Retreatment of DAA failures: An issue but for how long?

David L. Wyles, MD
Chief Division of Infectious Diseases
Denver Health Medical Center
Associate Professor of Medicine
University of Colorado Health Sciences

What we won't talk about and why…

- Interferon treatment failures
  - Retreatment options are well defined and efficacious
- DAA + interferon failures
  - Well represented (PI + Peg/RBV failures) in DAA trials
  - DAA regimens efficacious in this setting
- Impact of RASs in non-DAA exposed patients (baseline RASs)

Case 1: GJ

- 57 AA male HIV and HCV GT1a
  - Cirrhosis F5/6 (bx 3/14); no h/o decompensation
  - U/S negative 7/16; EGD w/o varices (2014)
  - Null responder to PEG/ RBV
  - Relapse after 12 weeks SOF + DCV (clinical trial)
    - No RBV
    - HCV RNA UD at week 4; relapse at SVR4 time point (250,000 IU/mL)
- HIV well controlled on DTG/ABC/3TC
- PMH
  - DMII; HTN
  - HBV and HAV immune

Case 1: Labs (OCT 2016)

- Chemistry:
  - Cr. 1.3; AST/ALT 39/25; TB 0.5; ALB 4.1
- CBC:
  - Hg 14.3; plt 107; INR 1.1
- HCV RNA: 3,457,502 IU/mL
- APRI = 0.91; Fib 4 = 4.16
- CD4: 509 (33%)
- HIV RNA: 25 (<20 on 7/19/16)

Additional test? What are his re-treatment options?

Considerations for Pts Who Failed a DAA-Based Regimen

1. Was initial therapy suboptimal (or submaximal)?
   - IFN + DAA vs DAA failure
   - Duration and RBV use
2. Stage of liver disease/host characteristics
3. Indications of other problems
   - Adherence?
   - Significant drug interactions?
4. What does the drug resistance profile look like?
   - What medication classes were used in the failing therapy?

Key HCV Resistance Concepts

1. HCV resistance associated substitutions (RASs) can be present without drug exposure
2. HCV RASs impacts treatment responses in specific situation
3. HCV is resistance is NOT absolute
4. Patient characteristics are just (if not more) important than RASs
5. Future regimens appear to obviate the need for most resistance testing
   - More from Professor Esteban

Resistance Characteristics of HCV Antiviral Classes

Class	Antiviral Potency	Genotype Activity	Resistance Barrier	FDA Approvals
NS3 Protease Inhibitors	+++ to ++++	1, 4 (± 2, 3, 6)	Low to High ↓	**Simeprevir** (2013) **Paritaprevir** (2014) **Grazoprevir** (2016) Voxilaprevir (2017)* Glecaprevir (2017)*
NS5B Nucleotide	++++	1-6	Very High	**Sofosbuvir** (2013)
NS5B Nonnucleoside	++	1	Low	**Dasabuvir** (2014)
NS5A Inhibitors	++++	1, 4, 6 (± 2, 3)	Low To High ↓	**Ledipasvir** (2014) **Daclatasvir** (2015) **Ombitasvir** (2014) **Elbasvir** (2016) **Velpatasvir** (2016) Pibrentasvir (2017)*

bated US FDA approvals

Resistance Testing Approaches

- Ultra-deep (or next-generation sequencing [NGS]) vs population (Sanger) sequencing
- What is broadly available:
  1. HCV NS5A drug resistance assay (LabCorp/Monogram Biosciences)
     - NGS with 10% detection level reported
  2. Hepatitis C viral RNA genotype 1/3 NS3/NS5 drug resistance assays (Quest Diagnostics)
     - RT-PCR with DNA sequencing
- Both assays now available for GT1 and GT3 HCV
  - GT1 assays are subtype specific

1. HCV NS5A Drug Resistance Assay Product Label. 2016.
2. Hepatitis C Viral RNA Genotype 1/3 NS3 and/or NS5 Drug Resistance Assay Product Labels. 2016

Examples: NS5A Resistance Genotyping

Drug			HCV GenoSure®		Assessment	Comments
	Generic Name	Brand/ Regimen	Region	Drug Resistance Associated Variants* Detected	Drug	
NS5AI	Daclatasvir		NS5A	M28V	DCV	Resistance Possible
	Elbasvir		NS5A	M28V	EBR	Resistance Possible
	Ledipasvir		NS5A	M28V	LDV	Resistance Possible
	Ombitasvir		NS5A	M28V	OBV	Resistance Possible

Important Definitions

- **Resistance Possible** - Resistance Associated Variants (RAVs) detected that (a) represent naturally-occurring polymorphisms or treatment-emergent variants associated with reductions in sustained virologic response (SVR) rates, (b) emerge during direct-acting antiviral (DAA)-treatment or relapse, and/or (c) may confer reductions in susceptibility based on *in vitro* data. Refer to prescribing information for specific details regarding the impact of these variants on treatment response in defined patient populations and when administered in combination with other antiviral agents.
- **None/Undetermined** - None; no RAVs detected. Undetermined: variants detected that have a subtle or uncertain impact on DAA-treatment responses.

Notes:

- All mutations are reported relative to the HCV genotype/subtype specific reference H77
- Assessment of drug susceptibility is based on detected mutations and is interpreted using a rules-based algorithm (version 4)
- Naturally-occurring polymorphisms may impact the emergence of resistance, leading to failure of DAA combination therapy
- Naturally-occurring DAA resistance-associated polymorphisms identified at baseline may impact SVR if the treatment regimen, or adherence, is suboptimal. The impact of these polymorphisms may vary in treatment-naïve and treatment-experienced patients and with varying disease states (e.g. non-cirrhotic vs cirrhotic)
- Reduced susceptibility to any one component of a DAA-containing regimen may be overcome by the activity of the other components of the regimen and/or longer treatment duration
- Treatment emergent RAVs may persist for prolonged periods of time and may impact subsequent treatment regimens

Region	Genotype	Summary of All Variants Observed
NS5A	1a	M28V, F36L, K107T, D126D/E, S131T, I144V, E171D, E181D, M226V, A245T, E256A/T, D285D/E, P299A, A310T, R311P, V315I, V326L, T328A, K331R, T367L, L368I, S389S/P, S383P, I388V, N392D, T395S, P405S, V410A, L428L/F

Comments: NS5A RAVs at position(s) 28, 30, 31 or 93 DETECTED. If considering an NS5A inhibitor-containing regimen, please refer to the prescribing information, or current guidelines, to determine the appropriate treatment regimen and duration.

HCV NS5A Drug Resistance Assay Product Label. 2016.

Baseline versus selected RAVs

Baseline

- Single variants
- Variable fold change
- Variable prevalence in viral population
- Any patient

Selected

- Multiple variants (w/ “linkage”)
- High fold change
- High prevalence in viral population
- “Difficult to treat” populations

Kitrinos K. #1949 EASL 2014. Wyles D. Dvory-Sobol H. EASL 2015. Cooper C. CID 2

Why NS3 PI resistance is not a big deal

1. Baseline RASs are not a significant clinical issue
   - RASs at key PI positions (R155, A156, D168) are rare (<1%) without drug exposure
   - No evidence for impact of Q80K with *recommended* SOF+SMV regimens

2. After failure selected PI RASs are “lost” rather quickly
   - Do they still have an impact, even if no longer detectable?

3. Non-PI options are available for sequencing of treatment
   - Eliminates the issue of a persistent effect

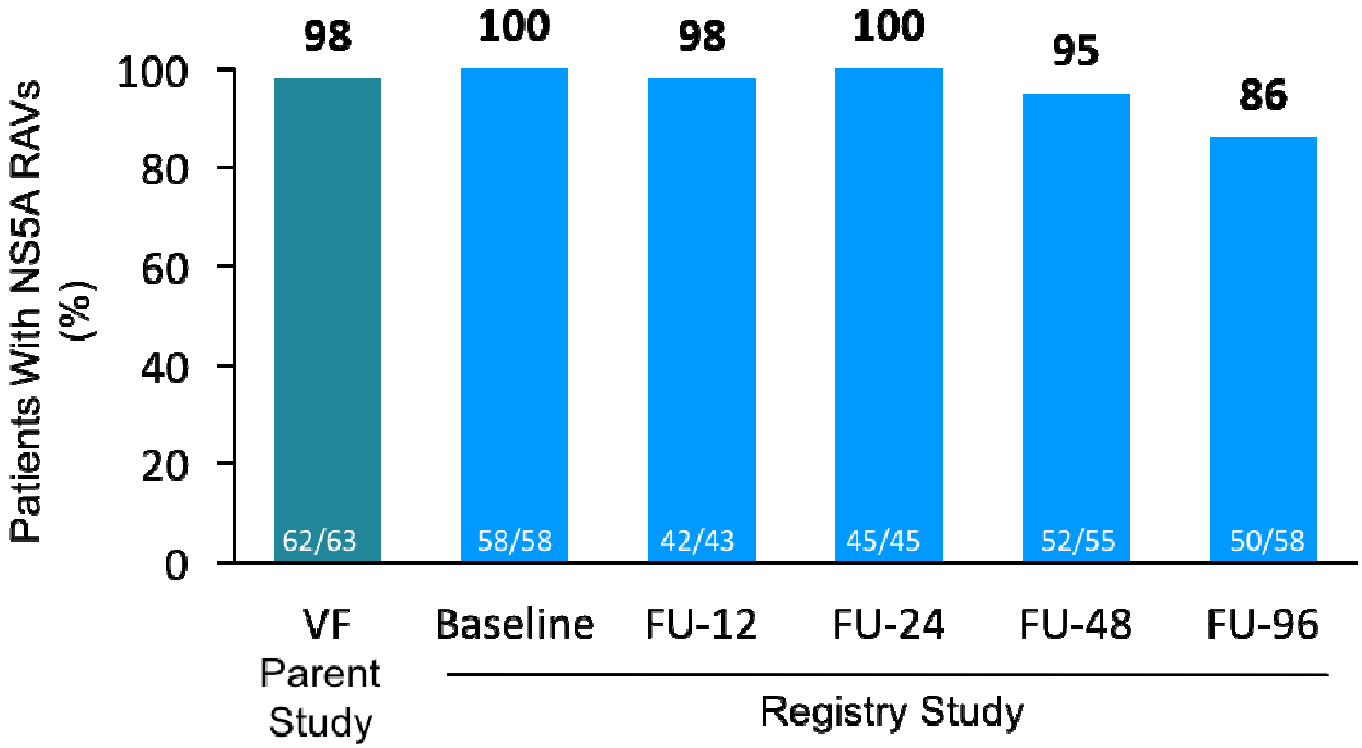
Rate of selection of NS5A resistance upon virologic failure

- Varies by regimen and duration
  - PI based
    - Vedroprevir + tegobuvir + LDV: >99%
    - GZR/EBR: 85%
    - 3D: 68%
  - Nucleotide based
    - SOF/LDV: 75%
      - 8 weeks: 65%
    - SOF/VEL: 93% (14/15; majority GT3 and with baseline RASs)
  - Nuc-based triple
    - SOF/5816/9857 (≤ 6 weeks): 0% (n=15)
    - SOF + GZR/EBR (≤ 8 weeks): 37% (n=30)

Kitrinos K. #AASLD 2014.Sulkowski M. Lancet 2014. Lawitz E. Lancet 2014. Sarrazin AASLD 2014. Kowdley K. NEJM 2013. Gane E. EASL 2015. Poordad F. EASL 2015. Zeuzem S. Ann Intern Med 2015. Hezode C. #THU-216 EASL 2016.

Durability of Treatment-Emergent NS5A RAVs

- Study assessing NS5A RASs in pts failing LDV-containing regimens (non-SOF)



Wyles D, Dvory-Sobol H. et al. #O059 EASL 2015

road Cross-Resistance With "Early Generation" NS5A

Fold Change	Genotype 1a				Genotype 1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
Ledipasvir	20x	> 100x	> 100x/ > 100x	> 1000x/ > 10,000		> 100x/--
Ombitasvir	> 1000x	> 100x	< 3x > 100x	> 10,000x/ > 10,000x	< 10x	20x/50x
Daclatasvir	> 100x	> 1000x	> 100x/ > 1000x	> 1000x/ > 10,000x	< 10x	20x/50x
Elbasvir	20x	> 100x	> 10x > 100x	> 1000x/ > 1000x	< 10x	> 100x/--
Velpatasvir	< 10x	< 3x	20x/50x	> 100x/ > 1000x	< 3x	< 3x/--
Pibrentasvir	< 3x	< 3x	< 3x	< 10x/< 10x	< 3x	< 3x/< 3x
Ruzasvir	< 10x	< 10x	< 10x	< 10x	< 10x	< 10x

et al. Antimicrob Agents Chemother. 2012;56:1588-1590. Cheng G, et al. EASL 2012. Abstract 1172. Zhao Y, et al. EASL 2012. Abstract A845. Yang G, e
stract 1199. Ng T, et al. CROI 2014. Abstract 639. Asante-Appiah E, et al. AASLD 2014. Abstract 1979.

When do the guidelines recommend RAS testing

Definitely	Probably	Maybe
All GT1a prior to EBR/GZR NS5A (EBR RASs) 8#, Q30, L31, and Y93 0% impacted not include M28V	Who: All GT1 DAA failure What: NS3 and NS5A	Who: • GT1a treatment experienced • GT3 non-cirrhotic (SOF + DCV • GT3 TE or cirrhosis (SOF/VEL What: NS5A (LDV RAVS or GT3 Y
: end to 16 weeks AND d RBV OR nsider other therapy	Action: 1. Select non-cross resistant therapy (if possible) 2. Add RBV (regardless) 3. Extend therapy	Action: 1. GT1a-consider RBV with LDV • 24wks + RBV with F4 2. GT3- add RBV to SOF+DCV 3. GT3 TE OR cirrhosis- add RB SOF/VEL (if Y93H)

Back to our patient:
HCV Genotypic Resistance Sequencing

	Drug		HCV GenoSure® NS3/4A		Assessment	
	Generic Name	Brand Name	Region	Drug Resistance Associated Mutations Detected	Drug	
PI	Boceprevir		NS3	None	BOC	Sensitive
			NS4A	None		
	Simeprevir		NS3	None	SMV	Sensitive
			NS4A	None		
	Telaprevir		NS3	None	TVR	Sensitive
			NS4A	None		

Region	Genotype	Summary of All Mutations Observed
NS5A	1a	T17S, L31M, F37L, T56A, T64A, R78K, Y93H, E171D, L176Q, N180H, L183P, T242A, R246H, E285D, Q288R, V298I, R305K, R307K, R311P, M313L, P319A, L326I, S328P, D331N, K348G, P350P/T, S364T, G381S, S396P, P400T, D402G, A406T, S437SDQ
NS5B	1a	I11V, T19S, L36M, L47Q, K81R, V85I, V116I, H118H/R, R120S, A210S, C213N, A218S, R250R/K, A300S, C316H, V321I, E333A, A338V, K355Q, R510K, Q514R, K523R, S549G, L564V, F572I, M573W, W574L

Resistance possible: DCV, EBR, LDV, OBV, VEL

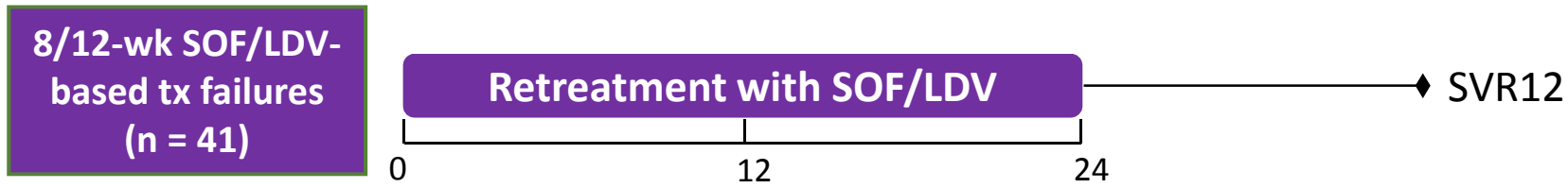
HCV NS5A Drug Resistance Assay Product Label. 2016.

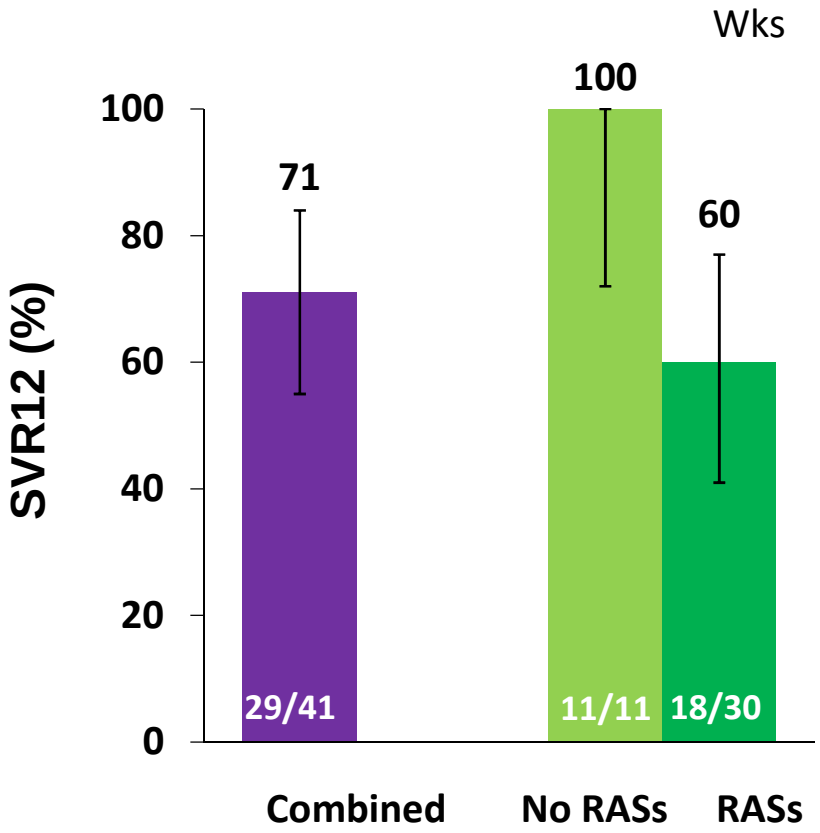
Based on his RAS testing how would you proceed?

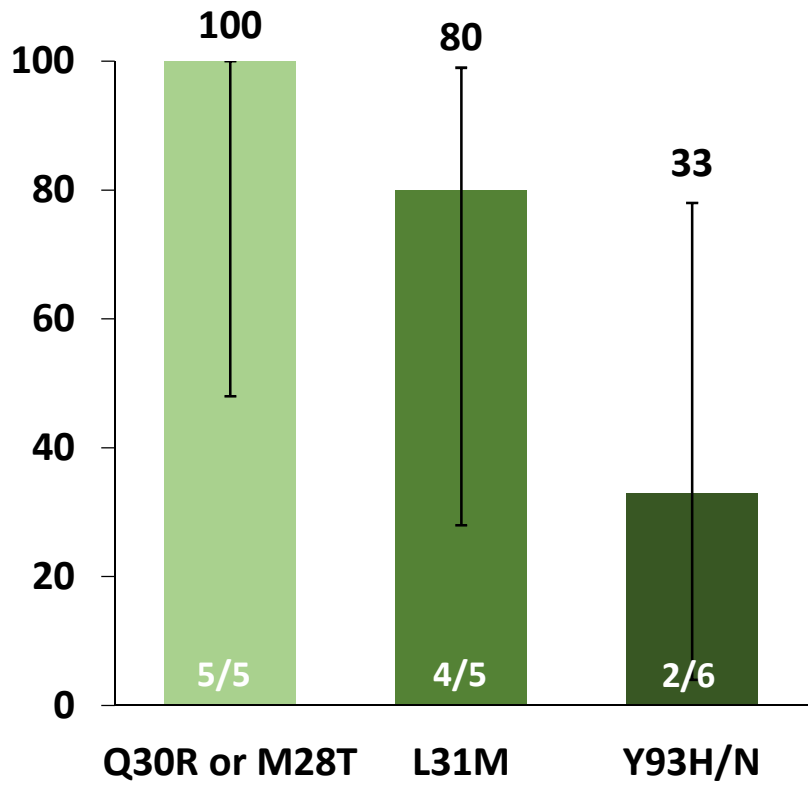
1. Yikes, defer!
2. I don’t know why I even sent the test: SOF/VEL + RBV for 24 weeks
3. Resistance is everything: SOF + SMV + RBV for 24 weeks
4. Kitchen sink 1: SOF + EBR/GZR + RBV 12 weeks
5. Kitchen sink 2: SOF + OBV/r/PTV + DSV + RBV 24 weeks

Retreatment of DAA failures

NS5A RASs Are Associated With Retreatment Failure



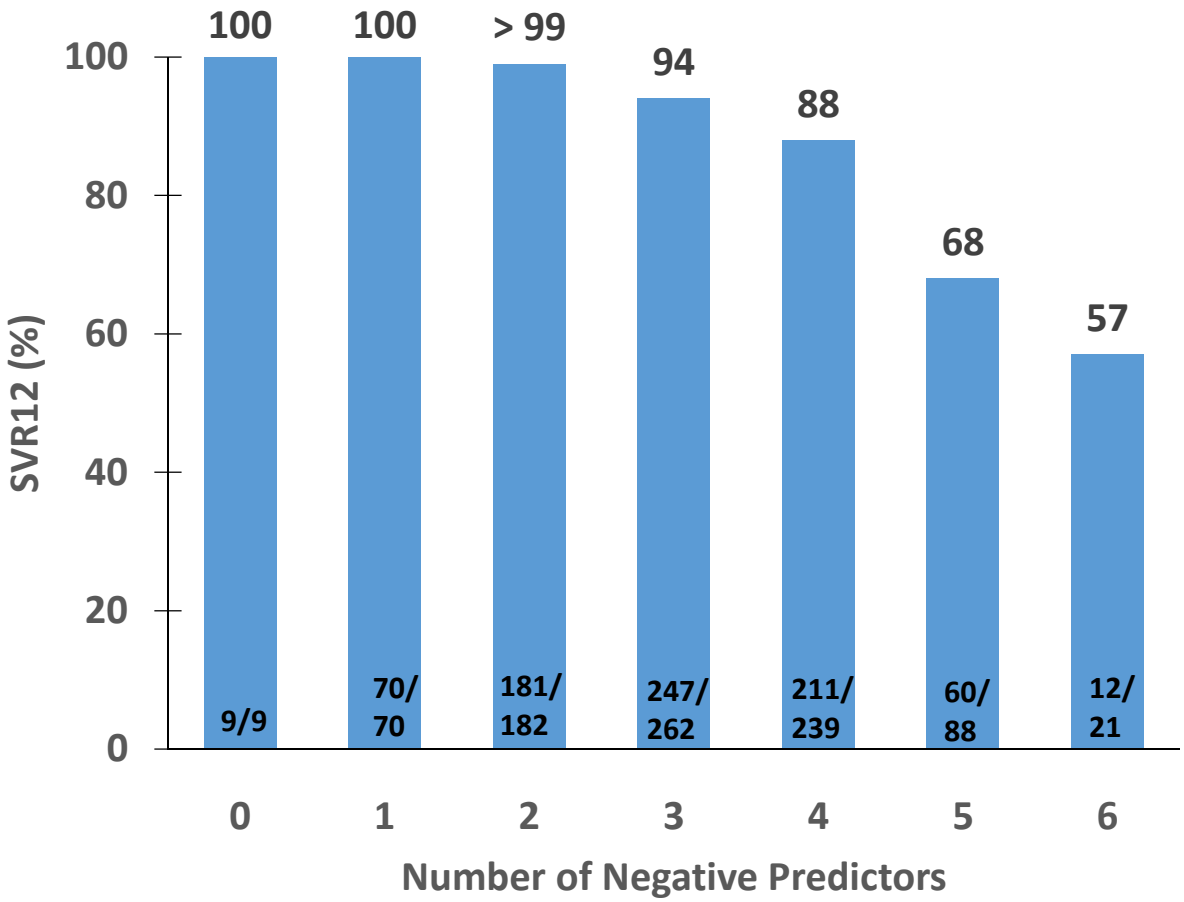




Lawitz E. #O005 EA

Impact of Multiple Negative Predictors on Response

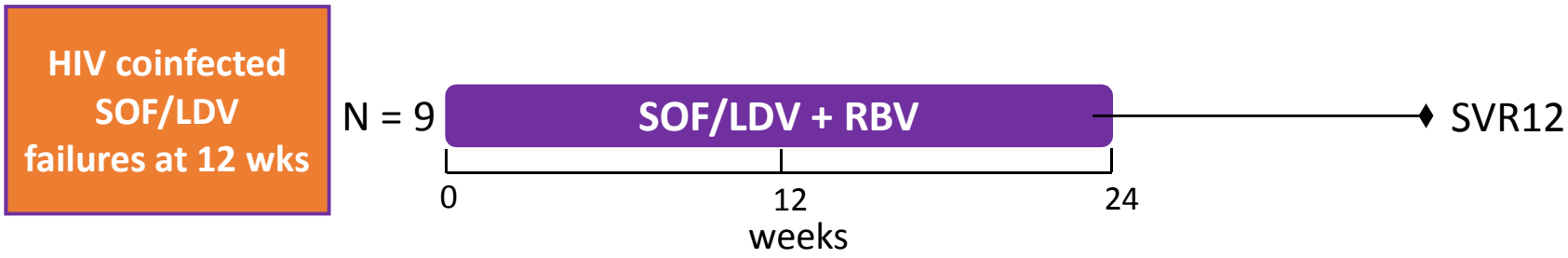
- Retrospective analysis of phase 2/3 studies of SOF + RBV ± PegIFN
- > 850 pts, genotypes 1, 2, and 3 HCV



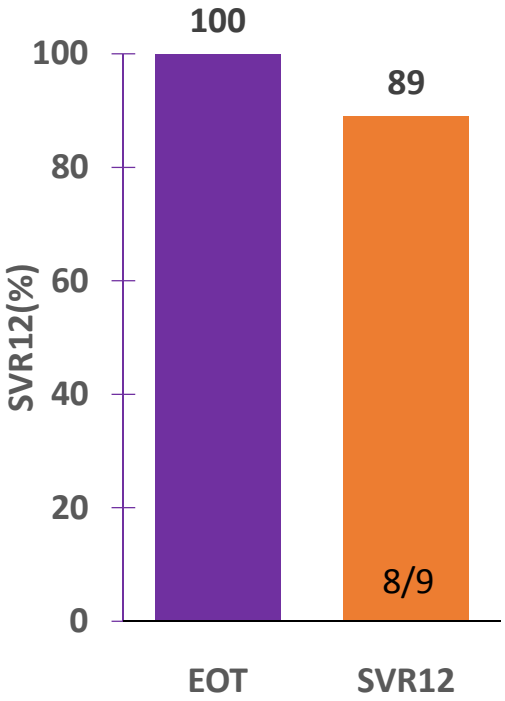
- Treatment experienced
- Cirrhosis
- HCV RNA*
- Male
- ≥ 75 kg
- IL28B non-CC
- NS5A RASs?

Foster GR, et al. EASL 2014. Abstra

What Roles Do RBV and Duration Play in Overcoming Resistance and Optimizing Retreatment?



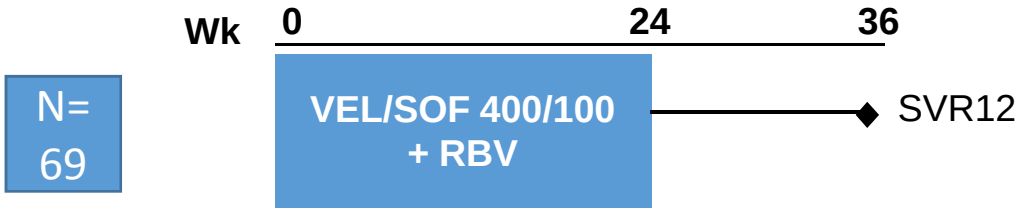
- Male: 78%
- 1a: 78%
- HCV RNA: 6.4 (± 0.8)
- Black: 100%
- Non-CC: 100%
- Cirrhosis: 22%
- NS5A RAVs: 78%



Failure
55-yr-old male
GT1a
No cirrhosis
L31M

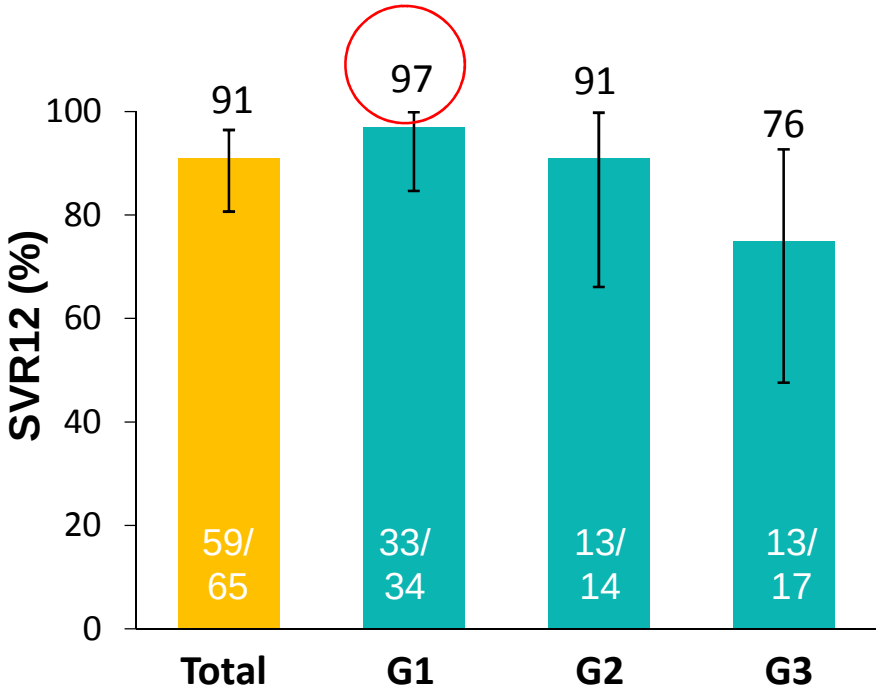
Cooper C. CID 2016.

What Roles Do RBV and Duration Play in Overcoming Resistance and Optimizing Retreatment?



26% cirrhosis
20% GT2
41% VEL 25mg
74% <12 weeks

Only 18% of GT1 with NS5A RASs

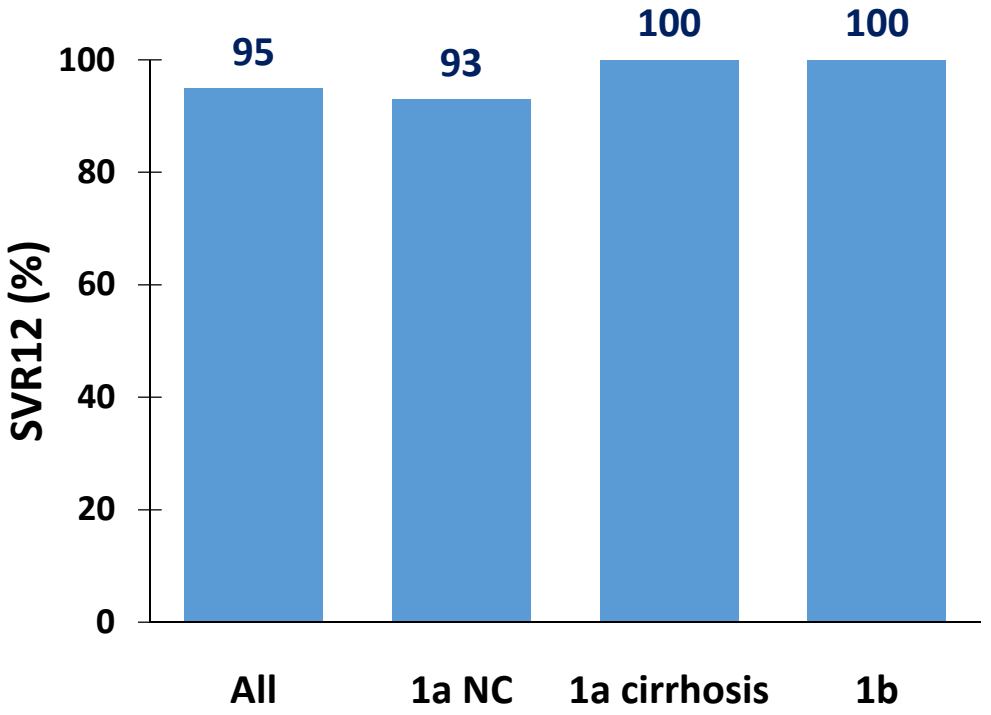


4 pts pending SVR12

Gane EJ, et al. EASL 2016. Abstract PS

Retreatment of DAA Failures with SOF + 3-D

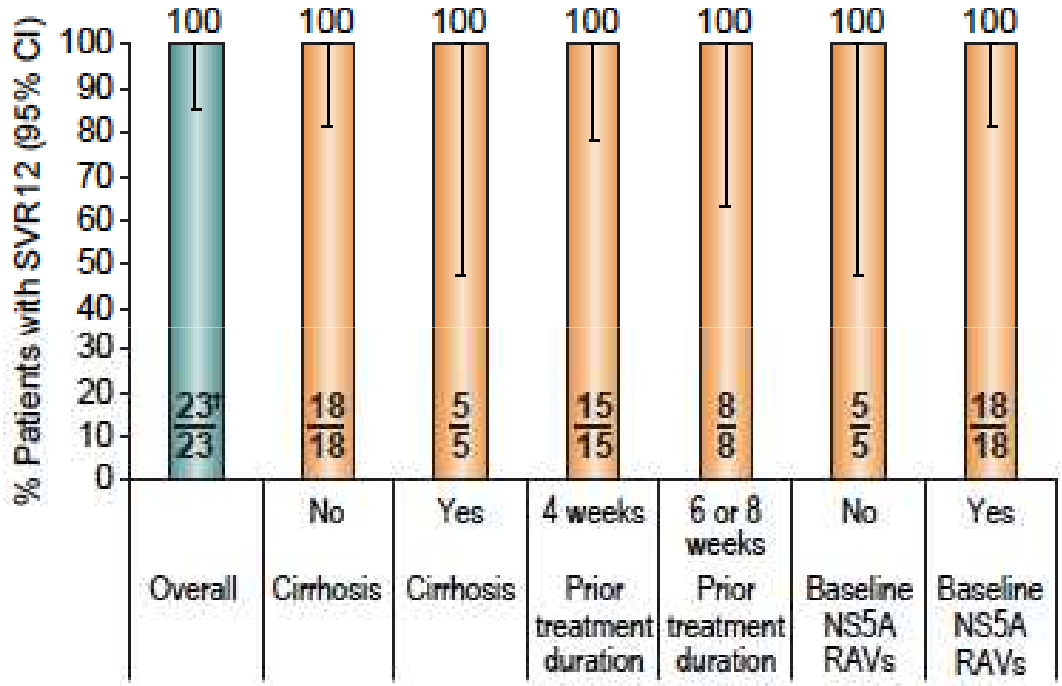
- 22 DAA-treated pts
  - 20 GT1a, 2 GT1b HCV pts
    - 6/20 with cirrhosis
  - 14/20 GT1a pts failed OBT/PTV/RTV + DSV
  - No SOF/LDV failures
- BL RASs (n)
  - D168E/V (5)
  - Y93C/F/H (4); Q30E/H/R (12)
- SOF + OBT/PTV/RTV + DSV
  - RBV for all GT1a
  - **GT1a tx: 12 wks for noncirrhotics, 24 wks for cirrhotics**



Poordad F, et al. EASL. Abstract SAT-156.

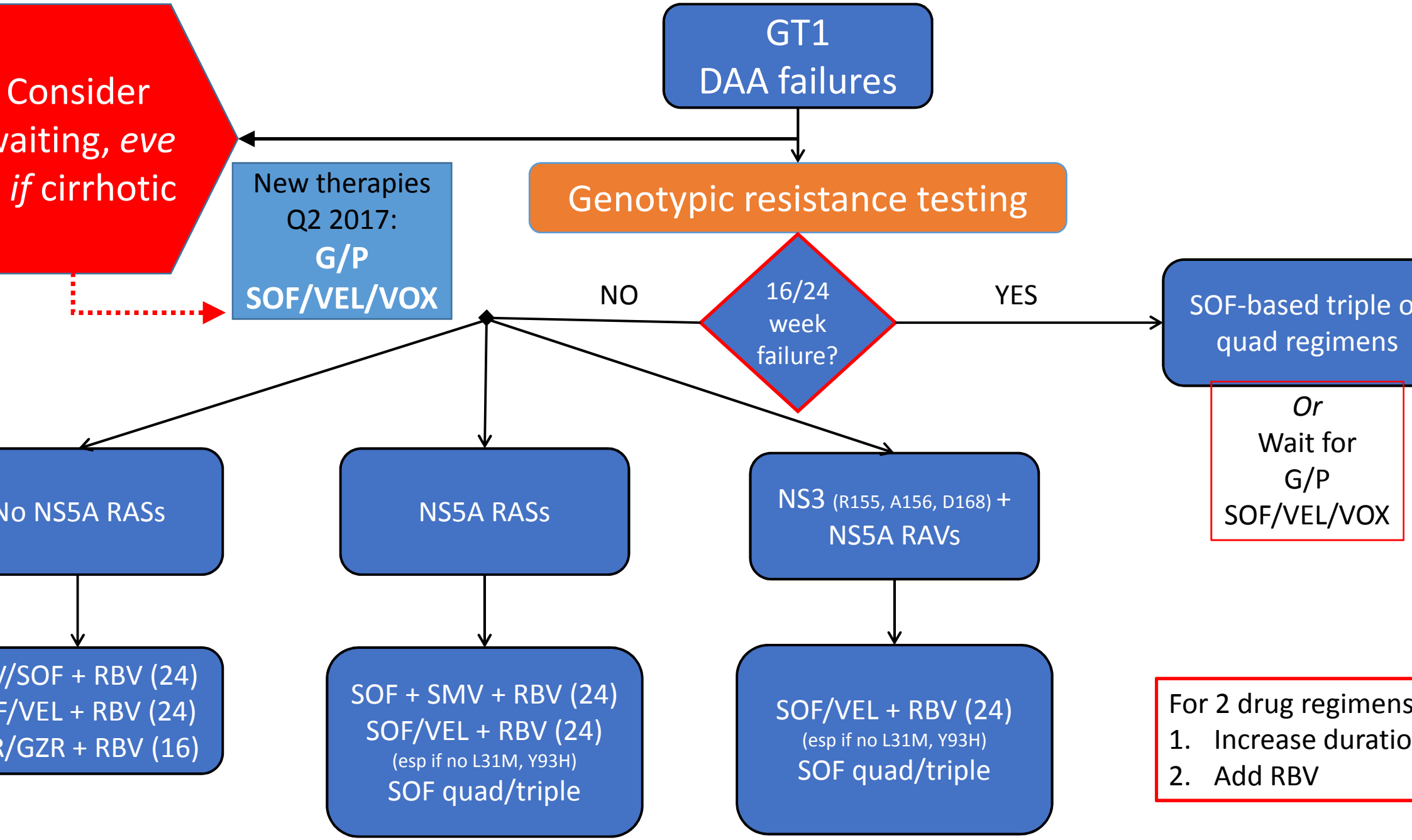
Retreatment of SOF + EBR/GZR Failures

- 25 pts who failed short course SOF + GZP/EBR (4-8 wks)
  - 22 GT1a, 3 GT1b
    - 20 failed 4 wks
  - 5 (20%) cirrhosis
  - 80% with NS5A RASs
  - 52% NS3 RASs
  - 44% NS3/NS5A RASs
- Received SOF + EBR/GZR + RBV for 12 wks

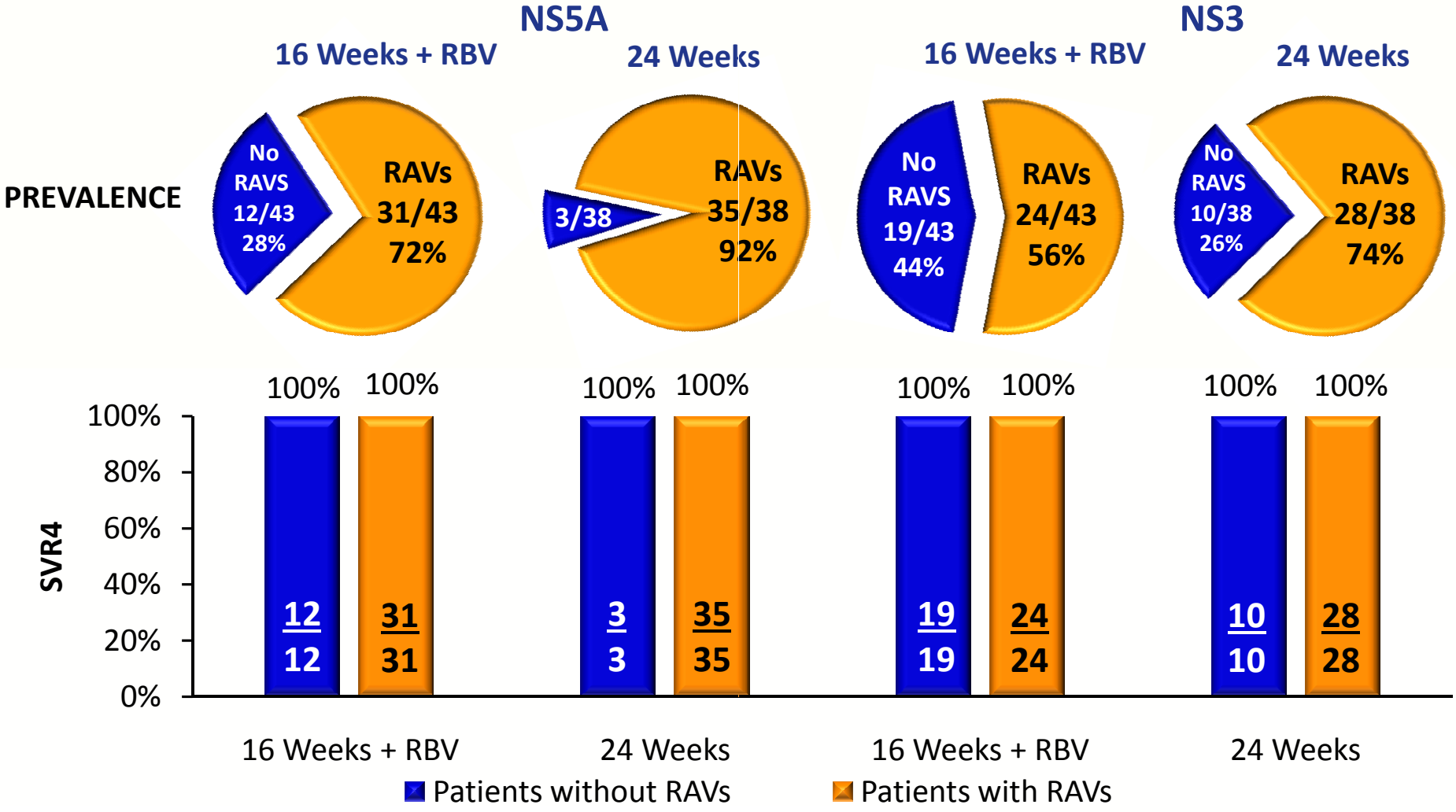


100% SVR12 (9/9) in pts with dual RASs

Lawitz E, et al. AASLD 2015. Abstract LB


GT1
DAA failures
Consider
vaiting, eve
if cirrhotic
New therapies
Q2 2017:
G/P
SOF/VEL/VOX
Genotypic resistance testing
NO
16/24
week
failure?
YES
SOF-based triple o
quad regimens
Or
Wait for
G/P
SOF/VEL/VOX
No NS5A RASs
NS5A RASs
NS3 (R155, A156, D168) +
NS5A RAVs
V/SOF + RBV (24)
F/VEL + RBV (24)
R/GZR + RBV (16)
SOF + SMV + RBV (24)
SOF/VEL + RBV (24)
(esp if no L31M, Y93H)
SOF quad/triple
SOF/VEL + RBV (24)
(esp if no L31M, Y93H)
SOF quad/triple
For 2 drug regimens
1. Increase duratio
2. Add RBV

No Impact of Baseline NS5A or NS3 RAVs on SVR4 (Resistance Analysis Population)



SVR4=proportion of patients with HCV RNA <15 IU/mL at 4 weeks after end of treatment.
*RAVs detected by next-generation sequencing with 15% sensitivity; NS5A RAV: any change from wild-type at 4 positions (28, 30, 31, or 93); NS3 RAVs = any change from wild-type at 14 positions (36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175).
† Excludes 1 patient from the 16-week group who withdrew after receiving 3 doses of study medication;

Wyles D et al. #193

Back to the case…

SOF + SMV + RBV was requested and approved.

- HCV RNA <15 IU/mL (detected) at week 4
- Undetectable at week 8
- Tolerated therapy well, no RBV dose reduction

- Pt late on refills
  - By week 24 still had ~3 weeks of meds left per pt

  - Stopped all therapy at week 28

- Achieved SVR 4 and 12

Acknowledgements

- UCSD AVRC
  - Kathy Nuffer
  - Rose-Marie Ramirez
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  - Lalo Cachay
  - Francesca Torriani
  - Craig Ballard
  - Brad Collwell
- UCSD HCV Clinic
  - Lucas Hill
  - Darcy Wooten
  - Chip Schooley

Questions? David.Wyles@dhha.org