# What is Known: Published Data on HCV Treatment Failure

**Presenter:**
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INSTITUTE OF HUMAN VIROLOGY


# Retreatment of Hepatitis C Studies and Questions

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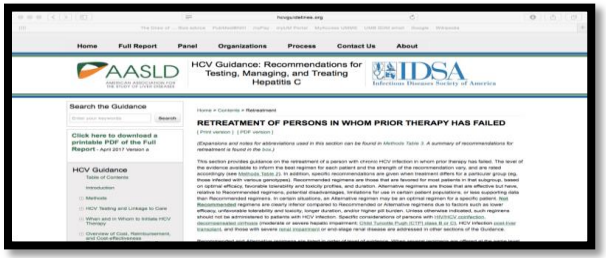
April 20th, 2017

# Background: Retreatment of HCV

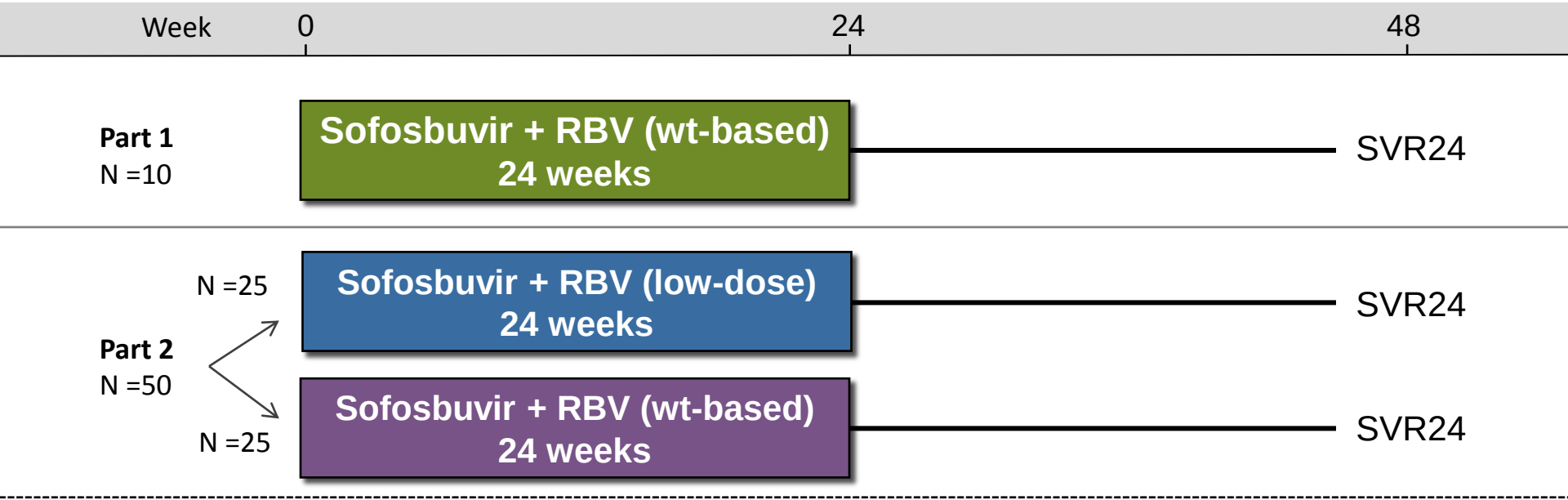
- HCV retreatment has changed with HCV treatment regimens
  - IFN/RBV
  - IFN/RBV + PI
  - SOF/RBV
  - NS5A-inhibitors
- AASLD/EASL guidelines address these, with varying levels of evidence
  - Patients may choose to defer retreatment if they can
  - If needed, retreatment should combine
    - a DAA with a high genetic barrier to resistance (SOF)
    - RBV if possible/tolerated
    - 1-2 other DAAs, preferably at least one from a novel class

# Background: HCV Treatment Failure

- Why do patients fail HCV treatment with DAAs?
  - Treatment experience
  - Fibrosis stage
  - Viral load
  - Immunodeficiency
  - Resistance
  - Adherence
  - Reinfection

# Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1
## NIH SPARE Trial: Design




**Drug Dosing**

Sofosbuvir: 400 mg once daily

Low-dose Ribavirin (divided bid): 800 mg/day

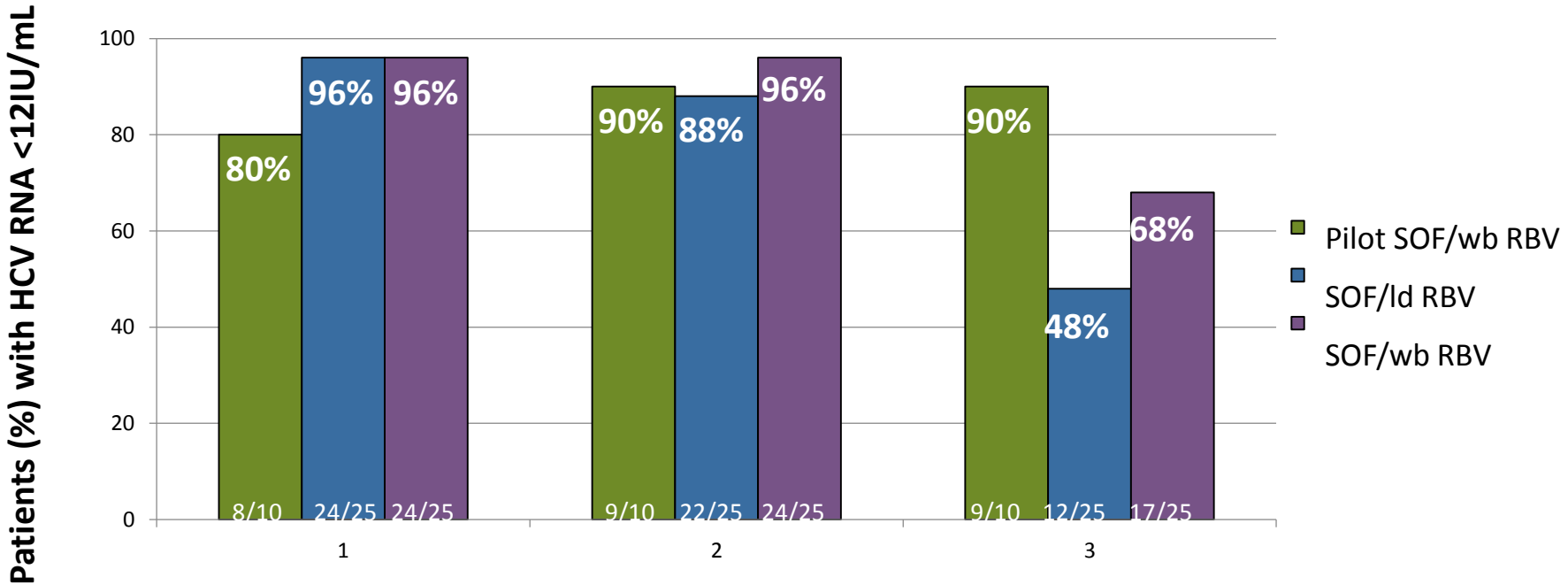
Weight-based Ribavirin (divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

**Source: Osinusi A, et al. JAMA. 2013;310:804-11.**

Slides adapated from HCV-Trials.com

# Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1
# NIH SPARE Trial: Results

## NIH SPARE : HCV <12 IU/ml by Study Timepoint

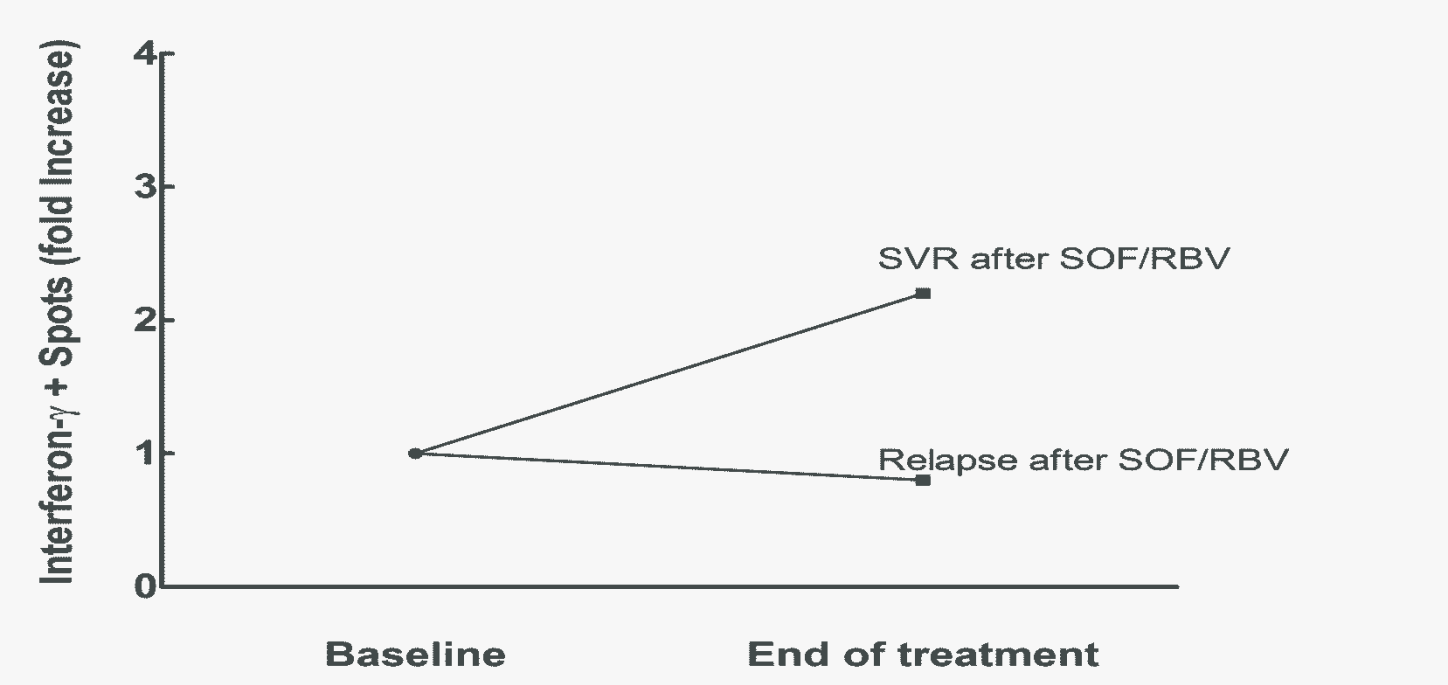



SOF = Sofosbuvir; RBV = Ribavirin; ld = Low dose; wb = Weight-based

**Source: Osinusi A, et al. JAMA. 2013;310:804-11.**

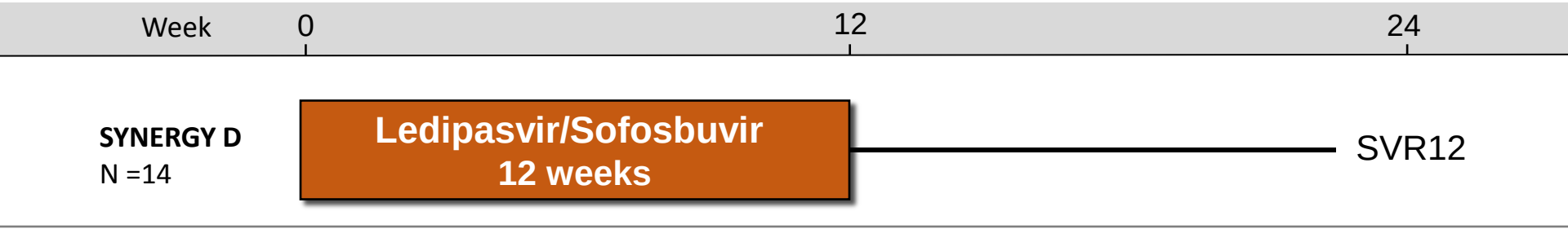
Slides adapted from HCV-Trials.com

# T cell response to HCV Treatment




Shrivastava *J Viral Hepat* 2017

# Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1
# NIH SYNERGY (Retreatment arm) Trial: Design



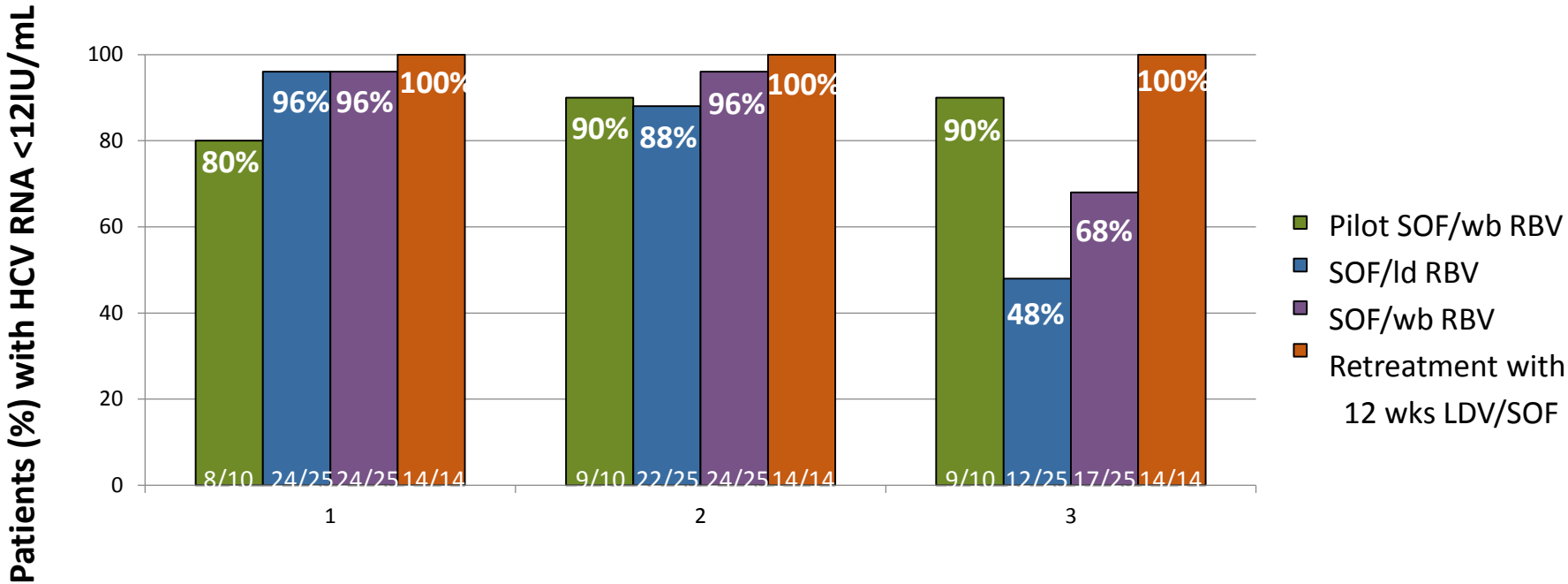

**Drug Dosing**

Ledipasvir/Sofosbuvir: 90mg/400 mg once daily

**Source: Osinusi A, et al. Ann Int Med. 2014;161:634-8.**

# Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1
# NIH SPARE Trial: Results

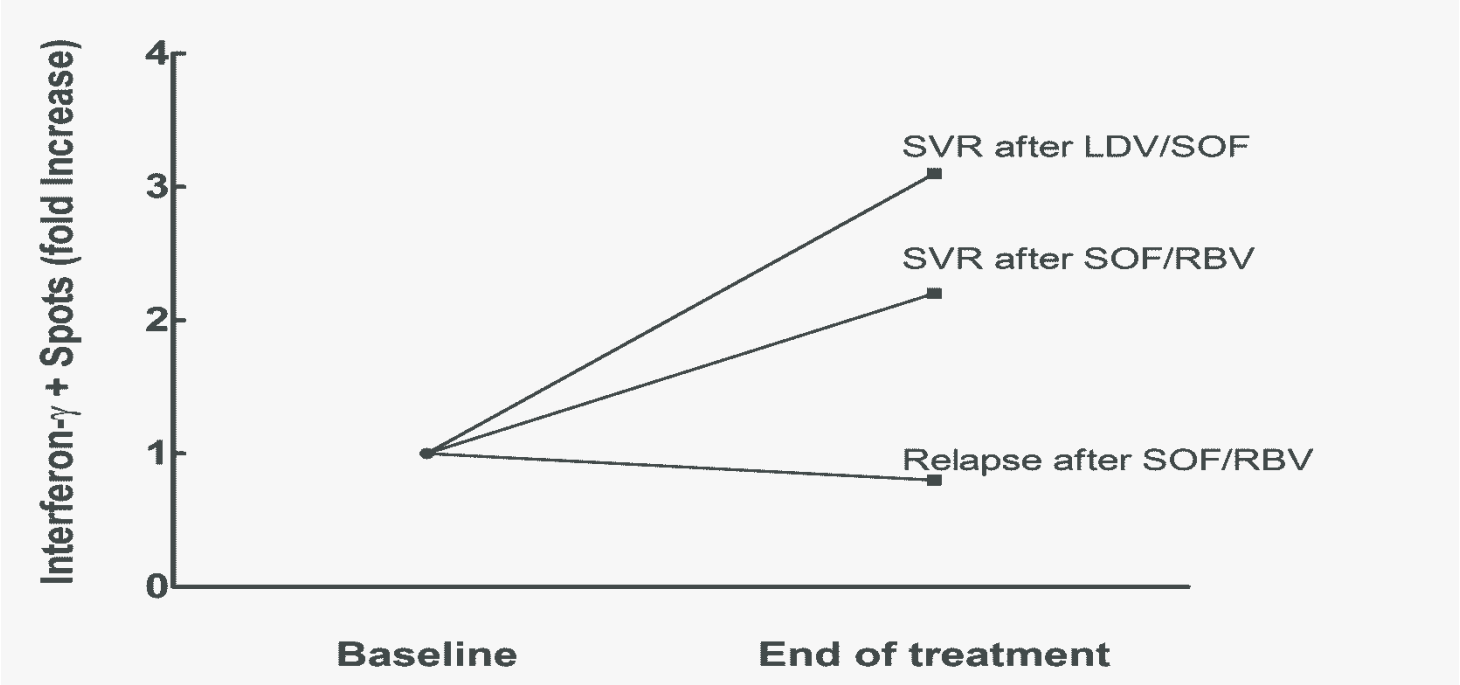
## NIH SPARE : HCV <12 IU/ml by Study Timepoint




SOF = Sofosbuvir; RBV = Ribavirin; LDV/ = Ledipasvir; ld = Low dose; wb = Weight-based

**Source: Osinusi A, et al. JAMA. 2013;310:804-11.**

# T cell response to HCV (re)Treatment

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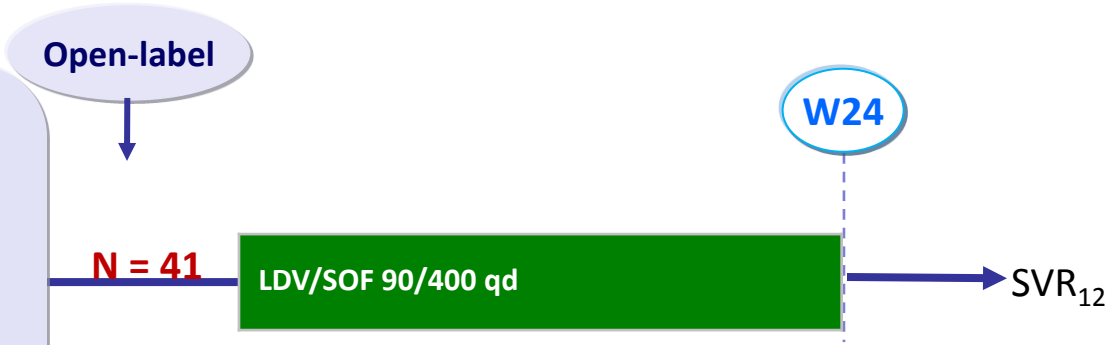
# LDV/SOF Failure Study: LDV/SOF for retreatment of genotype 1 with prior failure to LDV/SOF

## Design

**Chronic HCV infection**
**Genotype 1**
**Failure to achieve SVR on LDV/SOF-containing regimen for 8 or 12 weeks**
**Compensated cirrhosis (liver biopsy or Fibrotest > 0.75 + APRI > 2) allowed**
**No HBV or HIV co-infection**




## Objective

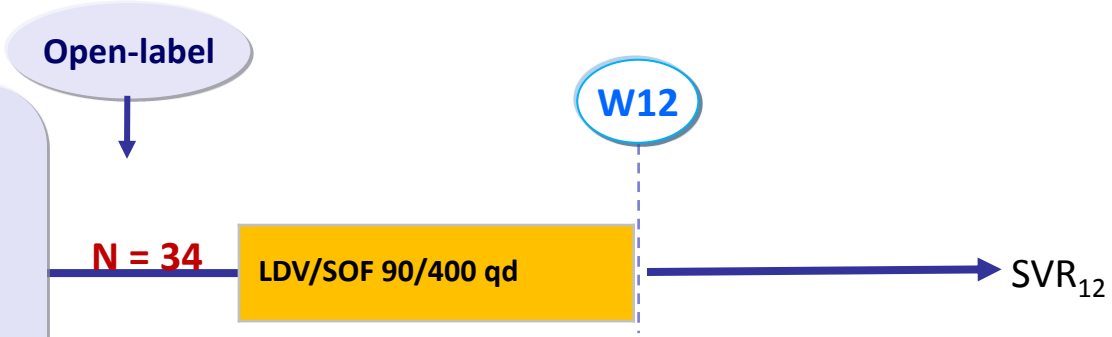
- Primary endpoint : $SVR_{12}$ (HCV RNA < 15 IU/ml) by intention to treat, with 2-sided 95% CI, no statistical hypothesis

*Lawitz E. EASL 2015, Abs. O005*

# SYNERGY D : LDV/SOF for retreatment of genotype 1 with prior failure to LDV/SOF/GS-9669 ± GS-9451

## Design

**Chronic HCV infection**
**Genotype 1**
**Failure to achieve SVR on LDV/SOF-containing regimen for 4 or 6 weeks**
**No HBV or HIV co-infection**




## Objective

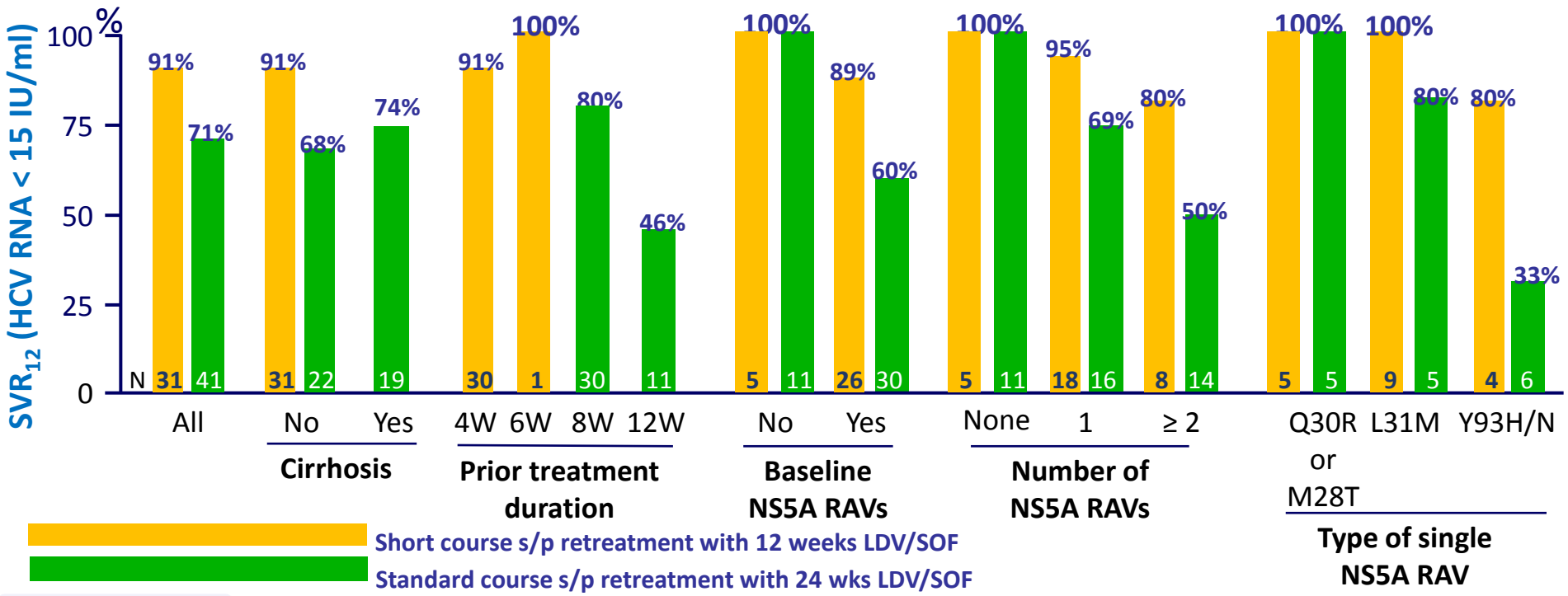
- Primary endpoint : $SVR_{12}$ (HCV RNA < 12 IU/ml) by intention to treat, with 2-sided 95% CI, no statistical hypothesis

*Wilson E. EASL 2015, Abs. LP09*
*Wilson E. CID 2016;62(3):280-8*

Slides adapated from HCV-Trials.com

*LDV/SOF Failure*

# LDV/SOF Failure and SYNERGY D Retreatment Studies

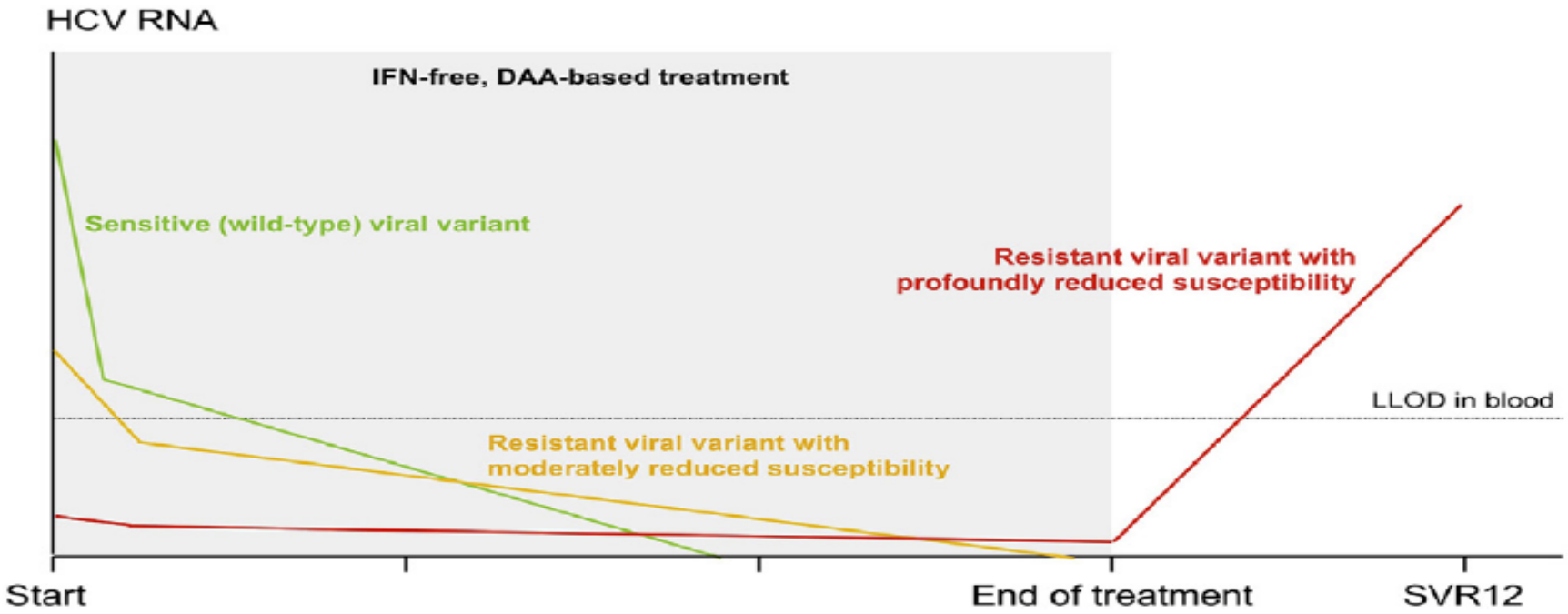



*LDV/SOF Failure*

*Lawitz E. EASL 2015, Abs. O005* *Wilson E. EASL 2015, Abs. LP09* *Wilson E. CID 2016:62(3):280-8*

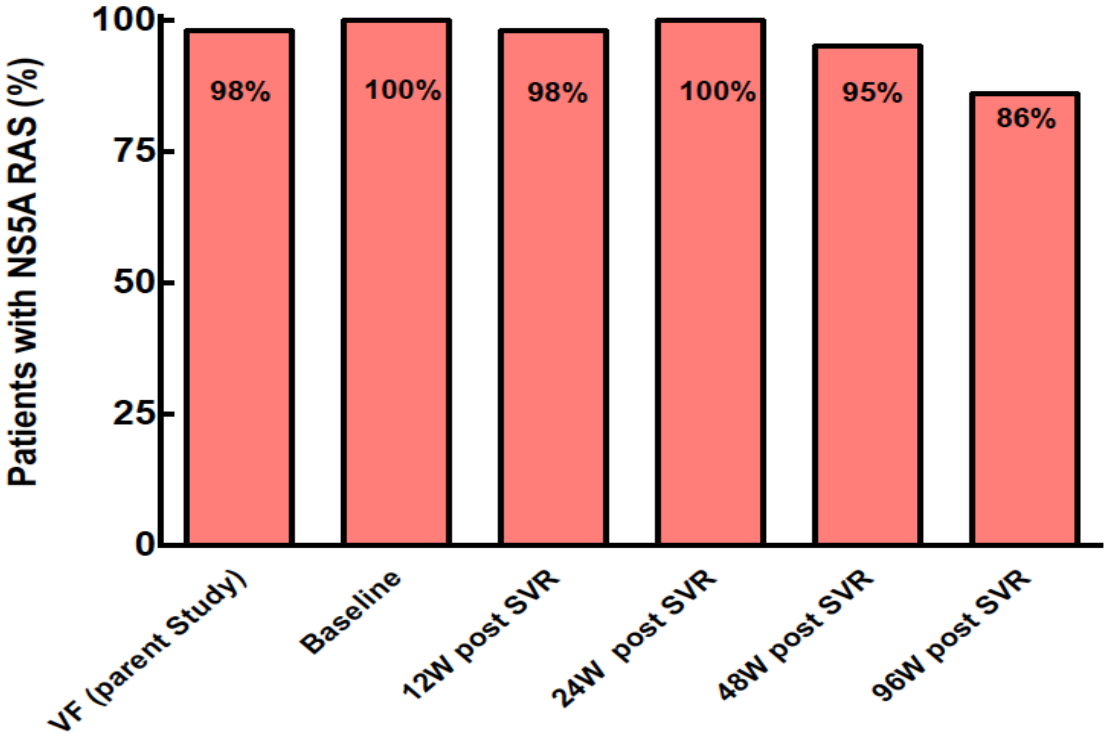
Slides adapted from HCV-Trials.com

# RAVS & Susceptibility of DAAs




Pawlotsky JM *Gastroenterology* 2016; 1-17

# Persistence of NS5A Mutants




Wyles D et al. EASL 2015

| NS5A Inhibitor | Amino Acid Position and Substitutions | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Genotype 1a | | | | | | | | | | | Genotype 1b | | |
| | M28 | | Q30 | | | L31 | | H58 | Y93 | | | L31 | | Y93 |
| | T | V | E | H | R | M | V | D | C | H | N | M | V | H |
| **Daclatasvir** (DCV) (77, 78) | 205 | – | 7,500 | 435 | 365 | 105 | 1,000 | – | 555 | 1,600 | 14,100 | 3 | 15 | 12 |
| **Elbasvir** (EBR) (79) | 15 | 1 | 56 | – | 16 | 10 | 61 | 6 | – | 220 | 929 | – | – | – |
| **Ledipasvir** (LDV) (77, 78) | 61 | – | 952-5,458 | 183 | 632 | 554 | – | 1,127 | 1,602 | 1,677-3,309 | 14,706 | – | – | 1,319 |
| **Ombitasvir** (OMV) (77, 80) | 8,965 | 58 | – | 3 | 800 | 2 | – | 243 | 1,675 | 41,383 | 66,740 | 1 | 8 | 77 |
| **Velpatasvir** (VEL) (87) | 8 | – | 18 | 2 | 2 | 16 | 68 | 7 | 4 | 609 | 2,758 | 2 | 3 | 3 |

No data <5 fold 5–100 fold >100 fold

Wilson, *Clin Micro Rev* 2017;30:23-42

# HCV Retreatment Studies GT-1

**Completed**

- LEPTON
- Rereatment
- GS-US-367-1168
- POLARIS-1
- POLARIS-4
- C-CREST 1 and 2 part C
- C-SURGE
- QUARTZ-1
- MAGELLAN-1, pt 1
- REVENGE

# HCV Retreatment Studies - Gilead

| | Prior Treatment | Retreatment regimen | Duration | N | $SVR_{12}$ | Outcome predictors |
|---|---|---|---|---|---|---|
| **LEPTON**<br>Gane *Gastroenterol* 2016 | Combination DAA | SOF/VEL/VOX | 6 weeks | 30 | 67% | **83% NS5A**<br>87% NS3 |
| **Retreatment**<br>Gane EASL 2016 | SOF/VEL or LEPTON | SOF/VEL + RBV | 24 weeks | 34 | 97% | 96% - RAVs<br>100% + RAVs |
| **GS-US-367-1168**<br>Lawitz *Gastroenterol* 2016 | NS5A or ≥2 classes DAAs | SOF/VEL/VOX | 12 weeks | 63 | 100% | No relapsers |
| Lawitz *Hepatology* 2016 | ≥ 1 DAA | SOF/VEL/VOX<br>± RBV | 12 weeks | 49 | 100%/96 % | 100% - RAVs<br>97% + RAVs |
| **POLARIS 1**<br>Bourliere AASLD 2016 | NS5A | SOF/VEL/VOX | 12 weeks | 150 | 97% | 98% - RAVs<br>96% + RAVs |
| **POLARIS 4**<br>Zeuzem AASLD 2016 | Non-NS5A | SOF/VEL<br>± VOX | 12 weeks | 144 | 97%/91 % | 94% - RAVs<br>100% + RAVs |
| Suda et al<br>*J Gastroenterol* 2017 | DCV/ASV | LDV/SOF + RBV | 12 weeks | 15 | 86.7% | |
| Akuta et al<br>*J Med Virol* 2017 | DCV/ASV | LDV/SOF | 12 weeks | 17 | 71% | |

# HCV Retreatment Studies - Merck

| | Prior Treatment | Retreatment regimen | Duration | N | $SVR_{12}$ | Outcome predictors |
|---|---|---|---|---|---|---|
| **C-CREST-1/2, pt C**<br>Serfaty AASLD 2016 | Uprifosbuvir + EBR or RZR | Uprifosbuvir/GZR/RZR + RBV | 16 weeks | 2 | 100% | No relapsers |
| | **Prior Treatment** | **Retreatment regimen** | **Duration** | **N** | **$SVR_8$** | **Outcome predictors** |
| **C-SURGE**<br>Wyles AASLD 2016 | LDV/SOF or EBR/GZR | Uprifosbuvir/GZR/RZR ± RBV | 16 weeks 24 weeks | 45<br>49 | 98%<br>100% | No relapsers* |
| | **Prior Treatment** | **Retreatment regimen** | **Duration** | **N** | **$SVR_8$** | **Outcome predictors** |
| **REVENGE**<br>De Ledinghen AASLD 2016 | SOF+(SMV,DCV,LDV) ± RBV | SOF+EBR/GZR + RBV | 16 weeks<br>24 weeks | 12<br>13 | 100%<br>100% | No relapsers |

# HCV Retreatment Studies - AbbVie

| | Prior Treatment | Retreatment regimen | Duration | N | $SVR_{12}$ | Outcome predictors |
|---|---|---|---|---|---|---|
| **QUARTZ-1**<br>Poordad AASLD 2016 | Combination DAA | PrOD + SOF ± RBV | 12 weeks<br>24 weeks<br>12 weeks | 14<br>6<br>2 | 93%<br>100%<br>100% | |
| **MAGELLAN-I**<br>Poordad *Hepatology* 2017 | Combination DAA | GLE/PIB ± RBV | 12 weeks | 50 | 96% | Gt1a, RAVs |

# HCV Retreatment Studies at ILC 2017

Saturday April 22nd Parallel Session HCV: DAA resistance and retreatment

- PS – 156 – F. Poordad, “MAGELLAN-1 Part 2: glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic hepatitis C virus genotype 1 or 4 and prior direct-acting antiviral treatment failure”
- PS – 157 – S. Chevaliez, “Effect of resistance-associated substitutions on retreatment of direct acting antiviral-exposed patients in the real-world setting (ANRS C022 HEPATHER)”
- PS – 158 – M.C. Cheung, “Re-treatment of patients with decompensated chronic hepatitis C virus cirrhosis using 24 weeks of SOF and an NS5A inhibitor, ± RBV, after failing 12 week course”
- PS – 159 – H. Wedemeyer, “Safety and efficacy of the fixed dose combination regimen of MK-3682/grazoprevir/ruzasvir in cirrhotic or non-cirrhotic patients with chronic HCV GT1 infection who previously failed a direct-acting antiviral regimen (C-SURGE)”

# Posters of interest at ILC 2017

- FRI-254 JL Callejo Panero et al, “Effectiveness of RBV with DAAs in treating non-cirrhotic patients with Gt1a or 4 HCV infection in real-world practice.”

- SAT-255 P Halfon et al, “Retreatment with Direct Active Antivirals of genotype 1, 3 and 4 chronic hepatitis C patients who previously failed an anti-NS5A- containing regimen in real world”

- SAT-287 U.V. Comandini et al, “Virological and clinical significance of detectable HCV-RNA below limit of quantification at End-of-Treatment in patients treated with direct antiviral agents”

- SAT-280 S.K. Roberts et al, “SOF/VEL/VOX results in high SVR12 rates when administered for 12 weeks in DAA-experienced patients or for 8 Weeks in DAA-naïve patients: an integrated analysis of the POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4 studies”

- SAT-288 V. Cento et al, “The challenge of HCV-retreatment after DAA-failure: real-life experience advocates for caution”

# HCV Retreatment Studies

Ongoing

- RESOLVE (NCT02745535) – combination DAA-experienced patients, 12 weeks SOF/VEL/VOX

Upcoming

- C-RESCUE (NCT03105349) – NS5A-experienced patients, 16 weeks EBR/GZR + SOF + RBV
- University of Florida HCV TARGET retreatment study in collaboration with AbbVie (NCT03092375) – SOF/NS5A-experienced (without PI) patients, GLE/PIB for 12 or 16 weeks ± RBV

# SHARED - Surveillance of Hepatitis C Antiviral Resistance, Epidemiology and Methodologies Study

- International epidemiological study
  - 12 sites in 10 countries
- Number of patients (projected): 1000+
- Characteristics
  - Viral genotype/subtype
  - Disease stage
  - Geographic region
  - Resistance data
    - Baseline: Yes, in a subset
    - At failure: Yes, in a subset
  - Treatment regimens
    - First treatment (regimen)
    - Second (re-)treatment regimen
    - Re-treatment outcome

Project Coordinator: **Anita Howe, PHD**
British Columbia Center for Excellence for HIV/AIDS

# Going Forward: HCV Retreatment

Guidelines have addressed retreatment strategies based on factors including

- resistance
- treatment duration
- the addition of ribavirin

Moving forward, it’s clear that other factors can also influence response to therapy, including

- immune-mediated factors
- poor adherence
- reinfection