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Non–Genotype 1 HCV Now and in the Near Future

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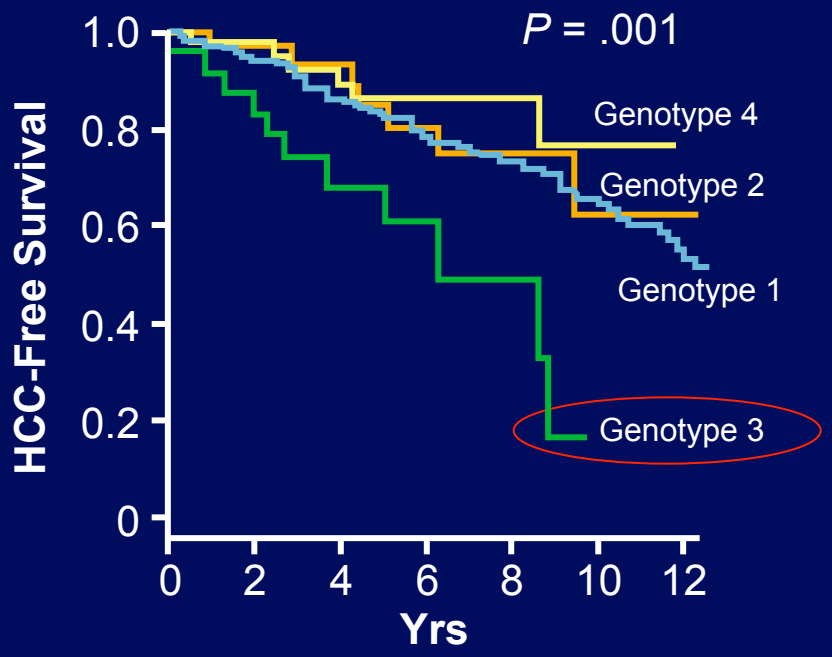
Genotype 3 HCV

Genotype 3 Is Important

- Second most common genotype globally[1]
  - 10% to 15% of HCV cases in the US
- Associated with more rapid progression of fibrosis and higher risk of HCC[2]
- Suboptimal responses to first-generation DAAs

HCC-Free Survival by Genotype[2]

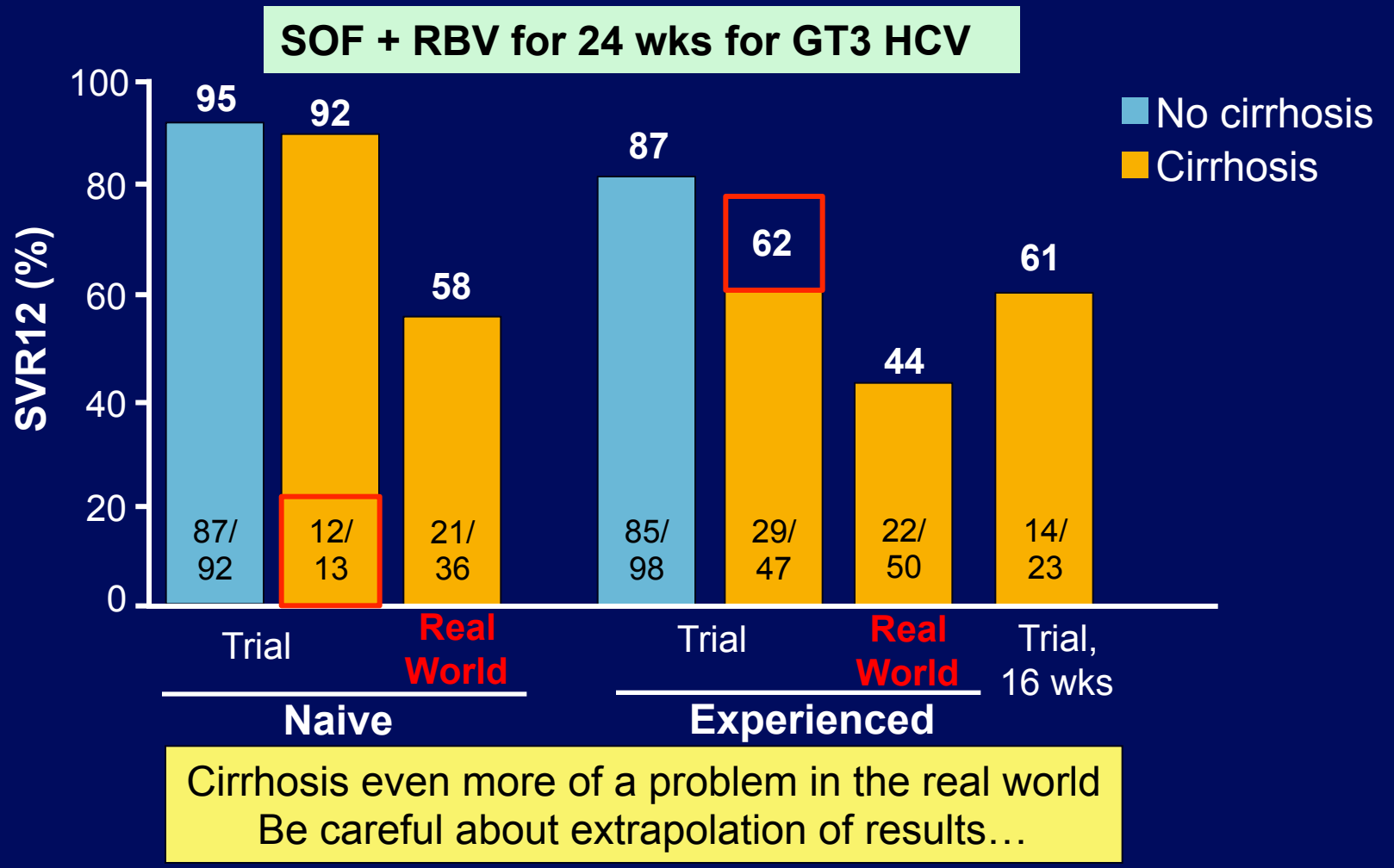


Genotype 1	251	207	166		85	56
Genotype 2	33	27	24		8	3
Genotype 3	25	20	10		3	1
Genotype 4	44	37	25		6	3

1. Messina JP, et al. Hepatology. 2015;61:77-87.
2. Nkontchou G, et al. J Viral Hepat. 2011;18:e516-e522.

Slide credit: clinicaloptions.com

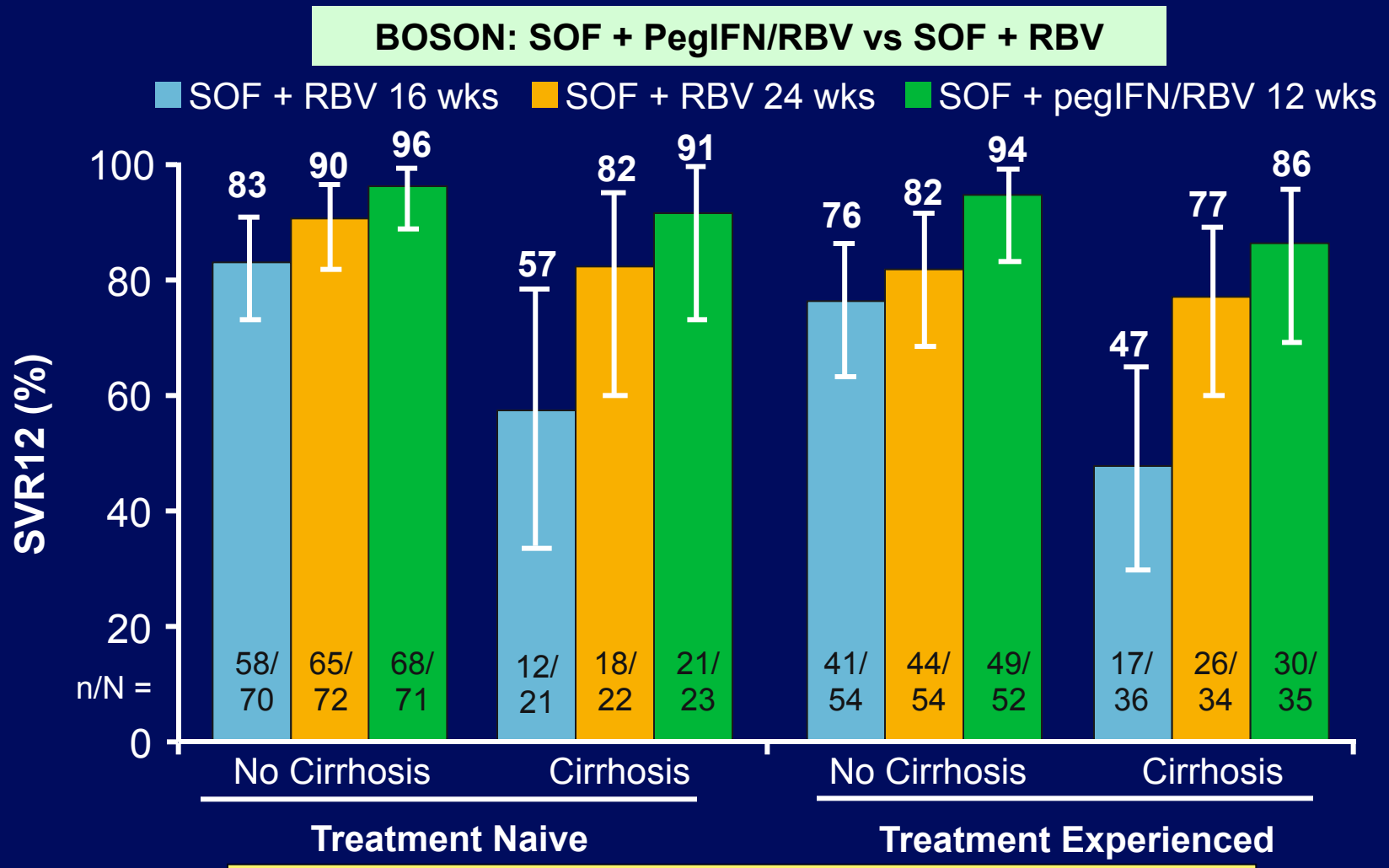
GT3: SOF + RBV Far From Ideal



Cirrhosis even more of a problem in the real world
Be careful about extrapolation of results…

Zeuzem S, et al. N Engl J Med. 2014;370:1993-2001. Feld JJ, et al. Clin Infect Dis. 2016; submitted. Jacobson IM, et al. N Engl J Med. 2013;368:1867-1877. Slide credit: clinicaloptions.com

Can PegIFN Still Be Used?



Clear advantage to SOF + pegIFN/RBV, especially in cirrhosis
Only 1 SOF + pegIFN/RBV discontinuation—good safety

Foster GR, et al. Gastroenterology. 2015;149:1462-1470.

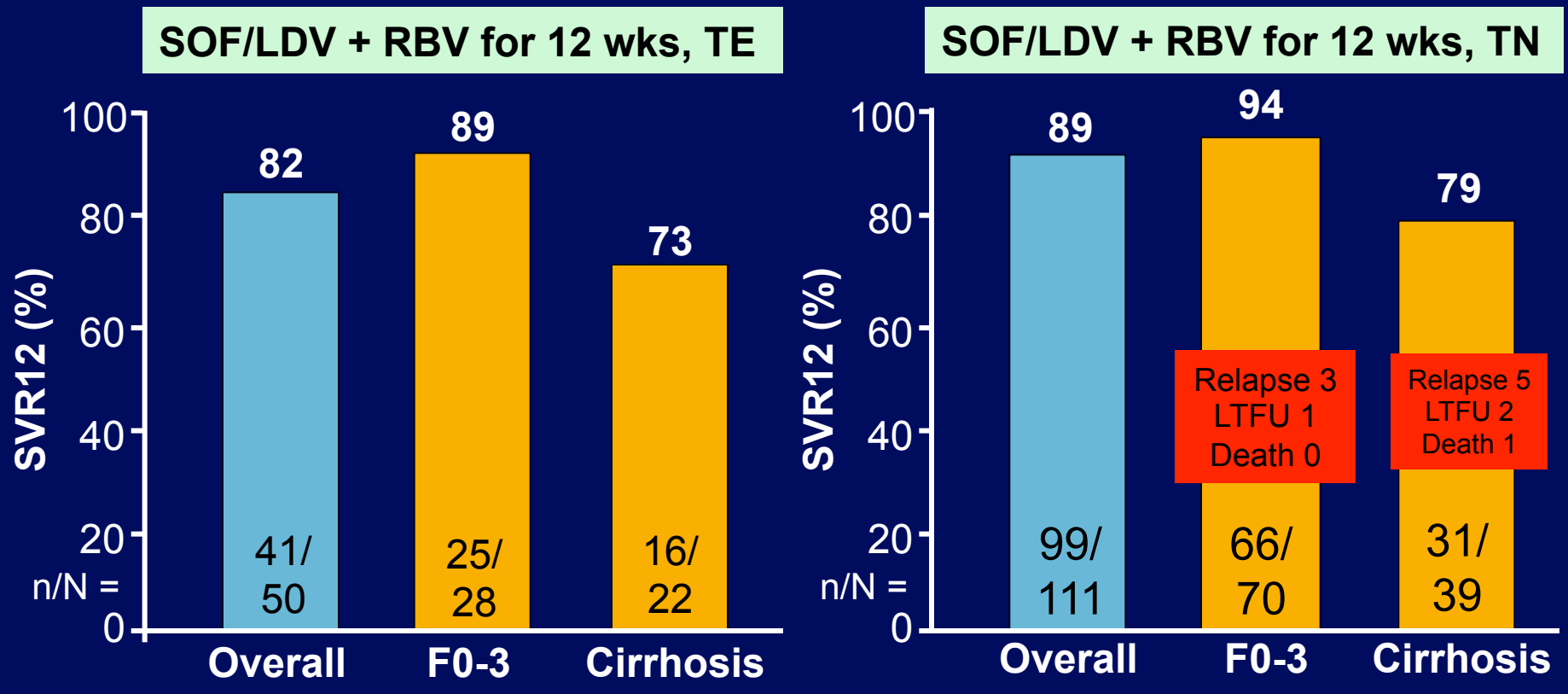
Slide credit: clinicaloptions.com

But Using PegIFN Is Not Ideal . . .
< 5% Uptake in HCV TARGET

Feld JJ, et al. Clin Infect Dis. 2016;submitted.

Slide credit: clinicaloptions.com

What About SOF/LDV for GT3 HCV?



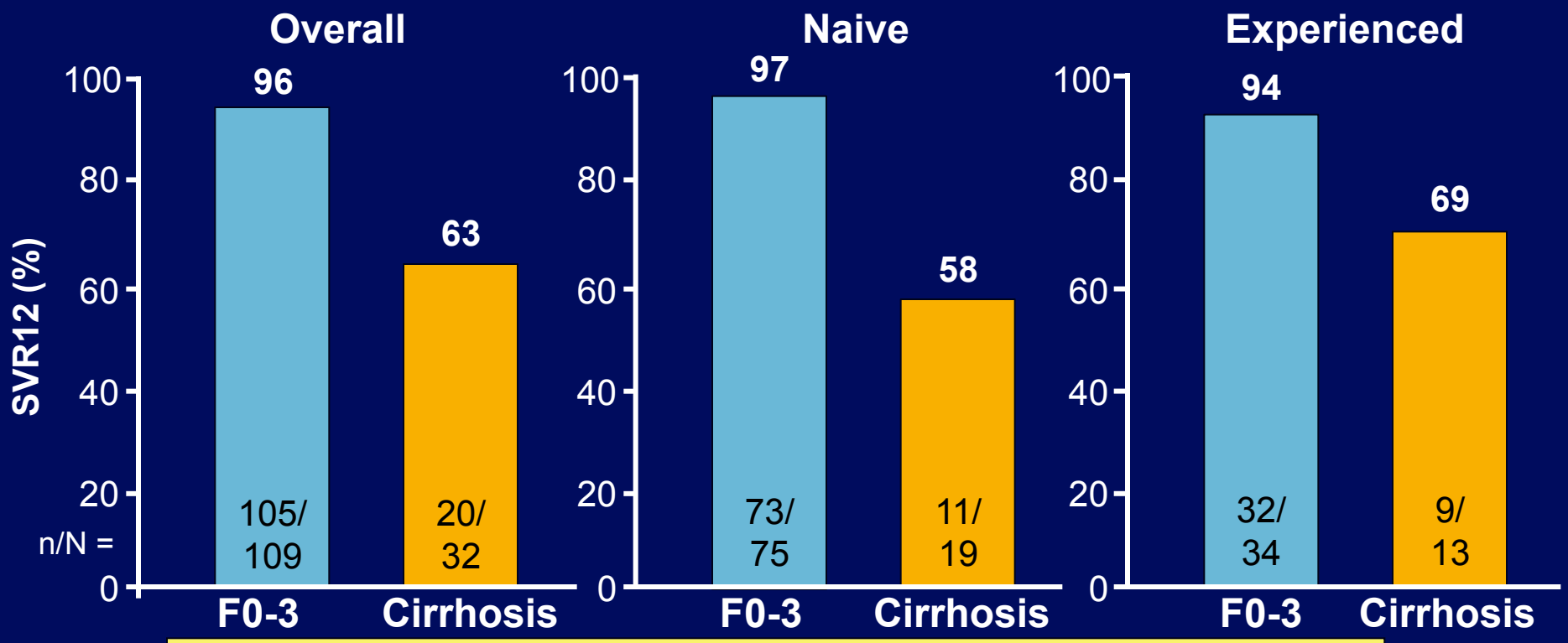
LDV not active against GT3 HCV in vitro…
Better than expected but still not optimal in cirrhotics

Gane EJ, et al. AASLD 2014. Abstract LB-11.
Feld J, et al. EASL 2016. Abstract SAT-183.

Slide credit: clinicaloptions.com

Is SOF + DCV More Effective in GT3 HCV?

ALLY-3: SOF + DCV for 12 wks for GT3 HCV



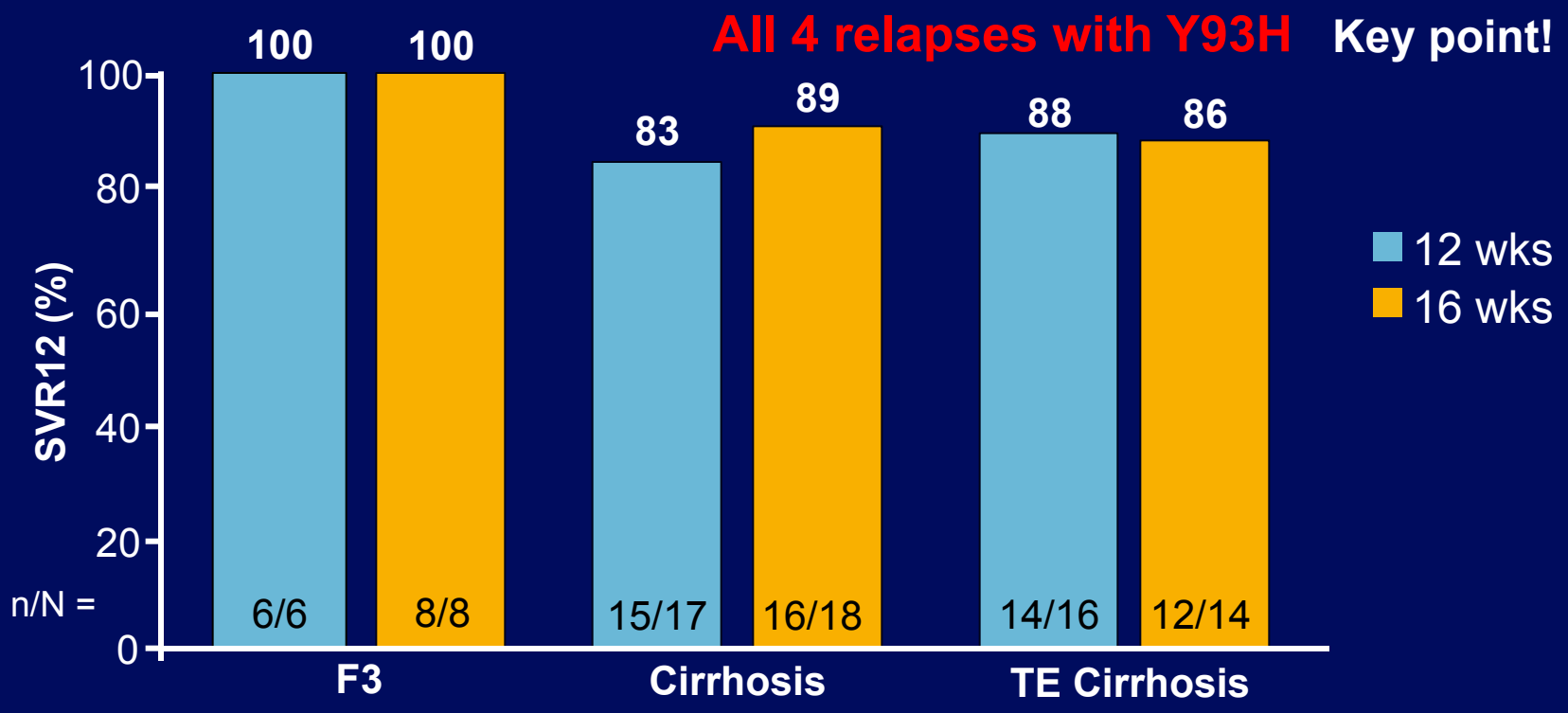
Very good IFN/RBV-free regimen for GT3 noncirrhotics
Unfortunately, not the answer for cirrhosis—at least not for 12 wks

Nelson DR, et al. AASLD 2014. Abstract LB-3.

Slide credit: clinicaloptions.com

Would Longer Help?

ALLY-3+: GT3 HCV pts with F3/F4 treated with SOF + DCV + RBV for 12 or 16 wks



Leaves us without a clear answer…RBV helpful but duration unclear

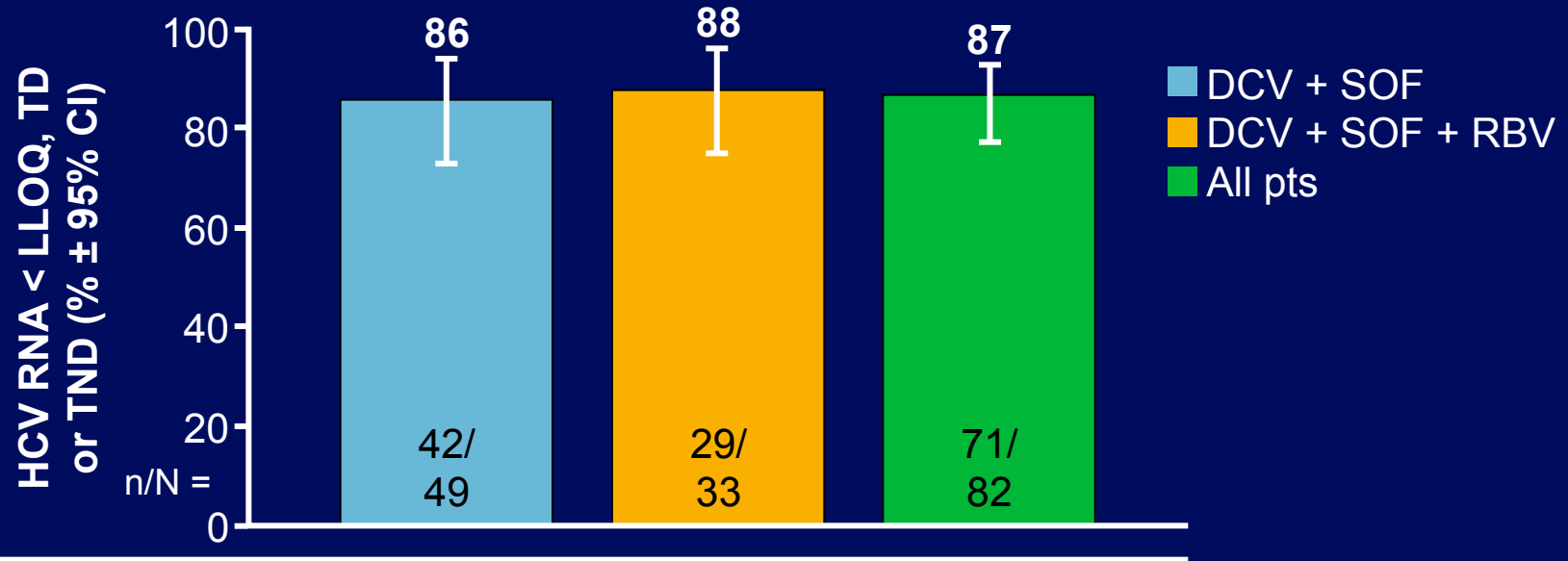
Leroy V, et al. AASLD 2015. Abstract LB-3.

Slide credit: clinicaloptions.com

Lessons From the "Real World"

GT3 HCV pts treated with SOF + DCV ± RBV for 24 wks in European EAP

- Pts with advanced liver disease (85% cirrhotic)



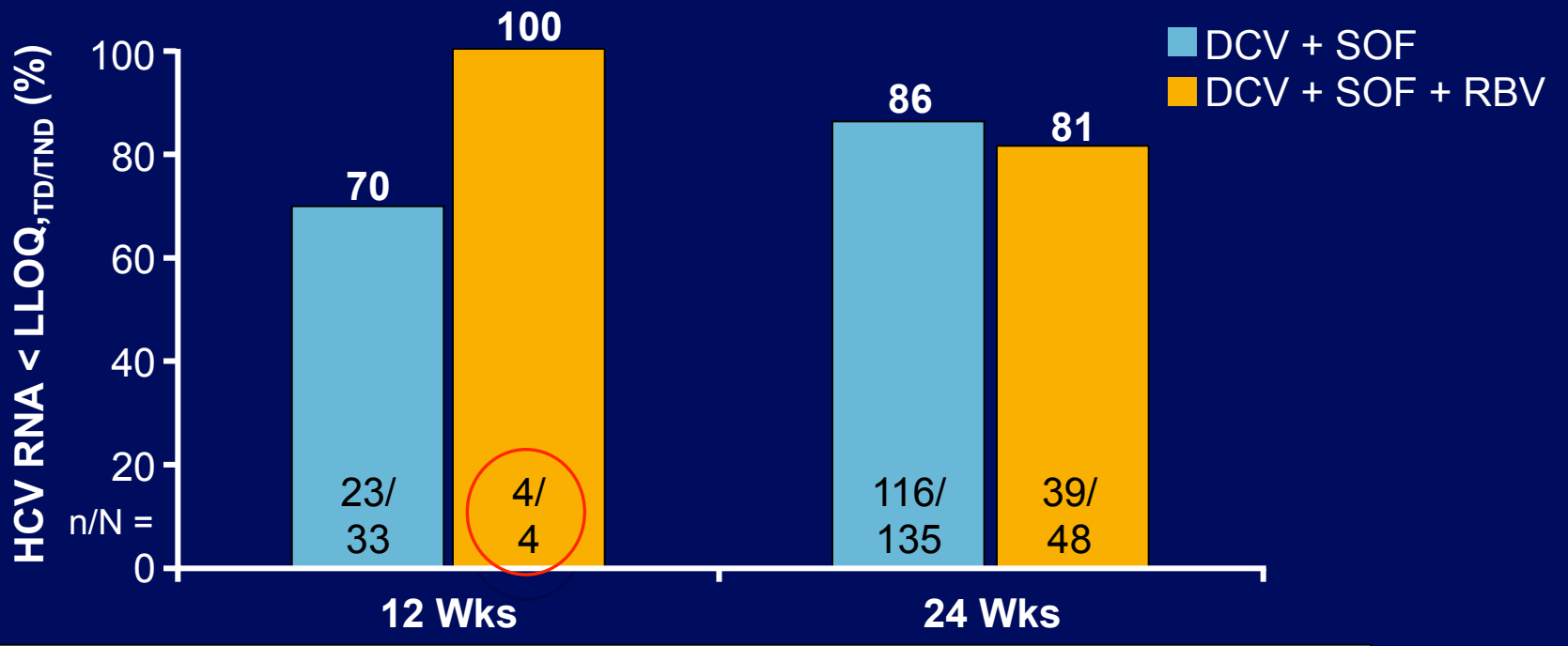
Not Achieving SVR12	7	4	11
Breakthrough	1	0	1
Relapse	3	3	6
Discontinuation (AE)	0	1	1
Death	3	0	3

Welzel TM, et al. AASLD 2015. Abstract 37.

Slide credit: clinicaloptions.com

Effective but Still Not Ideal in Cirrhosis

Cirrhotic GT3 HCV pts treated with SOF + DCV ± RBV for 12 or 24 wks in French EAP



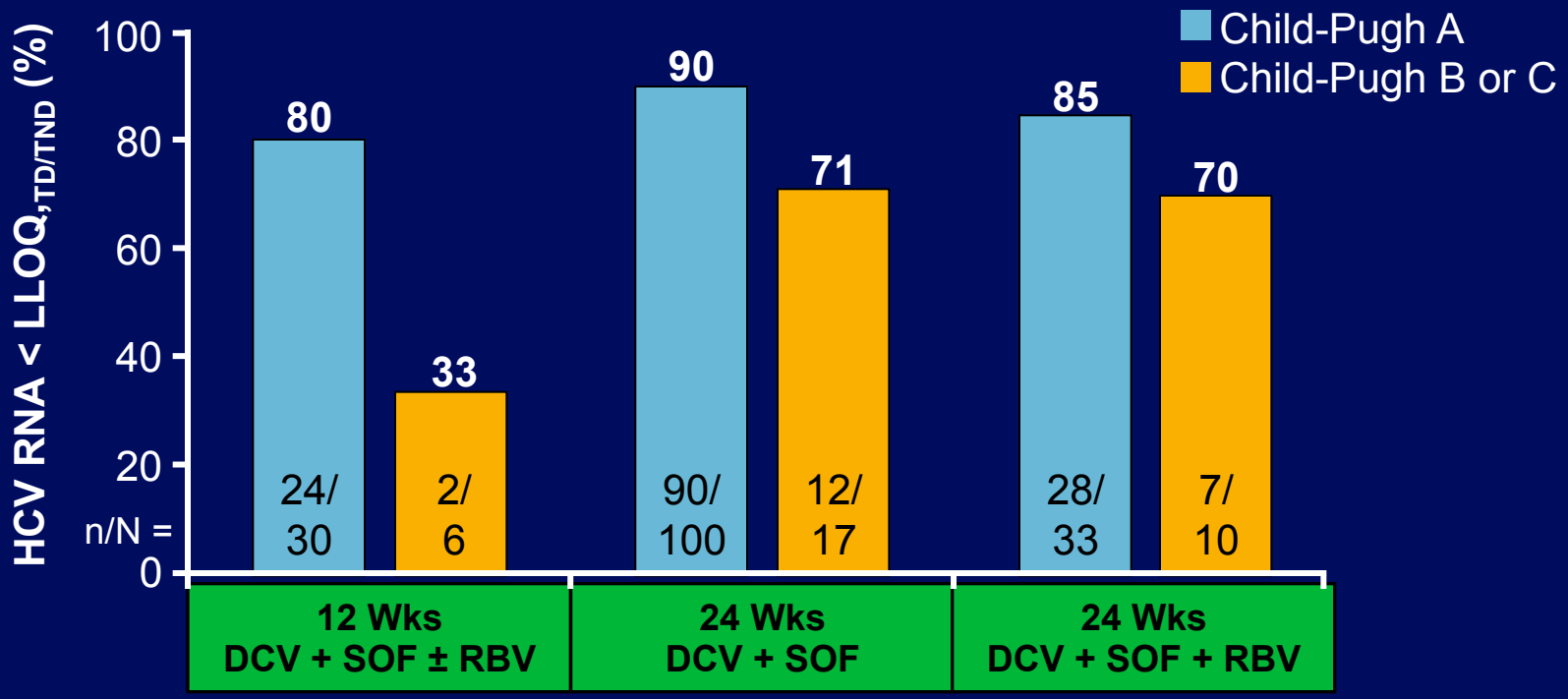
24 wks necessary
Unclear role of RBV
No real trial data…hard to interpret

Hezode C, et al. AASLD 2015. Abstract 206.

Slide credit: clinicaloptions.com

Less Effective With Decompensation

GT3 HCV pts in French EAP treated with SOF + DCV ± RBV for 12 or 24 wks



SOF + DCV is not ideal therapy for pts with advanced cirrhosis

Hezode C, et al. AASLD 2015. Abstract 206.

Slide credit: clinicaloptions.com

Summary of Current Therapy

- SOF + RBV for 24 wks
  - Suboptimal SVR rates, particularly in pts with cirrhosis
- SOF + PegIFN/RBV for 12 wks
  - Good option if you can convince pts to take it!
- SOF + DCV
  - Great for noncirrhotic pts
  - For cirrhotic pts: 16-24 wks with RBV reasonable but not ideal . . . concern that failure will affect future options
- SOF/LDV + RBV
  - Better than expected; similar to SOF + DCV for noncirrhotics but RBV clearly needed

Slide credit: clinicaloptions.com

AASLD/IDSA Guideline Recommendations: Genotype 3 HCV

Prior Treatment	No Cirrhosis	Compensated Cirrhosis
Naive	▪ **SOF + DCV for 12 wks** ▪ **SOF + pegIFN/RBV for 12 wks** ▪ SOF + RBV for 24 wks	▪ **SOF + DCV ± RBV for 24 wks** ▪ **SOF + pegIFN/RBV for 12 wks** ▪ SOF + RBV for 24 wks
Experienced ▪ PegIFN/RBV	▪ **SOF + DCV for 12 wks** ▪ **SOF + pegIFN/RBV for 12 wks**	▪ **SOF + DCV + RBV for 24 wks** ▪ **SOF + pegIFN/RBV for 12 wks**
▪ SOF + RBV	▪ **SOF + DCV + RBV for 24 wks** ▪ **SOF + pegIFN/RBV for 12 wks**	▪ **SOF + DCV + RBV for 24 wks** ▪ **SOF + pegIFN/RBV for 12 wks**

Bold = recommended regimen.

- Decompensated cirrhosis
  - SOF + DCV + low-initial dose RBV for 12 wks

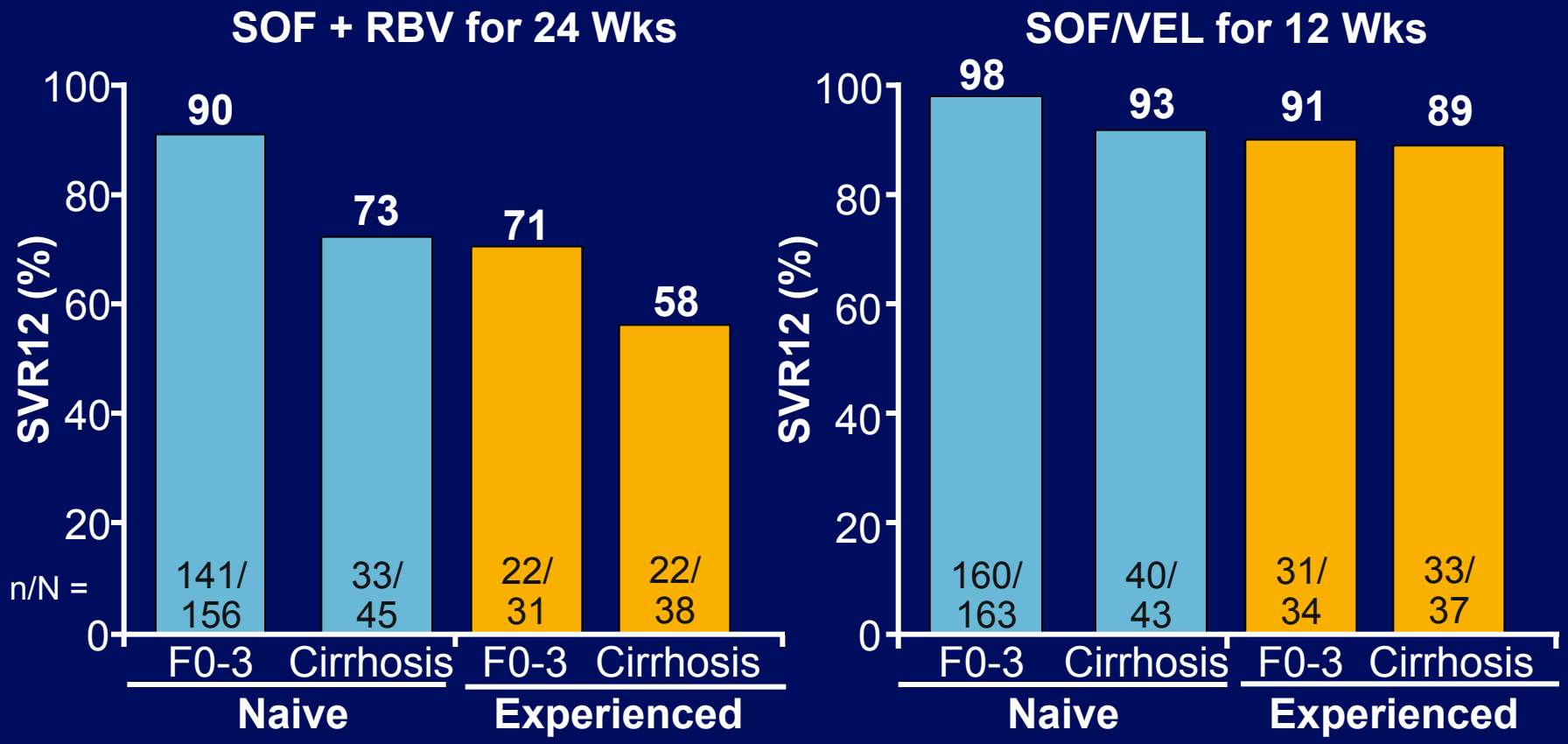
AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

What's Coming?

Pangenotypic Treatment Option Coming Soon

ASTRAL 3: SOF + velpatasvir (GS-5816) (NS5A) for 12 wks vs SOF + RBV for 24 wks in treatment-naive and treatment-experienced pts with GT3 HCV

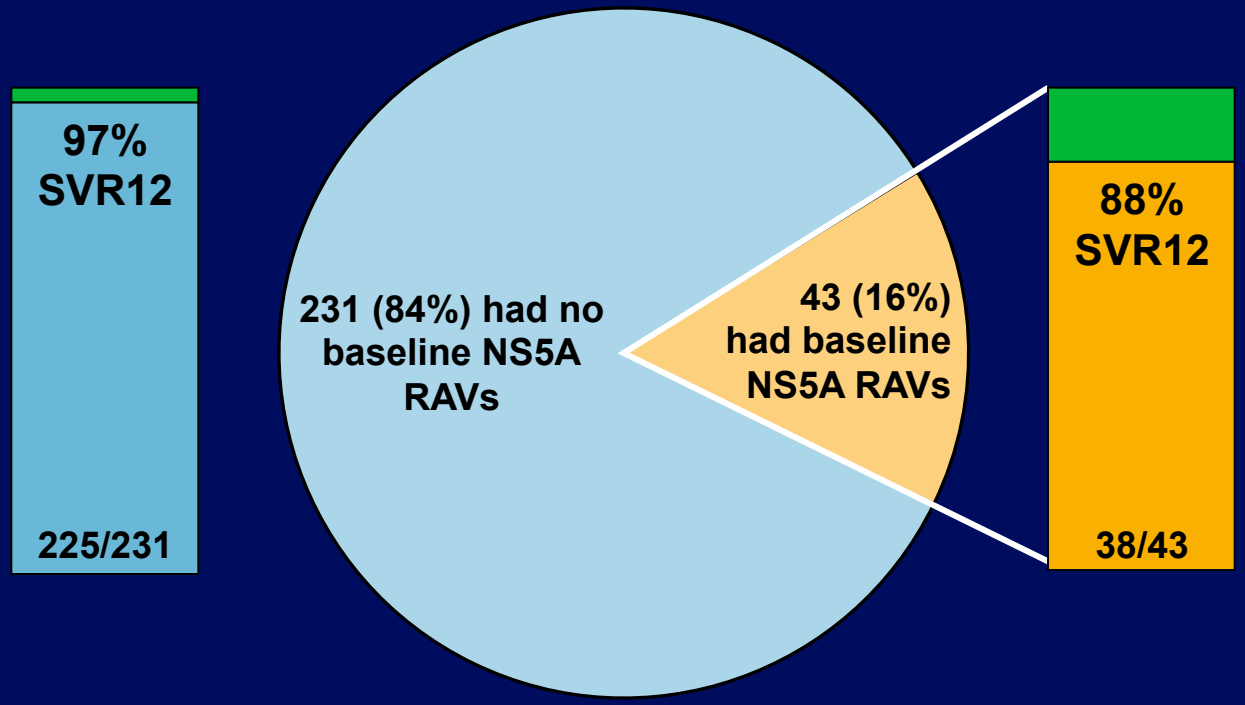


Foster GR, et al. N Engl J Med. 2015;373:2608-2617.

Slide credit: clinicaloptions.com

Avoiding Future Failure . . .

- ASTRAL 3: SVR12 rate with SOF/VEL relative to presence/absence of NS5A RAVs:



- Failing with an NS5A today may impair responses for the future . . .

Foster GR, et al. N Engl J Med. 2015;373:2608-2617.

Slide credit: clinicaloptions.com

SOF/VEL Safety (ASTRAL 1)

Pts,* n (%)	Placebo (n = 116)	SOF/VEL (n = 624)
All AE	89 (77)	485 (78)
Grade 3/4 AE	1 (< 1)	18 (3)
Serious AE	0	15 (2)
Discontinued due to AE	2 (2)	1 (< 1)
Death	0	1 (< 1)
Laboratory abnormalities, grade 3/4	14 (12)	45 (7)
Hb < 10 g/dL	0	2 (< 1)
Hb < 8.5 g/dL	0	0

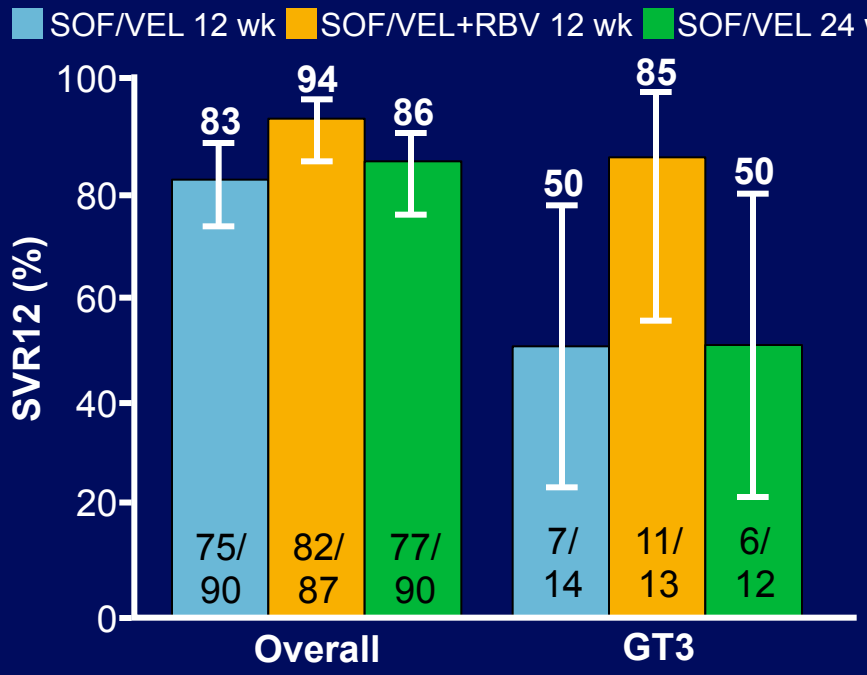
*Pts with GT1, 2, 4, 5, 6 HCV.

Headache, fatigue, nausea most common . . .
equal for treatment and placebo

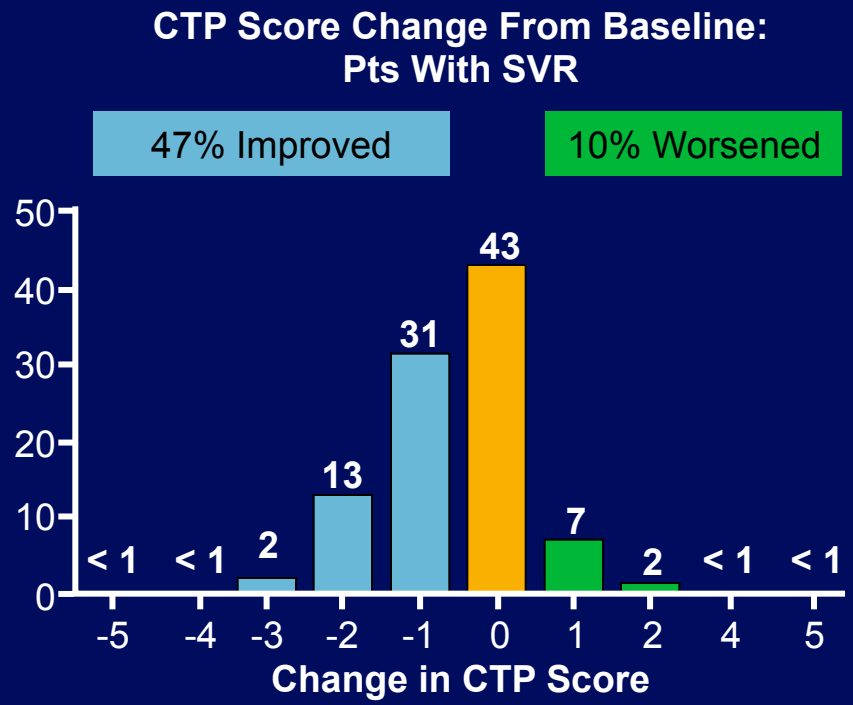
Feld JJ, et al. N Engl J Med. 2015;373:2599-2607.
Feld JJ, et al. AASLD 2015. Abstract LB-2.

Challenges Still Remain . . .

ASTRAL 4: SOF/VEL ± RBV for 12 wks or SOF/VEL for 24 wks in pts with CP-B cirrhosis



	Overall			GT3		
Breakthrough, n	-	1	1	-	1	1
Relapse, n	11	2	7	6	1	4
LTFU, n	1	-	3	-	-	-
Death, n	3	2	2	1	-	1



AEs consistent with clinical sequelae of advanced liver disease, RBV toxicity

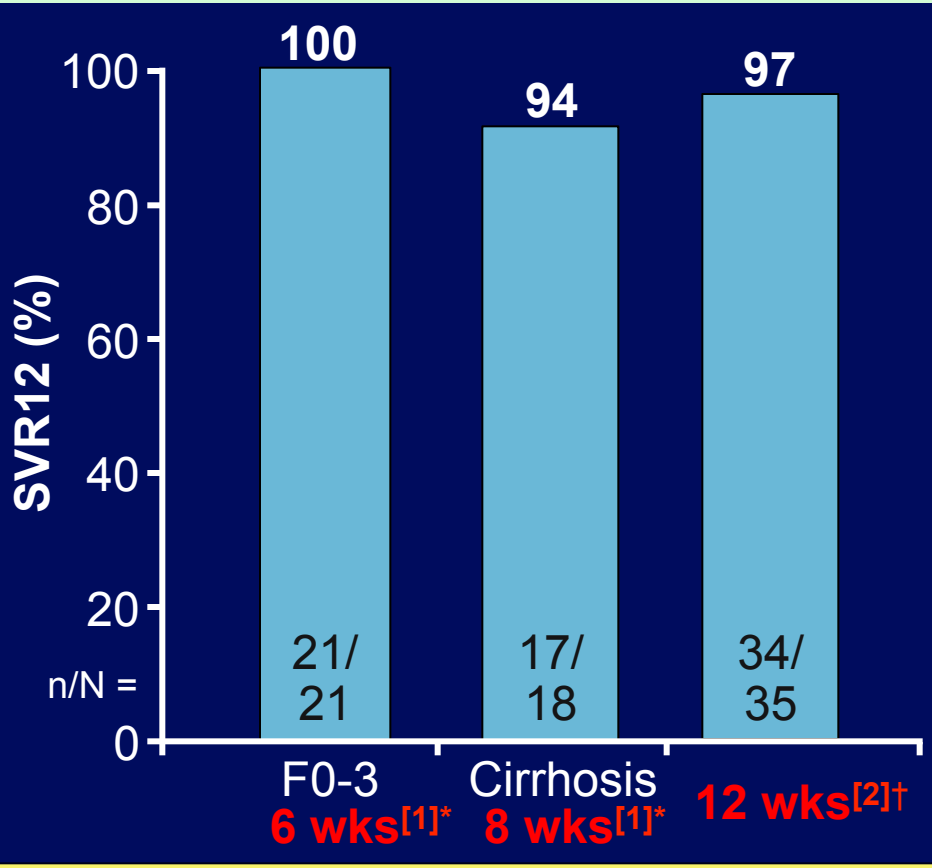
RBV won't go away… still helpful in advanced cirrhosis

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

Slide credit: clinicaloptions.com

Would Another Drug Help?

SOF/VEL + GS-9857 (PI) for 6-12 wks in pts with GT3 HCV



* Treatment-naive pts
†Tx-experienced cirrhotic and noncirrhotic pts

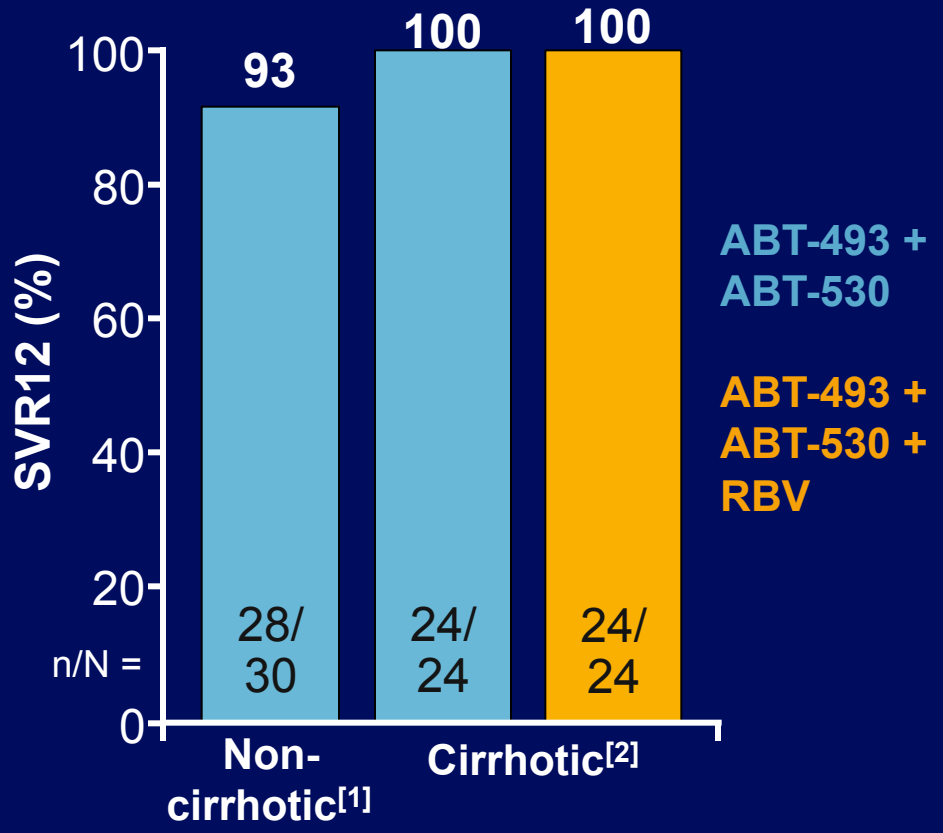
Looks promising across genotypes and for retreatment

1. Gane EJ, et al. EASL 2016. Abstract SAT-138.
2. Lawitz E, et al. EASL 2016. Abstract PS008.

Slide credit: clinicaloptions.com

Another Promising New Regimen

SURVEYOR-II:
ABT-493 (PI) + ABT-530 (NS5A) ± RBV for 12 wks in pts with GT3 HCV



Safety Outcome, Cirrhotic Pts n (%)[2]	ABT-493 + ABT-530 (n = 24)	ABT-493 + ABT-530 + RBV (n = 24)
Any AE	21 (88)	20 (83)
Serious AEs	1 (4)	2 (8)
AEs occurring in ≥ 10% pts		
▪Headache	3 (13)	8 (33)
▪Fatigue	2 (8)	6 (25)
▪Nausea	2 (8)	6 (25)
▪URTI	4 (17)	2 (8)
▪Dizziness	2 (8)	4 (17)
▪Diarrhea	5 (21)	0

1. Kwo PY, et al. AASLD 2015. Abstract 248.
2. Kwo PY, et al. EASL 2016. Abstract LBO1.

Slide credit: clinicaloptions.com

Genotypes 2, 4, 5, and 6 HCV

The Other Genotypes

- All have effective regimens with SVR rate > 90%[1]
- Goals for future regimens
  - Ribavirin free
  - Shorter duration
- Ideal regimen
  - Pangenotypic
  - Short duration
  - Well tolerated

1. AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

Genotype 2 HCV

Genotype 2 HCV

- Initial genotype to have interferon-free, highly effective regimen
- Challenges
  - First-line therapy contains ribavirin
- Goal
  - Ribavirin-free, short-duration regimen

Slide credit: clinicaloptions.com

AASLD/IDSA Guideline Recommendations: Genotype 2 HCV

Pt Subgroup	SOF + RBV	SOF + DCV	SOF + PegIFN/RBV
Treatment naive or pegIFN/RBV failures	**Recommended** No cirrhosis: 12 wks Cirrhosis: 16-24 wks	**Recommended if RBV ineligible** No cirrhosis: 12 wks Cirrhosis: 16-24 wks	**Alternative** for pegIFN/RBV failures with cirrhosis 12 wks

AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

SOF + DCV for GT2 HCV

- ALLY-2: open-label study that included 19 pts with GT2 HCV
- HIV/HCV pts; treatment-naive pts randomized 2:1 to receive either 12 or 8 wks of treatment; previously treated pts received 12 wks of treatment
- Regimen: SOF 400 mg + DCV 60 mg daily (with dose adjustment for HIV ARVs); no RBV

SVR12, GT2 HCV n/N (%)	Naive 12 Wks	Naive 8 Wks	Experienced 12 Wks	Combined 12 Wks
Overall	11/11 (100)	5/6 (83)	2/2 (100)	13/13 (100)
Cirrhotic	--	--	1/1 (100)	1/1 (100)
Noncirrhotic	11/11 (100)	5/6 (83)	1/1 (100)	12/12 (100)

12-wk regimen effective in small sample size; 8 wks less effective

Wyles DL, et al. N Engl J Med. 2015;373:714-725.

AASLD/IDSA Guideline Recommendations: Genotype 2 HCV

Pt Subgroup[1]	SOF + RBV	SOF + DCV	SOF + PegIFN/RBV
Treatment naive or pegIFN/RBV failures	**Recommended** No cirrhosis: 12 wks Cirrhosis: 16-24 wks	**Recommended if RBV ineligible** No cirrhosis: 12 wks Cirrhosis: 16-24 wks	**Alternative** for pegIFN/RBV failures with cirrhosis 12 wks
SOF + RBV failures*	--	**Recommended** ± cirrhosis ± RBV 24 wks†	**Recommended if IFN eligible** ± cirrhosis 12 wks†

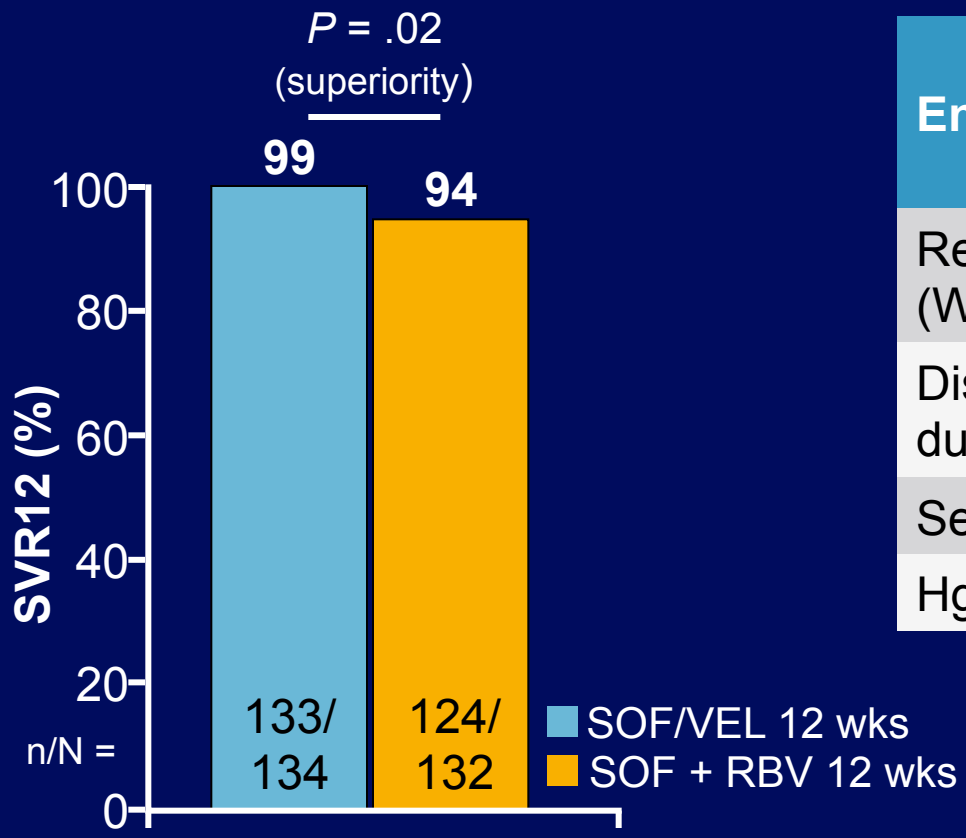
*Limited data for genotype 2 SOF failures. †Level C: consensus opinion of experts, case studies, or standard of care.

- Recombinant GT2k/1b HCV observed in 15% of pts in analysis of 279 pts in Germany, Israel, and Italy[2]
  - SOF + RBV appears less effective for these pts; pts may benefit from GT1b Tx

1. AASLD/IDSA. HCV guidelines. April 2016.
2. Susser S, et al. EASL 2016. Abstract PS001.

What About Sofosbuvir/Velpatasvir?

ASTRAL 2: SOF/VEL vs SOF + RBV for 12 wks in TN/TE pts with GT2 HCV



Endpoint, n (%)	SOF/VEL (n = 134)	SOF + RBV (n = 132)
Relapse (Wk 12)	0	6 (5)
Discontinuations due to AE	1 (1)	0
Serious AEs	2 (1)	2 (2)
Hgb < 10 g/dL	0	6 (5)

Foster GR, et al. N Engl J Med. 2015;373:2608-2617.

Slide credit: clinicaloptions.com

Genotype 4 HCV

Genotype 4

- Multiple highly effective regimens
- Challenges
  - Some regimens include ribavirin
- Goal
  - Ribavirin-free, short-duration regimen

Slide credit: clinicaloptions.com

AASLD/IDSA Guideline Recommendations: Genotype 4 HCV

Pt Subgroup	OBV/PTV/ RTV	EBV/GRZ	SOF/LDV	SOF + RBV	SOF + PegIFN/RBV
Treatment naive, ± cirrhosis	**Recommended** + RBV 12 wks	**Recommended** 12 wks	**Recommended** 12 wks	--	**Alternative** if IFN eligible 12 wks
PegIFN/RBV failures, without cirrhosis	**Recommended** + RBV 12 wks	**Recommended** Relapse: 12 wks Others*: + RBV 16 wks	**Recommended** 12 wks	**Alternative** if RBV eligible and IFN ineligible 24 wks	**Alternative** if IFN eligible 12 wks
PegIFN/RBV failures, cirrhosis	**Recommended** + RBV 12 wks	**Recommended** Relapse: 12 wks Others*: + RBV 16 wks	**Recommended** 24 wks or 12 wks + RBV if eligible	**Alternative** if RBV eligible and IFN ineligible 24 wks	**Alternative** if IFN eligible 12 wks

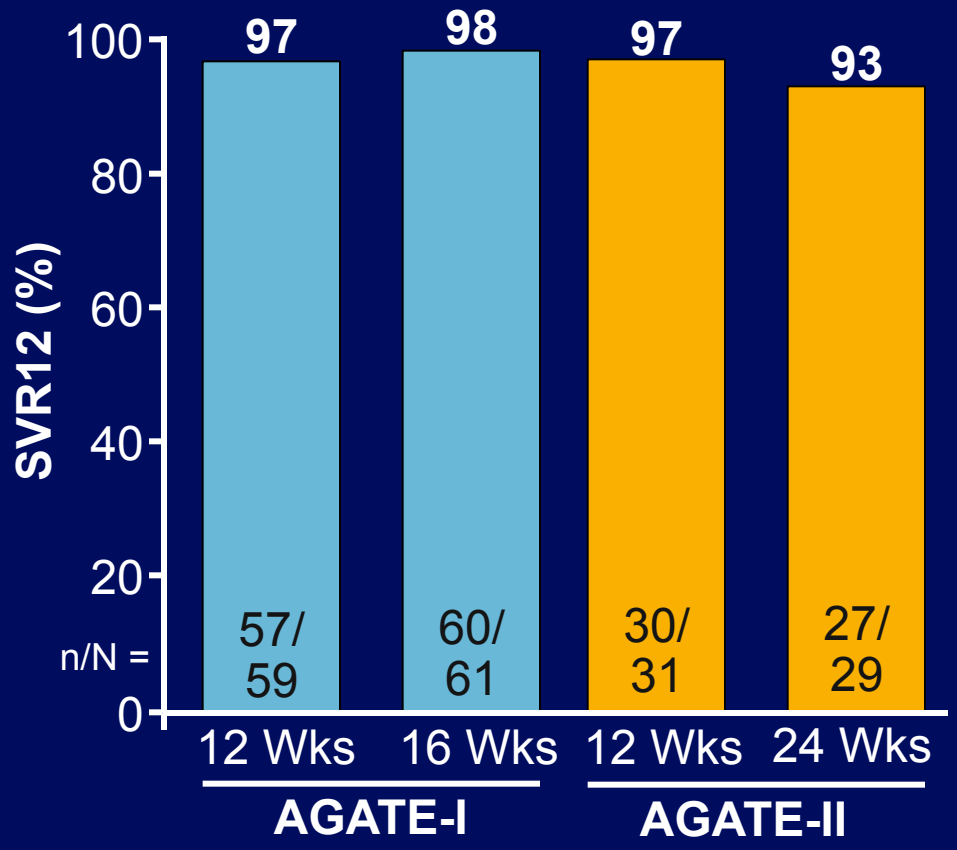
*Prior on-treatment failure to suppress or breakthrough.

AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

OBV/PTV/RTV + RBV for GT4 HCV

- PEARL-I: guided 12 wks and need for RBV in noncirrhotics[1]
- Treatment in compensated cirrhosis?
  - Regimen: OMB/PTV/RTV + RBV
  - AGATE-I: 12 vs 16 wks[2]
  - AGATE-II: 12 vs 24 wks[3]
- AASLD/IDSA recommendation: 12 wks + RBV with cirrhosis[4]



1. Hézode C, et al. Lancet. 2015;385:2502-2509.
2. Asselah T, et al. EASL 2016. Abstract SAT-278.
3. Waked I, et al. EASL 2016. Abstract SAT-166.
4. AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

Elbasvir/Grazoprevir for GT4 HCV

Trial, GT4 HCV Pt Subgroup, % (n/N)	EBV/GRZ 12 Wks	EBV/GRZ + RBV 12 Wks	EBV/GRZ 16 Wks	EBV/GRZ + RBV 16 Wks
NAIVE				
C-EDGE[1]	100 (18/18)	--	--	--
C-EDGE HIV/HCV[2]	96 (27/28)	--	--	--
C-SCAPE[3]	90 (9/10)	100 (10/10)	--	--
EXPERIENCED				
C-EDGE[4]	78 (7/9)	93 (14/15)	60 (3/5)	100 (8/8)

12-wk regimen effective for TN pts;
longer regimens and/or RBV may be needed for TE pts

1. Zeuzem S, et al. Ann Intern Med. 2015;163:1-13. 2. Rockstroh JK, et al. Lancet HIV. 2015;2:e319-e327. 3. Brown A, et al. EASL 2015. Abstract P0771. 4. Kwo PY, et al. EASL 2015. Abstract P0886.

Sofosbuvir/Velpatasvir for GT4 HCV

ASTRAL 1: SOF/VEL vs PBO for 12 wks in TN/TE pts with GT1, 2, 4, 5, 6 HCV

Parameter	All GTs on SOF/VEL (n = 624)	GT4 on SOF/VEL (n = 116)
Cirrhosis, %	19.4	23.3
SVR12, % (n/N)	99.0 (618/624)	100 (116/116)

Feld JJ, et al. N Engl J Med. 2015;373:2599-2607.

Slide credit: clinicaloptions.com

Genotypes 5 and 6 HCV

Genotypes 5 and 6

- Challenges
  - Limited data
- Goal
  - Ribavirin-free, short-duration regimen

Slide credit: clinicaloptions.com

AASLD/IDSA Guideline Recommendations: Genotypes 5 and 6 HCV

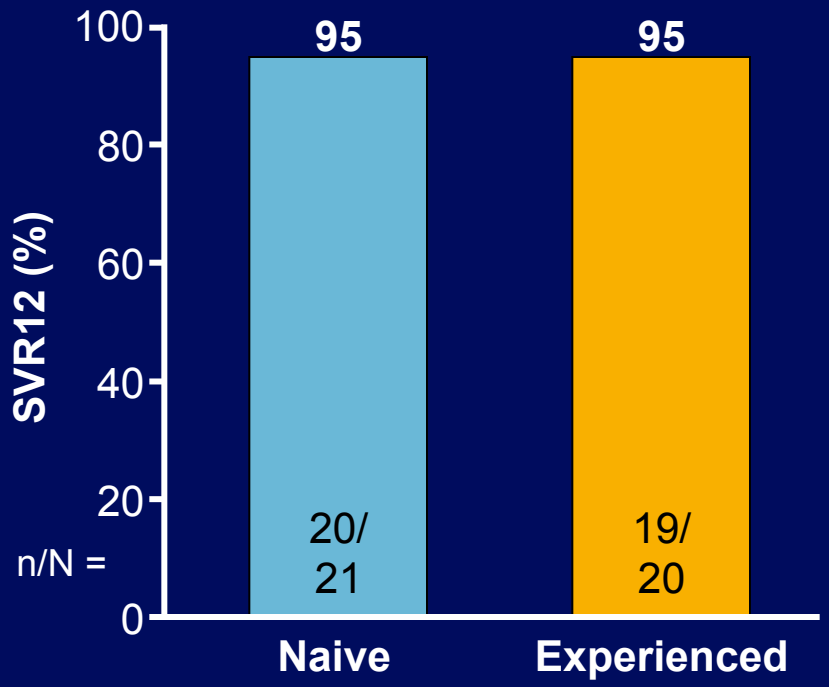
Pt Subgroup	SOF/LDV	SOF + PegIFN/RBV
Treatment naive, ± cirrhosis	**Recommended** 12 wks	**Alternative** if IFN eligible 12 wks
PegIFN/RBV failures, ± cirrhosis	**Recommended** 12 wks	**Alternative** if IFN eligible 12 wks

AASLD/IDSA. HCV guidelines. April 2016.

Slide credit: clinicaloptions.com

Sofosbuvir/Ledipasvir for GT5 HCV

SOF/LDV for 12 wks in TN/TE pts with GT5 HCV
Open-label, multicenter, single-arm phase II trial



12-wk SOF/LDV effective for Tx-naive and Tx-experienced pts

Abergel A, et al. Lancet Infect Dis. 2016;16:459-464.

Slide credit: clinicaloptions.com

What About Elbasvir/Grazoprevir for Genotypes 5 and 6 HCV?

- Not currently included in AASLD/IDSA guidance
- FDA approval not received for genotype 5 or 6
- Genotype 6: limited data
  - C-EDGE (phase III trial): included 10 treatment-naive pts with genotype 6 HCV[1]
    - Elbasvir/grazoprevir 12 wks without ribavirin
    - SVR12 8/10 (80%)

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

Sofosbuvir/Velpatasvir for GT5 and 6 HCV

ASTRAL 1: SOF/VEL vs PBO for 12 wks in TN/TE pts with GT1, 2, 4, 5, 6 HCV

Parameter	All GTs on SOF/VEL (n = 624)	GT5 on SOF/VEL (n = 35)	GT6 on SOF/VEL (n = 41)
Cirrhosis, %	19.4	14.3	14.6
SVR12, % (n/N)	99.0 (618/624)	97.1 (34/35)	100 (41/41)

Feld JJ, et al. N Engl J Med. 2015;373:2599-2607.

Slide credit: clinicaloptions.com

Summary

- Genotype 3 HCV
  - Noncirrhotics
    - SOF + DCV for 12 wks very effective
    - SOF + RBV for 24 wks or SOF + pegIFN/RBV for 12 wks acceptable
  - Cirrhotics
    - May consider waiting for promising options in the near future, including:
      - SOF/VEL ± GS-9857
      - ABT-493 + ABT-530
- Genotypes 2, 4, 5, 6 HCV
  - Effective regimens available
  - Progress continues with potent, shorter durations

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