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HCV Alert: New Data on Resistance to DAAs and Implications for Therapy

Nezam H. Afdhal, MD, FRCPI
Professor of Medicine
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

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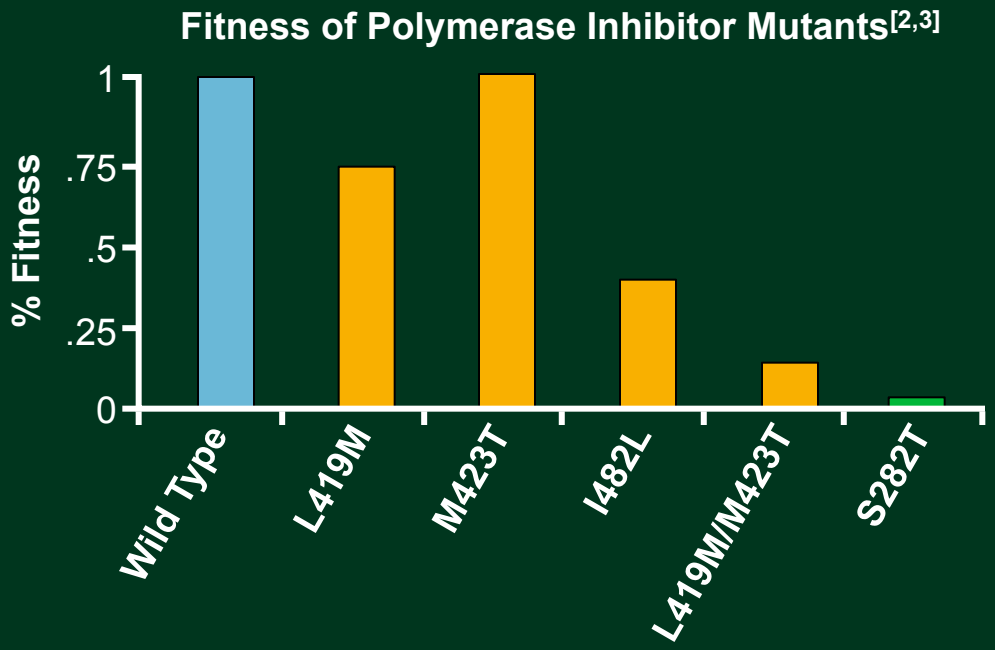
Virologic Barriers to Resistance

Genetic barrier

- Number and type of nucleotide changes required for a virus to acquire resistance to an antiviral regimen[1]

Viral fitness

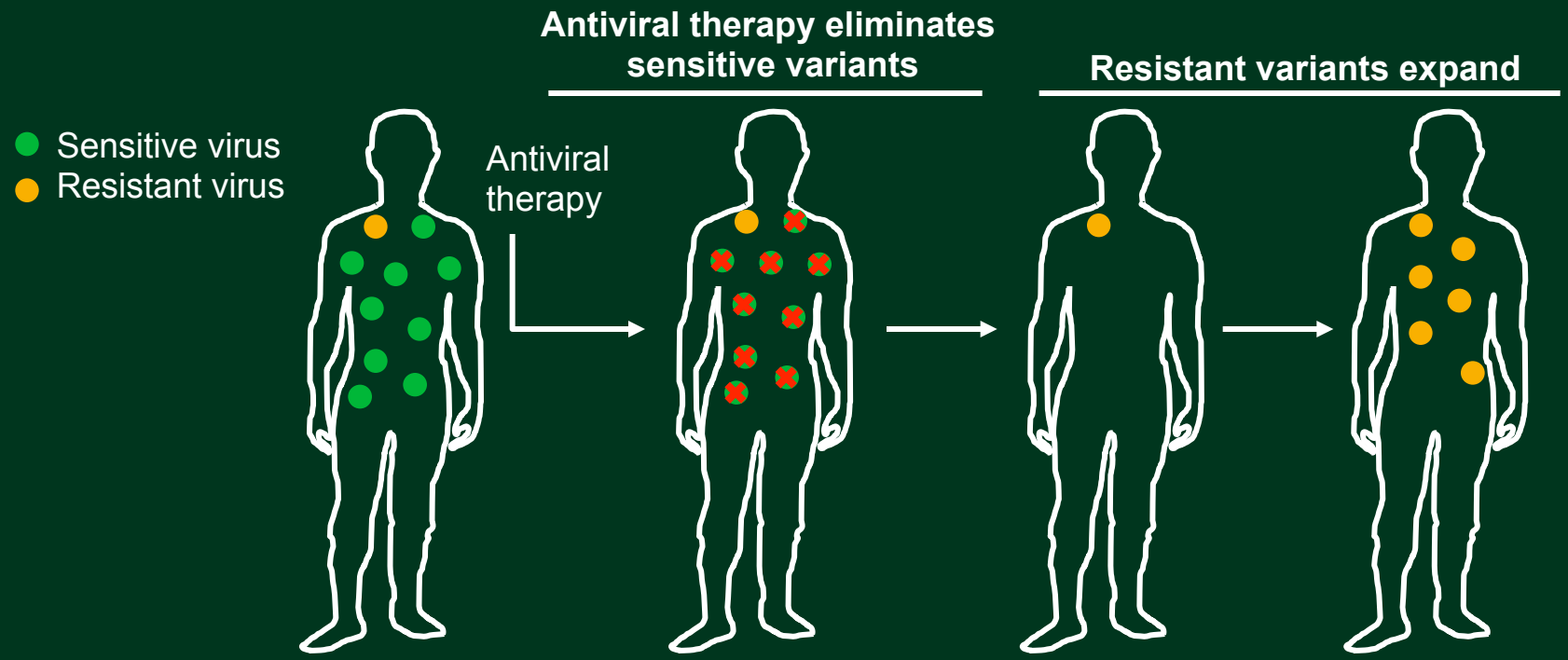
- Relative capacity of a viral variant to replicate in a given environment



1. Rong L, et al. Sci Transl Med. 2010;2:30ra32. 2. Le Pogam S et al. J Virol. 2006;80:6146-6154. 3. Le Pogam S, et al. J Infect Dis. 2010;202:1510-1519

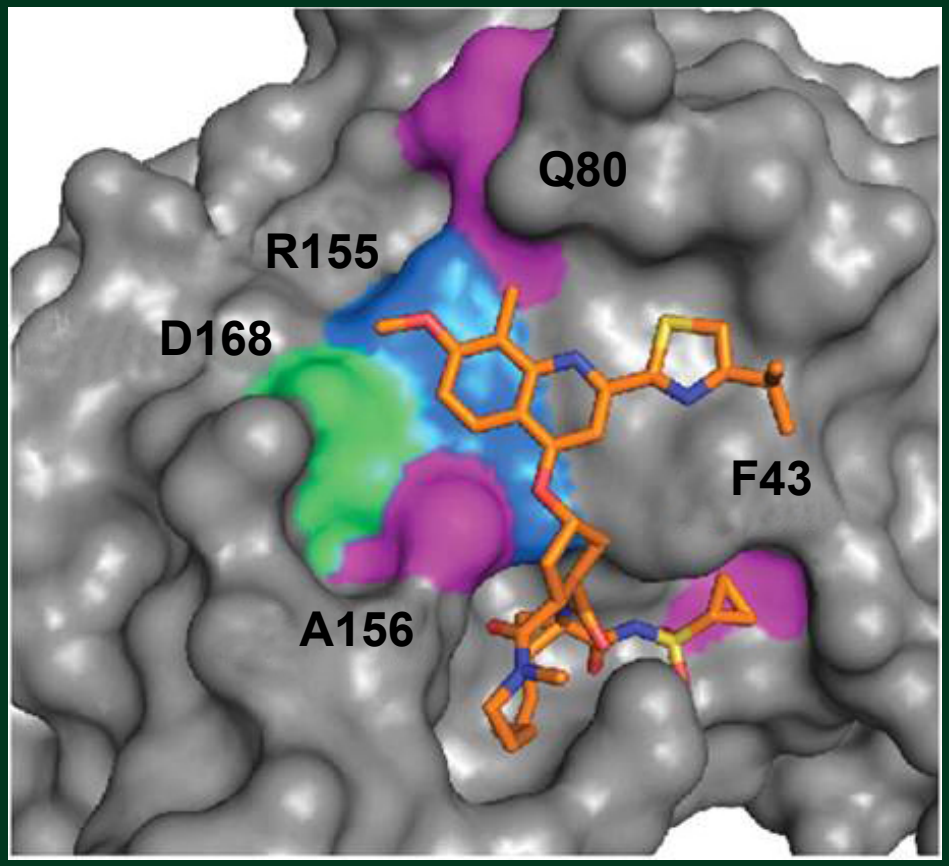
Resistant Variants Are Present Before and Can Be Selected During Treatment

- HCV is a mixture of related but distinct populations of virions in each pt[1]
- Most resistant variants are unfit and may be undetectable prior to therapy[2,3]

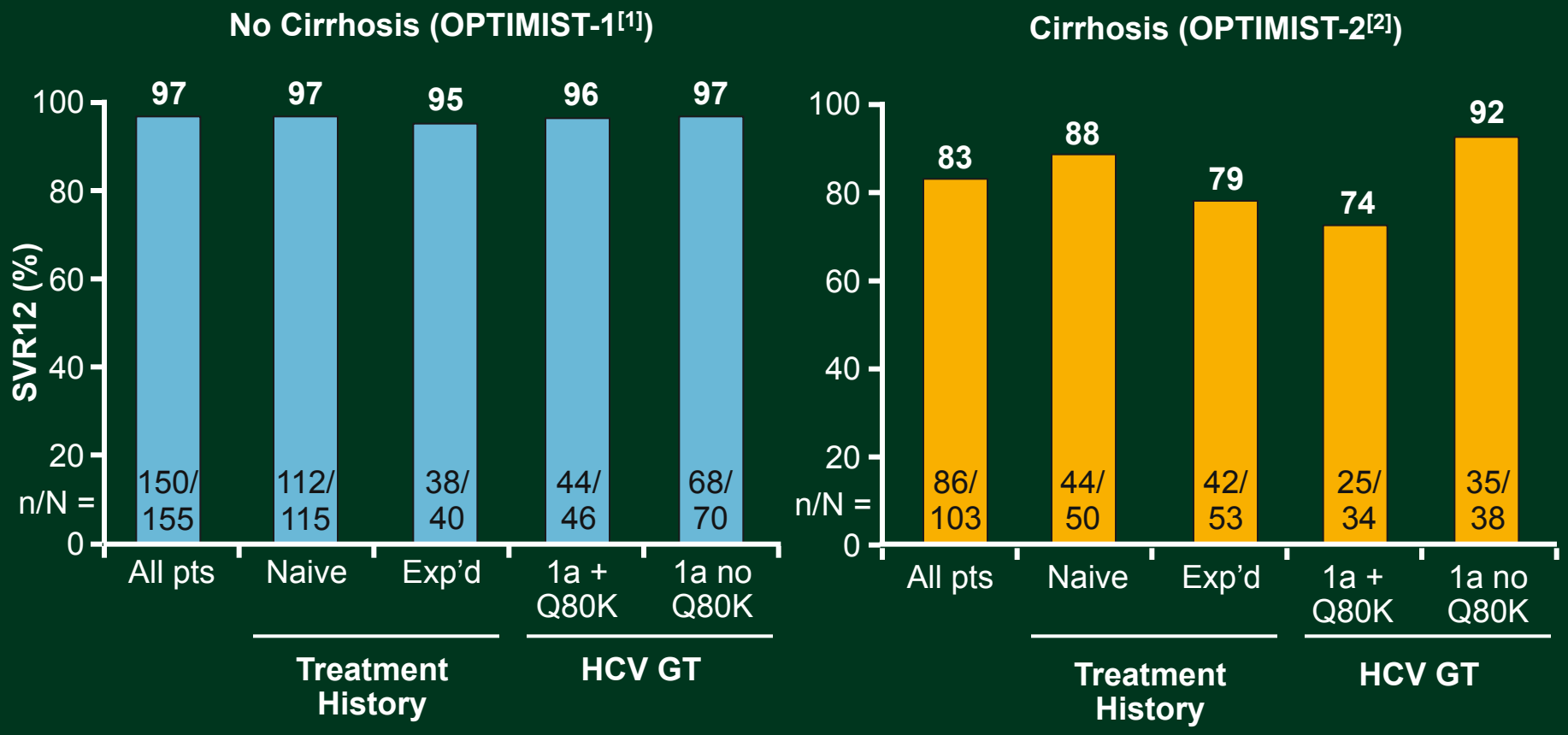


1. Pawlotsky JM. Clin Liver Dis. 2003;7:45-66. 2. Kuntzen T, et al. Hepatology. 2008;48:1769-1778.
3. Bartels DJ, et al. J Infect Dis. 2008;198:800-807. Image reproduced and adapted with permission from Forum for Collaborative HIV Research. www.hivforum.org

HCV NS3/4A Protease Resistance



Impact of Treatment Exp, Q80K Depends on Cirrhosis (12 Wks' SMV + SOF in GT1)



1. Kwo P, et al. EASL 2015. Abstract LP14. 2. Lawitz E, et al. EASL 2015. Abstract LP04.

OPTIMIST-2: Resistance Analysis in GT1 Cirrhotics in Whom SMV + SOF Failed

- Treatment-emergent NS3 mutations detected in 79% (11/14) of evaluable pts who did not achieve SVR12
  - Observed at position 168, R155K, or combinations
- NS5B polymorphism S282T not detected at baseline or at time of treatment failure
- No NS3 baseline polymorphisms observed aside from Q80K

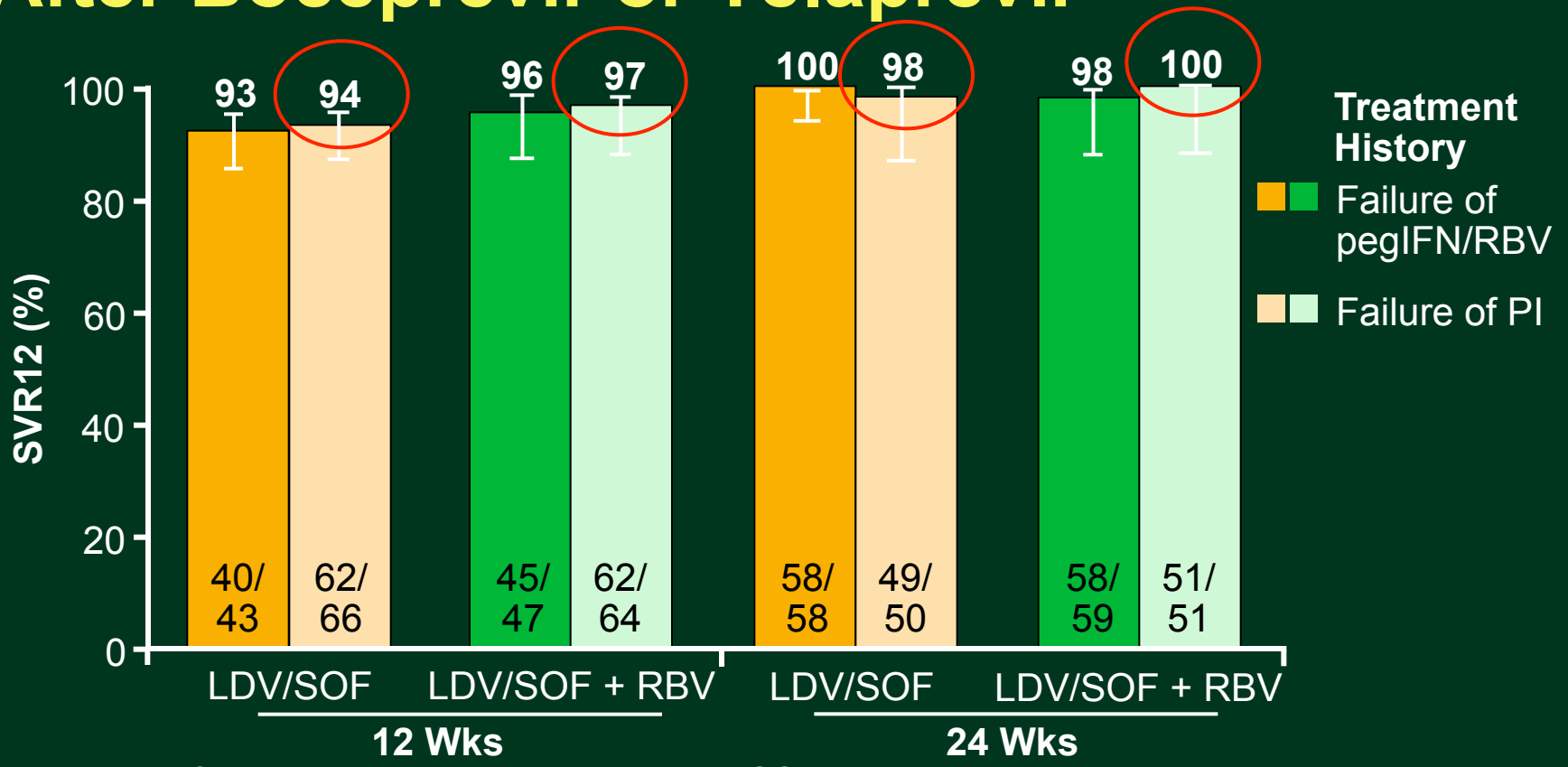
Lawitz E, et al. EASL 2015. Abstract LP04.

AASLD/IDSA Guidance for Resistance Testing When Considering SMV + SOF

- In pts with both genotype 1a HCV infection and compensated cirrhosis, if considering SMV + SOF, test for Q80K polymorphism
  - If Q80K variant is present, consider a regimen other than SMV + SOF
- Applies to treatment-naive and treatment-experienced pts
- Q80K testing not required for:
  - Pts with genotype 1b HCV infection
  - Pts without cirrhosis
  - Pts in whom you are considering other DAAs

AASLD/IDSA/IAS-USA. HCV Guidance.

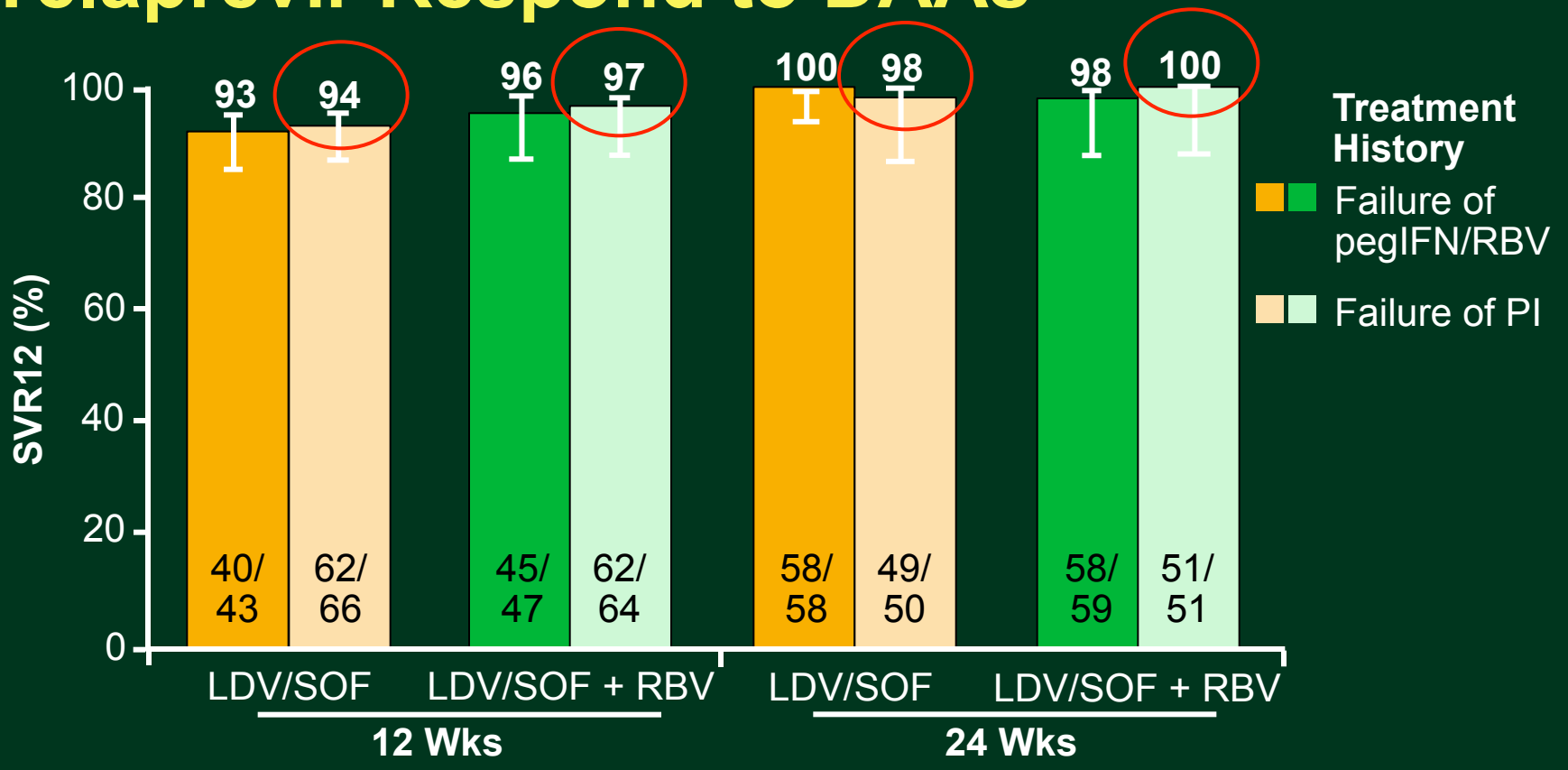
ION-2: DAAs Effective Against NS3 RAVs After Boceprevir or Telaprevir



- Virologic failure: 1 breakthrough in 24-wk LDV/SOF + RBV due to nonadherence; 11 relapses (7 in 12-wk LDV/SOF, 4 in 12-wk LDV/SOF + RBV)
- 14% of pts had NS5A RAVs at baseline; 89% of these achieved SVR12; 71% of pts had NS3 RAVs at baseline; 98% of these achieved SVR12

Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

ION-2: NS3 RAVs After Boceprevir or Telaprevir Respond to DAAs



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Afdhal N, et al. N Engl J Med. 2014;370:1483-1493.

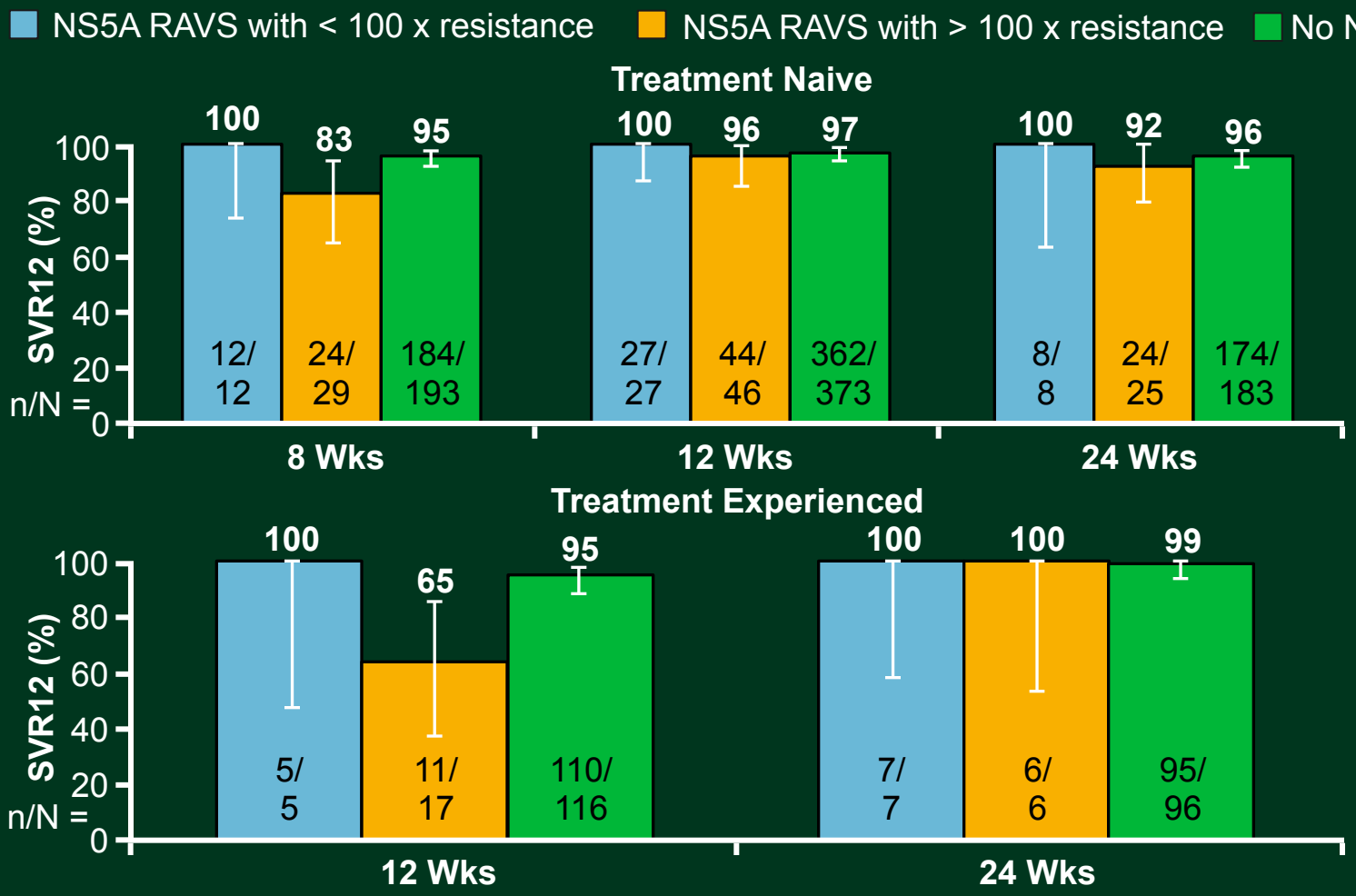
Resistance Analysis of Select NS5A Inhibitors in Genotype 1 HCV

Fold-Change in EC50	Genotype 1a				Genotype 1b	
Position	**M28T**	**Q30R**	**L31M/V**	**Y93H/N**	**L31V**	**Y93H/N**
FDA approved						
Daclatasvir[1,3]	> 100 x	> 1000 x	> 100 x	> 1000 x	< 10 x	< 100 x
Ledipasvir[1]	20 x	> 100 x	> 100 x	> 1000 x		> 1000 x/?
Ombitasvir[2]	> 1000 x	> 100 x	< 3 x > 100 x	> 10,000 x	< 10 x	< 100 x

> 100 x 3 to 100 x < 3 x

1. Cheng G, et al. EASL 2012. Abstract 1172. 2. Krishnan P, et al. Antimicrob Agents Chemother. 2015;59:979-987. 3. Yang G, et al. EASL 2013. Abstract 1199. 4. Ng T, et al. CROI 2014. Abstract 639.

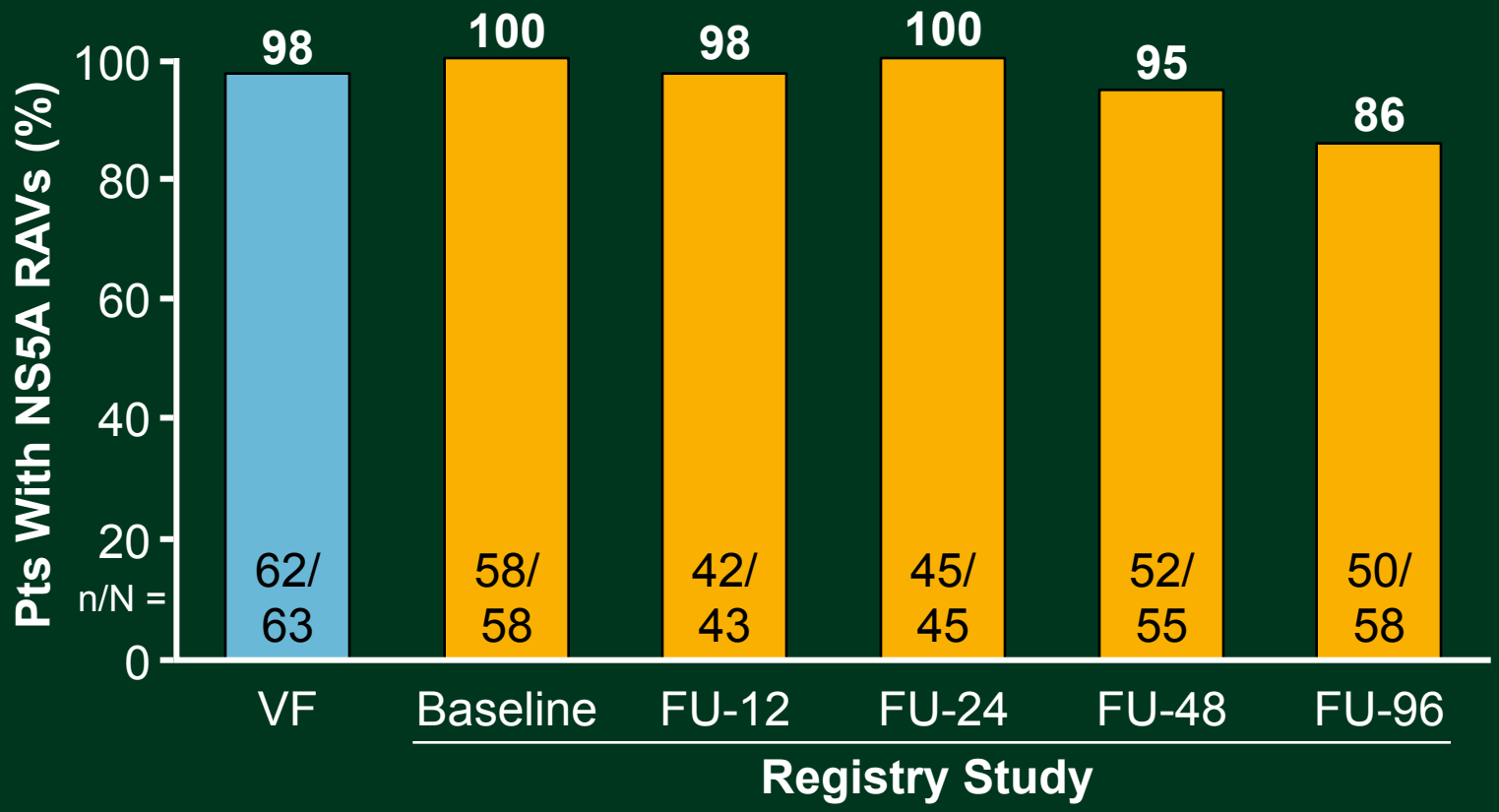
Impact of Duration of LDV/SOF on SVR12 in Pts With Baseline NS5A Resistance



Sarrazin C. AASLD 2014. Abstract 1926.

Durability of Treatment-Emergent NS5A RAVs After Virologic Failure

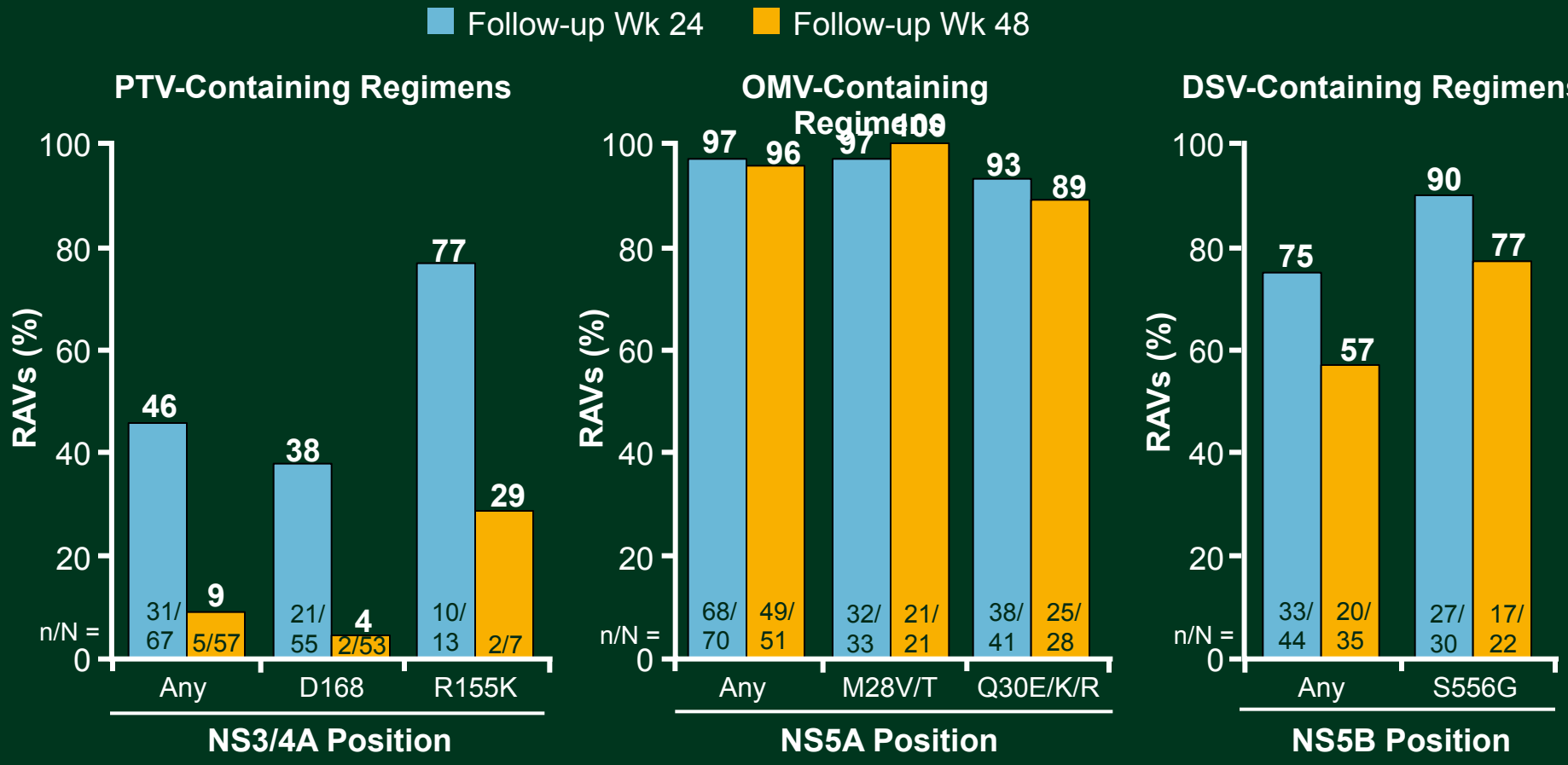
- Study of pts not achieving SVR after receiving LDV without SOF



- NS5A RAVs persisted in majority of pts for 96 wks

Dvory-Sobol H, et al. EASL 2015. Abstract O059.

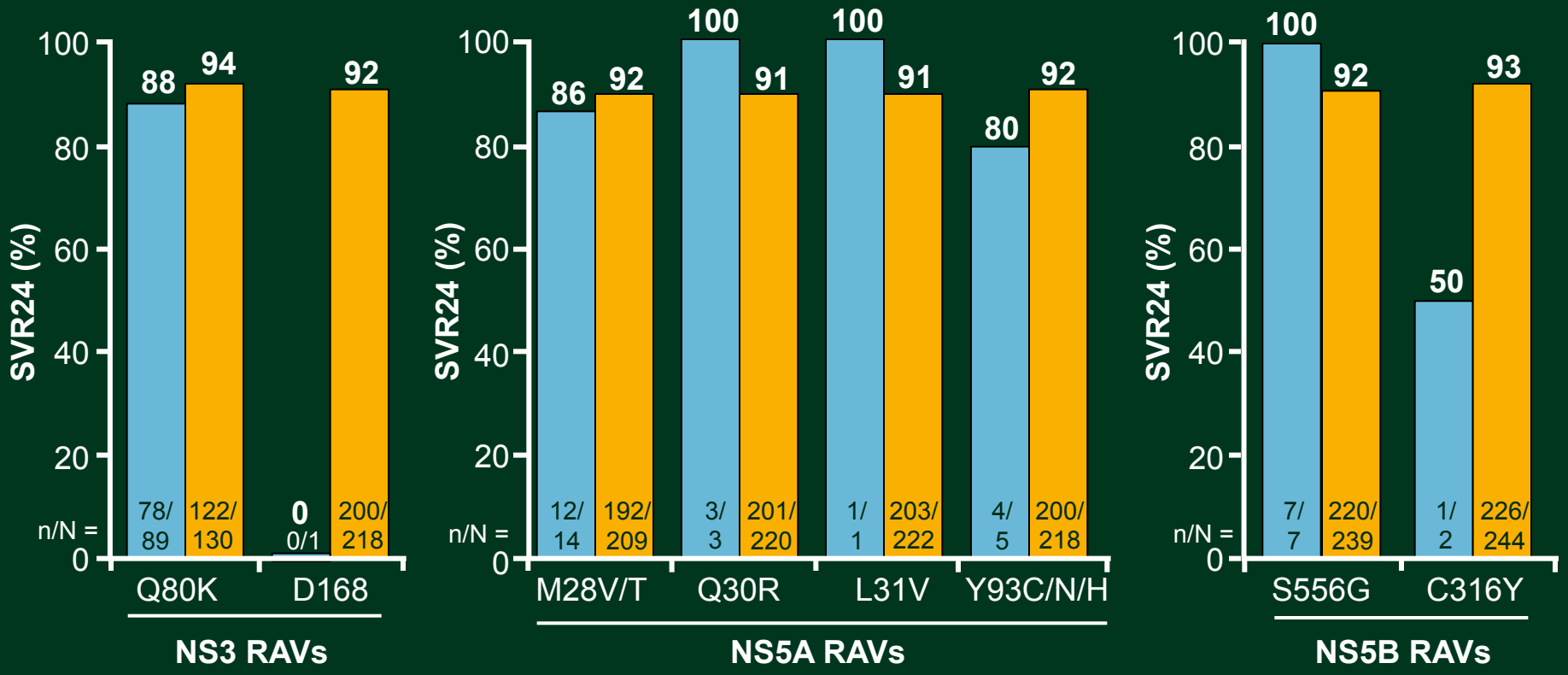
Pooled Analysis: RAV Persistence After Failure of PTV/RTV-, OMV-, DSV-Based Tx



Krishnan P. EASL 2015. Abstract O057.

AVIATOR: No Impact of Baseline RAVs in GT1a Pts Treated With OMV/PTV/RTV + DSV

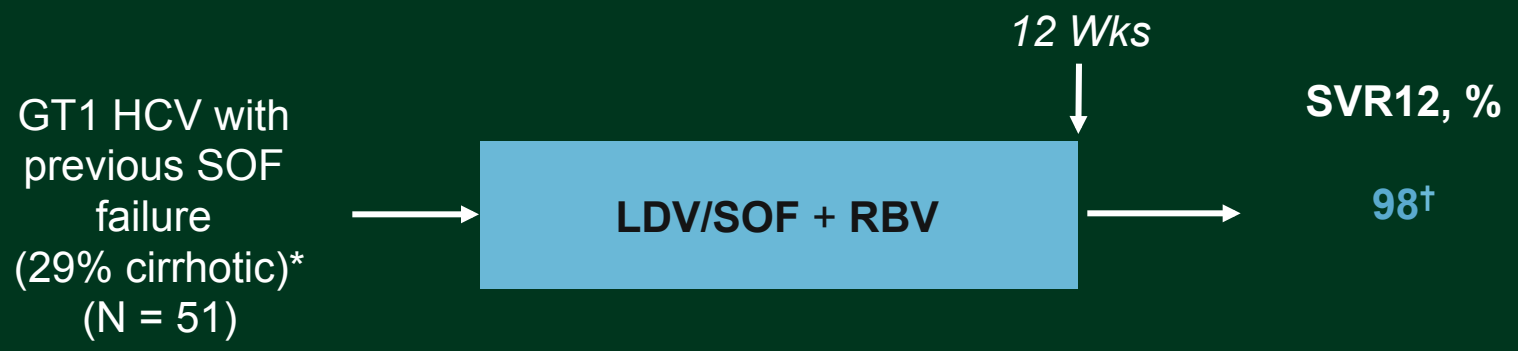
- Treatment naive pts or null responders to previous pegIFN/RBV
- All differences in SVR24 with vs without baseline RAVs were nonsignificant



Krishnan P, et al. Antimicrob Agents Chemother. 2015;59:5445-5454.

LDV/SOF + RBV in GT 1 HCV Pts With Previous Failure on Sofosbuvir Regimens

- Phase II trial

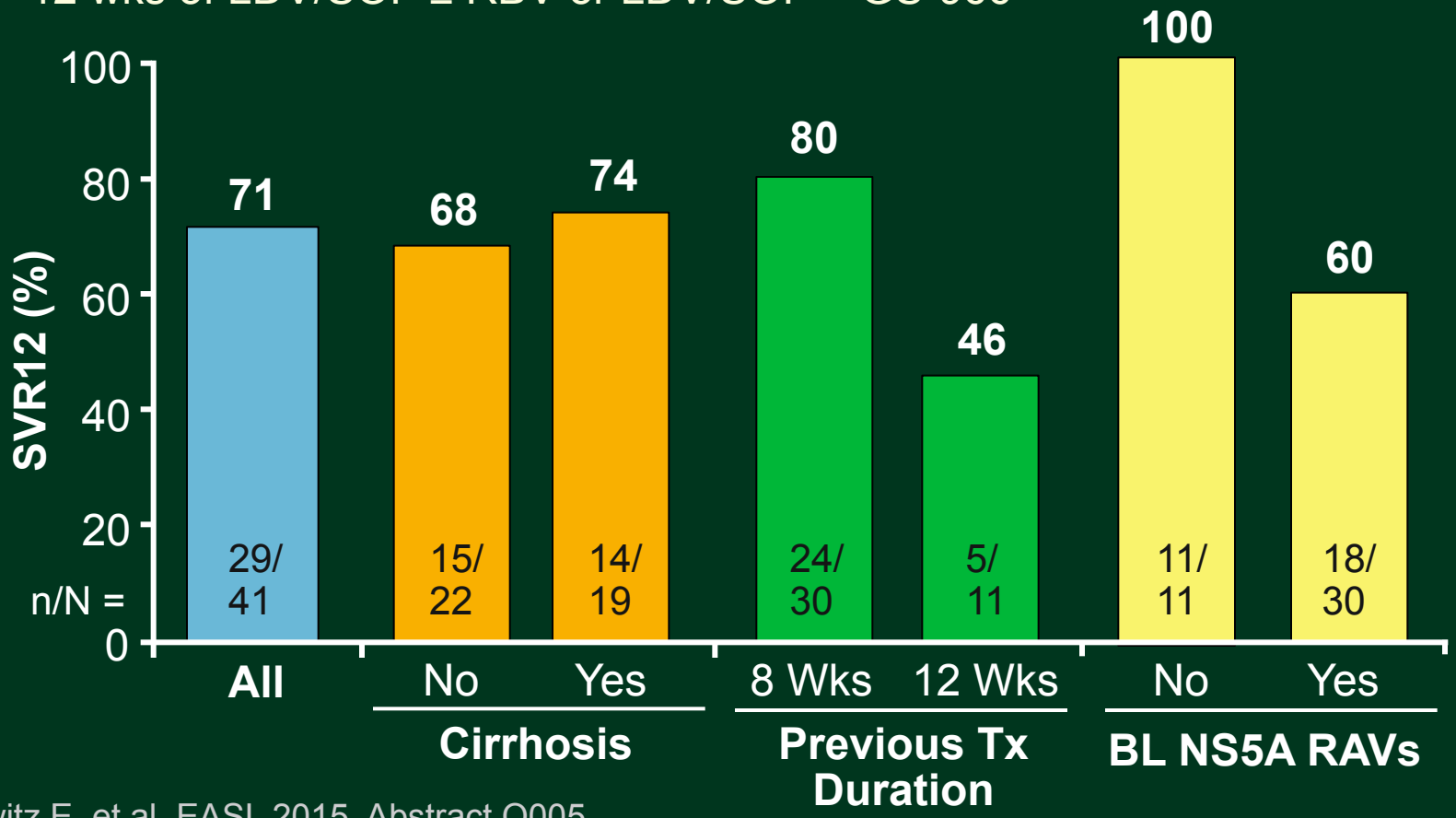


*25 pts (49%) were previously treated with SOF + pegIFN/RBV, 21 (41%) with SOF ± RBV, 5 (10%) with SOF placebo plus pegIFN/RBV or GS-0938 monotherapy, 1 (2%) with SOF monotherapy.
†1 pt who relapsed found to have GT3a HCV infection and enrolled in error.

Wyles DL, et al. Hepatology. 2015;61:1793-1797.

24 Wks of LDV/SOF Retreatment After Failure of 8-12 Wks of LDV/SOF-Based Tx

- GT1 HCV–infected pts with and without cirrhosis previously treated with 8 or 12 wks of LDV/SOF ± RBV or LDV/SOF + GS-966



Lawitz E, et al. EASL 2015. Abstract O005.

24 Wks of LDV/SOF After Failure of LDV/SOF-Based Tx: Effect of Baseline RAVs

SVR12 by Baseline NS5A RAVs, n/N (%)	LDV/SOF for 24 Wks
Number of RAVs	
▪ 0	11/11 (100)
▪ 1	11/16 (69)
▪ ≥ 2	7/14 (50)
Single NS5A RAV	
▪ Q30R or M28T	5/5 (100)
▪ L31M	4/5 (80)
▪ Y93H/N	2/6 (33)

- NS5B variants emerged during retreatment in 33% of pts (4/12) with virologic failure
  - **S282T: n = 2**; L159F: n = 1; **S282T + L159F: n = 1**

Lawitz E, et al. EASL 2015. Abstract O005.

GT1 Pts With NS5A Failure: Who Needs Resistance Testing?

- If previous failure of any NS5A inhibitors (including DCV + SOF, LDV/SOF, OMV/PTV/RTV + DSV) and minimal liver disease, deferral preferred pending further data
  - If cirrhosis or other need for urgent treatment, test for NS3 and NS5A RAVs
- Applies to genotype 1a and 1b HCV infection
- NS3 and NS5A testing not required for:
  - Previous failure of NS3/4A PIs (including simeprevir, boceprevir, telaprevir)
  - Previous failure of NS5B inhibitors (sofosbuvir)
  - Tx-naive pts (unless considering SMV + SOF in cirrhotic GT1a)

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Selecting Treatment Based on Resistance Testing Results

- If genotype 1a or 1b HCV infection and previous failure with any NS5A inhibitors and cirrhotic or other need for urgent treatment:

RAV Testing Result	Retreatment Regimen	Duration
No NS5A RAVs	Ledipasvir/sofosbuvir + ribavirin	24 wks
NS5A but no NS3 RAVs	Simeprevir + sofosbuvir + ribavirin	24 wks
NS5A and NS3 RAVs	Retreatment in a clinical trial setting	

AASLD/IDSA/IAS-USA. HCV Guidance.

Is Ribavirin Required for Pts With Cirrhosis?

- Integrated analysis of > 500 pts with cirrhosis treated with LDV/SOF ± RBV
- Treatment-experienced pts had previously received HCV PI

SVR12, %	Total (N = 513)	Treatment Naive (n = 161)	Treatment Experienced (n = 352)
Overall	96	98	95
12 wks ± RBV	95	97	94
24 wks ± RBV	98	99	98
Without RBV	95	96	95
With RBV	97	99	96
12 wks without RBV	92	96	90
12 wks with RBV	96	98	96
24 wks without RBV	98	97	98
24 wks with RBV	100	100	100

- Although NS5A resistance not measured, RBV overcomes shorter treatment duration in patients with HCV cirrhosis and prior treatment failure

Reddy KR, et al. Hepatology. 2015;62:79-86.

Is Ribavirin Required for Pts With Cirrhosis and NS5A RAVs?

- Integrated analysis of > 500 pts with cirrhosis treated with LDV/SOF ± RBV
- Treatment experienced patients had previously received HCV PI

SVR12, % (n/N)18	With NS5A RAVs	Without NS5A RAVs
Overall	91 (86/94)	98 (407/417)
12 wks without RBV	88 (23/26)	95 (86/91)
12 wks with RBV	94 (32/34)	97 (164/169)
24 wks without RBV	85 (17/20)	100 (113/113)
24 wks with RBV	100 (14/14)	100 (44/44)

Reddy KR, et al. Hepatology. 2015;62:79-86.

Personal Recommendations for Resistance in GT3 and GT4 HCV Infection

- **Genotype 3**
  - Treatment failures on daclatasvir should be tested for NS5A RAVs
  - BOSON: Adding pegIFN to SOF/RBV appears to help overcome virologic failure due to resistance in GT3[1]
    - Improved SVR12 vs SOF/RBV alone in both treatment-naive and treatment-experienced pts, with or without cirrhosis
- **Genotype 4**
  - Resistance testing should be performed if considering retreatment after LDV/SOF failure
  - Use SMV/SOF/RBV for NS5A RAVs

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

Summary

- Baseline RAVs (especially NS5A) are present in treatment-naive pts
- Treatment-emergent RAVs (including multidrug-resistant RAVs) seen in treatment failure and in all DAA classes and rarely with SOF
- NS3 RAVs have low replication efficacy and disappear over 9-18 mos
  - If considering SMV + SOF: In treatment-naive and treatment-experienced pts with both genotype 1a HCV infection and compensated cirrhosis, ensure no Q80K
- NS5A treatment-emergent RAVs persistent and a clinical challenge
  - If failure with any NS5A inhibitors (including DCV + SOF, LDV/SOF, OMV/PTV/RTV + DSV), and treatment is urgent, test for NS3 and NS5A RAVs
    - Use SMV + SOF + RBV if NS5A but no NS3 RAVs
    - Use LDV/SOF + RBV if no NS5A RAVs
    - Treat in clinical trial if both NS5A and NS3 RAVs present
- Resistance testing may be of benefit in treatment failures