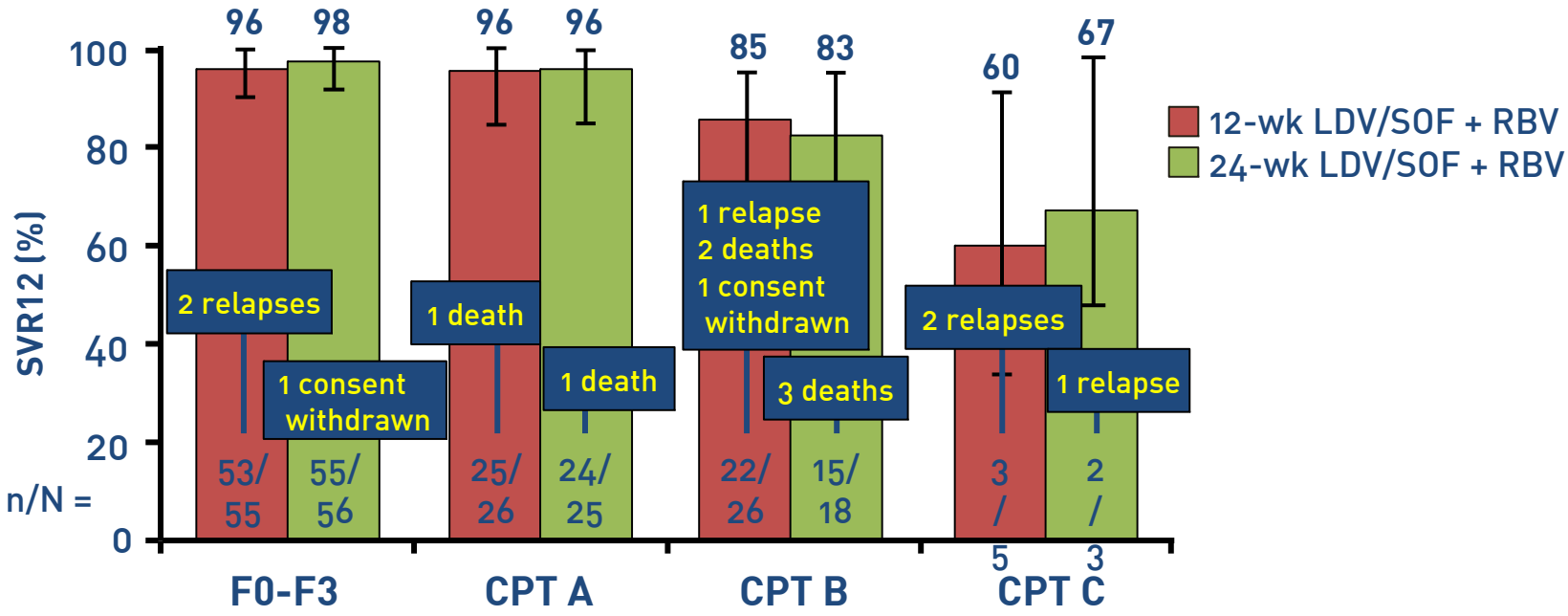
SVR12 with LDV/SOF + RBV in Gt1 patients with decompensated cirrhosis



Pts, n (%)	CPT B		CPT C	
	12 Wks (n = 30)	24 Wks (n = 29)	12 Wks (n = 23)	24 Wks (n = 26)
AE	29 (97)	27 (93)	23 (100)	26 (100)
SAE	3 (10)	10 (34)	6 (26)	11 (42)
Treatment-emergent, -related SAEs	2 (7)	0	0	2 (8)
Treatment discontinuation due to AE	0	1 (3)	0	2 (8)

Flamm SL, et al. AASLD 2014. Abstract 239. Reproduced with permission.

SVR12 SVR12 with LDV/SOF + RBV in Gt1 post-OLT patients



- In the 24-wk arm, 8 pts with CPT B and 1 pt with CPT C have not reached the follow-up Wk 12 visit
- MELD scores improved from baseline through follow-up Wk 4 in 15/48 pts with CPT A and 8/41 pts with CPT B disease

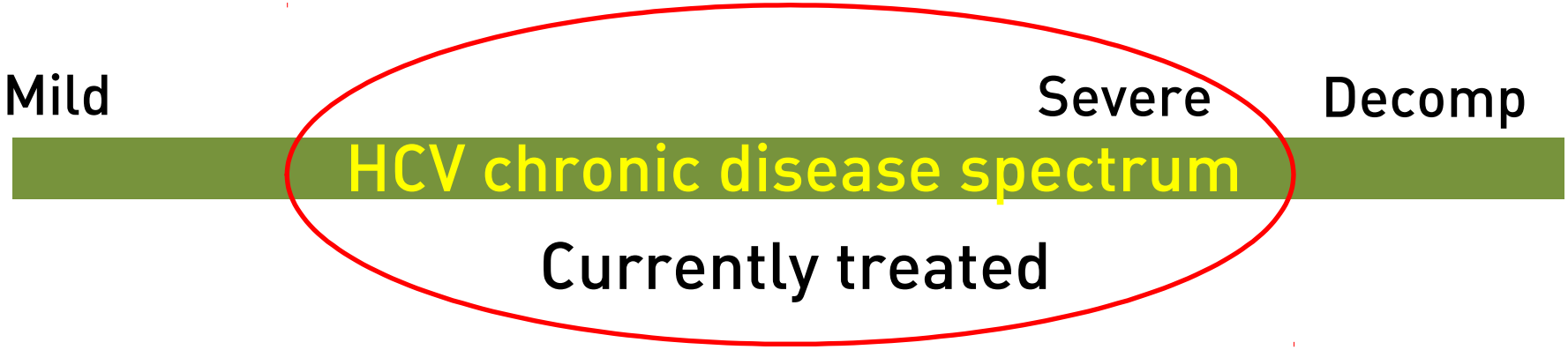
Reddy RT, et al. AASLD 2014. Abstract 8.

	Liver Impairment			
	mild	*moderate*	*severe compensated*	
Teleprevir	↓ 0.85	↓ 0.54		*SS, HCV-*
Boceprevir	↔	1.32	1.45	
Simeprevir		↑2.44	↑5.22	*SS, HCV-*
Sofosbuvir		↑1.26 (↑1.18**)	↑1.43 (↔1.09**)	*Parent (SS, HC GS 331007 m*
Ledipasvir	no adjustment	no adjustment		*SS, HCV-*
ABT 450r	↓ 0.71	↑1.62	↑10.23	
Ombitasvir (ABT-267)	0.92	0.70	0.45	*Single do*
Dasabuvir (ABT-333)	1.17	0.84	4.19	
Faldeprevir		↔	↔	*No change in*
Asunaprevir	↓ 0.79	↑ 9.8	↑ 32	*SS, HCV-, con* *↑PK in >60 y*
Daclatasvir	↓ 0.57	↓ 0.62 unbound ↔	↓ 0.64 unbound ↔	*Single dose, H*
MK5172	↑1.62	↑4.88		*SS, 100mg/20*
MK8742	↔	↔		*Single dose*

	VICTIM of DDI	PERPETRATOR of DDI	DDI pot
Teleprevir	Substrate for CYP 3A4, PgP	Inhibits CYP 3A4, PgP, OATP1B1/2 ? Protein binding	Significan
Boceprevir	Substrate for aldoketoreductase, CYP 3A4, PgP, BCRP	Inhibits CYP 3A4, PgP, OCT 1&2	Significan
Simeprevir	Substrate for CYP 3A4, PgP	Inhibits OATP1B1, MRP2 Mild inhibitor gut CYP 3A4, PgP	Moderate
Sofosbuvir	cathepsin A, esterases, kinases PgP & BCRP substrate (parent)	Weak inhibitor of gut PgP & BCRP	Low
Ledipasvir	Primarily excreted unchanged (>90% faeces), PgP / BCRP substrate	Weak inhibitor of PgP/BCRP, ?OATP1B1/3	?
ABT450r	Substrate for CYP 3A4, PgP, OATP1B1/3	Weak inhibitor PgP/BCRP (gut), ?OATP1B1/3	
Ombitasvir (ABT-267)	Substrate for PgP, BCRP (CYP 3A4)	Weak inhibitor of UGT1A1	Moderate Significan
Dasabuvir (ABT-333)	Substrate of CYP 2C8 > 3A4 > 2D6, Substrate of PgP, BCRP	Weak inhibitor of UGT1A1	
Daclatasvir	Substrate for CYP 3A4, PgP	Inhibits OATP1B1/3 & PgP	Moderate
Asunaprevir	Substrate for OATP1B1/2B1 CYP 3A4	Inhibits CYP2D6 (mod) & OATP1B1/3 (weak), ?BCRP, Weak CYP3A4 inducer	?
Faldeprevir	Substrate for CYP 3A4, PgP, OATP1B1 & MRP2	Inhibitor of CYP 3A4, 2C9, UGT1A1, Probably inhibits OATP1B1/3, MRP2	Moderate
MK-5172	Substrate for CYP 3A4, PgP, ? OATP1B1	Inhibits CYP 2C8, weak inhibitor of UGT1A1, ? BCRP	Moderate
MK-8742	Substrate for CYP 3A4, PgP, ?OATP1B1	weak inhibitor of UGT1A1	Moderate

IFN free DAA have expanded the pool of treatable patients

- IFN-free combination regimens dominate the treatment landsca
- SOF-based regimens are effective in “real-world” settings
- Safety demonstrated in noncirrhotic and cirrhotic patients



- By enrolling new patients at the extreme of the spectrum
- By enforcing need for mass screening for HCV

Who should be treated: EASL recommendations 2014

In principle, all patients with chronic HCV infection, but in a situation of limited availability:

- F3-F4: Priority
- F2: Reasonable
- F0-F1: Debatable

Informed deferral of treatment for patients with mild disease

EASL Online Recommendations on Treatment of Hepatitis C, April 2014

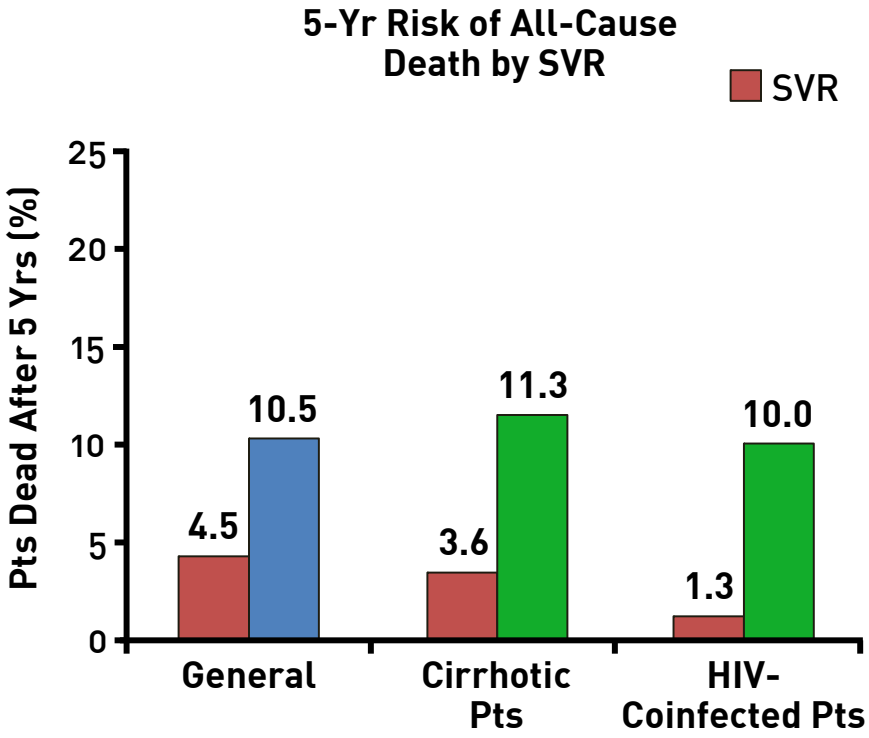
AASLD/IDSA: Patients With F3/F4 Fibrosis Have Highest Priority for HCV Treatment

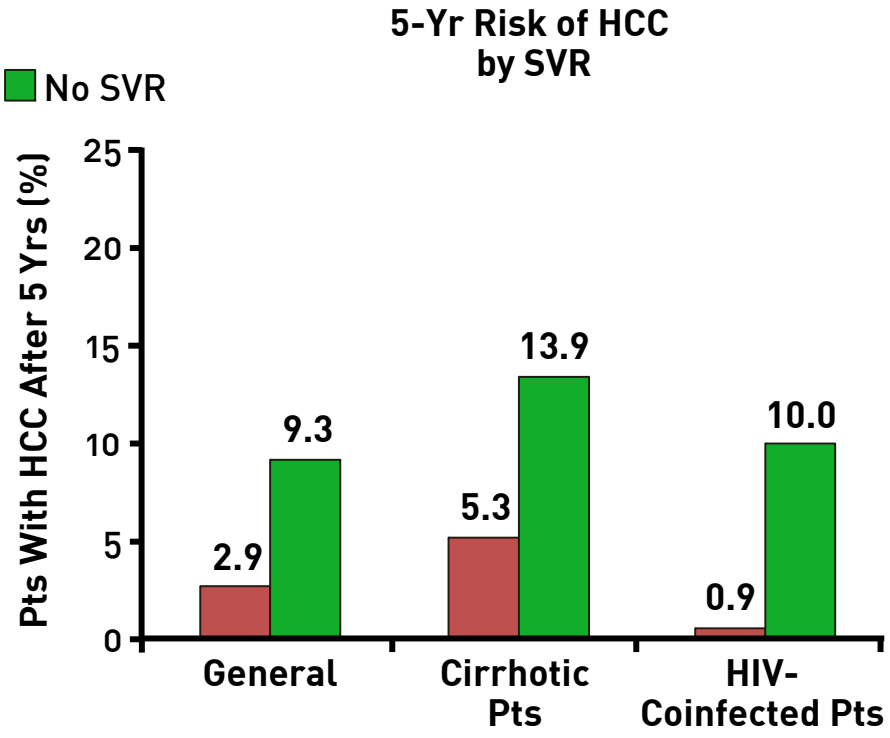
- When constrained resources prevent treatment of all HCV infection cases, highest priority should be given to patients with advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C
- Based on available resources, treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority

AASLD/IDSA HCV Management Guidance. October 2014.

SVR associated with reduced 5-Yr risk of death and HCC in all populations

- SVR on IFN-based therapy was associated with substantial benefit vs no SVR
  - 62% to 84% reduction in all-cause mortality, 90% reduction in liver transplantation, 68% to 79% reduction in HCC

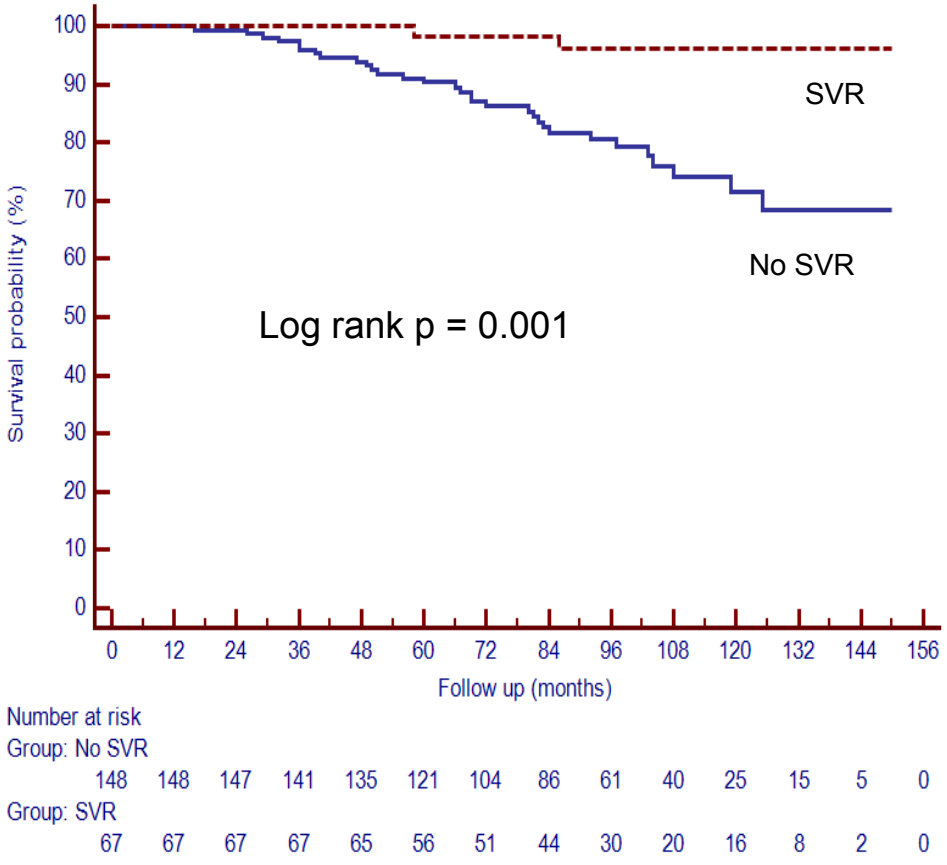




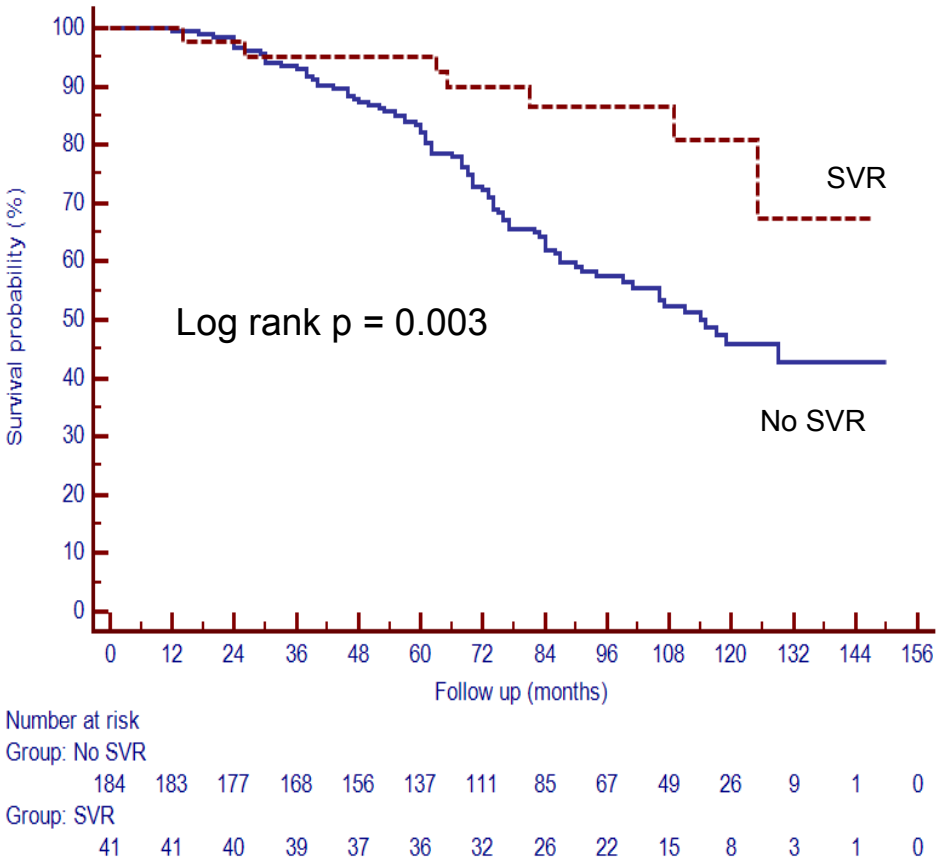
Hill AM, et al. AASLD 2014. Abstract 44.

Survival after P/R treatment in 440 patients with HCV cirrhosis, C-P A5-6 (mean follow-up 7.7 yrs)

No esophageal varices before P/R

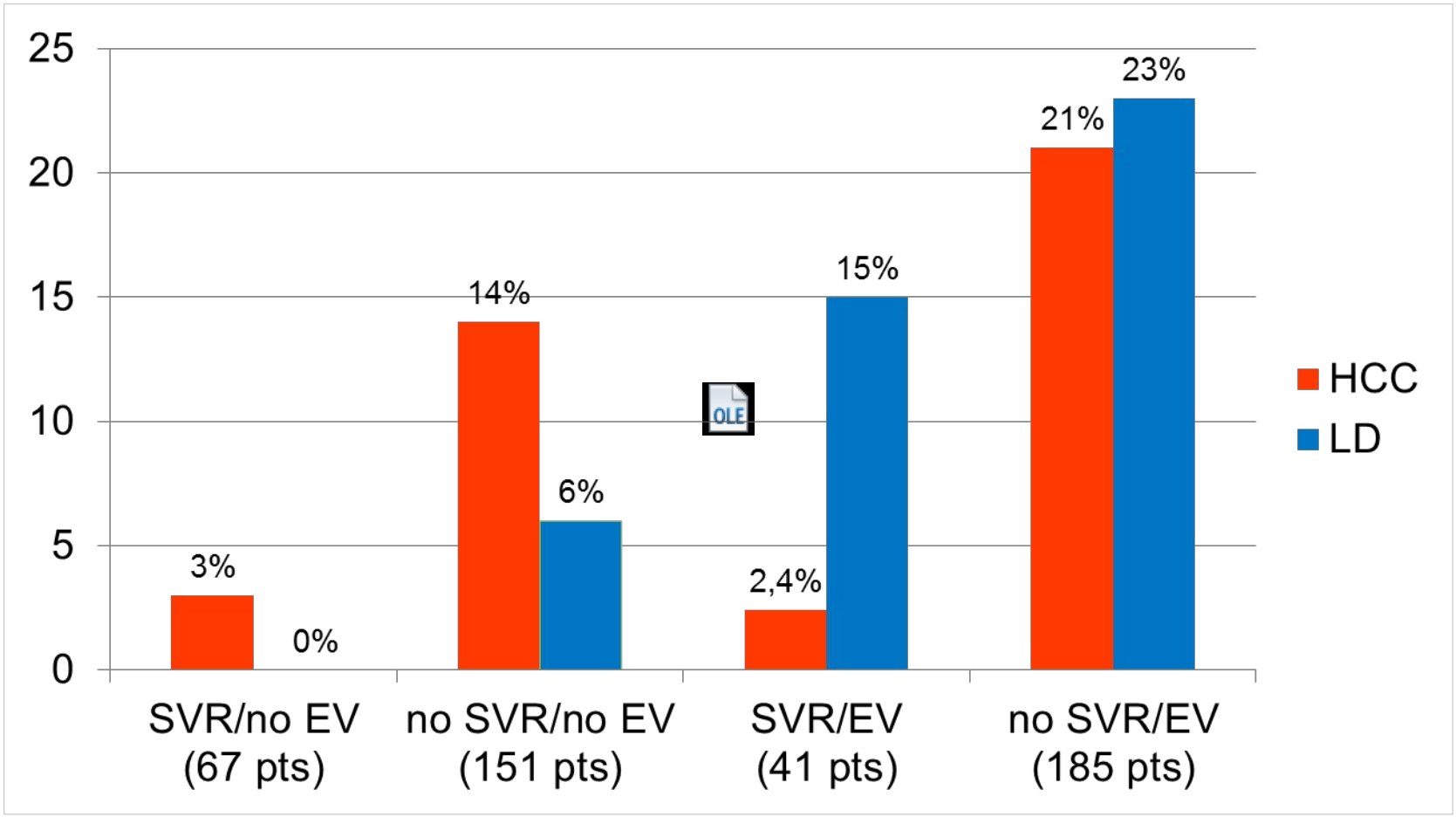


Esophageal varices before P/R



Di Marco V, submitted

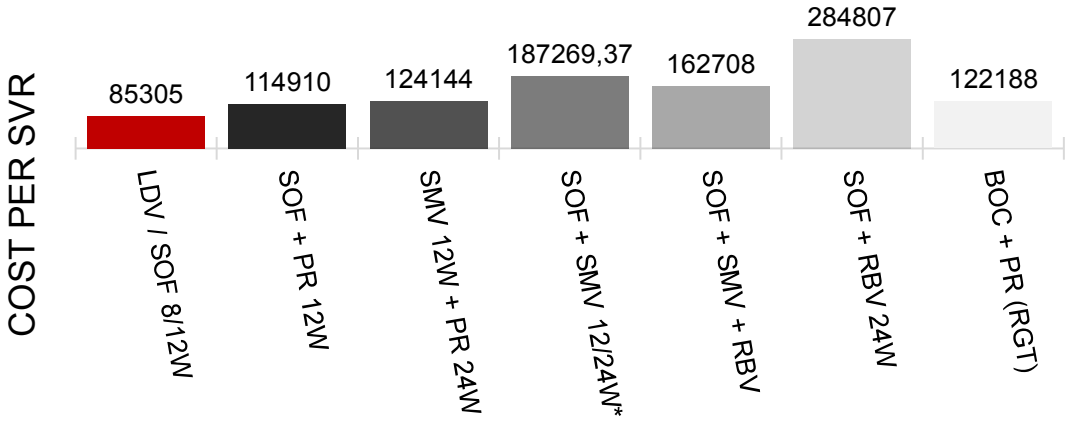
Deaths due to HCC or liver decompensation after P/R treatment in 440 patients with HCV cirrhosis



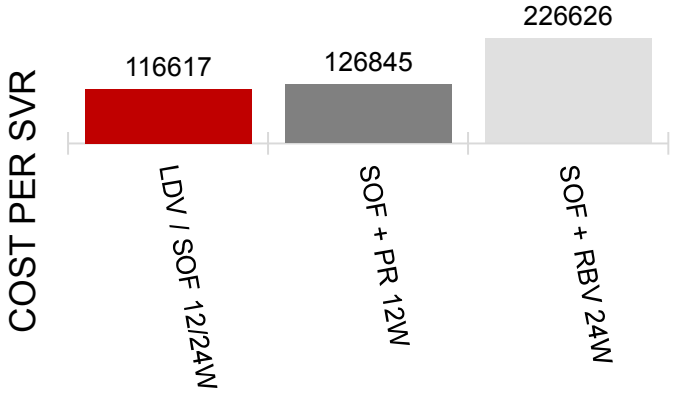
Di Marco V, submitted

Cost per SVR for GT1 HCV Patients

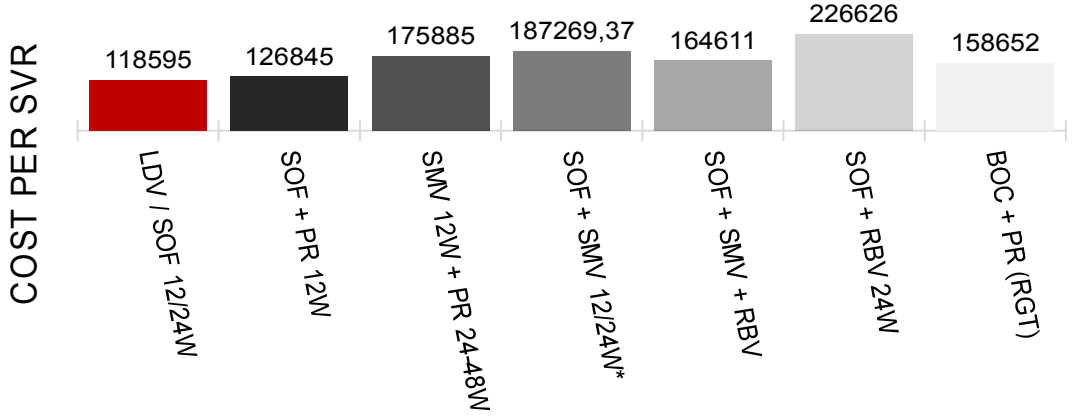
GT1, TREATMENT-NAIVE



GT1, TREATMENT-EXPERIENCED (PI+PR-EXPERIENCED)



GT1, TREATMENT-EXPERIENCED (PR-EXPERIENCED)

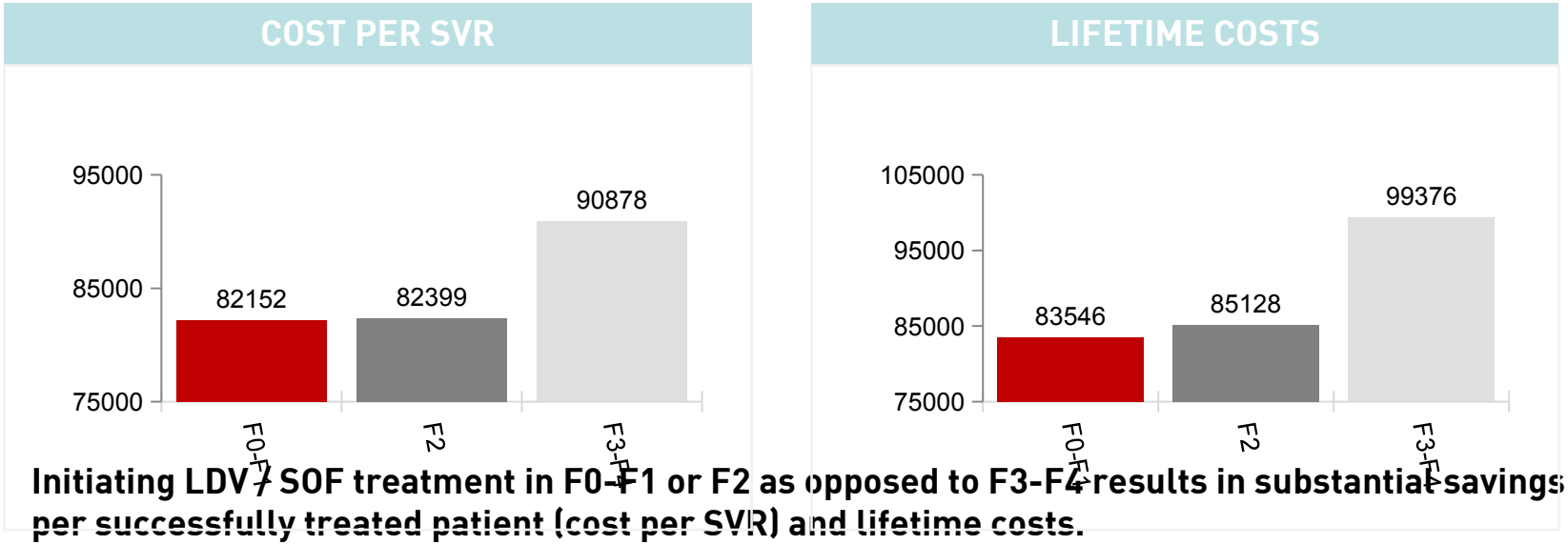


**SOF+SMV data from Phase IIb study and 12W regimen for NC, 24W regimen for CC patients as per label*

Younossi, AASLD, 2014, Poster #1754

Evaluation of Health Outcomes from LDV/SOF Treatment of Patients with Early vs. Advanced Liver Fibrosis

Initiating LDV/SOF treatment at F0-F1 and F2 rather than F3-F4 reduces lifetime costs of treatment, and has a lower cost per SVR



Initiating LDV / SOF treatment in F0-F1 or F2 as opposed to F3-F4 results in substantial savings per successfully treated patient (cost per SVR) and lifetime costs.

Ahmed A, AASLD, 2014, #1751


Hepatologist
HCV