

# **NS5A Resistance: What we Know and What we Think we Know**

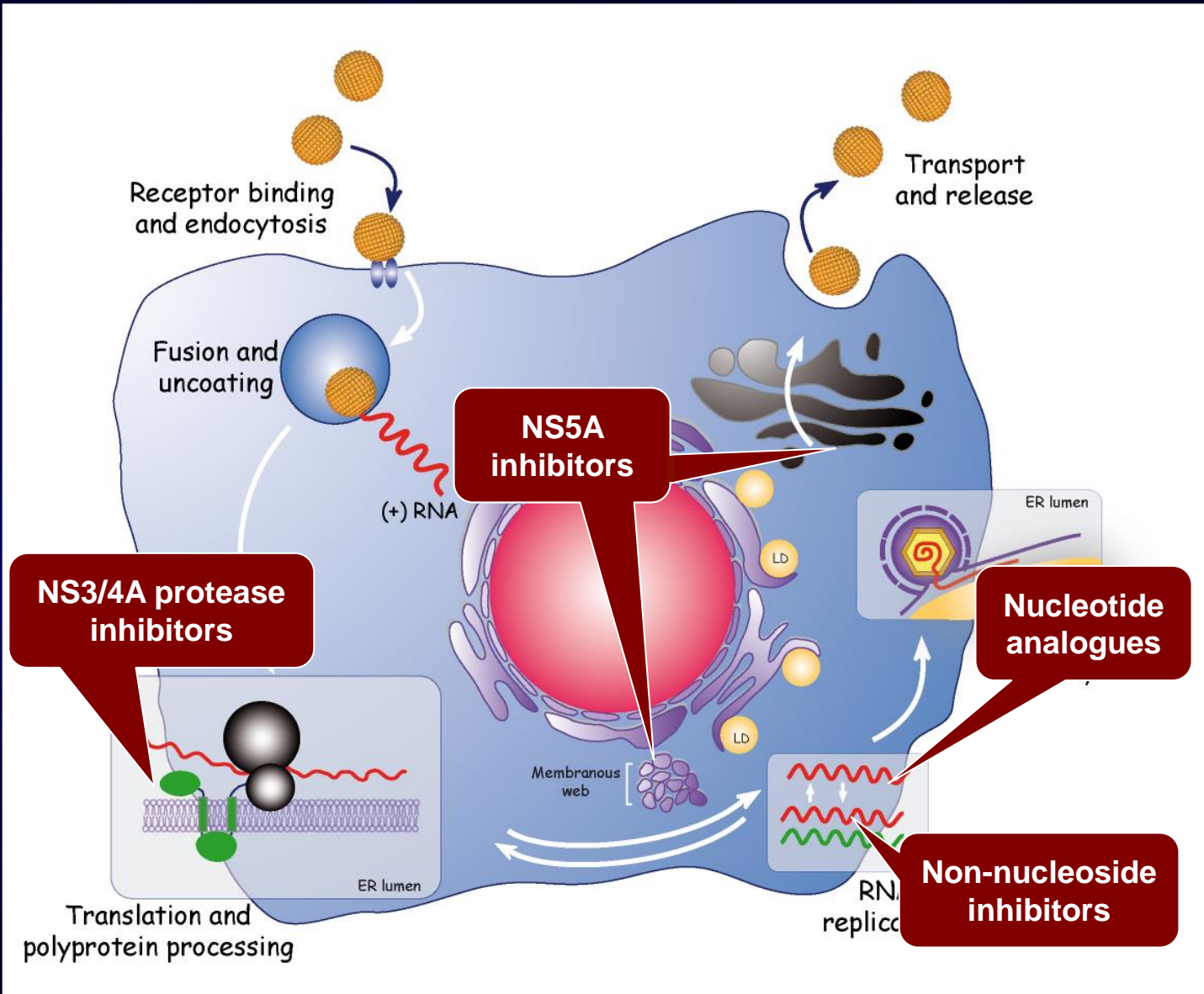
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**National Reference Center for Viral  
Hepatitis B, C and delta  
Department of Virology & INSERM U955**

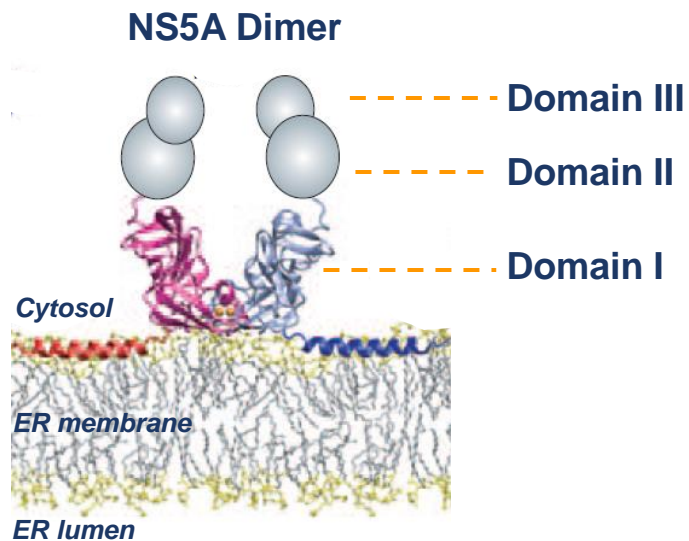
**Henri Mondor Hospital  
University of Paris-Est  
Créteil, France**

# Available HCV DAA Classes



***NS5A RAVs***

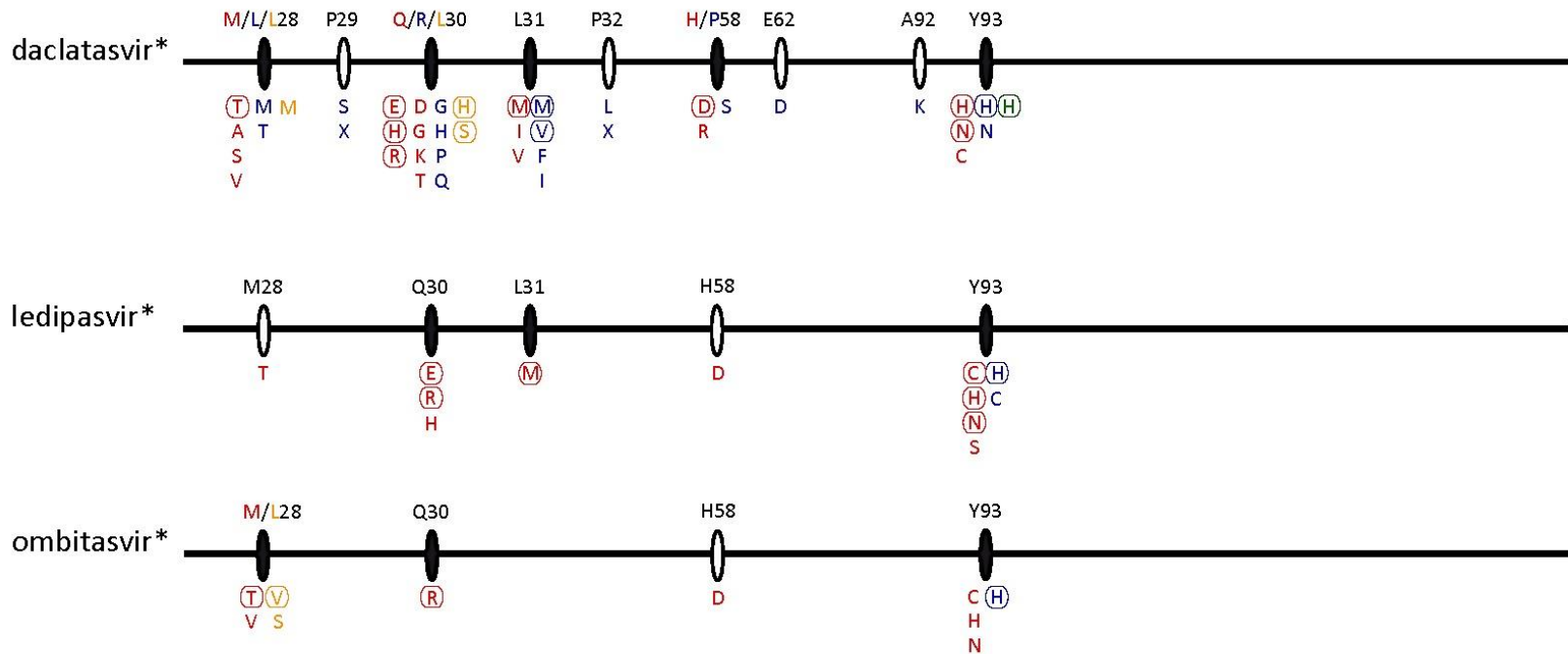
# NS5A Protein



- Required for HCV RNA replication
- Required for HCV viral particle assembly
- May be involved in the release of HCV particles

# NS5A Inhibitor Resistance

## *Low barrier to resistance*

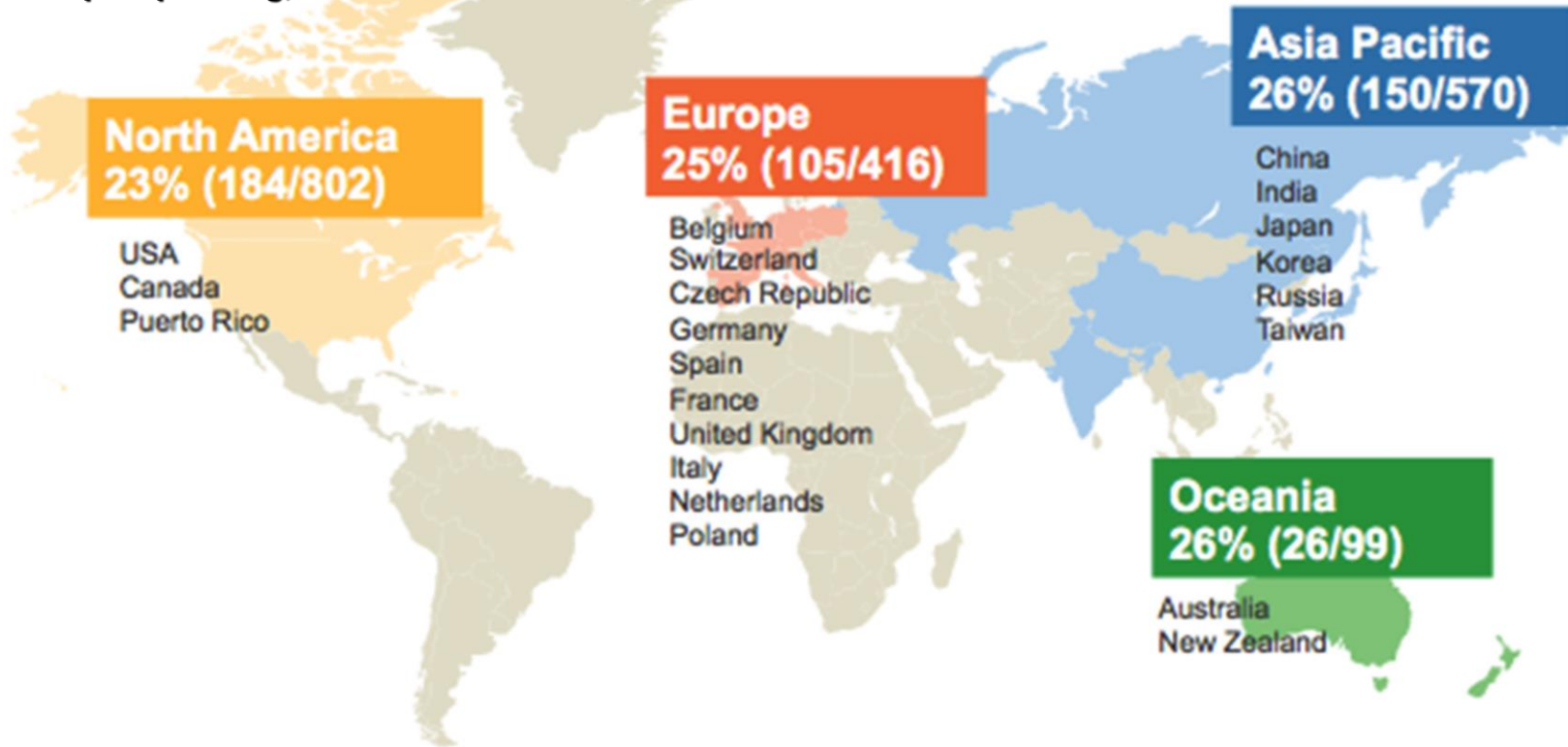


Genotype and subtype designations: 1a - red, 1b - blue, 3a - green, X - amino acid deletion  
4 - orange (daclatasvir - genotype 4, ombitasvir - genotype 4d)

# ***Prevalence of Baseline NS5A RAVs***

# Prevalence of NS5A RAVs

Deep sequencing, 1% cutoff



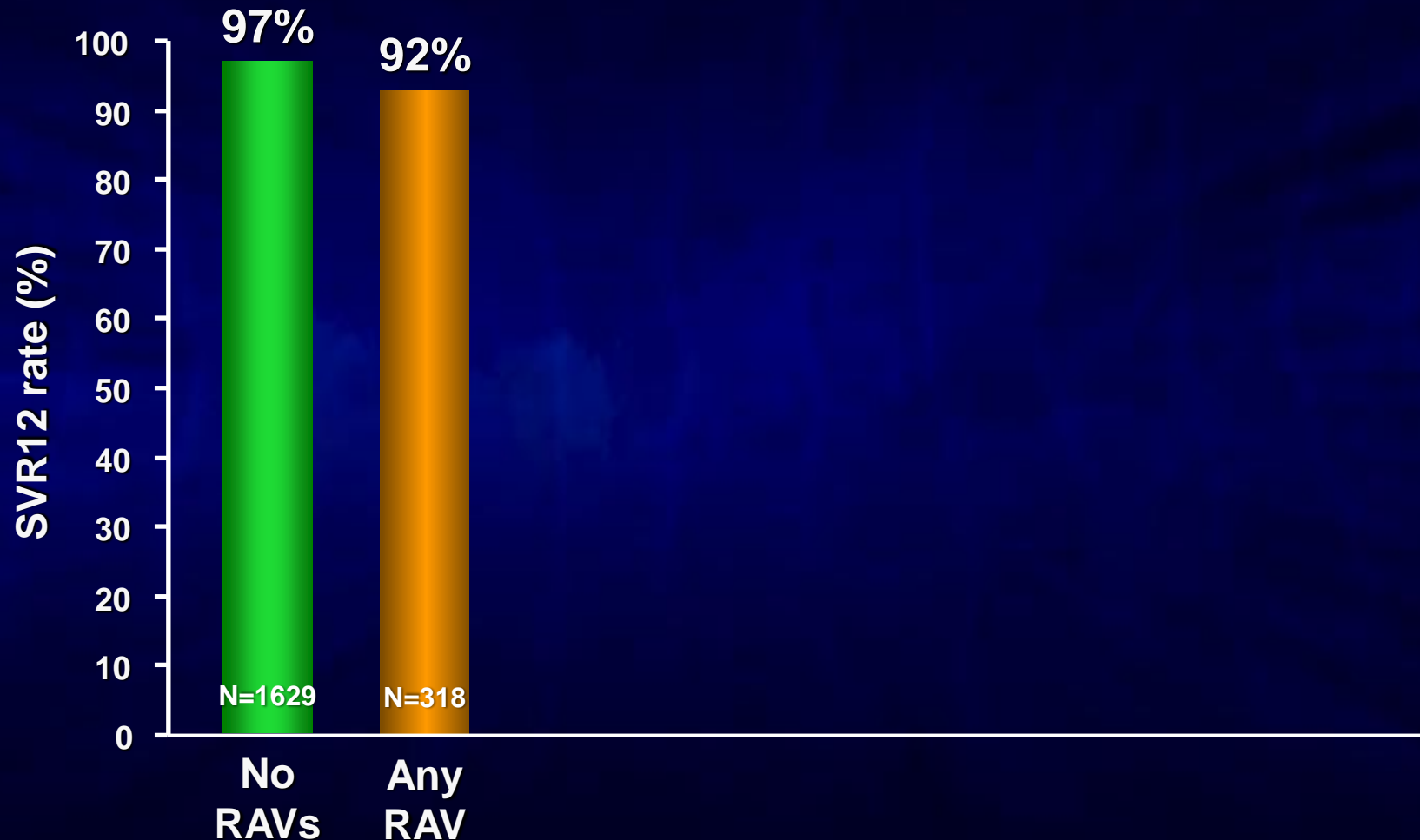
◆ Using a 15% cut-off, prevalence of NS5A RAVs was 16% in North America, 17% in Europe; 20% in Asia Pacific, 19% in Oceania

***Influence of Baseline RAVs on  
IFN-Free Treatment Outcomes***



# SVR According to Baseline NS5A RAVs

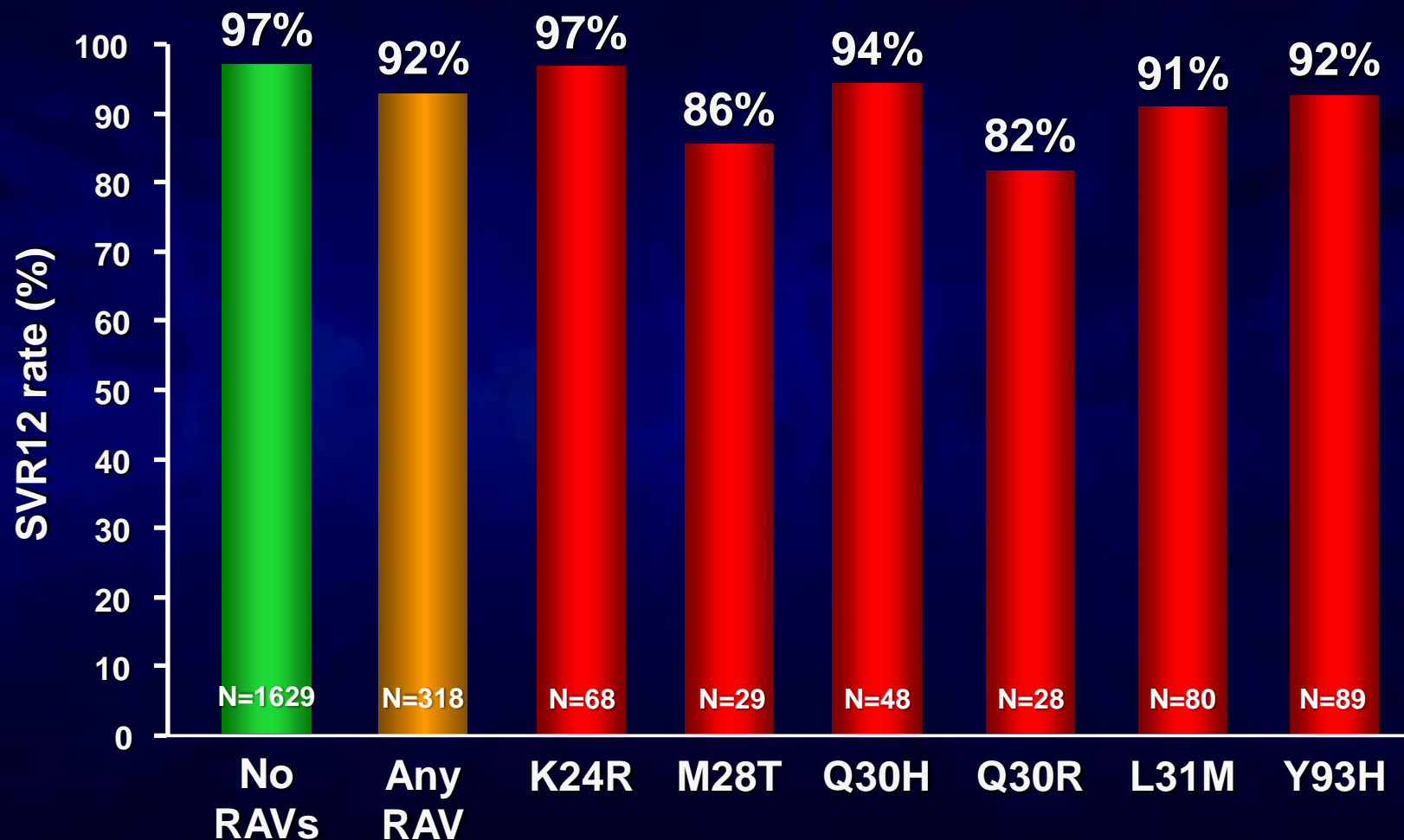
## ION-1/2/3- Sofosbuvir/Ledipasvir $\pm$ RBV



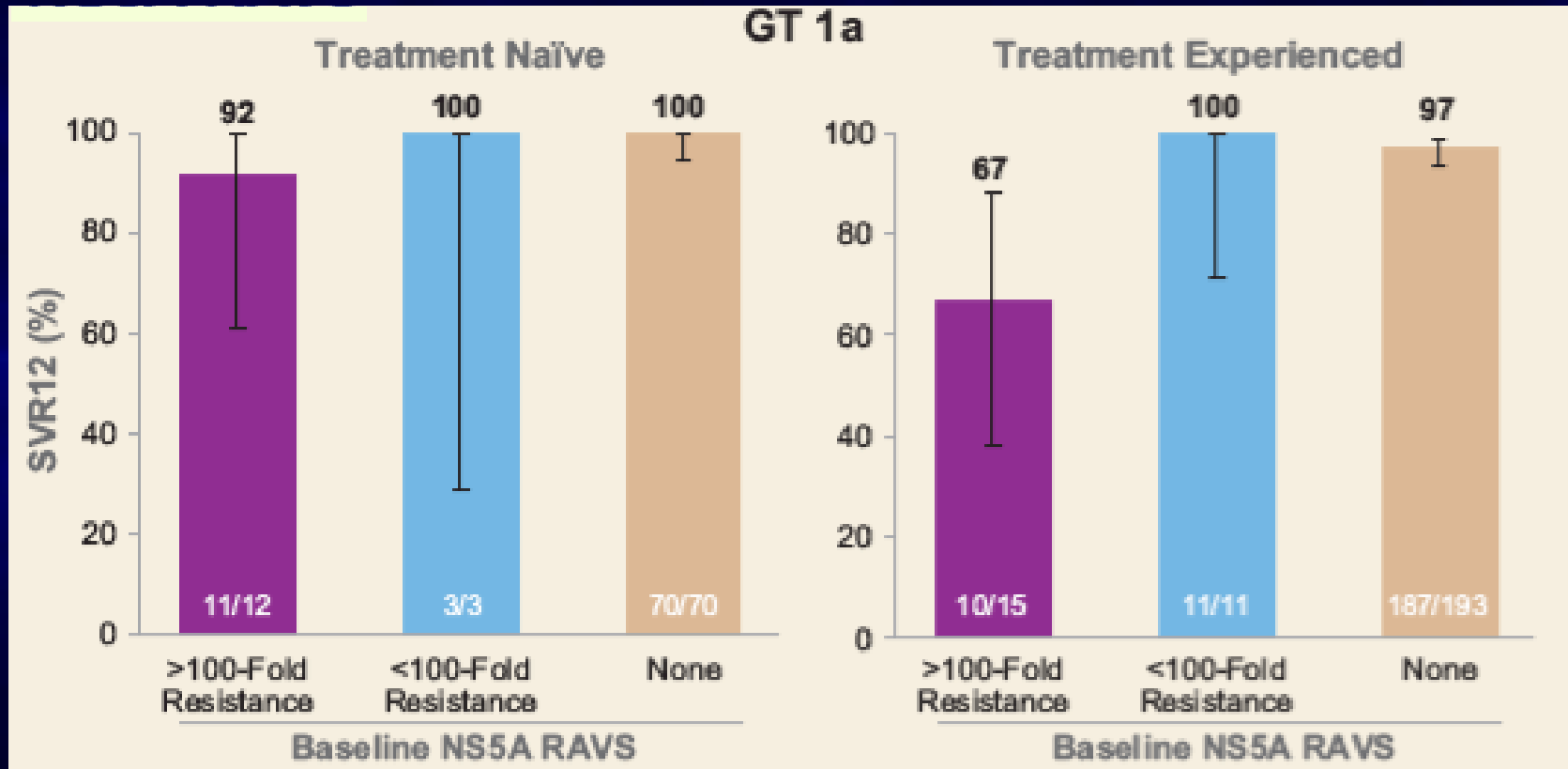
(Dvory-Sobol et al., International Workshop on Antiviral Drug Resistance, June 2014)

# SVR According to Baseline NS5A RAVs

*ION-1/2/3- Sofosbuvir/Ledipasvir ± RBV*



# SVR to Sofosbuvir/Ledipasvir According to NS5A RAVs (513 cirrhotic patients)

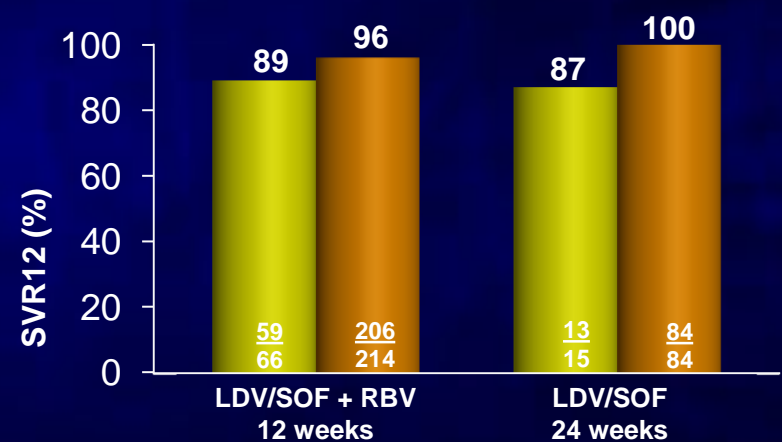
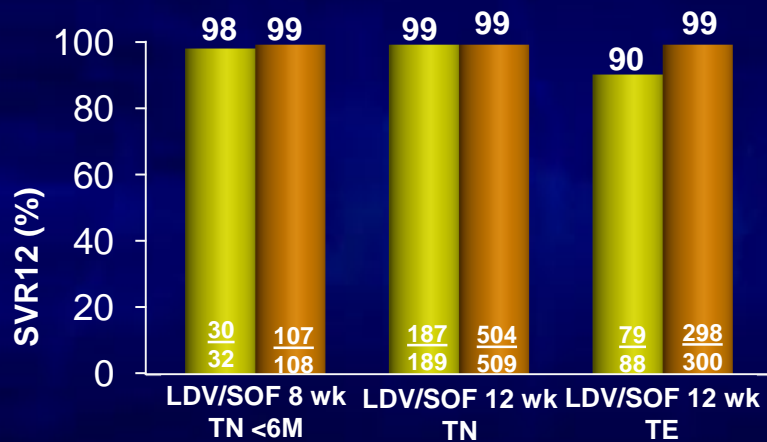


# Influence of NS5A RAVs

## Sofosbuvir-Ledipasvir

*No cirrhosis*

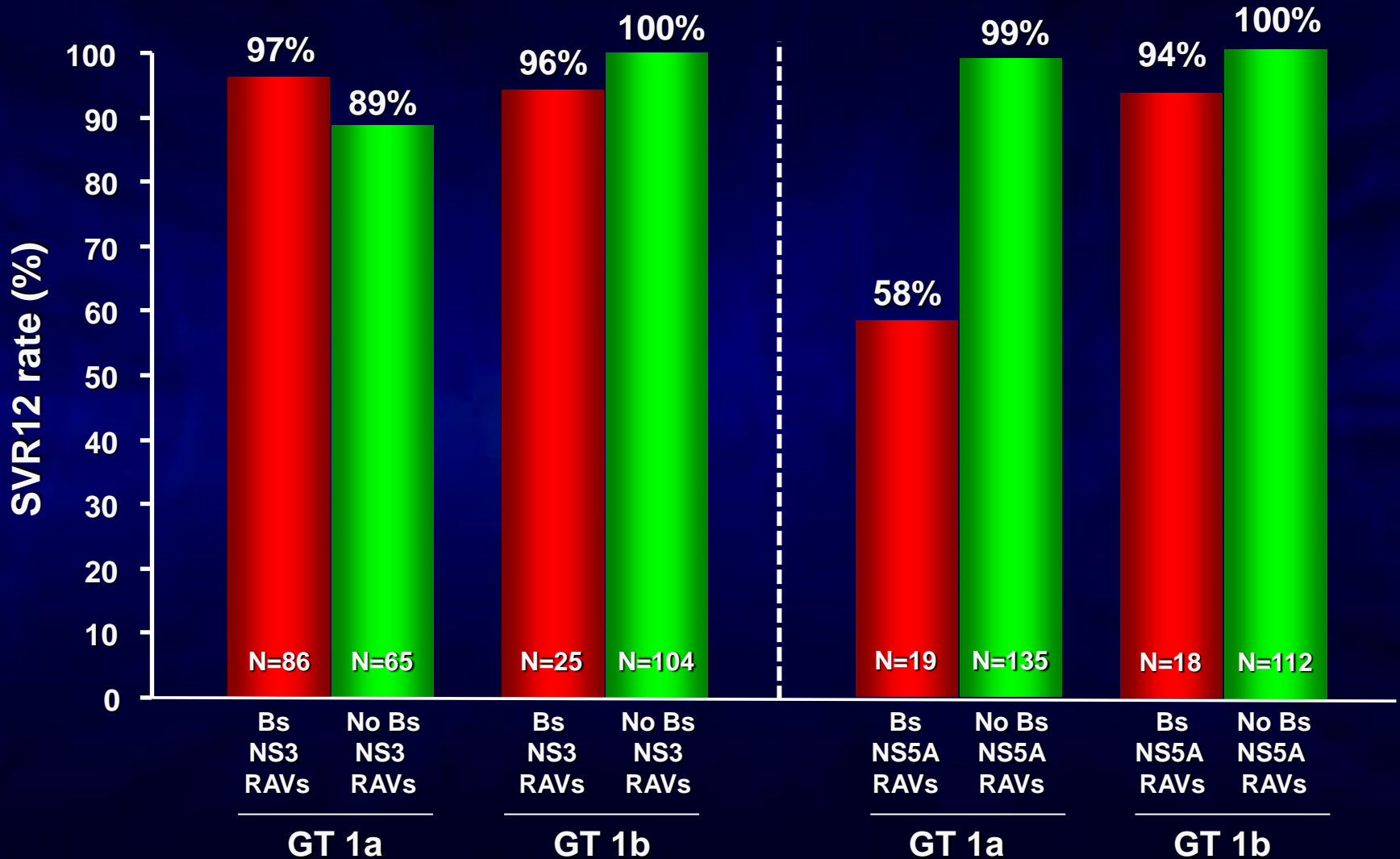
*Cirrhosis*



■ With RAVs ■ No RAVs

# Grazoprevir + Elbasvir

C-EDGE TN- Phase III, Rx-naïve, Gt 1, w/o cirrhosis, 12 weeks



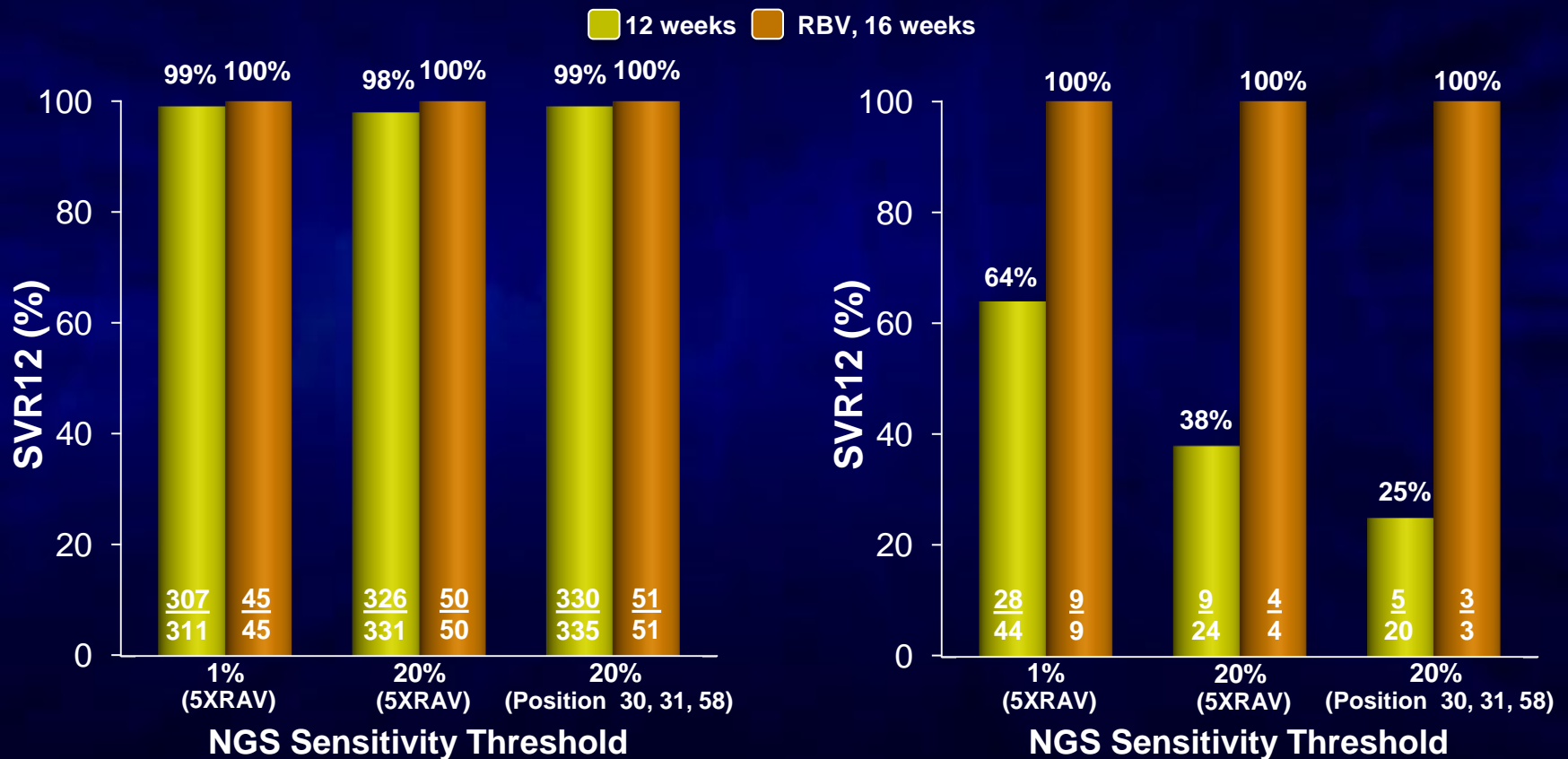
(Zeuzem et al., Ann Intern Med 2015; epub ahead of print)

# Influence of NS5A RAVs

## Grazoprevir-Elbasvir

No Baseline NS5A RAVs

With Baseline NS5A RAVs

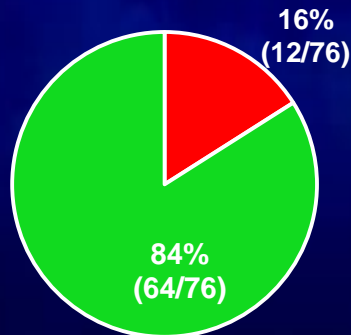


***Selection of RAVs in Patients  
who Fail to Achieve an SVR***

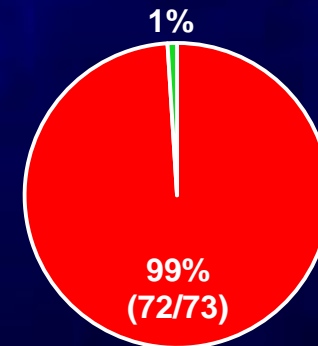
# Selection of RAVs in Patients who Failed after LDV (no SOF)

Patients who failed after a ledipasvir-containing treatment (without sofosbuvir)

Before LDV Treatment



At Virologic Failure With LDV Treatment



■ Patients without NS5A RAVs  
■ Patients with NS5A RAVs



# Treatment Failures in SAPPHERE-2

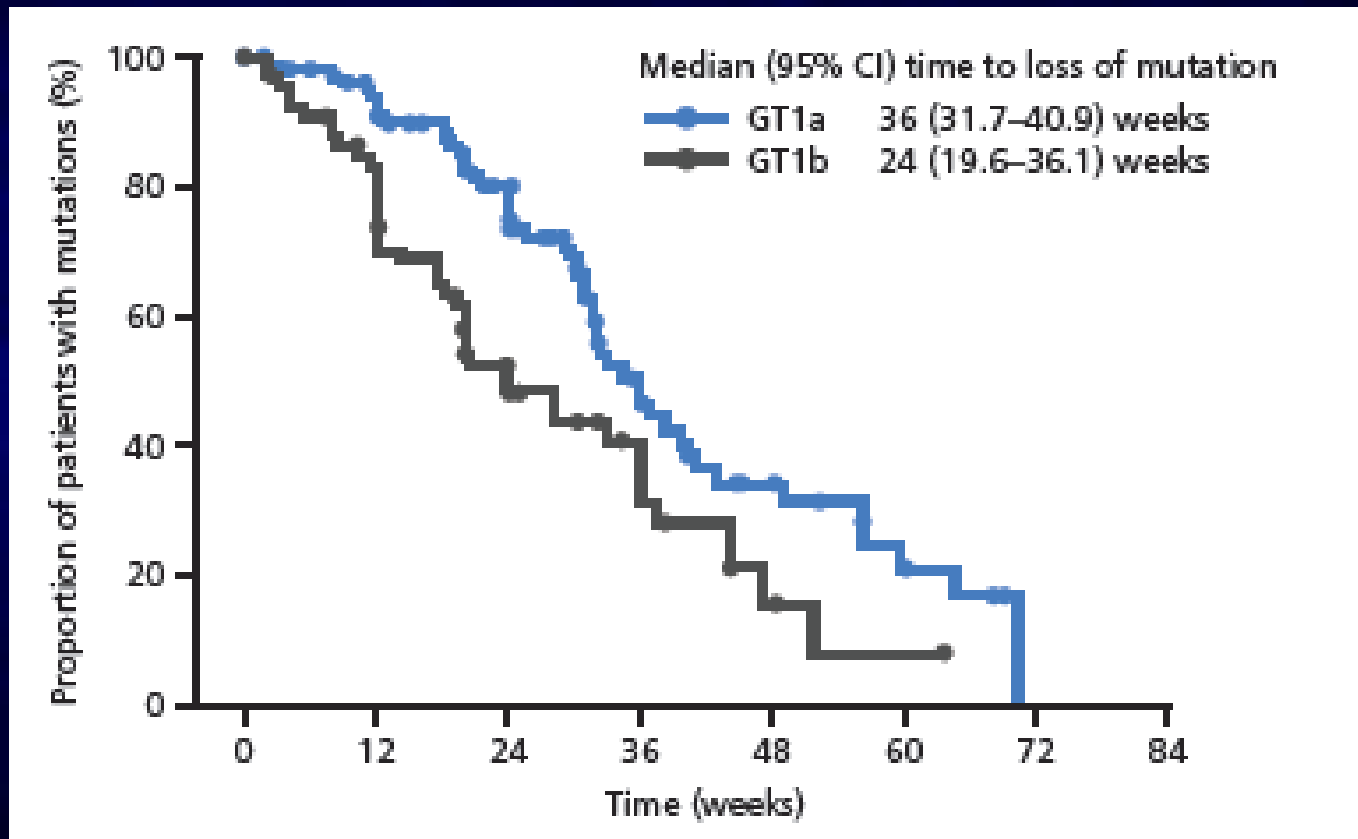
*Genotype 1, Rx-experienced, 3D ± Ribavirin*

**Virologic failure in 7/297 patients (2.4%)**

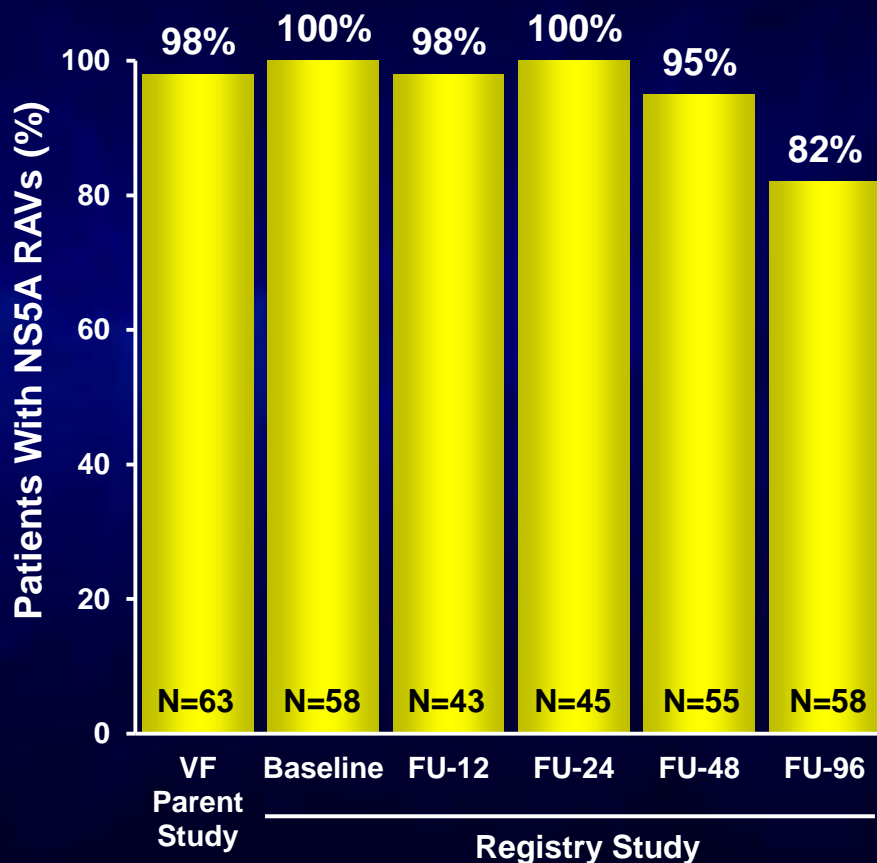
| Patient | Type of |                      |             |             |                |
|---------|---------|----------------------|-------------|-------------|----------------|
|         | GT      | Virologic Failure    | NS3         | NS5A        | NS5B           |
| 1       | 1a      | Relapse at PT Week 2 | D168Y       | M28V, Y93L* | S556G          |
| 2       | 1a      | Relapse at PT Week 4 | none        | M28V        | none           |
| 3       | 1a      | Relapse at PT Week 4 | V36A, D168V | M28V, Q30R  | S556G          |
| 4       | 1a      | Relapse at PT Week 8 | none        | none        | none           |
| 5       | 1a      | Relapse at PT Week 8 | D168V       | Q30R        | none           |
| 6       | 1b      | Relapse at PT Week 2 | Y56H, D168A | Y93H*       | C316N*, S556G* |
| 7       | 1b      | Relapse at PT Week 4 | none        | none        | none           |

***Post-treatment RAV Persistence  
in Patients who Fail to Achieve an SVR***

# Replacement of PI-Resistant Viruses by Wild-Type Viruses



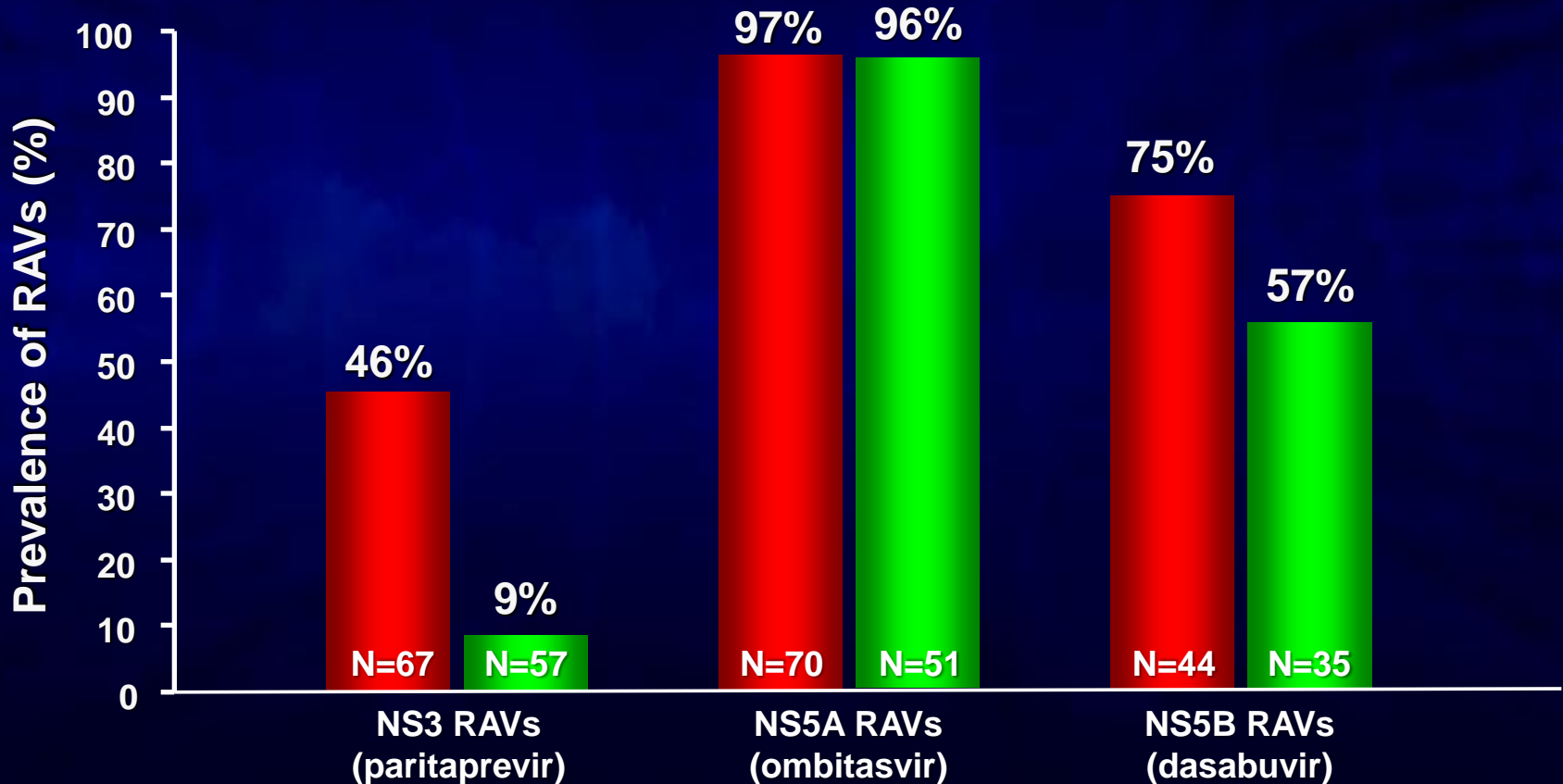
# Persistence of RAVs in Patients who Failed after LDV (no SOF)



# Persistence of RAVs in Patients who Relapsed after 3D

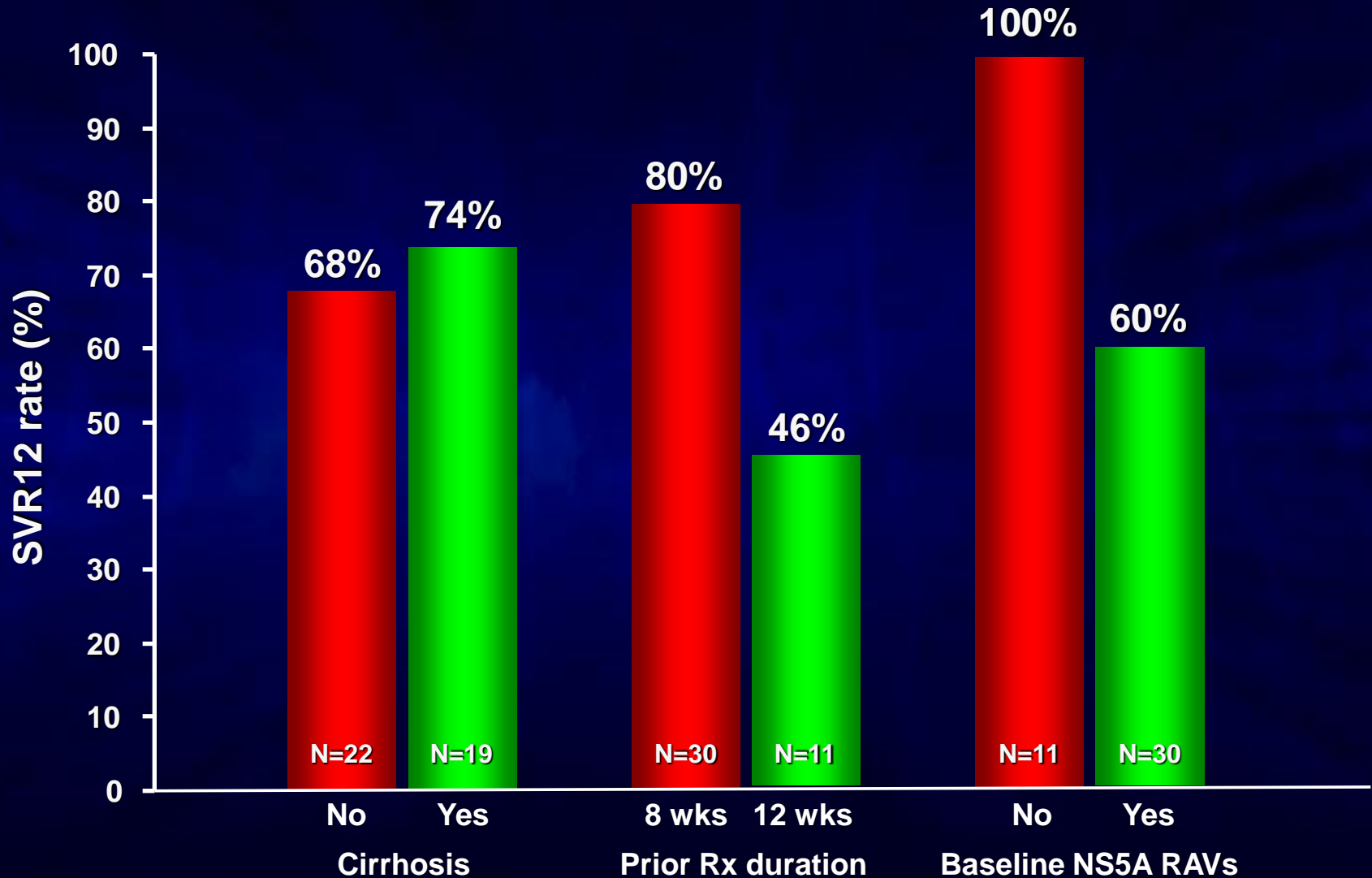
67/2510 patients with genotype 1a and virologic failure after 3D

■ 24 wks post-treatment  
■ 48 wks post-treatment



***Retreatment of Patients with Persistent  
RAVs after IFN-free regimen failure***

# Retreatment of Patients who Failed 8 or 12 Weeks of LDV/SOF with LDV/SOF 24 Weeks



# Retreatment of Patients who Failed an IFN-Free Regimen

- Recommendations are based on indirect evidence and subject to change when more data become available
- The retreatment regimen should contain
  - Sofosbuvir because of the high barrier to resistance
  - 1 or 2 other DAA(s), if possible with no cross-resistance with the DAA(s) already administered
  - Ribavirin
- Treatment duration should be 12 or 24 weeks (24 weeks recommended in F3-F4)



# Retreatment Options

- **Sofosbuvir + Daclatasvir + Simeprevir**
- **Sofosbuvir + 3D**
- **Sofosbuvir + Grazoprevir + Elbasvir**

# ***Utility of HCV Resistance Testing***

# Utility of HCV Resistance Testing

- **Lack of standardization of the assays**
- **Best timing for testing**
  - **Prior to therapy**
  - **At the time of relapse**
  - **At the time of retreatment**
- **Guidelines for interpretation and retreatment decisions**



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