CLINICAL CARE OPTIONS®
HIV

CLINICAL CARE OPTIONS®
HEPATITIS

Genotype 1 HCV in 2016: Clinical Decision Making in a Time of Plenty

Ira M. Jacobson, MD
Chair, Department of Medicine
Mount Sinai Beth Israel
Senior Faculty and Vice-Chair,
Department of Medicine
Icahn School of Medicine at
Mount Sinai
New York, New York

Supported by educational grants from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen Therapeutics, Merck, and ViiV Healthcare.

About These Slides

- Please feel free to use, update, and share some or all of these slides in your noncommercial presentations to colleagues or patients
- When using our slides, please retain the source attribution:

Slide credit: clinicaloptions.com

- These slides may not be published, posted online, or used in commercial presentations without permission. Please contact permissions@clinicaloptions.com for details

Disclosures

Ira. M. Jacobson, MD, has disclosed that he has received funds for research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck; has served on speaker bureaus for AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Janssen; and has received consulting fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept, Janssen, Merck, and Trek.

New Regimens and Data for Genotype 1 HCV Infection

AASLD Guidance

Updated February 24, 2016

- AASLD guidance stratifies regimens as **"recommended"** and **"alternative"**

AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

AASLD: Recommended and *Alternative* Regimens for GT1 Without Cirrhosis

	Nucleotide			No nucleotide	
Population	**LDV/SOF**	**DCV + SOF**	**SMV + SOF**	**GZR/EBR**	**OBV/PTV/RTV + DSV**
GT1a	12 wks	12 wks	12 wks	12 wks *16 wks + RBV†*	12 wks + RBV
GT1b	12 wks	12 wks	12 wks	12 wks	12 wks

†If NS5A RAVs present.

■ Recommended ■ *Alternative*

AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

AASLD: Recommended and *Alternative* Regimens for GT1 With Compensated Cirrhosis

	Nucleotide			No nucleotide	
Population	**LDV/SOF**	**DCV + SOF**	**SMV + SOF**	**GZR/EBR**	**OBV/PTV/RTV + DSV**
GT1a					
▪Naive	12 wks	*24 wks ± RBV*	*24 wks ± RBV**	12 wks *16 wks + RBV†*	*24 wks + RBV*
▪PR exp	12 wks + RBV or 24 wks	*24 wks ± RBV*	*24 wks ± RBV**	12 wks *16 wks + RBV†*	*24 wks + RBV*
GT1b					
▪Naive	12 wks	*24 wks ± RBV*	*24 wks ± RBV*	12 wks	12 wks
▪PR exp	12 wks + RBV or 24 wks	*24 wks ± RBV*	*24 wks ± RBV*	12 wks	12 wks

*Not with Q80K.
†If NS5A RAVs present.

■ Recommended ■ *Alternative*

AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

Grazoprevir/Elbasvir: Approved Jan 2016

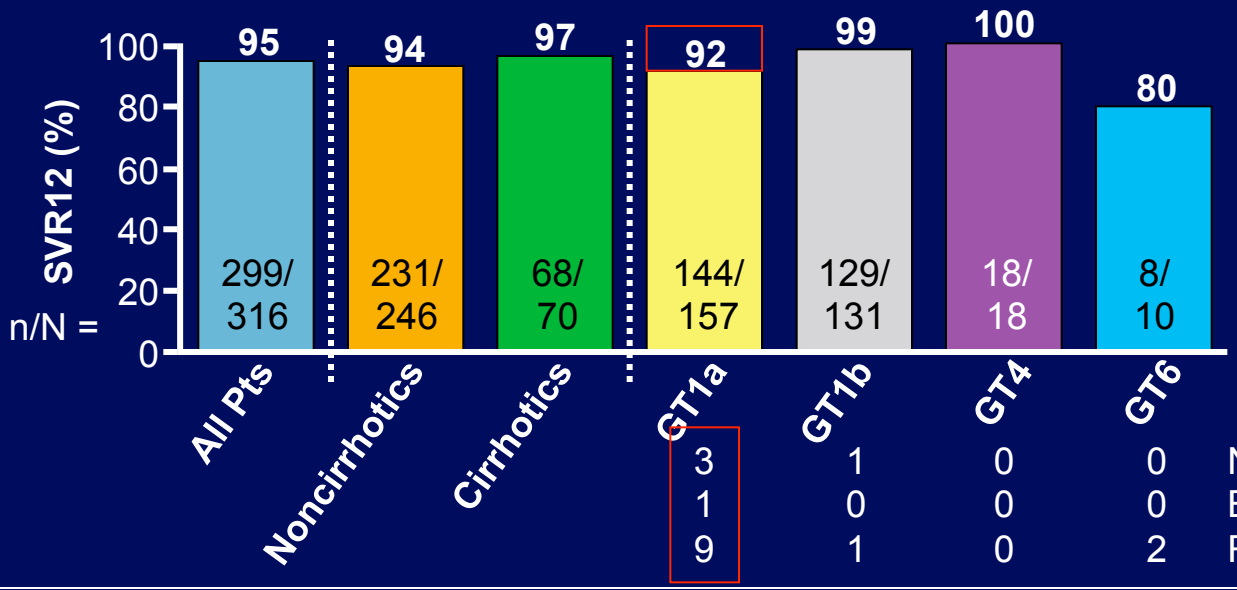
- Genotype 1a, with/without compensated cirrhosis, treatment naive or treatment experienced
  - Without NS5A RAVs: GZR/EBR, 12 wks
  - With NS5A RAVs: GZR/EBR + RBV, 16 wks*
    - RAVs at positions 28, 30, 31, 93
- Genotype 1b, with/without compensated cirrhosis, treatment naive or treatment experienced
  - GZR/EBR, 12 wks
    - RAV testing not indicated

*Listed as “alternative” regimen.

AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

C-EDGE TN: 12 Wks of GZR/EBR in Genotype 1, 4, or 6

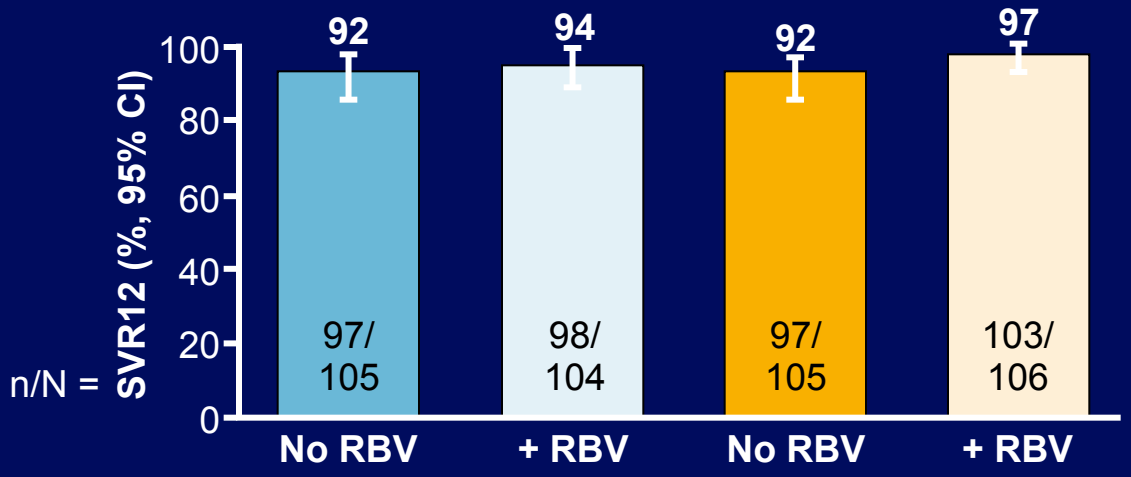


- Good safety and tolerability profile
  - No drug-related serious AEs; 2 deaths unrelated to drug
  - No concurrent ALT/bilirubin increase
- Lower SVR12 rates in pts with BL NS5A RAVs (2/9, 22%); associated with > 5-fold loss of EBR susceptibility
- Virologic failure only if baseline HCV RNA > 800,000 IU/mL

Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Slide credit: clinicaloptions.com

C-EDGE TE: 12 or 16 Wks of GZR/EBR ± RBV in Treatment-Experienced GT1, 4, or 6



n/N =	No RBV	+ RBV	No RBV	+ RBV
Breakthrough	0	0	1	0
Rebound	0	0	2	0
Relapse	6	6	4	0
LTFU/early d/c	2	0	1	3

*ITT population.

- Virologic failures driven by RAVs
- Analysis from AASLD 2015 shows that presence of baseline NS5A RAVs by population sequencing or next-generation sequencing (with 10% to 20% cutoff) is predictive of failure

Kwo P, et al. EASL 2015. Abstract P0886. Jacobson I, et al. AASLD 2015. Abstract LB22.

Slide credit: clinicaloptions.com

C-EDGE TE: Efficacy of 12 Wks of GZR/EBR ± RBV by Baseline RAVs

		SVR12, n/N (%)		
	Total	NS3 Variants Not Detectable	NS3 RAVs ≤ 5-Fold Shift	NS3 RAVs > 5-Fold Shift
GT1a	95%	107/112 (96)	104/111 (94)	0
GT1b	99%	133/135 (99)	9/9 (100)	1/1 (100%)

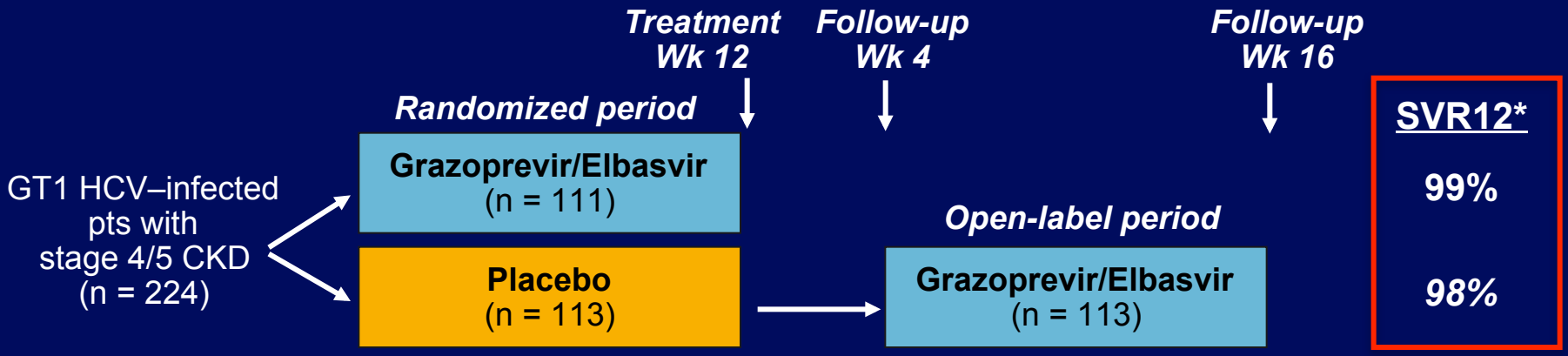
		NS5A Variants Not Detectable	NS5A RAVs ≤ 5-Fold Shift	NS5A RAVs > 5-Fold Shift
GT1a	95%	190/192 (99)	10/10 (100)	11/21 (52)
GT1b	99%	127/127 (100)	0	16/18 (89)

- Should baseline RAV testing be done with this regimen?
  - The NS5A RAVs that matter are in the 28, 30, 31, and 93 positions

Kwo P, et al. EASL 2015. Abstract P0886.

Slide credit: clinicaloptions.com

C-SURFER: Grazoprevir/Elbasvir in Pts With GT1 HCV and Stage 4/5 CKD



Grazoprevir/elbasvir dosed orally 100 mg/50 mg once daily. This study also included a pharmacokinetic analysis (n = 11) in which pts were treated as in the randomized grazoprevir/elbasvir study group.

*Modified full analysis set population.

- 76% on dialysis
- 34% with diabetes
- 52% GT1a, 48% GT1b
- 6% cirrhosis

Roth D, et al. Lancet. 2015;386:1537-1545
Roth D, et al. Kidney Week 2015. Abstract SA-PO1100.

Slide credit: clinicaloptions.com

Daclatasvir + Sofosbuvir

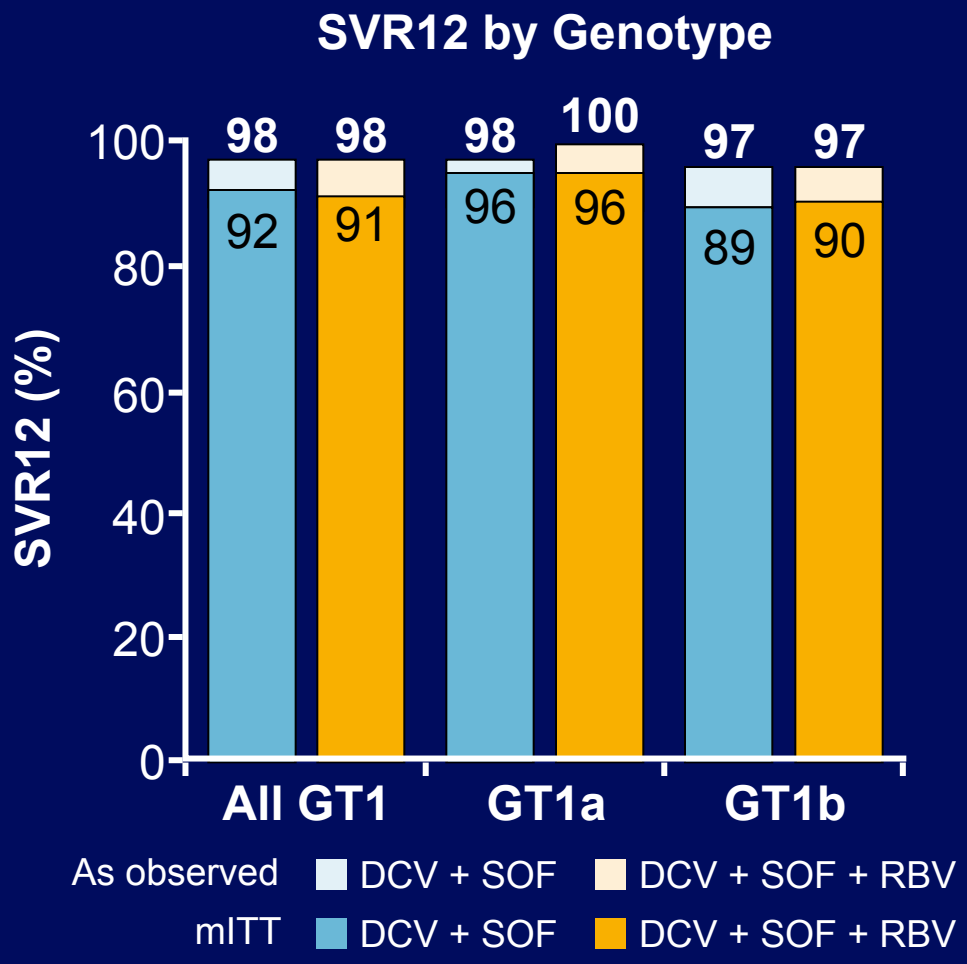
- Genotype 1a or 1b, treatment naive or experienced, without cirrhosis
  - DCV + SOF, 12 wks
- Genotype 1a or 1b, treatment naive or experienced, with compensated cirrhosis
  - DCV + SOF ± RBV, 24 wks*

*Listed as “alternative” regimen

AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

DCV + SOF ± RBV for 24 Wks in GT1 Pts With Advanced Liver Disease



Welzel T, et al. EASL 2016. Abstract SAT-275.

Slide credit: clinicaloptions.com

Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir

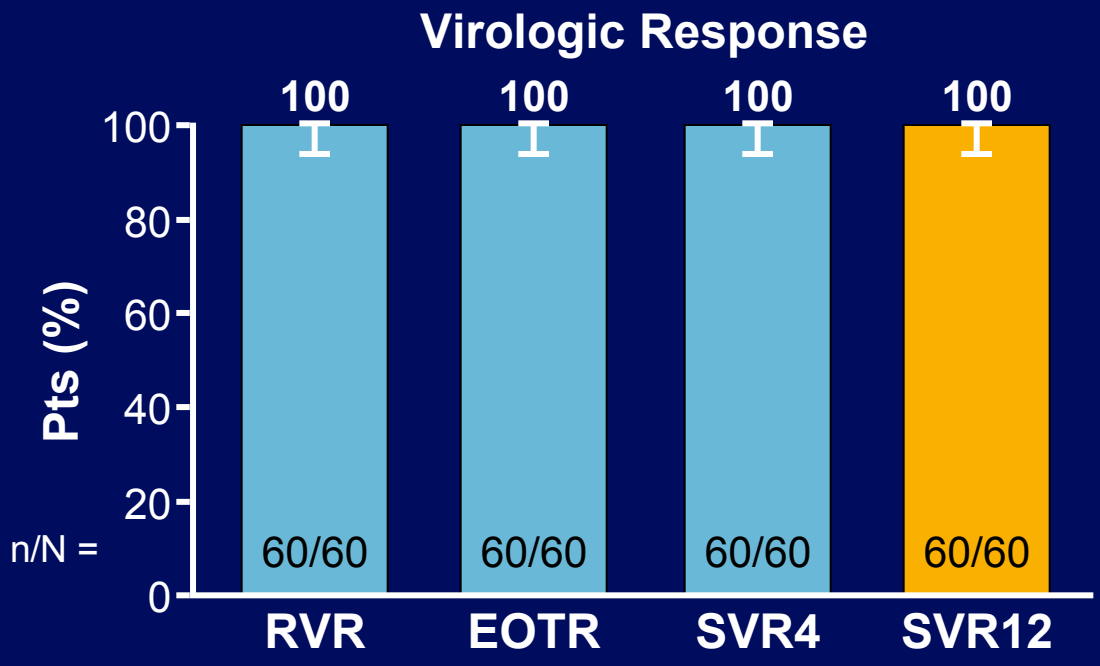
- Genotype 1a, treatment naive or experienced
  - No cirrhosis: OBV/PTV/RTV + DSV + RBV, 12 wks
  - With compensated cirrhosis: OBV/PTV/RTV + DSV + RBV, 24wks*
    - RAV testing not indicated
- Genotype 1b, with/without compensated cirrhosis, treatment naive or experienced
  - OBV/PTV/RTV + DSV, 12 wks
    - RAV testing not indicated

*Listed as “alternative” regimen.

AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

TURQUOISE III: 12 Wks of OBV/PTV/RTV + DSV Without RBV in Cirrhotic GT1b Pts



AASLD guidance now recommends OBV/PTV/RTV + DSV **12 wks without RBV** for GT1b cirrhotics

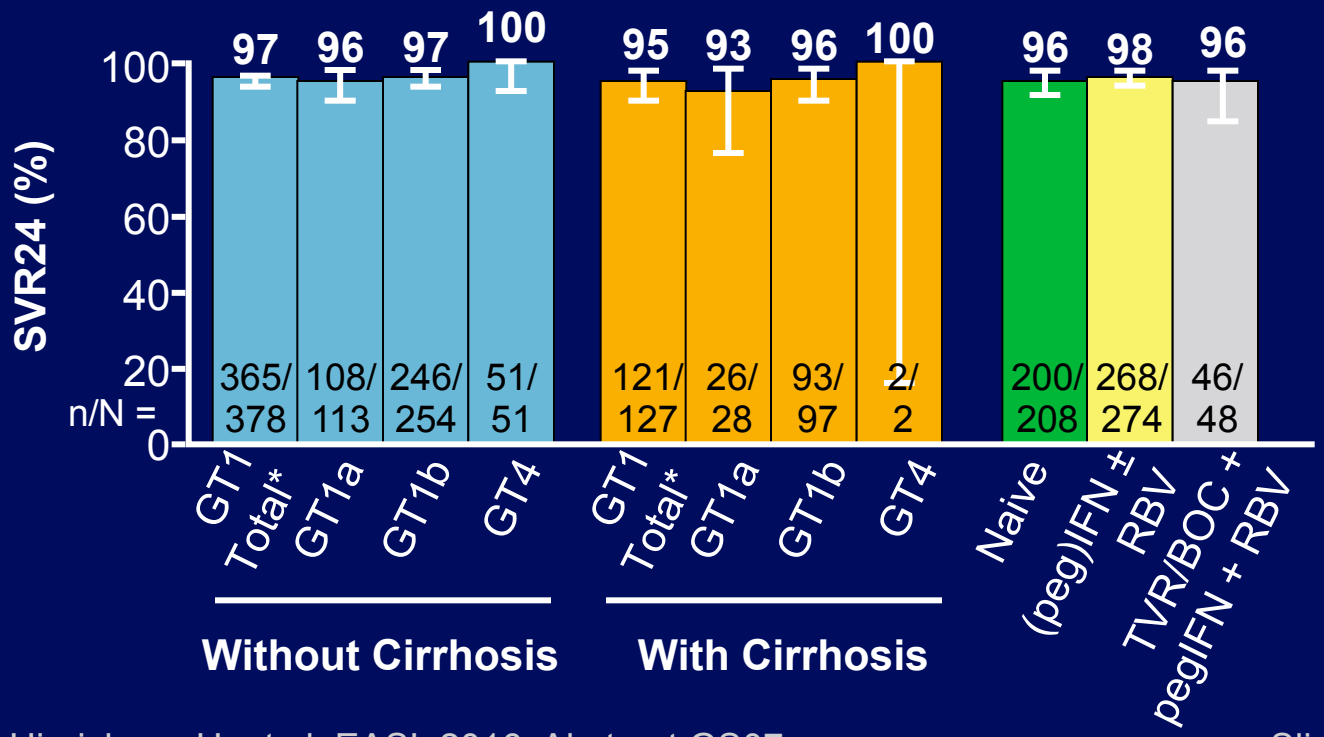
Still need 24 wks + RBV for GT1a cirrhotics, naive or experienced

Poordad F, et al. AASLD 2015. Abstract 1051.
AASLD/IDSA. HCV Guidance. April 2016.

Slide credit: clinicaloptions.com

Real-World Efficacy of OBV/PTV/RTV ± DSV ± RBV: German HCV Registry Cohort

- Efficacy population (complete follow-up): n = 543; safety population (initiated treatment): n = 1017
  - GT1: 88%; GT4: 12%; cirrhosis: 22% (CTP B/C: 7%); tx experienced: 59%



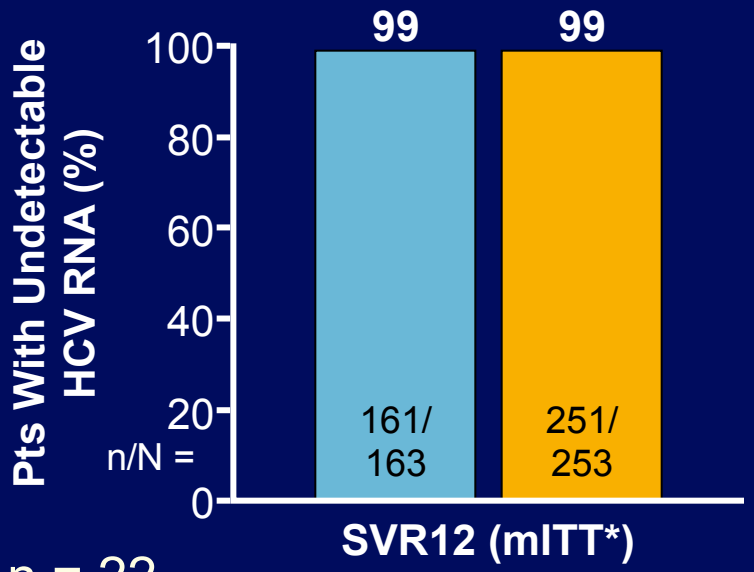
*Includes 13 pts with mixed or unknown GT1 subgenotype infection, all of whom achieved SVR.

Hinrichsen H, et al. EASL 2016. Abstract GS07.

Slide credit: clinicaloptions.com

Real-World Efficacy of OBV/PTV/RTV ± DSV ± RBV: Israeli Cohort

- Efficacy population (complete follow-up): n = 432; safety population (initiated treatment): n = 661
  - GT1: 100%; cirrhosis: 62% (CTP A/B: 98.5%/1.5%); tx exp'd: 62%



*Excludes pts who did not achieve SVR12 for reasons other than virologic failure.

  - Post LT: n = 22
    - SVR12 mITT/overall: 82%/86%; 4 discontinued due to serious AEs, one of which achieved SVR

Zuckerman E, et al. EASL 2016. Abstract PS004.

Slide credit: clinicaloptions.com

Real-World Safety of OBV/PTV/RTV ± DSV ± RBV: German and Israeli Cohorts

- Most common AEs across both cohorts[1,2]: fatigue, pruritus, headache, insomnia, nausea, diarrhea (Israeli), anemia (German)
  - Serious AE: 2.1% to 3.8%
  - D/c for AE: 1.5% to 3.0%
  - 3 deaths deemed unrelated to HCV therapy: stroke, MI, multiple organ failure
- In Israeli cohort, 20 pts discontinued for AEs[2]
  - Serious AE: n = 12
  - Decompensation: n = 8
- In Israeli cohort, several factors identified as significant predictors of hepatic decompensation[2]

Factor	*P* Value
Age older than 75 yrs	.005
Platelets < 90,000/mL	.03
Albumin < 3.5 g/dL	.048
CTP score ≥ 7	.07
MELD score > 10	.01
Previous decompensation	< .001

1. Hinrichsen H, et al. EASL 2016. Abstract GS07.
2. Zuckerman E, et al. EASL 2016. Abstract PS004.

Ledipasvir/Sofosbuvir for GT1 Tx-Naive Noncirrhotics With HCV RNA < 6 M IU/mL:

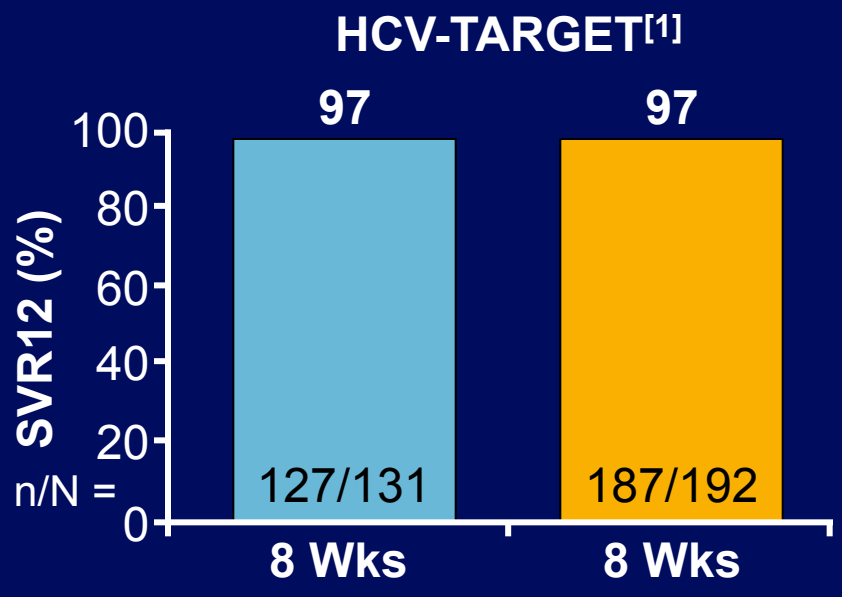
Are 8 wks sufficient? Or are 12 wks better?

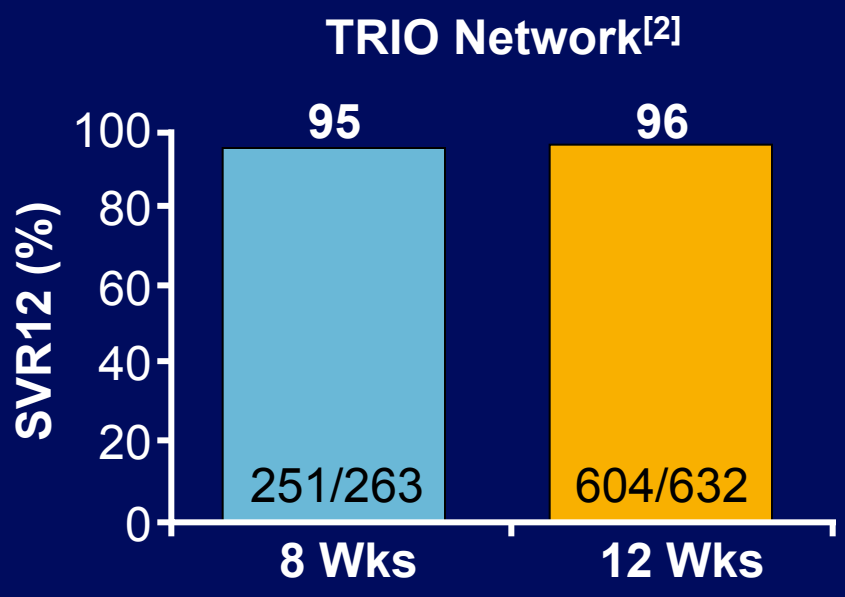
- Established by retrospective analysis of ION-3
- Many clinicians were initially uncomfortable
- What do "real-world" data show?

Slide credit: clinicaloptions.com

8 vs 12 Wks of LDV/SOF in Pts With GT1 HCV: HCV-TARGET and TRIO Network

- Treatment-naive, noncirrhotic pts with GT1 HCV
  - HCV RNA < 6 M IU/mL in HCV-TARGET

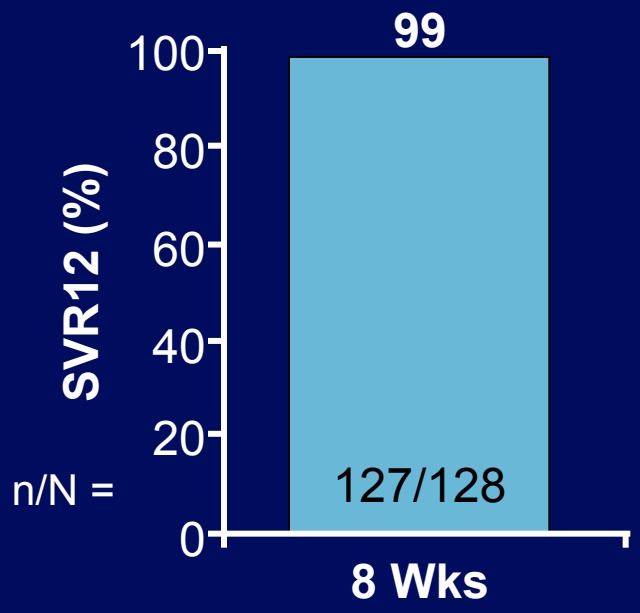




1. Terrault N, et al. AASLD 2015. Abstract 94.
2. Curry M, et al. AASLD 2015. Abstract 1046.

8 Wks of LDV/SOF in Pts With GT1 HCV: German Real-World Single-Center Study

- Pts noncirrhotic (100%) and primarily treatment naive (97%), GT1 (98%), and HCV RNA < 6 M IU/mL (96%)

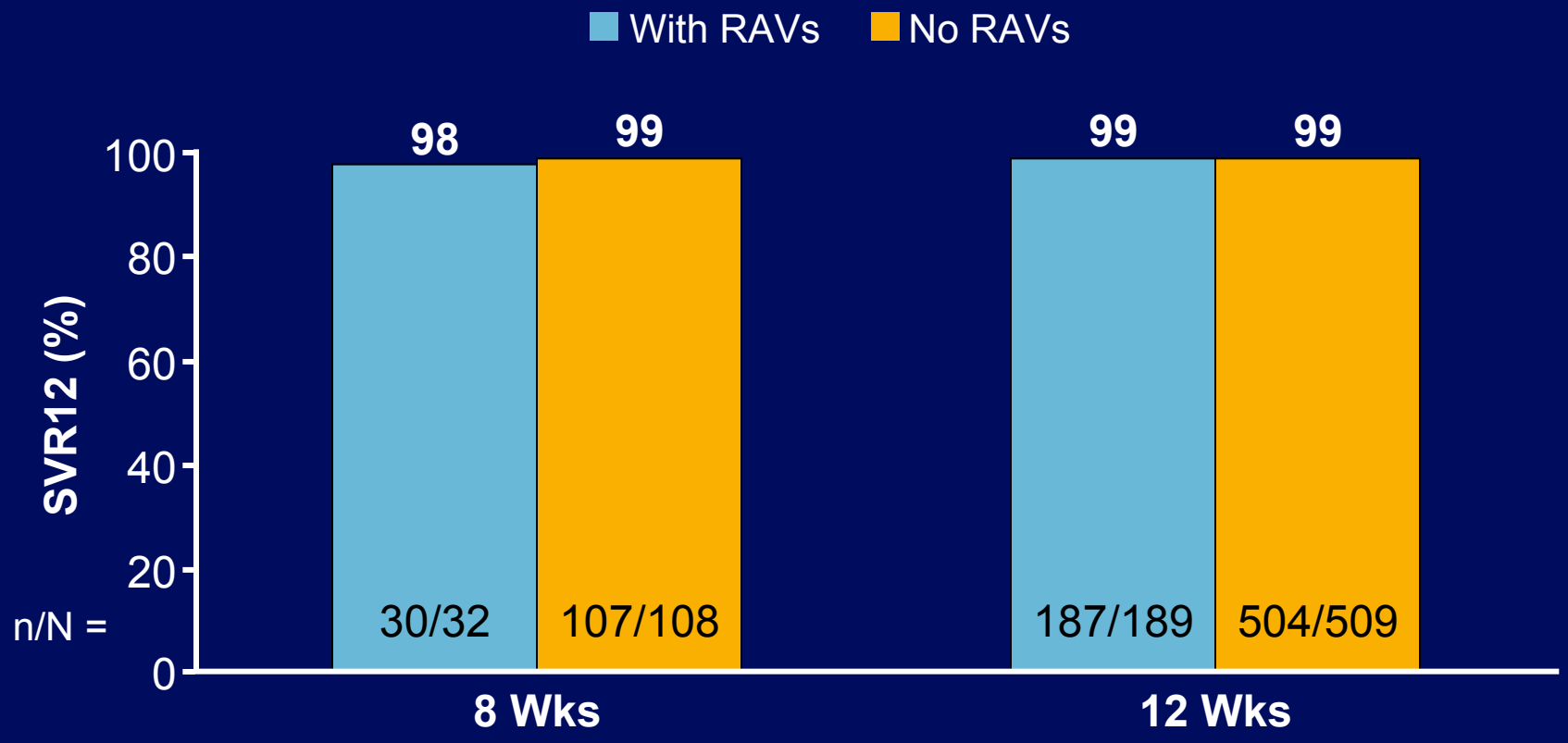


Buggisch P et al, EASL 2016. Abstract SAT-242.

Slide credit: clinicaloptions.com

LDV/SOF: SVR12 by Treatment Regimen and Duration in Pts Without Cirrhosis

- Pooled data from multiple trials, HCV RNA < 6 M IU/mL in 8-wk arm



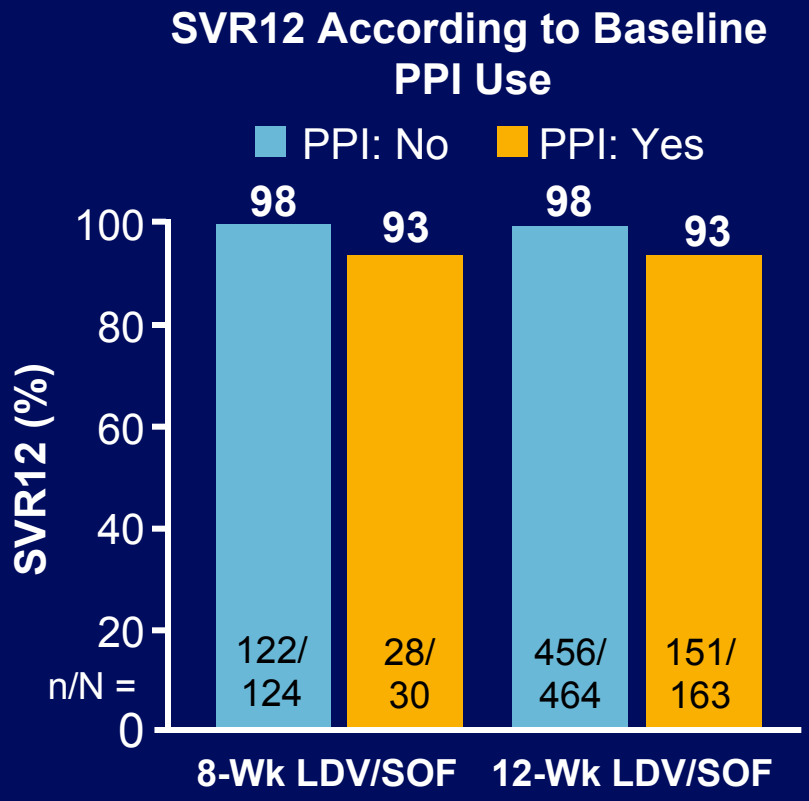
Zeuzem S, et al. AASLD 2015. Abstract 91.

Slide credit: clinicaloptions.com

PPIs and Ledipasvir: Does Acid Suppression Matter?

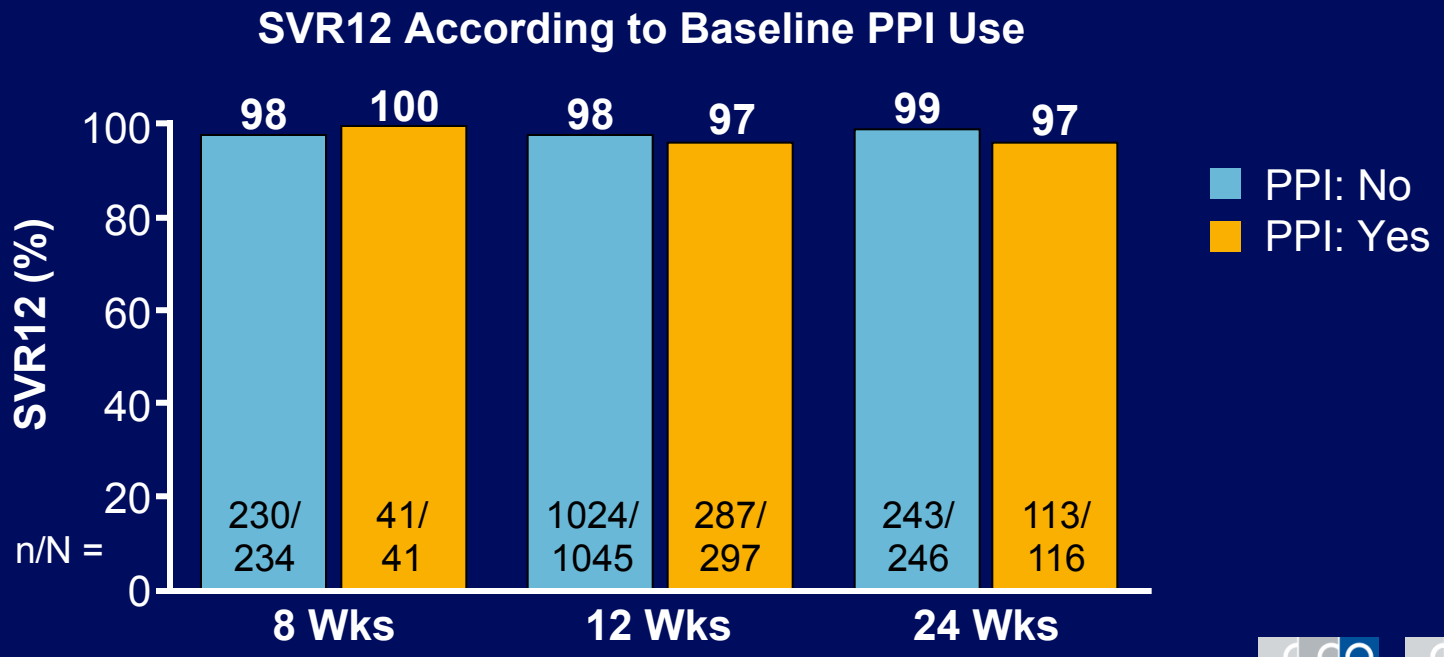
HCV-TARGET: Effect of PPI Use?

- Pts treated according to local standards of care at 44 academic/ 17 community medical centers in North America/ Europe
- Virologic outcome known for 1074 pts



TRIO Network: No Effect of PPI Use?

- Real-world data from 2034 pts with GT1 HCV receiving LDV/SOF
- A per protocol analysis (n = 1979) showed no effect of PPIs on SVR



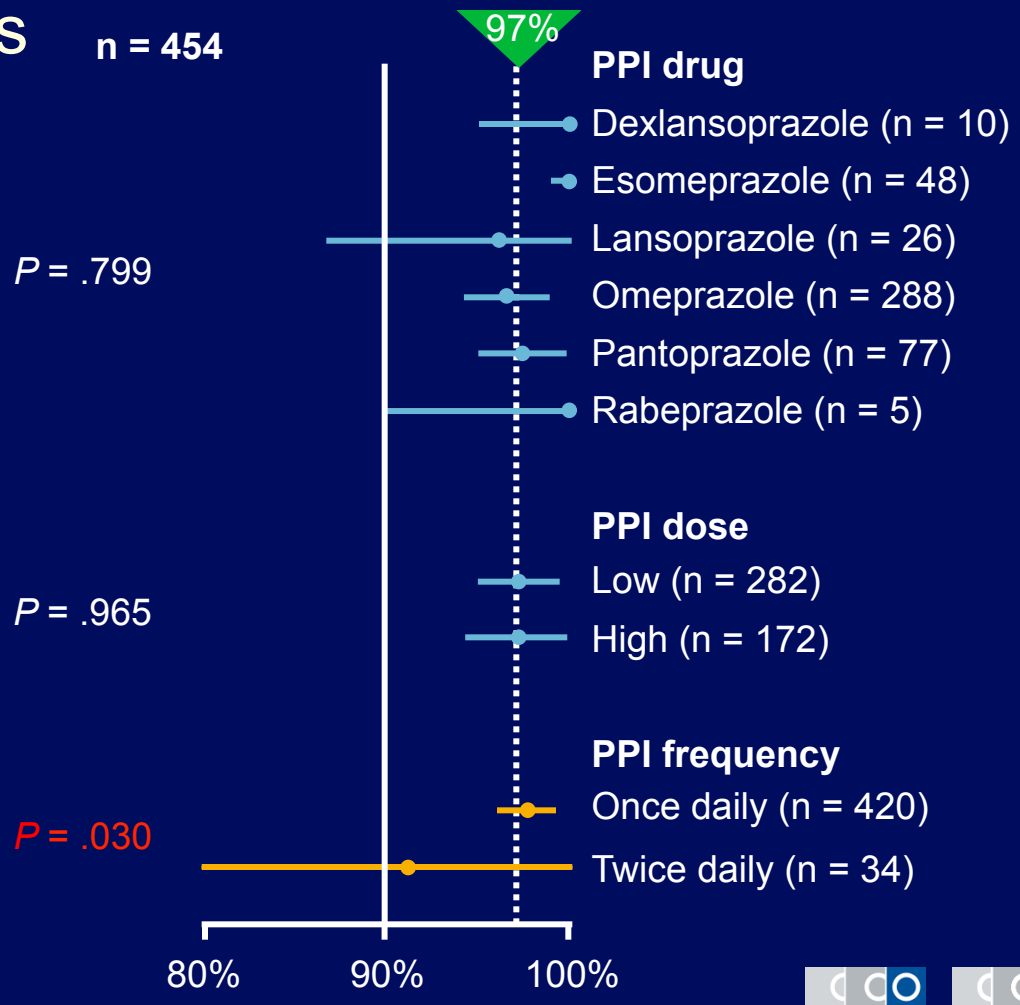
Afdhal N, et al. EASL 2016. Abstract LBP519.

Slide credit: clinicaloptions.com

TRIO Network: Predictors of Response to LDV/SOF by PPI Usage

- Per protocol analysis (n = 1979)

"Caution with use of high dose PPIs with LDV/SOF"



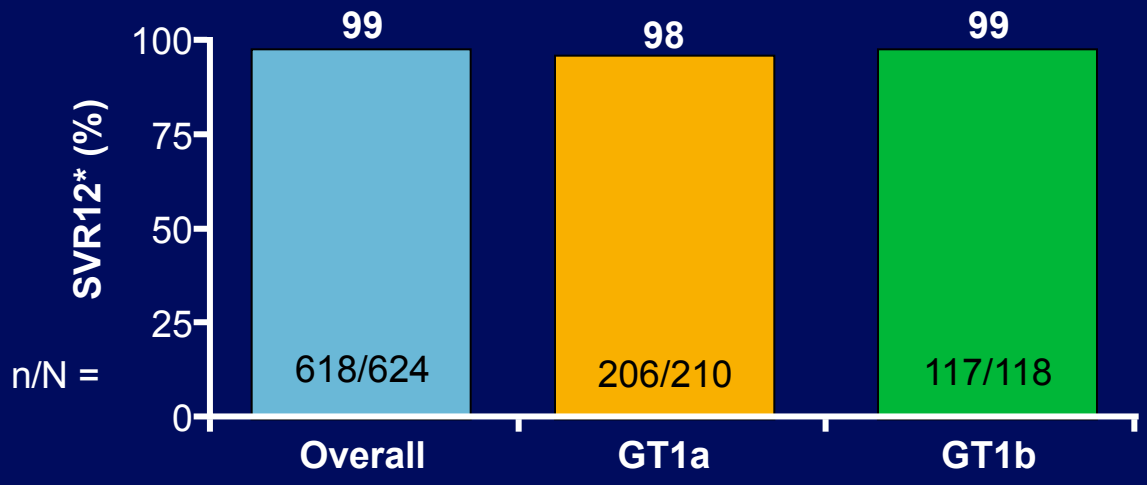
Afdhal N, et al. EASL 2016. Abstract LBP519.

Slide credit: clinicaloptions.com

New Regimens

ASTRAL-1: VEL/SOF FDC for 12 Wks in GT1/2/4/5/6 With and Without Cirrhosis

- Velpatasvir (GS-5816): pangenotypic HCV NS5A inhibitor
- GT3 pts evaluated in separate study
- 19% cirrhosis, 32% treatment experienced



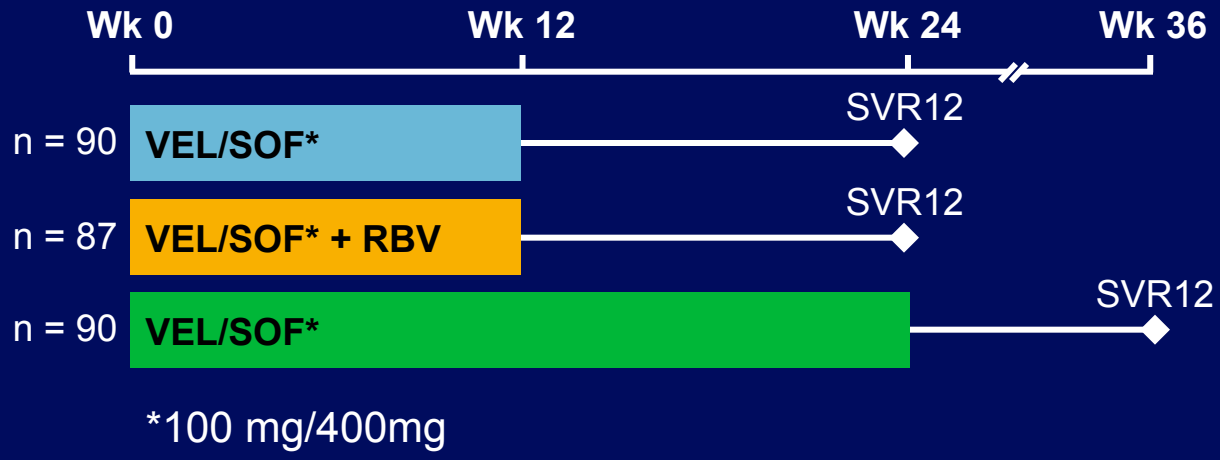
*HCV RNA < 15 IU/mL

Feld JJ, et al. AASLD 2015. Abstract LB-2.

Slide credit: clinicaloptions.com

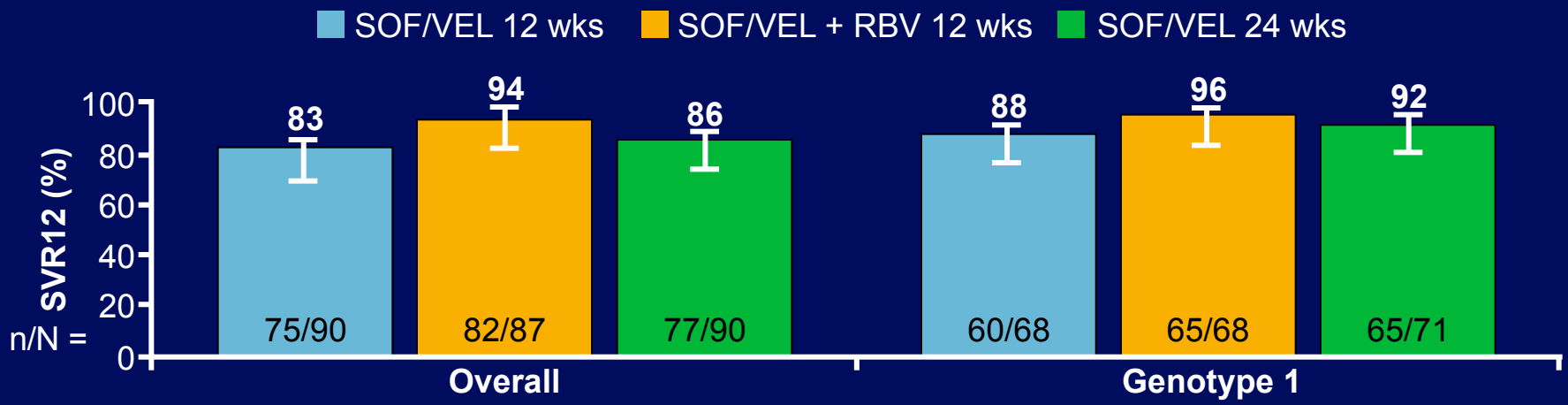
ASTRAL-4: VEL/SOF FDC for HCV in Pts With Decompensated Liver Disease

- Treatment-naive or treatment-experienced pts with GT1-6 HCV infection and CTP B cirrhosis (N = 267)
  - 55% treatment experienced; 95% MELD < 15; 75% to 83% ascites; 58% to 66% encephalopathy
  - GT1: 78%; GT3: 15%, GT2/4/6: 8%



Charlton MR, et al. AASLD 2015. Abstract LB-13.

ASTRAL-4: VEL/SOF FDC for HCV in Pts With Decompensated Liver Disease



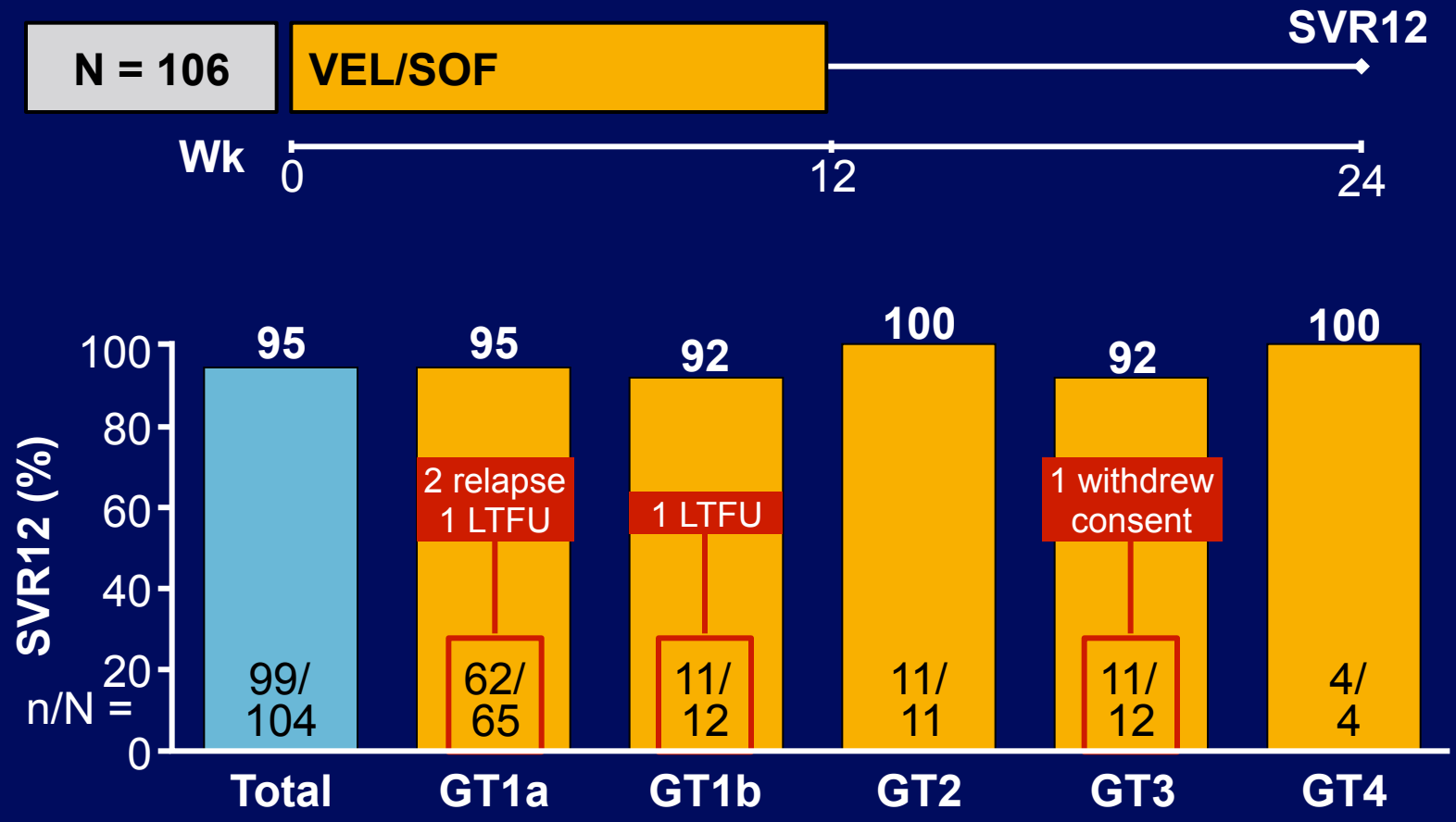
	Overall			Genotype 1		
Breakthrough, n	-	1	1	-	-	-
Relapse, n	11	2	7	5	1	3
LTFU, n	1	-	3	1	-	3
Death, n	3	2	2	2	2	-

- D/c due to AE: 3% (n = 9)
- Death due to AE: 3% (n = 9)
- Fatigue (29%); nausea (23%); HA (22%); anemia (13%; 31% in RBV arm)
- AE more frequent with RBV
- RBV arm: Hb < 10 mg/dL, 23%; Hb < 8.5 mg/dL, 7%
- RBV decreased in 37% and d/c in 17%

Charlton MR, et al. AASLD 2015. Abstract LB-13

Slide credit: clinicaloptions.com

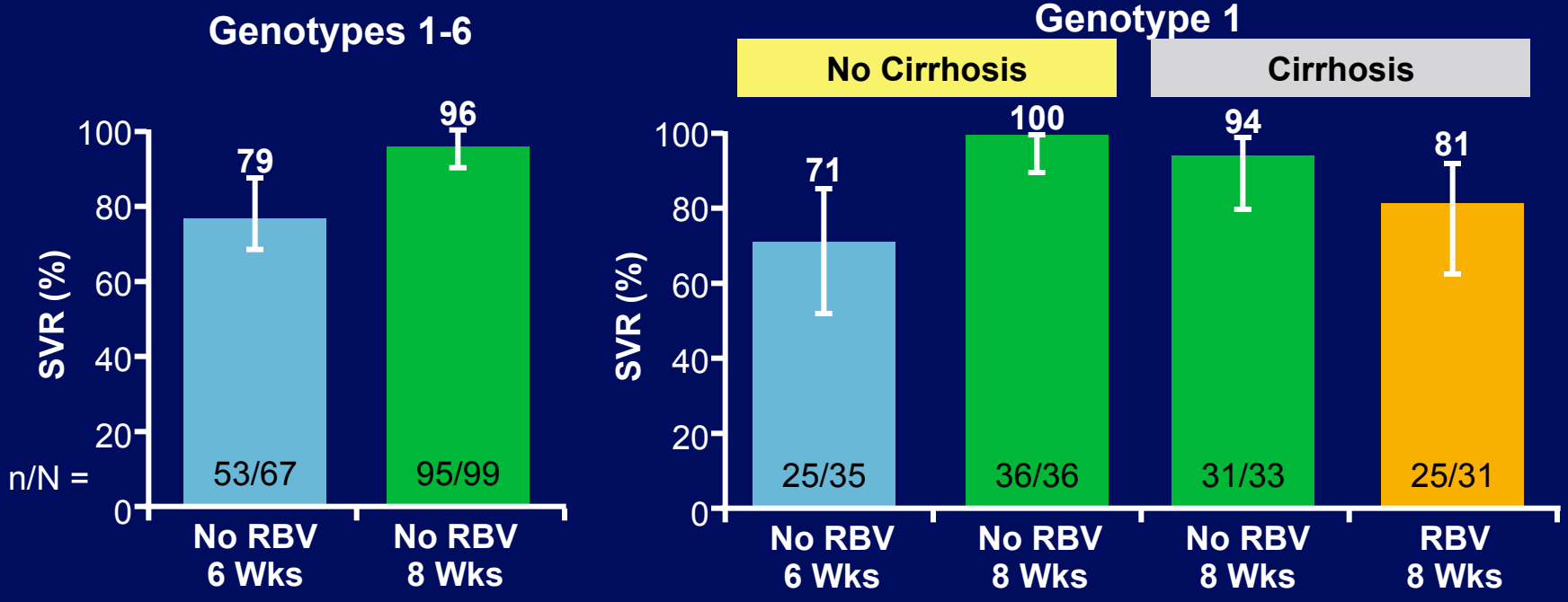
ASTRAL-5: VEL/SOF FDC for 12 Wks in Pts Coinfected With HCV and HIV-1



Wyles D, et al. EASL 2016. Abstract PS104.

Slide credit: clinicaloptions.com

VEL/SOF + GS-9857 for 6 or 8 Wks in Treatment-Naive Pts With GT1-6 HCV



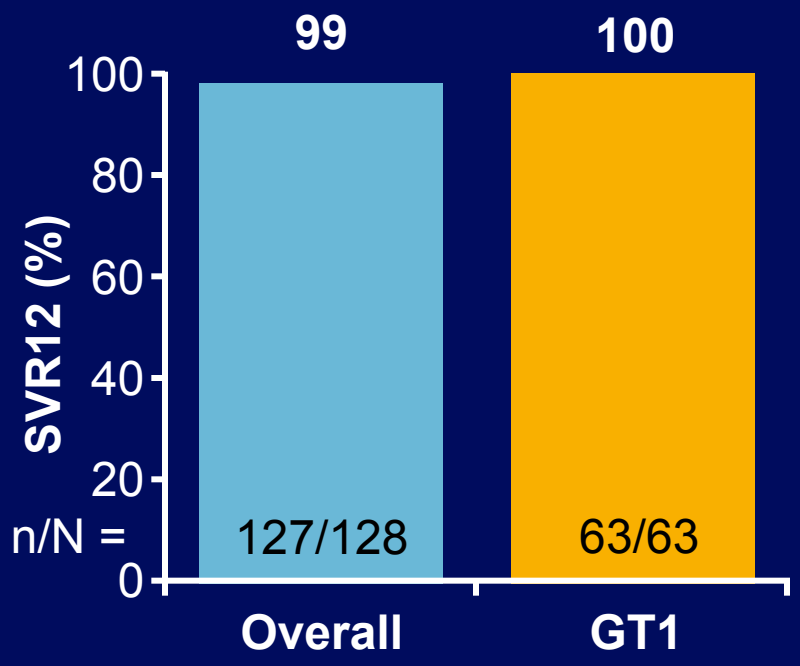
- 8 wks of VEL/SOF + GS9857 highly effective including pts with RAVs and cirrhosis
  - Single tablet QD in phase III
  - 6 wks had high relapse
- No benefit of RBV with 8 wks
- Will the triplet be used as primary first-line treatment or as salvage treatment for persons who fail current DAAs?

Gane EJ, et al. EASL 2016. Abstract SAT-138.

Slide credit: clinicaloptions.com

VEL/SOF + GS-9857 for 12 Wks in Treatment-Experienced GT1-6 HCV

BL Characteristics (N = 128)	VEL/SOF + GS-9857
Cirrhosis, n (%)	61 (48)
Mean HCV RNA, log_{10} IU/mL (range)	6.3 (3.8-8.1)
HCV genotype, n (%)	
▪ 1	63 (49)
▪ 2	21 (16)
▪ 3	35 (27)
▪ 4/6	9 (7)
DAA experience, n (%)	
▪ None (GT2-6 only)	27 (21)
▪ 1 DAA class	36 (28)
▪ ≥ 2 DAA classes	65 (51)



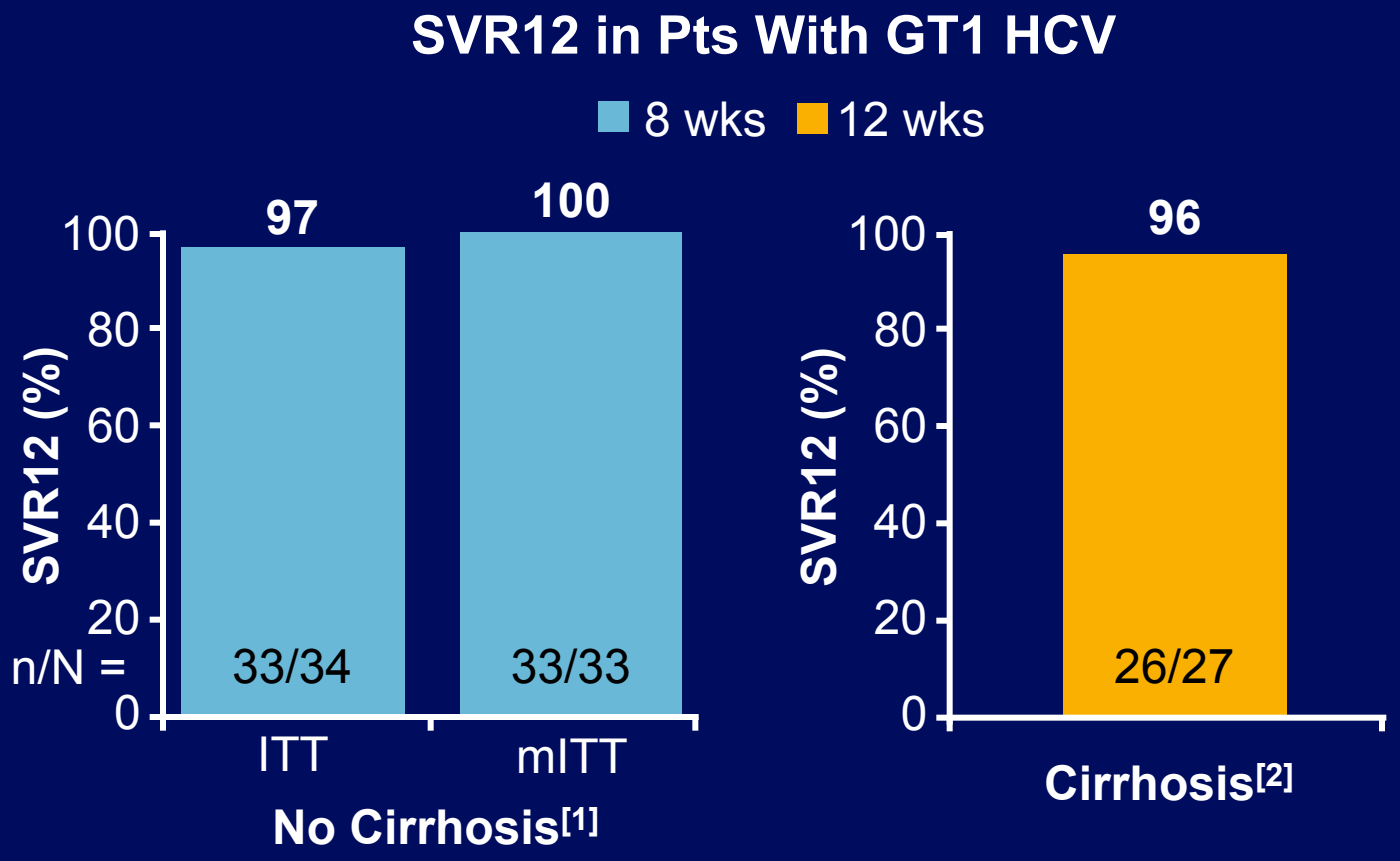
- 1 pt relapsed at posttreatment Wk 8

Lawitz E, et al. EASL 2016. Abstract PS008.

Slide credit: clinicaloptions.com

SURVEYOR-I/II: ABT-493 + ABT-530 for 8 or 12 Wks in Pts With GT1 or 2 HCV

- Open-label, treatment naive or pegIFN/RBV experienced

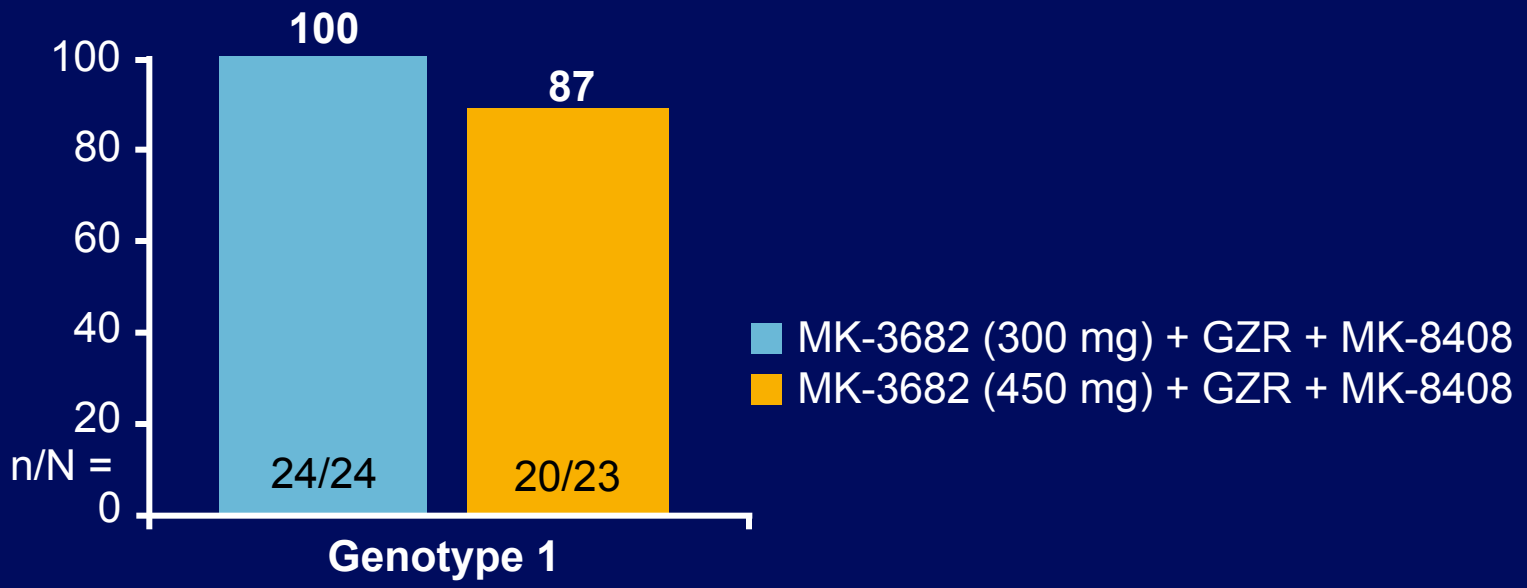


1. Poordad F, et al. EASL 2016. Abstract SAT-157.
2. Gane EJ, et al. EASL 2016. Abstract SAT-135.

Slide credit: clinicaloptions.com

C-CREST 1 and 2: MK-3682/GZR/MK-8408 for 8 Wks in Tx-Naive Noncirrhotic Pts

- GT1, 2, or 3 without cirrhosis (N = 240)



- In GT1 arm, no impact of baseline NS5A, NS3, or NS5B RAVs on SVR12

Gane EJ, et al. EASL 2016. Abstract 139.

Slide credit: clinicaloptions.com

Conclusions

- 5 highly effective regimens approved for GT1 HCV
  - Newest is GZR/EBR, which requires RAV testing in GT1a
- Need for extended therapy and/or RBV in cirrhotics depending on regimen, GT1 subtype, and prior treatment status
- Real-world data reflect efficacy in clinical trials
- Data support 8 wks of LDV/SOF in GT1 treatment-naive noncirrhotics with HCV RNA < 6 M IU/mL
- High-dose PPIs should be avoided with LDV (same likely to be the case with VEL based on clinical trial designs)

Slide credit: clinicaloptions.com

New Regimens in Development

- Promising regimens
  - VEL/SOF (likely to be approved in June 2016)
  - Second-generation 2-drug regimen of ABT-493/ ABT-530
  - Triplet regimens of PI/NS5A/Nuc
- New regimens may offer 8-week option for noncirrhotics
- High SVR rates in DAA failures

Slide credit: clinicaloptions.com

Go Online for More CCO Coverage of HIV!

Multimedia modules featuring video of expert faculty discussions of controversies and challenging cases

Downloadable slidesets for your own study or presentations

clinicaloptions.com/hcv