State of The Art Therapy for HCV

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Conflicts of Interest

- Speaker and consultancy fees received from
- AbbVie, BI, BMS, Gilead, Janssen, Roche, Merck, Novartis, Springbank, Achillion, Idenix

HCV – Effective Antivirals

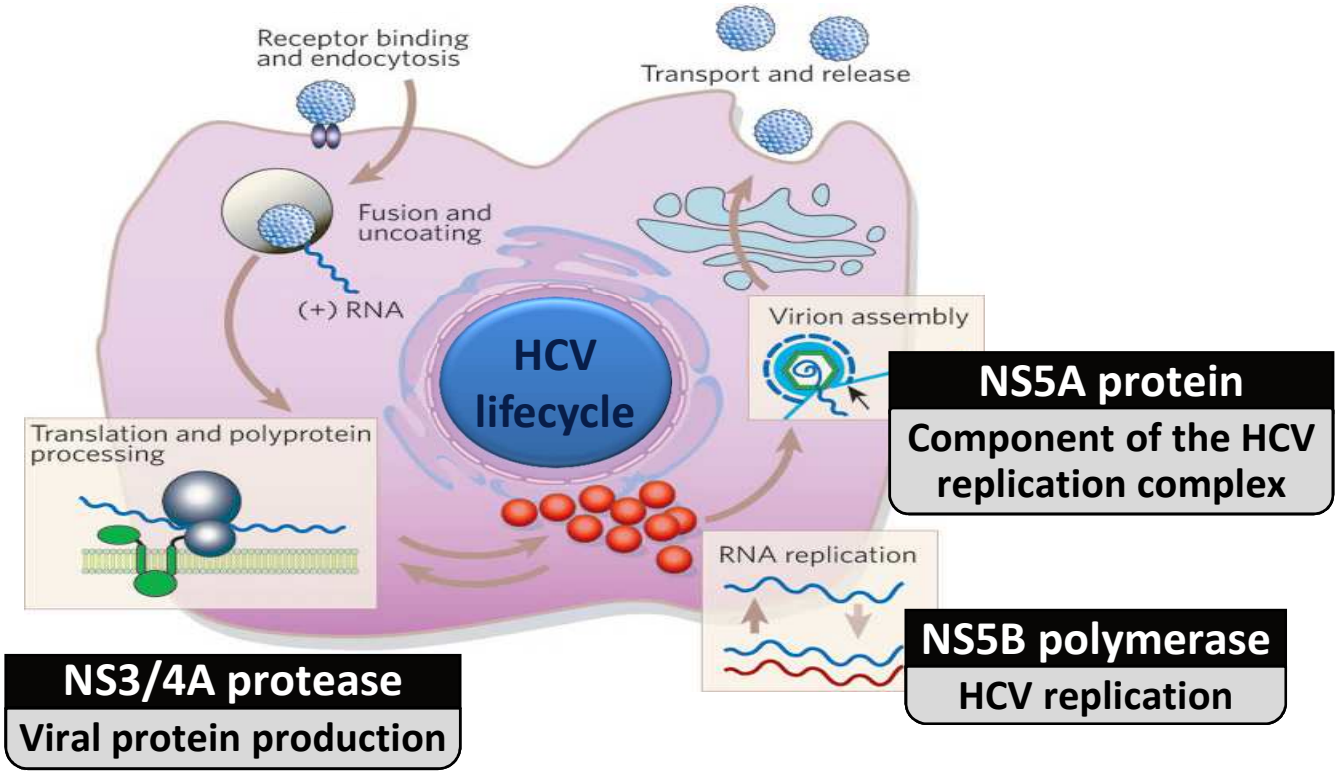
- The drugs
- The patients

HCV –New Antivirals

- The drugs
- The patients

HCV Targets

Most DAAs currently in development target one of three viral proteins: NS3/4A, NS5A, and NS5B



- RAV = resistance-associated variants.

- Bartenschlager R & Lohmann V. *J Gen Virol* 2000; **81:**1631–1648; Sarrazin C & Zeuzem S. *Gastroenterology* 2010; **138:**447–462.

Genotype 1 without Interferon

- Two strategies emerging:-
- Sofosbuvir + anything
- Potent protease + 1 or 2 other drugs

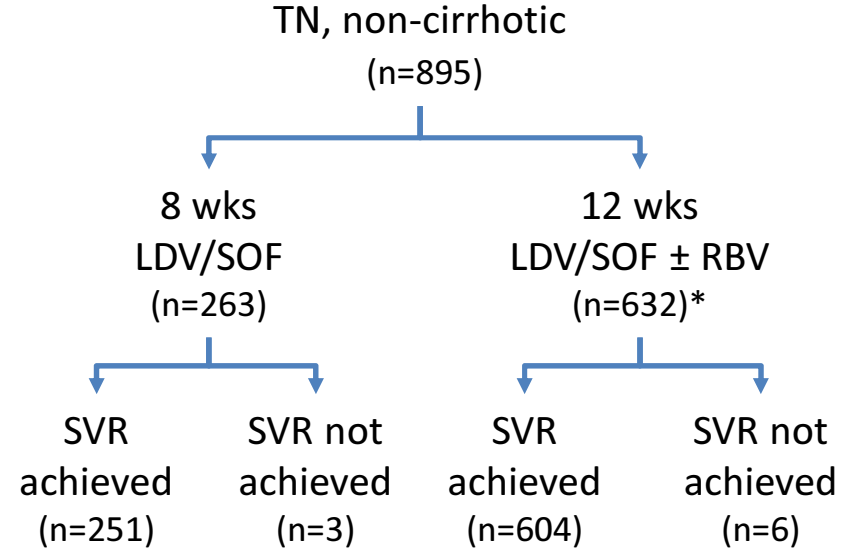
Sofosbuvir based regimes

- You can add sofosbuvir to anything and HCV dies
- (Simeprevir, daclatasvir, Channel No 5)

(One of the above is wrong)

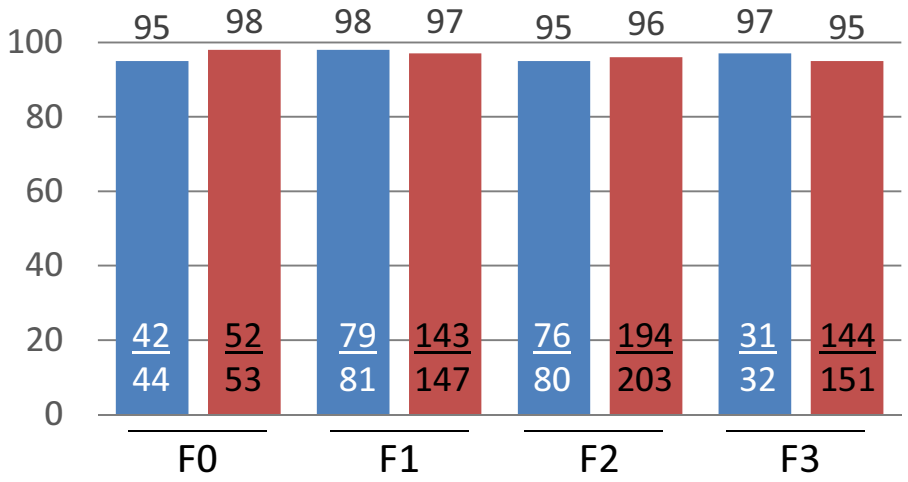
Real-world experience (TRIO Network): 8 or 12 week LDV/SOF in treatment-naive patients with **non-cirrhotic**, G1 HCV

Patient disposition

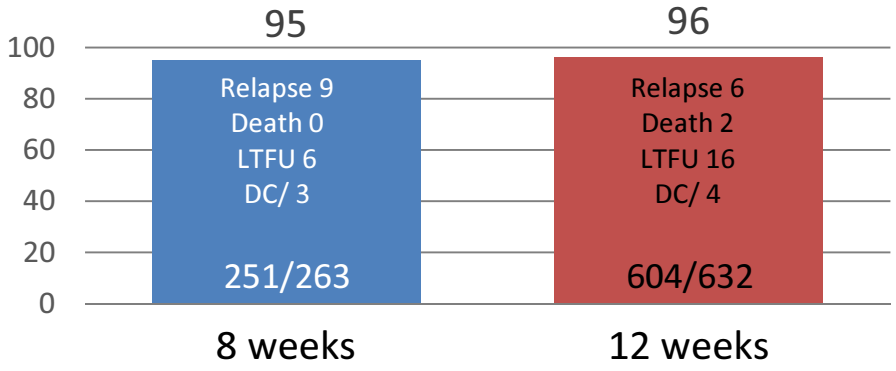


*21 Patients were on 12 weeks of LDV/SOF+RBV

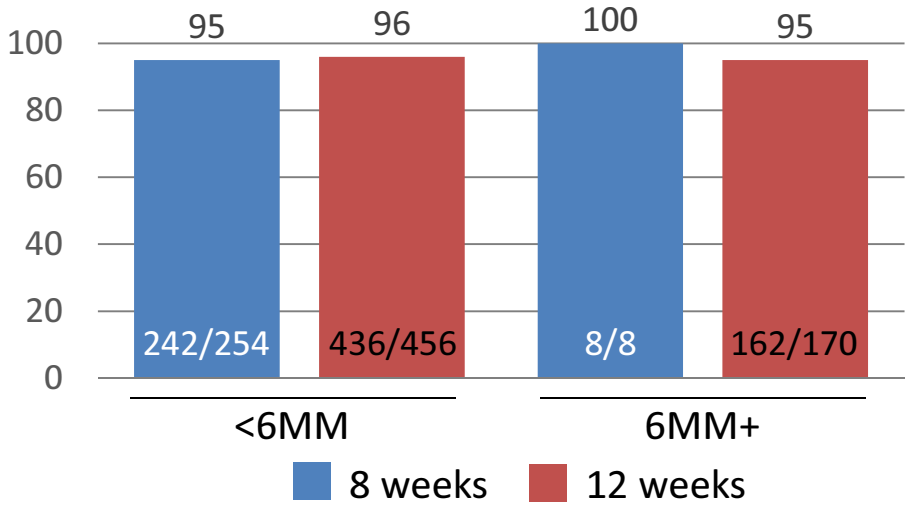
SVR12 by fibrosis



SVR12 by duration



SVR12 rates by baseline viral load



Curry M, et al. AASLD 2015, San Francisco. #1046

Real-world experience from the TRIO Network: Failure with all-oral DAA regimens

SVR rates inside vs outside FDA guidelines

	LDV/SOF ± RBV	VKP ± RBV	SMV + SOF ± RBV	Total
Outside guidelines	85% (115/135)	83% (5/6)	63% (5/8)	84% (125/149)
Inside guidelines	95% 1391/1462)	93% (38/41)	82% (27/33)	95% 1456/1536)
Total	94% 1506/1597)	91% (43/47)	78% (32/41)	94% 1581/1685)

Predictors of response

Variable	Full population distribution, % (n)	Treatment failure distribution, % (n)	p-value
Platelets <100k/mL Platelets 100l+/mL	11% (170) 89% (1320)	40% (19) 60% (29)	<0.001
Cirrhosis No cirrhosis	31% (504) 69% (1138)	70% (35) 30% (15)	<0.001
Outside FDA guidelines Inside FDA guidelines	10% (149) 90% (1536)	33% (17) 37% (34)	<0.001
Male Female	58% (975) 42% (710)	76% (39) 24% (12)	0.008

- Real life regimens for G1 when applied according to guidelines have achieved SVR rates comparable to clinical trials

Patients outside of guidelines: G1a on VKP without RBV, tx failure cirrhotic patients on 12 weeks of VKP ± RBV, LDV/SOF without RBV, or SMV + SOF ± RBV

Afdhal N, et al. AASLD 2015, San Francisco. #LB-17

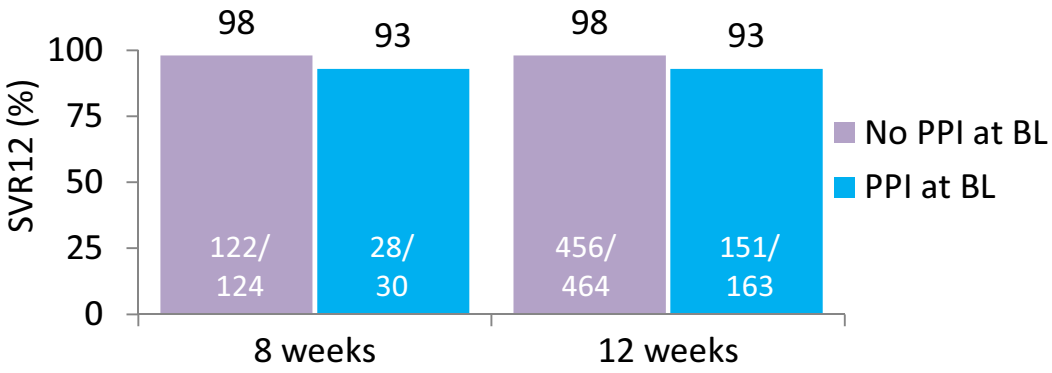
Treatment outcomes with 8-, 12- and 24-week regimens of SOF/LDV: Analysis of a multicenter prospective, observational study

- TARGET Registry: Pts treated according to local standards of care at academic (n=44) and community medical centers (n=17) in North America and Europe: N=2321 started Tx, virologic outcome known for 1074

SVR, by regimen

Regimen	SVR12, n/N (%)
SOF/LDV 8 wks	150/154 (97)
SOF/LDV 12 wks	607/627 (97)
SOF/LDV 24 wks	153/161 (95)
SOF/LDV 12 wks + RBV	86/89 (97)
SOF/LDV 24 wks + RBV	12/13 (92)

SVR, by use of proton pump inhibitor (PPI) at BL

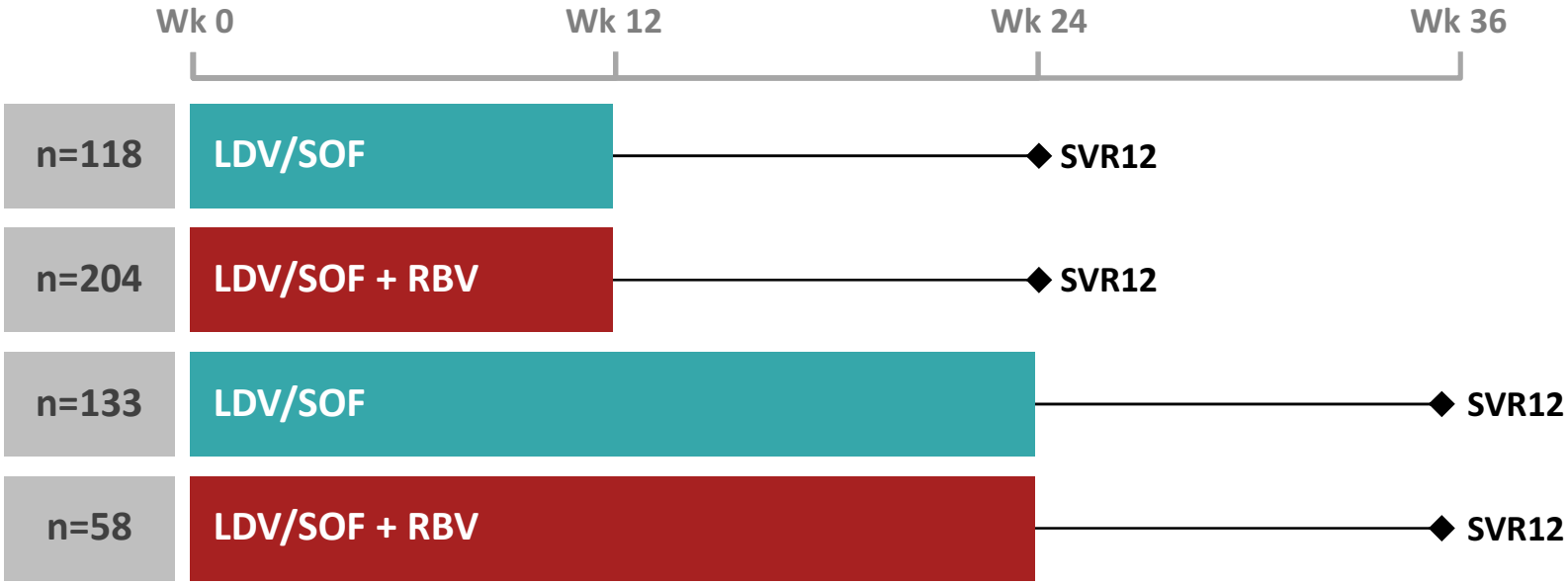


- SOF/LDV-containing 8 and 12-wk treatment regimens are generally safe, well tolerated, and highly effective across a broad spectrum of patients and clinical practices
- 8-week regimen underutilized
- Overall SVR rates high, although PPI use associated with higher rate of VF

Terrault N, et al. AASLD 2015, San Francisco. #94

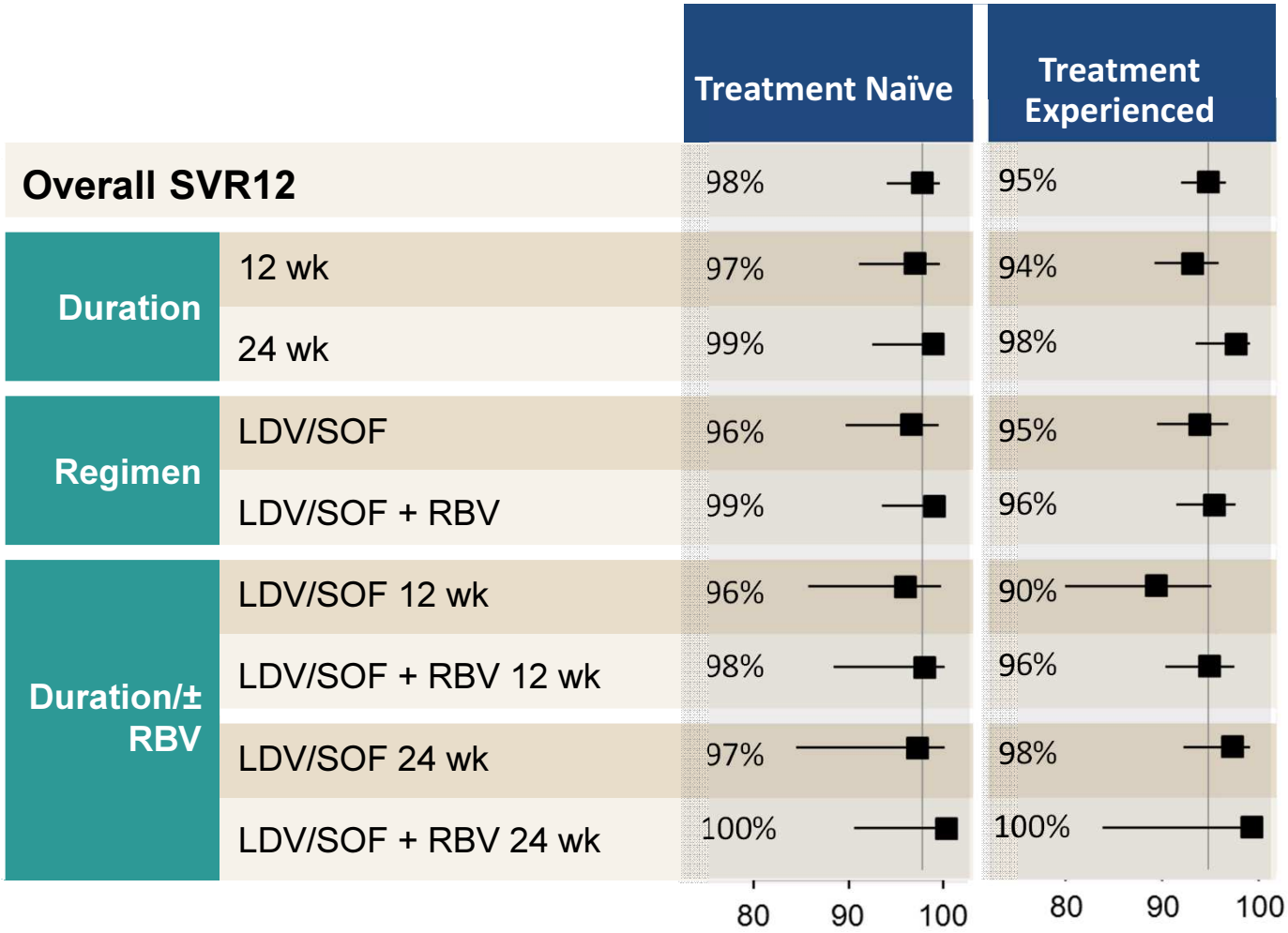
An Integrated Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with LDV/SOF±RBV

- 513 patients with HCV GT 1, compensated cirrhosis
- Pooled data from Phase 2 and 3 LDV/SOF ± RBV studies
  - LONESTAR, ELECTRON, ELECTRON-2, Japan phase 3 study, ION-1, ION-2, SIRIUS
- Primary efficacy endpoint: SVR12



Bourliere, AASLD, 2014, Oral #82

Results: SVR12 by Treatment Regimen



Among TE cirrhotic patients, 12 weeks of LDV/SOF + RBV resulted in similar SVR rates to 24 weeks of LDV/SOF alone

Bourliere, AASLD, 2014, Oral #82

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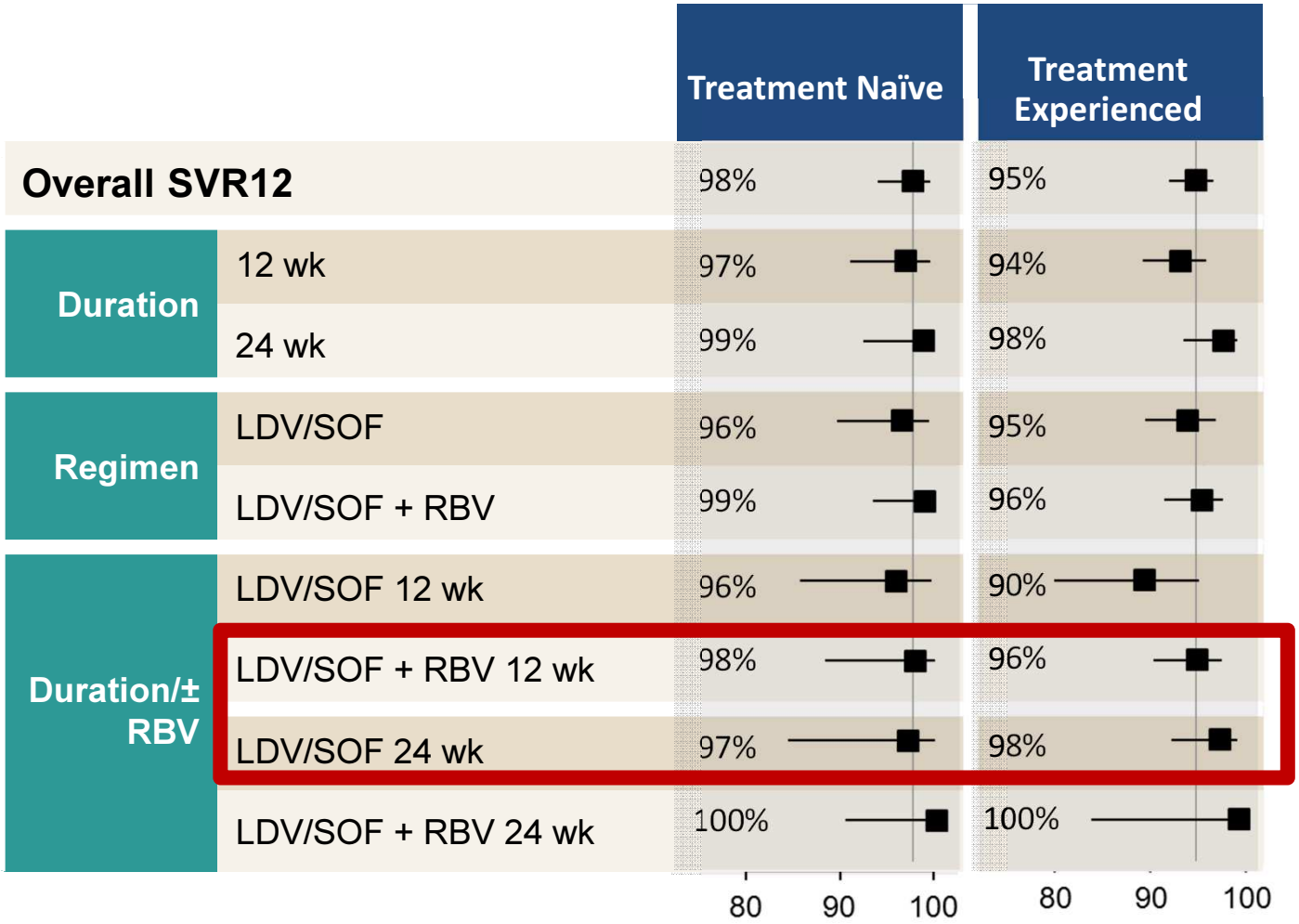


Among TE cirrhotic patients, 12 weeks of LDV/SOF + RBV resulted in similar SVR rates to 24 weeks of LDV/SOF alone

Bourliere, AASLD, 2014, Oral #82

Sofosbuvir + Ledipasvir

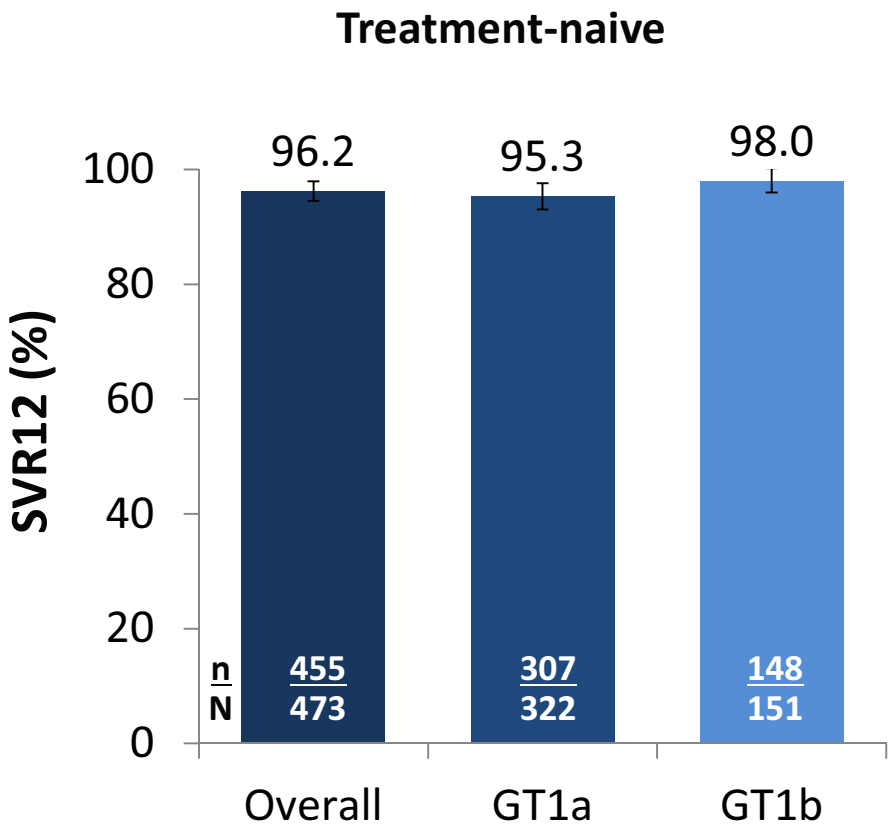
- A single tablet
- Cures most G1 in 8 weeks – side effect free
- Cures cirrhosis in 12 weeks

  (needs ribavirin, some side effects)

Genotype 1 without Interferon

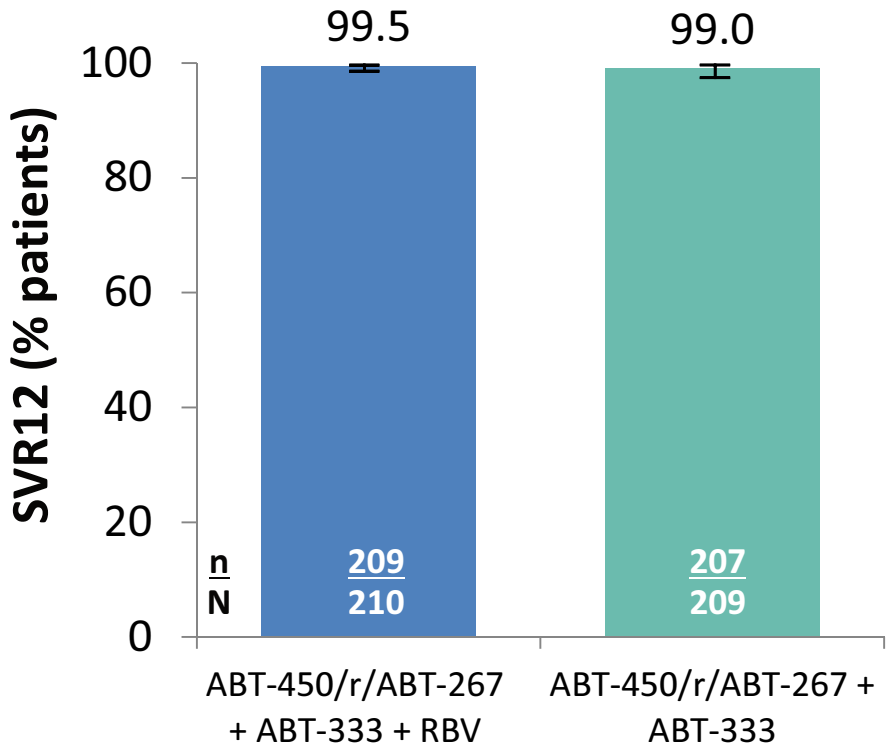
- Two strategies emerging:-
- Sofosbuvir + anything
- Potent protease + 1 or 2 other drugs

SAPPHIRE-I: GT1 treatment-naive patients — SVR12 rates by HCV GT1 subtype



Error bars: 95% CI.

PEARL-III: SVR rates with 3D ± RBV in GT1b treatment-naive patients



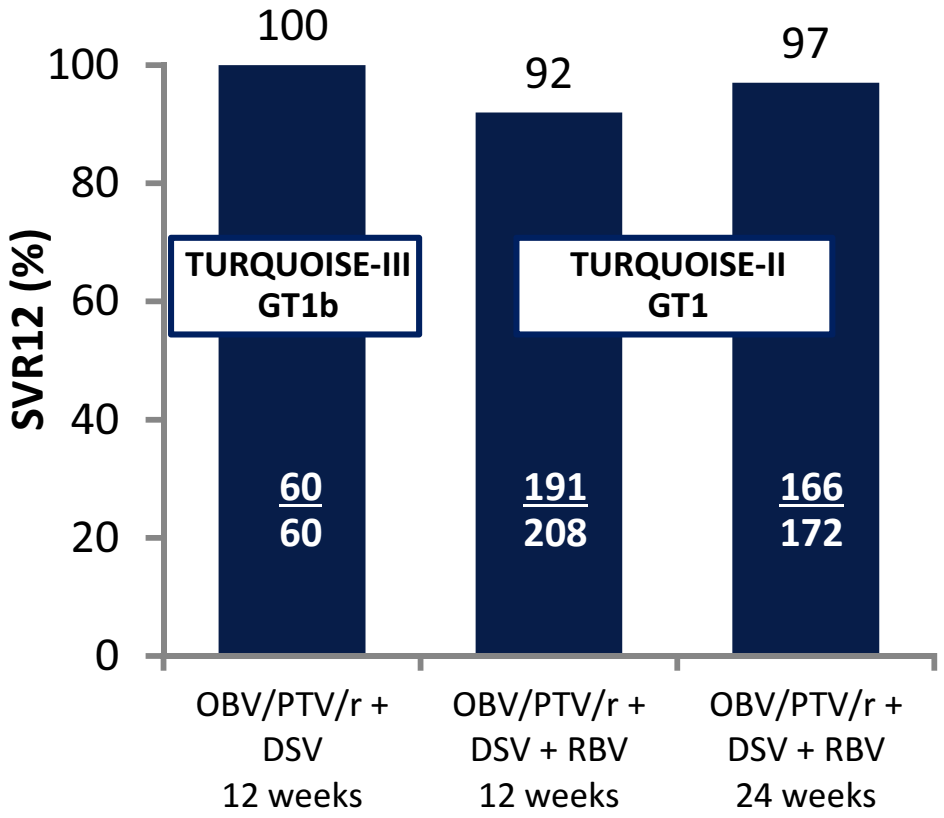
Error bars: 95% CI.

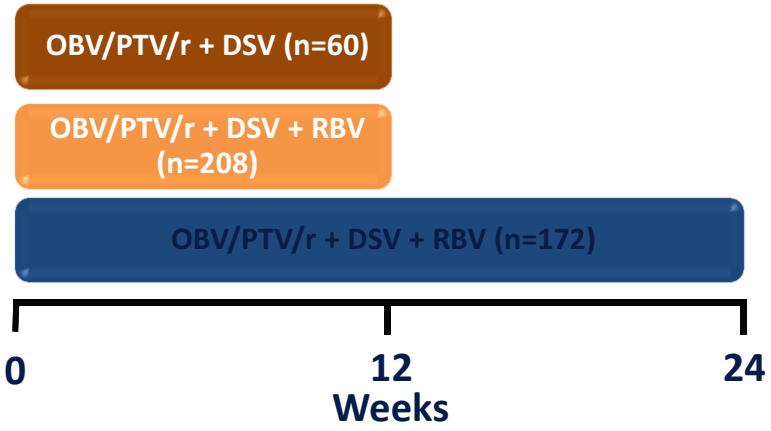
- Ferenci P, *et al. NEJM 2014;370:1988*].

TURQUOISE-II and -III: patients with compensated cirrhosis – study design and SVR12

TURQUOISE-III
HCV GT1b, treatment-naive or -experienced, cirrhotic

TURQUOISE-II
HCV GT1, treatment-naive or -experienced, cirrhotic





100% of cirrhotic GT1b patients treated with OBV/PTV/r + DSV achieved SVR12

- Feld JJ, *et al. J Hepatol* 2015; ePub ahead of print; Viekirax Summary of Product Characteristics (accessed November 2015).

AbbVie Regimes

- For naïve 1a patients (+/- cirrhosis):-
  12 weeks ‘3D’ with ribavirin

- For naïve 1b patients (- cirrhosis)
  12 weeks ‘3D’ without ribavirin
  (?? add ribavirin for cirrhosis)

- For experienced patients with cirrhosis extend for 24 weeks in 1a non-responders

Genotype 1 HCV

- Sorted!
- At present NHSE funds patients with cirrhosis
- NICE recommend that ALL patients get treated
  (Final confirmation of NICE due soon)

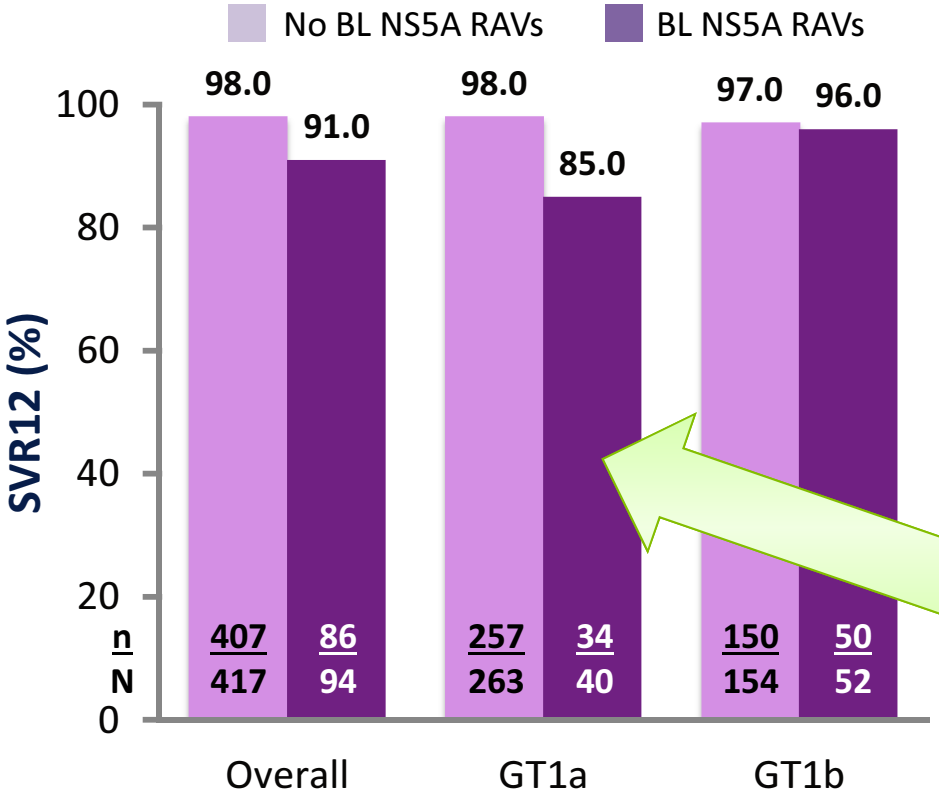
Emerging Issues - Resistance

- Current story is that Resistance Associated Variants (RAVs) have no impact on SVR

- Is this really true?

SOF/LDV and NS5A RAVs

Pooled analysis (phase 2/3 trials*) of 513 cirrhotic patients with GT1 treated with LDV/SOF ± RBV for 12 or 24 weeks. SOF has a high barrier to resistance



BL NS5A RAVs were detected in 18% of genotypable isolates

9% of GT1a-infected patients and 17% of GT1b-infected patients had NS5A RAVs that conferred a >100-fold shift in EC_{50}

SVR12 rates were lower in patients with BL RAVs and GT1a infection. However, the high barrier to resistance provided by SOF improves SVR12 rates

- * LONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, and SIRIUS trials. Presence of RAVs was evaluated by deep sequencing with assay cut-offs of 1%.

Sarrazin C, *et al. J Hepatol* 2015; **62**(Suppl):S620 (poster presentation).

RAVS

- They matter (sometimes)

- Is it worth hunting them down?

- Strategy A –
- Ignore them and worry about them in the failures
- Strategy B –
- Spend a fortune finding them first time round

Genotype 2

- 80% of Genotype 2 patients respond to 24 weeks of Peg+Riba

- (Patients who respond rapidly may have duration reduced to 12 weeks)

Genotype 2
Sofosbuvir + Ribavirin for 12 weeks

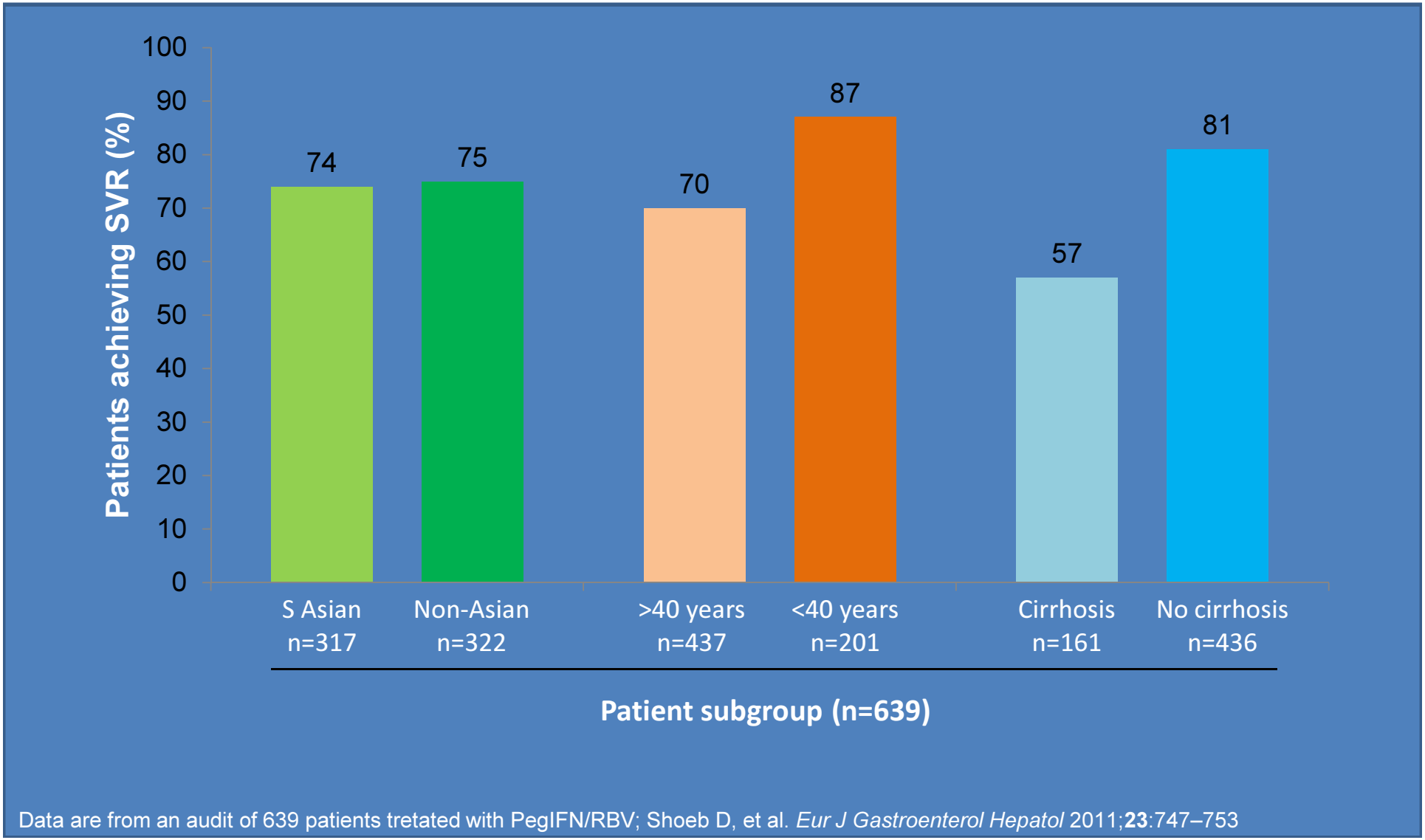
NAIVE		EXPERIENCED			
G2		G2 12 WEEKS		G2 16 WEEKS	
Non Cirrhosis	Cirrhosis	Non Cirrhosis	Cirrhosis	Non Cirrhosis	Cirrhosis
92%	94%	96%	60%	100%	78%

Jacobson NEJM 2013

Genotype 2

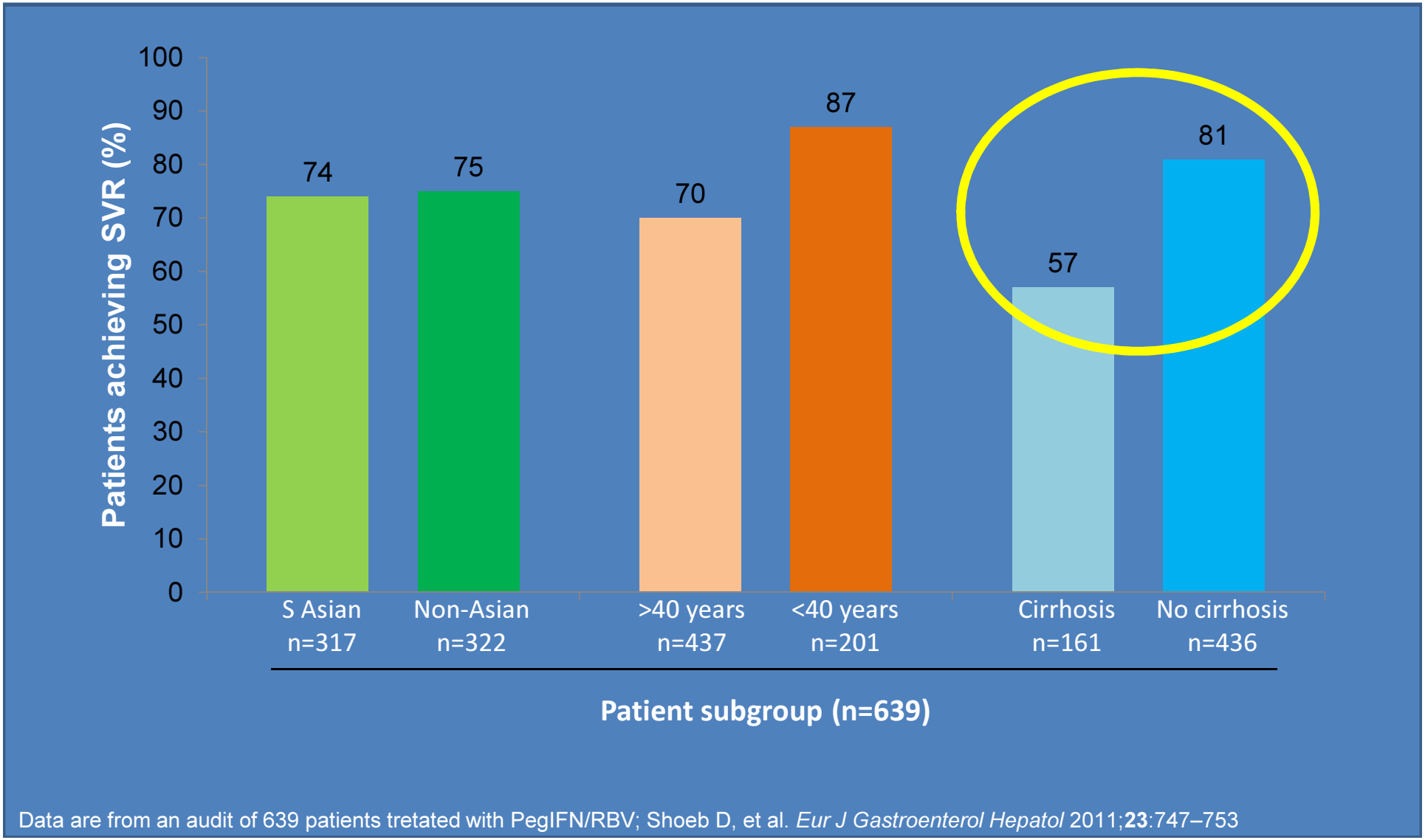
- Interferon works (and is cheap)
- Interferon is going to stay as first line for easy patients
- ‘Hard to cure patients’ may get tablet only therapy

Genotype 3
PegIFN + Ribavirin



Data are from an audit of 639 patients tretated with PegIFN/RBV; Shoeb D, et al. *Eur J Gastroenterol Hepatol* 2011;**23**:747–753

Genotype 3
PegIFN + Ribavirin



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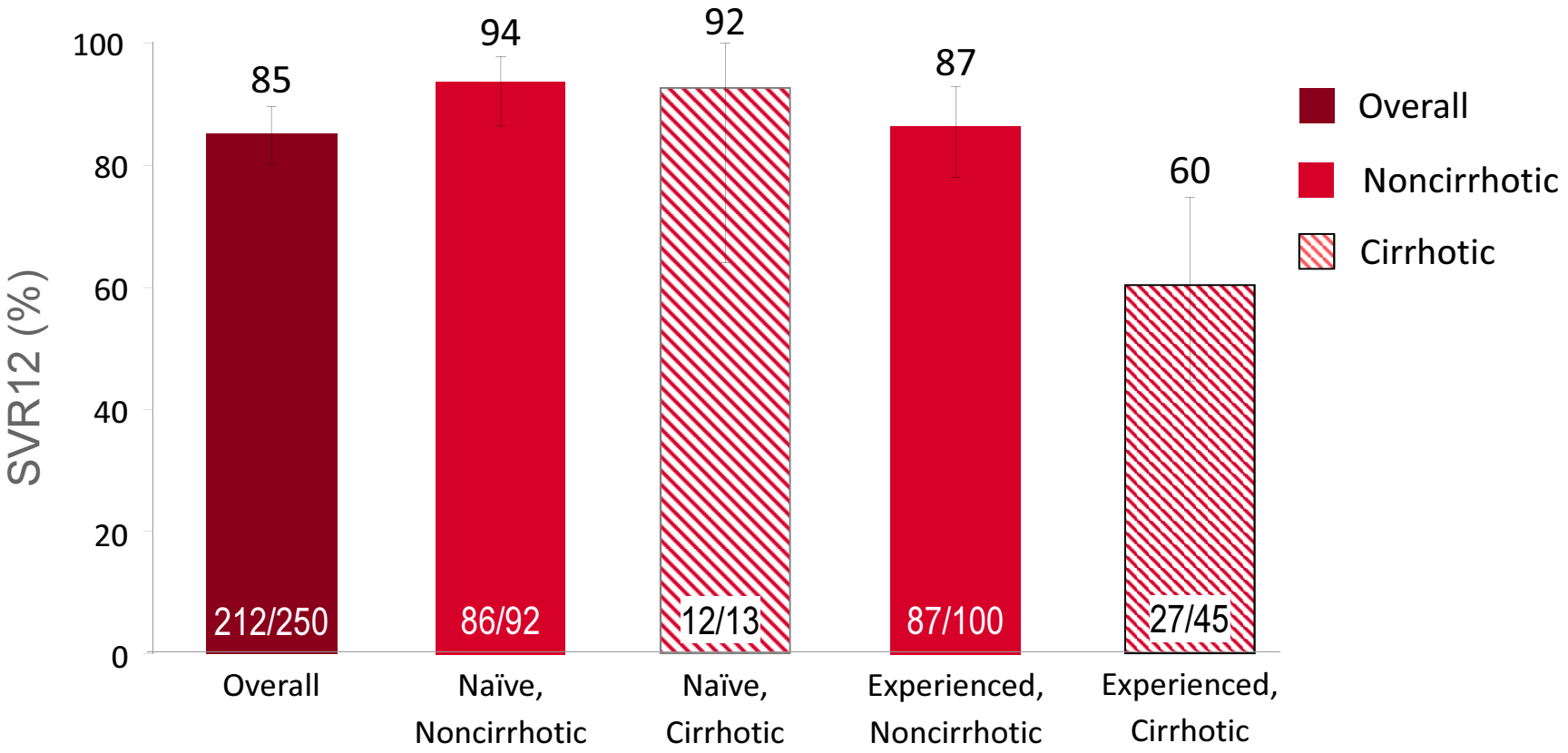
Sofosbuvir struggles with G3

Sofosbuvir for G3 24 weeks therapy



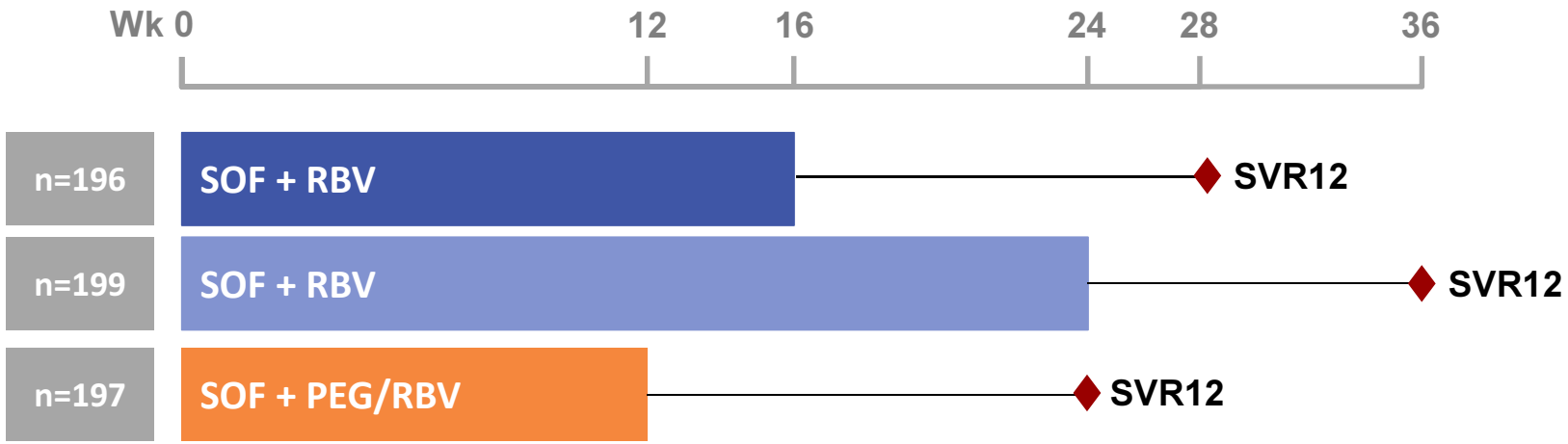
Valence NEJM 2014

Sofosbuvir for G3

- 12 weeks sofosbuvir is £35K
- 24 weeks sofosbuvir is £70K

- 24 weeks sofosbuvir is NEVER going to get NHSE support

Treating Genotype 3 BOSON

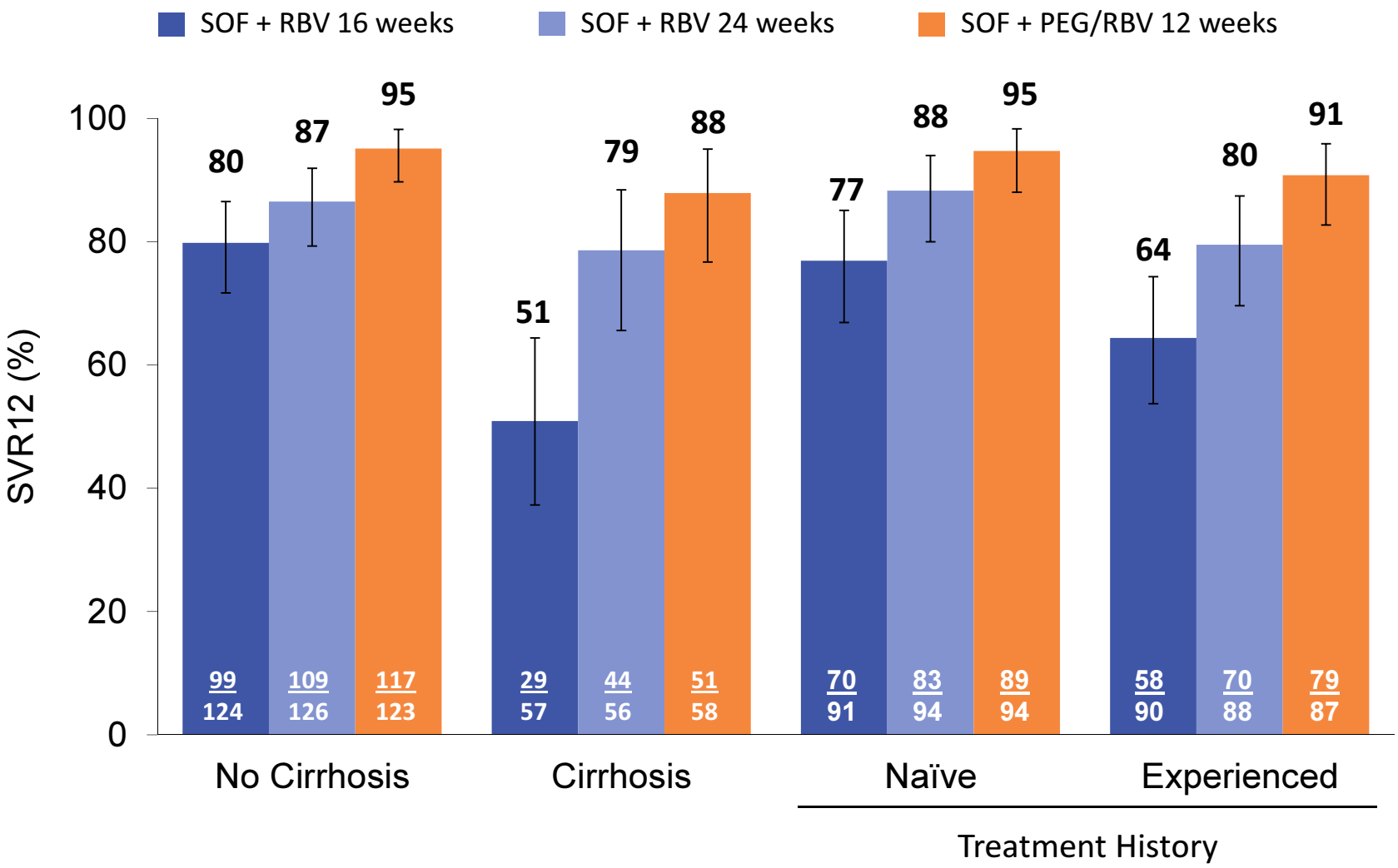


- Multicenter study, open-label, randomized (1:1:1) study at 80 sites in UK, Australia, USA, Canada, and New Zealand
- GT 2 patients: treatment experienced (TE) with cirrhosis
- GT 3 patients: TE or treatment naïve (TN), with or without cirrhosis
- Stratification
  - Cirrhosis
  - HCV Genotype
  - Prior HCV treatment
- ♦ Platelets ≥60,000 cells/mm^3

BOSON study - Demographics

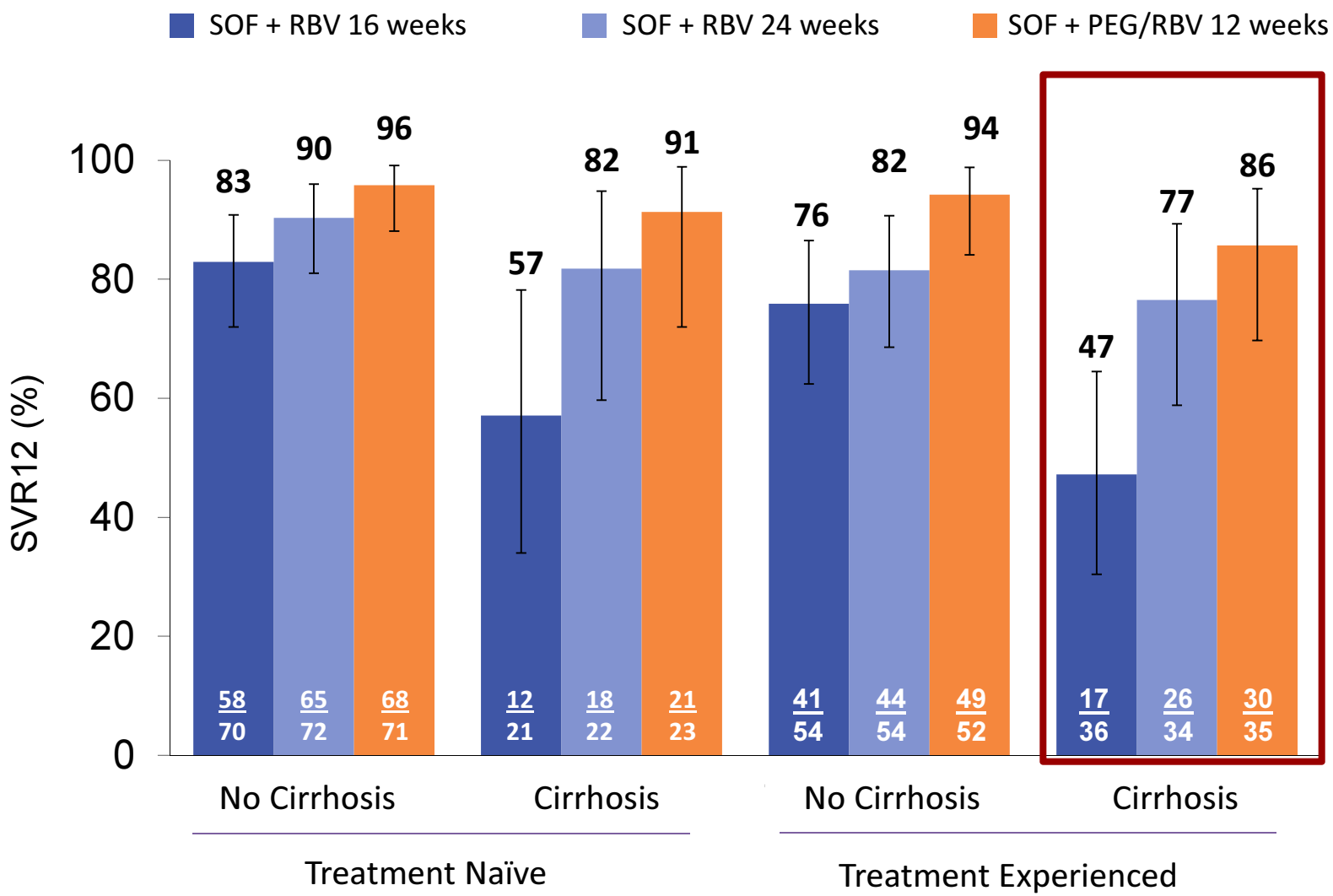
	SOF + RBV 16 weeks n=196	SOF + RBV 24 weeks n=199	SOF + PEG/RBV 12 weeks n=197	Total N=592
Mean age, y (range)	51 (20-69)	49 (23-71)	50 (19-73)	50 (19-73)
Male, n (%)	134 (68)	129 (65)	132 (67)	395 (67)
Asian, n (%)	28 (14)	26 (13)	25 (13)	79 (13)
Mean BMI, kg/m^2 (range)	28 (18-50)	28 (18-55)	28 (19-45)	28 (18-55)
IL28B CC, n (%)	75 (38)	73 (37)	78 (40)	226 (38)
HCV genotype 3, n (%)	181 (92)	182 (92)	181 (92)	544 (92)
Mean baseline HCV RNA, log_{10} IU/mL (range)	6.3 (4.0-7.6)	6.2 (3.3-7.6)	6.3 (3.7-7.5)	6.3 (3.3-7.6)
Treatment experienced, n (%)	105 (54)	105 (53)	103 (52)	313 (53)
Cirrhosis, n (%)	72 (37)	73 (37)	74 (38)	219 (37)

Results: SVR12 in GT 3



- intervals.

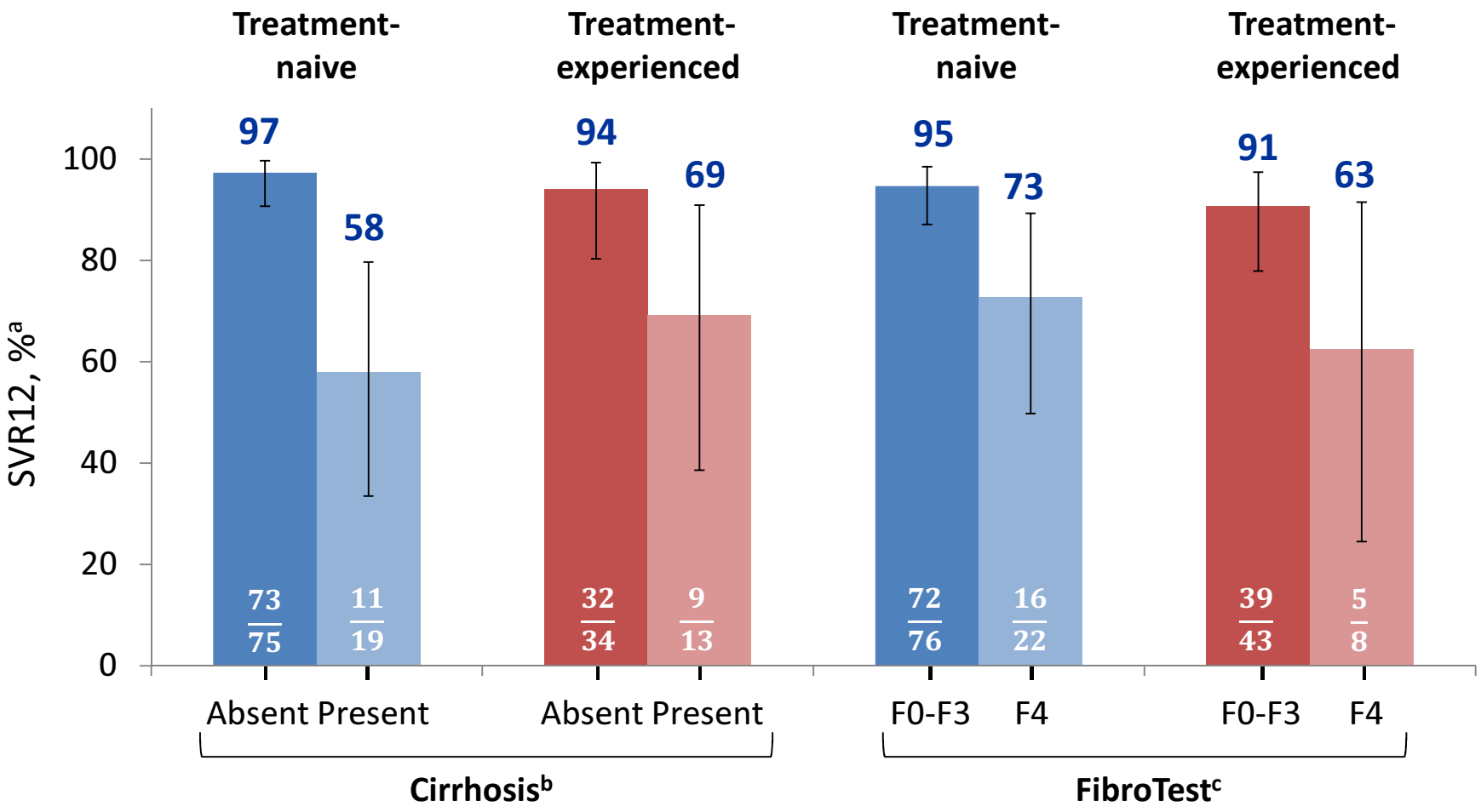
SVR12 in GT 3
by Treatment History and Cirrhosis Status



Genotype 3

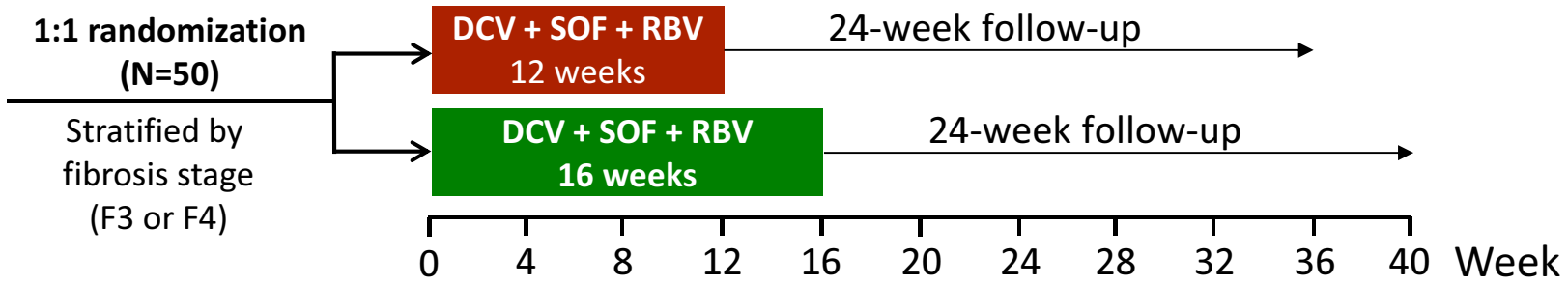
- The best way to cure ‘difficult’ Genotype 3 is with Interferon and sofosbuvir

G3 Without Interferon



[a] HCV RNA < LLOQ (25 IU/mL); error bars reflect 95% confidence intervals.
[b] Cirrhosis determined by liver biopsy (METAVIR > F3), FibroScan (> 14.6 kPa), or FibroTest score ≥ 0.75 and aspartate aminotransferase to platelet ratio index > 2.
[c] FibroTest assessments could have been performed up to Day 1 (baseline).

ALLY-3+ Phase 3 Study: All-oral treatment with DCV + SOF + RBV for 12 or 16 weeks in HCV G3-infected patients with advanced fibrosis or cirrhosis

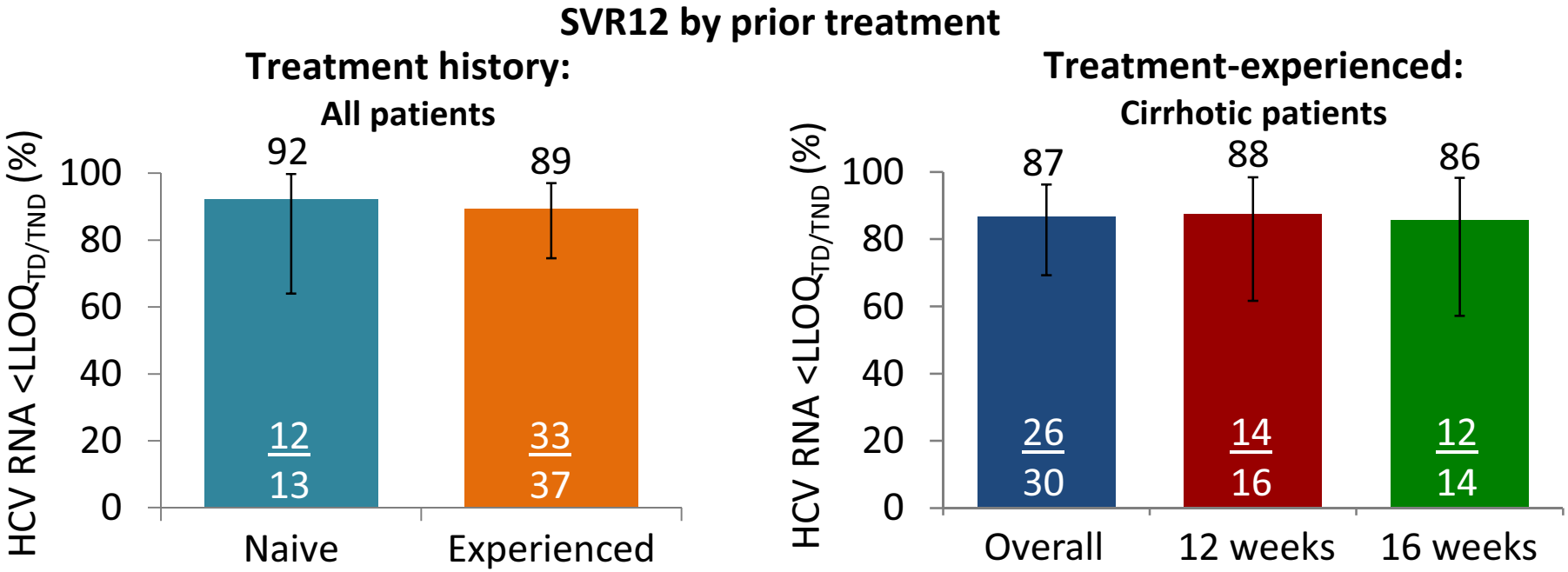


Demographics	DCV + SOF + RBV 12 weeks, n=24	DCV + SOF + RBV 16 weeks, n=26
Age, median (range) yrs	53.0 (36–73)	56.0 (42–62)
Male, n (%)	18 (75)	22 (85)
Race, n (%)		
White	23 (96)	26 (100)
Asian	1 (4)	0
IL28B non-CC, n (%)	13 (54)	15 (58)
HCV RNA, median (range) $\log_{10}$ IU/mL	6.70 (4.6–7.6)	6.91 (4.7–7.8)
HCV RNA category (IU/mL), n (%)		
≥ 2 million	18 (75)	20 (77)
≥ 6 million	11 (46)	15 (58)

Demographics cont.	DCV + SOF + RBV 12 weeks, n=24	DCV + SOF + RBV 16 weeks, n=26
Fibrosis stage, n (%)		
Advanced fibrosis (F3)	6 (25)	8 (31)
Cirrhosis (F4)	18 (75)	18 (69)
Albumin, med (range) g/L	43.0 (33–47)	42.5 (34–48)
Platelets, median (range) × 10^9 cells/L	161 (63–299)	155 (84–324)
Prior HCV Tx-experience, n (%)		
Naive	6 (25)	7 (27)
Experienced	18 (75)	19 (73)
IFN-based	15 (63)	16 (62)
SOF-based	3 (13)	3 (12)

Leroy V, et al. AASLD 2015, San Francisco. #LB-3

ALLY-3+ Phase 3 Study: All-oral treatment with DCV + SOF + RBV for 12 or 16 weeks in HCV G3-infected patients with advanced fibrosis or cirrhosis



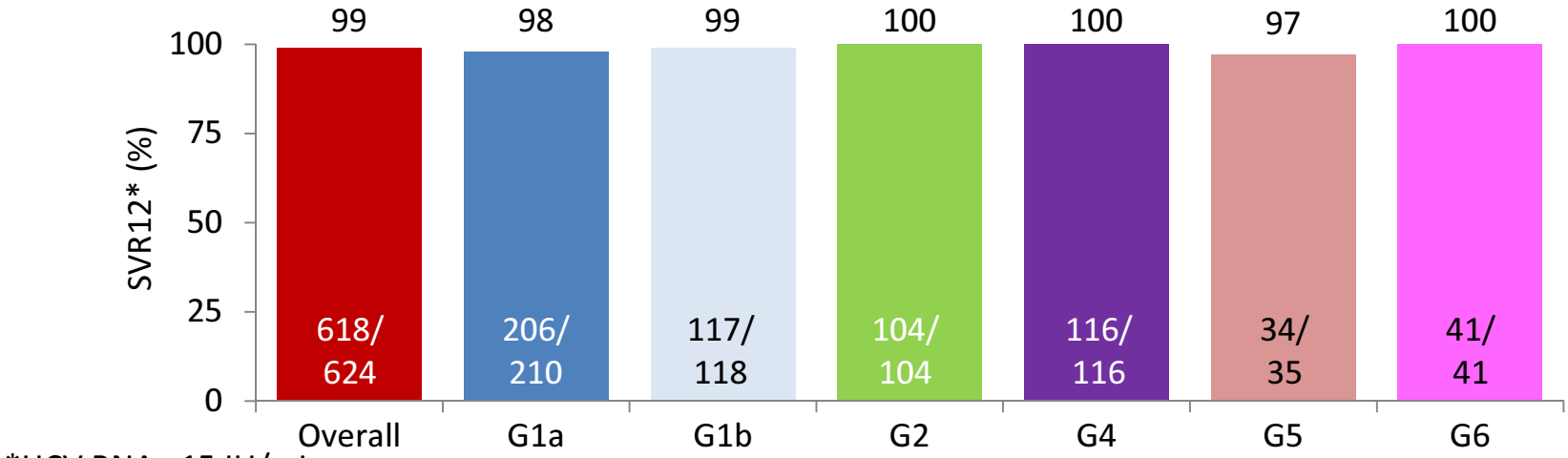
- Efficacious (90% SVR12) for G3 patients with advanced fibrosis or compensated cirrhosis, a population in urgent need of treatment
  - Comparable SVR12 for 12- (88%) and 16-weeks (92%)
  - No on-treatment VFs; two relapses in each treatment arm
- 100% SVR12 among patients with advanced fibrosis, 86% among patients with cirrhosis

Leroy V, et al. AASLD 2015, San Francisco. #LB-3

Genotype 3

- For people without cirrhosis – most drugs work (Interferon is cheapest)
- For people with cirrhosis – interferon and sofosbuvir is best (and cheapest)
- For people who can not take interferon sofosbuvir+ daclatasvir works well –
- ? 12 weeks ? Longer?

Phase 3 evaluation of SOF/VEL FDC for 12 weeks in naive and experienced G1, 2, 4, 5, 6 patients with and without cirrhosis: ASTRAL-1 study



*HCV RNA <15 IU/mL

- **No pts in the PBO group had HCV RNA <15 IU/mL at any timepoint**

Virologic failure, n (%)	
On-treatment failure	0
Post-treatment relapse	2 (<1)
Other reasons for classification as failure to achieve SVR 12, n (%)	
Lost to follow-up	2 (<1)
Withdrew consent	1 (<1)
Death	1 (<1)

Feld JJ, et al. AASLD 2015, San Francisco. #LB-2

Phase 3 evaluation of SOF/VEL FDC for 12 weeks in naive and experienced G1, 2, 4, 5, 6 patients with and without cirrhosis: ASTRAL-1 study

Parameter	Placebo for 12 wks (n = 116)	SOF-VEL for 12 wks (n = 624)
Patients discontinuing treatment due to AE	2 (2)	1 (<1)
Patients with SAEs	0	15 (2)[†]
Patients with any AE	89 (77)	485 (78)
Common adverse events*		
Headache	33 (28)	182 (29)
Fatigue	23 (20)	126 (20)
Hematologic events, n (%)		
Hemoglobin concentration <10 g/dL	0	2 (<1)
Lymphocyte count <350 to <500 per mm^3	0	3 (<1)
Neutrophil count 500 to <750 per mm^3	0	4 (1)
Platelet count 25,000 to <50,000/mm^3	0	1 (<1)

*Adverse events occurring in ≥20% of patients in any arm

- Treatment with the once daily, all-oral, single tablet regimen of SOF/VEL for 12 weeks is well tolerated and results in high SVR12 rates in tx-naive / -experienced G1, 2, 4, 5, and 6 patients with and without cirrhosis

Feld JJ, et al. AASLD 2015, San Francisco. #LB-2

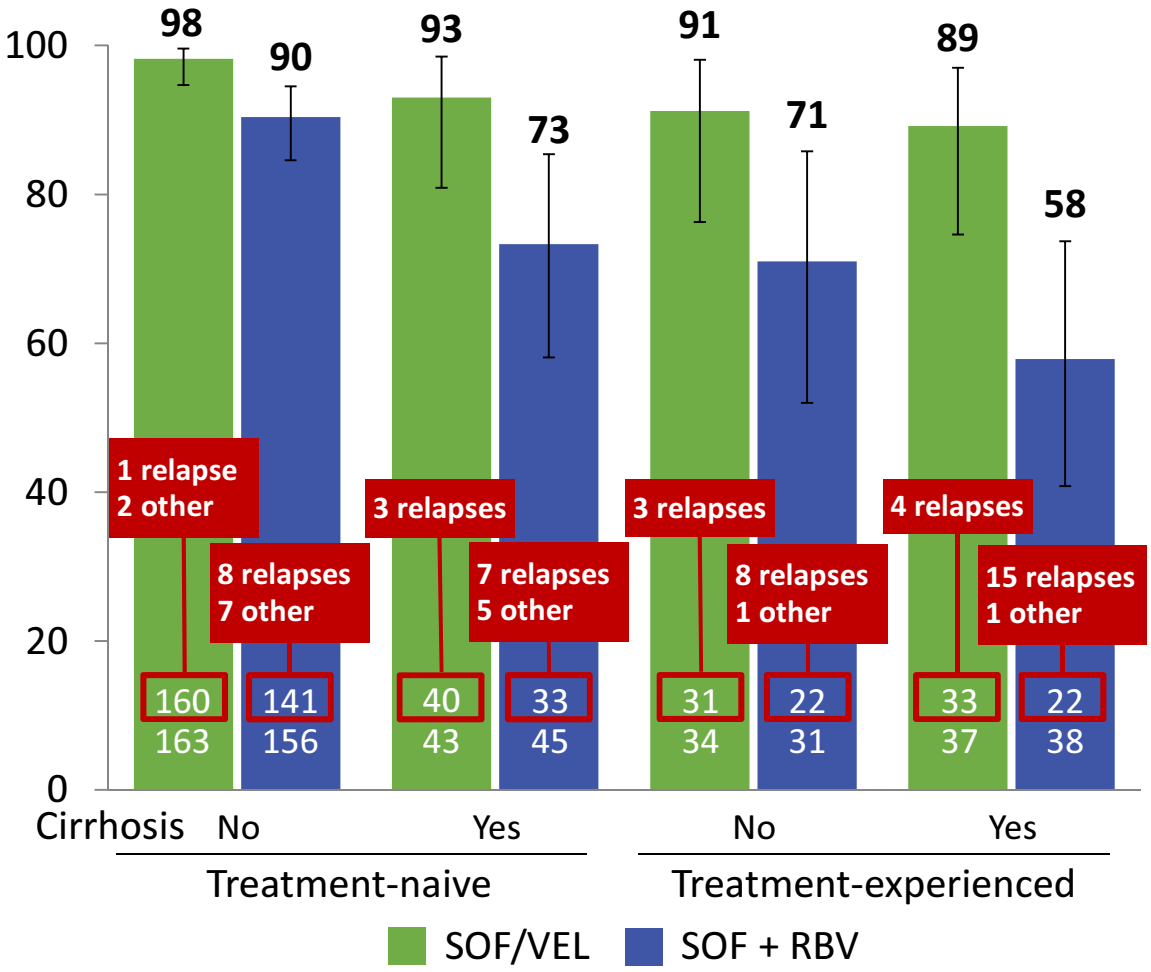
ASTRAL-3 Phase 3 Study: SOF/VEL FDC for 12 weeks compared to SOF + RBV for 24 weeks in G3 HCV infected patients

	SOF/VEL 12 weeks n=277	SOF + RBV 24 weeks n=275
Mean age, y (range)	49 (21–76)	50 (19–74)
Male, n (%)	170 (61)	174 (63)
White, n (%)	250 (90)	239 (87)
Mean BMI, kg/m^2 (range)	26 (17–48)	27 (17–56)
Cirrhosis, n (%)	80 (29)	83 (30)
Treatment experienced, n (%)	71 (26)	71 (26)
IL28B CC, n (%)	105 (38)	111 (40)
HCV RNA, $\log_{10}$ IU/mL (range)	6.2 (3.7–7.5)	6.3 (3.6–7.5)

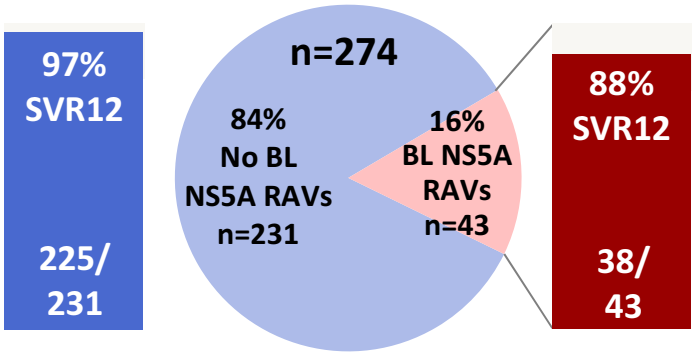
Foster GR, et al. NEJM 2015

ASTRAL-3 Phase 3 Study: SOF/VEL FDC for 12 weeks compared to SOF + RBV for 24 weeks in G3 HCV infected patients

SVR12 by cirrhosis and treatment history



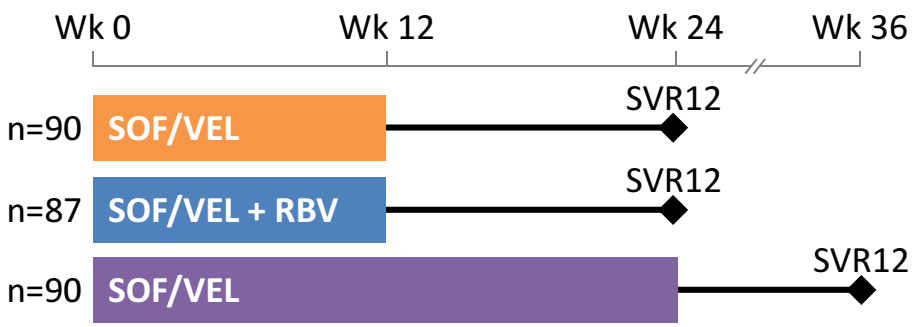
Resistance analysis



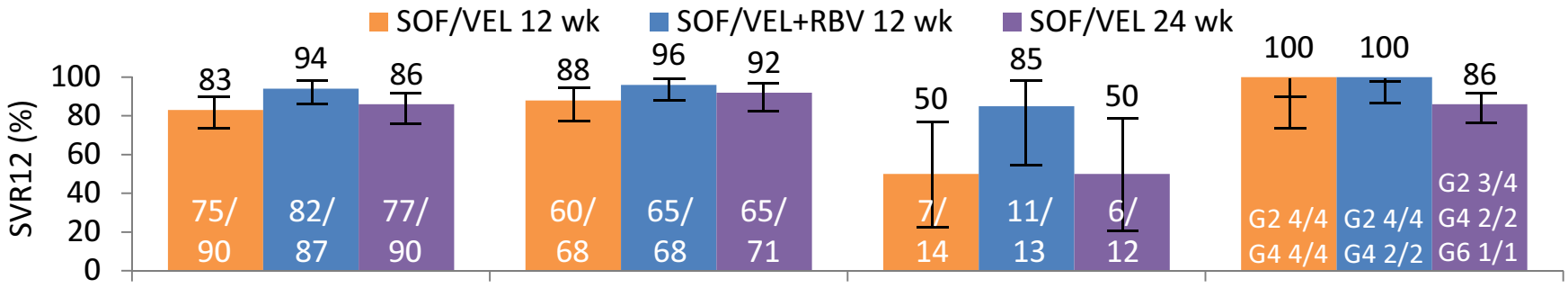
- 95% SVR12 rate in G3 infection
  - Superior to SOF + RBV for 24 weeks
  - 91% SVR12 in cirrhosis
- Well tolerated and lacked toxicities associated with RBV
- Simple, safe, highly effective,

Foster GR, et al. NEJM 2015

SOF/VEL FDC for treatment of HCV in patients with decompensated liver disease: The Phase 3 ASTRAL-4 study



- 267 treatment naive or experienced G1–6 with Child B cirrhosis
  - 65% treatment experienced
  - MELD <15 = 95%
  - Ascites 65–75%; encephalopathy 58–66%



	Overall			G1			G3			G2, 4, and 6		
Breakthrough, n	-	1	1	-	-	-	-	1	1	-	-	-
Relapse, n	11	2	7	5	1	3	6	1	4	-	-	-
LTFU, n	1	-	3	1	-	3	-	-	-	-	-	-
Death, n	3	2	2	2	2	-	1	-	1	-	-	1

Safety

- d/c due to AE 3%; death 3% (9)
- AE more frequent with RBV
- Fatigue (29%); nausea (23%); HA (22%); anemia (13%; 31% in RBV arm)
- RBV dose: Hb <10 = 23%; Hb <8.5 = 7%
- RBV decreased in 37% and d/c in 17%
- Bili <3 x ULN

Charlton MR, et al. AASLD 2015, San Francisco. #LB-13

HCV –New Antivirals

- The drugs

- The patients

HCV – The Patients

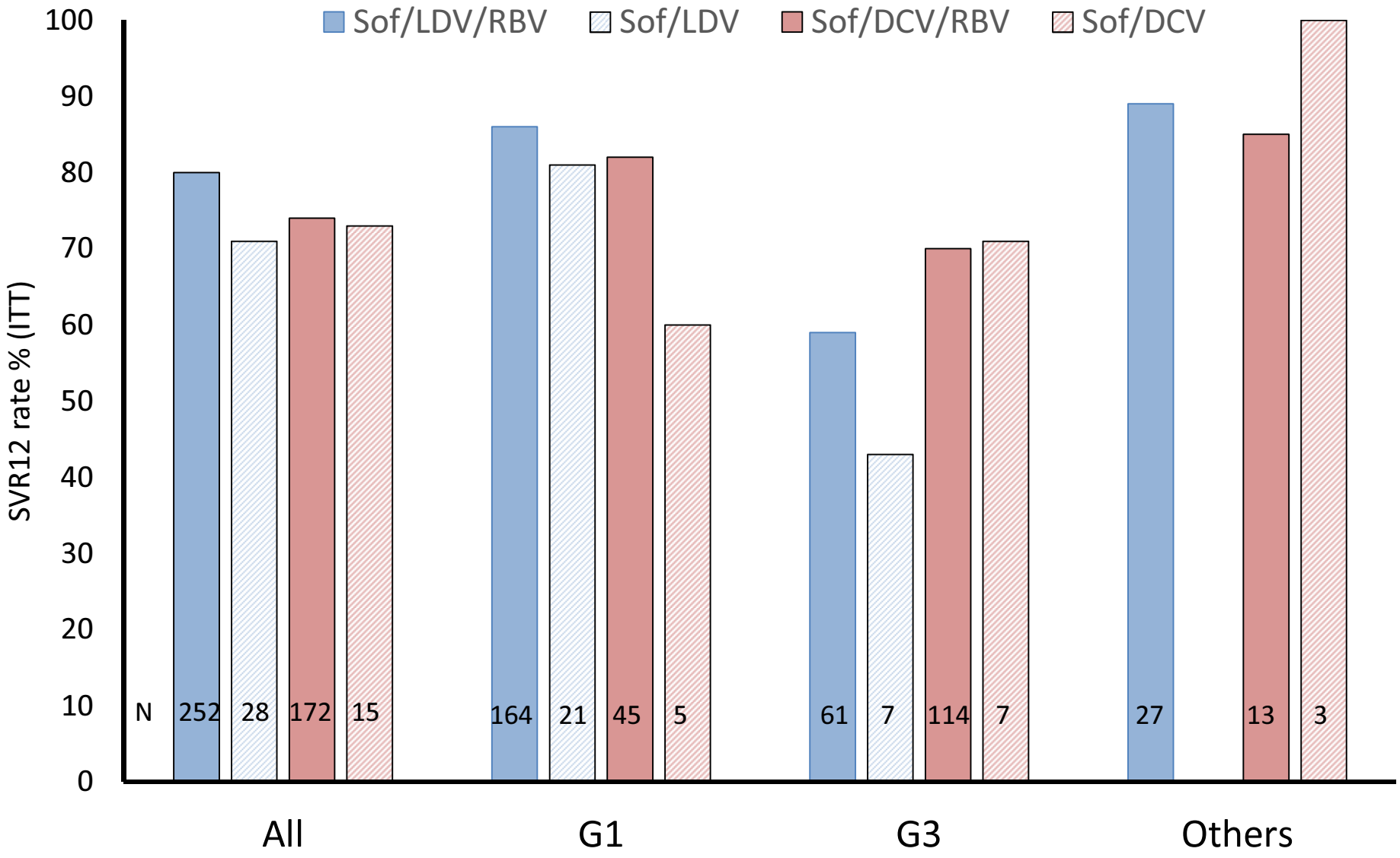
- Four populations:-

- Decompensated cirrhosis
- Cirrhosis
- Transmitters
- Stable mild/moderate

English EAP Program
Inclusion Criteria

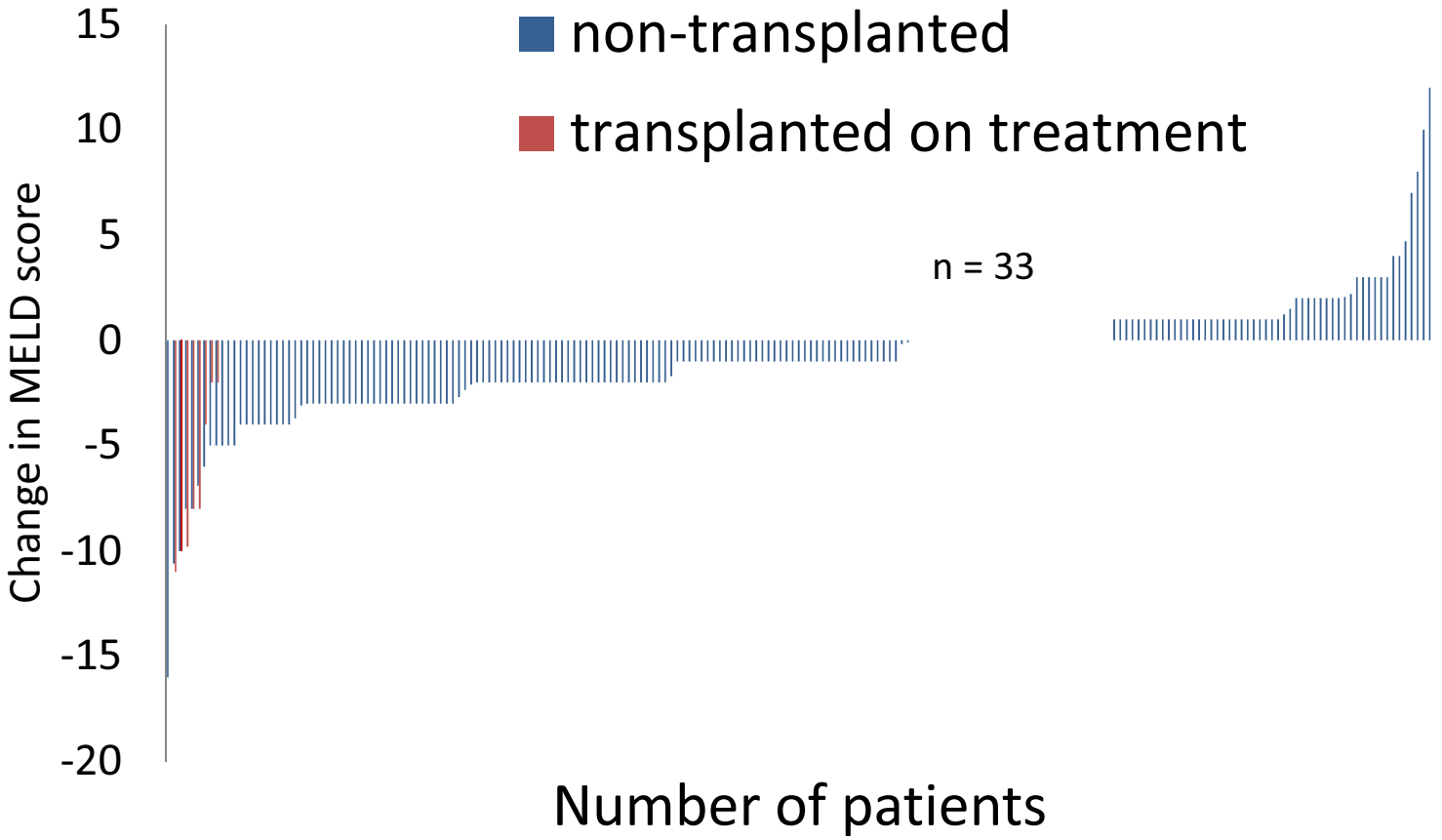
- Decompensated cirrhosis with ascites/variceal bleed/encephalopathy
- CTP score ≥7
- Non-hepatic manifestation likely to lead to irreversible damage in 12 months and intolerant to or failed Peg/Riba
- Exceptional circumstances by panel review

SVR12 by Genotype and Regime



SVR12 defined as HCV RNA at 12 weeks post-treatment < 30 IU/ml

Functional Outcome Change in MELD: Baseline – Follow up week 4



Comparative MELD scores available for 220 patients
(3 patients who died are not plotted)

HCV – The Patients

- Even the sickest patients benefit
- Care needed to select the right patient

HCV – The Patients

- Even the sickest patients benefit
- Care needed to select the right patient

What to do

- DISCUSS – transplant centre/MDT
- These tricky patients need consensus and experience

HCV – The Patients

- Cirrhosis – excellent response with new drugs

Non-cirrhotics G2 and 3

- Offer Peg/Riba

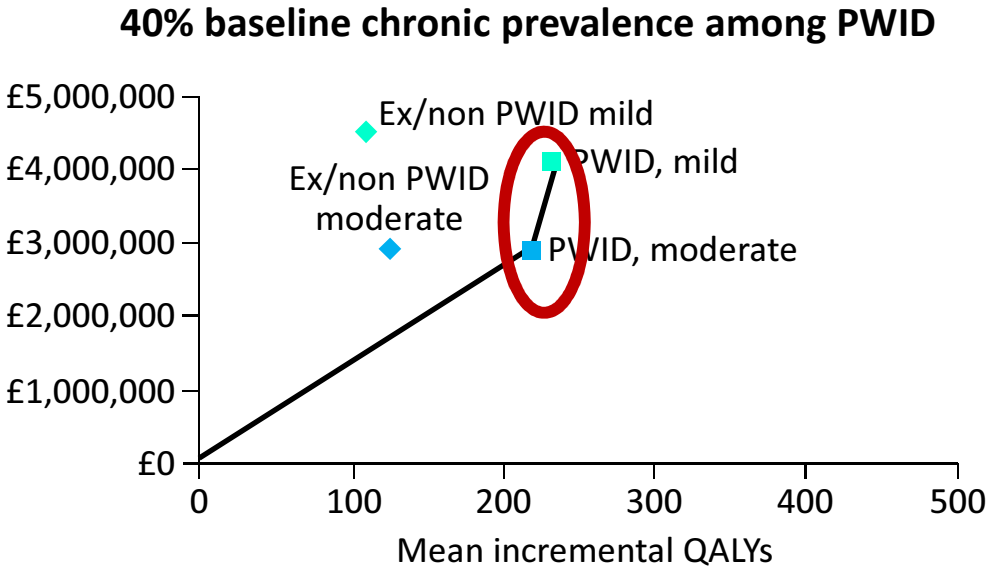
- All oral drugs will not be affordable any time soon!

Non-cirrhotics G1

- ‘Harvoni’ and ‘Viekirax/Exviera’ are NICE approved
- You can not treat everyone immediately
- You need to set up local prioritisation

Who should be prioritized for HCV antiviral treatment? A cost-effectiveness analysis including individual and population prevention benefits

- Dynamic HCV transmission and disease progression cost-effectiveness model to compare prioritization of HCV treatment using IFN-free DAAs
- Willingness to pay threshold (WTP) at £30,000 (~$50,000) per QALY gained



- After treating cirrhotics in population with 20% or 40% chronic prevalence among people who inject drugs (PWID) it is more cost effective to prioritize treatment to PWID at earlier disease stages because of substantial prevention benefits

- Treating HCV in PWID is highly cost effective

Martin NK, et al. AASLD 2014, Boston. #1752

HCV – who needs therapy now?

- Logically we should treat transmitters next

BUT

- Transmitters have no political clout
- Transmitters are expensive to treat

HCV - The New Drugs

- Exciting times
- Most patients can now be cured, many will get all oral therapies
- We need to prioritise sensibly