# Treatment of Chronic Hepatitis C

LUIS S. MARSANO, MD, FACG, FAASLD, AGAF, FASGE
Professor of Medicine
Jewish Hospital Distinguished Chair in Hepatology
Division of Gastroenterology, Hepatology and Nutrition
University of Louisville and Louisville VAMC
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# Disclaimer

- No conflict of interest to report.
- Several of the treatment protocols described are not within FDA label but they are inside the “Practice Guidelines Recommendations” from the AASLD and IDSA.

# Summary Treatment Tables

# Agents and Regimens Currently Used

| Combinations | Type of Antiviral | | | | |
|---|---|---|---|---|---|
| | NS3 | NS5A | Non-Nuc NS5B | Nuc NS5B | RBV |
| | "previr" | "asvir" | "buvir" | "buvir" | |
| Simeprevir + sofosbuvir | ⊙ | | | ⊙ | |
| Ledipasvir/sofosbuvir FDC (HARVONI) | | ⊙ | | ⊙ | |
| Paritaprevir/r/Ombitasvir FDC (TECHNIVIE or PrO) + Dasabuvir (VIEKIRA Pak and XR or PrOD or 3D) | ⊙ | ⊙ | ⊙ | | ⊙ RBV only for 1a or F3-4 |
| Sofosbuvir + ribavirin | | | | ⊙ | ⊙ |
| Daclatasvir + sofosbuvir | | ⊙ | | ⊙ | |
| Grazoprevir + Elbasvir (ZEPATIER) | ⊙ | ⊙ | | | |
| Velpatasvir + Sofosbuvir (EPCLUSA) | | ⊙ | | ⊙ | |
| Sofosbuvir + Velpatasvir + Voxilaprevir (Vosevi®) | ⊙ | ⊙ | | ⊙ | |
| Glecaprevir + Pibrentasvir (Mavyret) | ⊙ | ⊙ | | | |

# Treatment of Hepatitis C ; Treatment Naïve or Relapse to PEG/RBV

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 1a or 1 unspecified | F0-2 Naïve with HCV-RNA < 6 Million& No African American: **SOF/LED 400/90** | **8** | 97% |
| | F0-2 with HCV-RNA > 6 Million or relapse: **SOF/LED 400/90** | **12** | 96% |
| | F0-2: **GZR 100 + EBR 50** (without M28, Q30, L31, or Y93 polymorphism) | **12** | 98% |
| | F0-2: **GLE 300 + PIB 120** | **8** | 99% |
| | F0-2: **SOF 400 + VEL 100** | **12** | 98% |
| | F0-2: **DAC 60 + SOF 400 (alt)** | **12** | 100% |
| | F0-2: **PrOD + RBV 1-1.2 (alt)** | **12** | 96% |
| | F0-2: **SOF 400 + SMV* 150 ± RBV 1-1.2 g** (No in Q80K mutation) **(alt)** | **12** | 93-96% |
| | F3-4: **SOF/LED 400/90** | **12** | 94% |
| | F3-4 comp: **GZR 100 + EBR 50** (without M28, Q30, L31, or Y93 polymorphism) | **12** | 98% |
| | F3-4c: **GLE 300 + PIB 120** | **12** | 99% |
| | F3-4: **SOF 400 + VEL 100** | **12** | 98% |
| | F3-4: **DAC 60 + SOF 400 (not recommended anymore)** | **24** (+/- RBV 1-1.2) | 100% |
| | F3-4 comp: **SOF 400 + SMV* 150 ± RBV 1-1.2 g** (No in Q80K mutation) **(not recommended)** | **24** | 93-96% |
| | F0-4 comp: **GZP 100 + EBV 50 + RBV 800-1400** (with M28, Y93, Q30, or L31 polymorphism) **(alt)** | **16** | 100% |
| | F3-4 comp: **PrOD + RBV 1-1.2 (not recommended anymore)** | **24** | 95% |

F4 comp = compensated cirrhosis = Child-Pugh A (5 or 6 points)

# Treatment of Hepatitis C ; Treatment Naïve or Relapse to PEG/RBV

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| *1b* | F0-2 Naïve with HCV-RNA < 6 Million & No African American: **SOF/LED 400/90** | **8** | 97% |
| | F0-2 with HCV-RNA > 6 Million, or F3-4: **SOF/LED 400/90** | **12** | 96% |
| | F0-2: **GZR 100 + EBR 50** | **12** | 99% |
| | F0-2: **GLE 300 + PIB 120** | **8** | 99% |
| | F0-2: **SOF 400 + VEL 100** | **12** | 99% |
| | F0-2: **PrOD** (without RBV) **(alt)** | **12** | 100 |
| | F0-2: **SOF 400 + SMV 150 ± RBV 1-1.2 g (alt)** | **12** | 93-96% |
| | F0-2: **DAC 60 + SOF 400 (alt)** | **12** | 100% |
| | F3-4 comp: **GZR 100 + EBR 50** | **12** | 99% |
| | F3-4c: **GLE 300 + PIB 120** | **12** | 99% |
| | F3-4 comp: **SOF/LED 400/90** | **12** | 94% |
| | F3-4: **SOF 400 + VEL 100** | **12** | 99% |
| | F3-4 comp: **PrOD +/- RBV 1-1.2 (alt)** | **12** | 99% |
| | F3-4 comp: **SOF 400 + SMV 150 ± RBV 1-1.2 g (not recommended anymore)** | **24** | 93-96% |
| | F3-4: **DAC 60 + SOF 400 (+/- RBV 1-1.2g) (not recommended anymore)** | **24** | 100% |

F4 comp = compensated cirrhosis = Child-Pugh A (5 or 6 points)

# Treatment of Hepatitis C ; Treatment Naïve or Relapse to PEG/RBV

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 2 | F0-4: **SOF 400 + VEL 100** | **12** | 100% |
| | F0-4c: **GLE 300 + PIB 120** | **F0-2: 8w;**<br>**F3-4c: 12w** | 100% |
| | **DAC 60 + SOF 400 (alt)** | F0-2: **12**<br>F3-4 comp: **16-24** | 100% |
| 3 | **SOF 400 + VEL 100** | **12** | 95%<br>(F0-2: 98%)(F3-4c:93%) |
| | F0-4c: **GLE 300 + PIB 120** | **F0-2: 8w;**<br>**F3-4c: 12w** | F0-2: 95%<br>F3-4c: 96% |
| | F0-2: **DCV 60 + SOF 400 (alt)** | **12** | F0-2: 97%;<br>(F3-4: 58%) |
| | F3-4: **DAC 60 + SOF 400 +/- RBV (alt)**<br>(RBV helped in CP-B&C) | F4 C-P B&C (+/- RBV 1-1.2): **24**<br>F3 & F4 CP-A (+/- RBV): **24** | 88% (78% w/o RBV)<br>92% (88% w/o RBV) |
| | F3-4c: **SOF 400 + Vel 100 + Vox 100** for **Y93H RAS** | **12** | 96-100% |

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

# Treatment of Hepatitis C ; Treatment Naïve or Relapse to PEG/RBV

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 4 | F0-4: **SOF/LED 400/90** | **12** | 95-100% |
| | F0-4c: **GZR 100 + EBV 60 +/- RBV** | **12** | 90-100% |
| | F0-4: **SOF 400 + VEL 100** | **12** | 100% |
| | F0-4c: **GLE 300 + PIB 120** | **F0-2: 8w;<br>F3-4c: 12w** | 100% |
| | F0-4c: **PrO + RBV 1-1.2 g (alt)** | **12** | 100% |
| 5 | F0-4**: SOF/LED 400/90** | **12** | 95% |
| | F0-4: **SOF 400 + VEL 100** | **12** | 97% |
| | F0-4c: **GLE 300 + PIB 120** | **F0-2: 8w;<br>F3-4c: 12w** | 100% |
| 6 | F0-4: **SOF/LED 400/90** | **12** | 96% |
| | F0-4: **SOF 400 + VEL 100** | **12** | 100% |
| | F0-4c: **GLE 300 + PIB 120** | **F0-2: 8w;<br>F3-4c: 12w** | 100% |

# Treatment of Hepatitis C; PEG-IFN/RBV Non-Responders

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 1a or 1 unspecified | F0-2: **SOF/LED 400/90** | **12** | 95% |
| | F0-2: **SOF 400 + VEL 100** | **12** | 98% |
| | F0-2: **GZR 100 + EBR 50** *(*no M28, Y93, Q30, or L31 polymorphism) | **12** | 100% |
| | F0-2: **GLE 300 + PIB 120** | **8** | 99% |
| | F0-2: **PrOD + RBV 1-1.2 g** **(alt)** | **12** | 96% |
| | F0-2: **SOF 400 + SMV* 150 ± RBV 1-1.2g (No in Q80K mutation)** **(alt)** | **12** | 93-96% |
| | F0-2: **DAC 60 + SOF 400** **(alt)** | **12** | > 82% |
| | F3-4 comp: **GZR 100 + EBR 50** *(*no M28, Y93, Q30, or L31 polymorphism) | **12** | 100% |
| | F3-4c: **GLE 300 + PIB 120** | **12w** | 98% |
| | F3-4: **SOF 400 + VEL 100** | **12** | 98% |
| | F3-4: **SOF/LED 400/90 + RBV 1-1.2 g** **(alt)** (pre-test for NS5A resistance; treat 24 weeks if > 100 fold resistance or use other regimen) | **12** | 96% |
| | F3-4: **DAC 60 + SOF 400 +/- RBV 1-1.2g** **(not recommended anymore)** | **24** | 60% no-RBV<br>82% w RBV |
| | F3-4 comp: **SOF 400 + SMV* 150 ± RBV 1-1.2g (No in Q80K mutation)** **(not recommended)** | **24** | 93-96% |
| | F3-4: **SOF/LED 400/90** **(alt)** | **24** | |
| | F3-4 comp: **PrOD + RBV 1-1.2** **(not recommended anymore)** | **24** | 95% |
| | F0-3: **GZR 100 + EBR 50 + RBV .8-1.4 g** (with M28, Y93, Q30, or L31 polymorphism) (alt) | **16** | 97% |

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

# Treatment of Hepatitis C; PEG-IFN/RBV Non-Responders

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 1b | F0-2: **SOF/LED 400/90** | **12** | 95% |
| | F0-2: **SOF 400 + VEL 100** | **12** | 99% |
| | F0-2: **GZR 100 + EBR 50** | **12** | 97% |
| | F0-2: **GLE 300 + PIB 120** | **8** | 99% |
| | F0-2: **PrOD** (no RBV) **(alt)** | **12** | 100% |
| | F0-2: **DAC 60 + SOF 400 (alt)** | **12** | 82% |
| | F0-2: **SOF 400 + SMV* 150 ± RBV 1-1.2 g (alt)** | **12** | 93-96% |
| | F3-4 comp: **GZR 100 + EBR 50** | **12** | 97% |
| | F3-4: **SOF 400 + VEL 100** | **12** | 99% |
| | F3-4c: **GLE 300 + PIB 120** | **12** | 99% |
| | F3-4 comp: **PrOD (alt)** | **12** | 99% |
| | F3-4: **SOF/LED 400/90 + RBV 1-1.2 g (alt)** (test for NS5A resistance) | **12** | 96% |
| | F3-4: **SOF/LED 400/90 (alt)** | **24** | 100% |
| | F3-4: **DAC 60 + SOF 400 +/- RBV 1-1.2 g (not recommended anymore)** | **24** | 82% |
| | F3-4 comp: **SOF 400 + SMV* 150 ± RBV 1-1.2 g (not recommended anymore)** | **24** | 93-96% |

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

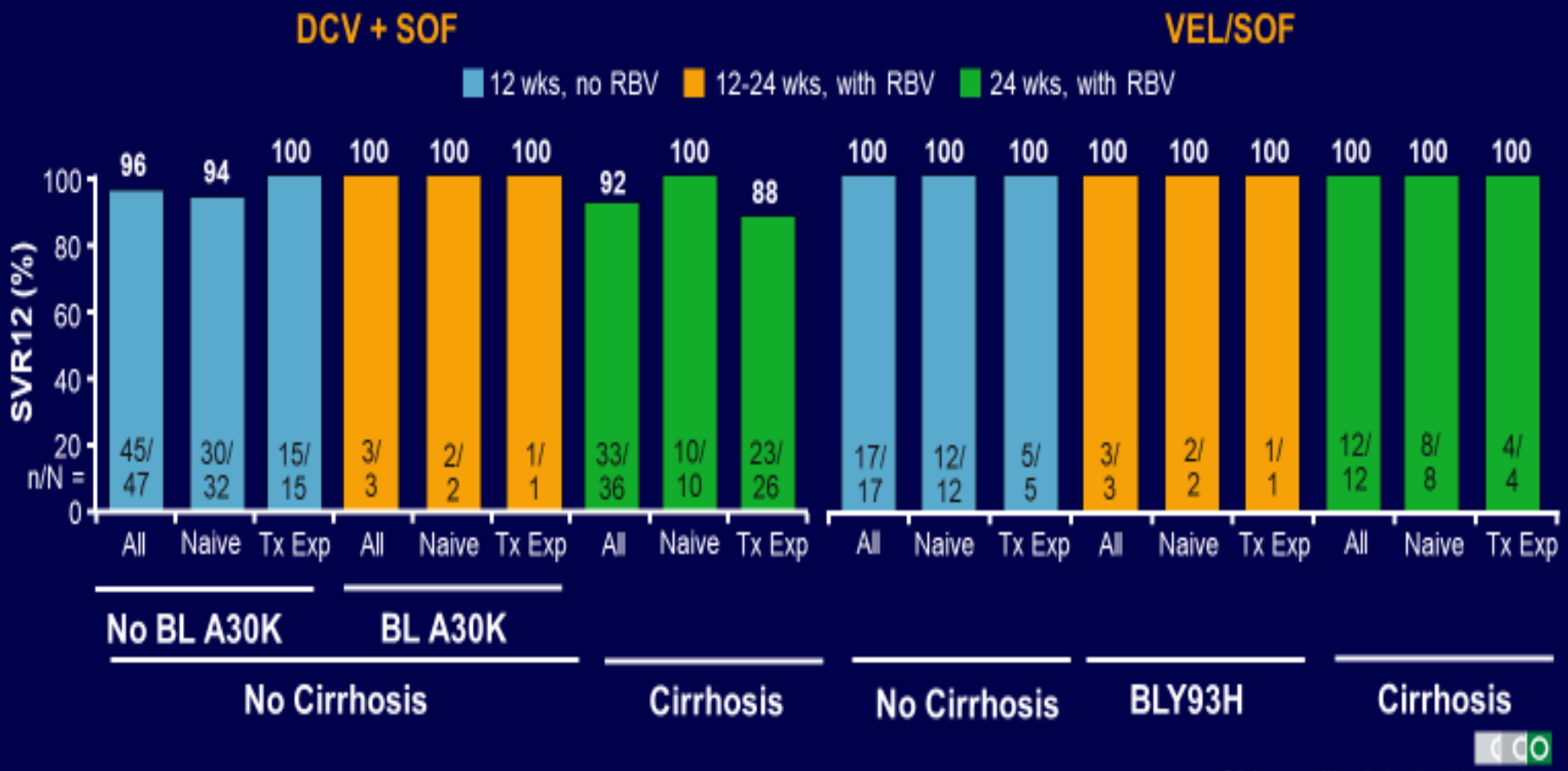
# Treatment of Hepatitis C; PEG-IFN/RBV Non-Responders

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 2 | F0-4: **SOF 400 + VEL 100** | **12** | 100% |
| | F0-4c: **GLE 300 + PIB 120** | **F0-2: 8w;<br>F3-4c: 12w** | 100% |
| | F0-2: **DAC 60 + SOF 400 +/- RBV 1-1.2 g (alt)**<br>F3-4c: **DAC 60 + SOF 400 +/- RBV 1-1.2 g (alt)** | **12<br>16-24** | ? |
| 3 | F0-2: **SOF 400 + VEL 100** | **12** | 94% |
| | F3-4c: **SOF 400 + VEL 100 + VOX 100** | **12** | 94-100% |
| | F3-4 comp: **GZR 100 + EBR 50 + SOF 400** | **12** | 100% |
| | F3-4: **SOF 400 + VEL 100 + RBV 1-1.2 g (alt)** | **12** | 89% |
| | F0-2: **DCV 60 + SOF 400 (alt)** | **12** | 94% |
| | F0-4c: **GLE 300 + PIB 120 (alt)** | **16** | 96% |
| | F0-2: **SOF 400 + VEL 100 + VOX 100** (when Y93H is present) **(alt)** | **12** | 94-100% |
| | F3-4: **DCV 60 + SOF 400 + RBV 1-1.2 g (not recommended)** | **24** | "Close to 100%" |

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

# DCV or VEL in Treatment-Experienced GT3 HCV Infection

- Real-world cohort of patients with GT3 HCV infection treated according to baseline NS5A RASs, previous treatment failure, and cirrhosis status (N = 167)




Vermehren J, et al. EASL 2017. Abstract PS-155. Reproduced with permission.

Slide credit: clinicaloptions.com

# Treatment of Hepatitis C; PEG-IFN/RBV Non-Responders

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 4 | F0-2: **SOF/LED 400/90** | **12** | 95% |
| | F0-2: **SOF 400 + VEL 100** | **12** | 100% |
| | F0-2: **GZR 100 + EBR 50 + RBV** | **16** | 97% |
| | F0-4c: **GLE 300 + PIB 120** | **8** | 100% |
| | F3-4 comp: **GZR 100 + EBR 50 + RBV** | **16** | 97% |
| | F3-4: **SOF 400 + VEL 100** | **12** | 100% |
| | F3-4c: **GLE 300 + PIB 120** | **12** | 100% |
| | F3-4: **SOF/LED 400/90 + RBV 1-1.2 g** (alt) | **12** | 95% |
| | F0-2: **PrO + RBV 1-1.2 g** (alt) | **12** | 100% |
| | F3-4: **SOF/LED 400/90** (alt) | **24** | 95% |
| 5 | F0-4: **SOF/LED 400/900** | **12** | 95% |
| | F0-4c: **GLE 300 + PIB 120** | **F0-2: 8w; F3-4c: 12w** | 100% |
| | F0-4: **SOF 400 + VEL 100** | **12** | 97% |
| 6 | F0-4: **SOF/LED 400/90** | **12** | 96% |
| | F0-4: **SOF 400 + VEL 100** | **12** | 100% |
| | F0-4c: **GLE 300 + PIB 120** | **F0-2: 8w; F3-4c: 12w** | 100% |
| | **GZR 100 + EBR 50 + RBV 1-1.2 g** (no FDA approved) | **16** | 97% |

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

# Treatment of Decompensated Cirrhosis
## (Child-Pugh class B or C)

| Genotype or w/o RBV | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 1 o 4 | **SOF/LED 400/90 + RBV 600-1200** increasing as tolerated | **12**<br>**24 if past SOF or NS5A, or w/o RBV** | 86% |
| | **SOF 400 + VEL 100 + RBV 1000-1200 mg** | **12**<br>**24 if past SOF or NS5A, or w/o RBV** | 94% in g1a; 100% g1b<br>100% in g4 |
| | **SOF 400/DCV 60 + RBV 600-1000 mg** | **12-24** with RBV<br><br>**24 if past SOF or NS5A, or w/o RBV** | 12: g1:83%; g4: 100% ;<br>24: close to 100% in g1<br>Unknown (without RBV) |
| 2 | **SOF 400 + VEL 100 + RBV 1000-1200 mg** | **12**<br>**24 if past SOF or NS5A, or w/o RBV** | 100% |
| | **SOF 400/DCV 60 + RBV 600-1000** | **12** (if Naive)<br>**24 if past SOF or NS5A, or w/o RBV** | 80% |
| | **SOF/LED 400/90 +/- RBV 600-1200**<br>**(no FDA approved)** | **12** | ? |
| 3 | **SOF 400/DCV 60 + RBV 600-1000** | **24** | 88% |
| | **SOF 400 + VEL 100 + RBV 1-1.2g** | **12 (24 if past SOF or NS5A or w/o RBV)** | 85% |
| 5 or 6 | **SOF 400 + VEL 100 + RBV 1000-1200 mg** | **12** | N/A |
| | **SOF 400 + LED 90 + RBV 600-1200 mg** | **12 (24 if past SOF or NS5A or w/o RBV)** | N/A |
| | **SOF 400 + VEL 100 + RBV 600-1200 mg** | **12 (24 if past SOF or NS4A or w/o RBV)** | N/A |

Ideally treated at the Transplant Center

# Treatment in Resistance to Direct Antiviral Agents

| No Response to Telaprevir or Boceprevir or Simeprivir | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| | F0-2: **SOF/LED 400/90** | **12** | 96% |
| | F0-4c: **GLE 300 + PIB 120** (Geno 1,2,4,5,6)<br>(Geno-3 is longer) | **Geno 1,2,4,5,6: 12w**<br>**Geno-3 (F0-4c): 16 w** | 100% |
| | F0-4: **SOF/VEL 400/100** | **12** | 100% |
| | F0-4 comp: **GZR 100 + EBR 50 + RBV .8-1.4 g (alt)** | **12 (16 with RAS mutant)** | 96% |
| | F3-4: **SOF/LED 400/90 + RBV 1-1.2 g (alt)** | **12** | 97% |
| | F3-4: **SOF/LED 400/90 (no longer recommended)** | **24** | 97% |
| | F3-4: **DAC 60 + SOF 400 +/- RBV 1-1.2 g (no longer recommended)** | **24** | 100% |
| **No Response to Sofosbuvir** | **Regimen** | **Duration (weeks)** | **SVR** |
| **Never Exposed to NS5A**<br>**Geno 1, 4, 5, 6**<br>**NS5A is (-) to RASs** | F0-4: **SOF 400 + VEL 100 + VOX 100** for **Geno 1a** | **12** | 97% |
| | F0-4: **SOF 400 + VEL 100** for **Geno 1b** | **12** | 96% |
| | F0-4: **GLE 300 + PIB 120** | **12** | |
| | F0-2: **SOF/LED 400/90 + RBV 1-1.2 g (alt)** | **12** | 100% |
| Genotype 2 or 3 failure to SOF/RBV+/- Peg-IFN<br>If in Urgent Need | F0-4: **Geno 2: SOF 400 + VEL 100** | **12** | 97% |
| | F0-4c: **Geno 2: GLE 300 + PIB 120** | **12**<br>**G3: F0-4c: 16 w (not recommended)** | 98%<br>96% |
| | **Geno 3 F0-4: SOF + VEL + VOX (add RBV 1-1.2 g if past NS4A failure)** | **12** | 96% |
| **Geno 1-6 NS5A Resistant** | **F0-4: SOF + VEL + VOX** | **12** | 96-100%<br>(g4:91%; g3:95%) |
| **Failures with SOF/VEL x 12w** | **SOF 400 + VEL 100 + RBV 1-1.2 g (not recommended)** | **24** | G-1: 98%<br>G-2: 100%<br>G-3: No RASs 100%;<br>G-3 with RASs: 77% |

RASs = Virus with “Resistance Associated Substitutions”

# Dose Adjustment for Renal Impairment

| Renal Impairment | eGFR / CrCl level (mL/min) | PEG-IFN | RBV | Sofosbuvir | Ledipasvir | Daclatasvir | Ombitasvir | Dasabuvir | Paritaprevir | Simeprevir |
|---|---|---|---|---|---|---|---|---|---|---|
| Mild | 50-80 | **PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1.5 µg/kg** | **Standard** | **Standard** | **Standard** | **Standard** | **Standard** | **Standard** | **Standard** | **Standard** |
| Moderate | 30-50 | **PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1 µg/kg (25% reduction)** | **Alternating doses 200 mg and 400 mg every other day** | **Standard** | **Standard** | **Standard** | **Standard** | **Standard** | **Standard** | **Standard** |
| Severe | <30 | **PEG-IFN (2a) 135 µg; PEG-IFN (2b) 1 µg/kg (50% reduction)** | **200 mg/d** | Limited data available | Data not available | Limited data available | Limited data available | Limited data available | Limited data available | **Standard** |
| ESRD with HD | | **PEG-IFN (2a) 135 µg/wk or PEG-IFN (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk** | **200 mg/d** | Limited data available | Data not available | Limited data available | Limited data available | Limited data available | Limited data available | Limited data available |

# Treatment of HCV in CKD 4/5 +/- Hemodialysis (GFR < 30 mL/min)

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| Geno 1-6<br>(F0-4c) | **GLE 300 + PIB 120** | **F0-2: 8**<br>**F3-4c: 12**<br>**Geno-3 with PR or SOF Failure: 16**<br>**PrOD or Zepatier Failure: 16** | 98-100% |
| 1 & 4<br>(F0-4comp)<br>(probably also 2, 5, 6) | **GZR 100 + EBR 50**<br>In genotype 1a with M28, Y93, Q30, or L31 polymorphism: GZR 100 + EBR 50 + RBV 100-200 mg | **12**<br>(16 week extension not needed) | 99% in geno-1 |
| 1a & 1 b<br>(F0-3) | **PrOD** (+ RBV 200 TIW in 1a)<br>(no longer recommended) | **12** | 90% |
| 2, 3, 5, 6<br>(F0-4comp) | **PegIFN + RBV 200** a day<br>(no longer recommended) | **24-48 weeks** | |

Patients with GFR > 30 mL/min can be treated with standard doses of other regimens

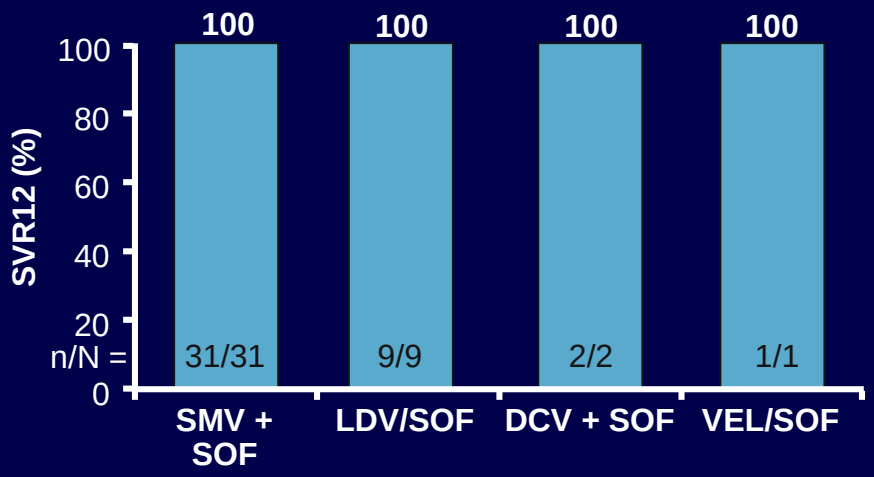
# Suggested RBV dose by Creatinine Clearance

Kamar N et al. Am J Kidney Dis. 2004;43:140-146 &
Bruchfeld A et al. Drug Monit. 2002;24:701-708

| Creatinine Clearance (Cockcroft-Gault) | >/= 100 mL/min | 80 mL/min | 60 mL/min | 40 mL/min | 20 mL/min | < 20 mL/min |
|---|---|---|---|---|---|---|
| RBV (mg/day) | 1200 | 1000 | 800 | 600 | 400 | 200 |

# SOF-Based, RBV-Free DAAs in Pts With HCV Infection and ESRD

- N = 43 pts mostly on dialysis (93%), treatment naive (79%), genotype 1a (65%), noncirrhotic (51%)
  - Mean baseline hemoglobin: 11.1 g/dL (range: 8.9-13.8 g/dL)
- Most pts treated for 12 wks (n = 36)




**Safety**

- No hepatic decompensation
- No dose adjustment of any regimen

Nazario H, et al. EASL 2017. Abstract FRI-220. Reproduced with permission.

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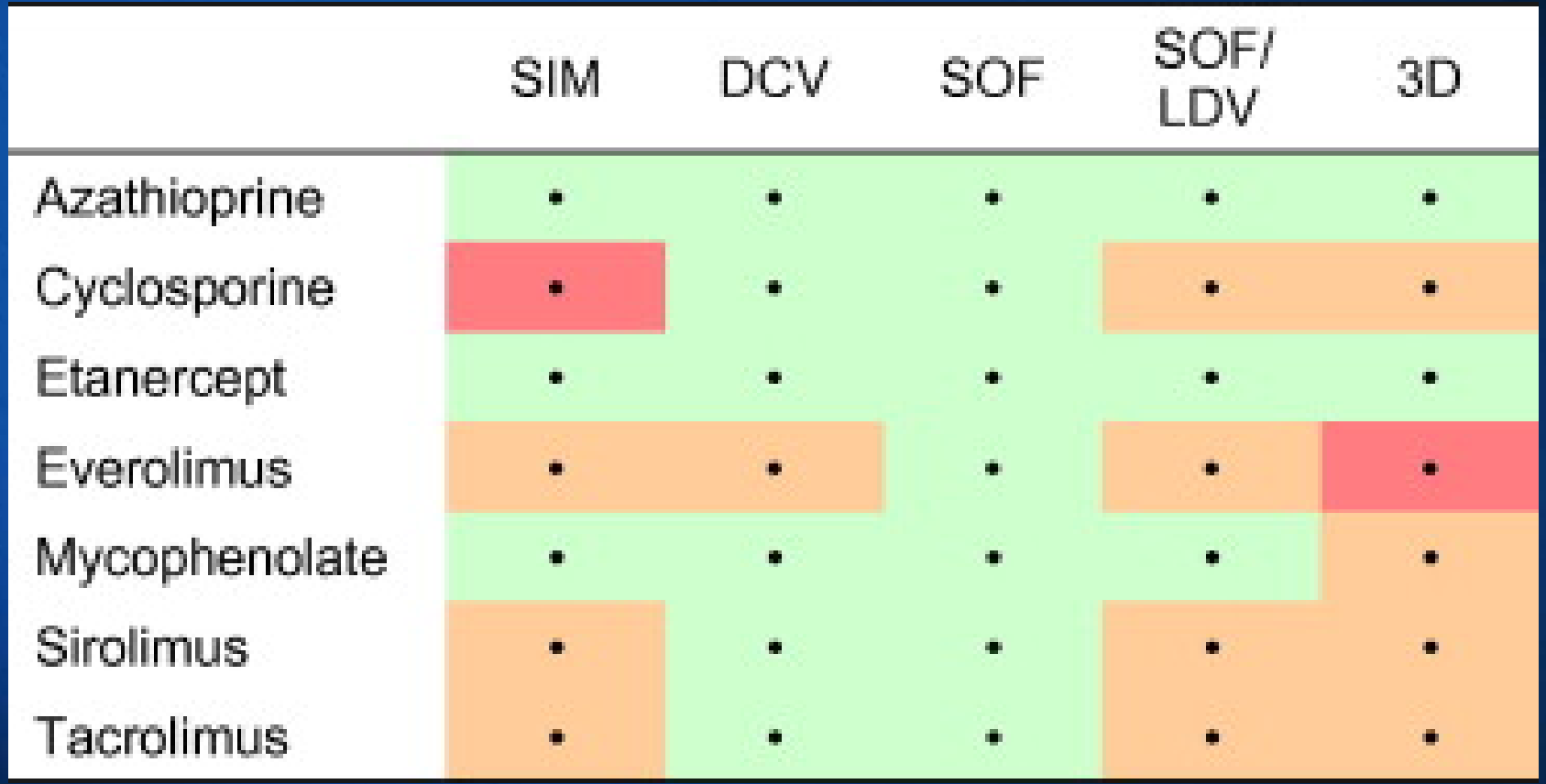
# DAAs and Immunosuppressants



| | SIM | DCV | SOF | SOF/ LDV | 3D |
|---|---|---|---|---|---|
| Azathioprine | • | • | • | • | • |
| Cyclosporine | • | • | • | • | • |
| Etanercept | • | • | • | • | • |
| Everolimus | • | • | • | • | • |
| Mycophenolate | • | • | • | • | • |
| Sirolimus | • | • | • | • | • |
| Tacrolimus | • | • | • | • | • |

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

# Dose Modifications with Cyclosporine and Tacrolimus

| | Cyclosporine | Tacrolimus |
|---|---|---|
| **Sofosbuvir** | 4.5-fold ↑ in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed | No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed |
| **Ledipasvir** | No data; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed | No data; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed |
| **Daclatasvir** | No interaction observed; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed | No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed |
| **Simeprevir** | 5.81-fold ↑ in SIM AUC; **combination is not recommended** | 85% ↑ in SIM AUC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed |
| **PrOD** | 5.8-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed | 57-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed |
| **PrO** | 4.3-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrO treatment, monitor CSA levels and titrate CSA dose as needed | 86-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrO treatment, monitor TAC levels and titrate TAC dose as needed |
| **Elbasvir/Grazoprevir** | 15-fold ↑ in GZR AUC and 2-fold ↑ in EBR AUC; **combination is not recommended** | 43% ↑ in TAC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed |
| **Gle/Pib** | 5-fold ↑ in GLE AUC with higher doses (400 mg) of CSA; **not recommended in patients requiring stable CSA doses >100 mg/day** | 1.45-fold ↑ in TAC AUC; no a priori dose adjustment, monitor TAC levels and titrate TAC dose as needed |
| **SOF/VEL/VOX** | 9.4-fold ↑ in VOX AUC; **combination is not recommended** | No data; no a priori dose adjustment |

# Treatment After Transplant

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 1 | F0-4: **SOF/LED 400/90 + RBV 1-1.2 g** (RBV: in decompensated, increase dose weekly if tolerated; start with 600 mg/day) | **12** | 96% |
| | F0-4c: **GLE/PIB** | **12** | 98% |
| | F0-4: **SOF/LED 400/90** | **24** | ? |
| | F0-4: **SOF 400 + DCV 60 +/- RBV 600-1000** | **12** (with RBV)<br>**24** (without RBV) | 1a: 97%<br>1b: 90% |
| | Only in F0-2: **PrOD + RBV 1-1.2 (alt)** (RBV: in decompensated, increase dose weekly if tolerated; start with 600 mg/day) [CSA :1/5 of usual dose when starting Viekira and follow daily levels; TAC do not give on 1st day of Viekira; monitor levels and then give 0.5 mg/week as determined by levels] | **24** | 1a: 97%<br>1b: 100% |
| | F0-4 comp: **SOF 400 + SIM 150 +/- RBV 1-1.2 g (alt)** (not in genotype 1a with Q80K mutation) | **12** | 92% |
| 4 | **SOF/LED 400/90 + RBV 1-1.2 g** (RBV: in decompensated, increase dose weekly if tolerated; start with 600 mg/day) | **12** | 96% |
| | F0-4c: **GLE/PIB** | **12** | 98% |
| | **SOF/LED 400/90** | **24** | ? |
| | **SOF 400 + DCV 60 + RBV 600-1000** | **12** (with RBV)<br>**24** (without RBV) | 91% |

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

# Treatment After Transplant

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| **2** | F0-4c: **GLE 300 + PIB 120** | **12** | 98% |
| | **Sofosbuvir (400 mg) and RBV 1-1.2 g** (RBV: if decompensated, start with 600 mg/day, and increase weekly as tolerated up to 1000 mg/day [<75 kg] or 1200 mg/ day [≥75 kg] 1200 mg depending on Clcr and hemoglobin). | **24** | ? |
| | **DAC 60 + SOF 400 +/- RBV 600-1200** (F0-4 comp) | **12** (with RBV)<br>**24** (without RBV) | ? |
| | **SOF/LED 400/90** if intolerant to RBV (no FDA approved) | **12** | ? |
| **3** | F0-4c: **GLE 300 + PIB 120** | **12** | 98% |
| | **SOF 400 + DCV 60 + RBV 600-1200 mg** | **12**<br>**24** without RBV<br>**24** with RBV for fibrosing cholestatic hepatitis | 91% |
| | **SOF/LED + RBV or VEL/SOF + RBV** (?) no enough data (no FDA approved) | | ? |
| **4,5, and 6** | F0-4c: **GLE 300 + PIB 120** | **12** | 98% |

# Treatment of HIV/HCV Co-infected Patients

- ***Patients with HCV-HIV co-infection should be treated with the same regimen as HCV mono-infected patients.***
- **LED/SOF (HARVONI):**
  - African-American patients respond less to Harvoni.
  - The theoretical risk of Renal damage from Tenofovir in patients receiving Atripla has not been seen in the clinical trials.
  - Treatments of only 8 weeks with Harvoni or with DAC + SOF are probably insufficient for co-infection; treat for 12 weeks.
  - Harvoni should not be given with Tenofovir if the GFR is < 60 mL/min, and should not be co-administer with Protease Inhibitors boosted with Ritonavir.
  - Tenofovir disoproxil fumarate levels are highest if administered with ritonavir- or cobicistat-containing regimens. Change to Tenofovir alafenamide.
- **PrOD (Viekira Pak):** should not be given to co-infected patients who are not receiving anti-HIV therapy.
- **DAC + SOF:** Patients receiving darunavir/r could have inferior response.
- **RIBAVIRIN:** Do not give to patients taking didanosine, stavudine, or zidovudine.
- ***DO NOT INTERRUPT ANTI-HIV THERAPY.***

| | Medication Interactions With HIV Antiretroviral Medications |
|---|---|
| DACLATASVIR | Daclatasvir requires dose adjustment with ritonavir-boosted atazanavir (decrease to 30 mg/d), cobicistat-boosted atazanavir (decrease to 30 mg/d), elvitegravir/cobicistat (decrease to 30 mg/d), and efavirenz or etravirine (increase to 90 mg/d). |
| SIMEPREVIR | Does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, dolutegravir, rilpivirine, and tenofovir. |
| ELBASVIR/ GRAZOPREVIR | Does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir. |
| GLECAPREVIR/ PIBRENTASVIR | Does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir. |
| LEDIPASVIR/ SOFOSBUVIR | Can be used with most antiretrovirals. Because this therapy increases tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min.<br>With Ledipasvir, Tenofovir disoproxil fumarate levels are highest if administered with ritonavir- or cobicistat-containing regimens. Change to Tenofovir alafenamide. |
| SOFOSBUVIR/ VELPATASVIR | Can be used with most antiretrovirals, but **not efavirenz, etravirine, or nevirapine**. Velpatasvir has the potential to increase tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min.<br>With Velpatasvir, Tenofovir disoproxil fumarate levels are highest if administered with ritonavir- or cobicistat-containing regimens. Change to Tenofovir alafenamide. |
| PrOD | Do not have substantial interactions: atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir.<br>The dose of ritonavir used for boosting atazanavir should be held when administered with paritaprevir/ritonavir/ombitasvir plus dasabuvir and then restored when HCV treatment is completed. Atazanavir (300 mg) should be administered at the same time as the fixed-dose HCV combination. |
| SOFOSBUVIR/ VELPATASVIR/ VOXILAPREVIR | Do not have substantial interactions: dolutegravir, emtricitabine, enfuvirtide, lamivudine, rilpivirine, and raltegravir.<br>With Velpatasvir, Tenofovir disoproxil fumarate levels are highest if administered with ritonavir- or cobicistat-containing regimens. Change to Tenofovir alafenamide. |

# HIV-HCV Genotype 1 Cheat Sheet

(Dr. Matt Cave)

| | HIV Backbone | HIV Brand Name | HIV Generic Names | Compatible HCV regimen |
|---|---|---|---|---|
| **Recommended HIV Regimens DHHS - 2015** | Integrase | **Triumeq** | dtg/abc/3tc | Harvoni, dcv/sof, sim/sof, GRZ + EBR, Viekira Pak probably OK (AASLD/IDSA) |
| | | **Tivicay/Truvada** | dtg/tdf/ftc | Harvoni, dcv/sof, sim/sof., GRZ + EBR, Viekira Pak probably OK (AASLD/IDSA) |
| | | **Stribild** | evg/cobi/tdf/ftc | NO DATA; ? dcv (30 mg) / sof |
| | | **Isentress/Truvada** | ral/tdf/ftc | Harvoni, Viekira Pak, dcv/sof, sim/sof, GRZ + EBR |
| | PI | **Prezista/r/Truvada** | drv/r/ftc/tdf | Harvoni, dcv/sof (dcv 30 mg given in Ally-2 but dose reduction not recommended in prescribing information). |
| **Alternate HIV Regimens DHHS - 2015** | NNRTI | **Atripla** | efv/tdf/ftc | dcv (90 mg) / sof, Harvoni |
| | | **Complera** | rpv/tdv/ftc | Harvoni, dcv/sof, sim/sof, GRZ + EBR |
| | PI | **Reyataz/r/Truvada** | atv/r+tdv/ftc | Viekira Pak (hold r), dcv (30mg) / sof |
| | | **Prezista/r/Ziagen/Epivir** | drv/r/abc/3tc | Harvoni, dcv/sof (dcv 30 mg given in Ally-2 but dose reduction not recommended in prescribing information). |

# Adolescents ≥12 Years Old or Weighing ≥35 kg, Without Cirrhosis or With Compensated Cirrhosis

| REGIMEN | Length (weeks) | SVR |
|---|---|---|
| ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-naive without cirrhosis or with compensated cirrhosis, or treatment-experienced without cirrhosis | 12 | 98% |
| ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-experienced with compensated cirrhosis | 24 | 98% |
| sofosbuvir (400 mg) plus weight-based ribavirin for patients with genotype 2 who are treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis | 12 | 100% |
| sofosbuvir (400 mg) plus weight-based ribavirin for patients with genotype 3 who are treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis | 24 | 97% |
| ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 4, 5, or 6 who are treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis | 12 | |

# Ribavirin and Teratogenicity

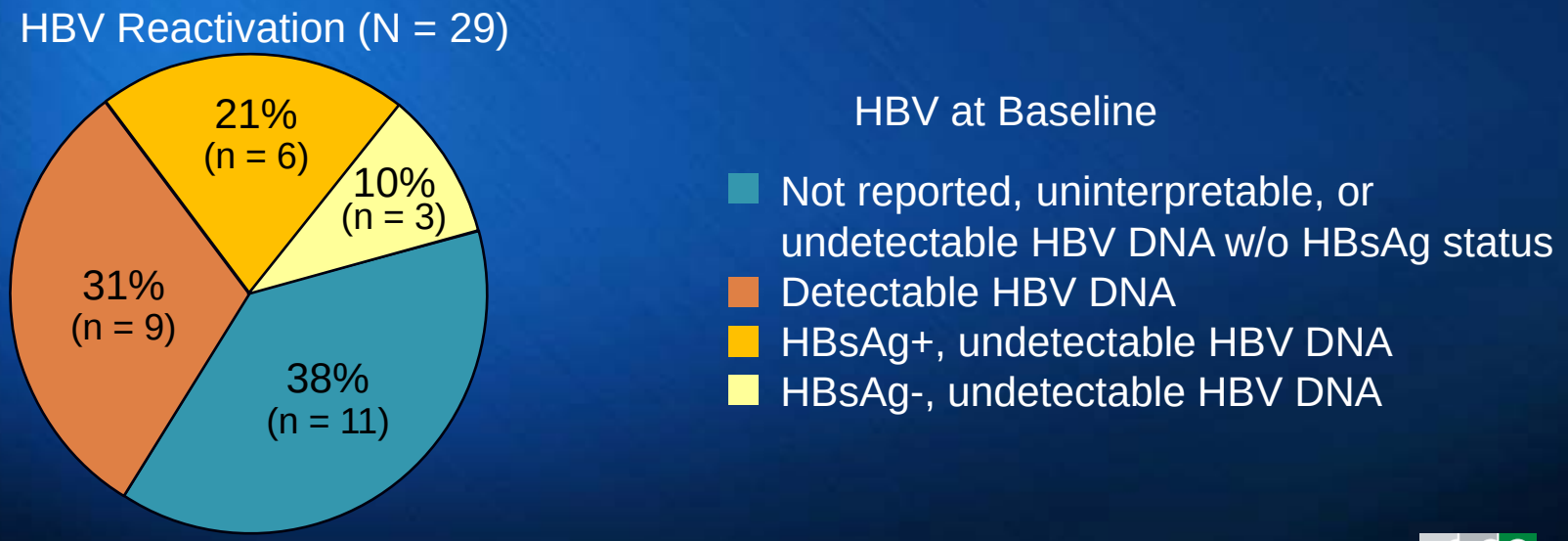
- Patients should be informed that Ribavirin is teratogenic.
- Ribavirin should not be started unless a pre-treatment pregnancy test has been negative.
- Women of childbearing potential and all males should use 2 methods of contraception during treatment and for 6 months after therapy.
- If pregnancy occurs, they should be advised of the significant teratogenic risk to the fetus.
- Physicians are strongly encouraged to report any pregnancy in a patient or partner, during treatment or 6 months after treatment to: Ribavirin Pregnancy Registry @ 1-800-593-2214

# Dosing for Ribavirin in Combination Therapy With Sofosbuvir for Adolescents ≥12 Years Old or Weighing ≥35 kg

| Body Weight (kg) | Daily Ribavirin Dosage (in 2 divided doses) |
|---|---|
| <47 | 15 mg/kg/day |
| 47–49 | 600 mg/day |
| 50–65 | 800 mg/day |
| 66–80 | 1000 mg/day |
| >80 | 1200 mg/day |

# HBV Reactivation in Pts Receiving DAAs: Postmarketing Cases Reported to FDA

- Case reports of HBV reactivation in pts receiving DAAs
  - Reactivation: increase in HBV DNA or seroconversion to HBsAg positive
- 29 confirmed cases in ~ 3 yrs (November 2013 to October 2016)
  - Pts from Japan (n = 19), US (n = 5), other (n = 5)
  - Most cases occurred within 4-8 wks of initiation
  - 2 deaths, 1 transplant, 6 hospitalizations, 10 DAA discontinuations

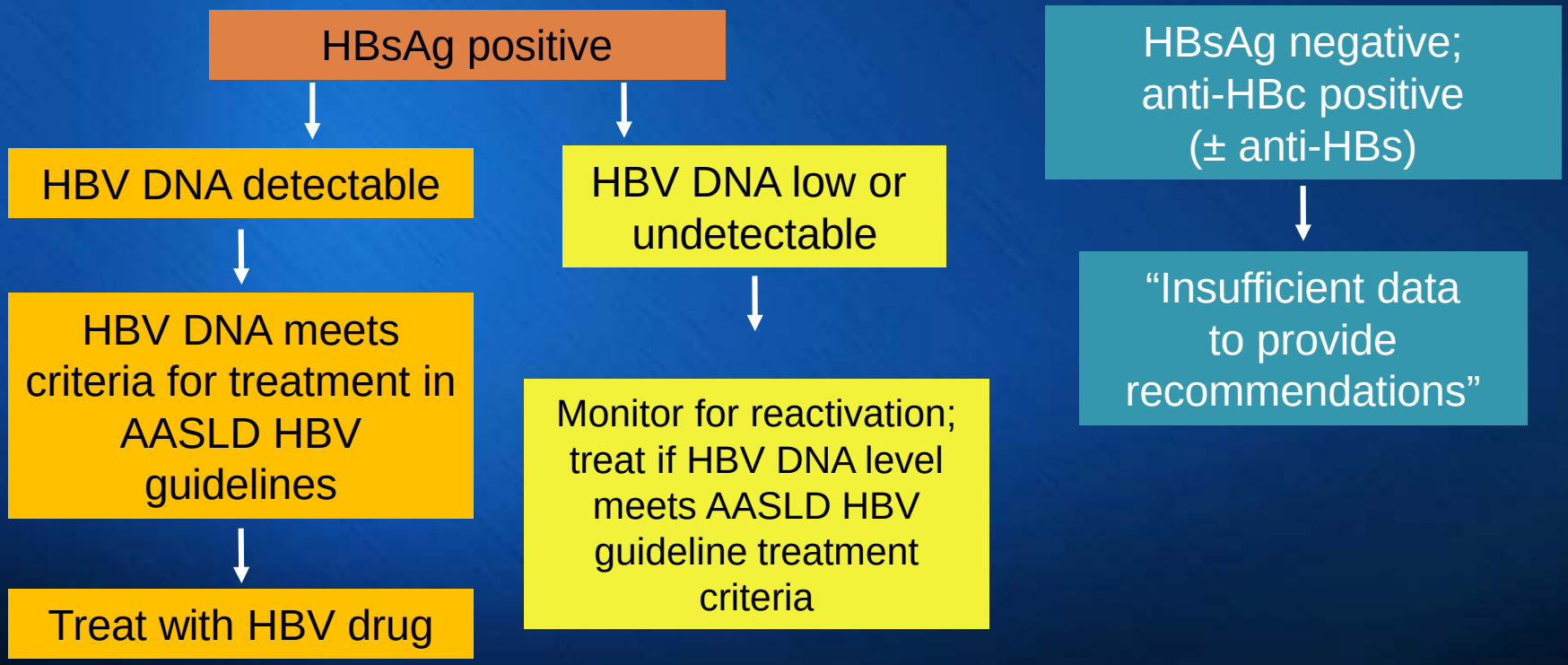



Bersoff-Matcha SJ, et al. AASLD 2016. Abstract LB17.

Slide credit: clinicaloptions.com

# HBV Testing and Monitoring During HCV DAA Therapy: AASLD/IDSA Guidance

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - No HBV markers: VACCINATE (this is not new)
  - HBV markers present:




AASLD/IDSA. HCV guidance. September 2016.
Graphic created by Ira M. Jacobson, MD.

Slide credit: clinicaloptions.com

# My recommendations

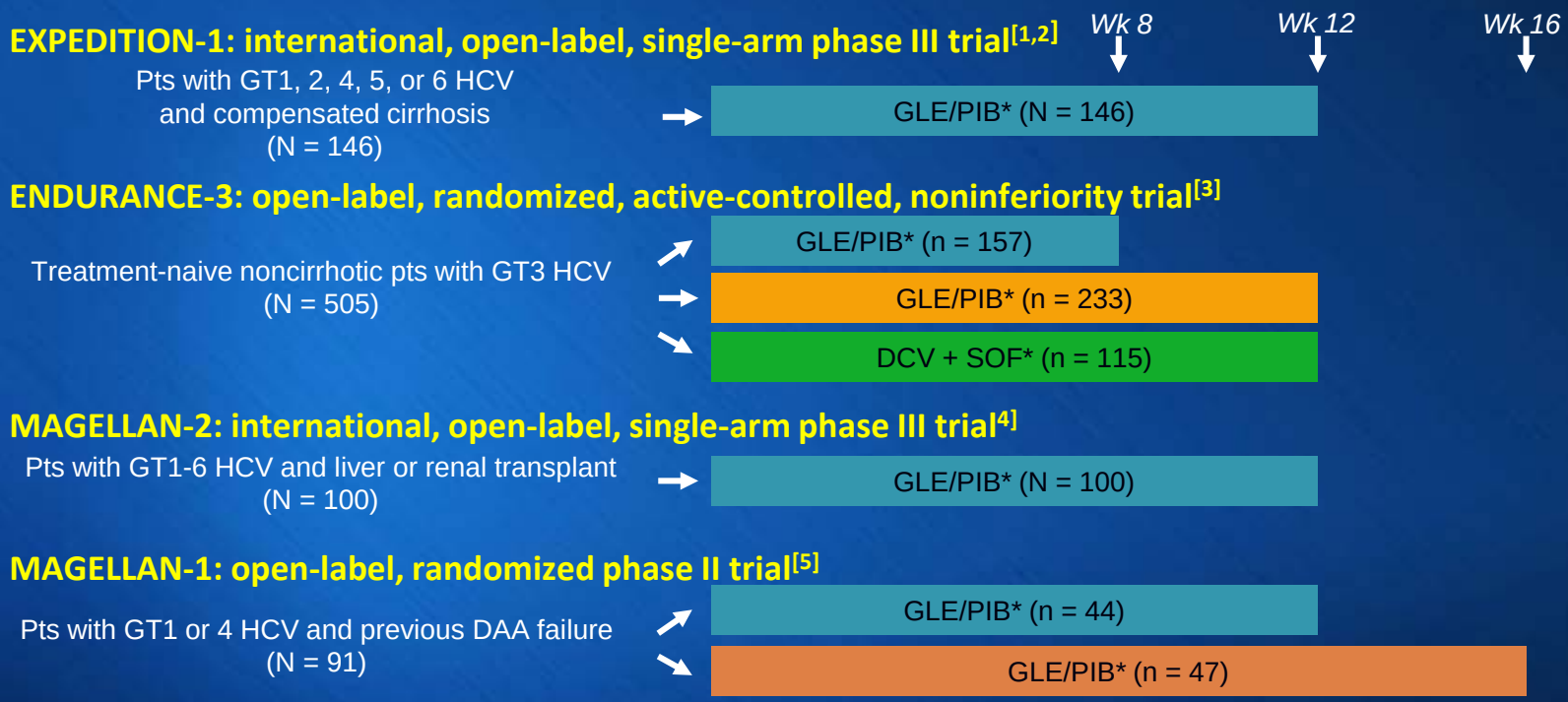
- If HBsAg(+) with HBV-DNA of 2000 IU/mL or higher:
  - Treat for chronic HBV
- If HBsAg (+) with HBV-DNA < 2000 IU/mL, or
  If HBsAg (-) but anti-HBc (+):
  - Monitor every 4 weeks with HBsAg (if it was negative) and HBV-DNA quantitation, during therapy and up to 8-12 weeks after EOT.

# Investigational HCV Treatments

# Summary of Investigational Direct-Acting Antivirals Discussed in This Slideset

| Drug | Abbreviation | Class |
|---|---|---|
| Glecaprevir | GLE | NS3/4A protease inhibitor |
| Voxilaprevir | VOX | NS3/4A protease inhibitor |
| Pibrentasvir | PIB | NS5A inhibitor |
| Ruzasvir | RZR | NS5A inhibitor |
| Uprifosbuvir (formerly MK-3682) | UPR | NS5B polymerase nucleotide inhibitor |

# Glecaprevir/Pibrentasvir for Treatment of HCV

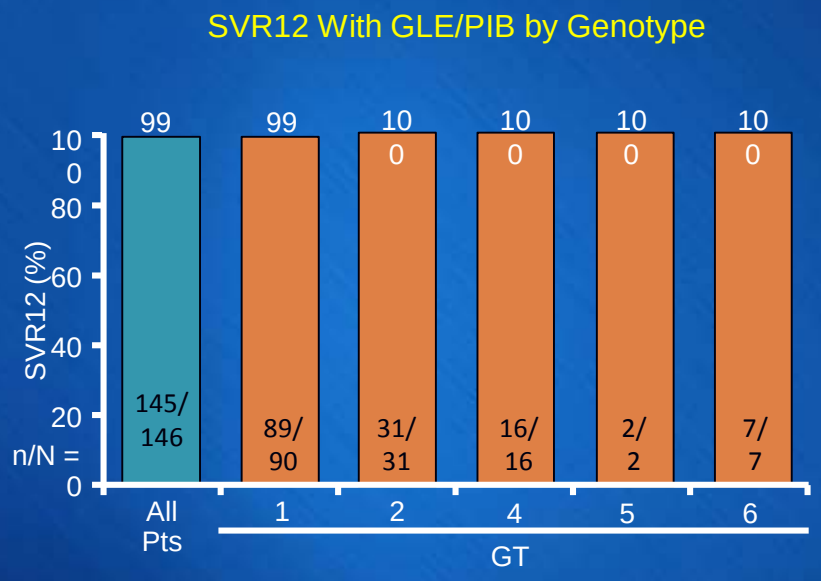



*Dosing: GLE/PIB, 300/120 mg. DCV + SOF, 60 mg + 400 mg QD.

Slide credit: clinicaloptions.com

References in slidenotes

# EXPEDITION-1: GLE/PIB in GT1, 2, 4, 5, or 6 HCV and Compensated Cirrhosis




- No AE-related discontinuations or DAA-related serious AEs
  - 1 death due to cerebral hemorrhage in pt with history of hemophilia deemed unrelated to study drug

| AE, n (%) | Pts (N = 146) |
|---|---|
| Any AE | 101 (69) |
| Any serious AE | 11 (8) |
| AEs occurring in ≥ 10% of pts | |
| ▪ Fatigue | 28 (19) |
| ▪ Headache | 20 (14) |
| ▪ Pruritus | 14 (10) |
| HCC | 2 (1) |

1 relapse in pt with GT1a HCV with new NS5Amutations (Q30R, H58D)

Slide credit: clinicaloptions.com

Forns X, et al. EASL 2017. Abstract GS-006. ClinicalTrials.gov. NCT02642432.
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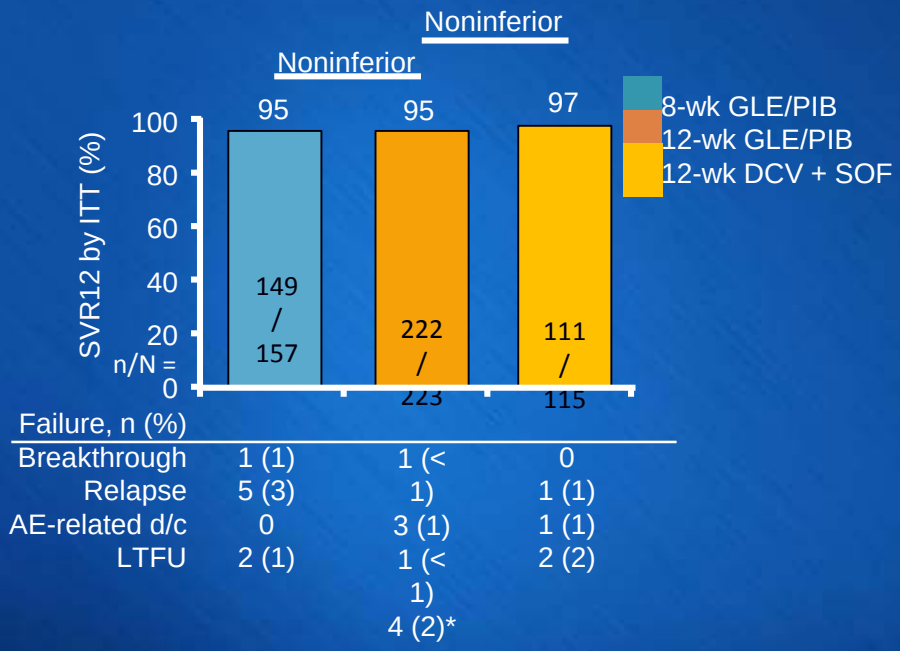
# ENDURANCE-3: GLE/PIB in GT3 HCV Without Cirrhosis




| Failure, n (%) | | | |
|---|---|---|---|
| Breakthrough | 1 (1) | 1 (< 1) | 0 |
| Relapse | 5 (3) | 3 (1) | 1 (1) |
| AE-related d/c | 0 | 1 (< 1) | 1 (1) |
| LTFU | 2 (1) | 4 (2)* | 2 (2) |

- Most pts had history of IDU (63% to 66%)

*2 other failures due to consent withdrawal and noncompliance.

- No serious AEs deemed related to study drug

| AE, n (%) | G/P 8 Wks (n = 157) | G/P 12 Wks (n = 233) | SOF + DCV (n = 115) |
|---|---|---|---|
| Any AE | | | |
| ▪ Possibly DAA related | 98 (62)<br>63 (40) | 177 (76)<br>112 (48) | 80 (70)<br>50 (43) |
| Serious AE | 3 (2) | 5 (2) | 2 (2) |
| AEs in ≥ 10% of pts | | | |
| ▪ Headache | 31 (20) | 60 (26) | 23 (20) |
| ▪ Fatigue | 20 (13) | 44 (19) | 16 (14) |
| ▪ Nausea | 19 (12) | 32 (14) | 15 (13) |

Grade ≥ 3 laboratory abnormalities: no clinically relevant ALT increases, 1 isolated bilirubin increase (G/P 8 wks), 1 isolated neutrophil count decrease (G/P 12 wks)

Foster GR, et al. EASL 2017. Abstract GS-007. Reproduced with permission

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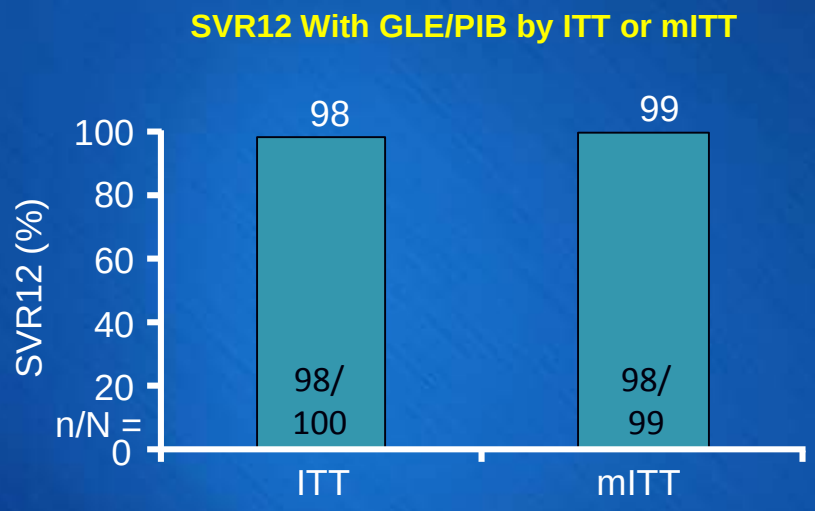
# MAGELLAN-2: GLE/PIB in GT1-6 HCV With Liver or Renal Transplant




1 relapse in pt with GT3a HCV; 1 pt LTFU

- No deaths during study, 1 pt with transplant rejection (unrelated to DAA)

| Safety Outcome, % | GLE/PIB (N = 100) |
|---|---|
| Any AE | 85 |
| Serious AE | 8 |
| ▪ DAA related | 2 |
| AEs leading to d/c | 1 |
| ▪ DAA related | 0 |
| AEs in ≥ 10% of pts | |
| ▪ Headache | 22 |
| ▪ Fatigue | 22 |
| ▪ Nausea | 12 |
| ▪ Pruritus | 12 |
| Grade ≥ 3 abnormality | |
| ▪ AST | 0 |
| ▪ ALT | 1 |
| ▪ Total bilirubin | 1 |
| ▪ CrCl | 2 |

Reau N, et al. EASL 2017. Abstract LBO-03. Reproduced with permission

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# MAGELLAN-1: GLE/PIB in GT1 or 4 HCV With Previous DAA Failure

- Of pts with both NS3 and NS5a RASs, 9/9 had previous failure with PI + NS5A
  - 5/9 had SVR12 on GLE/PIB

| SVR12, n/N (%) | GLE/PIB | |
|---|---|---|
| | 12 Wks (n = 44) | 16 Wks (n = 47) |
| Overall SVR12 | 39/44 (89) | 43/47 (91) |
| SVR12 according to previous DAA class | | |
| ▪ PI only | 14/14 (100) | 13/13 (100) |
| ▪ NS5A only | 14/16 (88) | 17/18 (94) |
| ▪ PI + NS5A | 11/14 (79) | 13/16 (81) |
| SVR12 according to baseline RAS | | |
| ▪ None | 13/13 (100) | 13/13 (100) |
| ▪ NS3 only | 2/2 (100) | 4/4 (100) |
| ▪ NS5A only | 20/24* (83) | 22/23† (96) |

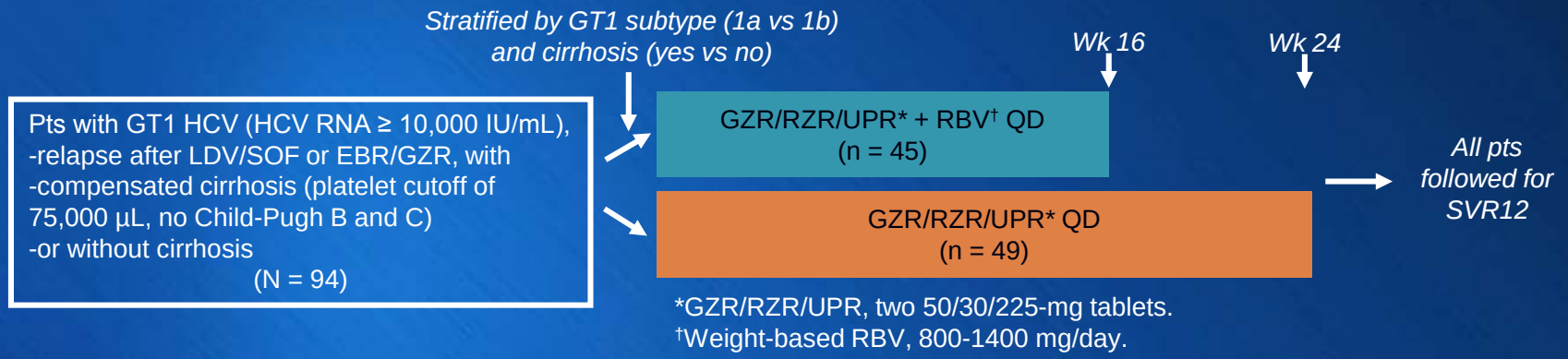
*Virologic failure: n = 3 relapse; n = 1 on treatment. †Virologic failure: n = 1 on treatment.

Slide credit: clinicaloptions.com

Poordad F, et al. EASL 2017. Abstract PS-156

# C-SURGE: GZR/RZR/UPR for GT1 HCV Pts Who Relapsed on Previous DAA Therapy

- Randomized, open-label phase II trial




Baseline characteristics:
- Noncirrhotic, 56%; compensated cirrhosis, 43%; unknown, 1%
- NS5A RASs, 84%;
- NS3 RASs, 65%;
- dual NS5A and NS3 RASs, 55%

Primary endpoints: SVR12 (HCV RNA < 15 IU/mL), safety

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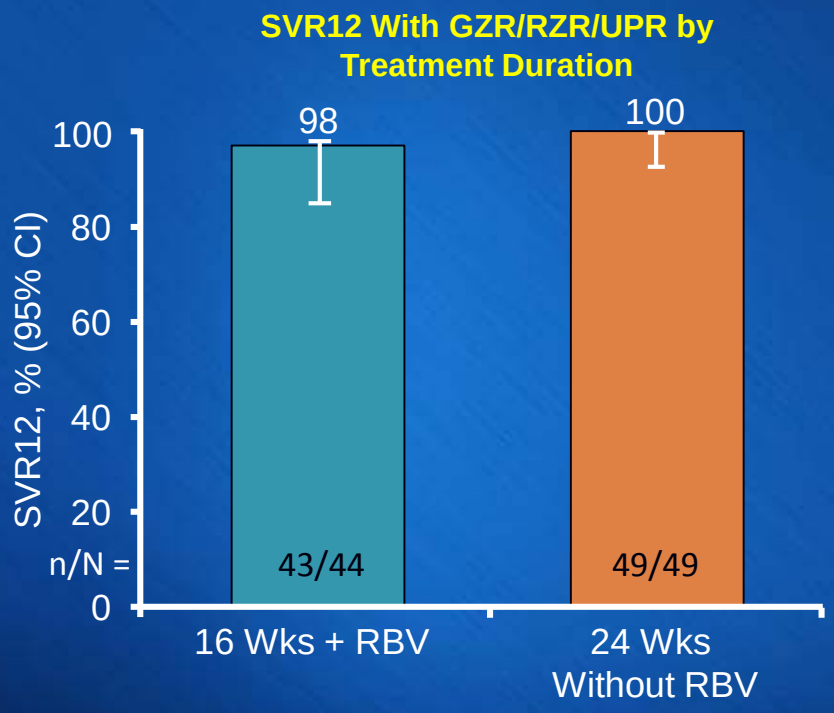
Wedemeyer H, et al. EASL 2017. Abstract PS-159

# C-SURGE: Efficacy and Safety Outcomes




- SVR12 achieved independent of presence of BL NS5A/NS3 RASs (including Y93)
- GZR/RZR/UPR + RBV arm had greater frequency of fatigue, pruritus, rash, decreased hemoglobin

| Safety Outcome, n (%) | 16 Wks + RBV (n = 44) | 24 Wks Without RBV (n = 49) |
|---|---|---|
| ≥ 1 AE | 40 (91) | 39 (80) |
| ▪ Drug-related AE | 32 (73) | 23 (47) |
| Any serious AE* | 1 (2) | 4 (8) |
| AEs occurring in ≥ 10% of pts | | |
| ▪ Fatigue | 21 (48) | 12 (24) |
| ▪ Headache | 6 (14) | 6 (12) |
| ▪ Diarrhea | 3 (7) | 5 (10) |
| ▪ Pruritus | 5 (11) | 0 |
| ▪ Rash | 6 (14) | 2 (4) |
| Hemoglobin < 10 g/dL | 4 (9) | 0 |

*All serious AEs deemed unrelated to study treatment.

Wedemeyer H, et al. EASL 2017. Abstract PS-159. Reproduced with permission.

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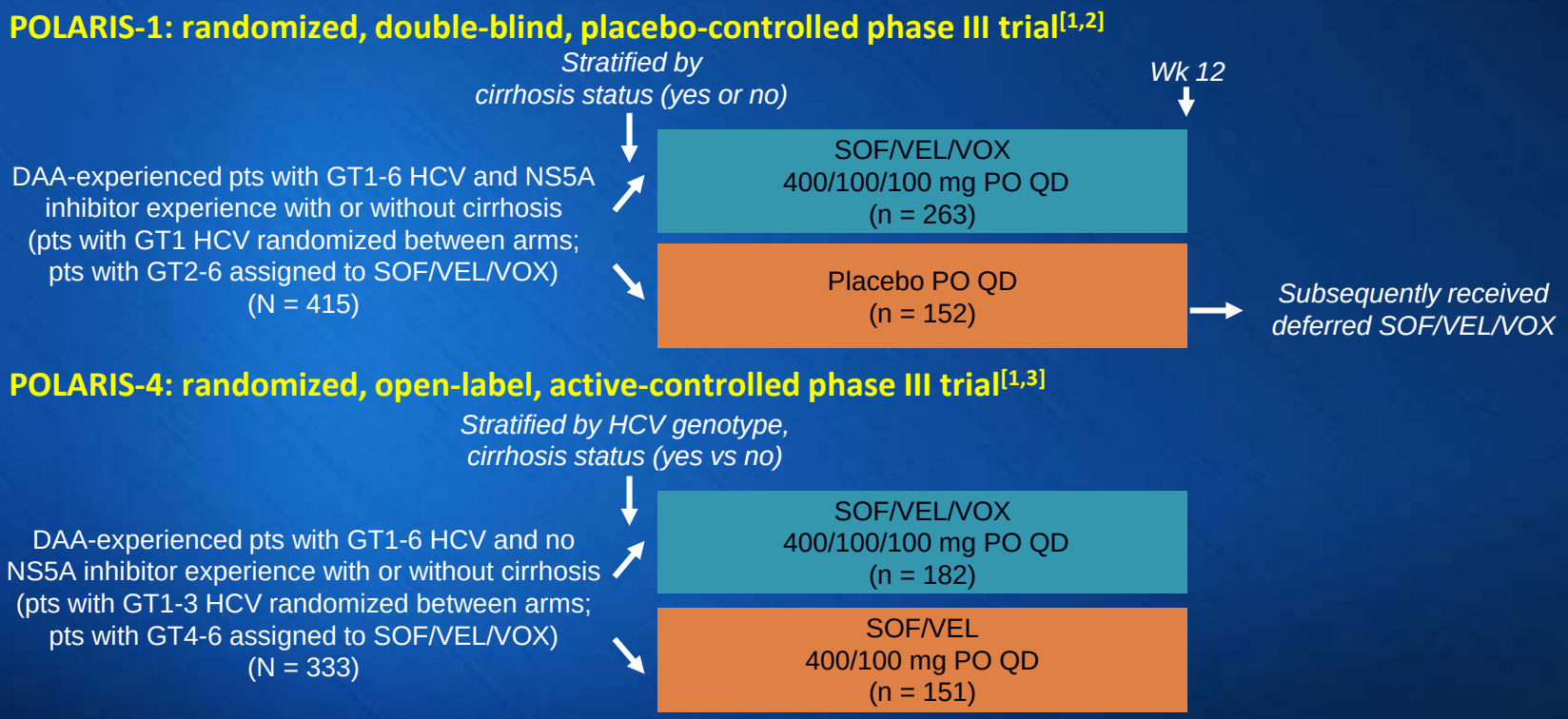
# POLARIS-1 and -4: SOF/VEL/VOX in DAA-Experienced Pts

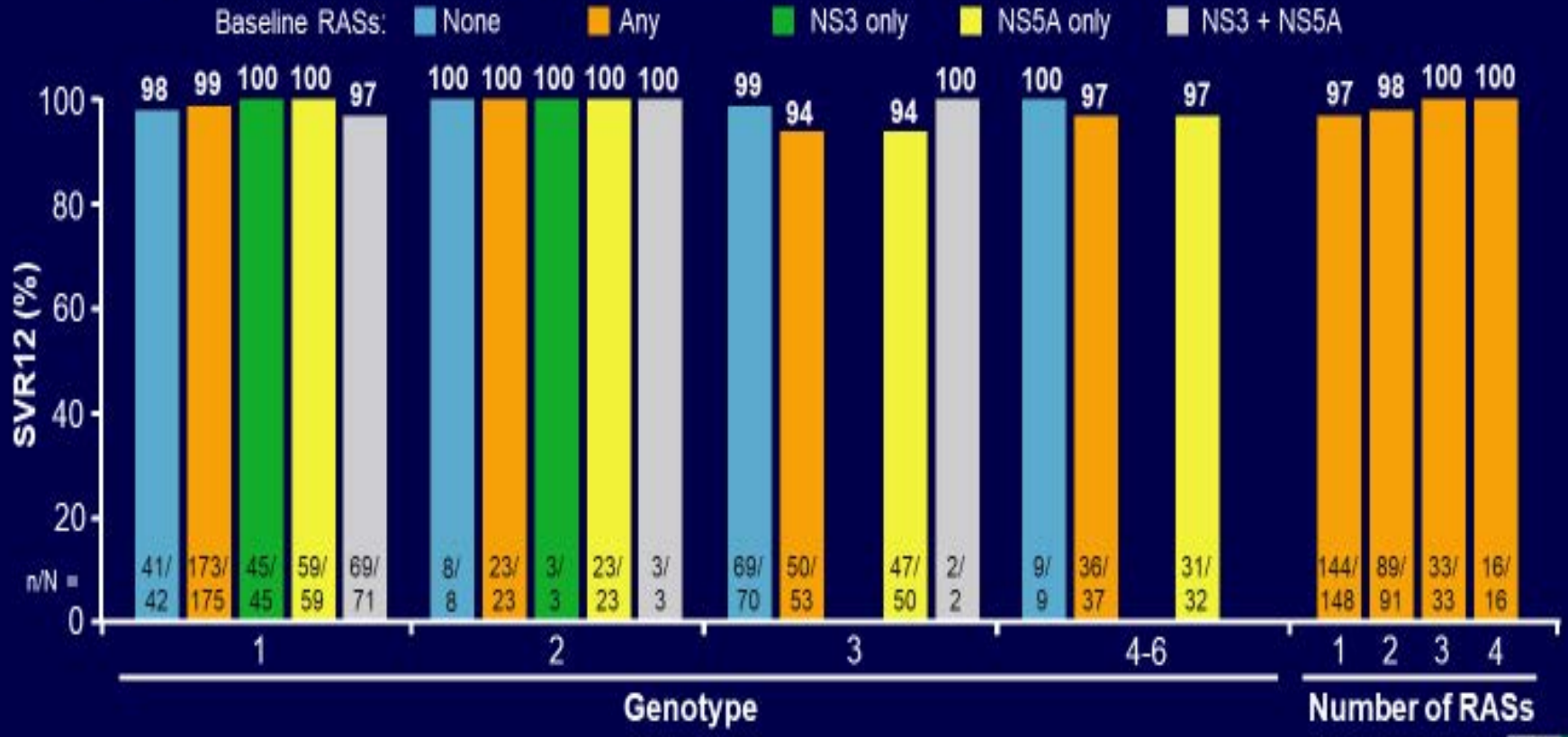



Slide credit: clinicaloptions.com

References in slidenotes

# POLARIS-1 and -4: Impact of Baseline RASs on 12-Wk SOF/VEL/VOX in DAA-experienced Pts

- Integrated analysis of data from SOF/VEL/VOX arms of 2 phase III trials of DAA-experienced pts with (n = 263) and without (n = 182) previous NS5A inhibitors, 46% with cirrhosis




Sarrazin C, et al. EASL 2017. Abstract THU-248. Reproduced with permission.

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# Evaluation and Management of Chronic Hepatitis C

# Hepatitis C Disease Burden: US

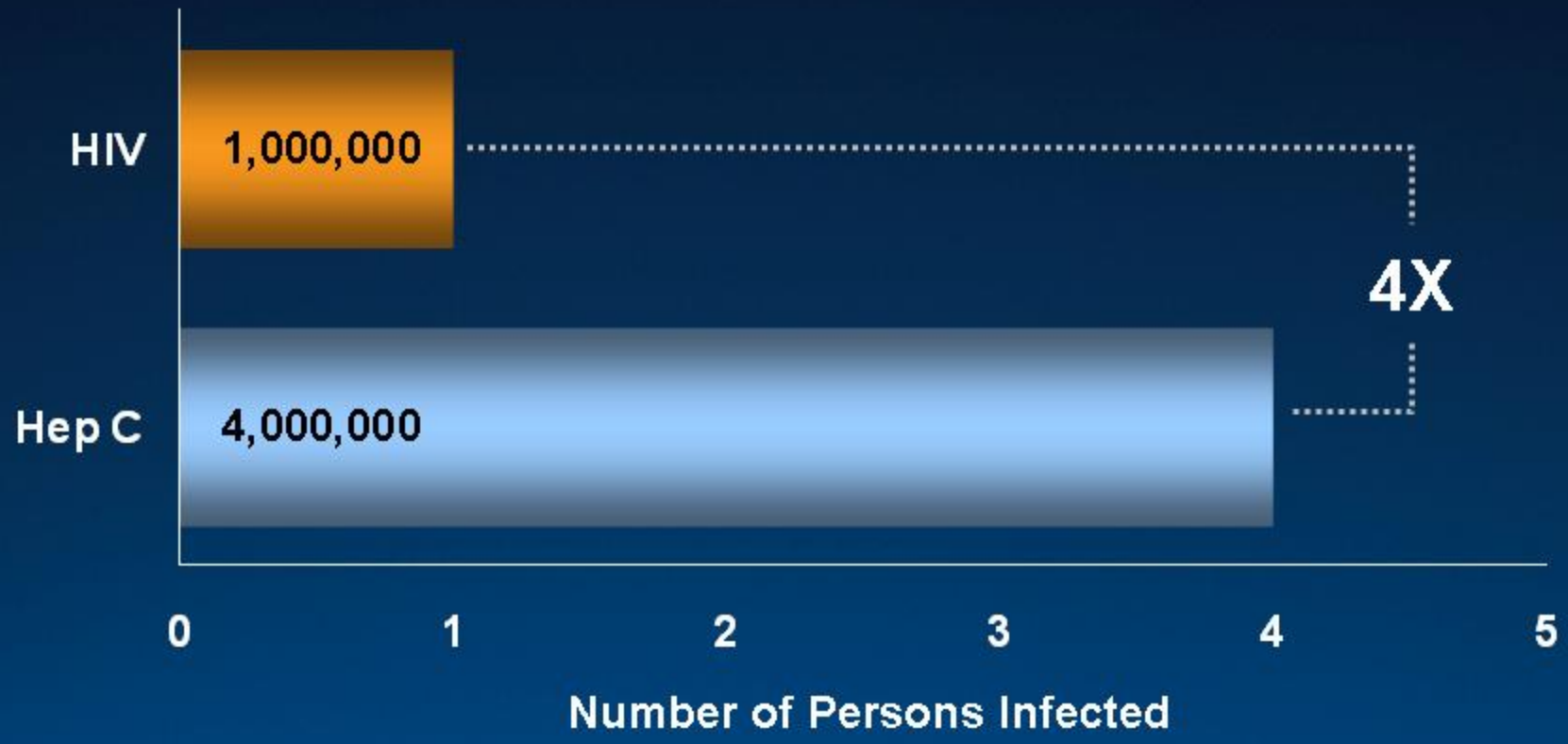
- Hepatitis C is the most common chronic blood-borne viral infection in the US[1]
  - ~ 1/2 of cirrhotic patients[2]
  - ~ 1/3 of HCC patients[3]
  - #1 reason for liver transplants[4]
  - #1 cause of death in HIV patients[5,6]

**It is estimated that 4 million Americans are infected with HCV[7]**

1. Alter M, et al. *N Engl J Med*. 1999;341:556-562; 2. NDDIC, 2006. Available at http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc; 3. NIH. *NIH Consens State Sci Statements*. 2002;19:1-46; 4. CDC Hepatitis Fact Sheet. http://www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm. Updated December 8, 2006; 5. Bica I et al. *Clin Infect Dis*. 2001;32:492-497; 6. Salmon-Ceron D et al. J Hepatol 2005;42:700-805; 7. Edlin B, et al. Presented at AASLD 2005. November 11-15, 2005; San Francisco, CA. Oral Presentation #44.

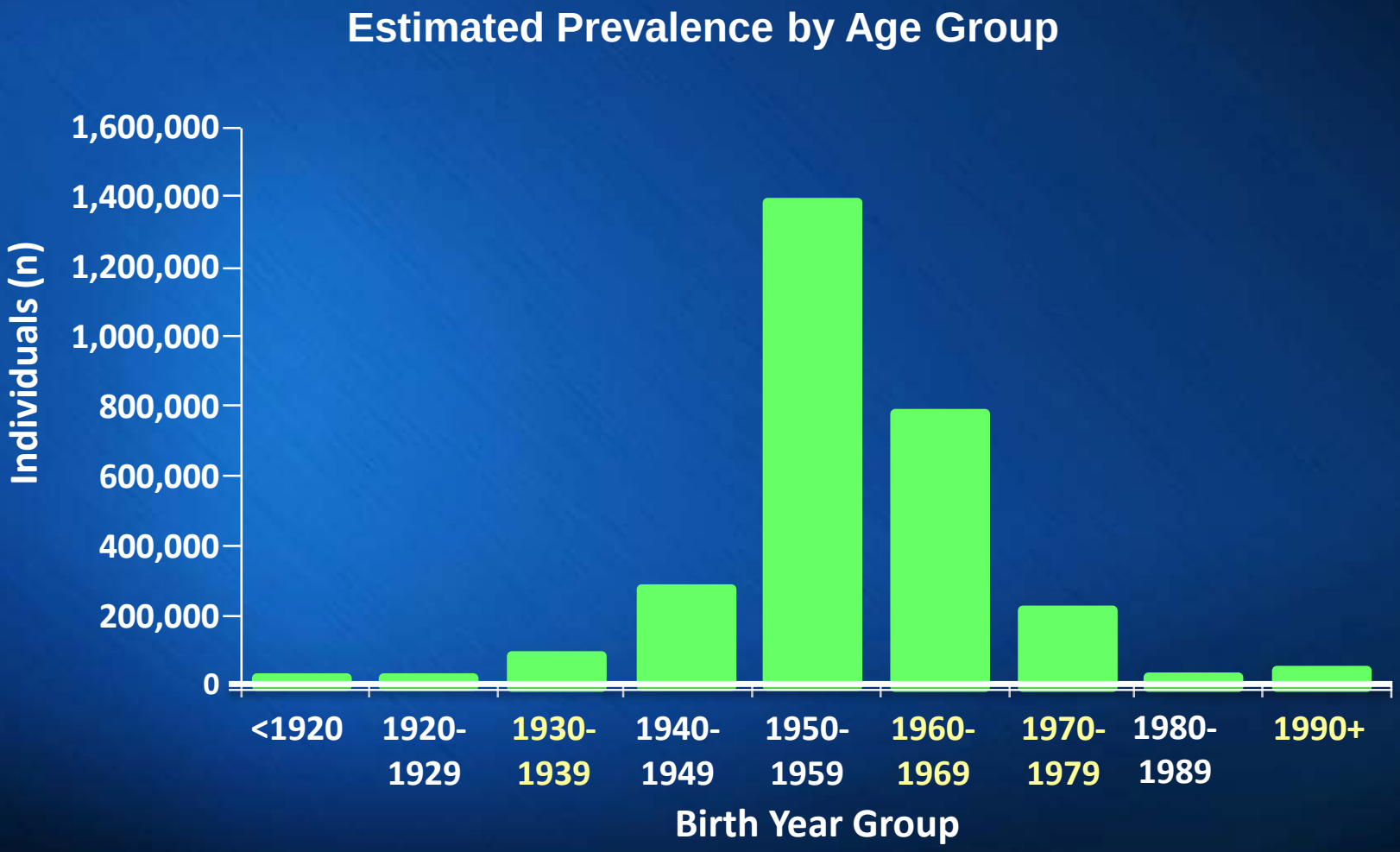
# Prevalence of Hepatitis C

- Hepatitis C is 4 times more prevalent than HIV[1,2]



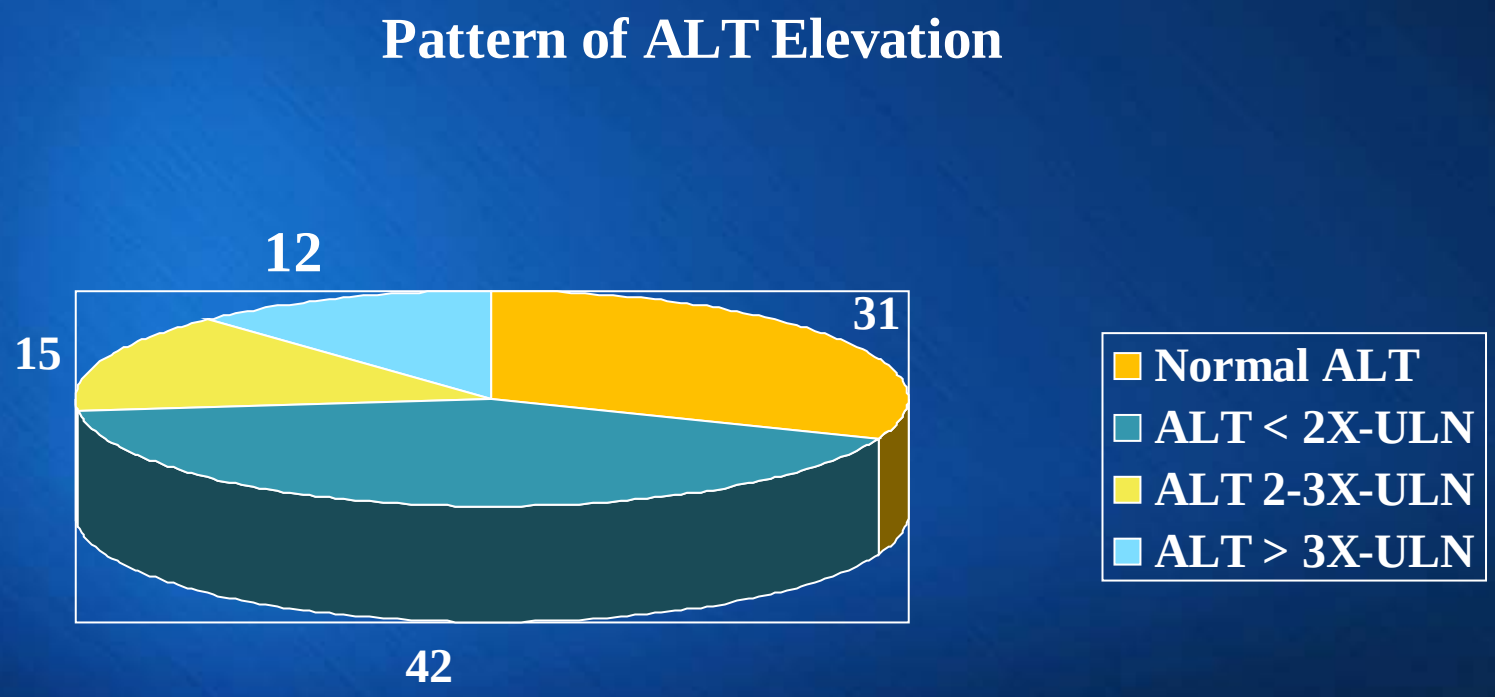

1. NIAID HIV/AIDS fact sheet. 2007. Available at: www.niaid.nih.gov/factsheets/hivinf.htm; 2. Edlin B, et al. Presented at AASLD 2005. November 11-15, 2005; San Francisco, CA. Oral Presentation #44.

# Two-Thirds of Those With Chronic HCV in the US Were Born Between 1946 and 1964




Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a Baby Boomer Epidemic of Liver Disease.* New York, NY: Milliman, Inc; 2009.

# Pattern of ALT Elevation Chronic HCV



# Factors Associated with Accelerated Fibrosis in HCV

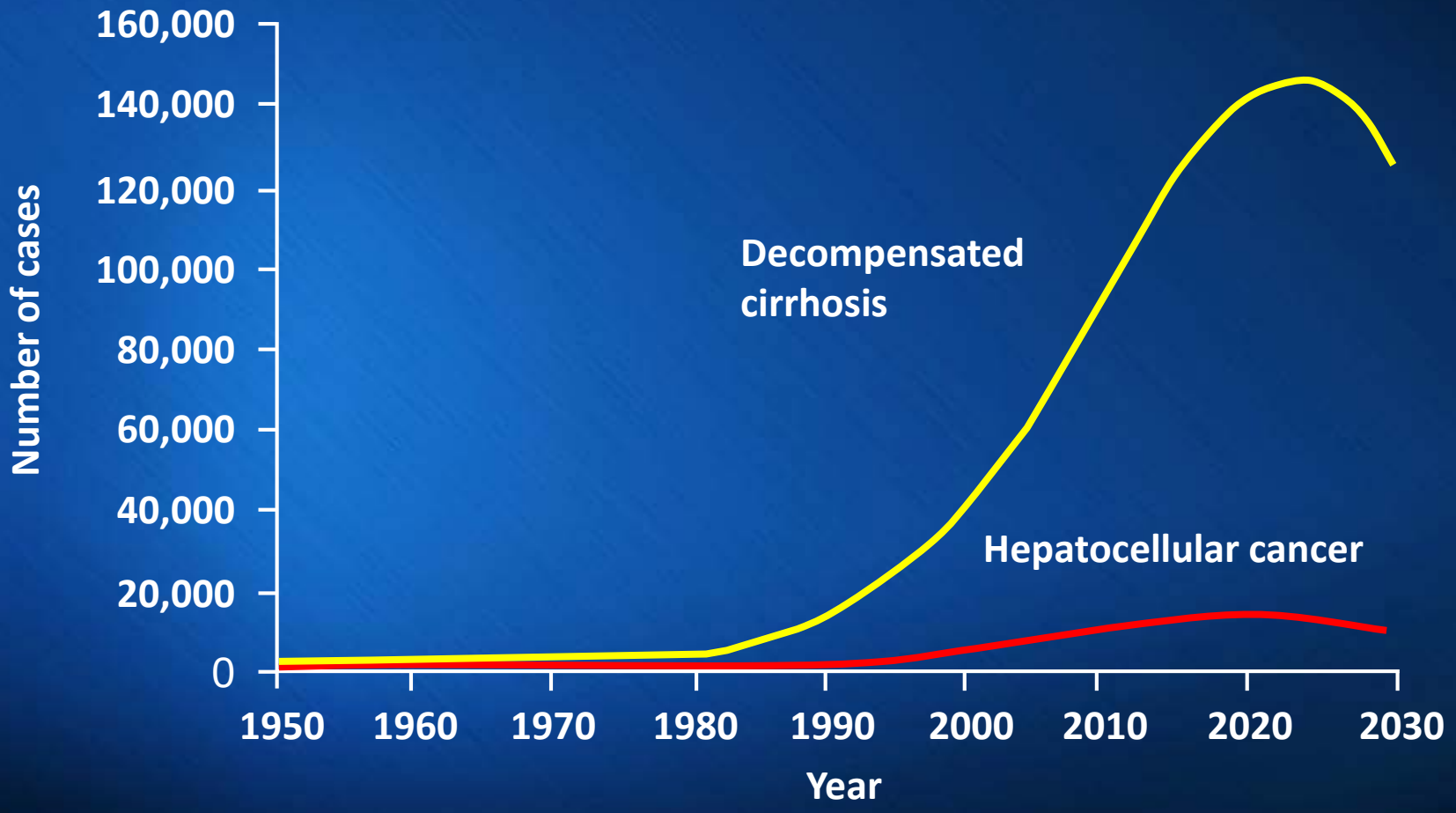
## Host Factors

- **Non-Modifiable**
  - Fibrosis stage
  - Inflammation grade
  - Older age at time of infection
  - Male gender
  - Organ transplant
- **Modifiable**
  - Alcohol consumption
  - Nonalcoholic fatty liver disease
  - Obesity
  - Insulin resistance

## Viral Factors

- Genotype 3
- Co-infection with HBV or HIV

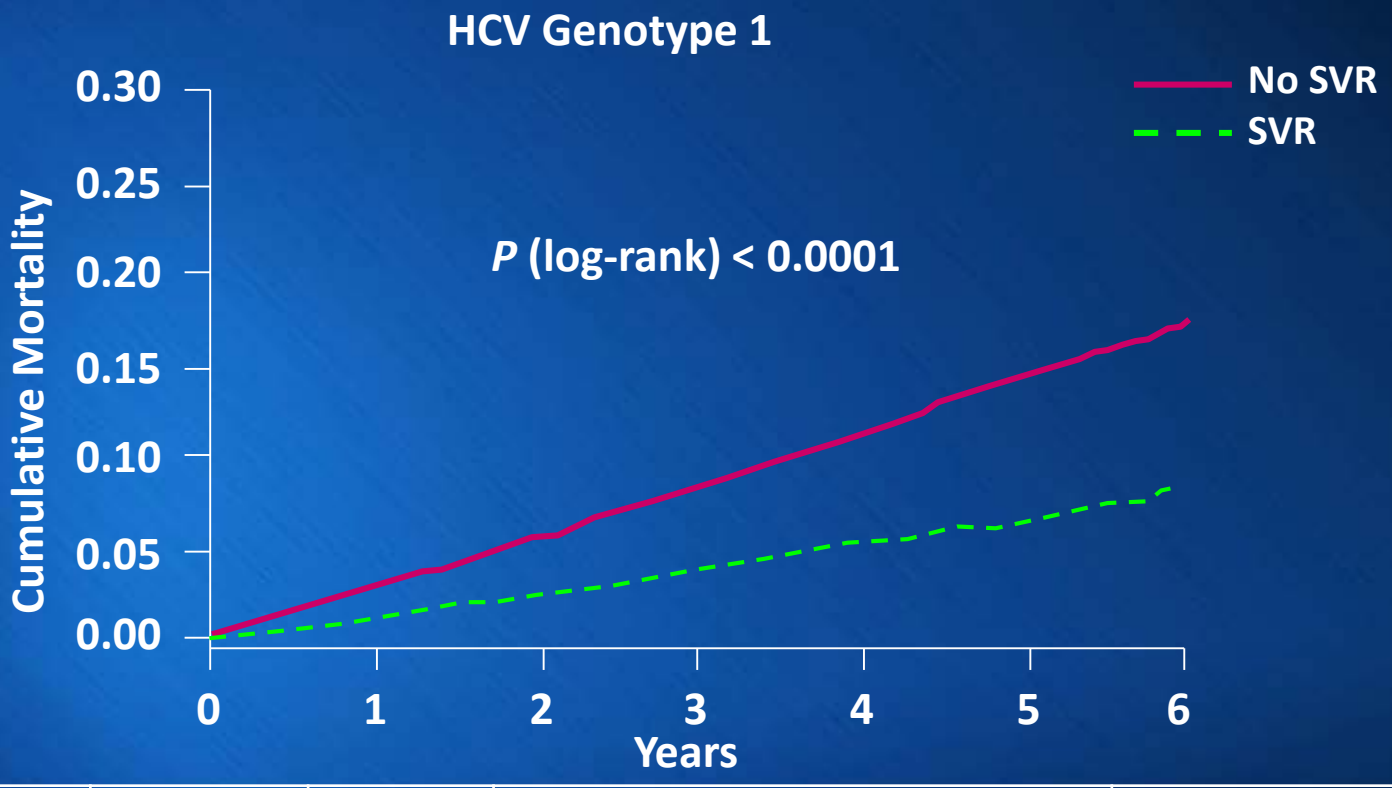
# Projected Cases of Hepatocellular Carcinoma and Decompensated Cirrhosis Due to HCV




Davis GL, et al. *Gastroenterology*. 2010;138(2):513-521

# SVR and Reduced Risk of All-Cause Mortality

## US VA Study: Treatment with Pegylated Interferon/Ribavirin




| Genotype | N | SVR | Hazard Ratio for Death with SVR | *P*-value |
|---|---|---|---|---|
| 1 | 12,166 | 35% | 0.70 | < 0.0001 |
| 2 | 2904 | 72% | 0.64 | 0.006 |
| 3 | 1794 | 62% | 0.51 | 0.0002 |

Backus L, et al. *Clin Gastroenterol Hepatol*. 2011;9:509-516.

# Who should be Tested for HCV?

- **HCV testing is recommended at least once for persons born between 1945 and 1965. Rating:** Class I, Level B

- **Other persons should be screened for risk factors for HCV infection, and**
  - **one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection. Rating:** Class I, Level B

## Who should be Tested for HCV?

# Behaviors, Exposures and Conditions with High HCV Risk

- ***Risk behaviors***
  - **Injection-drug use (current or ever, including those who injected once)**
  - **Intranasal illicit drug use**

- ***Other medical conditions***
  - **HIV infection**
  - **Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase (ALT) levels**

## Who should be Tested for HCV?

# Behaviors, Exposures and Conditions with High HCV Risk

- ***Risk exposures***
  - Long-term hemodialysis (ever)
  - Getting a tattoo in an unregulated setting
  - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood
  - Children born to HCV-infected women
  - Prior recipients of transfusions or organ transplants, including persons who:
    - were notified that they received blood from a donor who later tested positive for HCV infection
    - received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
    - received clotting factor concentrates produced before 1987
    - were ever incarcerated

# Recommendations for patients with HCV

- Avoid sharing toothbrushes and dental or shaving equipment.
- Cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
- Stop using illicit drugs and enter substance abuse treatment.
- If continue to inject drugs should:
  - avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment;
  - use new sterile syringes and filters and disinfected cookers; clean the injection site with a new alcohol swab; and dispose of syringes and needles after one use in a safe, puncture-proof container.

# Recommendations for patients with HCV

- Do not donate blood
- Discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
- MSM with HIV infection and those with multiple sexual partners or sexually transmitted infections should use barrier precautions to prevent sexual transmission.
  - Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
- Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

# Treatment of Chronic Hepatitis C
# AASLD/IDSA Guidelines + FDA

*http://www.hcvguidelines.org/*

# Who should be treated for HCV

- ***Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions.***
  - A 15-year follow-up study of patients with early (F0-1) chronic hepatitis C showed a survival of:
    - 92% in patients who were cured (SVR),
    - 87% in non-treated patients, and
    - 82% in those patient who did not respond to therapy.
- Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications are given high priority.

Hepatitis C shortens the life expectancy of all infected patients and its eradication improves survival.

## Who should be treated for HCV

## **Highest Priority** (Highest Risk for Severe Complications)

- Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
- Organ transplant recipients
- Type 2 or Type 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)
- Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis

# Who should be treated for HCV
# High Priority

## Owing to High Risk for Complications

- Fibrosis (Metavir F2)
- HIV-1 coinfection
- HBV coinfection
- Other coexistent liver disease (eg, NASH)
- Debilitating fatigue
- Type 2 Diabetes mellitus (insulin resistant)
- Porphyria Cutanea Tarda

## Owing to Transmission Risk

- MSM with high-risk sexual practices
- Active injection drug users
- Incarcerated persons
- HCV-infected women of child-bearing potential wishing to get pregnant
- Persons on long-term hemodialysis

All Patients should be counseled on ways to decrease transmission and minimize the risk of reinfection.

# Evaluation of Liver Fibrosis: Serum Fibrosis Tests + TLE and Liver Biopsy

- Transient Liver Elastograpy (TLE): Cutoff Values*
  - 8.4 to 9.5 kPa correlates with Metavir F2;
  - 9.6 to 12.7 kPa with F3; and
  - 12.8 or higher kPa with F4 or cirrhosis.
- The measurement range overlap between stages.
- When the elastography and FibroTest (e.g.: Fibro Sure, Fibro Test-ActiTest) results agreed, liver biopsy examination confirmed the stage of fibrosis in:
  - 84 percent of cases for F ≥2 fibrosis,
  - 95 percent for F ≥3 fibrosis, and
  - 94 percent for F = 4 fibrosis
- If serum fibrosis markers are discordant with TLE, do liver biopsy.

*Afdhal N et al. Clin Gastroenterol Hepatol 2015;13:772-779

# Drugs to Treat Hepatitis C

- Interferon
- PEGylated-Interferon (Peg-IFN)
- Ribavirin
- **Direct Antiviral Agents**

# Interferon Ineligible

## Definition

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- History of depression
- Clinical features consistent with depression
- A baseline neutrophil count below 1500/µL
- A baseline platelet count below 90,000/µL
- A baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

MOST PATIENTS REFUSE TO BE TREATED WITH IFN

# Agents and Regimens Currently Used

| Combinations | Type of Antiviral | | | | |
|---|---|---|---|---|---|
| | NS3 | NS5A | Non-Nuc NS5B | Nuc NS5B | RBV |
| | "previr" | "asvir" | "buvir" | "buvir" | |
| Simeprevir + sofosbuvir | ⊙ | | | ⊙ | |
| Ledipasvir/sofosbuvir FDC (HARVONI) | | ⊙ | | ⊙ | |
| Paritaprevir/r/Ombitasvir FDC (TECHNIVIE or PrO) + Dasabuvir (VIEKIRA Pak and XR or PrOD or 3D) | ⊙ | ⊙ | ⊙ | | ⊙ RBV only for 1a or F3-4 |
| Sofosbuvir + ribavirin | | | | ⊙ | ⊙ |
| Daclatasvir + sofosbuvir | | ⊙ | | ⊙ | |
| Grazoprevir + Elbasvir (ZEPATIER) | ⊙ | ⊙ | | | |
| Velpatasvir + Sofosbuvir (EPCLUSA) | | ⊙ | | ⊙ | |
| Sofosbuvir + Velpatasvir + Voxilaprevir (Vosevi®) | ⊙ | ⊙ | | ⊙ | |
| Glecaprevir + Pibrentasvir (Mavyret) | ⊙ | ⊙ | | | |

# Before Treatment

- Check for Co-Infection (HBV, HIV)
  - Vaccinate for HAV, HBV, Pneumonia, as appropriate.
- Evaluate the Fibrosis Stage of the Disease, previous therapies, and the Viral Load and Genotype.
  - In “decompensated cirrhosis” (Child-Pugh B or C), **DO NOT USE “NS3 containing regimens”** like Simeprevir, Paritaprevir (PrOD/PrO), nor Grazoprevir (Zepatier); liver failure risk.
- Evaluate Potential Interactions of the Antiviral Regimen with all the drugs that the patient is taking (prescription, OTC, or Complementary/Alternative).
  - Eliminate what is not indispensable.

# Before Treatment

- Genotype 1a; if planning to use:
  - SIMEPREVIR, check “NS3 Resistance Panel” for Q80K mutation. Do not use if Q80K mutation is present.
  - ELBASVIR, check for “NS5A Polymorphism (M28, Y93, Q30, L31)” (present in 11%) to decide length of therapy and addition of RBV (16 weeks with resistant polymorphism vs 12 weeks)
  - LEDIPASVIR, check for “NS5A Polymorphism”; with Y93 polymorphism (4%) SVR is 20% lower (96% vs 75%)
- Plan for anti-conceptive therapy, especially if Ribavirin will be used.
- Inform the patient that he/she must not start nor discontinue any medication without previous discussion with you or with another Physician or Pharmacist who will evaluate the effects of this change on the hepatitis C treatment.

# NS5A Resistance-Associated Substitutions (RASs) with Potential for Clinical Significance

| Wild-type Amino Acid (sensitive) | Position | Substitution Amino Acid |
|---|---|---|
| M | 28 | A/G/T |
| Q | 30 | D/E/H/G/K/L/R |
| L | 31 | F/M/V |
| Y | 93 | C/H/N/S |

Genotypes 1a and 3 are the most affected

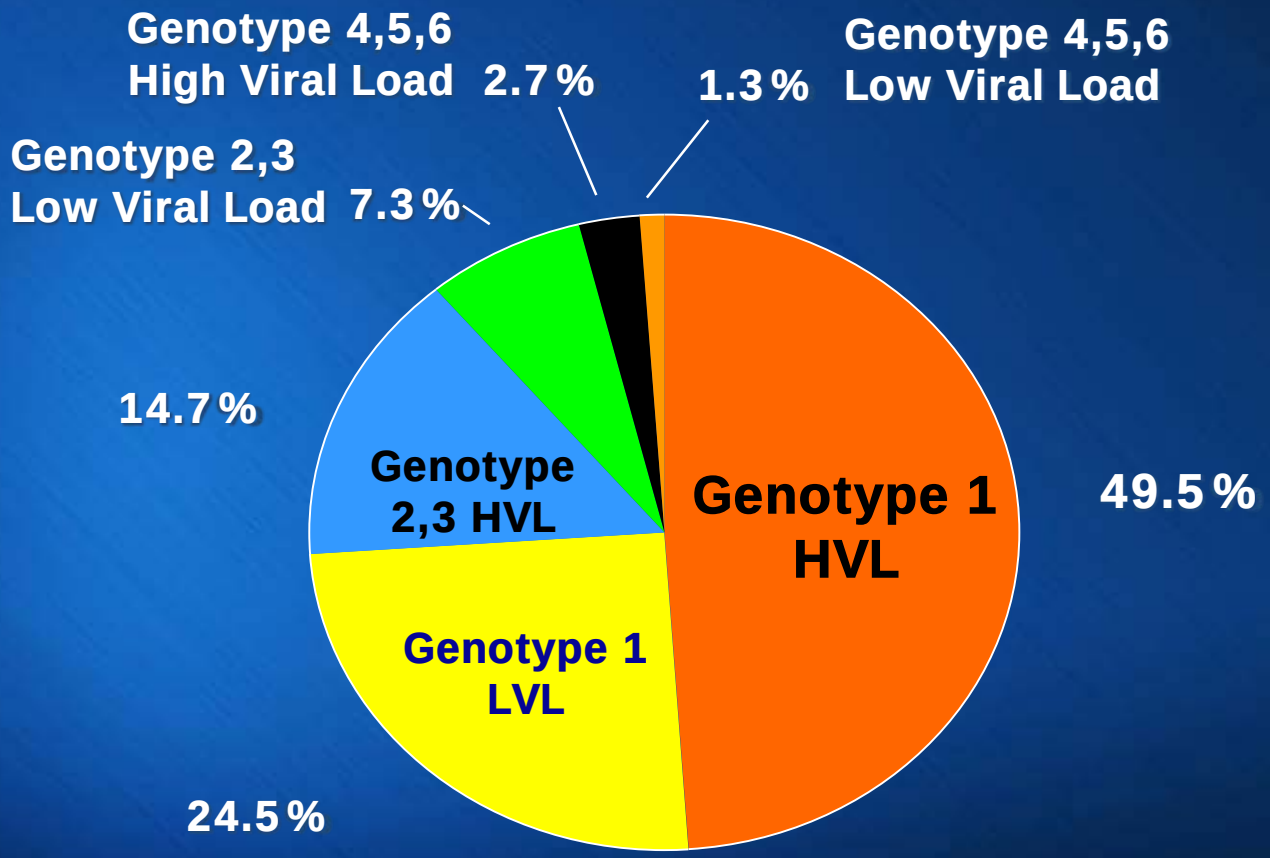
# Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice

| RECOMMENDED | RATING |
|---|---|
| **Elbasvir/grazoprevir**<br>NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir. If present, weight-based ribavirin should be added and treatment should be extended to 16 weeks, or a different recommended therapy used. | I, A |
| **Ledipasvir/sofosbuvir**<br>NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients without cirrhosis being considered for ledipasvir/sofosbuvir. If >100-fold resistance is present, treatment should include 12 weeks of therapy with weight-based ribavirin, or a different recommended therapy. | I, A |
| NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with cirrhosis being considered for ledipasvir/sofosbuvir. If >100-fold resistance is present, treatment should include 24 weeks of therapy with weight-based ribavirin, or a different recommended therapy used. | I, A |
| **Sofosbuvir/velpatasvir**<br>NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients (with or without cirrhosis) and treatment-naive patients with cirrhosis being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added. | I, A |
| **Daclatasvir plus sofosbuvir**<br>NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients without cirrhosis being considered for 12 weeks of daclatasvir plus sofosbuvir. If Y93H is present, weight-based ribavirin should be added. | I, B |
| NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis being considered for 24 weeks of daclatasvir plus sofosbuvir. If Y93H is present, treatment should include weight-based ribavirin, or a different recommended therapy used. | I, B |

# Before Treatment

- Patients scheduled to receive an HCV NS3 protease inhibitor (paritaprevir, simeprevir, grazoprevir) should be assessed for a history of decompensated liver disease and for severity of liver disease using CTP score. Rating: Class I, Level A
  - Patients with current or prior history of decompensated liver disease or with a current CTP score of 7 or greater should NOT receive treatment with regimens that contain NS3 protease inhibitors due to increased area under the curve (AUC) and/or lack of safety data.
  - Similarly, patients with a CTP score of 5 or 6, who cannot be closely monitored for laboratory or clinical symptoms during treatment, should not receive treatment with a regimen that contains paritaprevir/ritonavir.
- All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc. Rating: Class IIa, Level B

# Genotype and Viral Load in US Patients




Alter et al. *N Engl J Med.* 1999;341;556-562.
Blatt et al. *J Viral Hepatitis.* 2000;7:196-202.

# Drug-Drug Interactions
## (Including “Herbals” and “Natural”)

# DAAs and Illicit Recreational Drugs

| | SIM | DCV | SOF | SOF/ LDV | 3D |
|---|---|---|---|---|---|
| Amphetamine | • | • | • | • | • |
| Cannabis | • | • | • | • | • |
| Cocaine | • | • | • | • | • |
| Diamorphine | • | • | • | • | • |
| Diazepam | • | • | • | • | • |
| Gamma-hy-droxybutyrate | • | • | • | • | • |
| Ketamine | • | • | • | • | • |
| MDMA (ecstasy) | • | • | • | • | • |
| Methamphetamine | • | • | • | • | • |
| Phencyclidine (PCP) | • | • | • | • | • |
| Temazepam | • | • | • | • | • |

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

| Concomitant Medications | Daclatasvir | Ledipasvir | Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir | Simeprevir | Sofosbuvir | Elbasvir/ Grazoprevir |
|---|---|---|---|---|---|---|
| Acid-reducing agents* | | X | X | | | |
| Alfuzosin/ tamsulosin | | | X | | | |
| Amiodarone | X | X | X | X | X | X |
| Anticonvulsants | X | X | X | X | X | X |
| Antiretrovirals* | See HIV section | See HIV section | See HIV section | See HIV section | See HIV section | See HIV section |
| Azole antifungals* | X** | | X | X | | X |
| Buprenorphine/ naloxone | | | X | | | |
| Calcineurin inhibitors* | | | X | X | | X |
| Calcium channel blockers* | X | | X | X | | X |
| Cisapride | | | X | X | | X |
| Digoxin | X | X | | X | | X |
| Ergot derivatives | | | X | | | |
| Ethinyl estradiol–containing products | | | X | | | |

*Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
**Requires a daclatasvir dose modification.

| Concomitant Medications | Daclatasvir | Ledipasvir | Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir | Simeprevir | Sofosbuvir | Elbasvir/ Grazoprevir |
|---|---|---|---|---|---|---|
| Furosemide | | | X | | | |
| Gemfibrozil | | | X | | | |
| Glucocorticoids* | X | | X (inhaled, intranasal) | X | | X |
| Herbals<br>St. John's wort<br>Milk thistle | X | X | X | X<br>X | X | X<br>X |
| Macrolide antimicrobials* | X** | | | X | | X |
| Other antiarrythmics* | | | X | X | | X |
| Phosphodiesterase type 5 inhibitors* | | | X | X | | X |
| Pimozide | | | X | | | |
| Rifamycin antimicrobials* | X | X | X | X | X | X |
| Salmeterol | | | X | | | |
| Sedatives* | | | X | X | | X |
| Statins* | X | X | X | X | | X |

*Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
**Requires a daclatasvir dose modification.

| Anti-HIV DRUG | Simeprevir | Sofosbuvir | Ledipasvir | Daclatasvir | Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD) | Paritaprevir, ritonavir, ombitasvir (PrO) | Grazoprevir/ Elbasvir |
|---|---|---|---|---|---|---|---|
| **Ritonavir-boosted atazanavir** | **No data** | No data | Ledipasvir ↑; atazanavir[a] ↑ (okay with TAF not TDF) | Daclatasvir ↑[b] | Paritaprevir ↑; atazanavir ↑ | **Paritaprevir ↑; atazanavir ↔** | **Grazoprevir ↑; elbasvir ↑; atazanavir ↑** |
| **Ritonavir-boosted darunavir** | **Simeprevir ↑ ; darunavir ↔** | Sofosbuvir ↑ ; darunavir ↔ | Ledipasvir ↑, darunavir[a] ↔ (okay with TAF not TDF) | Daclatasvir ↑; darunavir ↔ | **Paritaprevir ↓/↑; darunavir ↓** | Paritaprevir ↑; darunavir ↔ | **Grazoprevir ↑; elbasvir ↑; darunavir ↔** |
| **Ritonavir-boosted lopinavir** | **No data** | No data | No data[a] | Daclatasvir ↑ ; lopinavir ↔ | **Paritaprevir ↑; lopinavir ↔** | **Paritaprevir ↑; lopinavir ↔** | **Grazoprevir ↑ ; elbasvir ↑; lopinavir ↔** |
| **Ritonavir-boosted tipranavir** | **No data** | **No data** | **No data** | **No data** | **No data** | **No data** | **No data** |
| **Efavirenz** | **Simeprevir ↓ ; efavirenz ↔** | Sofosbuvir ; efavirenz ↔ | Ledipasvir ↓ ; efavirenz ↓[a] | Daclatasvir ↓[b] | **No pharmacokinetic data[c]** | **No data** | **Grazoprevir ↓ ; elbasvir ↓ ; efavirenz ↓** |
| **Rilpivirine** | Simeprevir ↔ rilpivirine ↔ | Sofosbuvir ↔; rilpivirine ↔ | Ledipasvir ↔; rilpivirine ↔ | No data | **Paritaprevir ↑; rilpivirine ↑** | **No data** | Grazoprevir ↔ ; elbasvir ↔ ; rilpivirine ↔ |

[a]Only problematic when administered with tenofovir disoproxil fumarate; tenofovir levels are increased.
[b]Decrease daclatasvir dose to 30 mg once daily with atazanavir; increase daclatasvir dose to 90 mg once daily with efavirenz or etravirine.
[c]PrOD administered with efavirenz led to premature study discontinuation owing to toxic effects.

| Anti-HIV DRUG | Simeprevir | Sofosbuvir | Ledipasvir | Daclatasvir | Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD) | Paritaprevir, ritonavir, ombitasvir (PrO) | Grazoprevir/ Elbasvir |
|---|---|---|---|---|---|---|---|
| **Etravirine** | No data | No data | No data | Daclatasvir ↓[b] | No data | **No data** | **No data** |
| **Raltegravir** | Simeprevir ↔; raltegravir ↔ | Sofosbuvir ↔; raltegravir ↔ | Ledipasvir ↔; raltegravir ↔ | No data | PrOD ↔; ↑ raltegravir | PrO ↔; raltegravir ↑ | Grazoprevir ↔; elbasvir ↔; raltegravir ↑ |
| **Cobicistat-boosted elvitegravir** | **No data** | Cobicistat ↑[a]; sofosbuvir ↑ (okay with TAF not TDF) | Cobicistat ↑[a]; ledipasvir ↑ (okay with TAF not TDF) | No data | No data | **No data** | **No data** |
| **Dolutegravir** | No data | No data | Ledipasvir ↔; dolutegravir ↔ | Daclatasvir ↔; dolutegravir ↑ | Paritaprevir ↓; dolutegravir ↑ | No data | Grazoprevir ↔; elbasvir ↔; dolutegravir ↑ |
| **Maraviroc** | No data | No data | No data | No data | No data | No data | No data |
| **Tenofovir disoproxil fumarate** | Simeprevir ↔; tenofovir ↔ | Sofosbuvir ↔; tenofovir ↔ | Ledipasvir ↔; tenofovir ↑ | Daclatasvir ↔; tenofovir ↔ | PrOD ↔; tenofovir ↔ | Pro ↔; tenofovir ↔ | Grazoprevir ↔; elbasvir ↔; tenofovir ↑ |

[a]Only problematic when administered with tenofovir disoproxil fumarate; tenofovir levels are increased.
[b]Decrease daclatasvir dose to 30 mg once daily with atazanavir; increase daclatasvir dose to 90 mg once daily with efavirenz or etravirine.
[c]PrOD administered with efavirenz led to premature study discontinuation owing to toxic effects.

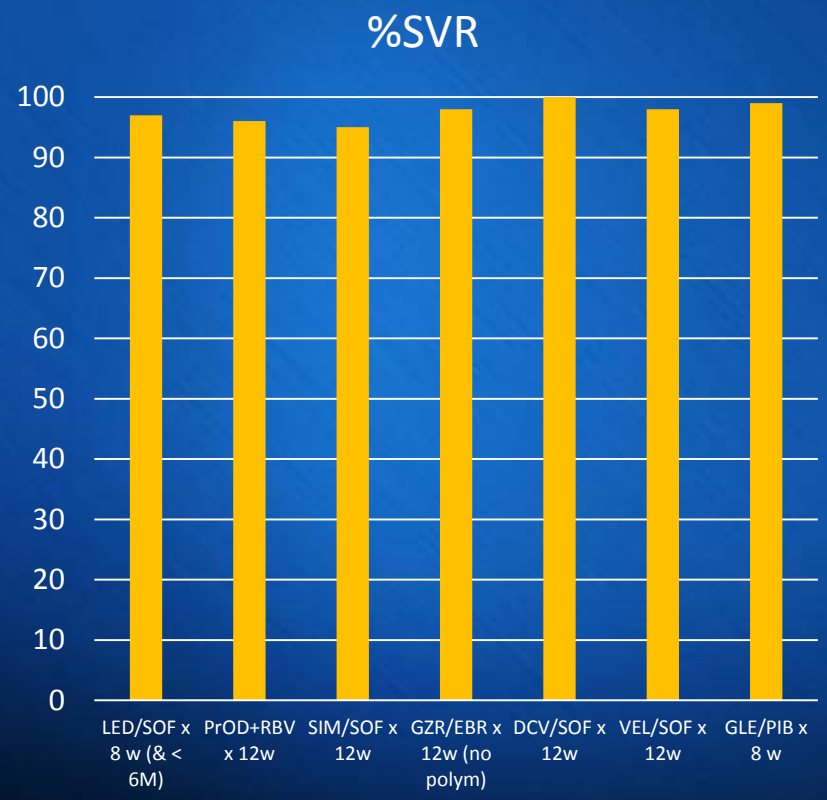
# Expected SVR with First Line Regimens

- Data is NOT comparative due to different populations, inclusion and exclusion criteria.
- There are not large head-to-head studies for true comparison

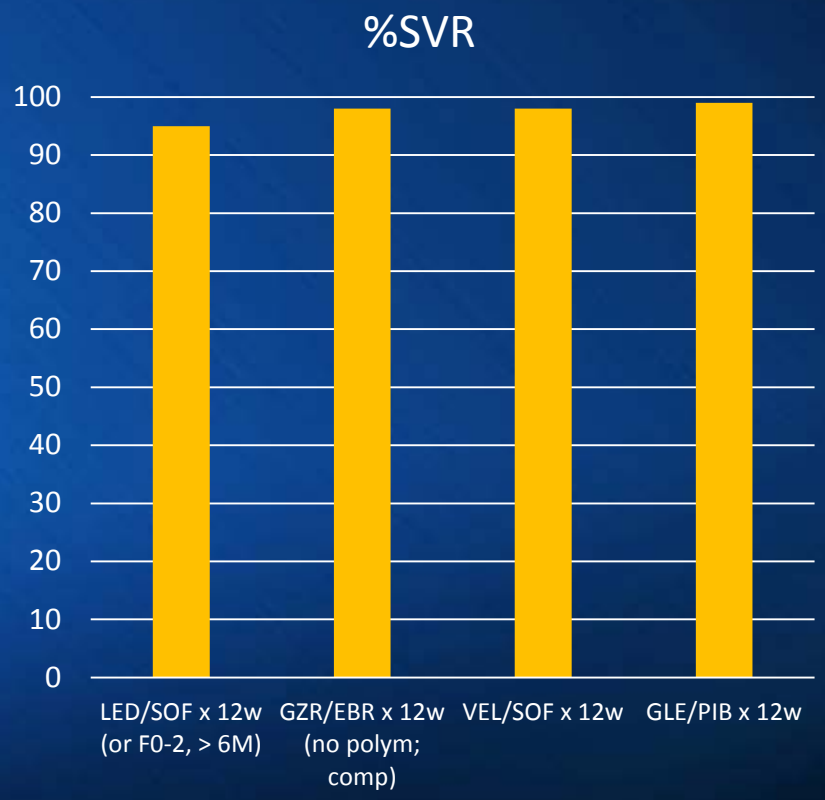
# NAÏVE: Genotype 1a or Unspecified

## First Line Therapy

### SVR in F0-2 only



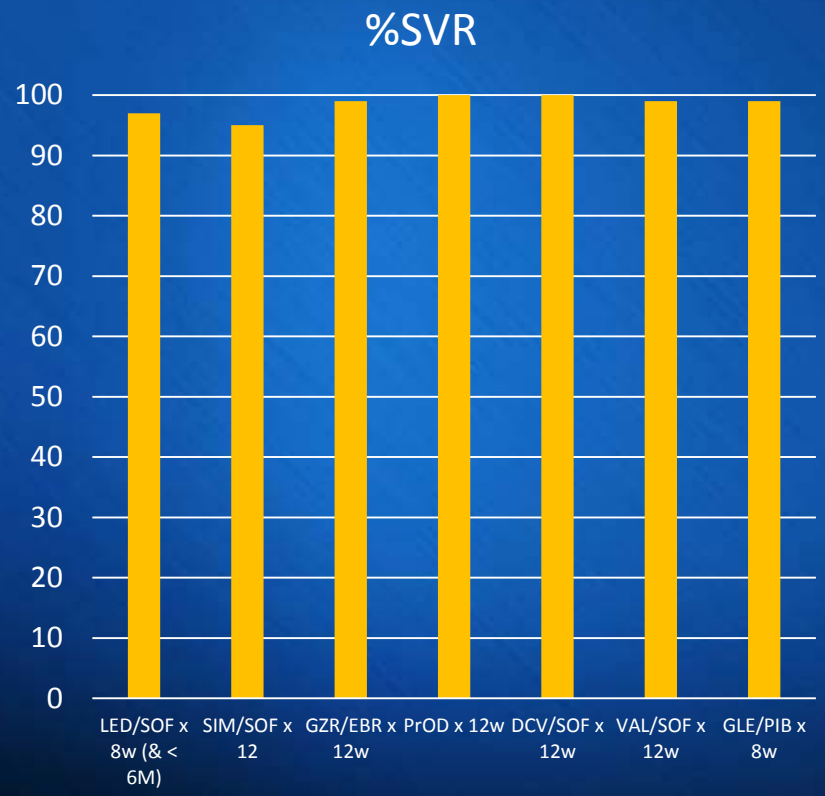

### SVR in F3-4



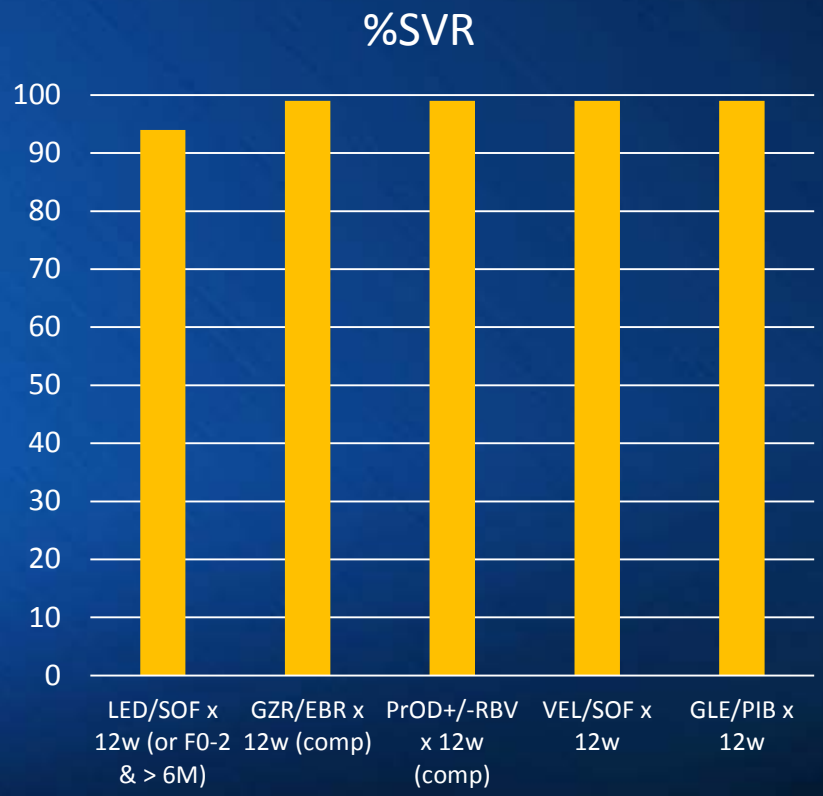
# Naïve: Genotype 1b

## First Line Therapy

### SVR in F0-2 only




### SVR in F3-4

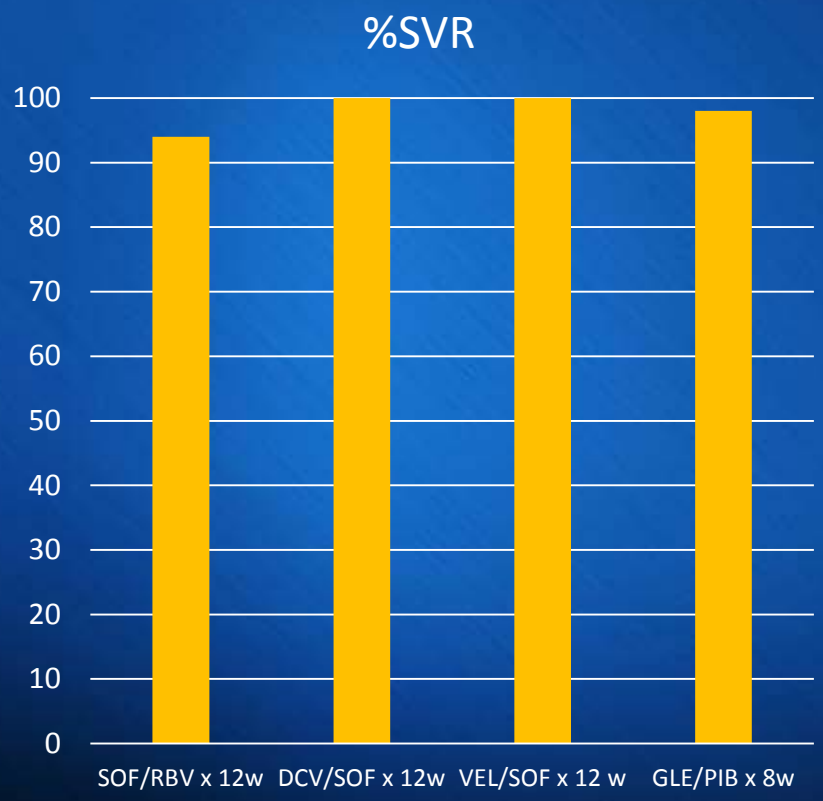



comp = compensated cirrhosis

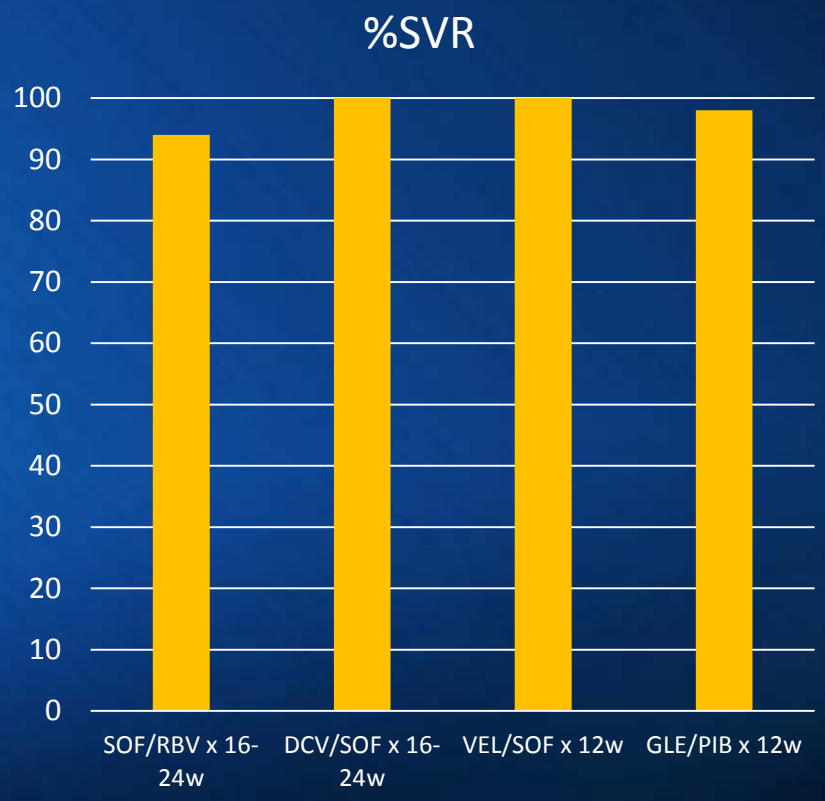
# Naïve: Genotype 2

## First Line Therapy

### SVR in F0-2 only



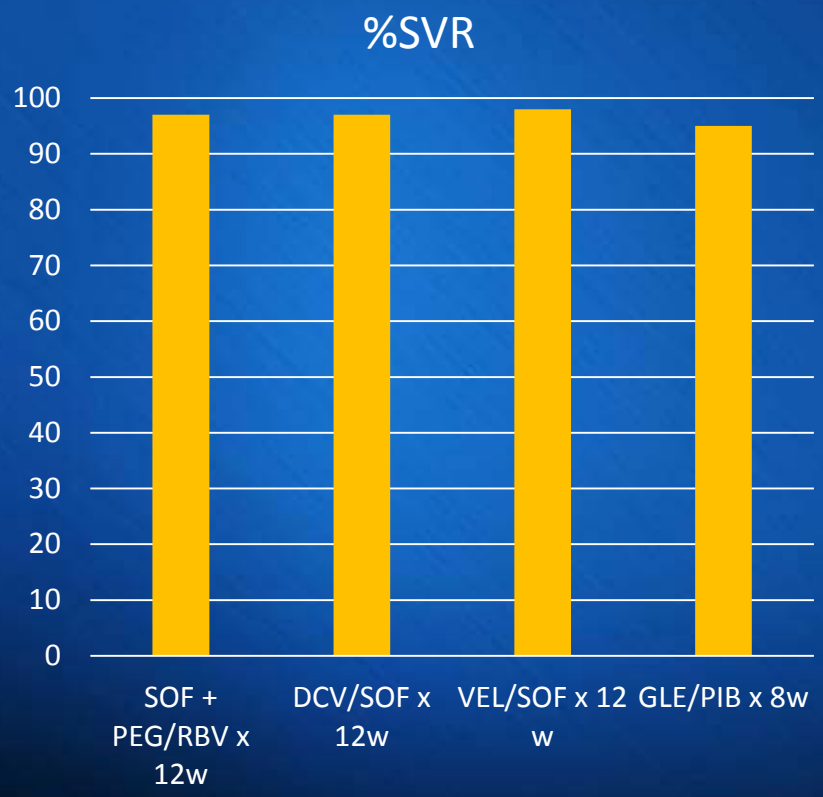

### SVR in F3-4



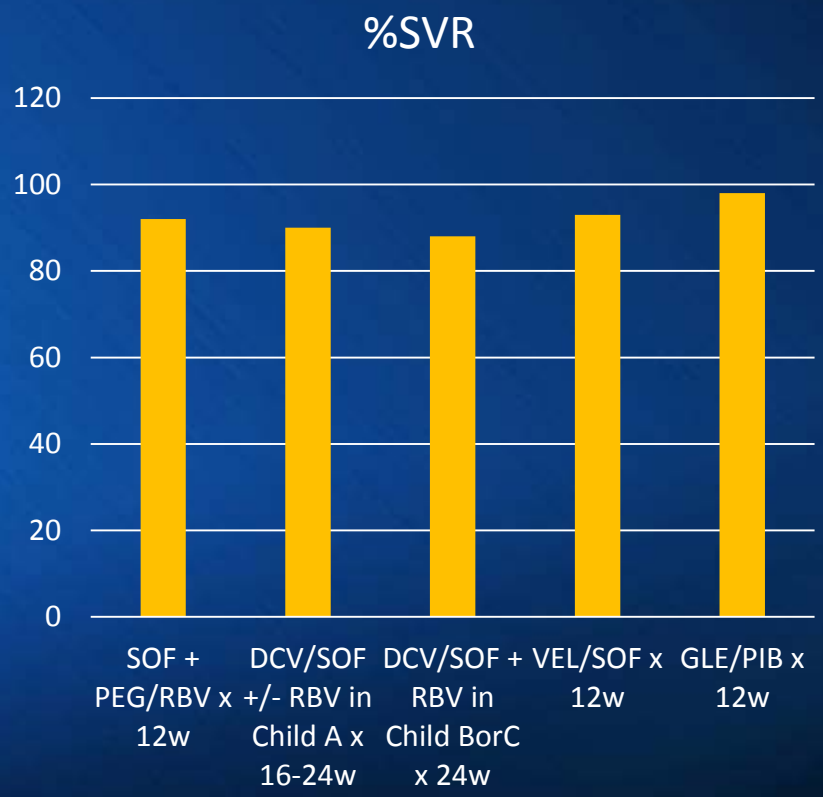
# Naïve: Genotype 3

## First Line Therapy

### SVR in F0-2 only



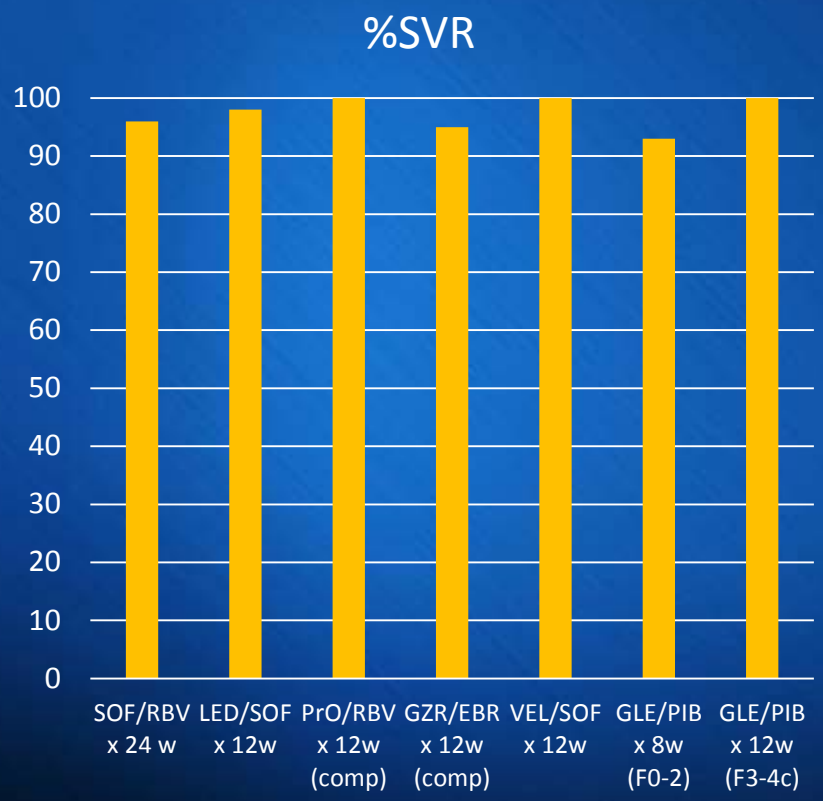

### SVR in F3-4



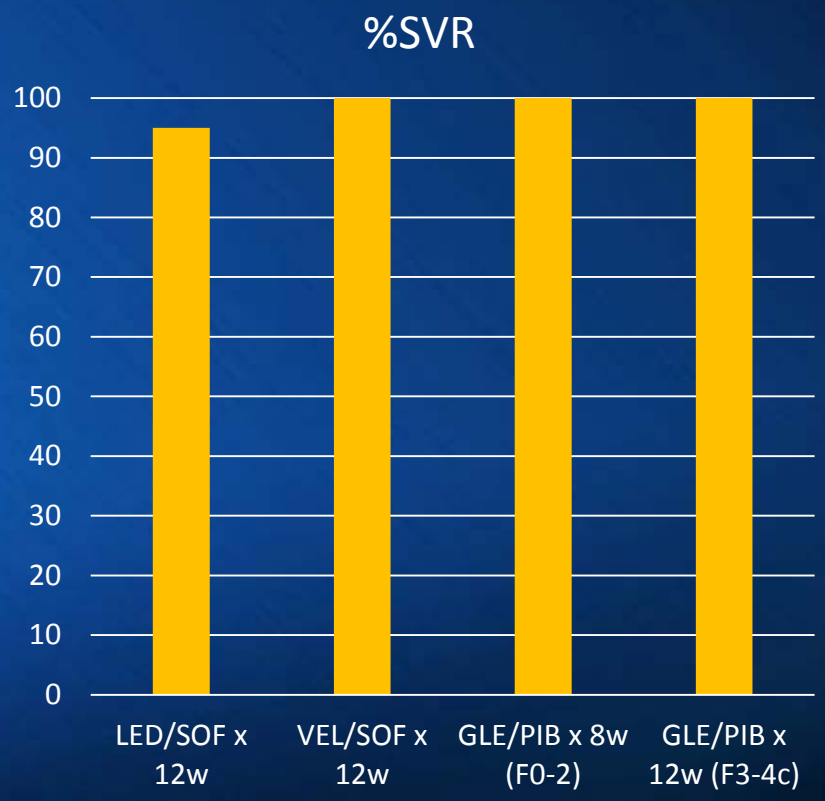
# Naïve: Genotypes 4, 5, and 6

## First Line Therapy

### SVR in Genotype 4



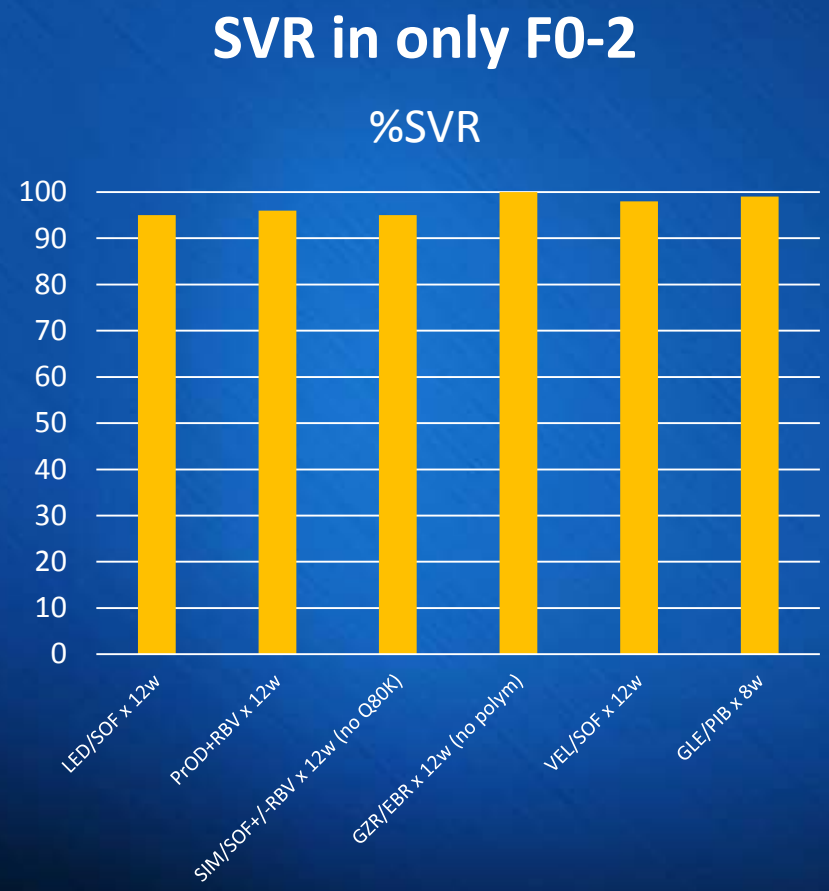

### SVR in Genotypes 5 & 6

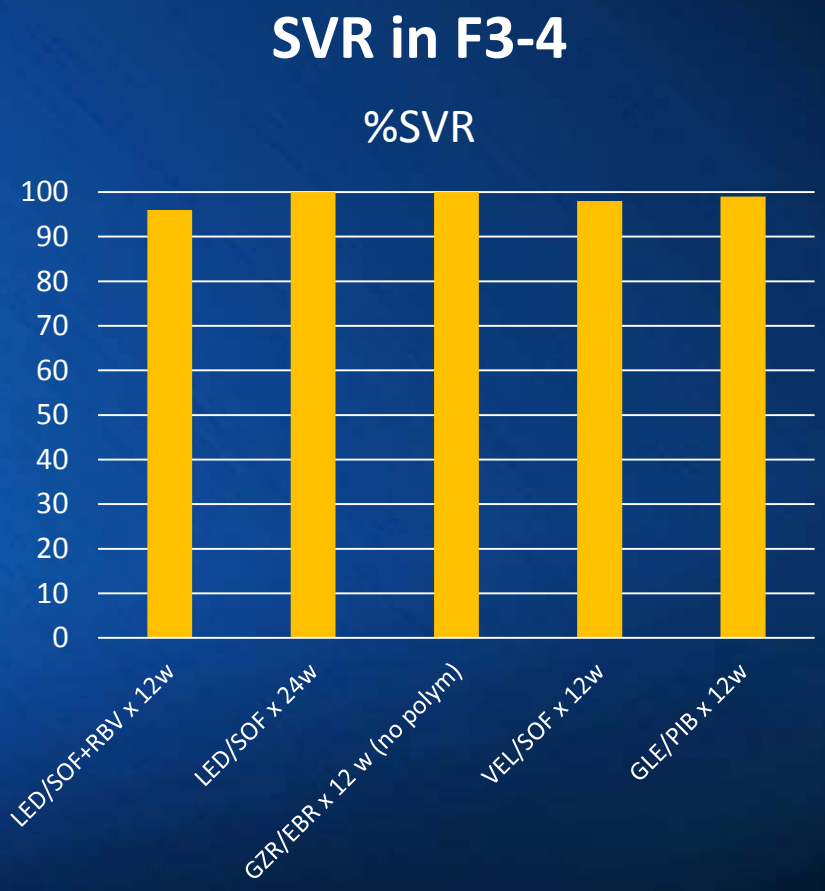



comp = compensated cirrhosis

# PegIFN NR: Genotype 1a or Unspecified

## First Line therapy

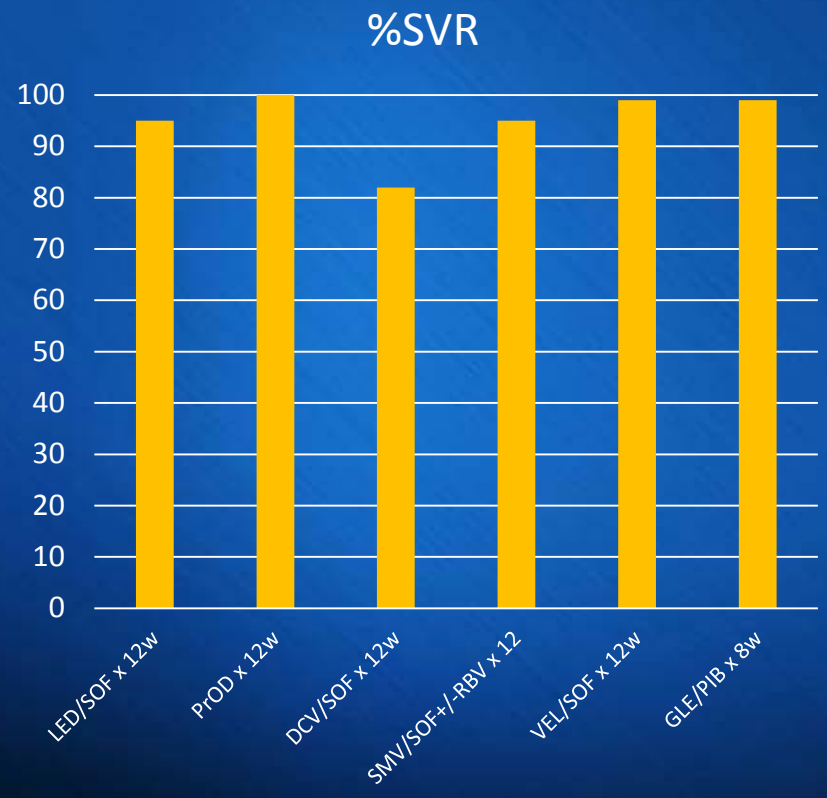


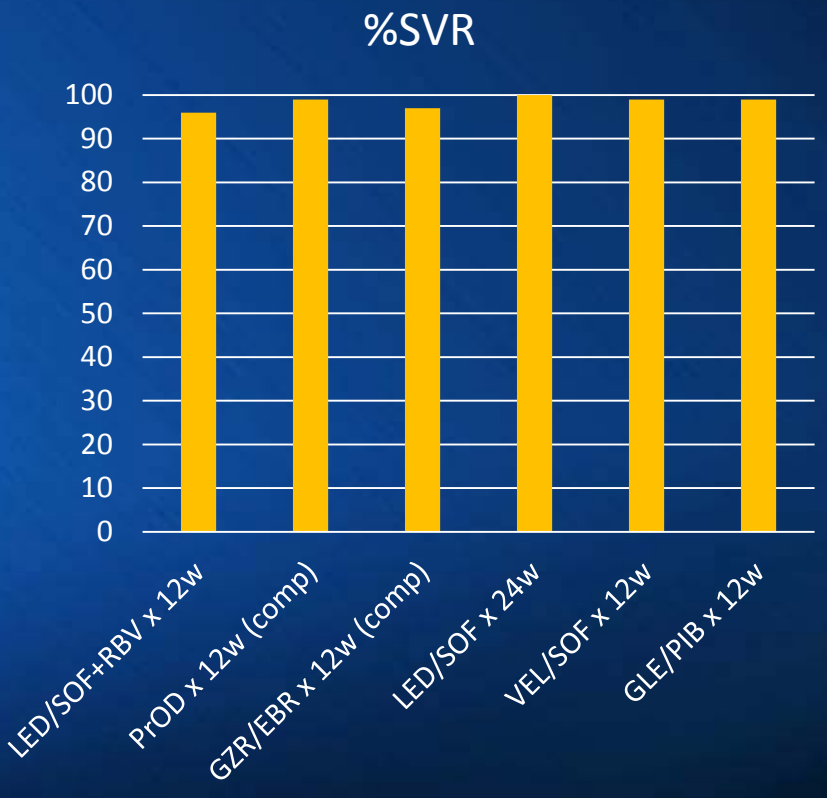
# PegIFN NR: Genotype 1b

## First Line Therapy

### SVR in F0-2 only

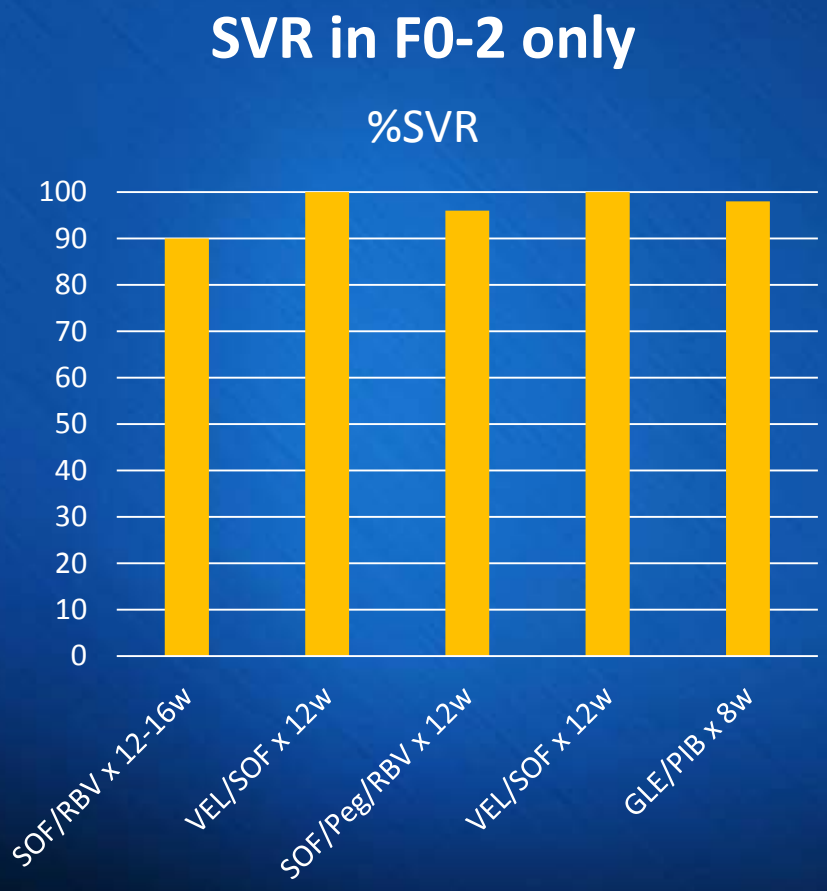


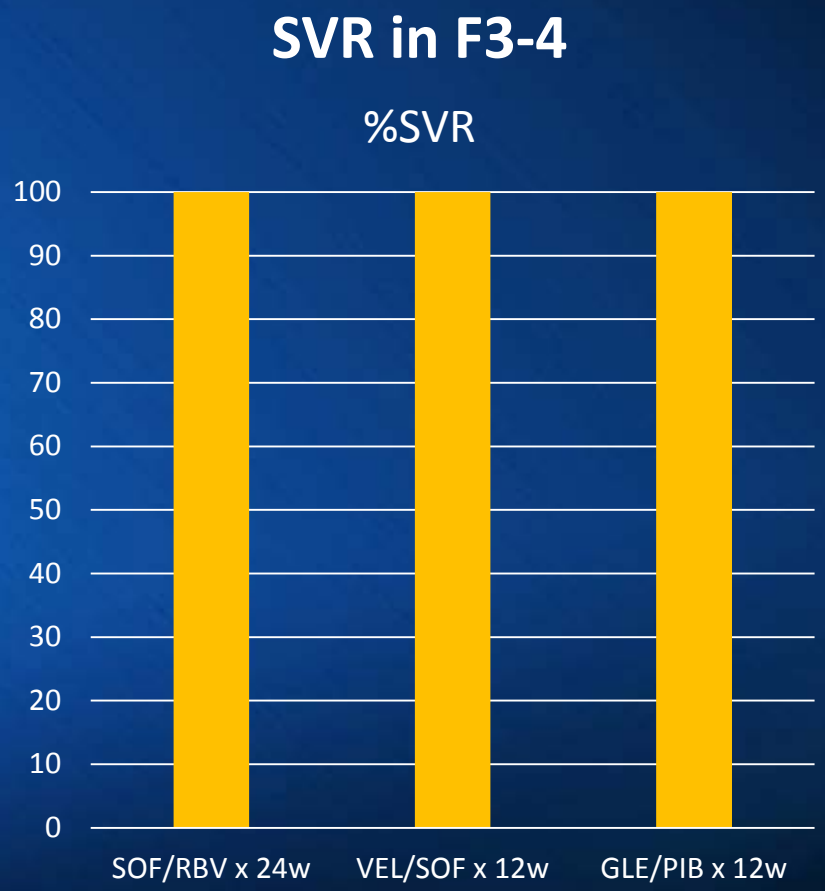

### SVR in F3-4




comp = compensated cirrhosis

# PegIFN NR: Genotype 2

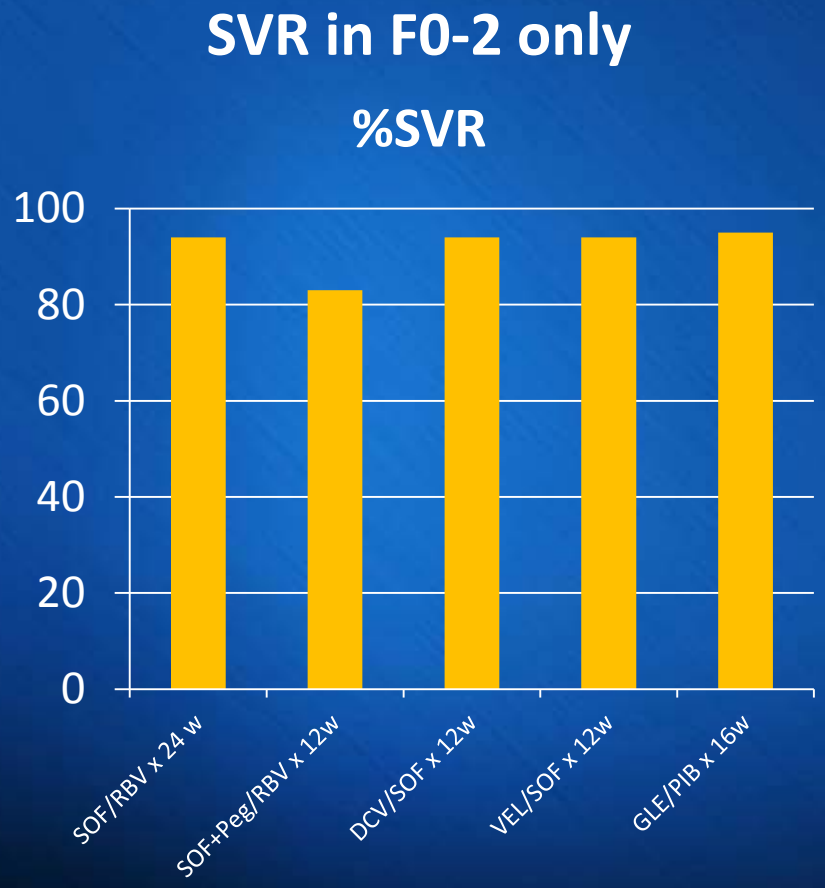


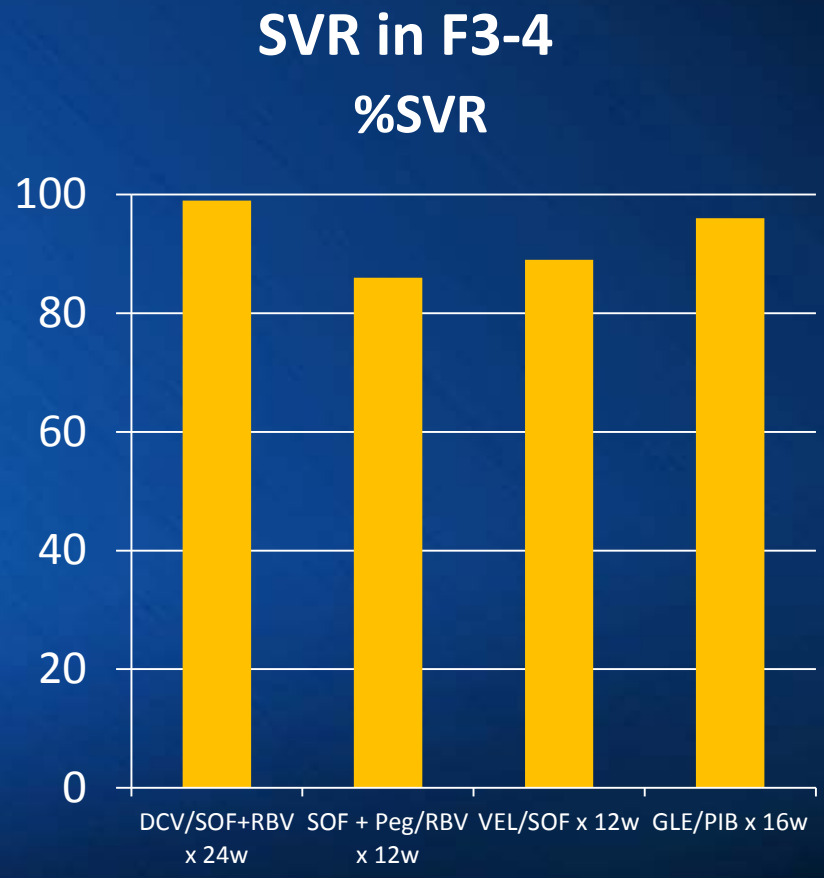




DCV/SOF +/- RBV is also recommended but there is not enough SVR data

# PegIFN NR: Genotype 3

## First Line Therapy

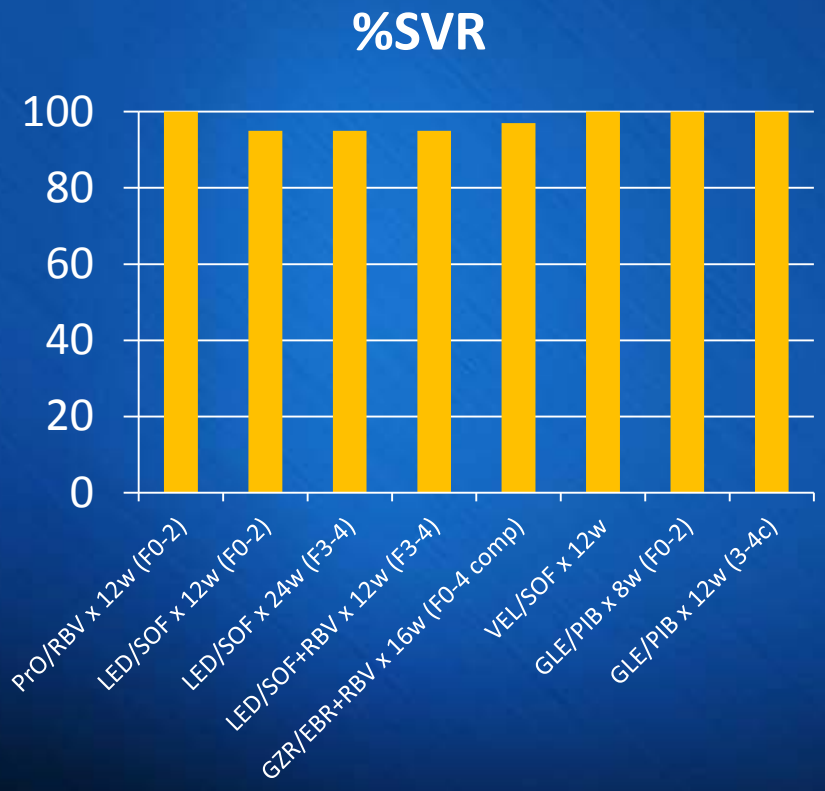


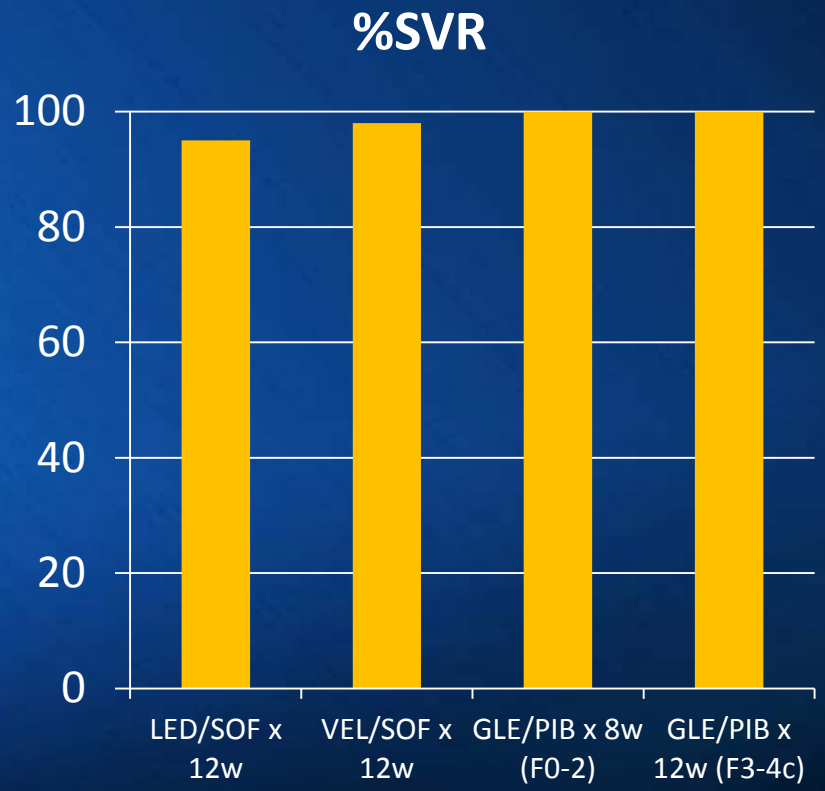
# PegIFN NR: Genotypes 4, 5, & 6

## First Line Therapy

### SVR Genotype 4




### SVR Genotypes 5 & 6




comp = compensated cirrhosis

# Treatment in Resistance to Direct Antiviral Agents

| No Response to Telaprevir or Boceprevir or Simeprivir | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| | F0-2: **SOF/LED 400/90** | **12** | 96% |
| | F0-2: **DAC 60 + SOF 400** | **12** | 95% ? |
| | F0-4c: **GLE 300 + PIB 120** (Geno 1,2,4,5,6)(Geno-3 is longer) | **F0-2: 8w; F3-4c: 12w<br>Geno-3 (F0-4c): 16 w** | 100% |
| | F0-4: **SOF/VEL 400/100** | **12** | 100% |
| | F0-4 comp: **GZR 100 + EBR 50 + RBV .8-1.4 g** | **12 (16 with RAS mutant)** | 96% |
| | F3-4: **SOF/LED 400/90 + RBV 1-1.2 g** | **12** | 97% |
| | F3-4: **SOF/LED 400/90** | **24** | 97% |
| | F3-4: **DAC 60 + SOF 400 +/- RBV 1-1.2 g** | **24** | 100% |
| **No Response to Sofosbuvir** | **Regimen** | **Duration (weeks)** | **SVR** |
| **Geno 1, 4, 5, 6<br>NS5A is (-) to RASs** | F3-4: **SOF/LED 400/90 + RBV 1-1.2** g | **24** | 100% |
| | F3-4: **SOF 400 + VEL 100 + RBV 1-1.2 g** | **24** | 96% |
| | F0-2 with urgent need for therapy: **SOF/LED 400/90 + RBV 1-1.2 g** | **12** | 100% |
| (Genotype 2 or 3 failure to SOF/RBV)<br>If in Urgent Need | **DAC 60 + SOF 400 + RBV 1-1.2** | **24** | 70%? |
| | **Geno 3 F0-4: SOF + VEL + VOX** | **12** | |
| | **SOF 400 + VEL 100 + RBV 1-1.2 g** | **12** | 91%(2), 76%(3) |
| | F0-4comp: **GZV 100 + EBR 50 + SOF 400 +/- RBV 1-1.2 g** | **12-16** | |
| **Geno 1-6 NS5A Resistant** | **F0-4: SOF + VEL + VOX** | **12** | 96-100%<br>(g4:91%; g3:95%) |
| **Geno 1 NS5A Resistant** | F0-4c: **GLE 300 + PIB 120** | **16** | 100% |
| **Geno 1, NS5A is (+) but NS3A is (-) to RASs** | **SMV/SOF 150/400** | **24** | ? |
| **Failures with SOF/VEL x 12w** | **SOF 400 + VEL 100 + RBV 1-1.2 g** | **24** | G-1: 98%<br>G-2: 100%<br>G-3: No RASs 100%;<br>G-3 with RASs: 77% |

RASs = Virus with "Resistance Associated Substitutions"

# Treatment of Decompensated Cirrhosis
## (Child-Pugh class B or C)

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| 1 o 4 | **SOF/LED 400/90 + RBV 600-1200** increasing as tolerated | **12**<br>**24** if SOF failure, or without RBV | 86% |
| | **SOF 400 + VEL 100 + RBV 1-1.2g** | **12** | 94% in g1a; 100% g1b<br>100% in g4 |
| | **SOF 400/DCV 60 + RBV 600-1000** | **12-24** with RBV<br><br>**24** without RBV | 12: g1:83%; g4: 100% -<br>24: close to 100% in g1<br>Unknown (without RBV) |
| | **GZR 50 + EBR 50 (C-P B, geno-1)**<br>**(no FDA approved)** | **12** | 95% |
| 2 | **SOF 400 + VEL 100 + RBV 1-1.2g** | **12** | 100% |
| | **SOF 400/DCV 60 + RBV 600-1000** | **12** (if Naive)<br>**24** (if previously treated) | 80% |
| | **SOF/LED 400/90 +/- RBV 600-1200**<br>**(no FDA approved)** | **12** | ? |
| 3 | **SOF 400/DCV 60 + RBV 600-1000** | **24** | 88% |
| | **SOF 400 + VEL 100 + RBV 1-1.2g** | **12** | 85% |
| 5, 6 | **SOF 400 + VEL 100 + RBV 1-1.2g** | **12** | N/A |

Ideally treated at the Transplant Center

# Treatment of HCV in CKD 4/5 +/- Hemodialysis (GFR < 30 mL/min)

| Genotype | Regimen | Duration (weeks) | SVR |
|---|---|---|---|
| Geno 1-6 (F0-4c) | **GLE 300 + PIB 120** | **F0-2: 8 w**<br>**F3-4c: 12 w**<br>**Geno-3 with PR or Sof Failure: 16 w**<br>**PrOD or Zepatier Failure: 16 w** | 98-100% |
| 1a & 1 b (F0-3) | **PrOD** (+ RBV 200 TIW in 1a) | **12** | 90% |
| 1 & 4 (F0-4comp) (probably also 2, 5, y 6) | **GZR 100 + EBR 50**<br>In genotype 1a with M28, Y93, Q30, or L31 polymorphism:<br>GZR 100 + EBR 50 + RBV 100-200 mg | **12**<br>**16** | 99% in geno-1 |
| 2, 3, 5, 6 (F0-4comp) | **PegIFN + RBV 200** a day | **24-48 weeks** | |

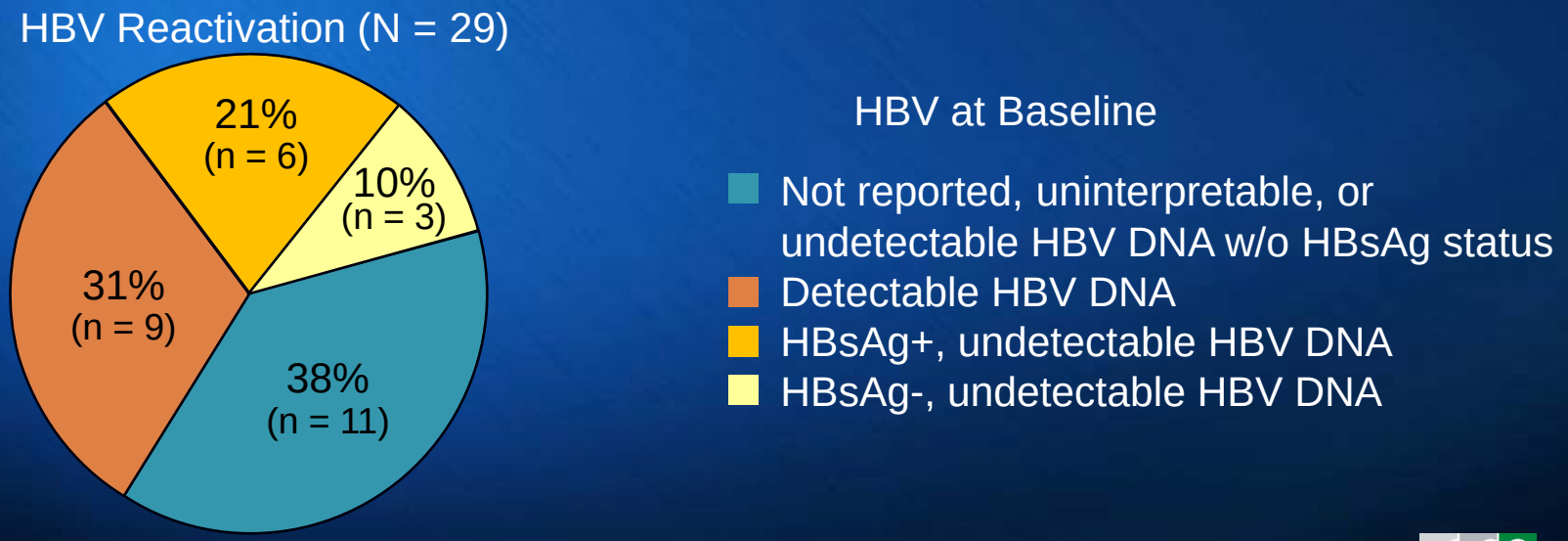
Patients with GFR > 30 mL/min can be treated with standard doses of other regimens

# Treatment of HIV/HCV Co-infected Patients

- ***Patients with HCV-HIV co-infection should be treated with the same regimen as HCV mono-infected patients.***
- **SOF/LED (HARVONI):**
  - African-American patients respond less to Harvoni.
  - The theoretical risk of Renal damage from Tenofovir in patients receiving Atripla has not been seen in the clinical trials.
  - Treatments of only 8 weeks with Harvoni or with DAC + SOF are probably insufficient for co-infection; treat for 12 weeks.
  - Harvoni should not be given with Tenofovir if the GFR is < 60 mL/min, and should not be co-administer with Protease Inhibitors boosted with Ritonavir.
- **PrOD (Viekira Pak):** should not be given to co-infected patients who are not receiving anti-HIV therapy.
- **DAC + SOF:** Patients receiving darunavir/r could have inferior response.
- **RIBAVIRIN:** Do not give to patients taking didanosine, stavudine, or zidovudine.
- ***DO NOT INTERRUPT ANTI-HIV THERAPY.***

# HBV Reactivation in Pts Receiving DAAs: Postmarketing Cases Reported to FDA

- Case reports of HBV reactivation in pts receiving DAAs
  - Reactivation: increase in HBV DNA or seroconversion to HBsAg positive
- 29 confirmed cases in ~ 3 yrs (November 2013 to October 2016)
  - Pts from Japan (n = 19), US (n = 5), other (n = 5)
  - Most cases occurred within 4-8 wks of initiation
  - 2 deaths, 1 transplant, 6 hospitalizations, 10 DAA discontinuations

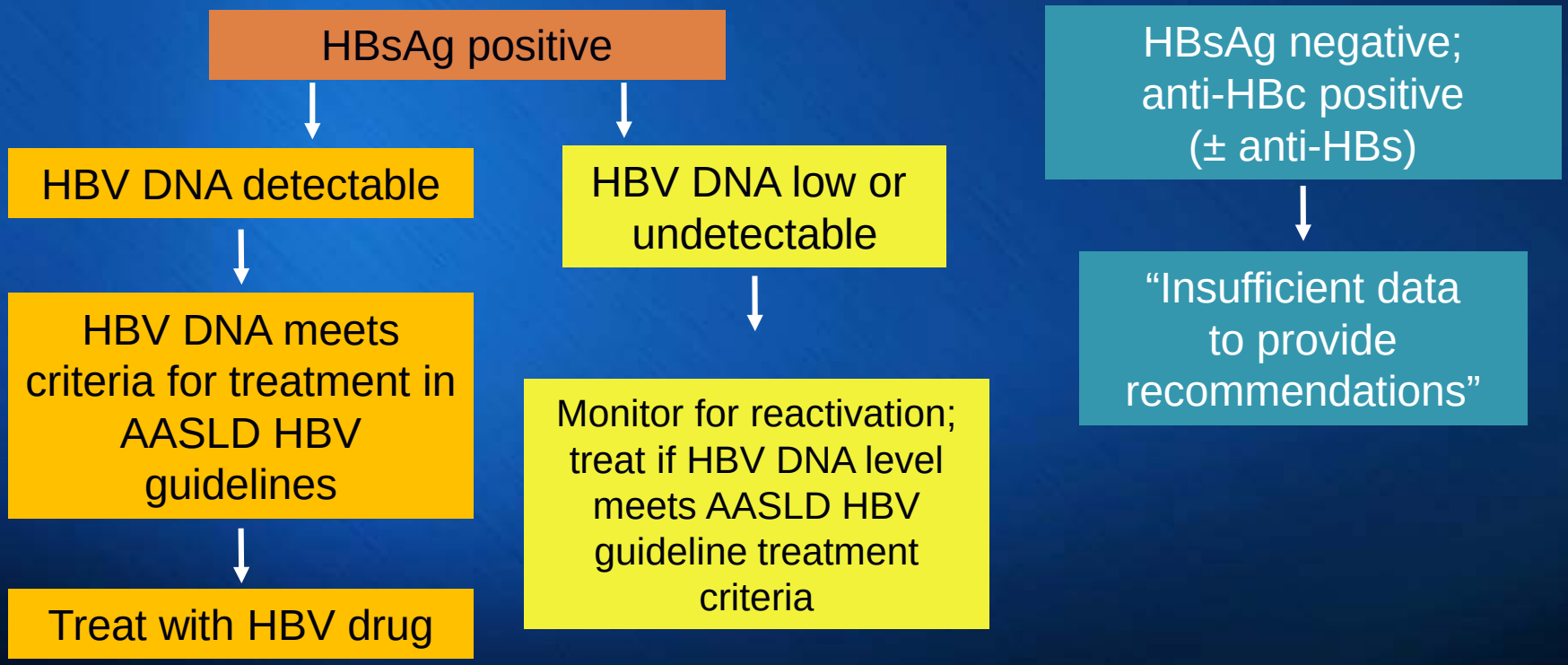



Bersoff-Matcha SJ, et al. AASLD 2016. Abstract LB17.

Slide credit: clinicaloptions.com

# HBV Testing and Monitoring During HCV DAA Therapy: AASLD/IDSA Guidance

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - No HBV markers: VACCINATE (this is not new)
  - HBV markers present:




AASLD/IDSA. HCV guidance. September 2016.
Graphic created by Ira M. Jacobson, MD.

Slide credit: clinicaloptions.com

# Follow up During Therapy

- Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (GFR), and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated.
  - More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving RBV) is recommended as clinically indicated.
- Thyroid-stimulating hormone (TSH) is recommended every 12 weeks for patients receiving IFN.

# Follow up During Therapy

- Any 10-fold increase in alanine aminotransferase (ALT) activity at week 4 should prompt discontinuation of therapy.
- Any increase in ALT of less than 10-fold at week 4 if accompanied by any weakness, nausea, vomiting, jaundice, or increased bilirubin, alkaline phosphatase, or international normalized ratio should also prompt discontinuation of therapy.
- Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should be closely monitored and repeated at week 6 and week 8. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.

# Follow up During Therapy

- Patients with compensated cirrhosis‡ who are receiving paritaprevir/ritonavir-based regimens should be assessed for clinical signs of decompensated liver disease (eg, ascites, encephalopathy) and for biochemical evidence of liver injury Rating: Class I, Level A
  - with a hepatic function panel at week 2 and week 4 of treatment, and as needed during the remainder of treatment.
  - Paritaprevir/ritonavir-based regimens should be discontinued if patients develop ascites or encephalopathy or a significant increase in direct bilirubin or ALT or AST.
- For HBsAg+ patients who are not already on HBV suppressive therapy Rating: Class IIa, Level B
  - monitoring of HBV DNA levels during and immediately after DAA therapy for HCV is recommended, and
  - antiviral treatment for HBV should be given if treatment criteria for HBV are met.

# Follow up During Therapy

- If quantitative HCV viral load is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6).
  - If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended.
- The significance of a positive HCV RNA test result at week 4 that remains positive, but lower, at week 6 or week 8 is unknown. No recommendation to stop therapy or extend therapy can be provided at this time.

# Management after Treatment

- Patients are considered “cured from hepatitis C” if the HCV-RNA is negative 12 weeks after the end of therapy.
  - Is reasonable to confirm cure 18 months after the end of therapy.
- Patients with “early disease” (F0-2) can be discharged if cured.
- Patients with “advanced disease” (F3-4) need long-term follow-up with:
  - Liver Ultrasound every 6 months to R/O HCC;
  - Clinical and Laboratory follow up for early detection of complications from cirrhosis or portal hypertension,
  - Patients with cirrhosis should be evaluated for gastro-esophageal varices with EGD.
- Non-Responder patients:
  - Need to be considered for re-treatment, under the care of a Hepatologist or other expert.
  - Should be evaluated for disease progression every 6-12 months with CBC, Hepatic Panel, and PT/INR.

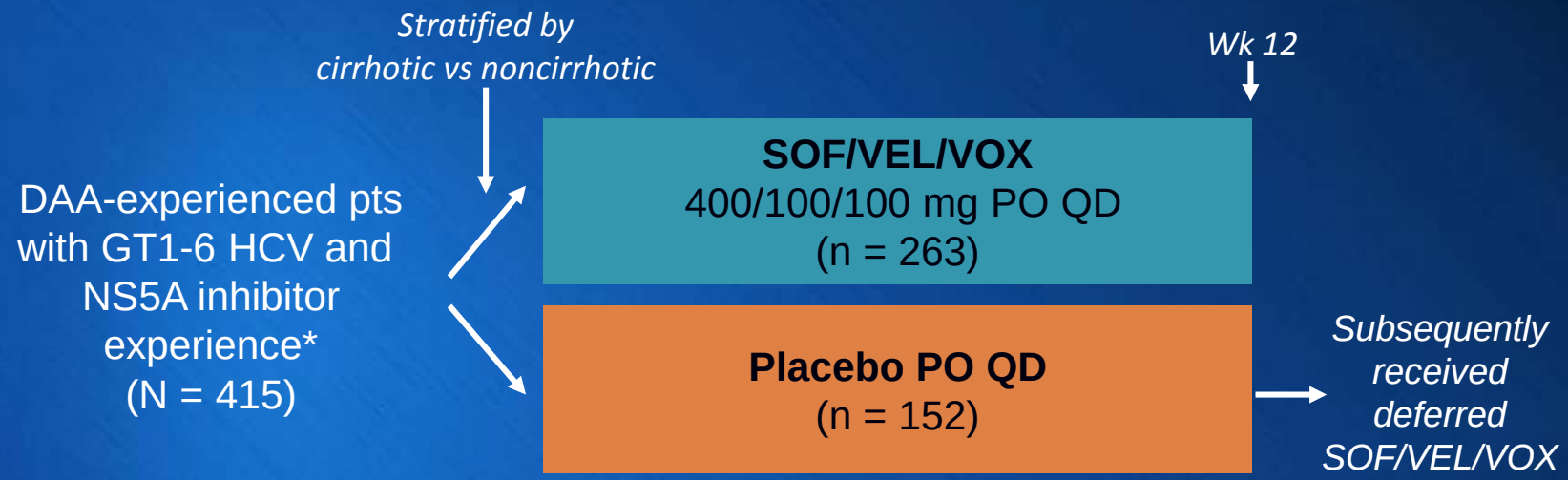
# Summary of Investigational Direct-Acting Antivirals Discussed in This Slideset

| Drug | Abbreviation | Class |
|---|---|---|
| Glecaprevir (formerly ABT-493) | GLE | NS3/4A protease inhibitor |
| Voxilaprevir | VOX | NS3/4A protease inhibitor |
| Pibrentasvir (formerly ABT-530) | PIB | NS5A inhibitor |
| Ruzasvir (formerly MK-8408) | RZR | NS5A inhibitor |
| MK-3682 | -- | NS5B polymerase nucleotide inhibitor |

Slide credit: clinicaloptions.com

# POLARIS-1: SOF/VEL/VOX (Vosevi®) for 12 Wks After NS5A Failure in GT1-6 HCV

- Randomized, double-blind, placebo-controlled phase III trial




*Pts with GT1 HCV at screening equally randomized between arms; pts with GT2-6 HCV assigned to active treatment arm.

- Previous NS5A treatment in SOF/VEL/VOX group (n = 263)
  - LDV, 51%; DCV, 27%; OBV, 11%; other, 13%
- Cirrhosis definition for POLARIS studies: METAVIR F4 or Ishak 5-6 on biopsy, *or FibroTest* > 0.75 + APRI > 2, *or FibroScan* > 12.5 kPa

Bourlière M, et al. AASLD 2016. Abstract 194.

Slide credit: clinicaloptions.com

# POLARIS-1: SVR12 Rates With 12-Wk SOF/VEL/VOX (Vosevi®) in Previous NS5A Failure

| SVR12, % (n/N) | SOF/VEL/VOX |
|---|---|
| Overall | 96 (253/263) |
| Cirrhosis status | |
| ▪ No cirrhosis | 99 (140/142) |
| ▪ Cirrhosis | 93 (113/121) |
| Baseline RAVs | |
| ▪ None | 98 (42/43) |
| ▪ Any | 96 (199/208) |

| SVR12, % (n/N) | SOF/VEL/VOX |
|---|---|
| Genotype | |
| ▪ 1a | 96 (97/101) |
| ▪ 1b | 100 (45/45) |
| ▪ 2 | 100 (5/5) |
| ▪ 3 | 95 (74/78) |
| ▪ 4 | 91 (20/22) |
| ▪ 5 | 100 (1/1) |
| ▪ 6 | 100 (6/6) |

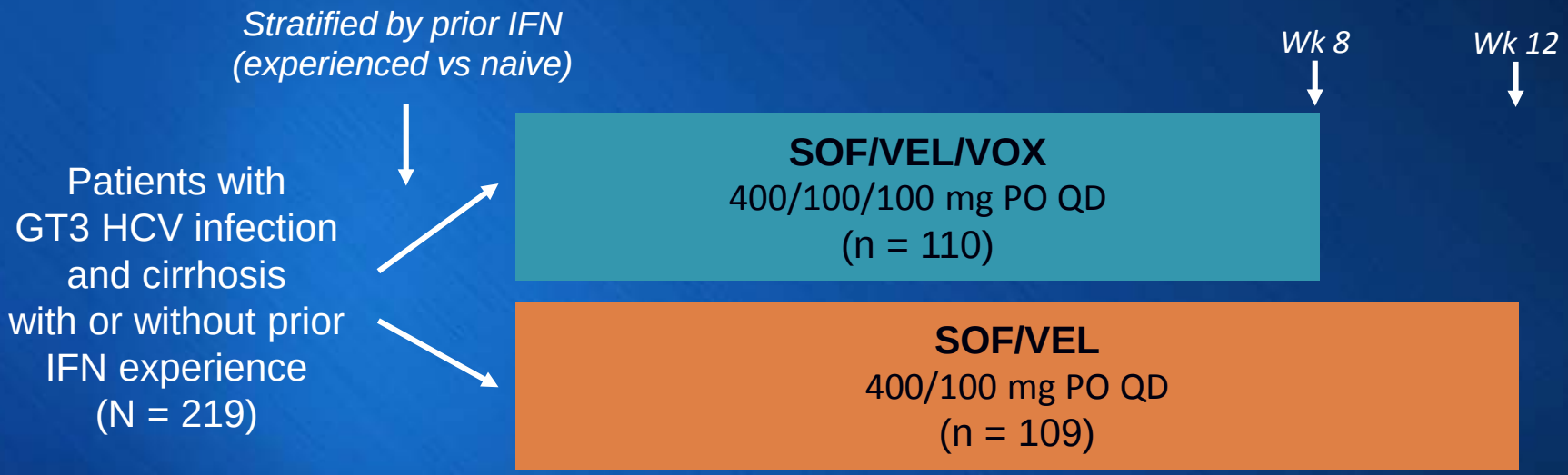
- 7 virologic failures; all cirrhotic pts (GT1a, n = 2; GT3, n = 4; GT4, n = 1)

Bourlière M, et al. AASLD 2016. Abstract 194.

Slide credit: clinicaloptions.com

# POLARIS-3: 8-Wk SOF/VEL/VOX (Vosevi®) vs 12-Wk SOF/VEL for Cirrhotic, DAA Naive GT3

- Randomized, open-label, active-controlled phase III trial

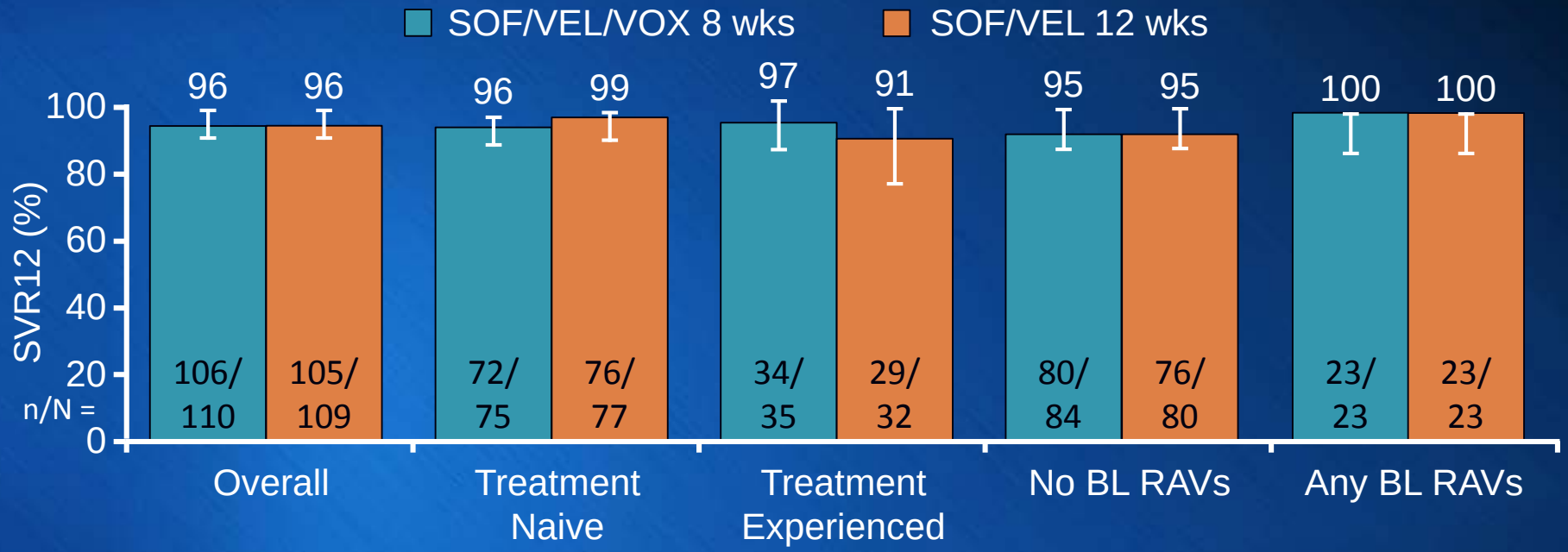



- IFN experience in 29% to 32% of pts

Foster GR, et al. AASLD 2016. Abstract 258.

Slide credit: clinicaloptions.com

# POLARIS-3: SVR12 Rates With 8-Wk SOF/VEL/VOX (Vosevi®) for Cirrhotic GT3 Pts

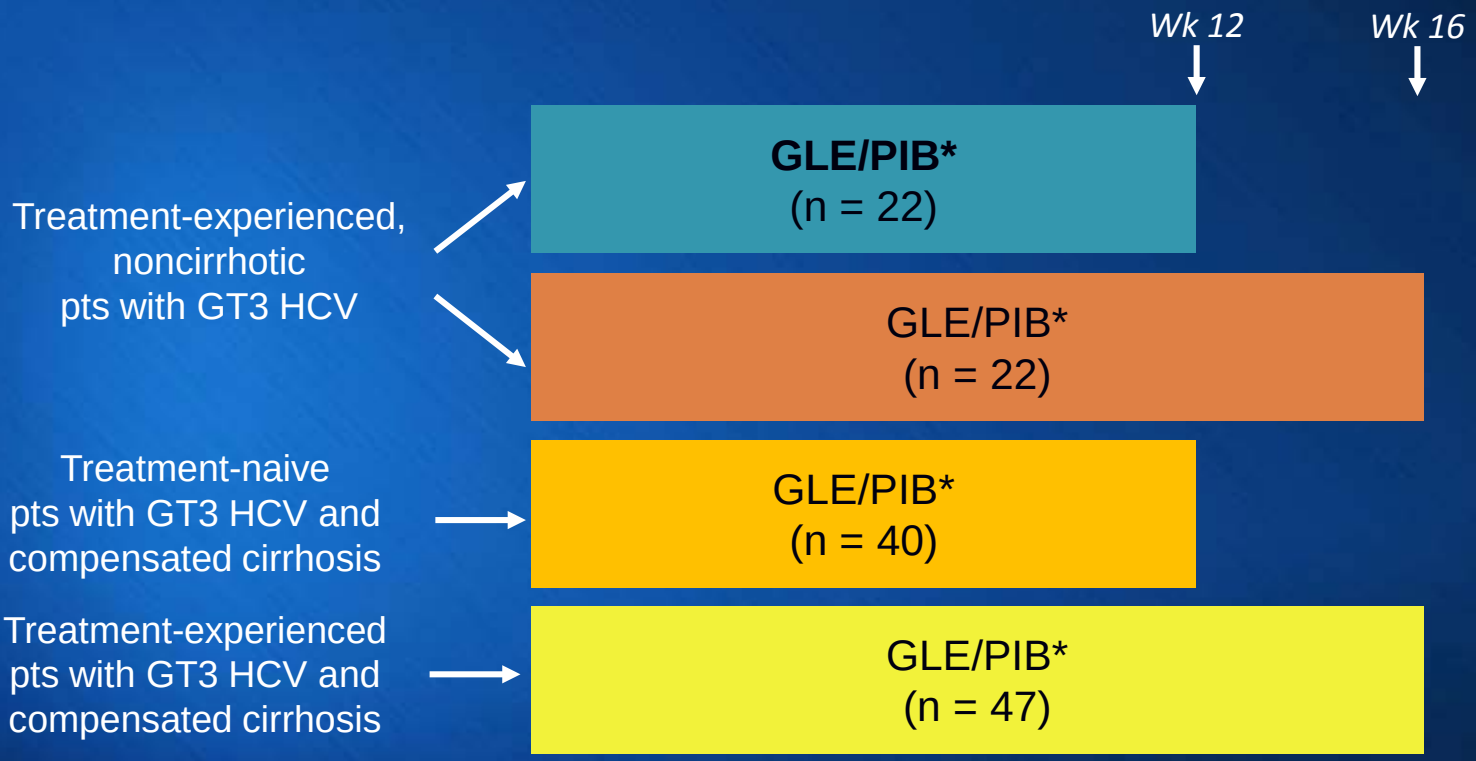



- Both regimens: *P* < .001 for superiority vs prespecified 83% goal
- Overall VF: SOF/VEL/VOX, n = 2 relapses; SOF/VEL, n = 1 each for relapse and on-treatment failure
- No treatment-emergent RAVs in SOF/VEL/VOX arm; Y93H in both virologic failures in SOF/VEL arm

Foster GR, et al. AASLD 2016. Abstract 258. Reproduced with permission. Slide credit: clinicaloptions.com

# SURVEYOR-II, Part 3: GLE/PIB (Mavyret) for Pts With GT3 HCV ± Cirrhosis

- Partially randomized, open-label phase II trial (N = 131)



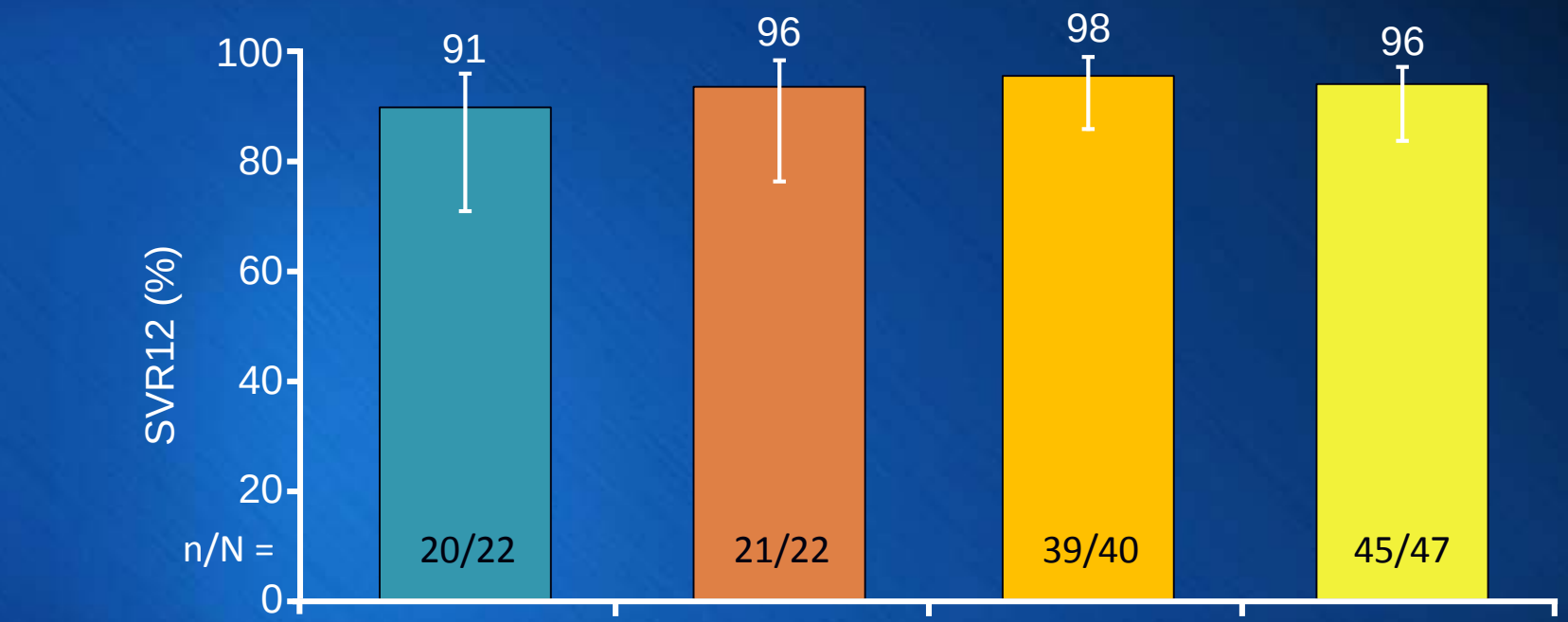

- Prior treatment experience consisted of IFN or pegIFN ± RBV or SOF + RBV ± pegIFN

*Dosing: GLE/PIB given as 3 coformulated 100/40 mg tablets QD for a total dose of 300/120 mg.

Wyles DL, et al. AASLD 2016. Abstract 113.

Slide credit: clinicaloptions.com

# SURVEYOR-II, Part 3: SVR12 Rates With GLE/PIB (Mavyret) for Pts With GT3 HCV ± Cirrhosis



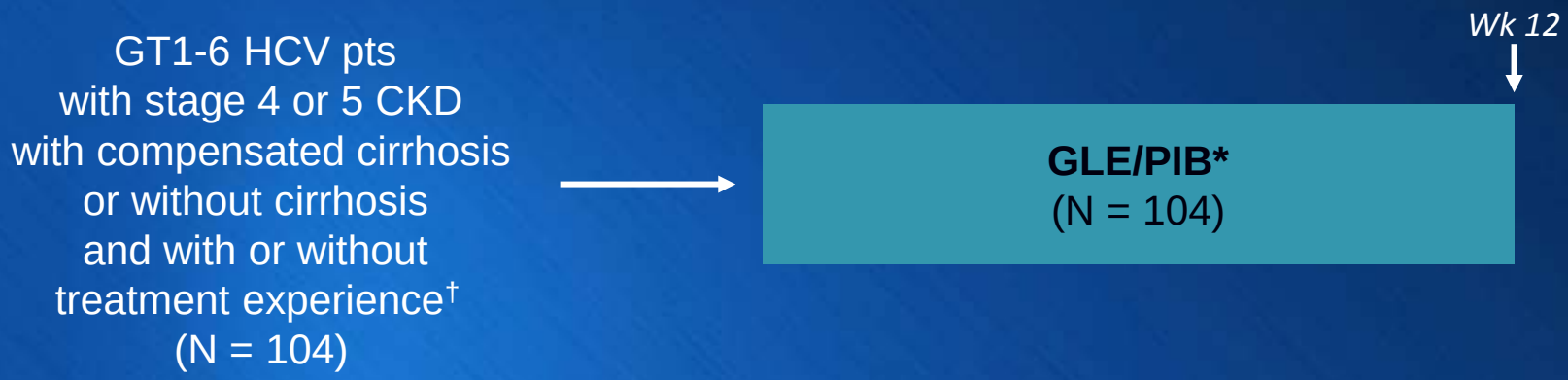

| | | | | |
|---|---|---|---|---|
| Tx Wks | 12 | 16 | 12 | 16 |
| Cirrhosis | - | - | + | + |
| Tx Experienced | + | + | - | + |
| Breakthrough | 0 | 0 | 0 | 1 |
| Relapse | 2 | 1 | 0 | 1 |
| LTFU | 0 | 0 | 1 | 0 |

Wyles DL, et al. AASLD 2016. Abstract 113. Reproduced with permission.

Slide credit: clinicaloptions.com

# EXPEDITION-IV: GLE/PIB (Mavyret) for Pts With GT1-6 HCV and Renal Impairment

- Open-label, single-arm phase III trial




- At baseline, 82% on hemodialysis; 19% cirrhotic; 42% treatment experienced
- SVR12 rate of **98%** (ITT; n/N = 102‡/104)

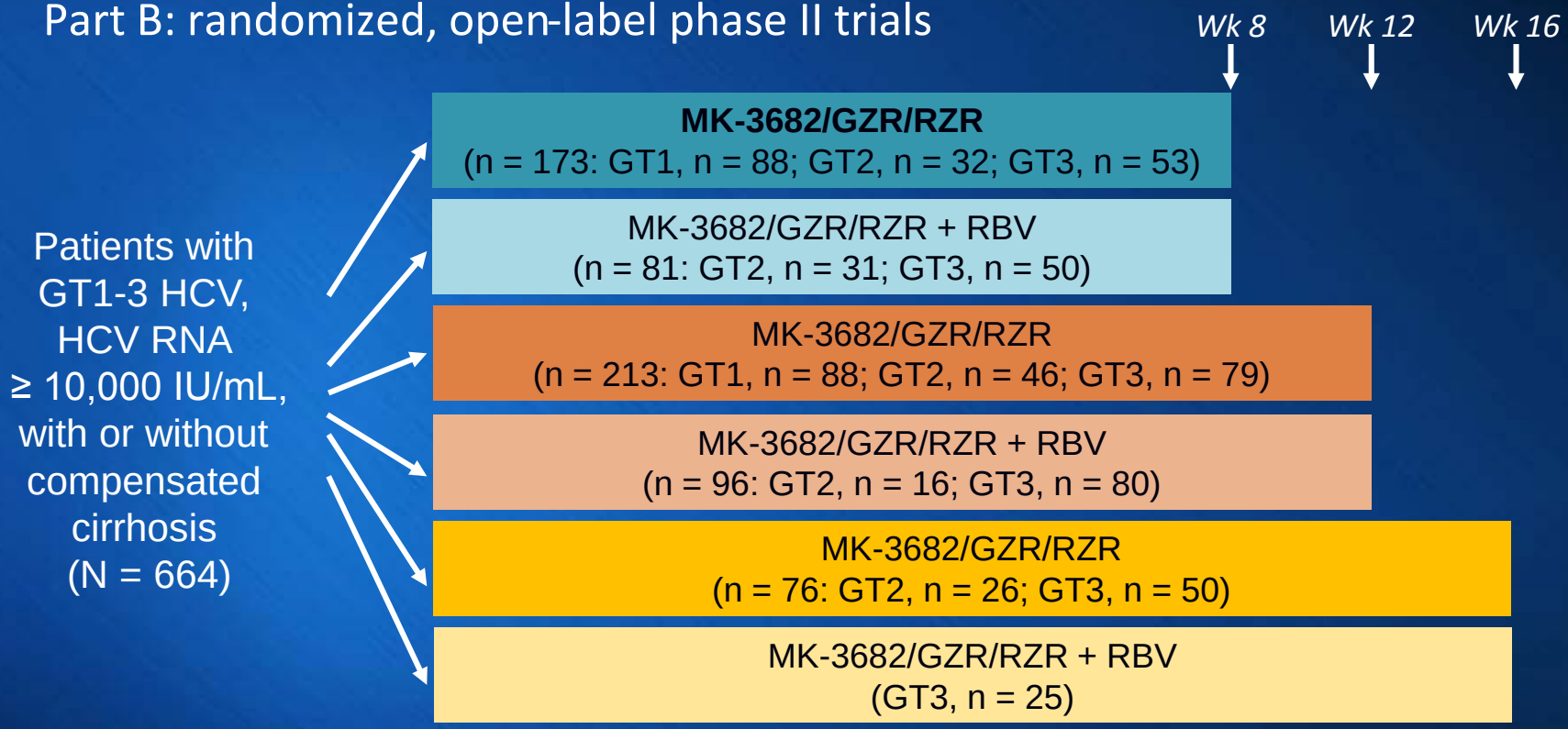
*Dosing: GLE/PIB given as 3 coformulated 100/40-mg tablets QD for a total dose of 300/120 mg.
†Prior treatment experience consisted of IFN or pegIFN ± RBV or SOF + RBV ± pegIFN.
‡1 pt d/c, 1 pt LTFU in ITT analysis of SVR12.

Gane EJ, et al. AASLD 2016. Abstract LB11.

Slide credit: clinicaloptions.com

# C-CREST 1 & 2: MK-3682/GZR/RZR ± RBV for Treating Pts With GT1-3 HCV

- Part B: randomized, open-label phase II trials



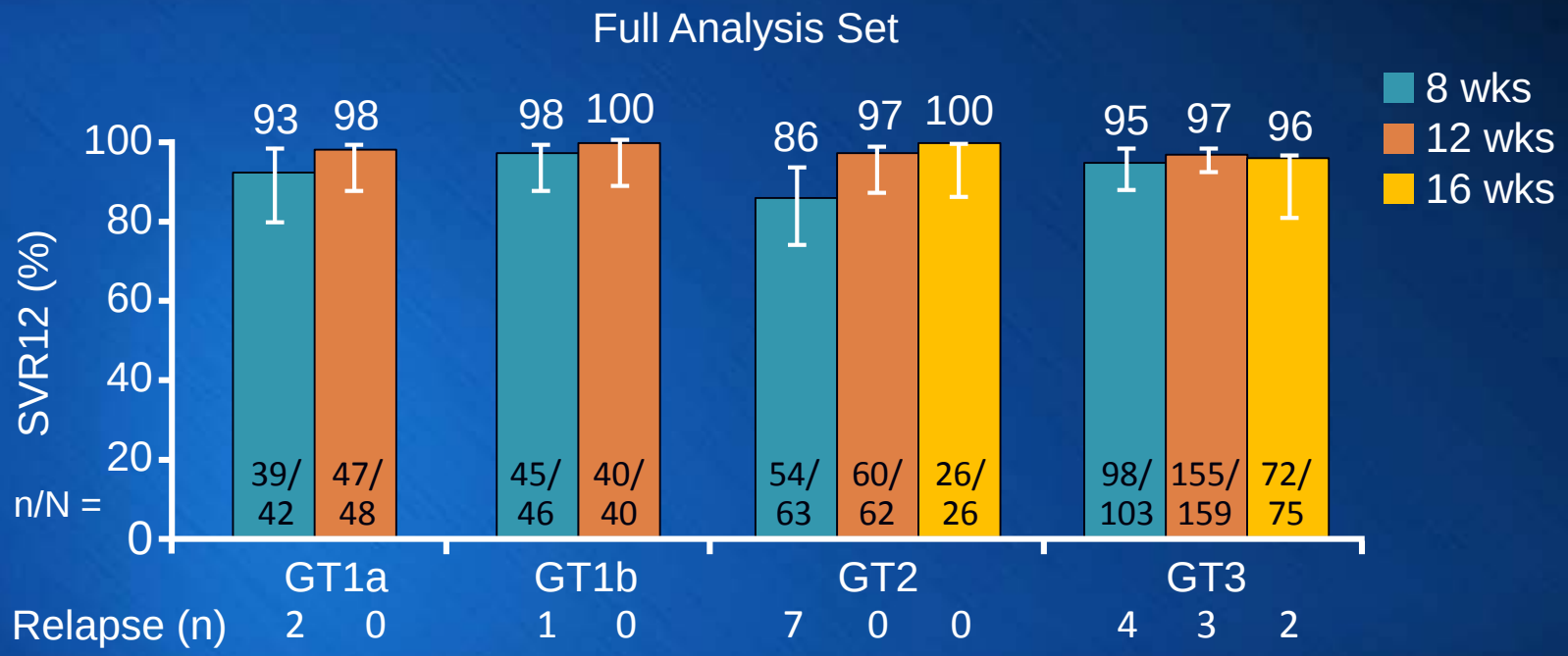

Dosing: MK-3682/GZR/RZR dosed as two 225/50/30-mg tablets QD. Pts with GT3 HCV could be treatment naive or have failed on pegIFN/RBV; all others treatment naive. Cirrhosis definition in notes.

- Baseline: 35% to 43% cirrhotic; 44% of GT3 pts had prior pegIFN/RBV

Lawitz E, et al. AASLD 2016. Abstract 110.

Slide credit: clinicaloptions.com

# C-CREST 1 & 2: Efficacy of MK-3682/ GZR/RZR ± RBV for Pts With GT1-3 HCV




- Presence of cirrhosis, use of ribavirin, prior tx experience did not impact SVR12 rates

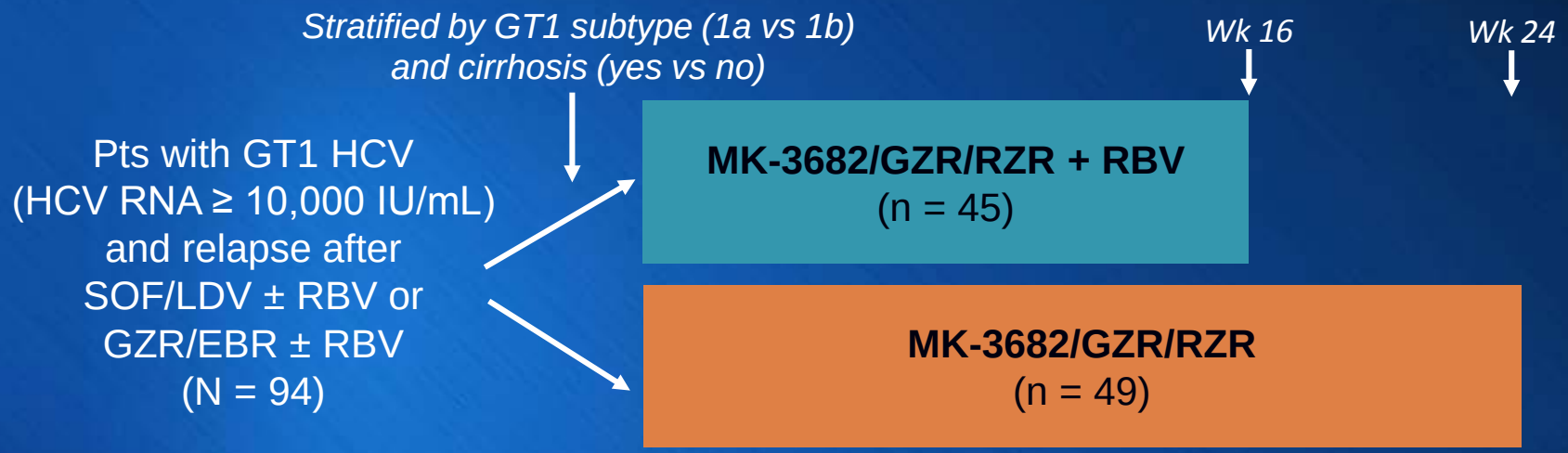
| SVR12 by Baseline RAV Presence, % (n/N) | GT2 HCV | | GT3 HCV | |
|---|---|---|---|---|
| | No L31M | L31M | No Y93H | Y93H |
| 8 wks | 94 (31/33) | 80 (20/25) | 98 (95/97) | 50 (2/4) |
| 12 wks | 100 (23/23) | 100 (28/28) | 99 (147/148) | 71 (5/7) |

Lawitz E, et al. AASLD 2016. Abstract 110. Reproduced with permission.

Slide credit: clinicaloptions.com

# C-SURGE: MK-3682/GZR/RZR for GT1 HCV Pts Who Relapsed on DAA Therapy

- Randomized, open-label phase II trial (interim analysis)



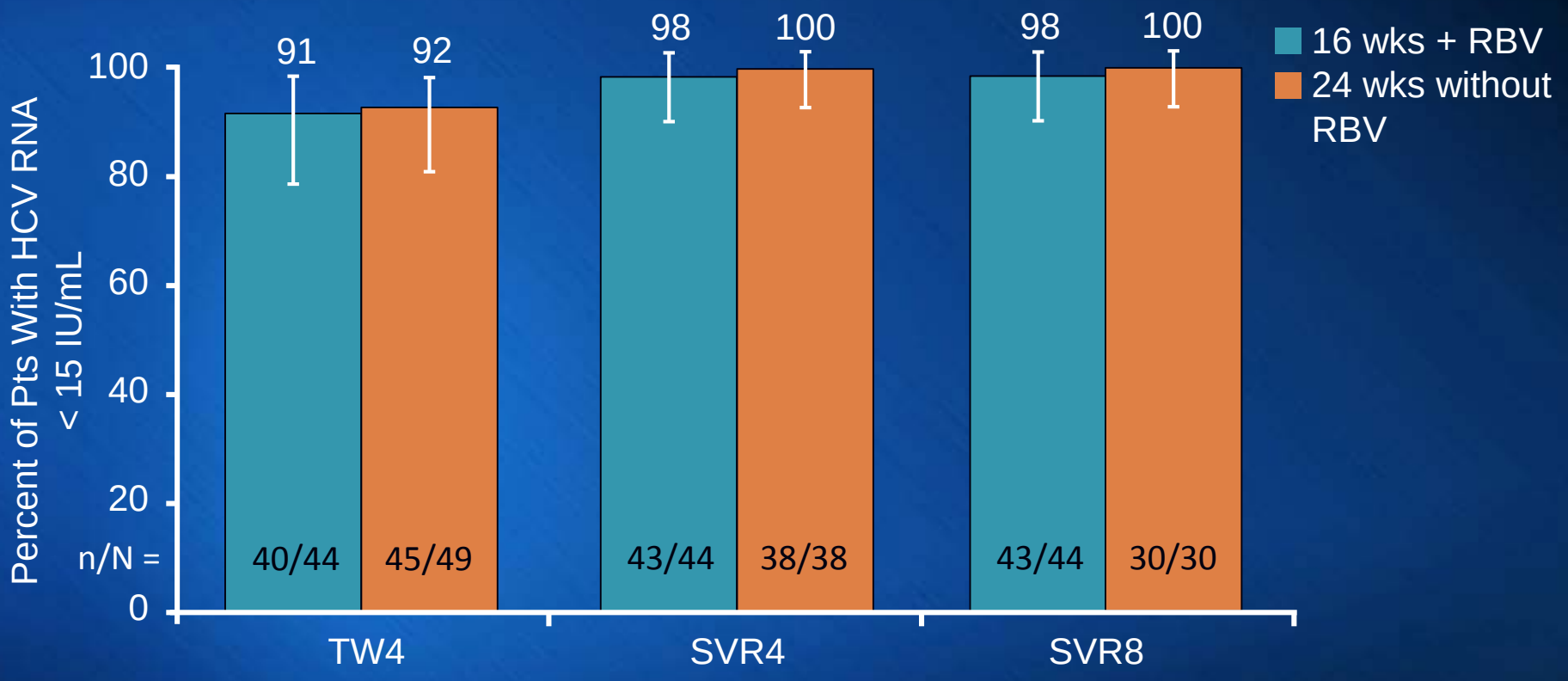

- Baseline characteristics:
  - Previous failing regimen: LDV/SOF 12-24 wks, 61%; LDV/SOF 8 wks, 15%; GZR/EBR 12 wks, 24%
  - NS5A RAVs, 84%; NS3 RAVs, 65%

Dosing: MK-3682/GZR/RZR two 225/50/30-mg tablets once daily; weight-based RBV (800-1400 mg/day).
Trial included compensated cirrhotic and noncirrhotic pts; cirrhosis definition in slidenotes.

Wyles DL, et al. AASLD 2016. Abstract 193.

Slide credit: clinicaloptions.com

# C-SURGE: SVR8 Rates With MK-3682/GZR/RZR for DAA Relapses




- No impact of NS5A or NS3 RAVs on SVR4, including Y93 RAVs
  - 4% of pts had ≥ 3 NS5A RAVs; 55% had dual NS5A and NS3 RAVs

Wyles DL, et al. AASLD 2016. Abstract 193. Reproduced with permission. Slide credit: clinicaloptions.com

# MK-3682/GZR/RZR Studies: Safety

| Outcome, % | C-CREST 1 & 2 Part B[1] MK-3682/GZR/RZR | | C-SURGE[2] MK-3682/GZR/RZR | |
|---|---|---|---|---|
| | No RBV (n = 462) | + RBV (n = 202) | + RBV, 16 Wks (n = 44) | 24 Wks (n = 49) |
| Any AE | 69 | 86 | 91 | 80 |
| Drug-related AE | 36 | 67 | 75 | 47 |
| D/c for AE | < 1 | 3 | 0 | 0 |
| Serious AE | 2 | 2 | 2 | 8 |
| Death | < 1* | 0 | 0 | 0 |
| AE in > 10% of pts | | | | |
| ▪ Fatigue | 15 | 29 | 48 | 24 |
| ▪ Headache | 19 | 27 | 14 | 12 |
| ▪ Nausea | 11 | 15 | NA | NA |
| ▪ Diarrhea | NA | NA | 7 | 10 |
| ▪ Pruritus | NA | NA | 11 | 0 |
| ▪ Rash | NA | NA | 14 | 4 |

*Deemed unrelated to study drug.

1. Lawitz E, et al. AASLD 2016. Abstract 110.
2. Wyles DL, et al. AASLD 2016. Abstract 193.

Slide credit: clinicaloptions.com

# Thank you for your attention

# Cost Effectiveness for IFN-Free Regimens
## (Dollars/QUALY) (Good value = $ 50,000 – 100,000)

- Genotype 1:
  - Naive: $ 0 - 31,452 (depending on cirrhosis).
  - IFN-Experienced: $ 84,744 – 178,295
- Genotype 2:
  - $35,500 - $238,000 (depending on cirrhosis)
- Genotype 3:
  - Up to $410,548
  - PEG-IFN + SOF + RBV is most cost effective
- Genotype 4:
  - $34,349 - $80,793 (depending on cirrhosis)

# End of Supplemental Slides

# SLAM-C: Sofosbuvir + Ledipasvir or Simeprevir for Acute HCV Infection

- Randomized, open-label, prospective pilot study
  - N = 29 pts with acute HCV infection at 6 drug rehabilitation centers (NYC)
- Group A (n = 14)
  - LDV/SOF 90/400 mg QD for 4 wks
- Group B (n = 15)
  - SOF 400 mg + SMV 150 mg QD for 8 wks

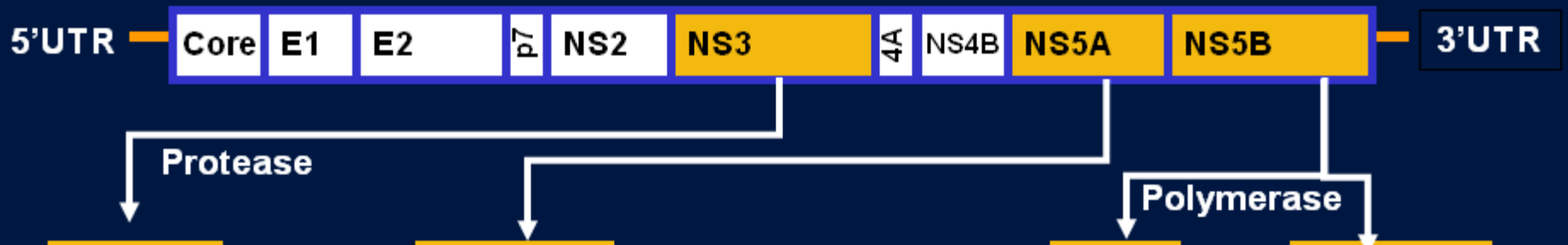
| Outcome, % (n/N) | LDV/SOF for 4 Wks (n = 14) | SOF + SMV for 8 Wks (n = 15) |
|---|---|---|
| SVR12 | | |
| ▪ All pts | 100 (14/14) | 87 (13/15) |
| ▪ Per protocol* | 100 (14/14) | 100 (13/13) |
| Retention through 20 wks | 93 (13/14) | 87 (13/15) |

*Excludes pts lost to follow-up or who discontinued for nonvirologic reasons.

Basu P, et al. AASLD 2015. Abstract 1074.

Slide credit: clinicaloptions.com

# Multiple Direct Acting Antivirals




Protease

Polymerase

**HCV PIs**

**Viral enzyme**
**Active site**

*Telaprevir*
*Boceprevir*
***Simeprevir***
Faldaprevir
Asunaprevir
***Paritaprevir***
***Grazoprevir***
Sovaprevir
ACH-2684

**NS5A Inhibitors**

**Non-enzyme**
**Replication complex**

***Daclatasvir***
***Ledipasvir***
***Ombitasvir***
ACH-3102
Ravidasvir
GSK2336805
Samatasvir
***Elbasvir***
***Velpatasvir***

**NS5B Nucs**

**Viral enzyme**
**Active site**

***Sofosbuvir***
VX-135
IDX20963
ACH-3422

**NS5B Non-nucs**

**Viral enzyme**
**Allosteric site**

***Dasabuvir***
Deleobuvir
BMS-791325
PPI-383
GS-9669
TMC647055

# Direct-Acting Antiviral Profiles

| | Direct-Acting Antiviral | | | | | |
|---|---|---|---|---|---|---|
| | NS3[1] | NS3[2] | NS5A[1] | NS5A[2] | Non Nuc NS5B | Nuc NS5B |
| Resistance profile | 🔴 | 🟡 | 🟡 | 🟢🟡 | 🔴 | 🟢 |
| Pan-genotypic efficacy | 🔴 | 🟢🟡 | 🟡 | 🟢🟡 | 🟡 | 🟢 |
| Efficacy | 🟡 | 🟢 | 🟢 | 🟢 | 🟡 | 🟢 |
| Adverse events | 🔴 | 🟢 | 🟡 | 🟢 | 🟡 | 🟡 |
| Drug-drug interactions | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟢 |

🟢 Good profile 🟡 Average profile 🔴 Least favorable profile

[1] 1st generation.
[2] 2nd generation.

# DAAs and HIV anti-Retrovirals

| | | SIM | DCV | SOF | SOF/ LDV | 3D |
|---|---|---|---|---|---|---|
| NRTIs | Abacavir | • | • | • | • | • |
| | Didanosine | • | • | • | • | • |
| | Emtricitabine | • | • | • | • | • |
| | Lamivudine | • | • | • | • | • |
| | Stavudine | • | • | • | • | • |
| | Tenofovir | • | • | • | • | • |
| | Zidovudine | • | • | • | • | • |
| NNRTIs | Efavirenz | • | • | • | •* | • |
| | Etravirine | • | • | • | • | • |
| | Nevirapine | • | • | • | • | • |
| | Rilpivirine | • | • | • | •* | • |
| Protease inhibitors | Atazanavir; atazanavir/ritonavir | • | • | • | •* | • |
| | Darunavir/ritonavir; darunavir/cobicistat | • | • | • | •* | • |
| | Fosamprenavir | • | • | • | •* | • |
| | Lopinavir | • | • | • | •* | • |
| | Saquinavir | • | • | • | •* | • |
| Entry/ Integrase inhibitors | Dolutegravir | • | • | • | • | • |
| | Elvitegravir/cobicistat | • | • | • | •* | • |
| | Maraviroc | • | • | • | • | • |
| | Raltegravir | • | • | • | • | • |

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

# DAAs and Lipid Lowering Drugs

| | SIM | DCV | SOF | SOF/ LDV | 3D |
|---|---|---|---|---|---|
| Atorvastatin | • | • | • | • | • |
| Bezafibrate | • | • | • | • | • |
| Ezetimibe | • | • | • | • | • |
| Fenofibrate | • | • | • | • | • |
| Fluvastatin | • | • | • | • | • |
| Gemfibrozil | • | • | • | • | • |
| Lovastatin | • | • | • | • | • |
| Pitavastatin | • | • | • | • | • |
| Pravastatin | • | • | • | • | • |
| Rosuvastatin | • | • | • | • | • |
| Simvastatin | • | • | • | • | • |

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

# DAAs and CNS Drugs

| | | SIM | DCV | SOF | SOF/ LDV | 3D |
|---|---|---|---|---|---|---|
| Anti-depressants | Amitriptyline | • | • | • | • | • |
| | Citalopram | • | • | • | • | • |
| | Duloxetine | • | • | • | • | • |
| | Escitalopram | • | • | • | • | • |
| | Fluoxetine | • | • | • | • | • |
| | Paroxetine | • | • | • | • | • |
| | Sertraline | • | • | • | • | • |
| | Trazodone | • | • | • | • | • |
| | Trimipramine | • | • | • | • | • |
| | Venlafaxine | • | • | • | • | • |
| Anti-psychotics | Amisulpiride | • | • | • | • | • |
| | Aripiprazole | • | • | • | • | • |
| | Chlorpromazine | • | • | • | • | • |
| | Clozapine | • | • | • | • | • |
| | Flupentixol | • | • | • | • | • |
| | Haloperidol | • | • | • | • | • |
| | Olanzapine | • | • | • | • | • |
| | Quetiapine | • | • | • | • | • |
| | Risperidone | • | • | • | • | • |

# DAAs and Cardiovascular Drugs

| | | SIM | DCV | SOF | SOF/ LDV | 3D |
|---|---|---|---|---|---|---|
| Antiarrythmics | Amiodarone | • | • | • | • | • |
| | Digoxin | • | • | • | • | • |
| | Flecainide | • | • | • | • | • |
| | Vernakalant | • | • | • | • | • |
| Antiplatelet and anticoagulants | Clopidogrel | • | • | • | • | • |
| | Dabigatran | • | • | • | • | • |
| | Warfarin | • | • | • | • | • |
| Beta blockers | Atenolol | • | • | • | • | • |
| | Bisoprolol | • | • | • | • | • |
| | Propranolol | • | • | • | • | • |
| Calcium channel blockers | Amlodipine | • | • | • | • | • |
| | Diltiazem | • | • | • | • | • |
| | Nifedipine | • | • | • | • | • |
| Hypertension and heart failure agents | Aliskiren | • | • | • | • | • |
| | Candesartan | • | • | • | • | • |
| | Doxazosin | • | • | • | • | • |
| | Enalapril | • | • | • | • | • |

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

| Concomitant Medications | Ledipasvir | Daclatasvir | Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir | Simeprevir | Sofosbuvir |
|---|---|---|---|---|---|
| **Acid-reducing agents*** | -Decrease Omeprazole not to exceed 20 mg a day. | | -Increase Omeprazole but do not exceed 40 mg a day ; decreases effect of Omeprazole. | | |
| **Alfuzosin/tamsulosin** | | | -Do not take with Viekira; can cause hypotension. | | |
| **Anticonvulsants** | -AVOID: Carbamazepine, Phenytoin; decrease Ledispavir | -CONTRAINDICATED: Phenytoin, Carbamazepine | -Do not take with Carbamazepine, phenytoin, Phenobarbital. Loss of effectiveness of Viekira. | -DO NOT USE; DECREASES SIMEPREVIR EFFECT: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin. | -DO NOT USE; DECREASES SOFASBUVIR EFFECT: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin |
| **Antiretrovirals*** | -with tenofovir only if CrCl >/= 60; -DO NOT USE with cobicistat, elvitegravir nor tipranavir | -Monitor for DAC adverse events: Atazanavir, fosanprenavir, darunavir/ritonavir. -Increase dose to 90 mg/d: Efavirenz, Etravirine | -Atazanavir without Ritonavir: give only 300 mg and only in am. Likely to elevate bilirubin. -Do not give Darunavir/Ritonavir -Do not give Lopinavir/Ritonavir -Do not give Rilpivirine (QT prolongation) -Do not give with Efavirenz (liver enzyme elevation). | -DO NOT USE; INCREASES SIMEPREVIR LEVELS: Cobicistat-containing product (elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate), Darunavir, Ritonavir -DO NOT USE; DECREASES SIMEPREVIR EFFECT: Efavirenz -DO NOT USE; VARIABLE EFFECT ON SIMEPREVIR: Atazanavir, Fosamprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir, Delavirdine, Etravirine, Nevirapine | -DO NOT USE; DECREASES SOFOSBIVIR EFFECT: tipranavir / ritonavir only. |
| **Azole antifungals*** | | -Monitor for DAC adverse events: Fluconazole. -Decrease DAC to 30/day: Itraconazole, Ketoconazole, Posaconazole, Voriconazole. | -Do not exceed Fluconazole 200 mg a day. -Avoid using Voriconazole. | -DO NOT USE; INCREASES SIMEPREVIR LEVELS: Itraconazole, Ketoconazole, Posaconazole, Fluconazole , Voriconazole. | |
| **Buprenorphine/ naloxone** | | | -No dose modification, BUT monitor closely for sedation and cognitive effects. | | |

| Concomitant Medications | Ledipasvir | Daclatasvir | Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir | Simeprevir | Sofosbuvir |
|---|---|---|---|---|---|
| **Calcineurin inhibitors*** | | | -Reduce CSA to 1/5$^{th}$ of original dose and monitor levels; readjust by blood levels at EOT. Monitor renal function.<br>-Tacrolimus: do not give in day 1 of Viekira; start day 2 with 0.5 mg a week adjusting dose and frequency by blood levels. Monitor renal function. | -MODEST EFFECT AND REQUIRES MONITORING: Cyclosporine, Tacrolimus, Sirolimus | |
| **Calcium channel blockers*** | | -Monitor for DAC adverse events: Diltiazem, Verapamil | - Dose reduce Amlodipine and monitor BP. | -USE WITH CAUTION AND MONITORING: Amlodipine, Diltiazem , Felodipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil | |
| **Cisapride** | | | X | -Increases Cisapride level | |
| **Digoxin** | -AVOID: increases Digoxin levels. | -Measure Digoxin level and decrease dose by 30-50%, and monitor level.<br>-Start Digoxin at lowest possible dose and monitor levels. | | -Increases Digoxin levels; reduce dose and monitor levels. | |
| **Ergot derivatives** | | | -Do not give with Ergotamine, dihydroergotamine, methylergonovine.; can cause ergot toxicity (vasospasm + ischemia). | | |
| **Ethinyl estradiol–containing products** | | | -Do not give with BCPs or patches (Lo Estrin, FE, Norinyl, Ortho Tri-Cyclen Lo, Ortho Evra), or Rings (NuvaRing), or hormone replacement (FEM HRT); Causes ALT elevation. | | |
| **Furosemide** | | | -Increases effect of furosemide; reduce dose or monitor. | | |

| Concomitant Medications | Ledipasvir | Daclatasvir | Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir | Simeprevir | Sofosbuvir |
|---|---|---|---|---|---|
| **Gemfibrozil** | | | -Do not take with Gemfibrozil (Lopid); causes QT prolongation. | | |
| **Glucocorticoids** | | -Increase DAC to 90 mg/d: Dexamethasone | -Inhaled, or Intranasal Fluticasone is absolved in excess and causes decreased cortisol levels. | -Decreases Simeprivir effect: Dexamethasone. | |
| **Herbals<br>St. John's wort<br>Milk thistle** | | -CONTRAINDICATED with St John's wort. | -Causes loss of activity of Viekira: St. John's wort | -DO NOT USE; DECREASES SIMEPREVIR LEVEL: St John's wort.<br>-DO NOT USE; INCREASE SIMEPREVIR LEVEL: Milk Thistle | -DO NOT USE; DECREASES SOFOSBUVIR EFFECT: St. John's wort |
| **Macrolide antimicrobials*** | | -Decrease DAC to 30 mg/d: Clarithromycin, Telithromycin.<br>-Increase DAC to 90 mg/d: Nafcillin, Rifapentine.<br>-Monitor for DAC adverse events: Ciprofloxacine, Erythromycin. | | -DO NOT USE: Erythromycin, Clarithromycin, Telithromycin; increases Simeprivir levels.<br>-Simeprevir also increases antibiotic level. | |
| **Other antiarrythmics*** | | -CONTRINDICATED: Amiodarone + SOF/DAC | -USE WITH CAUTION AND MONITORING: Amiodarone, Bepridil, Disipyramide, Flecainidine, Lidocaine (systemic), Mexiletine, Propafenone, Quinidine; increases antiarrhythmic effect; follow drug levels. | -USE WITH CAUTION AND MONITORING: Digoxin, Amiodarone, Disopyramide, Flecainide, Mexiletine, Propafenone, Quinidine | |
| **Phosphodiesterase type 5 inhibitors*** | | | -Revatio CONTRAINDICATED because effect is increased; risk of visual disturbance, hypotension, priapism, and syncope. | -USE WITH CAUTION AND MONITORING: Sildenafil , Tadalafil , Vardenafil all need dose adjustment when treating pulmonary hypertension. | |

| Concomitant Medications | Ledipasvir | Daclatasvir | Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir | Simeprevir | Sofosbuvir |
|---|---|---|---|---|---|
| **Pimozide** | | | -Do not give Pimozide with Viekira; risk of cardiac arrhythmias. | | |
| **Rifamycin antimicrobials** | -AVOID; Decreases Ledipasvir level. | -CONTRAINDICATED: Rifampin | -Rifampin causes loss of effect of Viekira. | -DO NOT USE; Decrease Simeprivir level: Rifampin, Rifabutin, Rifapentine | -DO NOT USE; DECREASES SOFOSBUVIR EFFECT: Rifampin, Rifabutin, Rifapentine |
| **Salmeterol** | | | -Not recommended due to increased risk of QT prolongation and sinus tachycardia. | | |
| **Sedatives** | | | - Do not give with Oral Midazolam nor Triazolam; prolonged sedation and respiratory depression.<br>-Alprazolam : consider dose reduction; effect is increased. | -USE WITH CAUTION AND MONITORING: Oral Midazolam and Triazolam | |
| **Simeprevir** | -AVOID: Increases levels of both drugs. | | | | |
| **Statins** | -Rosuvastatin: AVOID; Increases rosuvastatin level and risk of myopathy and rhabdomyolysis. | -Monitor for Myopathy and other side effects: Atorvastatin, Fluvastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin. | -CONTRAINDICATED with Lovastatin and Simvastatin ; risk of myopathy and rhabdomyolysis.<br>-Limit Rosuvastatin to 10 mg/d .<br>-Limit Pravastatin to 40 mg/d. | -Rosuvastatin max 10 mg, -Atorvastatin max 40 mg, -Simvastatin lowest possible dose, -Pitavastatin lowest possible dose, -Pravastatin lowest possible dose, -Lovastatin lowest possible dose | |

| Concomitant Medications | Ledipasvir | Daclatasvir | Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir | Simeprevir | Sofosbuvir |
|---|---|---|---|---|---|
| **Anticoagulants** | | -Do not use in Renal Impairment: Dabigatran etexilate mesylate | - | | |
| **Antidepressants** | | -Decrease DAC to 30 mg/d: Nefazodone | | | |
| **Eugeroics** | | -Increase DAC to 90 mg/d: Modafinil | | | |
| **Antihypertensives** | | -Increase DAC to 90 mg/d: Bosentran. | | | |
| | | | | | |
| | | | | | |