Case

63 year old woman now with:

- HCV GT 1b, HCV RNA 6.2 x 10^6 IU/mL
- Asymptomatic except for fatigue
- Normal exam
- ALT 72 IU/mL, Bili 0.9 mg/dL, INR 1.1, Albumin 3.9 g/dL, Creatinine 0.7 mg/dL
- Normal EGD
- Mild splenomegaly with few small venous collaterals

- Three indeterminate lesions – 2 LR4, 1 LR3

Prior HCV Treatment

In 2012: Liver biopsy demonstrated Stage II Fibrosis
Asymptomatic. Normal Lab. Imaging negative.
Clinical Trial: DAC + ASV + RBV x 12 weeks
Relapsed

In 2015: FibroScan 11.9 kPa; c/w Stage III/IV Fibrosis
Asymptomatic. Normal Lab.
Imaging with areas of transient hypervascularity.

She was anxious about the possible stage progression and hypervascularities and wanted re-treatment.

Would you have considered re-treatment in 2015?

Question 1

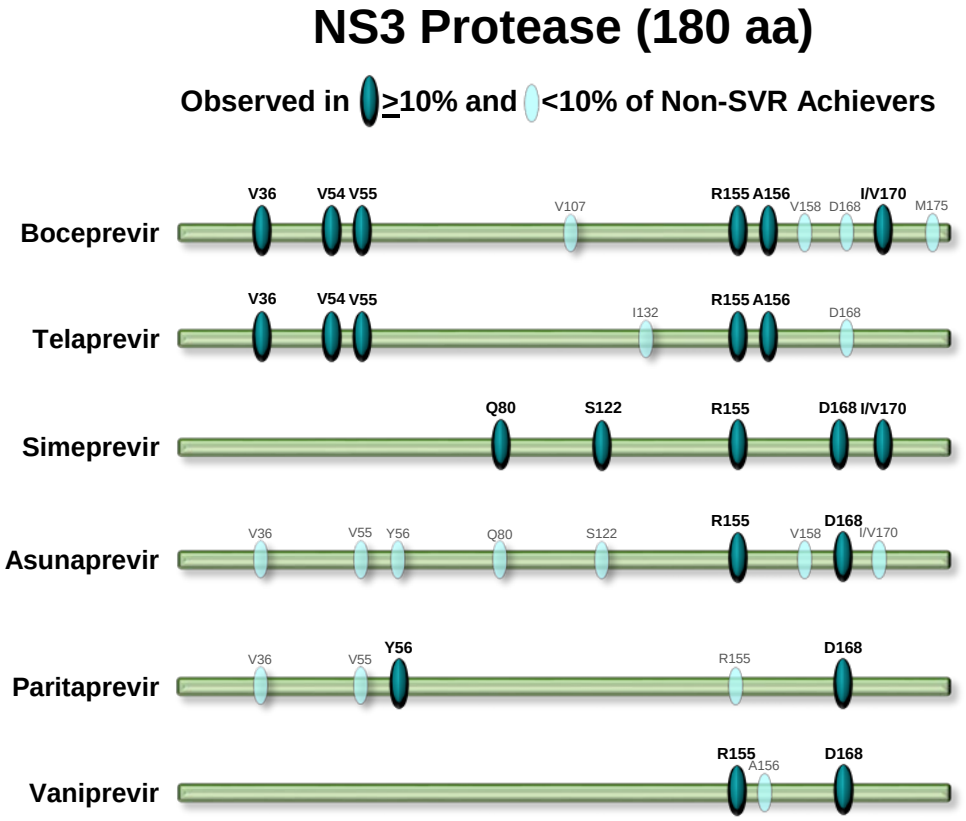
HCV GT1, treatment experienced (dual DAA – protease inhibitor (Asunaprevir) + NS5a inhibitor (Daclatasvir), F3/F4 Fibrosis Stage.

What would you have recommended for re-treatment?

1. Ledipasvir/sofosbuvir
2. Paritaprevir/ombitasvir/dasabuvir
3. Simiprevir/Sofosbuvir
4. Add Ribavirin
5. Lengthen Duration (from 12 to 24 Weeks)
6. Wait for other Treatment Options

NS3 RAVs Observed With Treatment

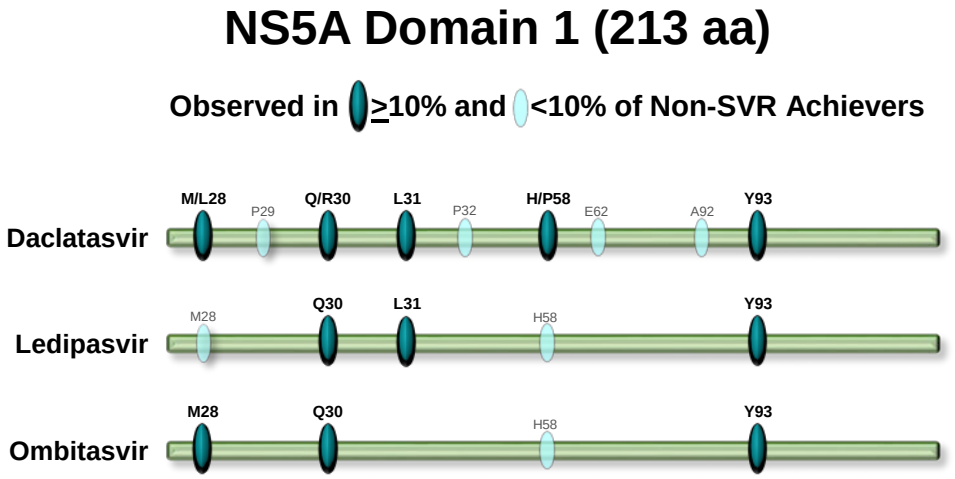
- Boceprevir, telaprevir
  - Activity in genotype 1
  - Low genetic barrier of resistance
  - Considerable cross-resistance
    - V36, T54, R155, A156
- Simeprevir, asunaprevir, paritaprevir, vaniprevir
  - Activity in multiple genotypes
  - Improved genetic barriers to resistance
  - R155 and D168 mutations substantially reduce activity



Lontok E, et al. *Hepatology*. 2015;62:1623-1632.

NS5A RAVs Observed With Treatment

- Broad genotypic coverage
- Relatively low barriers to resistance
- Most common NS5A RAV in patients not achieving SVR12
  - Daclatasvir
    - Genotype 1a: M28T, Q30E/H/R, L31M, H58D, Y93H/N
    - Genotype 1b: L31M/V, Y93H
    - Genotype 4: Q30H/S
  - Ledipasvir
    - Genotype 1a: Q30E/R, L31M, Y93C/H/N
    - Genotype 1b: Y93H
  - Ombitasvir
    - Genotype 1a: M28T, Q30R
    - Genotype 1b: Y93H
    - Genotype 4d: L28V



Lontok E, et al. *Hepatology*. 2015;62:1623-1632.

Decision

HCV GT1, treatment experienced (dual DAA – protease inhibitor (Asunaprevir) + NS5a inhibitor (Daclatasvir), F3/F4 Fibrosis Stage.

What we decided to do:

1. Ledipasvir/sofosbuvir
2. Paritaprevir/ombitasvir/dasabuvir
3. Simiprevir/Sofosbuvir
4. Add Ribavirin
5. Lengthen Duration (from 12 to 24 Weeks)
6. Wait for other Treatment Options

Case

She was treated with Ledipasvir/Sofosbuvir for 24 weeks. She refused RBV initially, but requested addition of RBV around week 12 of treatment. RBV was added, and was administered from weeks 12 to 24.

She relapsed 12 weeks after stopping treatment.

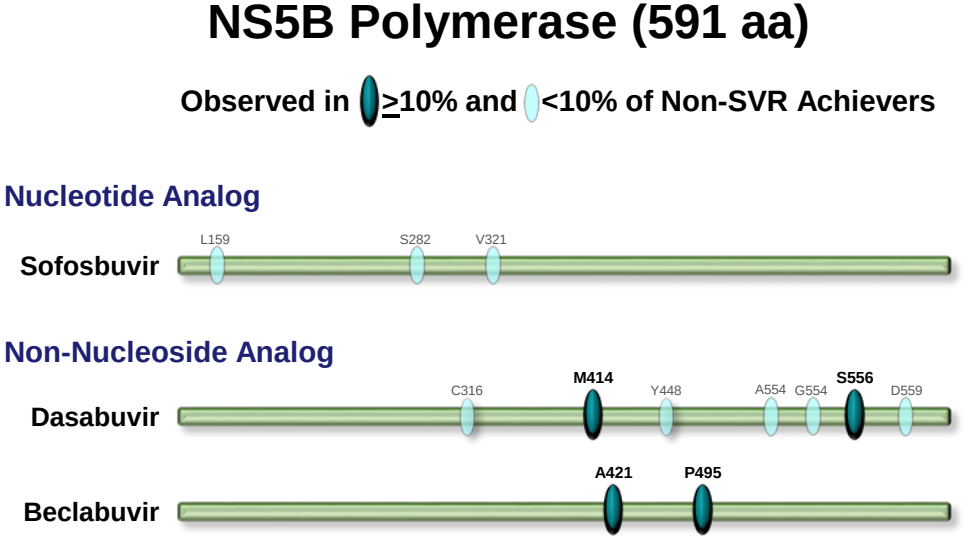
She is upset!

Treatment did not work!
Have we created an HCV SuperBug?

Significant co-pay of several thousand US dollars!

NS5B RAVs Observed With Treatment

- No cross-resistance across nucleotide (sofosbuvir) and non-nucleotide (dasabuvir) polymerase inhibitors
- High barrier to resistance (sofosbuvir)
- Most common RAVs detected in non-SVR12 achievers
  - Sofosbuvir
    - Genotype 2: S282T
    - Genotype 3: L159F and V321A
  - Dasabuvir
    - Genotype 1a: M414T, S556G
    - Genotype 1b: S556G
  - Beclabuvir
    - Genotype 1a: A421V, P495L/S



Lontok E, et al. *Hepatology*. 2015;62:1623-1632.

Question 2

Failed two DAA regimens: PI inhibitor (Asunaprevir) + NS5a inhibitor (Daclatasvir) and NS5b nuc inhibitor (Sofosbuvir) + NS5a inhibitor (Ledipasvir). F3/F4 Fibrosis Stage with possible HCC.

What do you recommend for the possible HCC?

1. Loco-Regional Therapy (LRT)

2. Surgical resection

3. Evaluate for Liver Transplantation
   A. Deceased donor
   B. Living donor

4. Other

Decision

Failed two DAA regimens: PI inhibitor (Asunaprevir) + NS5a inhibitor (Daclatasvir) and NS5b nuc inhibitor (Sofosbuvir) + NS5a inhibitor (Ledipasvir). F3/F4 Fibrosis Stage with multi-centric HCC.

What we have done for the HCC:

1. Loco-Regional Therapy (LRT)

2. Surgical resection

3. Evaluate for Liver Transplantation
   A. Deceased donor
   B. Living donor

4. Other – Followup Imaging for LR5 HCC

Question 3

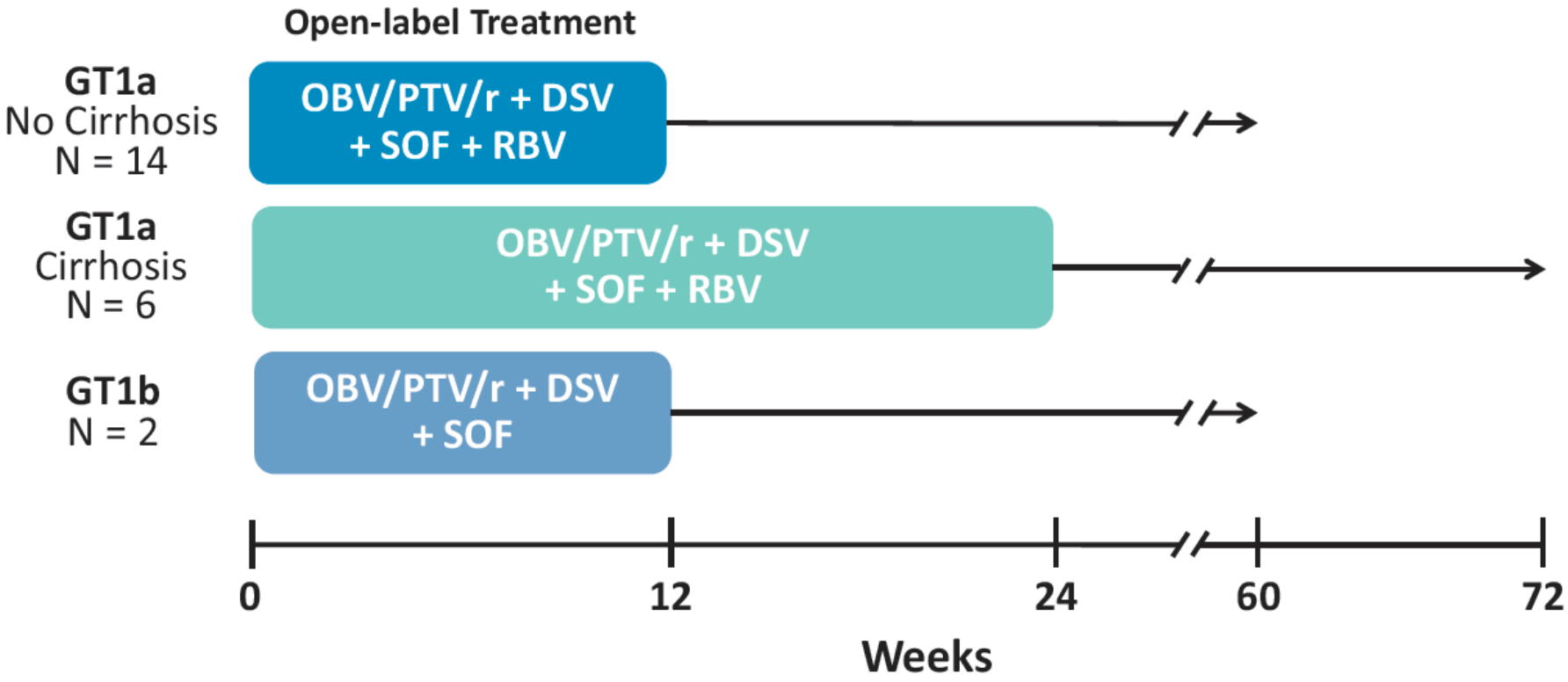
What do you recommend for treatment of the HCV?

1. Treat Now – or “Pre-transplant”
2. Treat after the potential transplant
3. Other

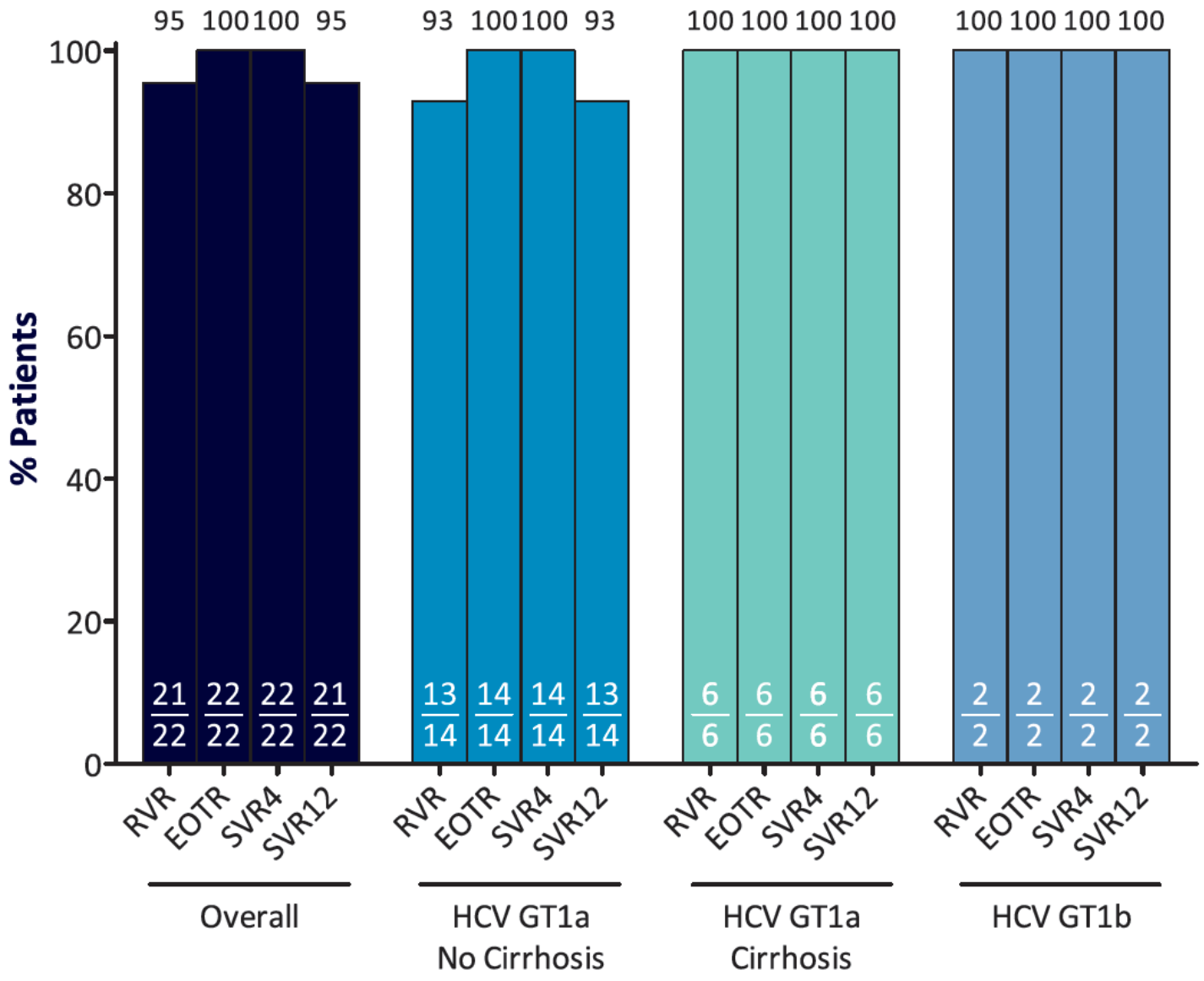
If you decide to Treat Now:

- What DAA regimen would you recommend?
- Would you use interferon?
- Would you use ribavirin?
- How long would you treat?

Sofosbuvir + Paritaprevir/Ombitasvir/Dasabuvir + Ribavirin


Open-label Treatment
GT1a
No Cirrhosis
N = 14
OBV/PTV/r + DSV
+ SOF + RBV
GT1a
Cirrhosis
N = 6
OBV/PTV/r + DSV
+ SOF + RBV
GT1b
N = 2
OBV/PTV/r + DSV
+ SOF
0
12
24
60
72
Weeks

Patient ID	GT	Response	Day sequenced	NS3 variant	NS5A variant	NS5B variant	Prior treatment
1	1a	Relapse	1	**Q80K**			TPV + PR
			PTW12	**Q80K**			
2	1a	SVR12	1	**Q80K**	**Q30E**	**Y448H**	SOF + PR
3	1a	SVR12	1	**V55A**, I170V	**M28V**, **Q30H**		OBV/PTV/r
4	1a	SVR12	1	**Q80K**	**M28V**, Q30R, **Y93C**/S		OBV/PTV/r
5	1a	SVR12	1	**Q80K**	M28V		SOF + RBV
6C	1a	SVR12	1	**Q80K**			OBV/PTV/r + DSV + RBV
7	1a	SVR12	1		**M28V**		OBV/PTV/r + DSV + RBV
8C	1a	SVR12	1	**Q80K**			OBV/PTV/r + DSV + RBV
9C	1a	SVR12	1	**Q80K**	Q30R	**S556G**	OBV/PTV/r + DSV + RBV
10	1a	SVR12	1	**Q80K**, D168V	**Q30R**, Y93H	**M414T**	OBV/PTV/r + DSV + RBV
11	1a	SVR12	1	**Q80K**	**M28V, Q30R**		OBV/PTV/r + DSV
12	1a	SVR12	1	**Q80K**	**M28V, Q30E**/G	**S556G**	OBV/PTV/r + DSV
13C	1a	SVR12	1	S122G	**H58D**		OBV/PTV/r + DSV
14C	1a	SVR12	1	**D168V**, I170V	M28T, **Q30R**	**L314H**	OBV/PTV/r + DSV + RBV
15	1a	SVR12	1	**D168E**	**Q30R, Y93F**	**M414I**	OBV/PTV/r + DSV + RBV
16	1a	SVR12	1	V55I, **Q80K**, **D168V**/H/A	**M28T**	**S556G**/R	OBV/PTV/r + DSV + RBV
17	1a	SVR12	1	**Q80K**, D168V/A/Y	**M28V, Q30R**	**S556G**	OBV/PTV/r + DSV + RBV
18C	1a	SVR12	1	**Q80K**	**Q30R**	**S556G**	OBV/PTV/r + DSV + RBV
19	1a	SVR12	1	S122G	**M28T**, Q30R/H	**S556G**	OBV/PTV/r + DSV
20	1a	SVR12	1	**Q80K**			TPV + PR
21	1b	SVR12	1	Q80R	**L31M**, **Y93H**		SMV + SAM + RBV
22	1b	SVR12	1			**S556G**	SMV + SOF


95 100 100 95
93 100 100 93
100 100 100 100
100 100 100 100
% Patients
100
80
60
40
20
0
21/22 22/22 22/22 21/22
13/14 14/14 14/14 13/14
6/6 6/6 6/6 6/6
2/2 2/2 2/2 2/2
RVR EOTR SVR4 SVR12
RVR EOTR SVR4 SVR12
RVR EOTR SVR4 SVR12
RVR EOTR SVR4 SVR12
Overall
HCV GT1a No Cirrhosis
HCV GT1a Cirrhosis
HCV GT1b

What is in the Pipeline?

DUAL DAA Regimens

Protease Inhibitor + Inhibitor of NS5A protein

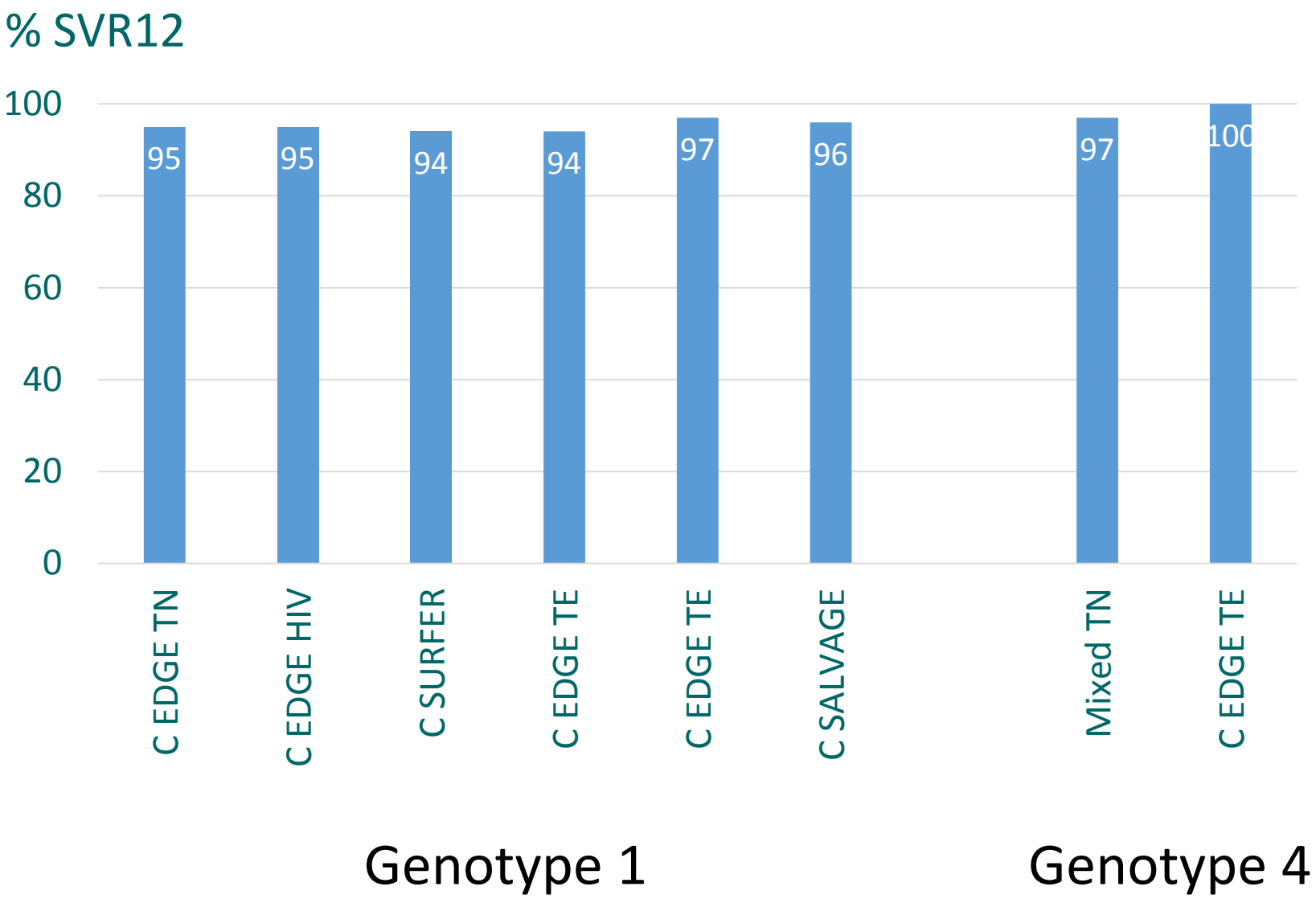
- Grazoprevir + Elbasvir GT 1, 4

Polymerase Inhibitor + NS5A protein inhibitor

- Sofosbuvir + Velpatasvir Pan-GT

Grazoprevir/Elbasvir (GRZ/ELB)

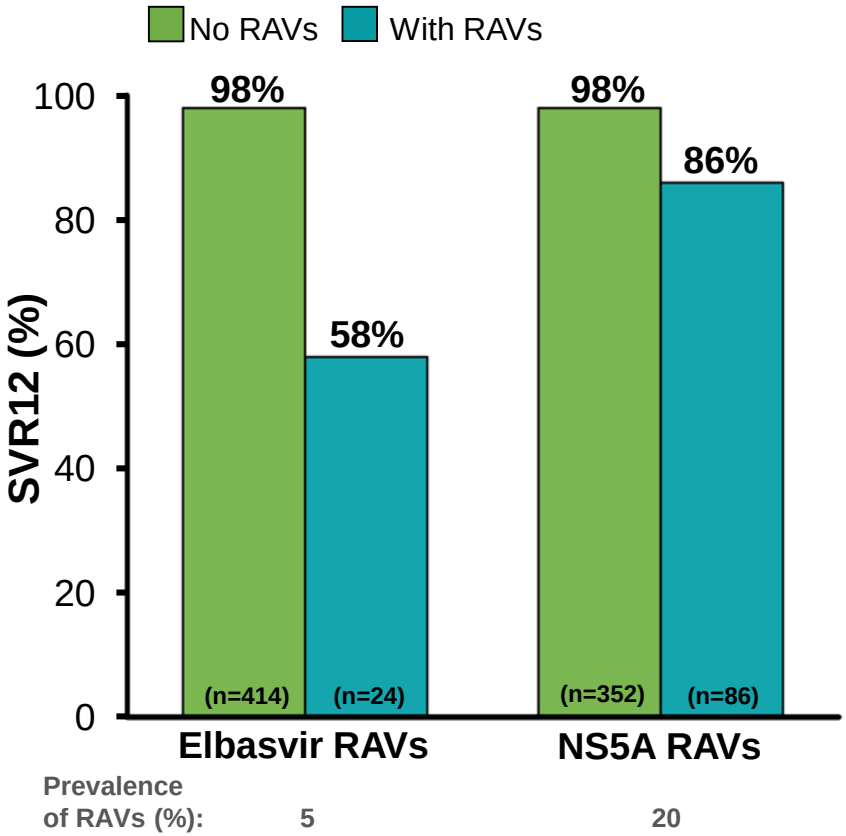
Trials of GRZ/ELB



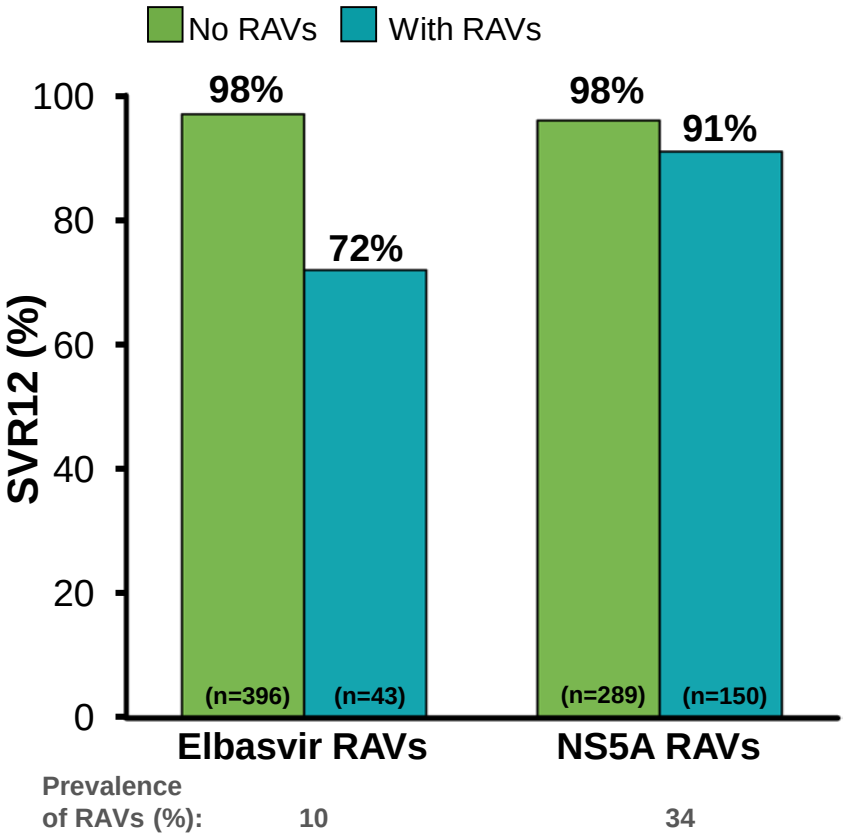
Impact of Baseline RAVs on SVR12 Rates: HCV Genotype 1a Treatment-Naïve, Prior PR Relapsers

Elbasvir/Grazoprevir for 12 Weeks

Population Sequencing



Next-Generation Sequencing*



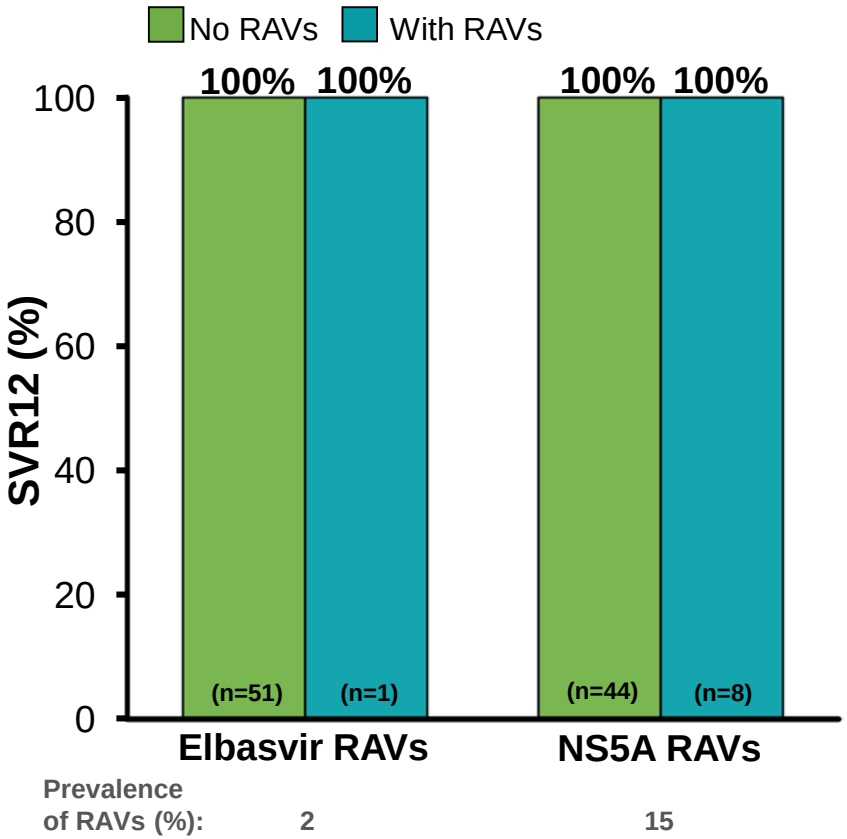
*1% cut-off.

Jacobson IM, et al. *Hepatology*. 2015;62(suppl S1):1393A-1394A. Abstract LB-22.

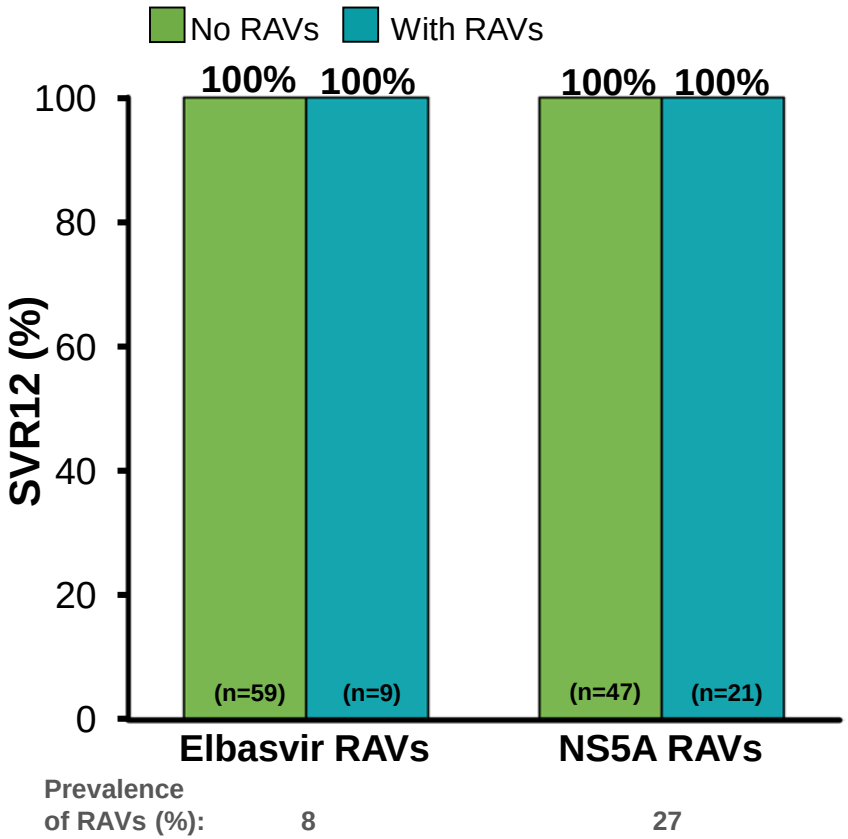
Impact of Baseline RAVs on SVR12 Rates: HCV Genotype 1a, Prior PR Nonresponders

Elbasvir/Grazoprevir + RBV for 16/18 Weeks

Population Sequencing



Next-Generation Sequencing*



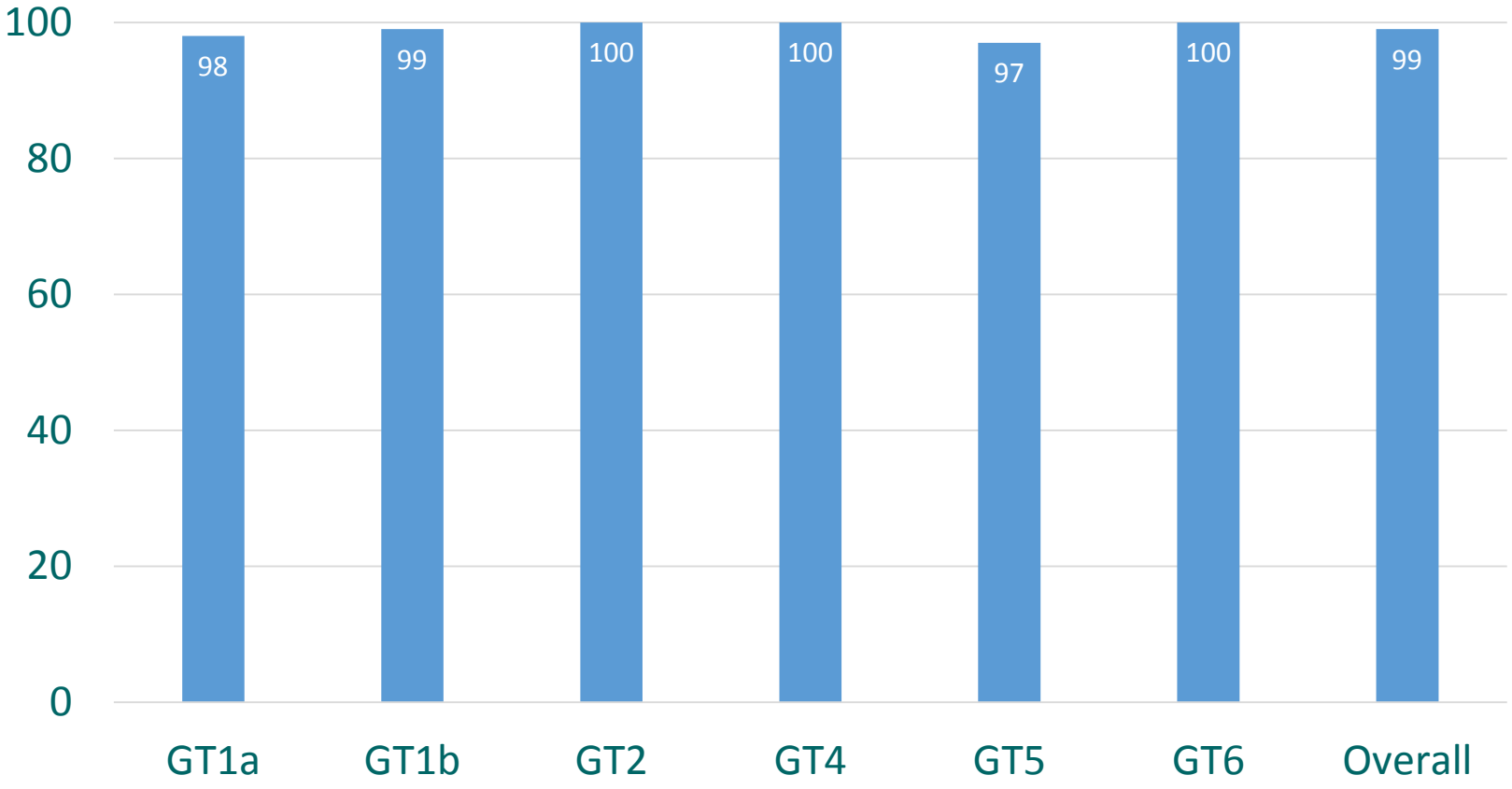
*1% cut-off.

Jacobson IM, et al. *Hepatology*. 2015;62(suppl S1):1393A-1394A. Abstract LB-22.

Velpatasvir / Sofosbuvir (VEL/SOF)

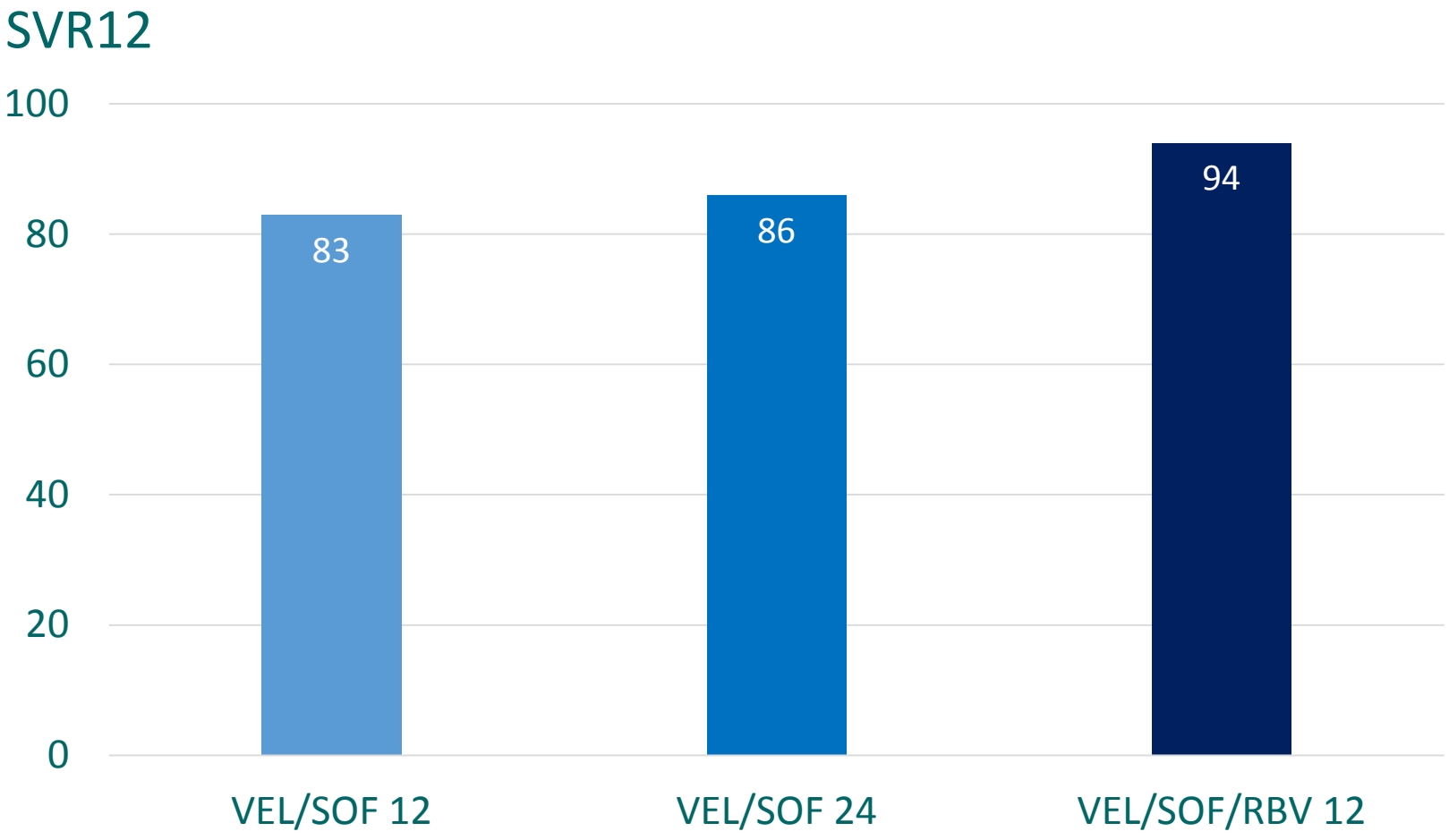
ASTRAL-1

SVR12



Astral-1 Trial: Phase 3, 624 patients, 8% Black, 19% Cirrhosis, 32% prior treatment. SVR in placebo group 0%.
SVR 99% in Compensated Cirrhosis, and 99% in Treatment Experienced.
SVR not affected by baseline NS5A RAVs. No on-Rx and only 2 post-Rx virologic failures.
N Engl J Med. 2015 Dec 31;373(27):2599-607.

ASTRAL-4 (CP B Cirrhosis)



ASTRAL-4: Phase 3, 267 patients with CP B Cirrhosis. 78% GT1, 4% GT2, 15% GT3, 3% GT4, 0 GT5, <1% GT6.
N Engl J Med. 2015 Dec 31;373(27):2618-28.

TRIPLE DAA Regimens

- Polymerase Inhibitor + NS5A Inhibitor + Protease Inhibitor

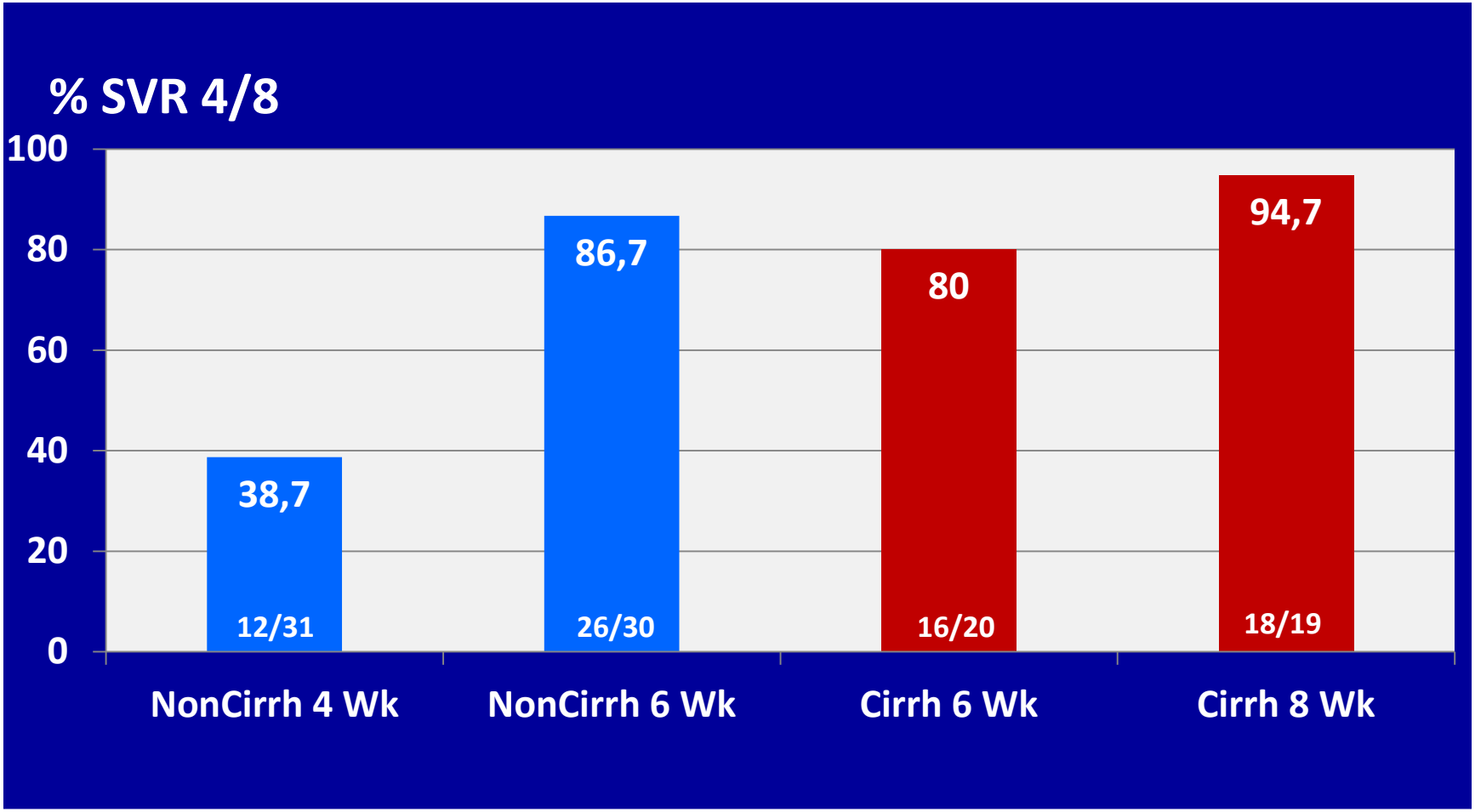
• Sofosbuvir + Elbasvir + Grazoprevir	GT 1
• Sofosbuvir + Velpatasvir + GS 9857	Pan-GT
• MK 3682 + Elbasvir + Grazoprevir	Pan-GT
• ACH 3422 + Odalasvir + Sovaprevir	GT 1
• TMC 647055r + Samatasvir + Simeprevir	GT 1
• Sofosbuvir + Daclatasvir + Simeprevir	GT 1,3,4

Sofosbuvir / Elbasvir / Grazoprevir

C-SWIFT study of HCV GT 1

Shortened Duration of Rx: GT1

SOFOSBUVIR 400 mg + ELBASVIR 50 mg + GRAZOPREVIR 100 mg



Lawitz E, et al. C-SWIFT: MK-5172 + MK-8742 + SOFOSBUVIR in Rx-Naïve Patients with HCV GT1 with and without cirrhosis. AASLD 2014. LB-33.

Sofosbuvir / Velpatasvir / GS 9857

POLARIS Studies 1,2,3,4

"Anybody can jump a motorcycle. The trouble begins when you try to land it." Evel Kneivel

Case

63 year old woman now with:

- HCV GT 1b, HCV RNA 6.2 x 10^6 IU/mL
- Asymptomatic except for fatigue
- Normal exam
- ALT 72 IU/mL, Bili 0.9 mg/dL, INR 1.1, Albumin 3.9 g/dL, Creatinine 0.7 mg/dL
- Normal EGD
- Mild splenomegaly with few small venous collaterals

- Three indeterminate lesions – 2 LR4, 1 LR3

Question 3

What do you recommend for treatment of the HCV?

Enrolled in clinical trial – POLARIS.*

She has been evaluated but not listed for LTx. She has potential donors for LDLT.