HCV: How to provide the best treatment with what I have

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Disclosures

David R Nelson, MD,

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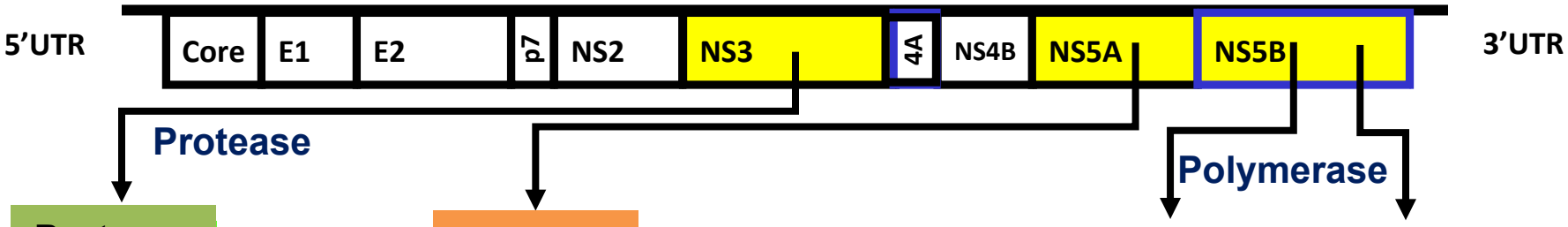
Key Points

- Six all-oral regimens are approved for chronic HCV treatment; two more coming in 2016
- Limited access and availability of some oral agents create the need to build the best treatment regimen from available drugs
- Treatment choice is often based on access, efficacy, safety, and cost balance
- Easy to treat populations allow more options for tailored therapy, while hard to treat populations (eg; Gen 3, decompensated, renal failure) require more select treatment regimens

Multiple Validated Drug Targets in 2016



Protease inhibitors

Simeprevir
Paritaprevir
Grazoprevir

NS5A Inhibitors

Ledipasvir Elbasvir
Daclatasvir Velpatasvir
Ombitasvir

NS5B Nucs

Sofosbuvir

NS5B Non-nucs

Dasabuvir

	DAA Regimens in Use	Direct Acting Antiviral Class
Current	Sofosbuvir + RBV	NUC
	Sofosbuvir + Simeprevir	NUC + PI
	Sofosbuvir + Ledipasvir	NUC + NS5A
	Paritaprevir + Ombitasvir + Dasabuvir +/- RBV	PI + NS5B + NNI
	Sofosbuvr + Daclatasvir	NUC + NS5A
	Asunaprevir + Daclatasvir	PI + NS5A
Pending approval	Grazoprevir + Elbasvir	PI + NS5A
	Sofosbuvir + Velpatasvir	NUC + NS5A

How to Provide the Best Treatment With What I Have?

Option #1: Have The Best Treatment

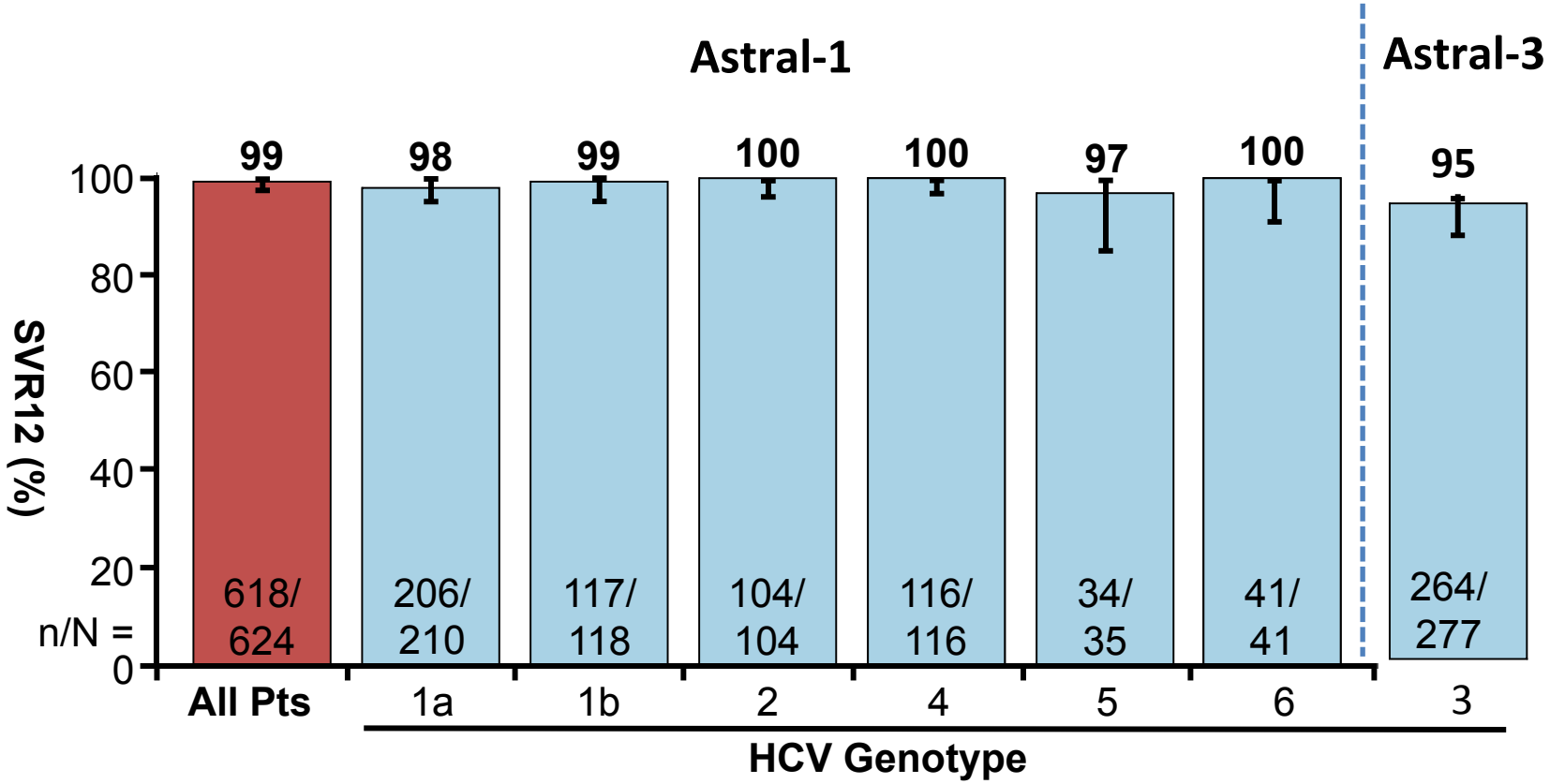
Key Attributes of "Best Treatment"

- Extremely high efficacy (>95%)
- Minimal toxicity
- Minimal drug-drug interactions
- Once daily dosing and no ribavirin
- Pangenotypic
- Short duration
- Low cost

Is this type of drug on the horizon ?

ASTRAL-1 and 3: SVR12 With Sofosbuvir/ Velpatasvir for 12 Weeks in GT1, 2, 3, 4, 5, 6 HCV

- Highly effective across all genotypes and stages of liver disease
- AE profile similar to placebo



Feld JJ, et al. N Engl J Med. 2015; Foster GR, et al. N Engl J Med. 2015

How to Provide the Best Treatment With What I Have?

Option #2: Build the best possible treatment regimen from available drugs

- Preferred treatment choices with multiple options are provided by most guidelines
- However, restrictions of access to drugs on formulary and of which patients can be treated alter the traditional physician-patient decision process
  - Ex: Market simulation survey* of 45 US academic centers in Aug 2015 showed that only 10% of physicians/patients had parity in drug choice selection
    - 90% of patients had a single "preferred" drug based on pricing agreements between commercial payors/Medicaid and Pharma

*HCV-TARGET survey

Balance of Efficacy, Safety, and Cost

Second Generation DAAs offer high level of safety and efficacy

Regimen	Type	SVR (%)	SAE (%)	DDR (%)	Cost/wk ($)	Cost/SVR ($)
P + R	Naïve	49.4 (42.7-56.2)	10.1 (7.2-14.0)	9 (5.3-14.9)	900	87449
P + R	NR	18.5 (15.2-22.4)	7.9 (5.5-11.3)	3.5 (2.1-5.7)	900	233514
TEL or BOC based with P/R	Naïve	74.5 (67.8-80.2)	9.4 (6.7-13.0)	11.9 (6.5-20.7)	2300	148188
TEL or BOC based with P/R	NR	62.6 (55.9-68.7)	13.7 (11.3-16.5)	12.5 (9.8-15.8)	2300	176358
SOF or SIM based with P/R	Naïve	90.3 (83.6-94.4)	5.4 (1.9-12.5)	2.5 (1.1-5.4)	6900	91694
SOF or SIM based with P/R	NR	95.9 (91.5-98.1)	6.8 (1.1-12.8)	1.9 (0.5-7.1)	6900	86340
DAA + R	Naïve	92.3 (82.9-96.7)	3.1 (1.3-6.8)	0.9 (0.3-2.6)	12200	158613
DAA +R	NR	95.9 (91.5-98.1)	3.3 (1.1-9.9)	1.9 (0.5-7.1)	12200	152659
2 DAA, No P/R	***Naïve***	***96.4 (93.6-98.0)***	***1.9 (0.6-5.7)***	***0.9 (0.3-2.7)***	***12000***	***149378***
2 DAA, No P/R	***NR***	***94.1 (88.9-97.0)***	***2.3 (0.6-8.8)***	***1.4 (0.3-6.5)***	***12000***	***153029***

Bansal A et al. World J Hepatol 2015;7:806-813
23 RCT including 9,354 pts

DDR: drug d/c rate

Case 1: Easy To Treat Population

34 year old Asian female, with baseline HCV RNA of 850,000 IU/ml and genotype 1b, mild fibrosis and the IL28B CC genotype.

AASLD and IDSA: Recommended HCV Regimens for This Patient

Duration of Therapy (weeks)

	Genotype 1a		Genotype 1b	
	No Cirrhosis	**With Cirrhosis***	**No Cirrhosis**	**With Cirrhosis***
Ledipasvir/sofosbuvir (90/400 mg qd)	12^	12	12^	12
Sofosbuvir (400 mg qd) + simeprevir (150 mg qd) ± RBV†‡	12 (no RBV)	24 (without Q80K)	12 (no RBV)	24
Ombitasvir/paritaprevir/r (25/150/100 mg qd) + dasabuvir (250 mg bid) ± RBV	12 (with RBV)	24‡ (with RBV)	12 (no RBV)	12 (no RBV)
Daclatasvir (60 mg qd)§ + sofosbuvir (400 mg qd) ± RBV	12 (no RBV)	24	12 (no RBV)	24

Weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]).; *Compensated cirrhosis.; †Role of RBV is unclear, awaiting results from larger phase 3 studies for clarification.; ‡12 weeks may be considered for some patients based on prior treatment history. §Dose may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively.; ^ FDA label: consider 8 weeks of therapy if HCV RNA < 6M IU/ml

AASLD and IDSA. http://www.hcvguidelines.org/full-report-view. Version December 11, 2015.

Easy to Treat Genotype 1 Patient
Multiple Pathways to High SVR

Regimen	SVR %
Tier 1	
Sofosbuvir + Ledipasvir x 8-12 wks	> 95%
Paritaprevir /ritonavir + Ombitasvir + Dasabuvir x 12 wks	> 95%
Sofosbuvir + Daclatasvir x 12 weeks	> 95%
Sofosbuvir + Simeprevir x 12 weeks	> 95%
Elbasvir/Grazoprevir x 12 weeks	> 95%
Tier 2	
PEG/RBV + Sofosbuvir x 12 weeks	> 95%
Asunaprevir + Daclatasvir x 24 weeks	> 85%
Tier 3	
PEG/RBV + Simeprevir x 24 weeks	> 90%
Sofosbuvir + Telaprevir x 12 weeks	> 90%
PEG/RBV x 24-48 weeks	> 85%

Case 2: Hard To Treat Population

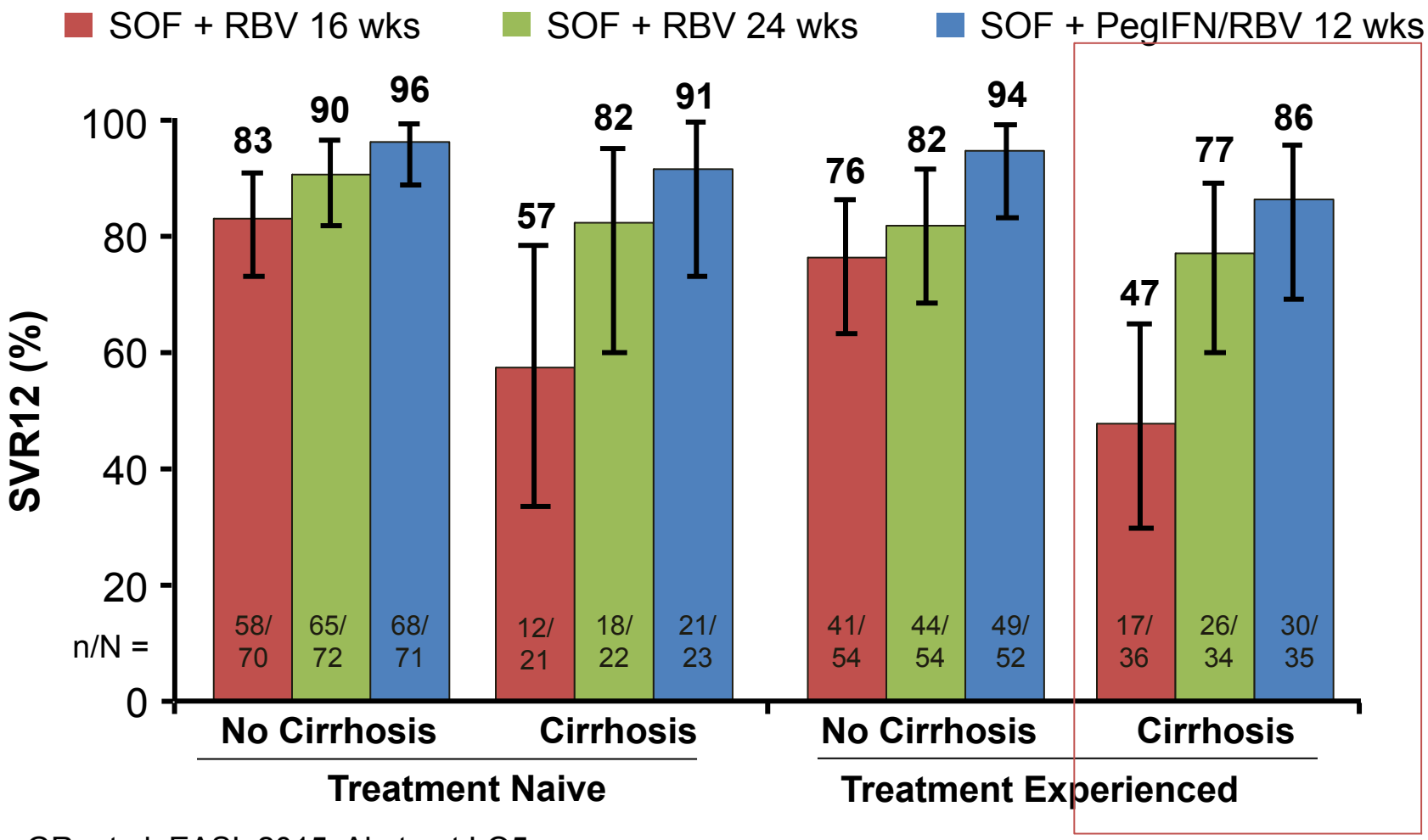
68 year old male, genotype 3, cirrhosis and failed prior therapy with PEG-IFN + ribavirin.

AASLD/IDSA recommendations for Gen 3, cirrhosis, TE Patients

Sofosbuvir (400 mg qd) + PR for 12 weeks
Daclatasvir (60 mg qd) + sofosbuvir (400 mg qd) ± RBV for 24 weeks

AASLD and IDSA. http://www.hcvguidelines.org/full-report-view. Version December 11, 2015.

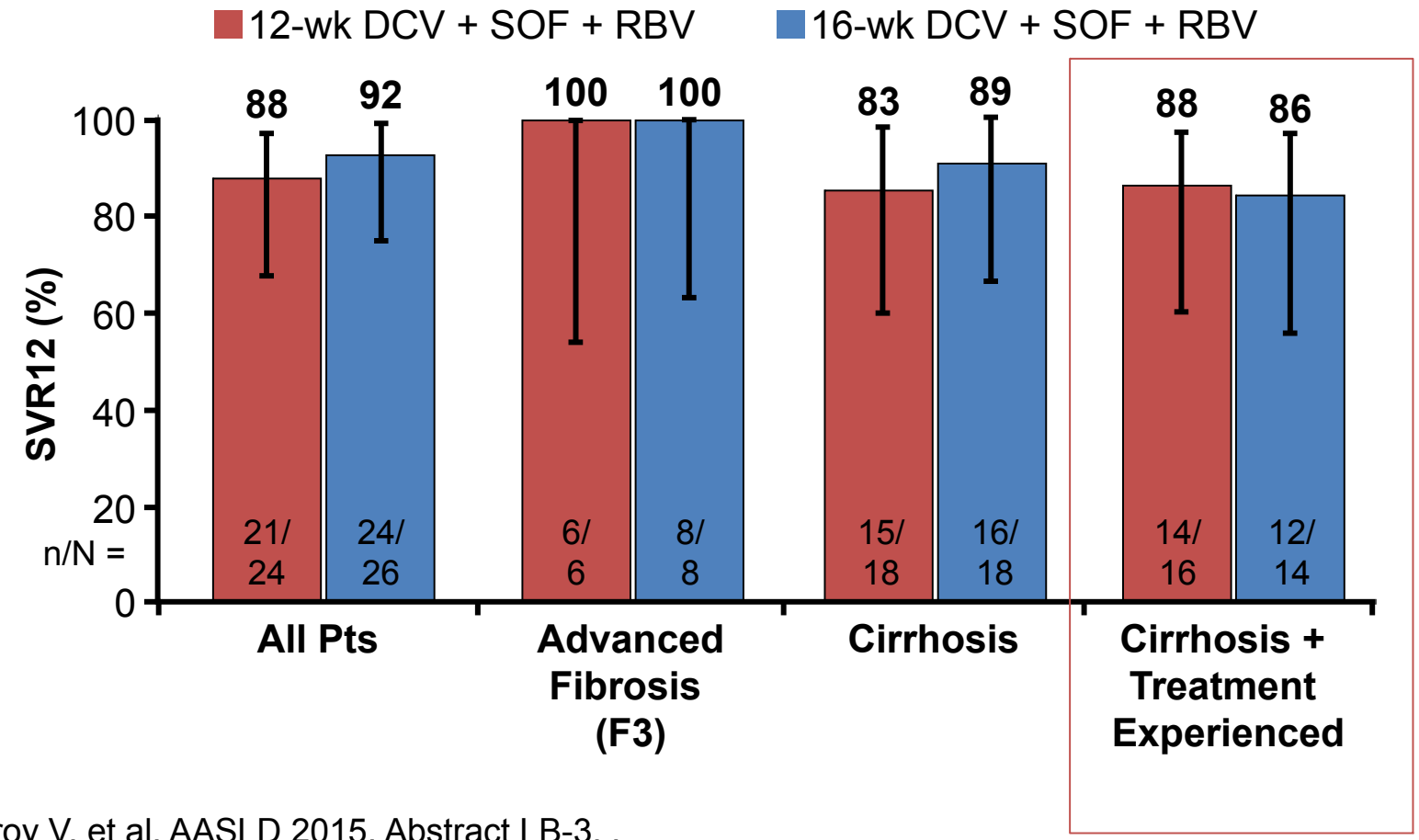
BOSON: SVR12 in GT3 by Tx History and Cirrhosis Status



Foster GR, et al. EASL 2015. Abstract LO5.

ALLY-3+: Longer Duration and RBV Improve Response in G3 Cirrhosis

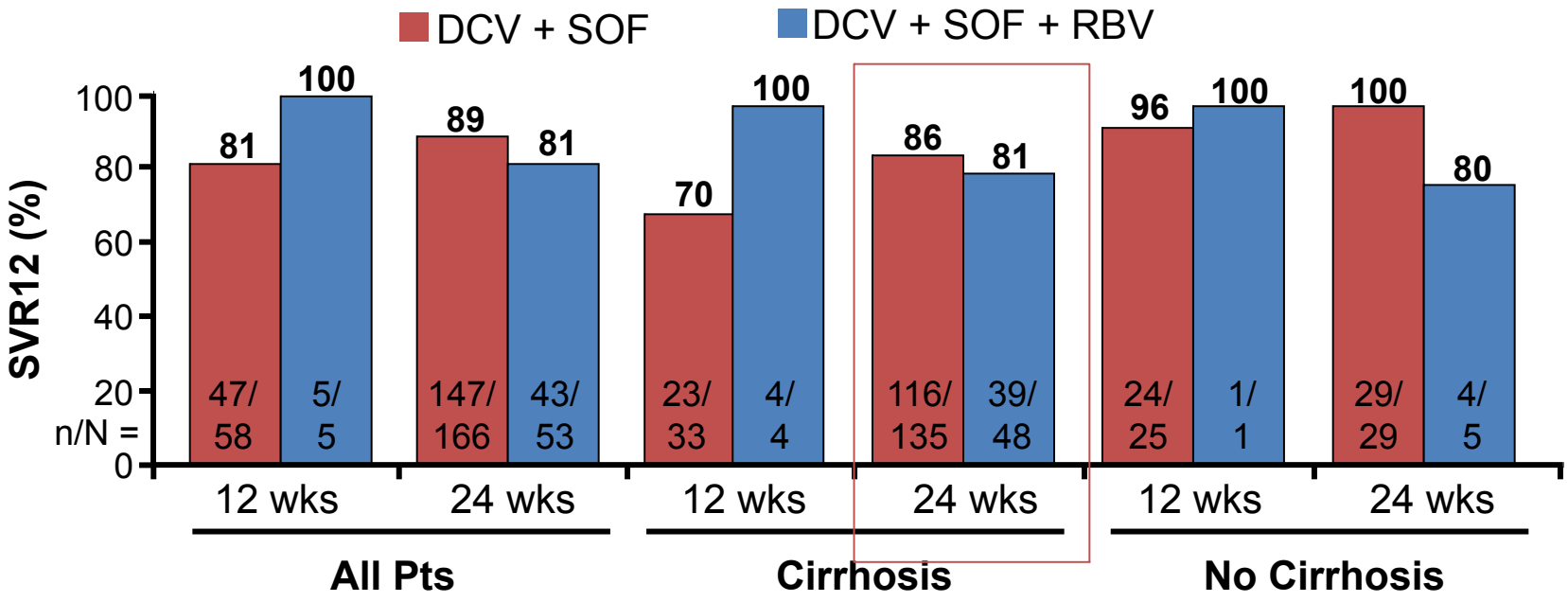
- No virologic failures or AE-related discontinuations



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

Interim Analysis: Daclatasvir + Sofosbuvir ± RBV in GT3 HCV in French CUP

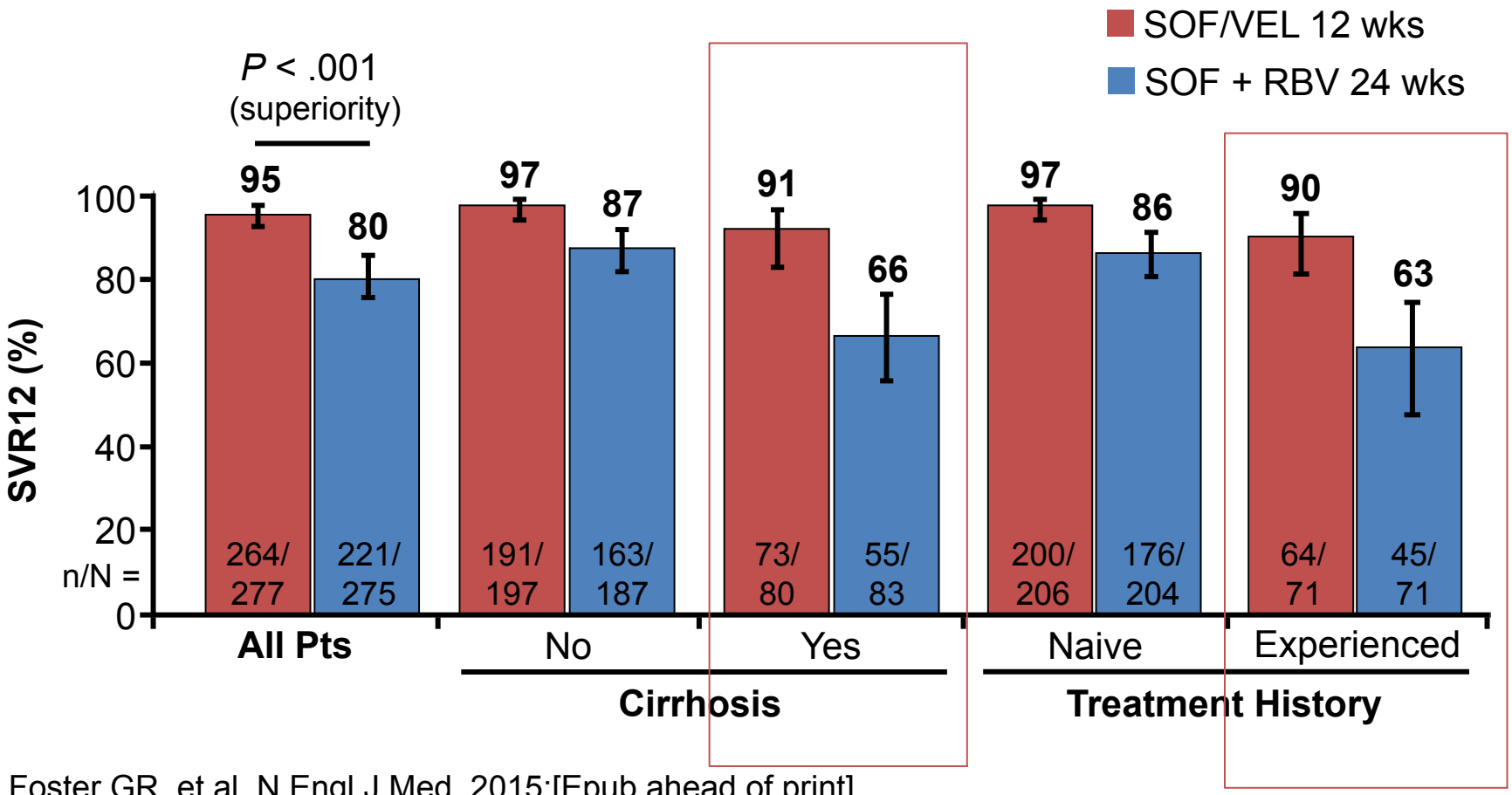
- Pts treated with DCV 60 mg + SOF 400 mg QD for 24 wks; RBV added or duration shortened to 12 wks per physician discretion
- Most common AEs: asthenia, sleep disorder, headache
  - Tx-related serious AEs (n = 1 each): hepatic decompensation, allergic dermatitis



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

ASTRAL-3 Open-Label Trial: SVR12, Safety With Sofosbuvir/Velpatasvir in GT3 HCV

- SVR12 rate numerically lower with vs without BL NS5A RAVs (88% vs 97%)
- Safety profile similar to ASTRAL-1

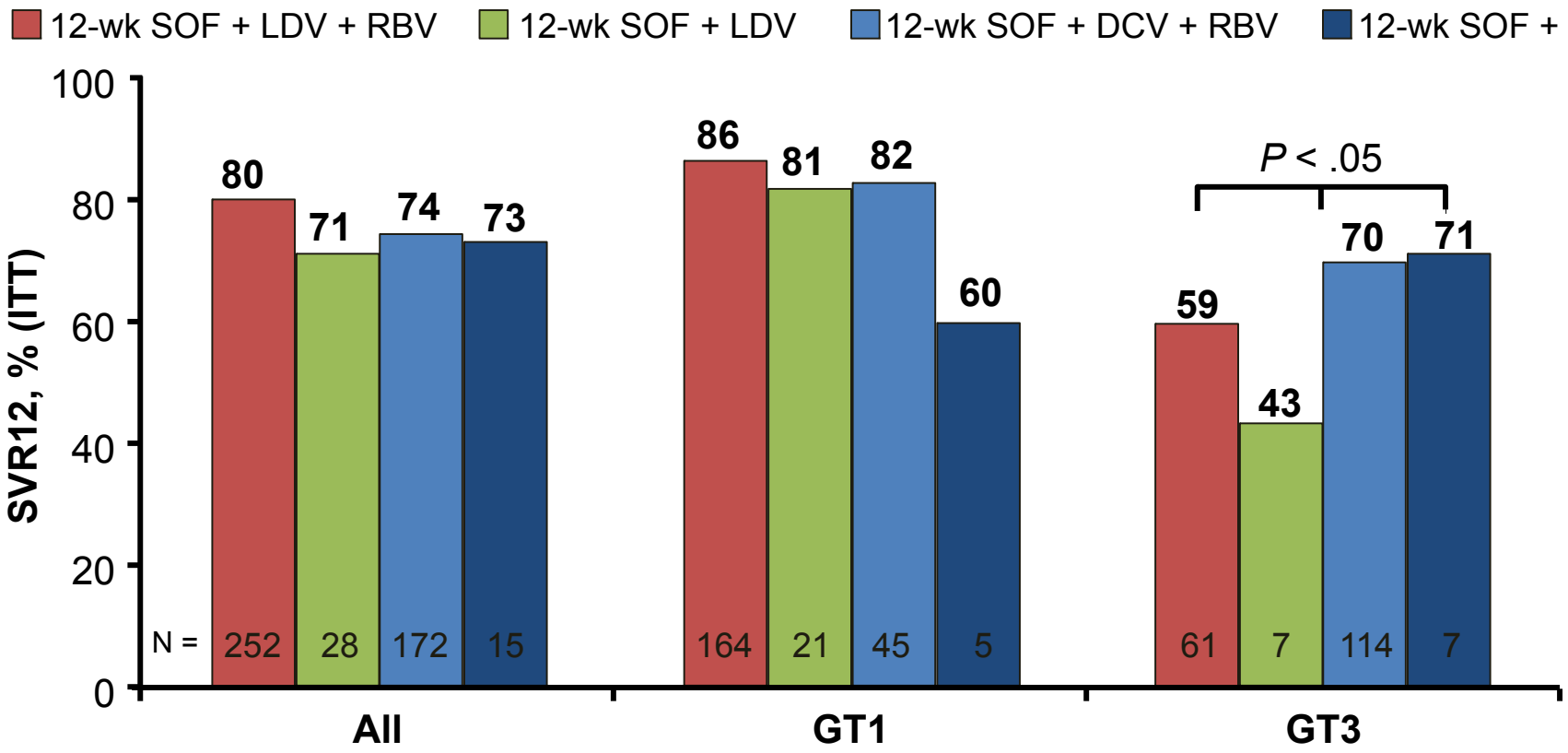


Foster GR, et al. N Engl J Med. 2015;[Epub ahead of print].

Case 3: Special HCV Populations With Very Limited Treatment Options

- AASLD/IDSA Recommendations for **Decompensated Cirrhosis**
  - Gen 1/4
    - Sofosbuvir + Daclatasvir + RBV x 12 wks
    - Sofosbuvir + Daclatasvir x 24 wks (RBV intolerant)
    - Sofosbuvir + Ledipasvir + RBV x 12 wks
  - Gen 2/3
    - Sofosbuvir + Daclatasvir + RBV x 12 wks
    - Sofosbuvir + RBV x 48 wks
  - **NOT recommended**
    - Interferon
    - Telaprevir, Boceprevir, or Simeprevir based regimen
    - Pariteprevir-, ombitasvir-, or dasabuvir-based regimens

SOF + NS5A Inhibitors ± RBV in Pts With Decompensated Cirrhosis: Efficacy

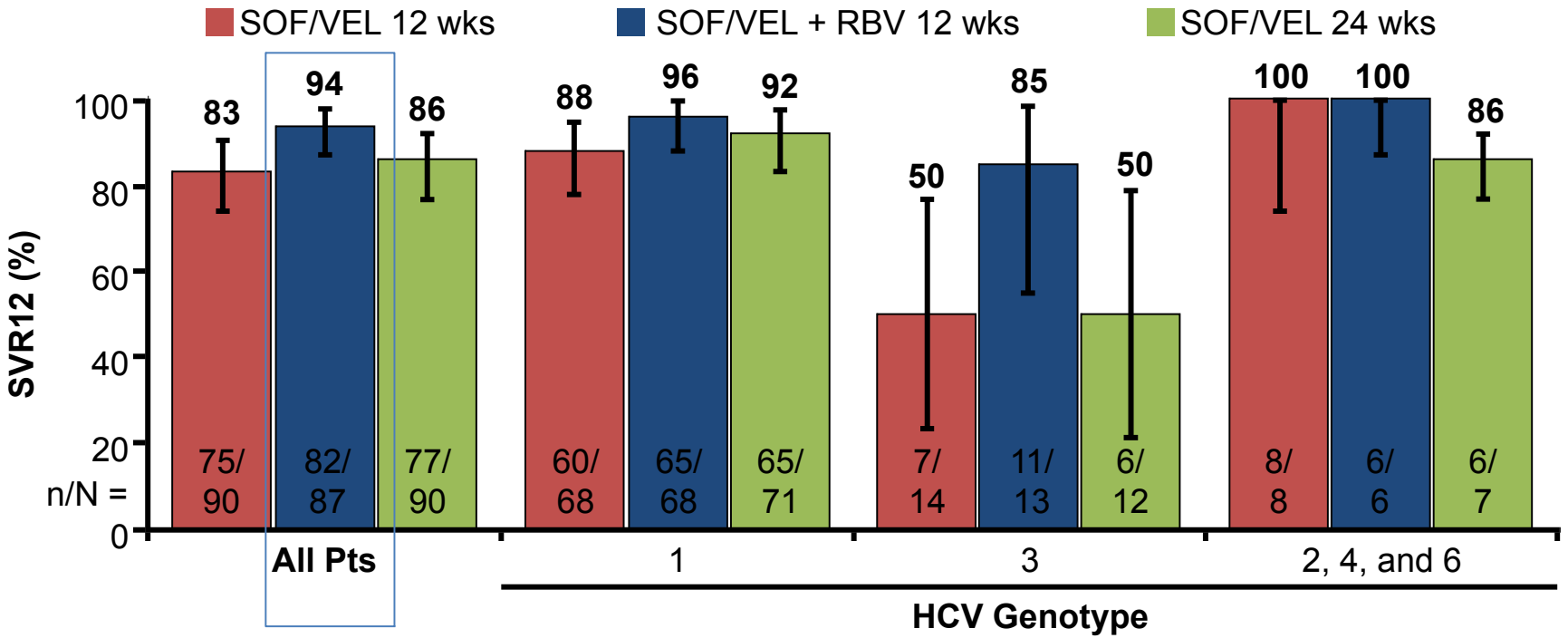


SVR12 among pts with other HCV GTs: 89% (n = 27) with SOF + LDV + RBV; 85% (n = 13) with SOF + DCV + RBV; 100% (n = 3) SOF + DCV

Foster GR, et al. EASL 2015. Abstract O002.

ASTRAL-4: Sofosbuvir/Velpatasvir in Decompensated Cirrhosis

- Open-label trial; HCC and liver transplantation excluded
- In pts with BL MELD > 15, SVR12, score improved in 84%, worsened in 8%; in pts with BL MELD < 15, SVR12, score improved in 52%, worsened in 27%
- AEs consistent with advanced liver disease and RBV toxicity



Charlton MR, et al. AASLD 2015. Abstract LB-13.
Curry MP, et al. N Engl J Med. 2015;[Epub ahead of print].

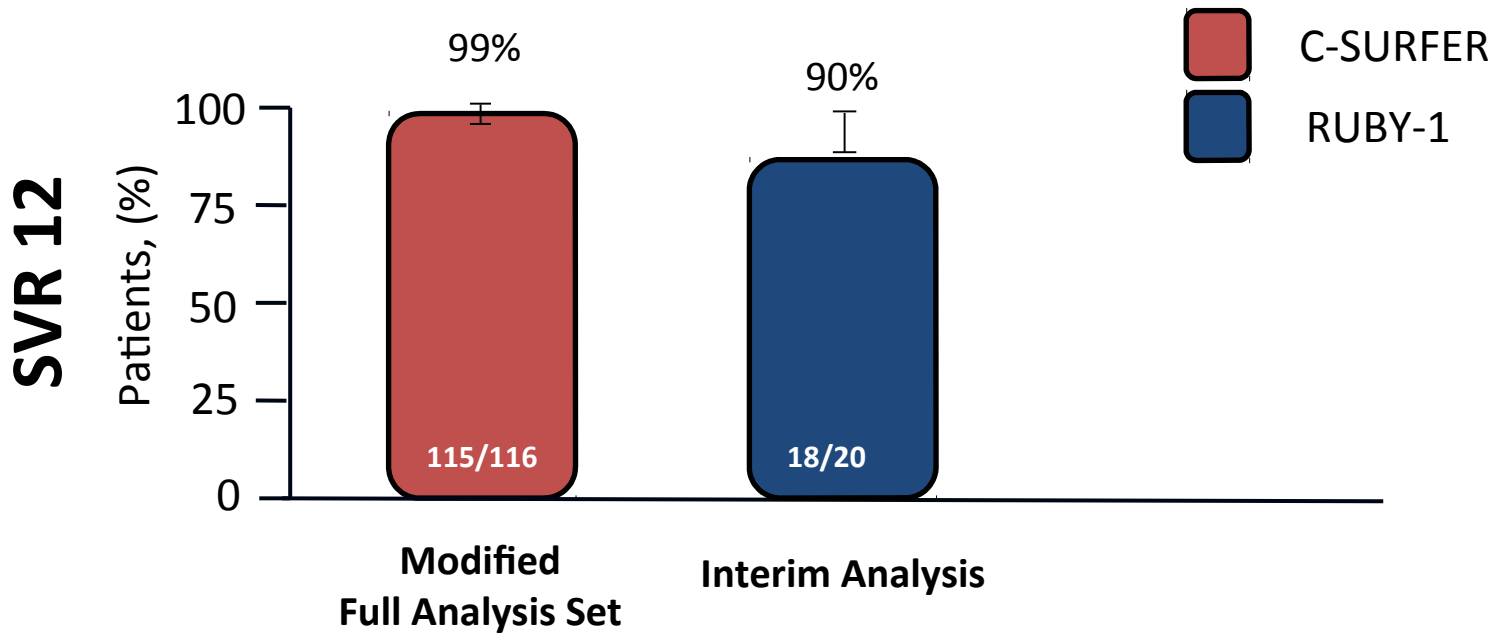
Case 4: Special HCV Populations With Very Limited Treatment Options

- AASLD/IDSA Recommendations for **Renal Impairment (CrCl < 30 ml/min)**
  - Gen 1/4
    - Ombitasvir/Paritaprevir/r ± Dasabuvir ± RBV
    - (coming: Grazoprevir + Elbasvir)
  - Gen 2/3/5/6
    - PEG-IFN + low-dose RBV x 12 wks
    - Sofosbuvir + RBV x 48 wks

HCV Treatment in Genotype 1 and Chronic Kidney Disease

C-SURFER: Grazoprevir + Elbasvir

RUBY-1: Ombitasvir/Paritaprevir/r + Dasabuvir ± RBV *



MFAS = primary efficacy analysis;
* Genotype 1a with RBV (200 mg qd), genotype 1b: no RBV

Roth D, et al EASL 2015; Pockros PJ, et al. *Hepatology*. 2015;62(suppl S1):716A-717A. Abstract 1039

What is the risk of using a **Step-up** approach (cheaper and less effective regimen) vs **Top-down** (best biologic agents)

- **Treatment failure**
  - Resistant associated variants increased
    - Harder to retreat and may restrict future options
  - Many times you only get one shot at treating a patient
    - Lost to follow-up
    - Payors restrict retreatment in US
- Solution
  - Use most effective regimen available to minimize failure
  - Payors/Pharma: Pay for cure, not treatment regimen

Summary

- Eight all-oral regimens will be approved for chronic HCV treatment by end of 2016
- Limited access and availability of some oral agents create the need to build the best treatment regimen from available drugs
- Treatment choice is often based on access, efficacy, safety, and cost balance
- Easy to treat populations allow more options for tailored therapy, while hard to treat populations (eg; Gen 3, decompenated, renal failure) require more select treatment regimens