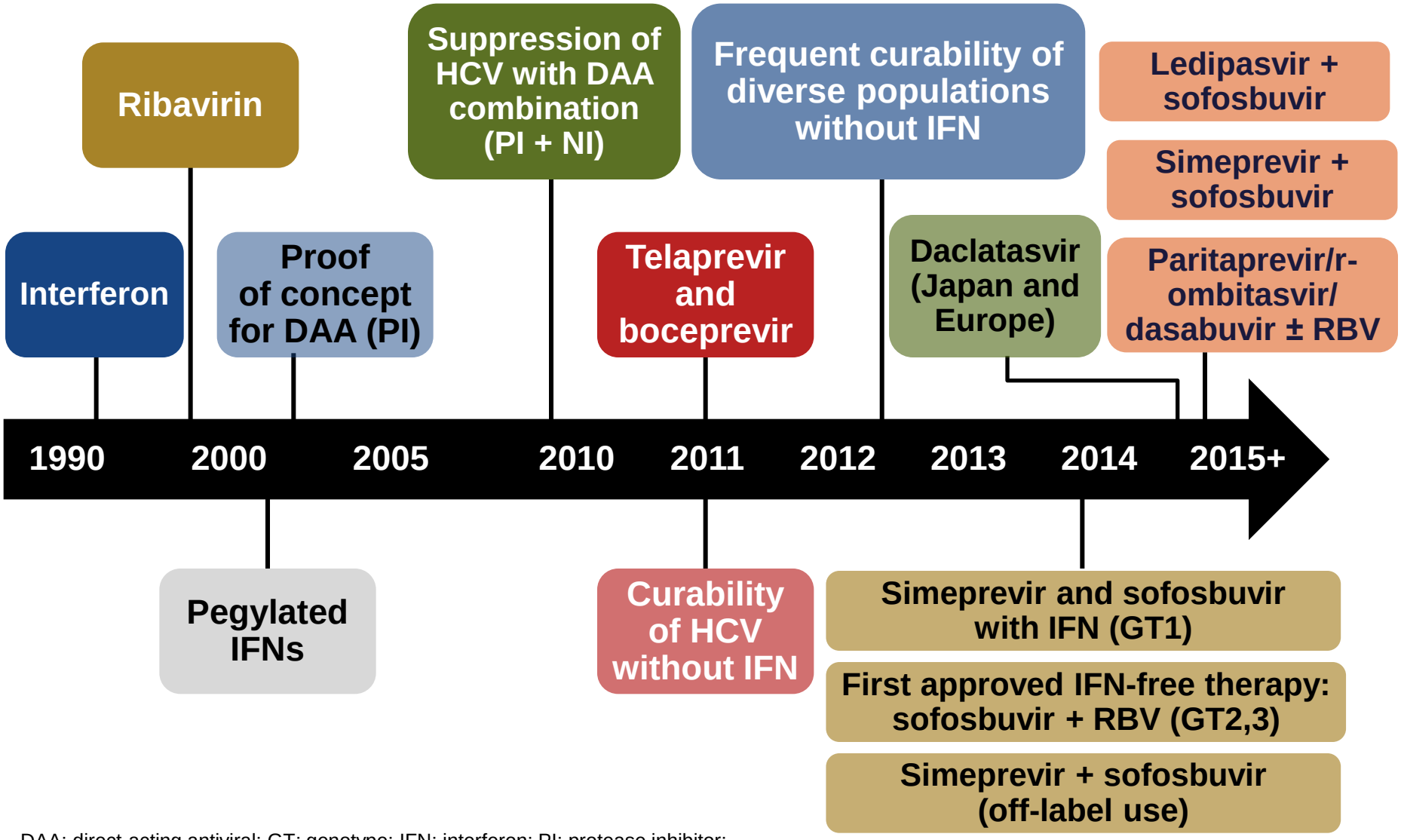
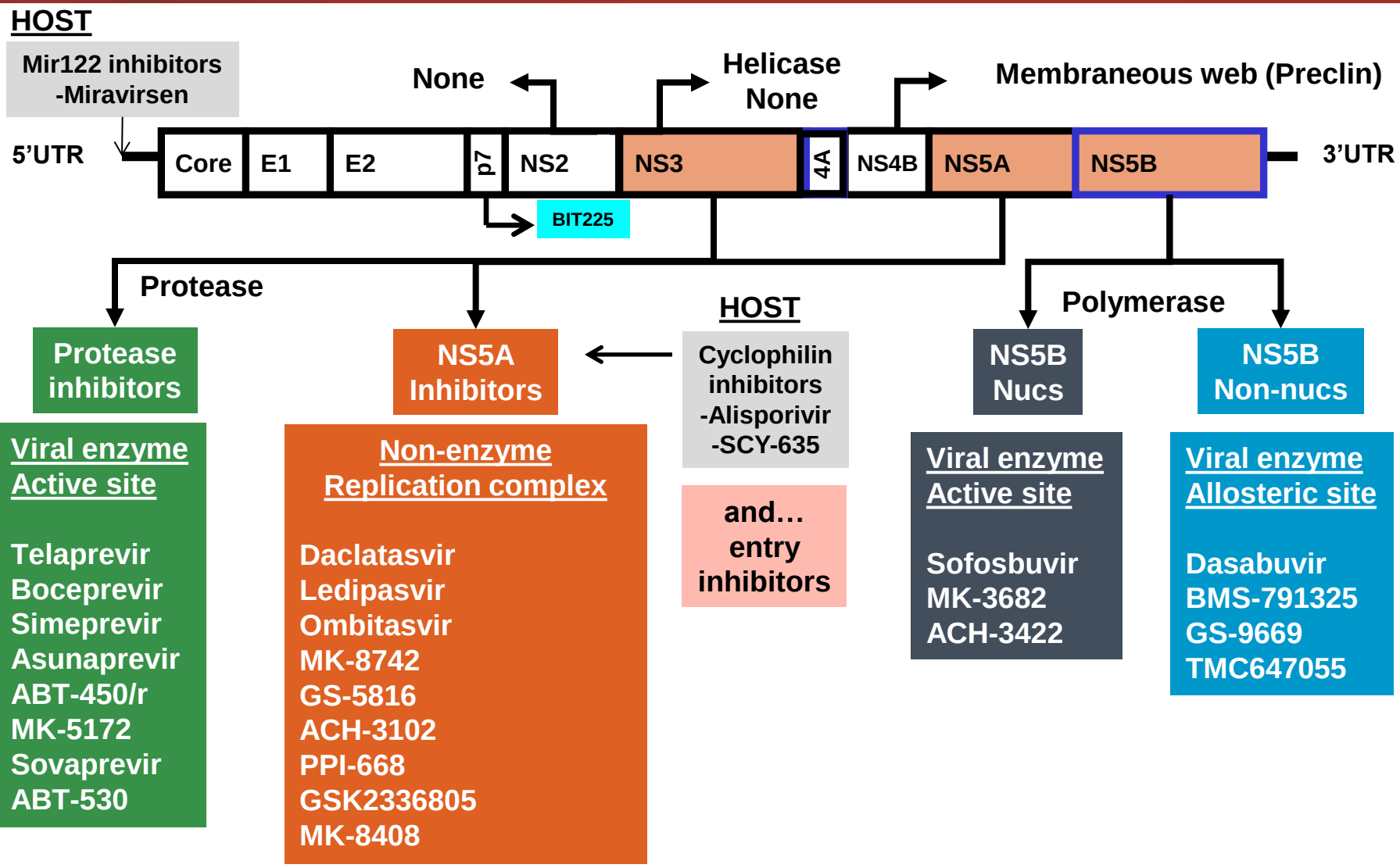
Future HCV Treatments

Evolution of HCV Therapy



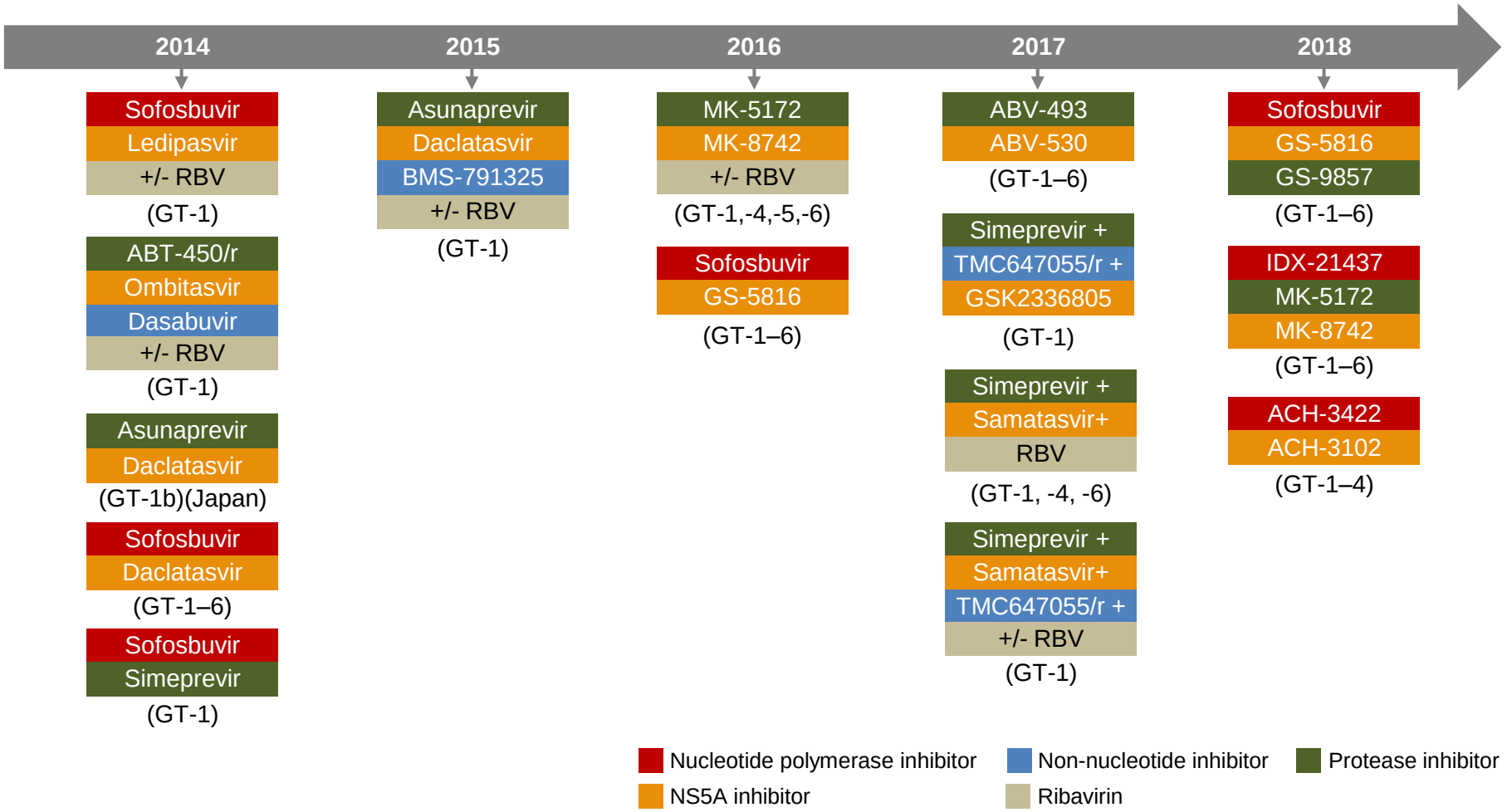
DAA: direct-acting antiviral; GT: genotype; IFN: interferon; PI: protease inhibitor; NI: nucleoside/nucleotide inhibitor; RBV: ribavirin; r: ritonavir.

Multiple Validated Drug Targets



Adapted from Dr John Link, adapted with permission
Not all-inclusive

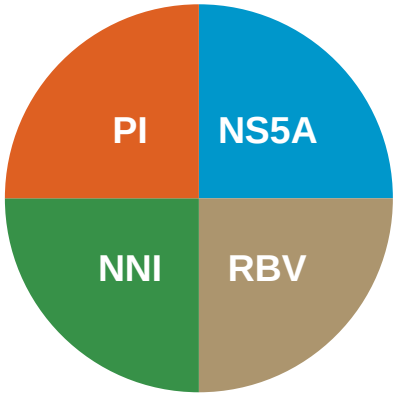
HCV Therapy: 2014 and Beyond

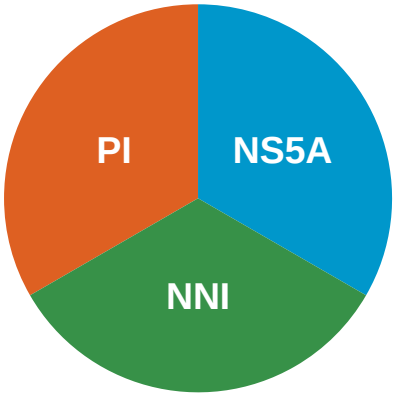


Sources: ClinicalTrials.gov, Competitive Monitoring, natap.org, clinicaloptions.com, corporate websites

Oral Regimens With ≥90% SVR for GT1 Patients

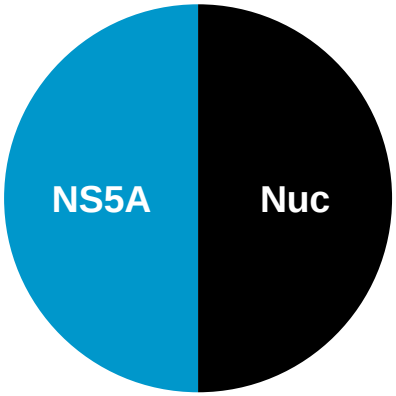
No nucleotide



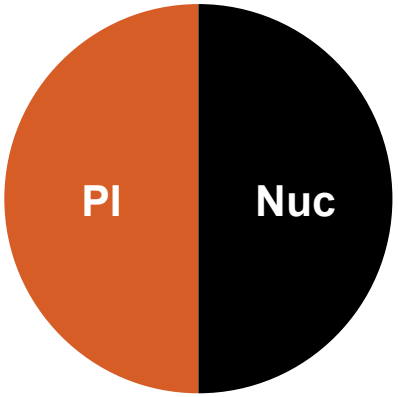


± RBV

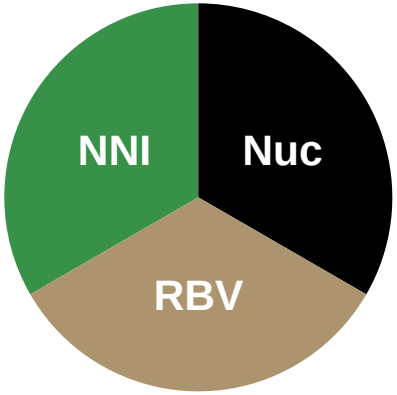
Nucleotide



± RBV



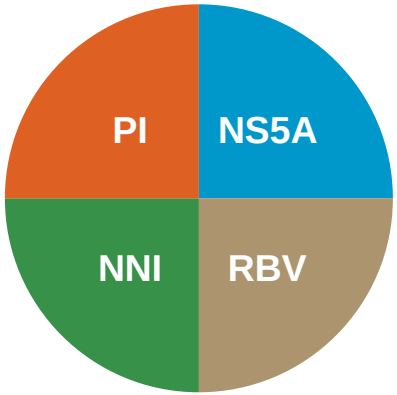
± RBV

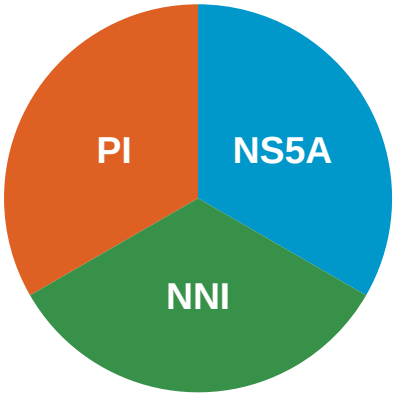


*'second generation'
NNI, non-nucleoside inhibitor; Nuc, nucleotide inhibitor.;PI, protease inhibitor

Oral Regimens With ≥90% SVR for GT1 Patients

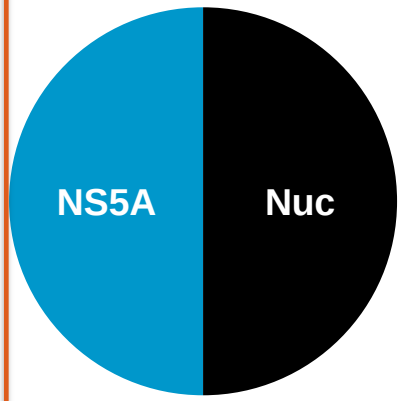
No nucleotide



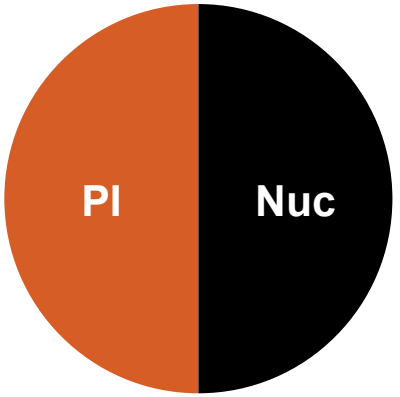


± RBV

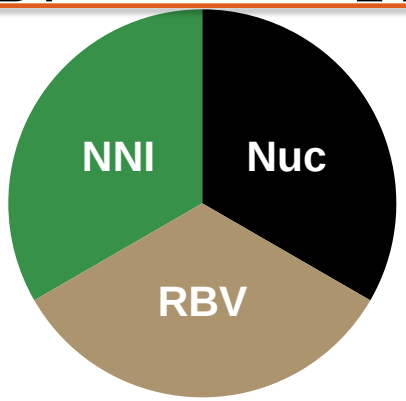
Nucleotide



± RBV



± RBV



*'second generation'
NNI, non-nucleoside inhibitor; Nuc, nucleotide inhibitor.;PI, protease inhibitor

The ION Studies Show That We Don't Need Ribavirin

Right?

Well…….

LDV/SOF + RBV 12 Weeks vs LDV/SOF 24 Weeks

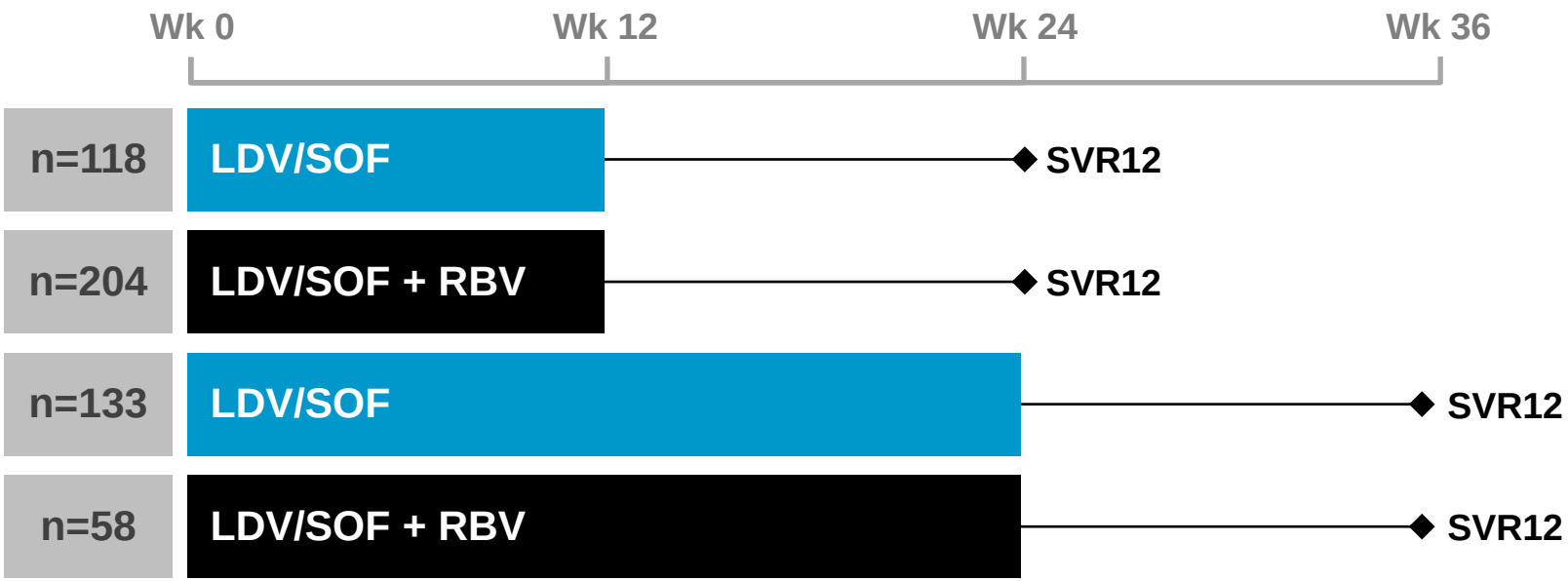
Cirrhotic G1 Patients with PR/PI Failure

- Double-blind: LDV/SOF with RBV placebo for 24 wks or matching placebo for 12 weeks followed by LDV/SOF + RBV for 12 wks
- 18% platelets <100,000 /uL, 13% albumin < 3.5 g/dL

	LDV/SOF+RBV 12 weeks (n=77)	LDV/SOF 24 weeks (n=77)	Total (n=154)
SVR12, n(%)	74 (96%)	75 (97%)	149(97%)
Discontinuations on active treatment, %	0	0	0
Relapse, n(%)	3(4%)	2(3%)	5(3%)

Bourliere M et al, AASLD 2014, LB-6

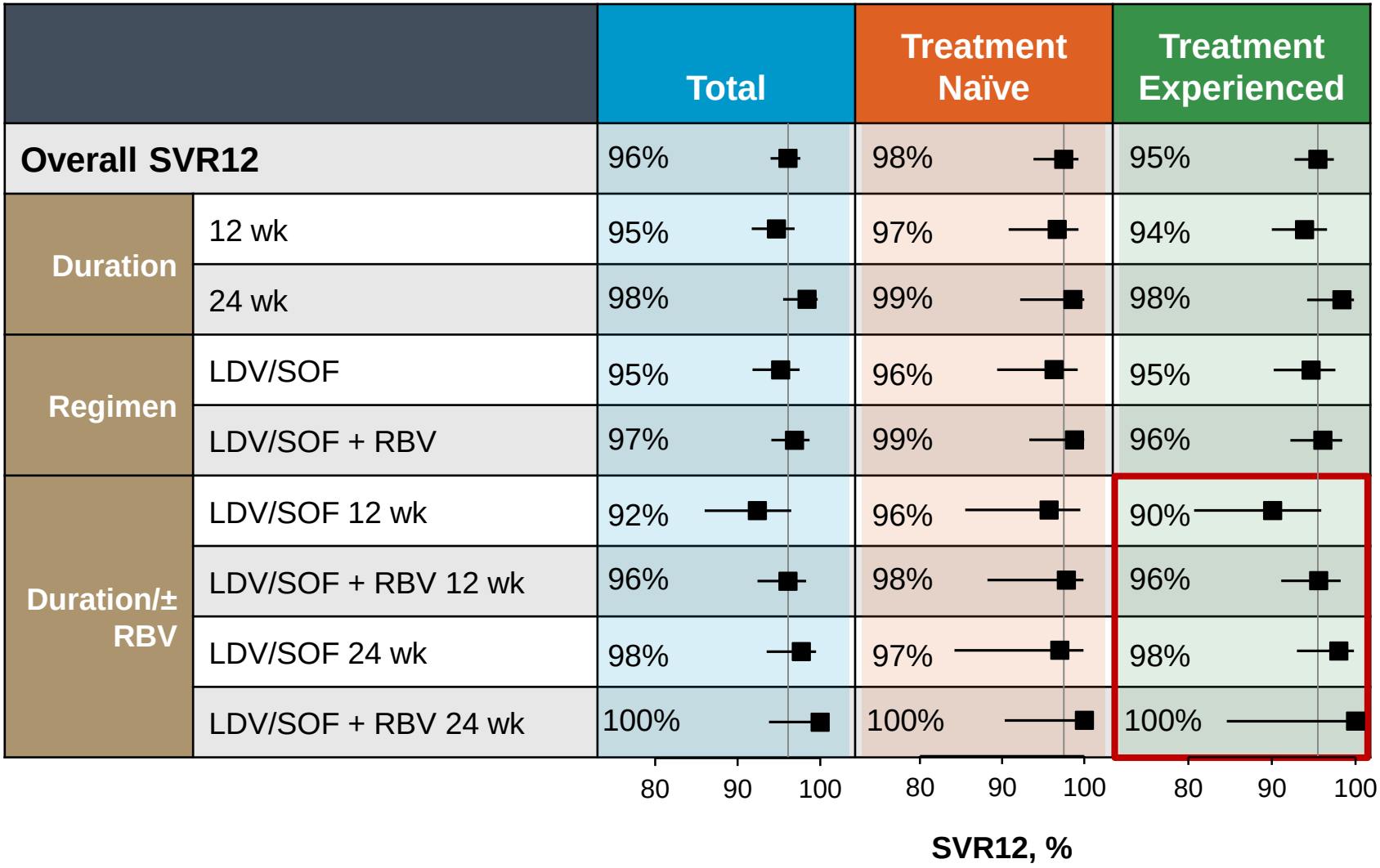
Integrated Analysis of Cirrhotic Patients From the Ledipasvir/Sofosbuvir Development Program



- 513 patients with HCV GT 1, compensated cirrhosis
- Pooled data from Phase 2 and 3 LDV/SOF ± RBV studies
  - LONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, SIRIUS
- Primary efficacy endpoint: SVR12

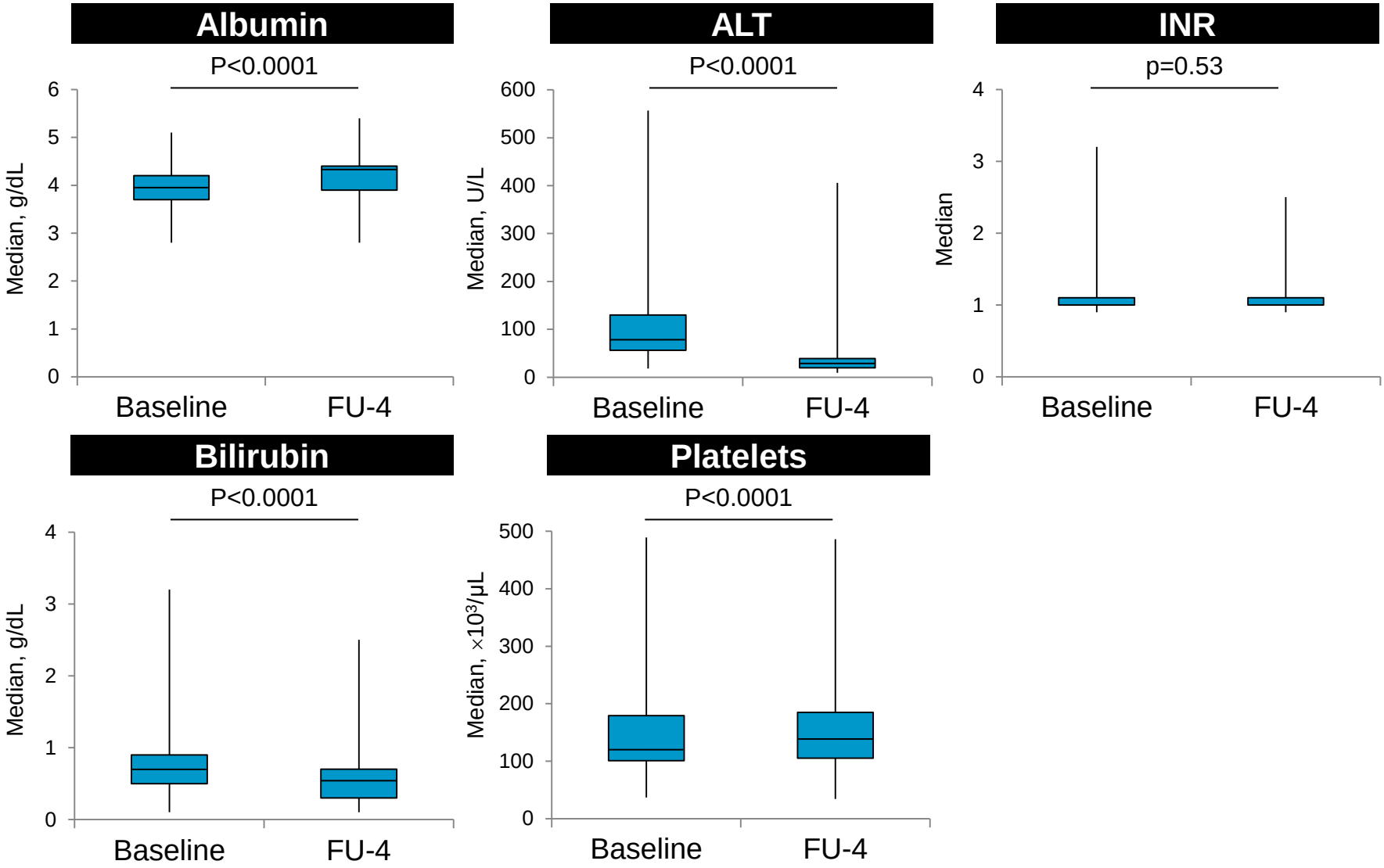
Bourliere M et al, AASLD 2014

Integrated Analysis: SVR12 by Treatment Regimen



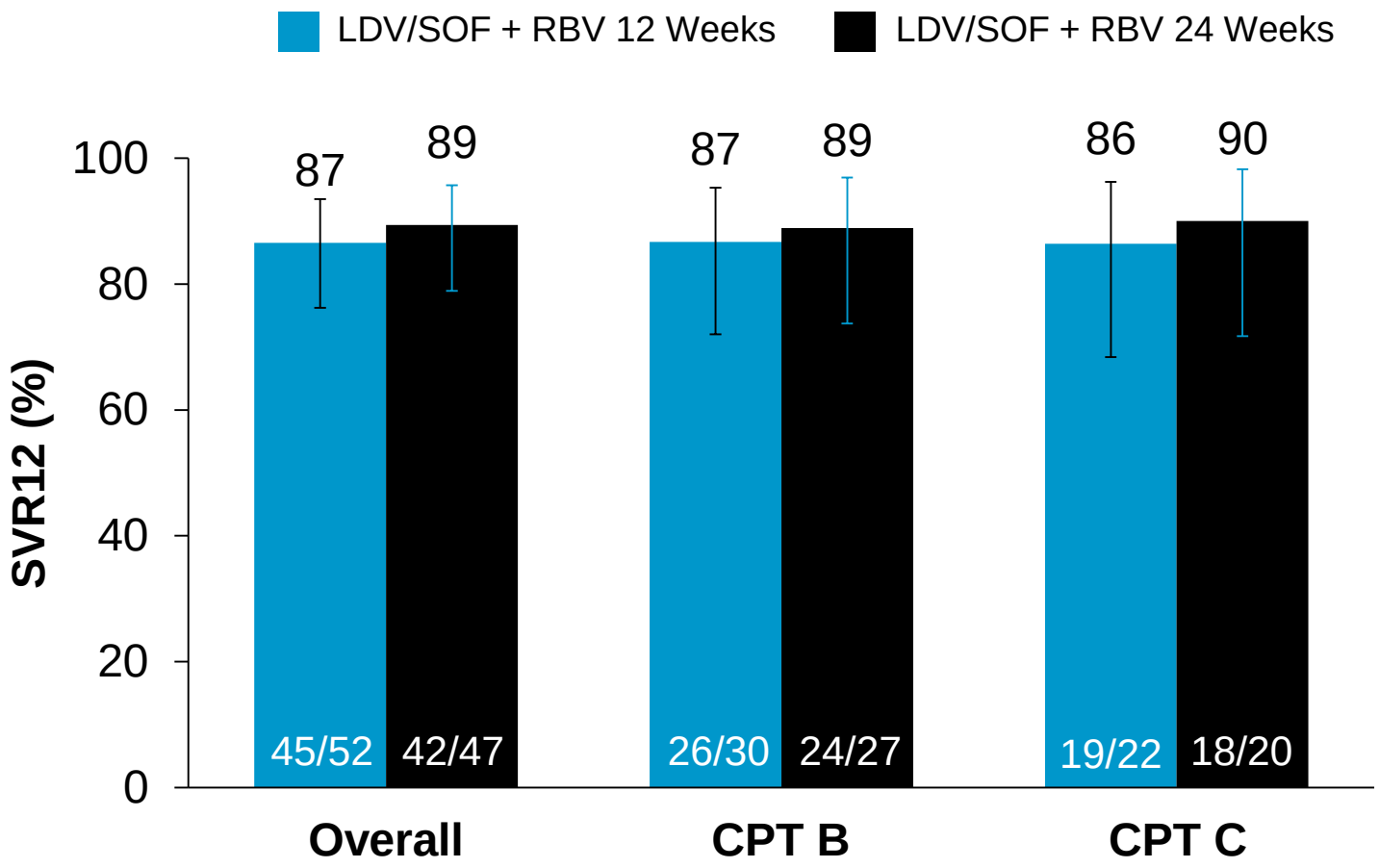
Bourliere M et al, AASLD 2014

Integrated Analysis: Response of Laboratory Parameters



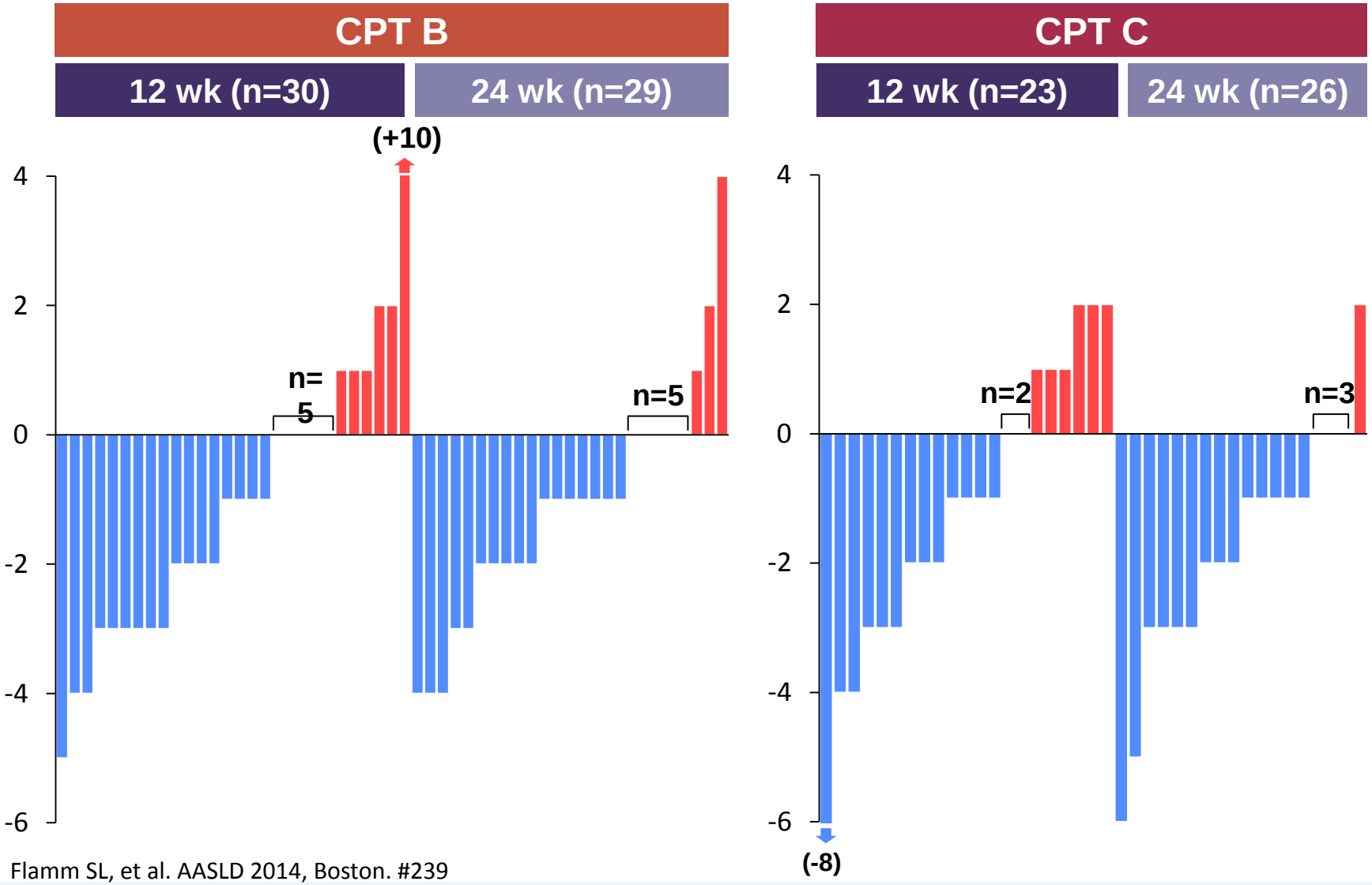
Bourliere M et al, AASLD 2014

Ledipasvir + Sofosbuvir + Ribavirin in Decompensated Cirrhotics: Genotypes 1 and 4, Childs-Pugh B and C



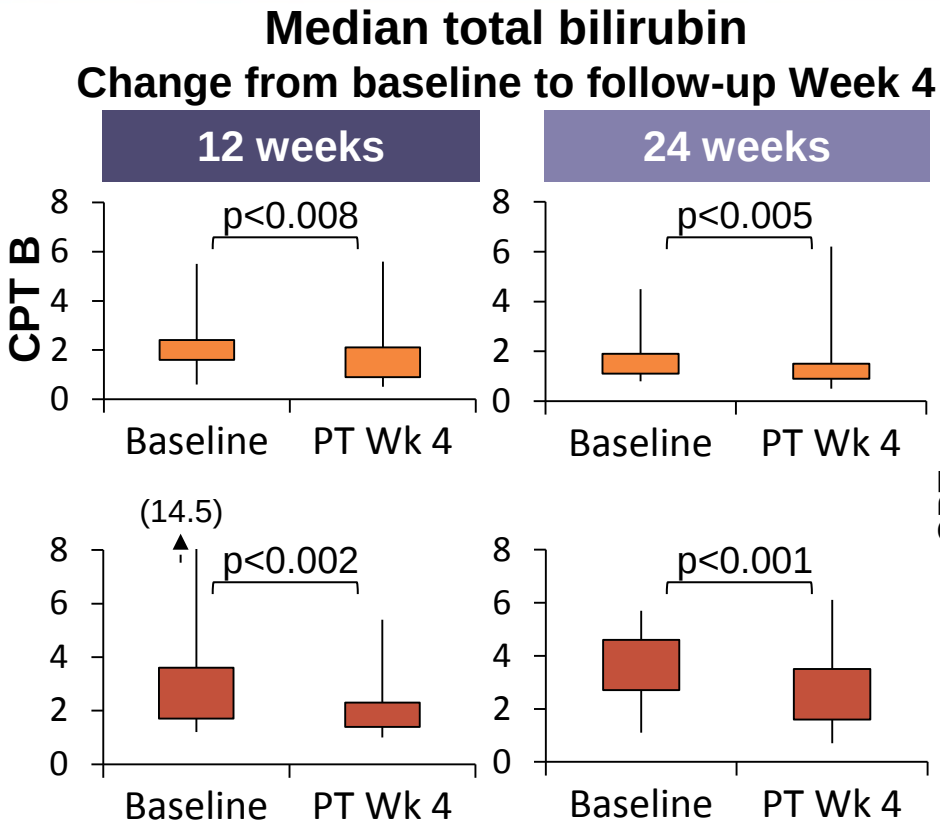
6 subjects (2 CPT B/24 Wk, 1 CPT C/12 Wk and 3 CPT C/24 Wk) excluded (transplant on study);
3 subjects CPT C/24 Wk have not reached SVR12.
Error bars represent 90% confidence intervals.
Flamm S et al, AASLD 2014

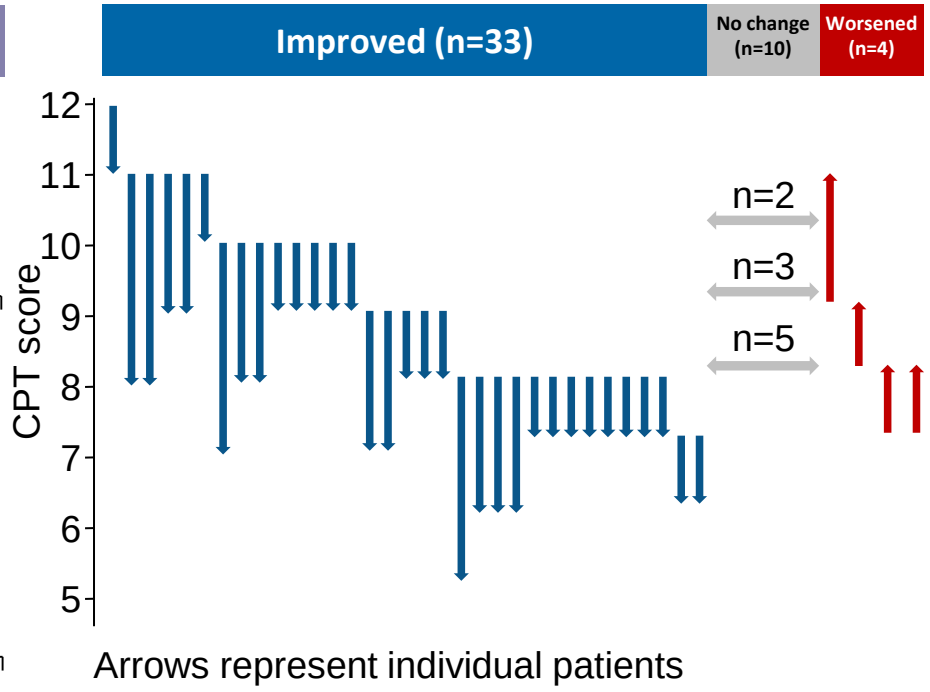
Ledipasvir + Sofosbuvir + Ribavirin in Decompensated Cirrhotics: Genotypes 1 and 4, Childs-Pugh B and C



Flamm SL, et al. AASLD 2014, Boston. #239

Ledipasvir + Sofosbuvir + Ribavirin in Decompensated Cirrhotics: Genotypes 1 and 4, Childs-Pugh B and C

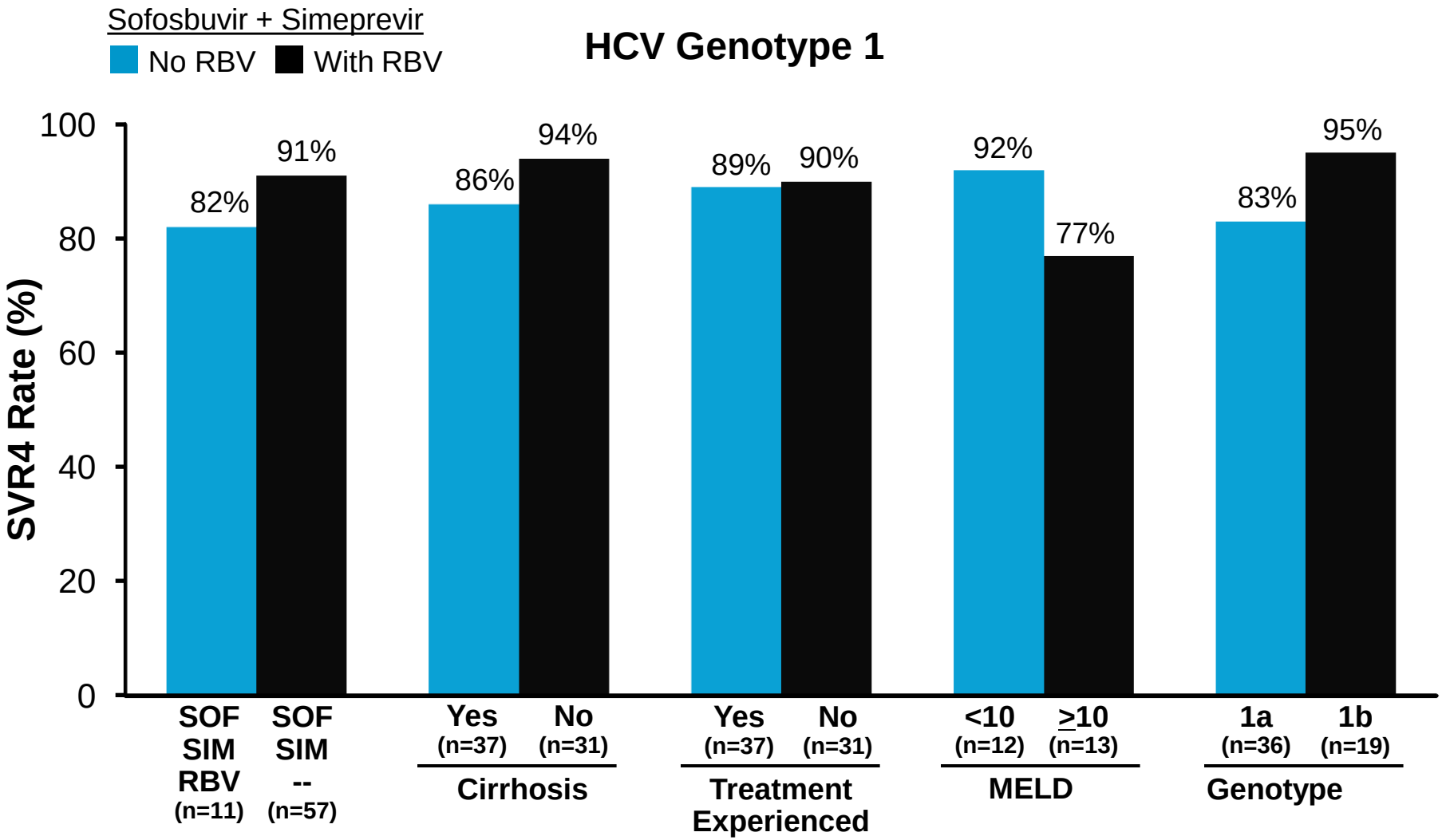




Treatment of Decompensated Cirrhotics: Is There a Point at Which HCV Cure is Too Little, Too Late?

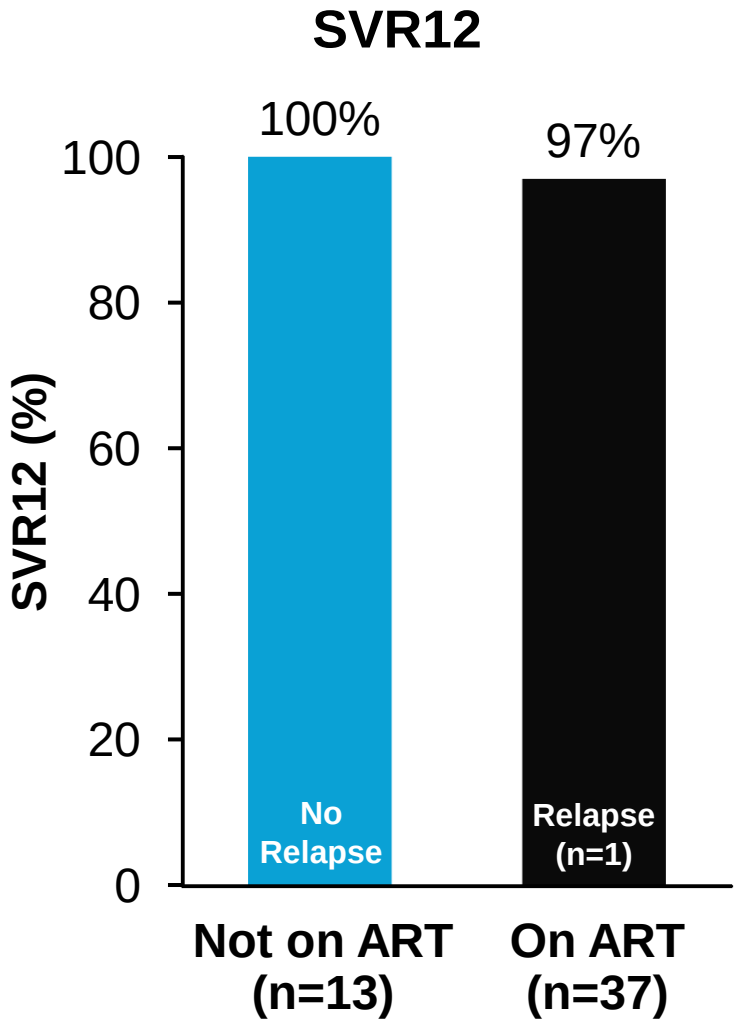
- Definable by:
  - MELD score?
  - Intractable ascites?
  - Recurrent encephalopathy?
- Better to wait till after transplant to treat?

HCV TARGET Study (Interim Results): Crude SVR4 Rates With Sofosbuvir + Simeprevir ± RBV in Recurrent HCV Post-Liver Transplantation



Brown RS, et al. *Hepatology*. 2014;60(suppl 1). Abstract LB-4.

ERADICATE Trial: Ledipasvir/Sofosbuvir in HCV Genotype 1 Patients With HIV Coinfection

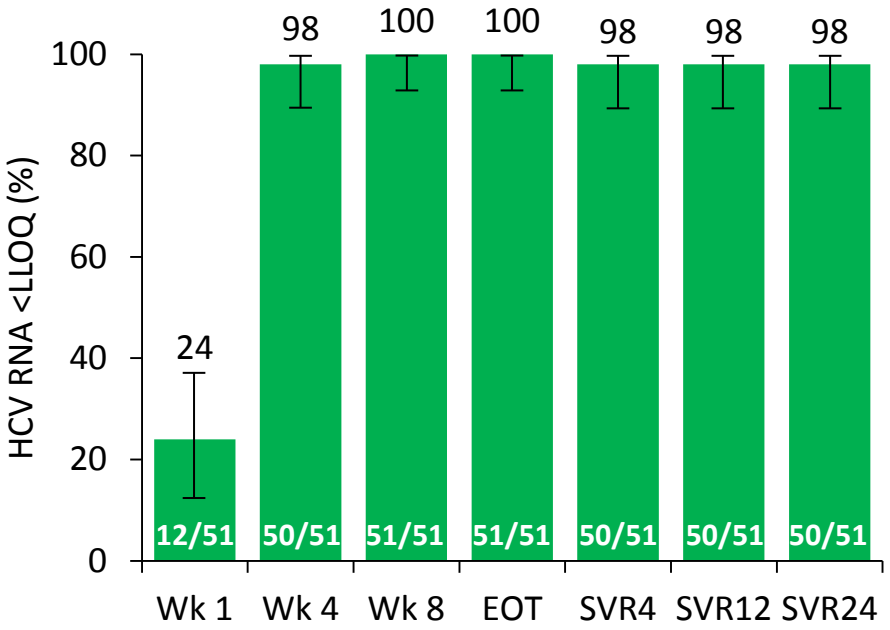


- No discontinuations due to adverse events
- Most common adverse events
  - Fatigue, insomnia, headache, nausea

Townsend KS, et al. *Hepatology*. 2014;60(suppl 1):240A-241A. Abstract 84.

Retreatment of Patients Who Failed Prior SOF-Based Regimens With SOF+LDV+RBV for 12 Weeks

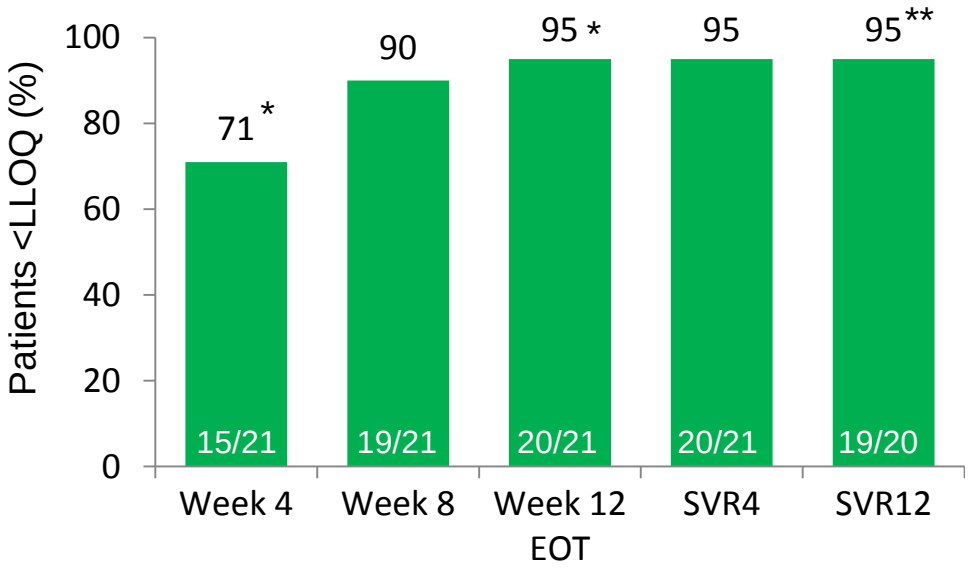
- 51 G1 SOF failures treated with 12 weeks SOF/LDV/RBV



- 1 relapser was incorrectly genotyped as G1a by LIPA but on sequencing was confirmed as G3a
- NS5A: 12% RAV, 6/6 achieved SVR

Wyles DL, et al. AASLD 2014, Boston. #235

Sofosbuvir + Ledipasvir for Genotype 4: NIAID SYNERGY Trial

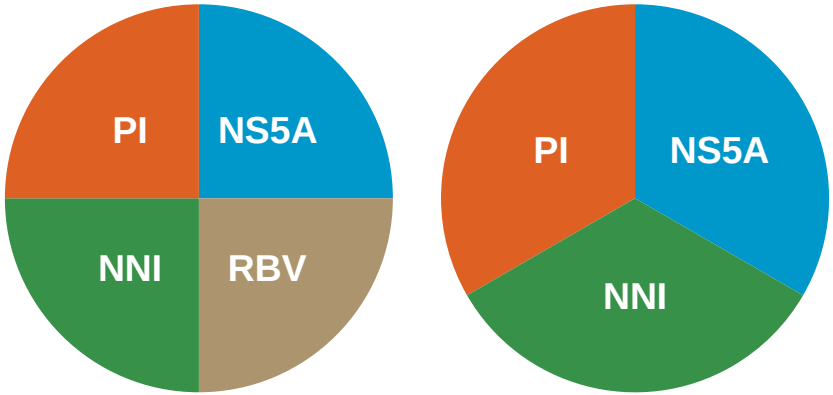


*1 dropout, counted as failure in ITT ** 1 pending

Kapoor R, et al. AASLD 2014, Boston. #240

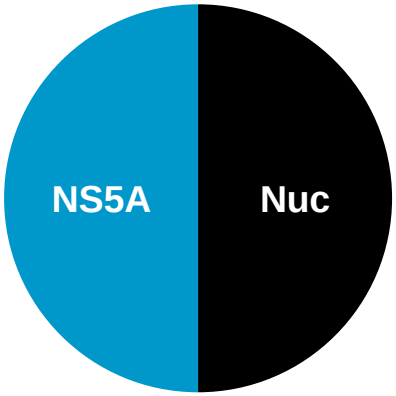
Oral Regimens With ≥90% SVR for GT1 Patients

No nucleotide

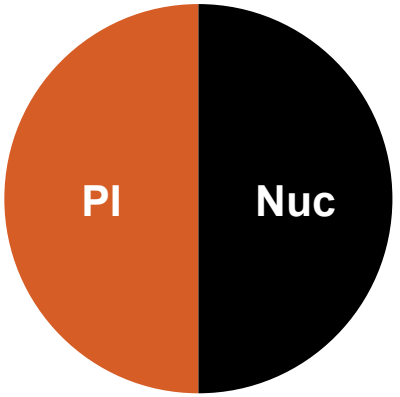


± RBV

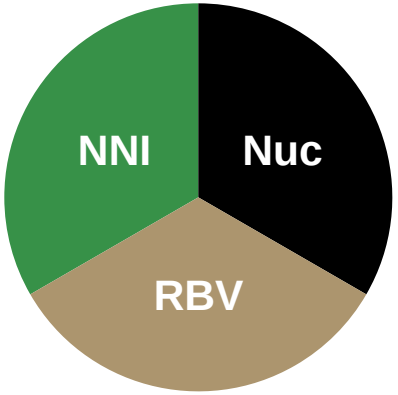
Nucleotide



± RBV

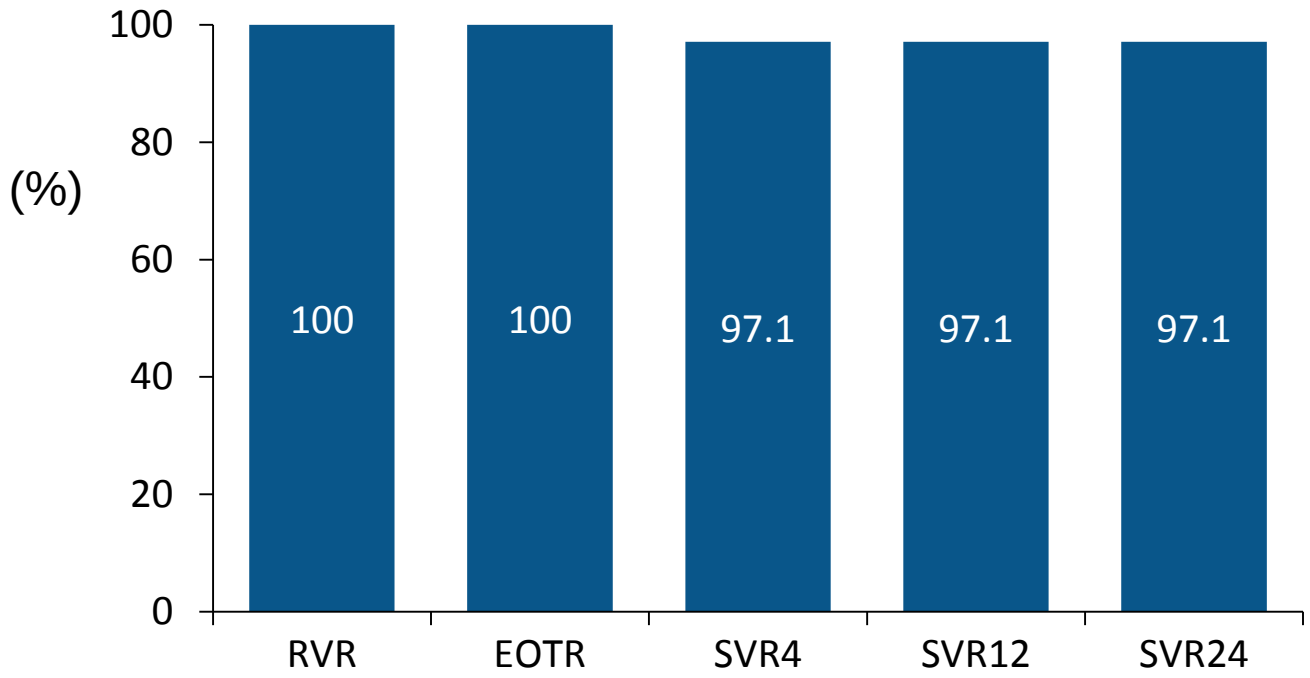


± RBV

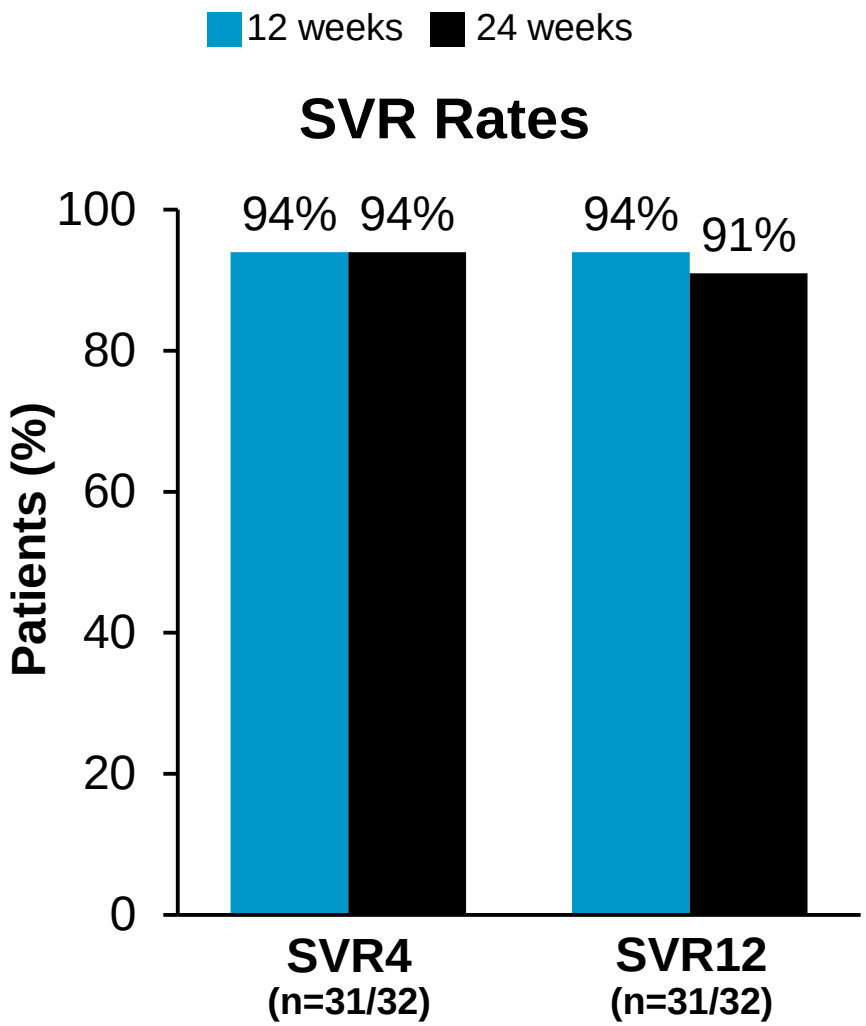


*'second generation'
NNI, non-nucleoside inhibitor; Nuc, nucleotide inhibitor.;PI, protease inhibitor

ABT-450/r/Ombitasvir + Dasabuvir + RBV 24 Weeks in Post-OLT with F0-2



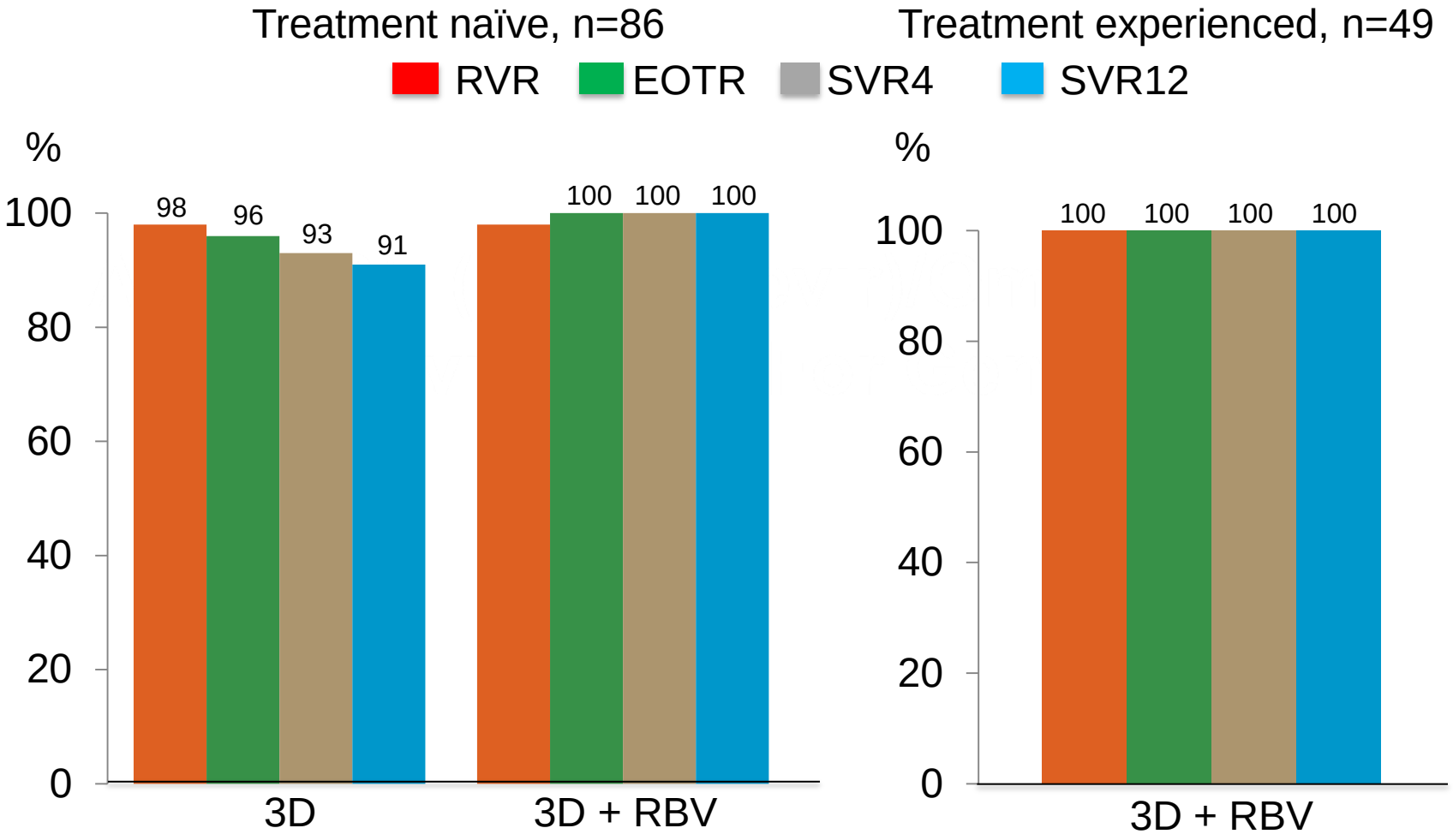
TURQUOISE-I: ABT-450/r/Ombitasvir + Dasabuvir + RBV in HCV Genotype 1 With HIV Co-Infection



Indirect hyperbilirubinemia seen mostly with atazanavir

Wyles DL, et al. *Hepatology*. 2014;60(suppl 1):1136A-1137A. Abstract 1939.

ABT-450/r (Paritaprevir)/Ombitasvir + Dasabuvir ± RBV For Genotype 4



Pol S, et al. AASLD 2014, Boston. #1928

PK and Safety Of ABT-450/R, Ombitasvir ± Dasabuvir in Subjects With Mild, Moderate, and Severe Renal Impairment Compared With Subjects With Normal Renal Function

- Phase 1 PK study in patients with renal impairment without HCV (4x 6 subjects)

G1a
G1b

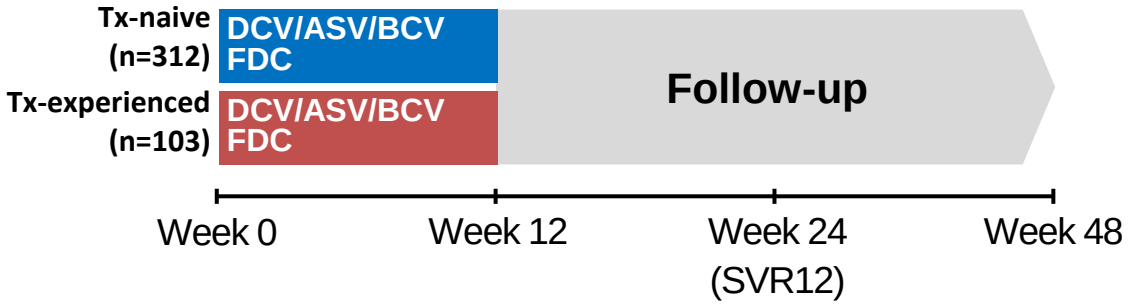
Renal function	Normal	Mild	Mod	Severe	Period 1 (7 days)	Washout 14 days	Period 2 (7 days)
Creat Cl (mL/min)	≥90	60–89	30–59	15–29	3D regimen		2D regimen

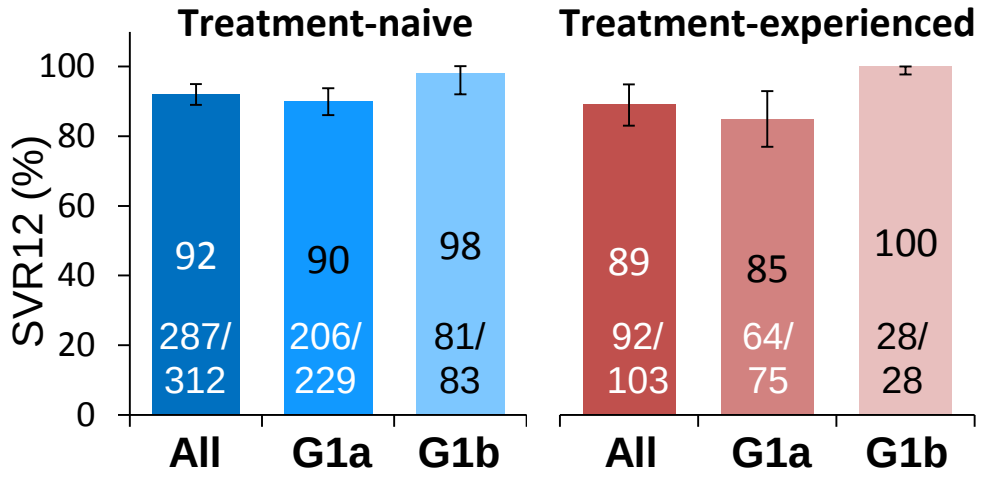
Changes in exposure in renal dysfunction, AUC (ng*h/ml)

	Renal dysfunction					
	Mild		Moderate		Severe	
	2-DAA	3-DAA	2-DAA	3-DAA	2-DAA	3-DAA
Ombitasvir	same	same	same	same	same	same
ABT-450	11%↑	20%↑	20%↑	37%↑	25%↑	50%↑
RTV	40%↑	42%↑	76%↑	80%↑	108%↑	114%↑
Dasabuvir	-	20%↑	-	37%↑	-	50%↑

Khatri A, et al. AASLD 2014, Boston. #238

Daclatasvir+Asunaprevir+Beclabuvir For Genotype 1: Noncirrhotic (UNITY-1)

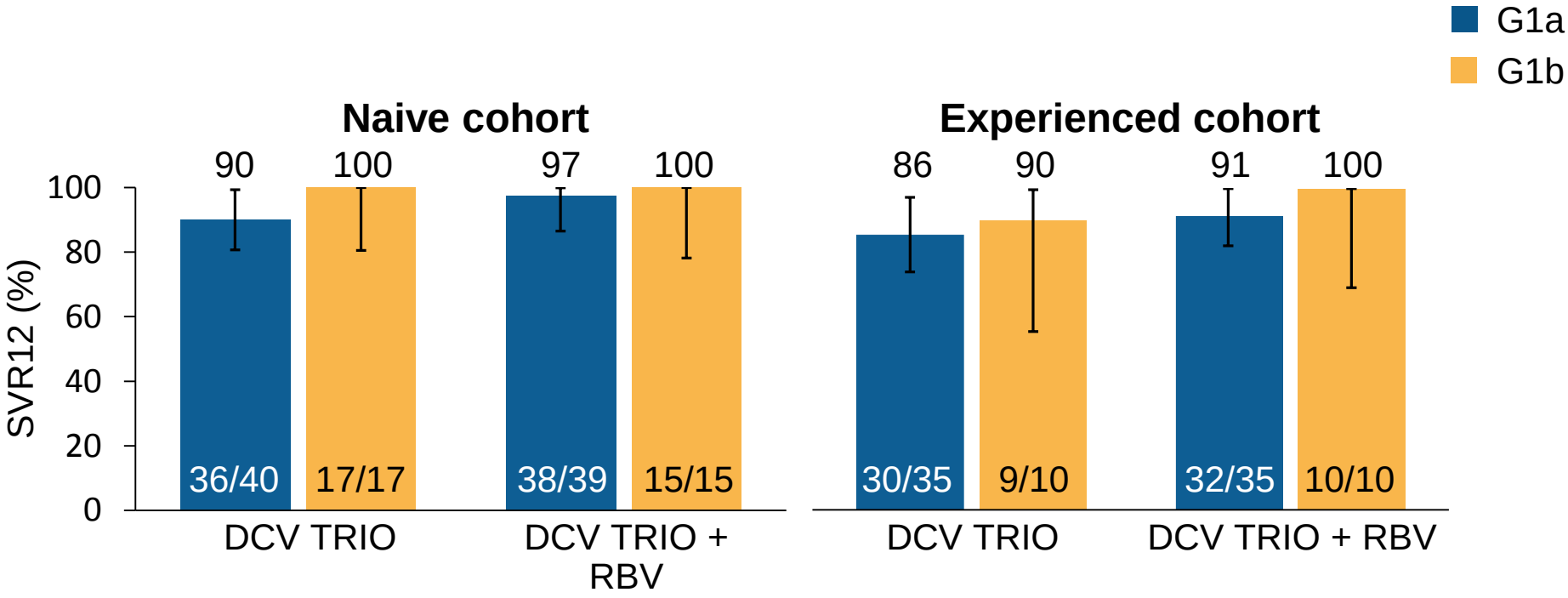




Breakthrough	2%	2%
Relapse	5%	6%

Poordad F, et al. AASLD 2014, Boston. #LB-7

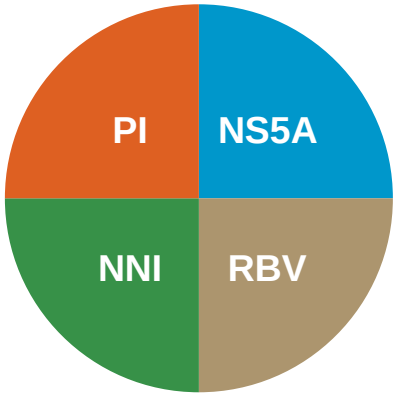
Daclatasvir+Asunaprevir+Beclabuvir + RBV for Genotype 1 Cirrhosis (UNITY-2)

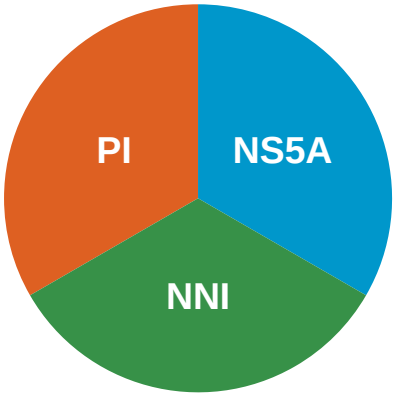


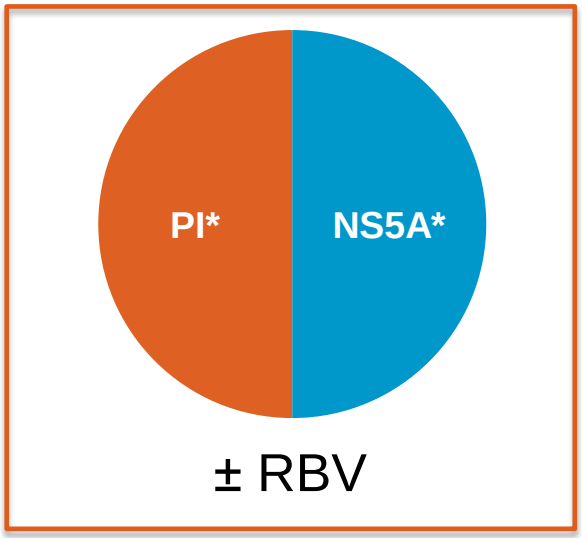
Poordad F, et al. AASLD 2014, Boston. #LB-7

Oral Regimens With ≥90% SVR for GT1 Patients

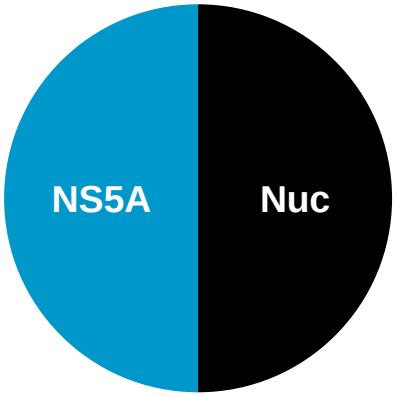
No nucleotide



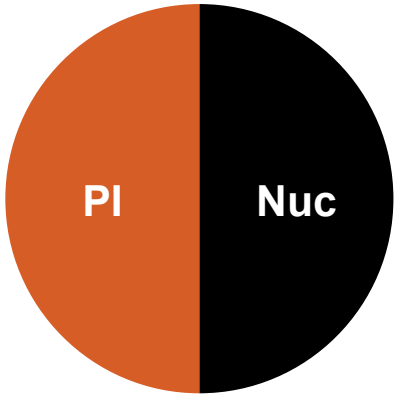




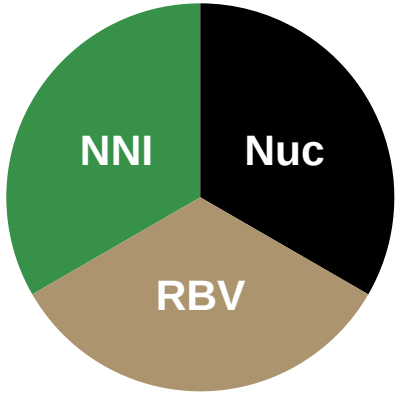
Nucleotide



± RBV



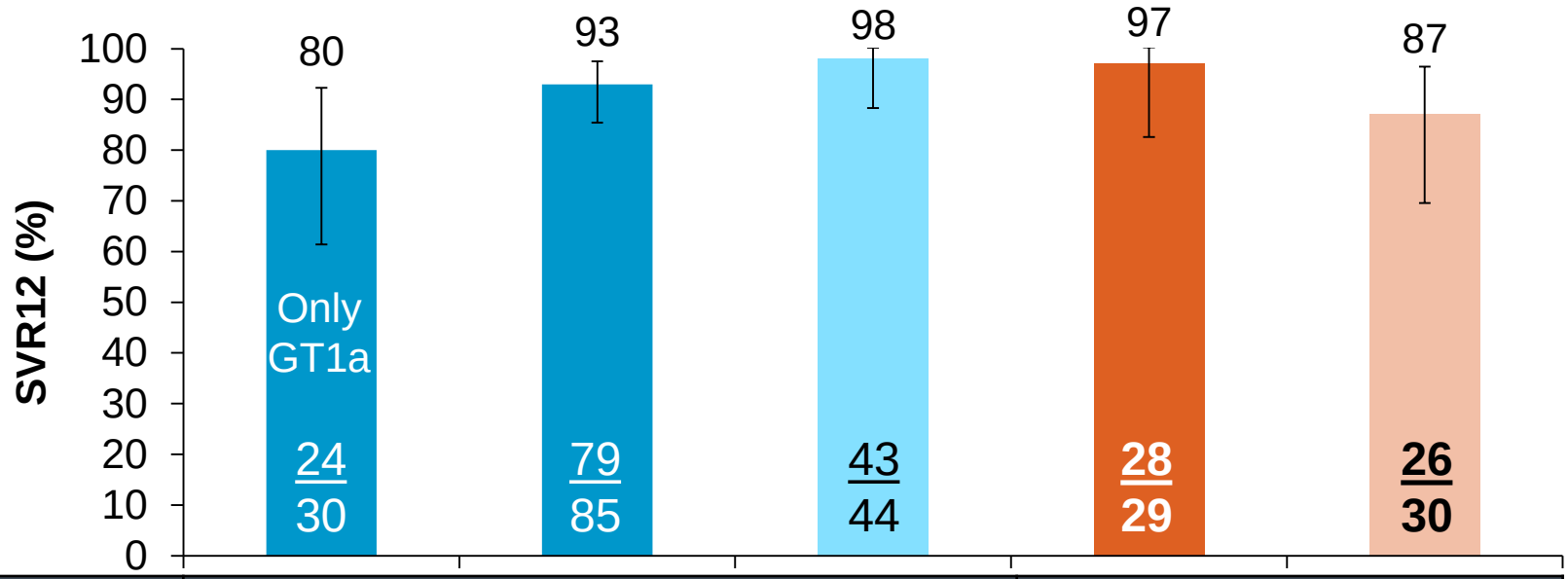
± RBV



*'second generation'

NNI, non-nucleoside inhibitor; Nuc, nucleotide inhibitor.;PI, protease inhibitor

MK-5172 + MK-8742 ± Ribavirin in HCV Mono-infected and HIV/HCV Co-infected Treatment-naïve, Non-cirrhotic Patients With HCV Gt1 Infection: The C-WORTHY Study



	HCV Mono-infected			HIV/HCV Co-infected	
Treatment Duration	8 weeks	12 weeks	12 weeks	12 weeks	12 weeks
RBV	+ RBV	+ RBV	No RBV	+ RBV	No RBV
LTFU* or Discontinued early not due to virologic failure	1	3	0	0	2
Breakthrough	0	1†	0	0	2
Relapse	5	2‡	1	1	0

* LTFU=Lost to follow-up

† Breakthrough was due to HCV GT2b (minor GT2b variant at baseline)

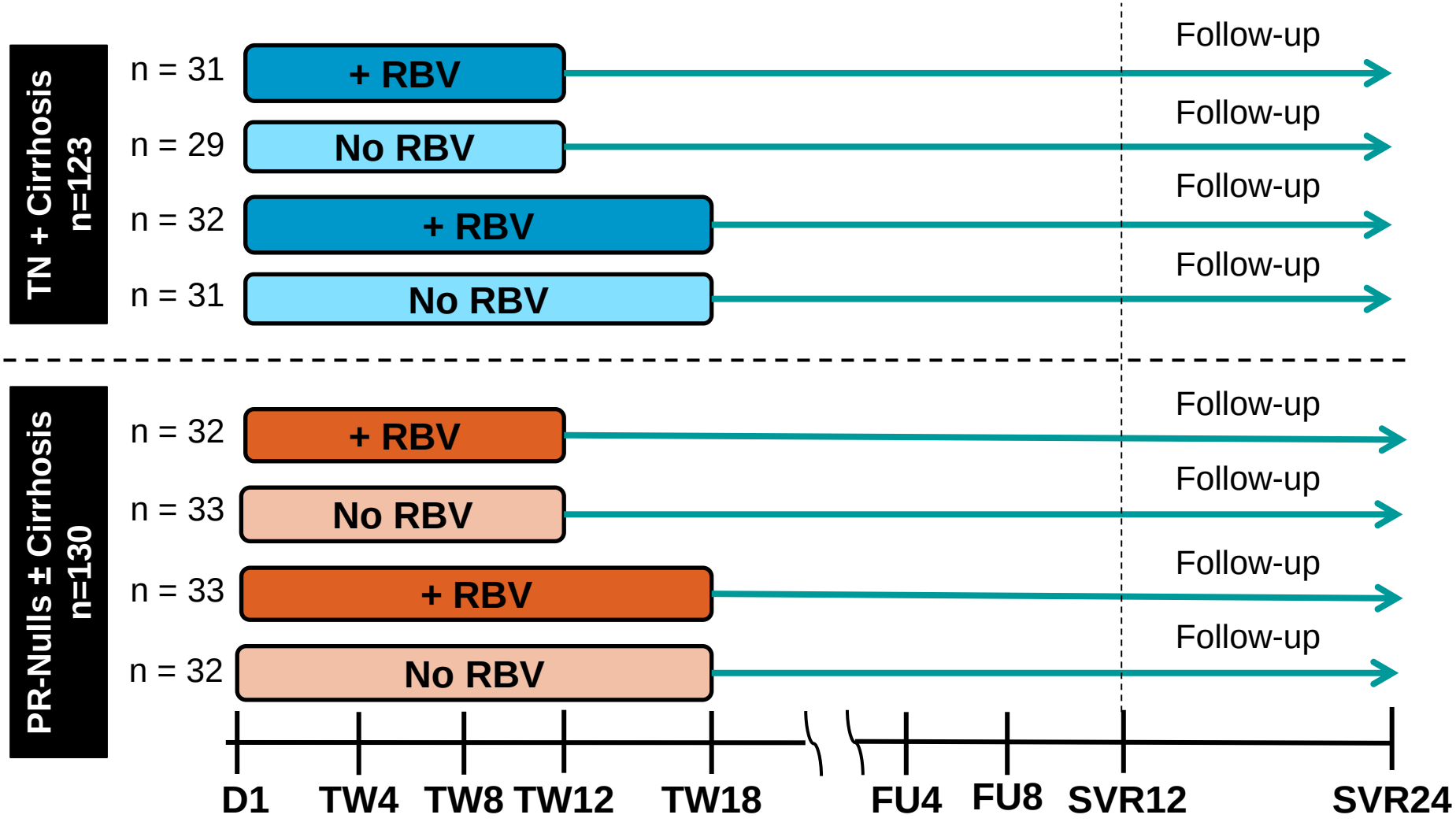
‡ One of the patients who relapsed did not receive grazoprevir and only received only elbasvir + RBV for the first month of treatment.

Adverse Event and Laboratory Safety Summary During Treatment

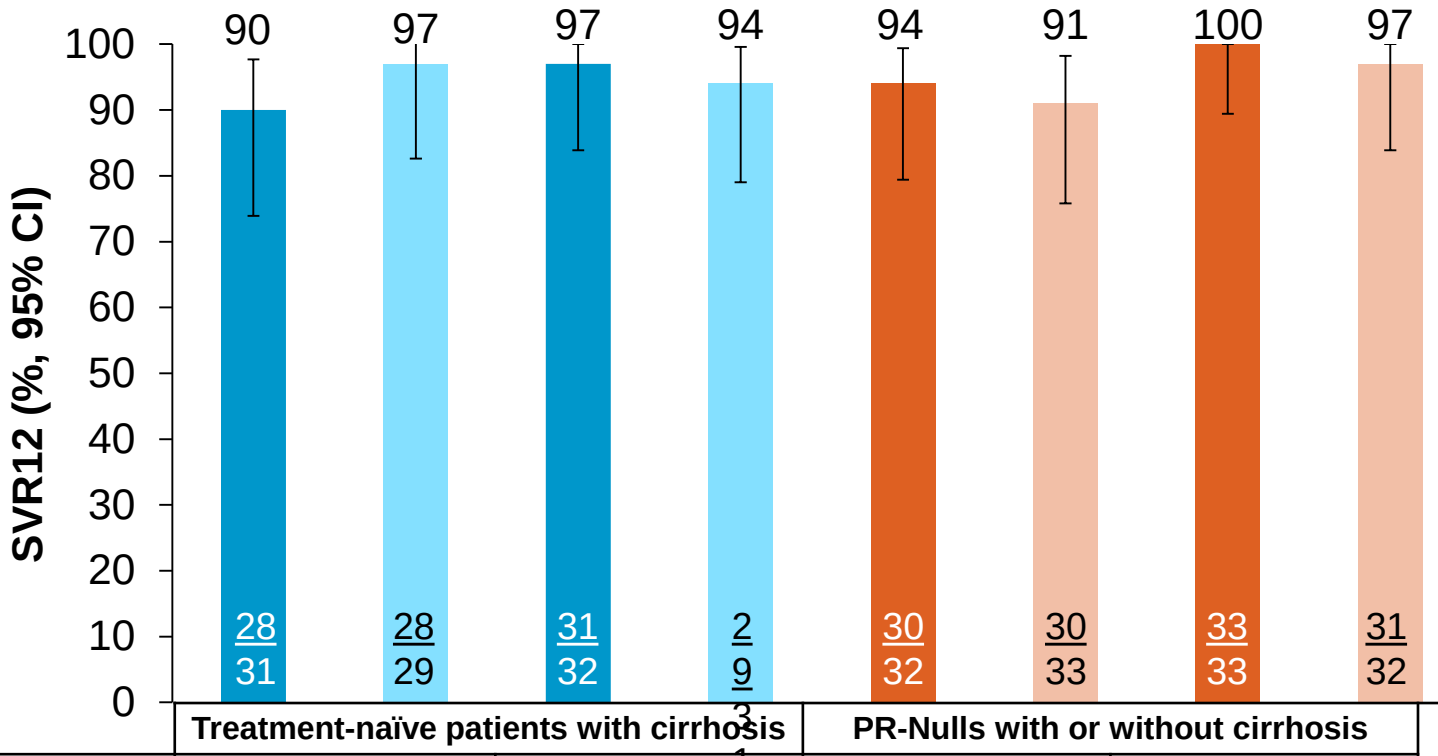
	HCV Mono-infected		HIV/HCV Co-infected	
	Grazoprevir + Elbasvir + RBV N=116*	Grazoprevir + Elbasvir (No RBV) N=43*	Grazoprevir + Elbasvir + RBV N=29	Grazoprevir + Elbasvir (No RBV) N=30
Serious adverse event	1† (1%)	0 (0%)	1‡ (3%)	1§ (3%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued due to AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hemoglobin <10 g/dL	10 (9%)	0 (0%)	1 (3%)	0 (0%)
Total bilirubin >5xULN	0 (0%)	0 (0%)	2 (7%)	0 (0%)
ALT/AST >2x to ≤5xULN after initial normalization	1 (1%)	1 (2%)	0 (0%)	1 (3%)
ALT/AST >5xULN after initial normalization	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Change in CD4 from baseline (cells/mm^3, mean (SD))	N/A	N/A	-47 (176)	52 (178)
HIV breakthrough	N/A	N/A	0 (0%)	0 (0%)

*One patient received RBV but was assigned the RBV-free arm. For the analysis of safety, this patient is in the + RBV group.
Serious AEs were: †nausea (related to study drug); ‡asthenia (related to study drug);
§Staphylococcal infection (not related to study drug)

C-WORTHY Study
Grazoprevir (100 mg QD) + Elbasvir (50 mg QD) ± RBV in Treatment Naïve Cirrhotics or Null Responders



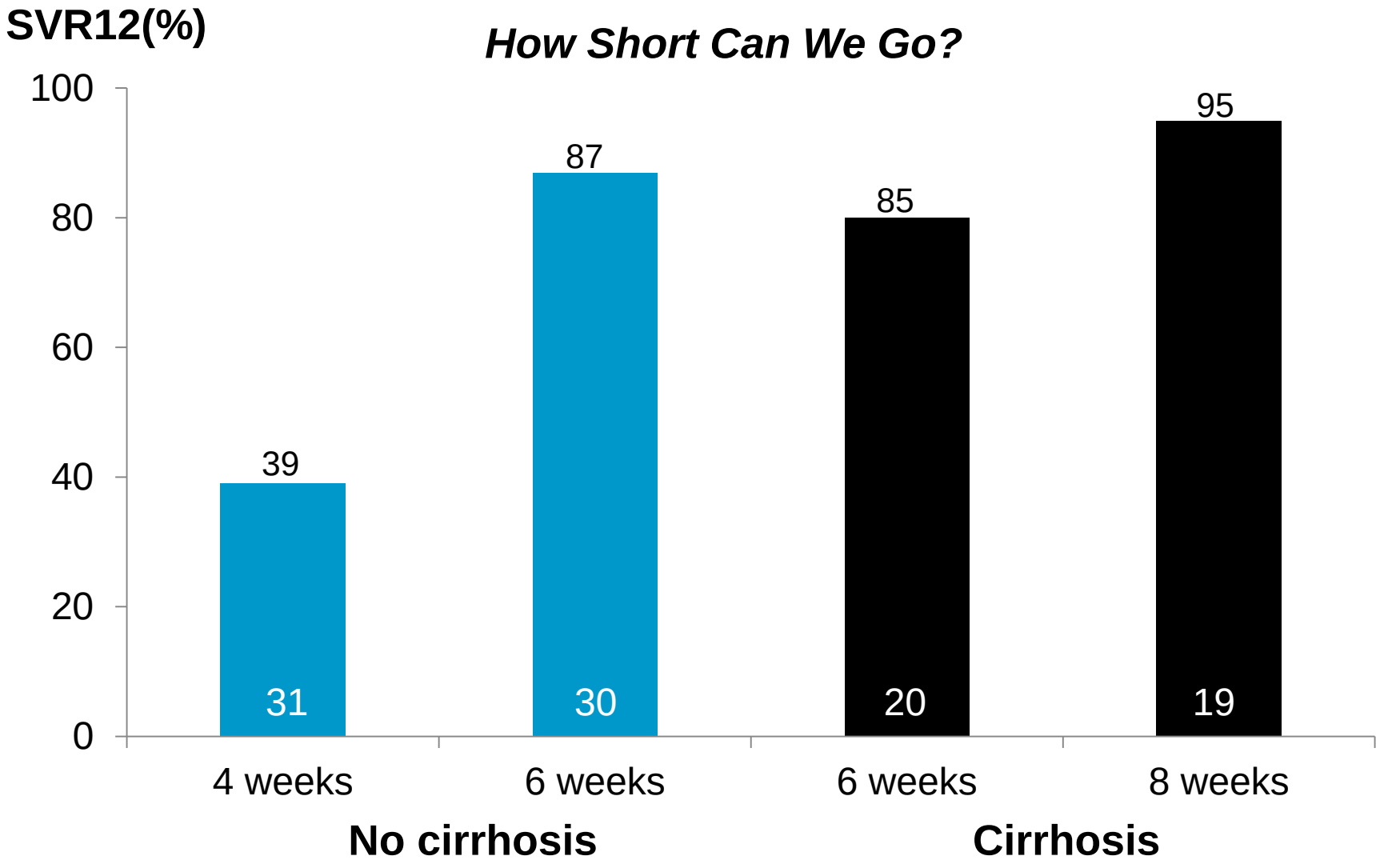
Primary Efficacy Results (% SVR12; ITT)
Null Responder Patients Cirrhosis



	Treatment-naïve patients with cirrhosis				PR-Nulls with or without cirrhosis				All patients
Treatment duration (weeks)	**12**		**18**		**12**		**18**		
RBV	+ RBV	No RBV	+ RBV	No RBV	+ RBV	No RBV	+ RBV	No RBV	
LTFU* or Discontinued early not due to virologic failure	0	0	1	0	2	0	0	0	3
Breakthrough	1	0	0	0	0	0	0	1	2
Relapse	2	1	0	2	0	3	0	0	8

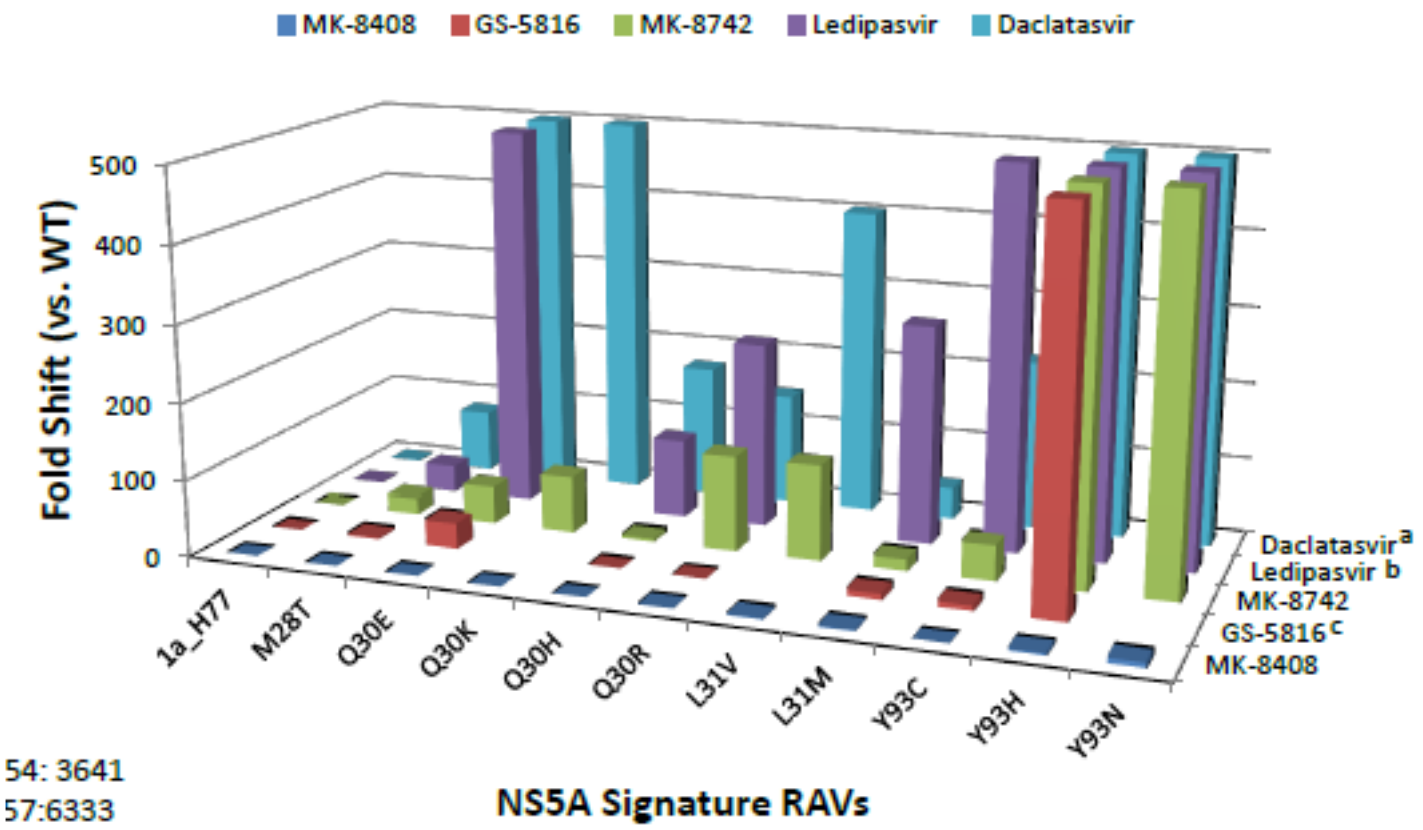
* LTFU=Lost to follow-up

C-SWIFT Study: Grazoprevir + Elbatasvir + Sofosbuvir for 4, 6, or 8 Weeks

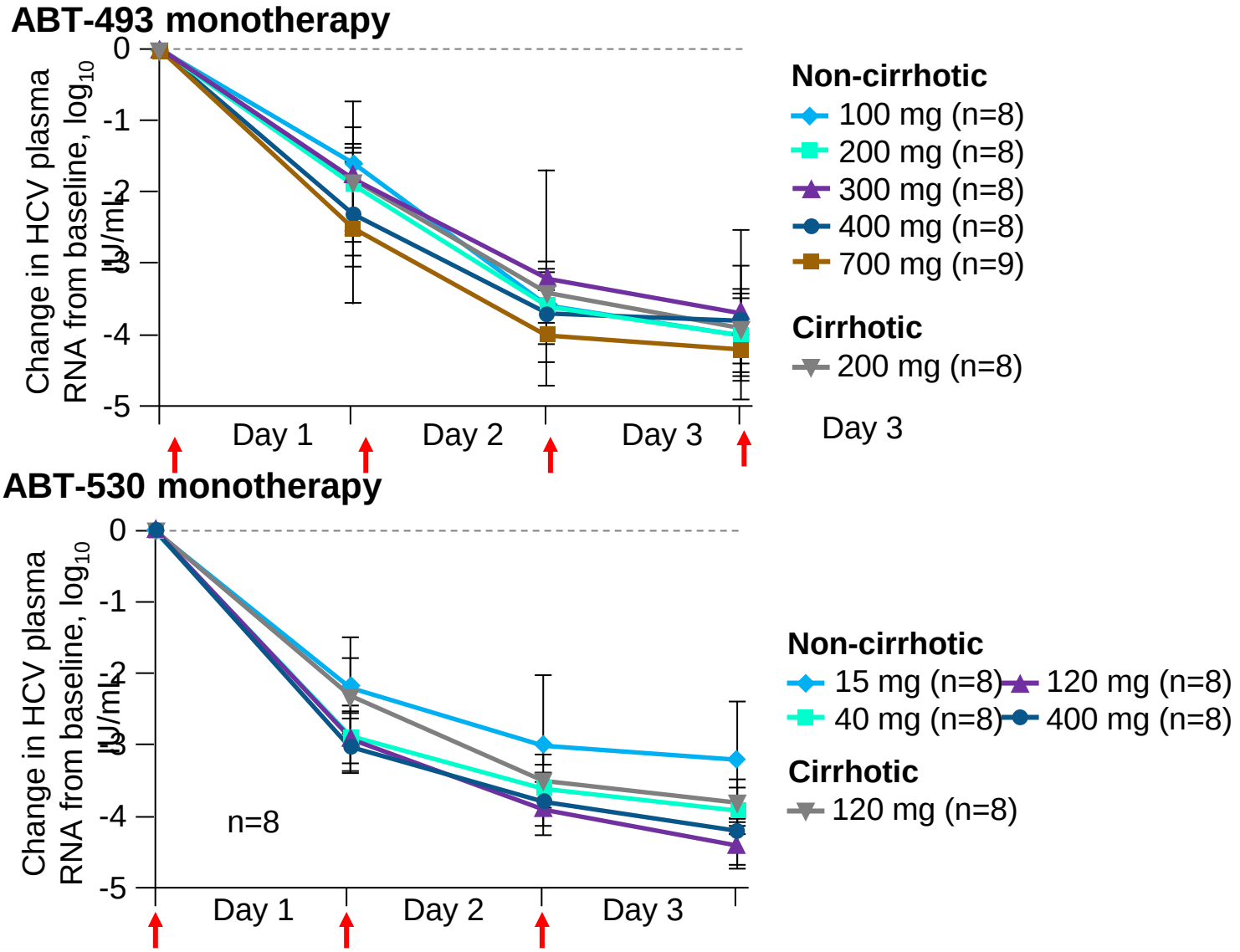


Lawitz E et al, AASLD 2014

MK-8408: A Second Generation NS5A Inhibitor



ABT-493 (Second generation PI) and ABT-530 (Second generation NS5A)



Lawitz E, et al. AASLD 2014, Boston. #1956

New DAA Regimens For Genotype 3

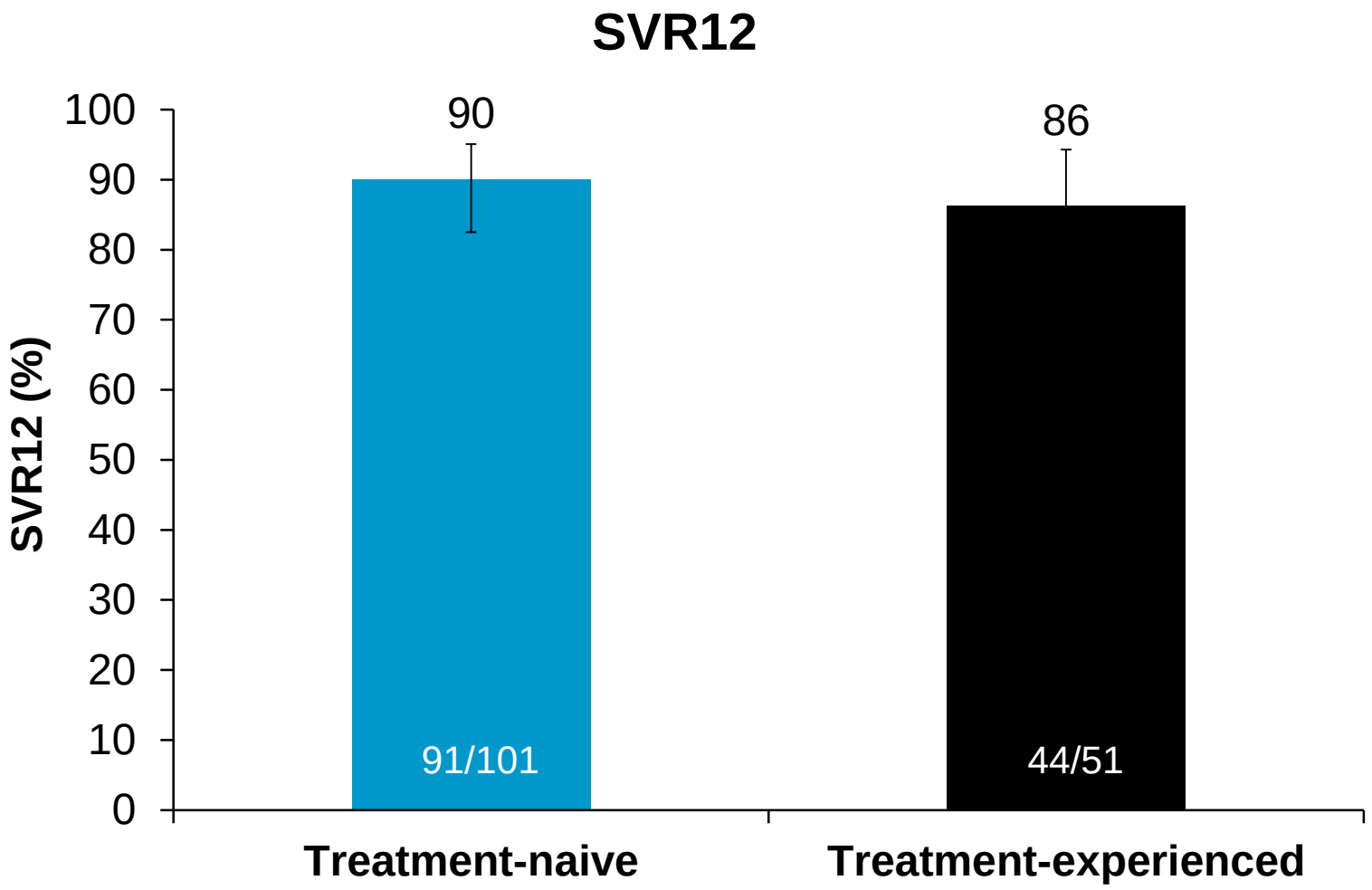
Variable EC50's for NS5A Inhibitors Against Genotype 3

EC50 (nM) in replicons

Drug	1a	1b	3a	4a
Daclatasvir	0.02	0.004	0.15	0.012
Ledipasvir	0.034	0.004	35	0.11
GS-5816	0.011	0.009	0.012	0.009
MK-8742	0.004	0.003	0.03	0.003
ACH-3102	0.02	0.007	<0.2	<0.2
IDX-719	0.0062	0.0024	0.017	0.002

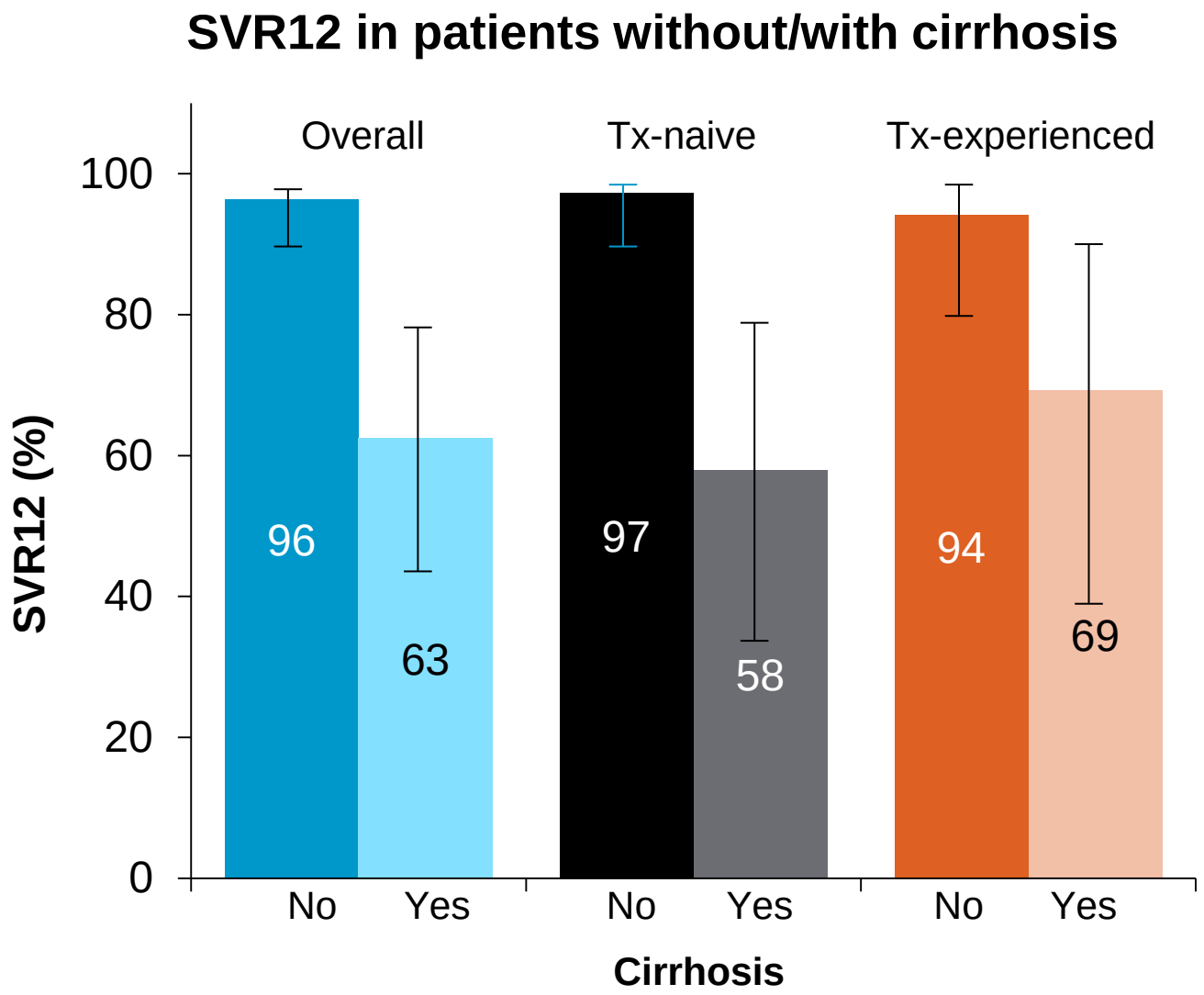
Gao M, *Current Opinion in Virology* 2013;3:514-20

ALLY-3 Study: 12-week Combination Treatment With DCV + SOF for HCV G3



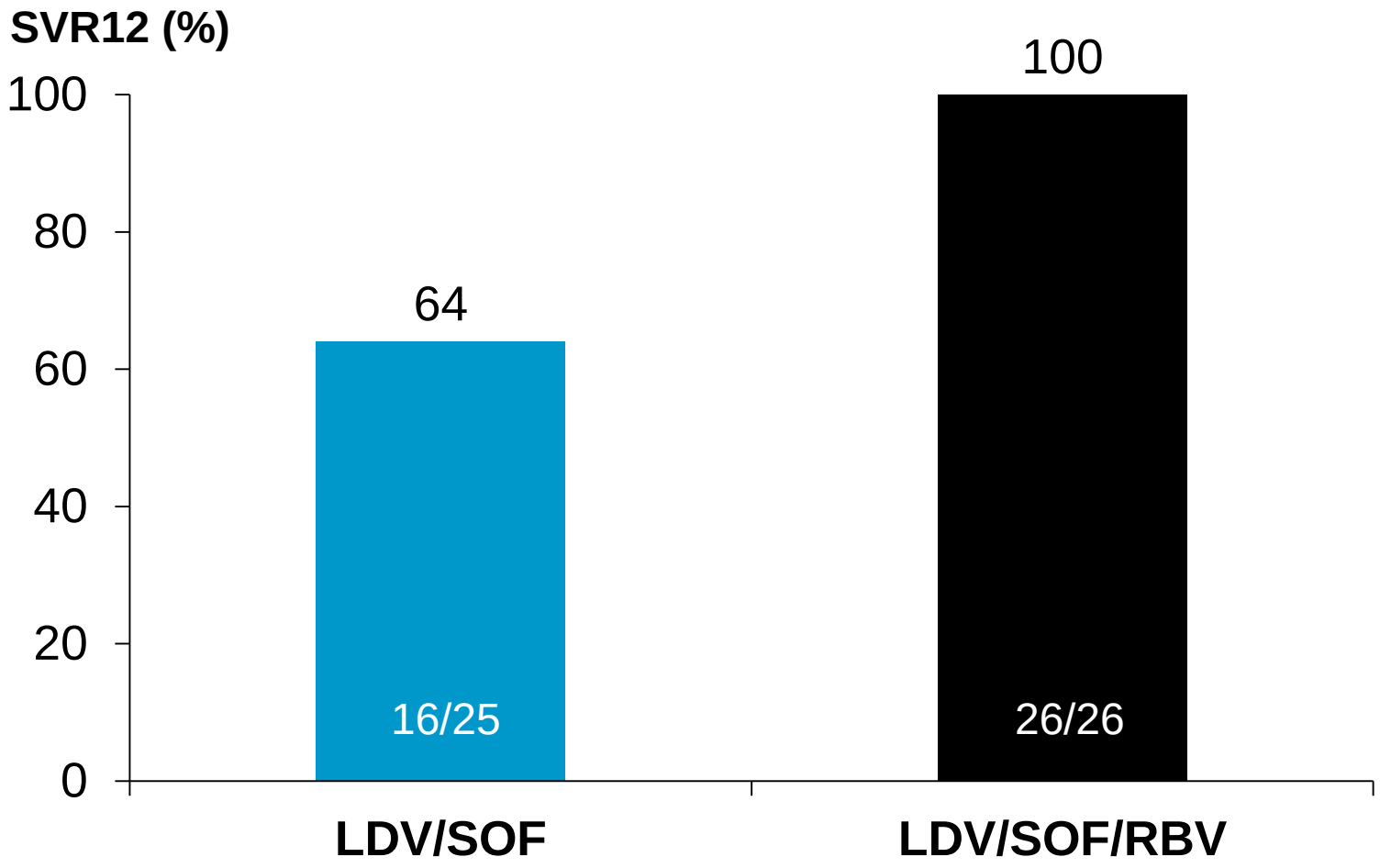
Nelson DR et al, AASLD 2014, LB-3

ALLY-3 Study: 12-week Combination Treatment With DCV + SOF for HCV G3



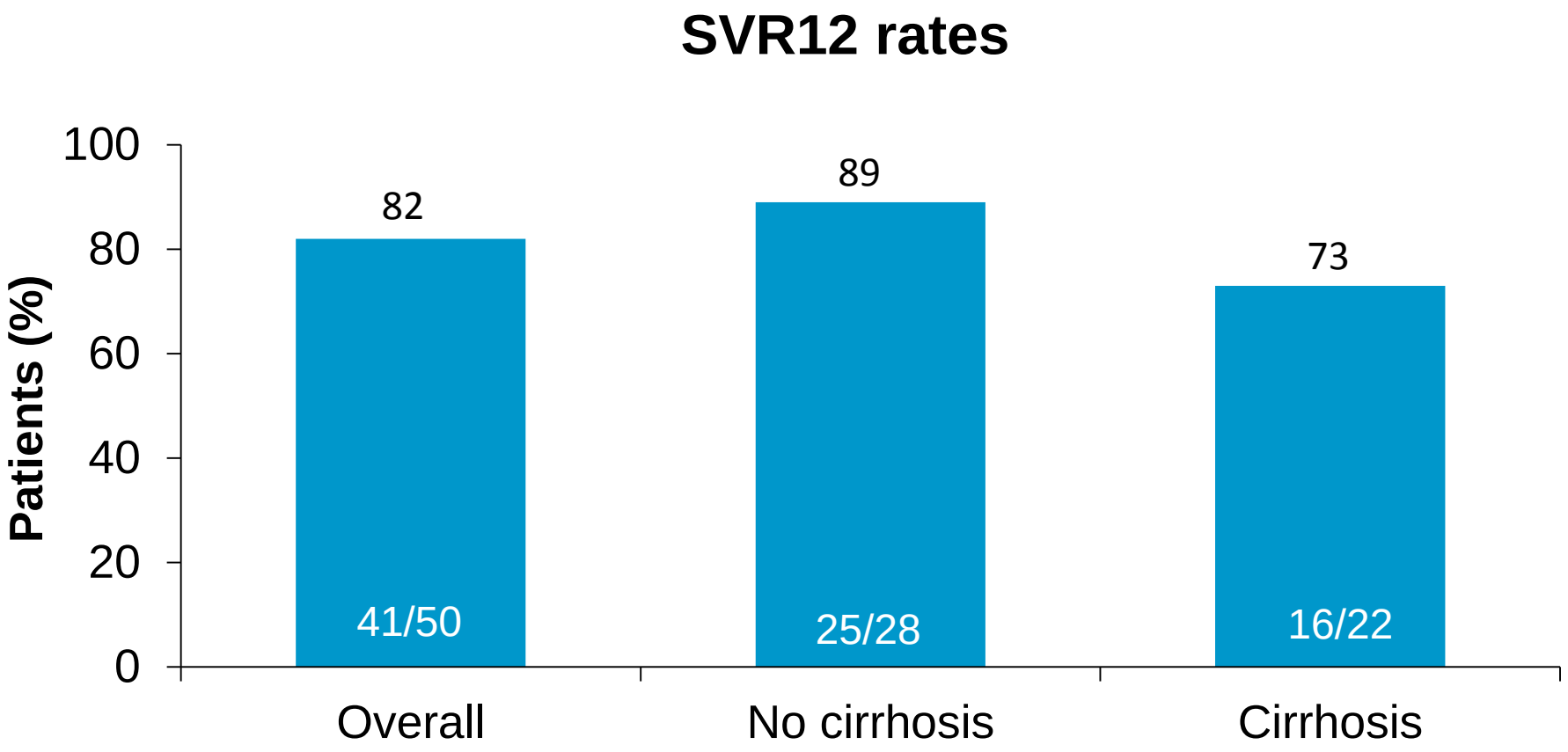
Nelson DR et al, AASLD 2014, LB-3

Ledipasvir/Sofosbuvir ± RBV 12 Weeks for Treatment-naïve Noncirrhotic G3



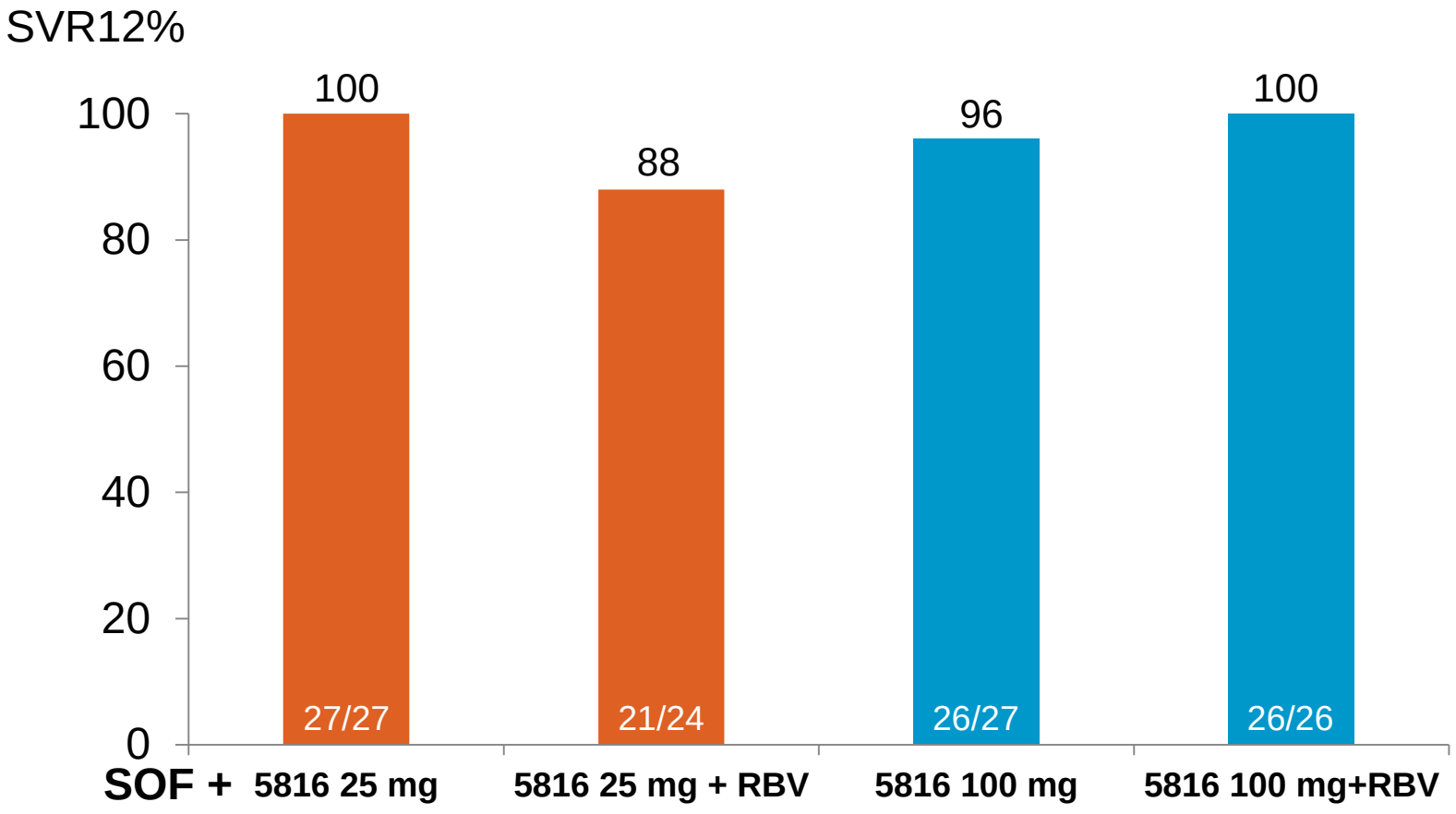
Gane E.J, et al. Presented at: EASL; 2014; London. Abstract O6.

Efficacy of LDV/SOF Regimens for 12 Weeks for Treatment Experienced Genotype 3



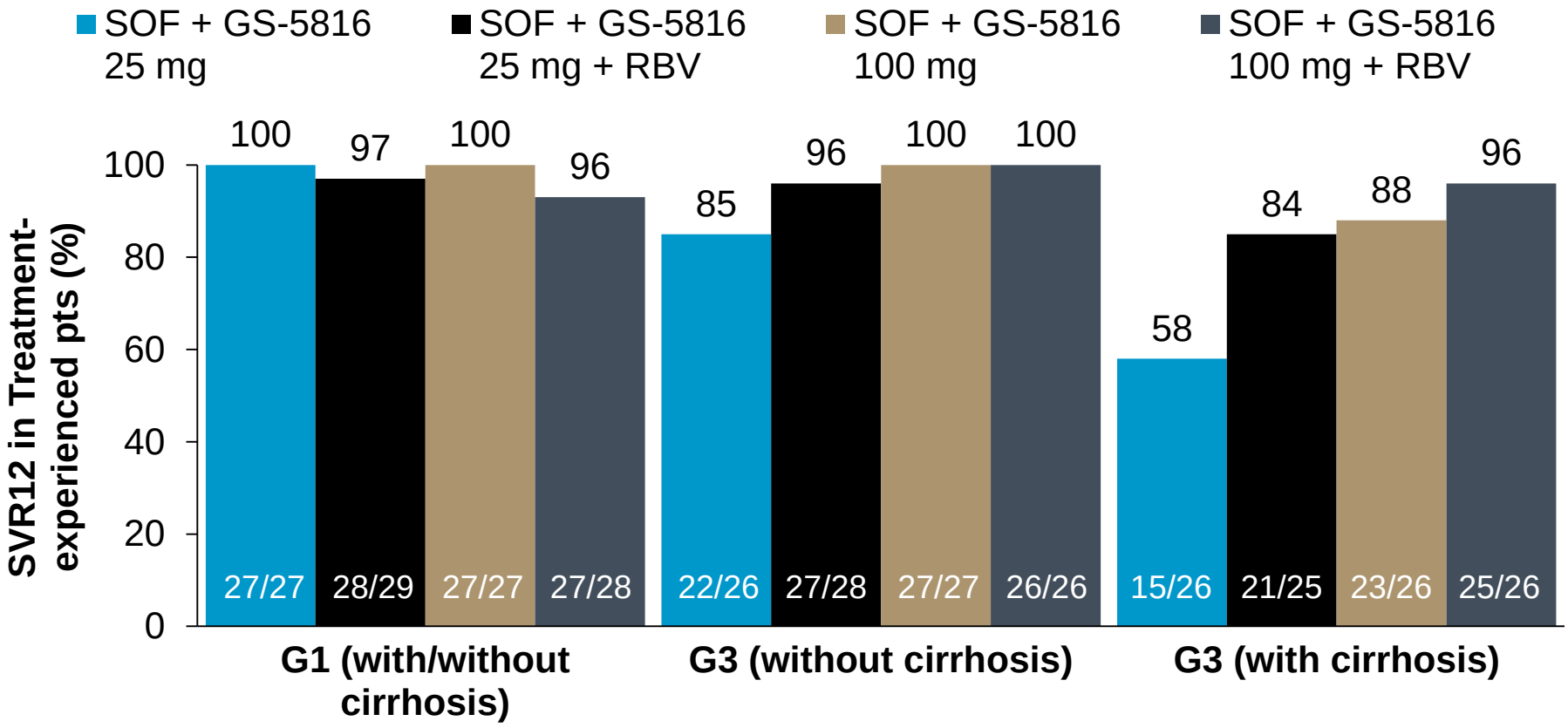
Gane EJ et al, AASLD 2014, LB-11

Once-daily SOF With GS-5816 for 8 Weeks ± RBV in Treatment-naive G3 Non-cirrhotics: ELECTRON-2 Study



Gane EJ et al, AASLD 2014, #79

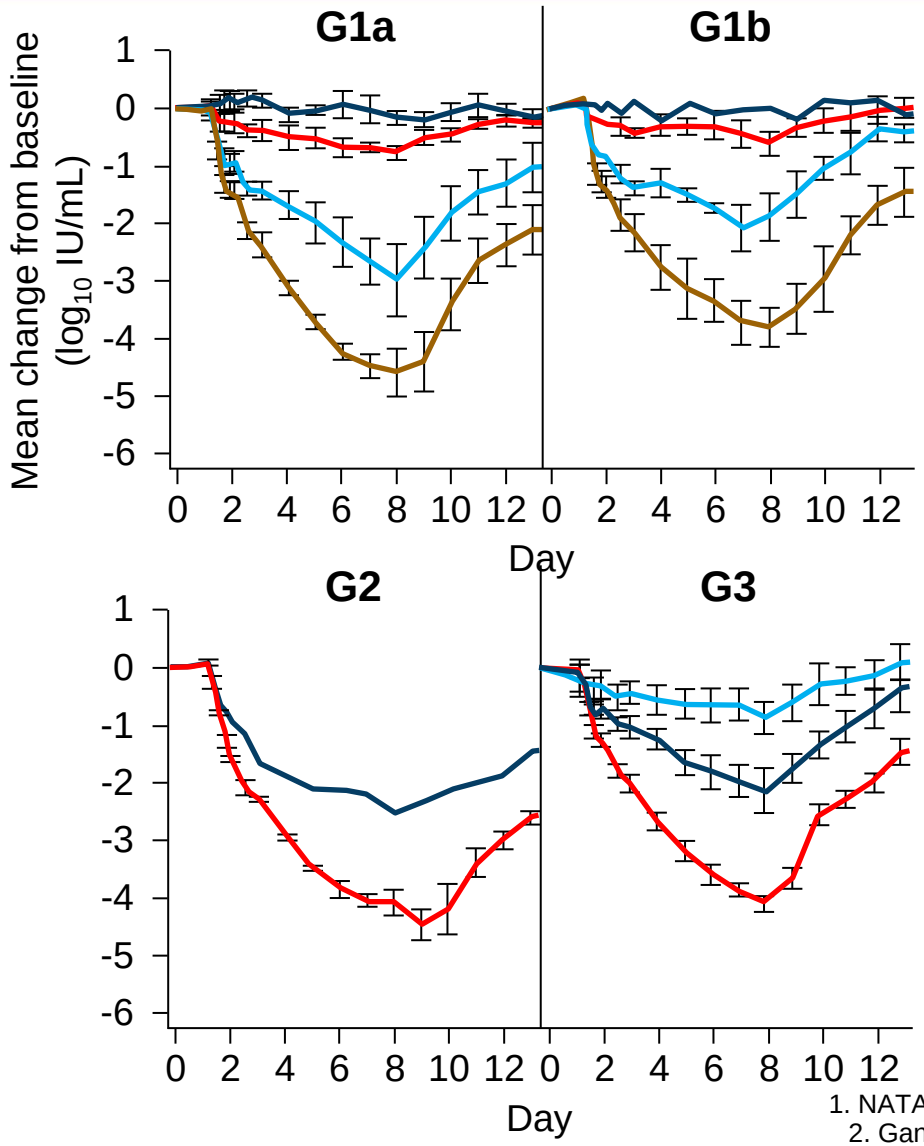
SOF + GS-5816 ± RBV for 12 Weeks in Treatment-experienced G1/3 Patients



- Post-treatment NS5A RAVs observed in all patients with virologic failure
- Good safety and tolerability

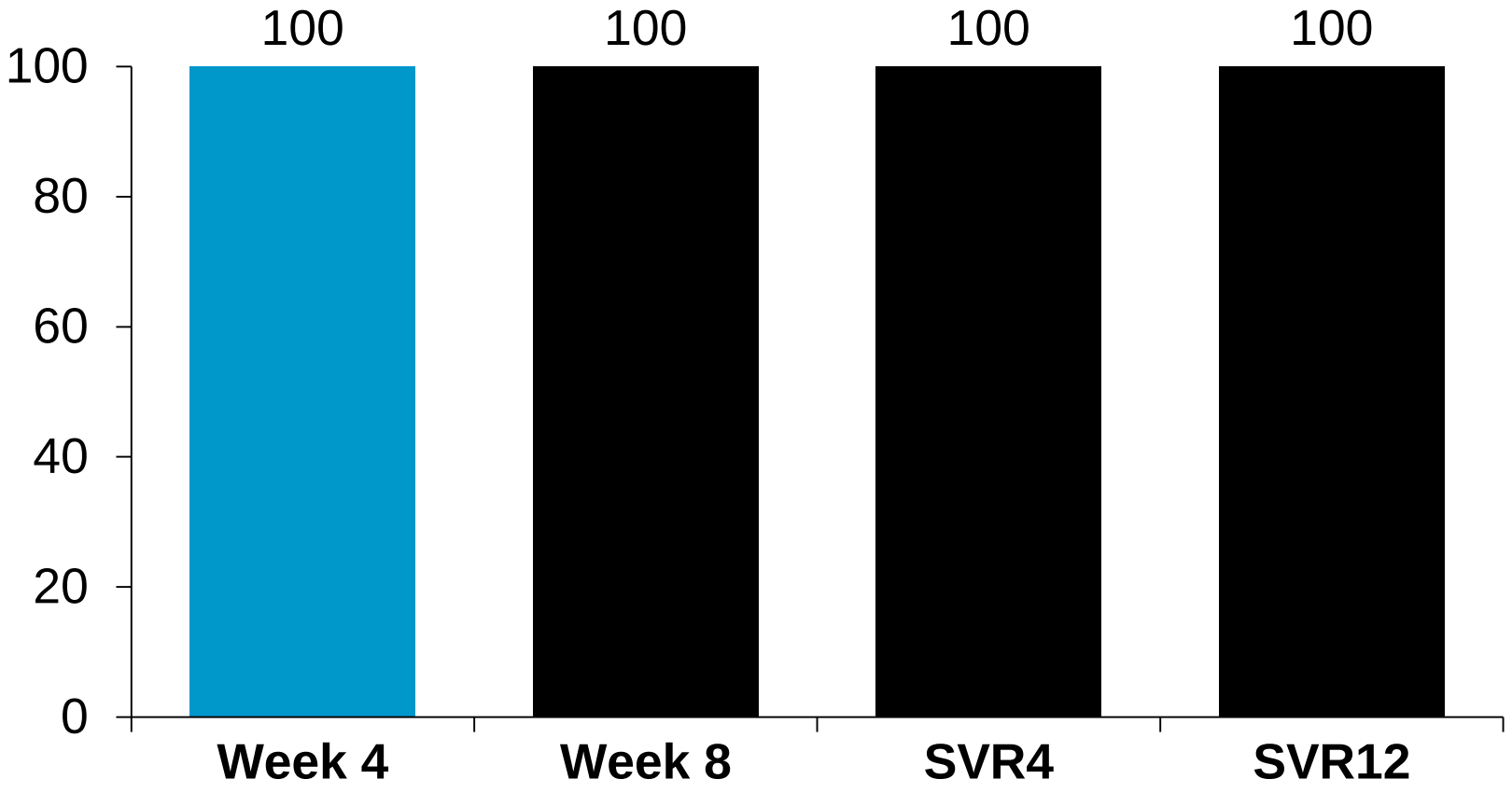
Pianko S, et al. AASLD 2014, Boston. #197

MK-3682 (Nucleotide): 7-day virologic data from proof-of-concept monotherapy study



1. NATAP Website. http://www.natap.org/2014/Pharm/Pharm_12.htm;
2. Gane E, et al. *Hepatology* 2014; Oct;60 (4 Supp 1); Abstract 1974

Interim SVR, Safety and Tolerability Results of 8-week Treatment With ACH-3102 and SOF in G1 Treatment-naive Patients: A Phase 2 'Proxy' Study, n=12



- Cohort 2: ACH-3102 + SOF 6 weeks (n=12) and 6 controls
  - 8/8 thus far have ETR; no SVR data
- Plans to combine ACH-3102 with ACH-3422 (nuc)

Gane EJ, et al. AASLD 2014, Boston. #LB-23

Conclusions

- Further refinements in therapy can be expected, but no reason to defer therapy any longer
- Cost issues may be attenuated as arena becomes more competitive
- Will need retreatment regimens for DAA failures: under development
- Decompensated cirrhotics and transplant recipients appear to be excellent candidates for therapy
- Our enthusiasm for ultra-short durations may need to be tempered
- Novel classes of antivirals, host factor antagonists, or immune modulators may not be needed