Azienda
ULSS12 Veneziana

SIMIT
SOCIETA' ITALIANA DI MALATTIE INFETTIVE E TROPICALI

Risultati del trattamento dei monoinfetti con Sofosbuvir, Simeprevir nella coorte veneziana. Confronto di esito con la coorte del trattamento con Boceprevir e Telaprevir

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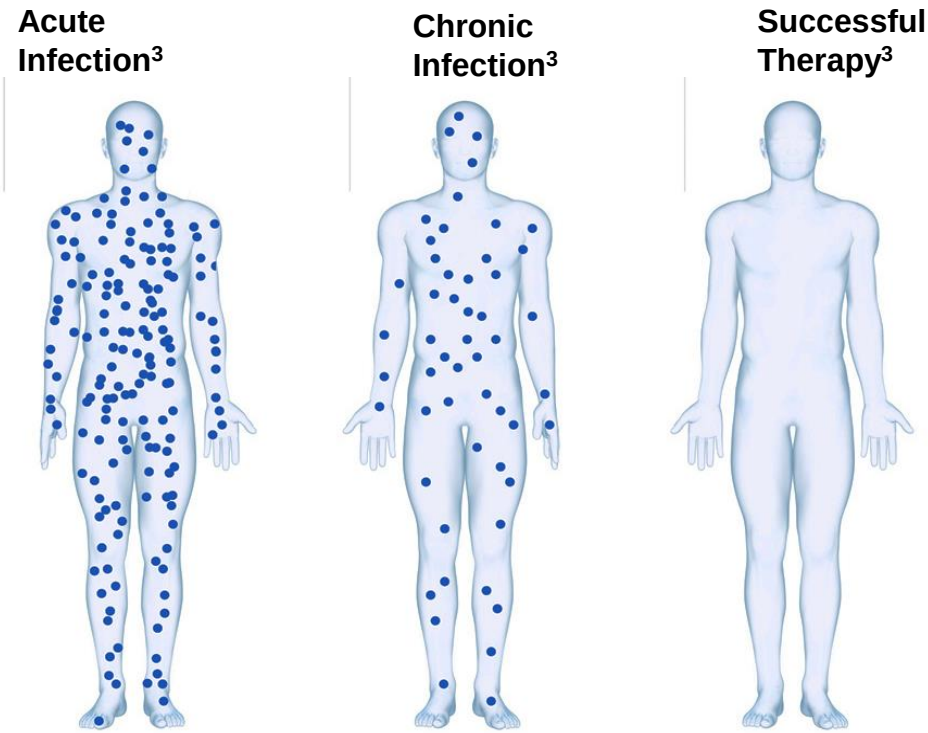
Unlike HIV and HBV infection a viral cure can be achieved in HCV infection

Achievement of a sustained virologic response (SVR) following completion of treatment is indicative of successful therapy and is synonymous with a cure



1. Soriano V, et al. *J Antimicrob Chemother*. 2008;62:1–4.
2. Smith BD, et al. *MMWR*. 2012;61(4):1-32.
3. Adapted from Metzner KJ. *Future Virol*. 2006;1:377-91

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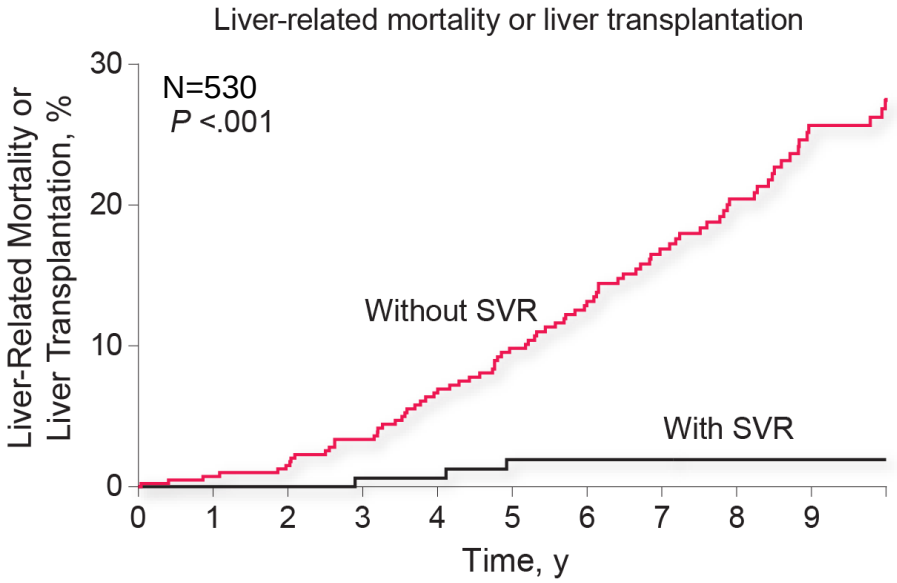
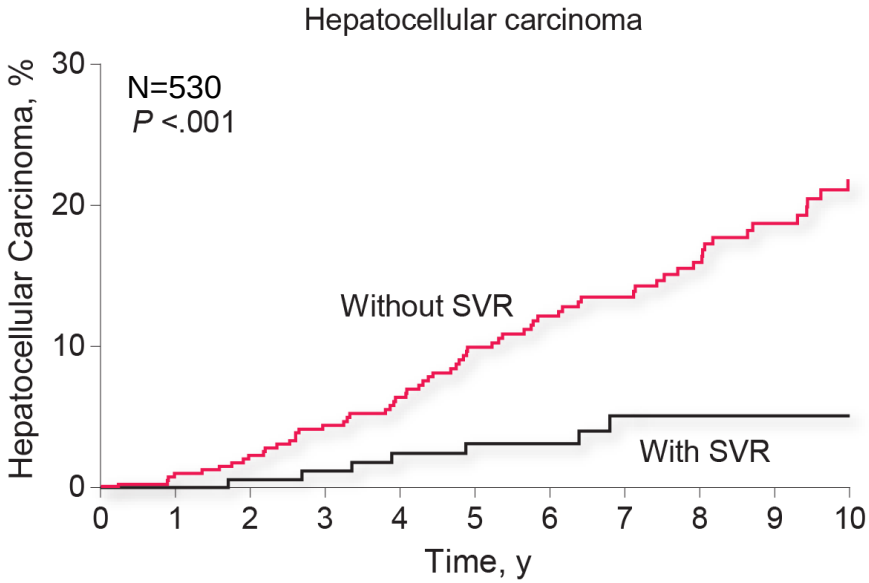
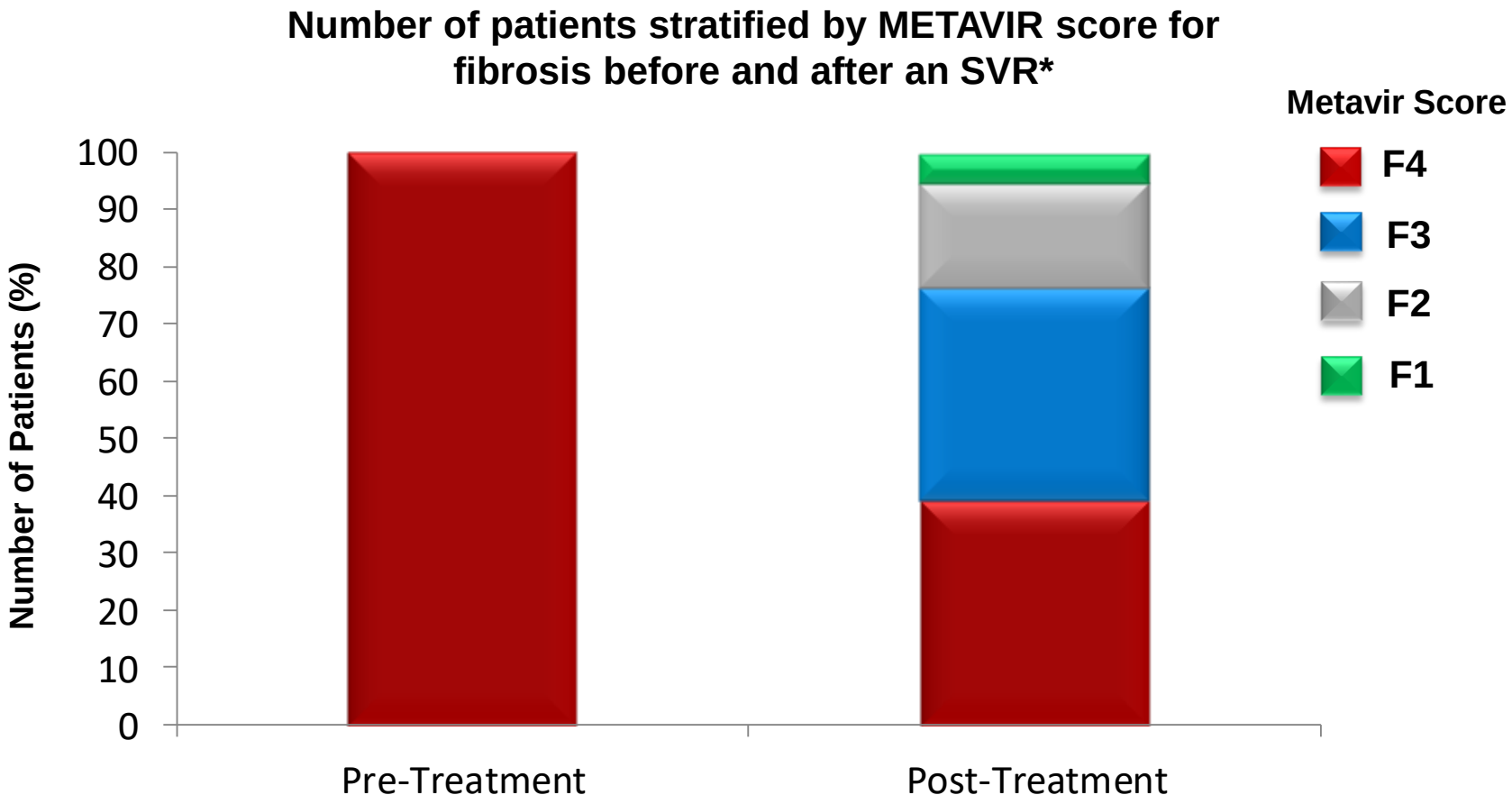
Sustained Virologic Response is associated with a reduction in liver-related mortality and HCC





van der Meer AJ, et al. *JAMA*. 2012; 308(24):2584-2593.

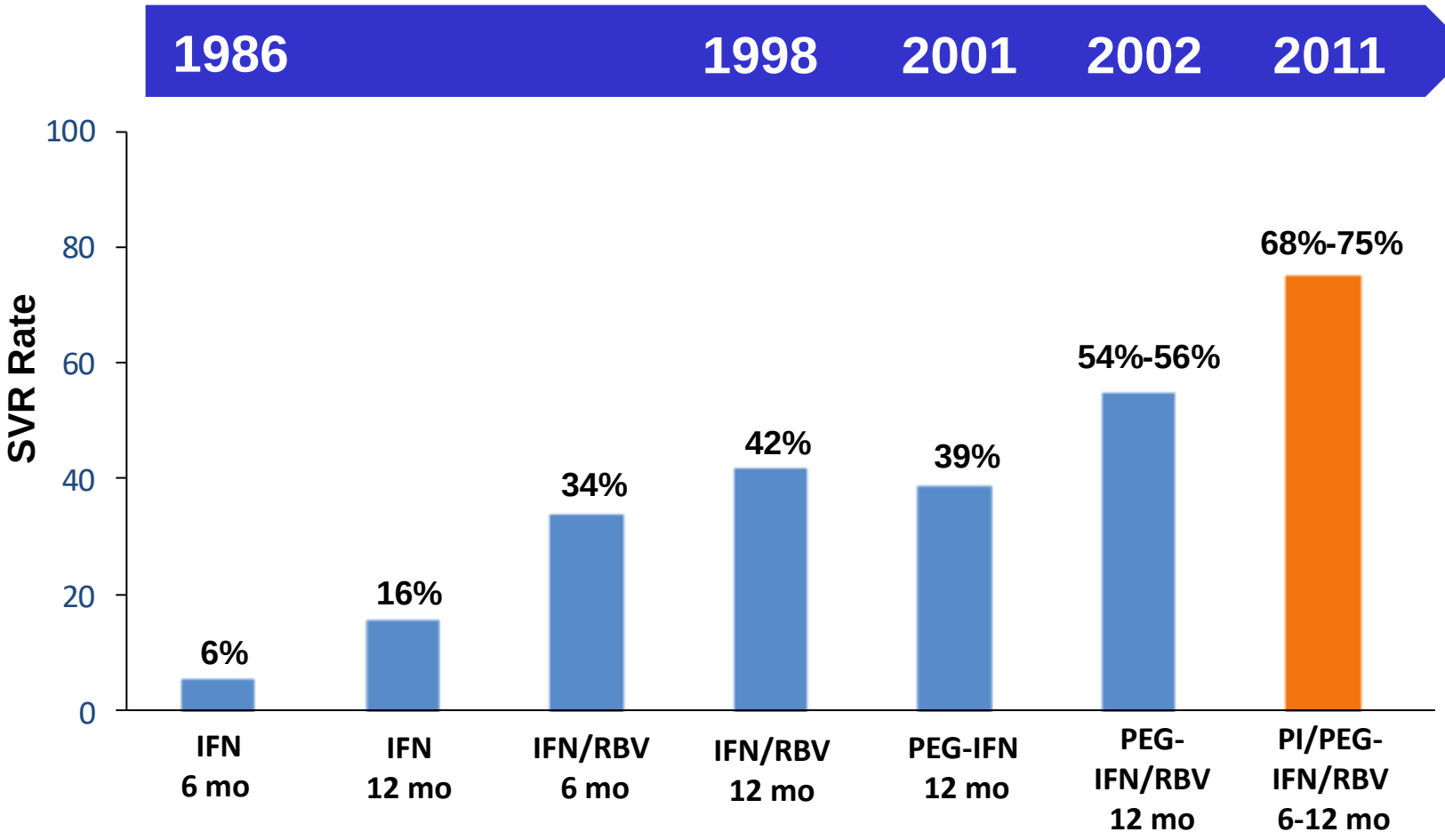
Cirrhosis regression is observed in over 60% of HCV patients achieving an SVR



***Median interval between pre- and post-treatment liver biopsies was 79 months**

D'Ambrosio R, et al. *Hepatology.* 2012;56:532-543.

SVR Rates in Patients With Genotype 1 HCV



Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2012. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2011.

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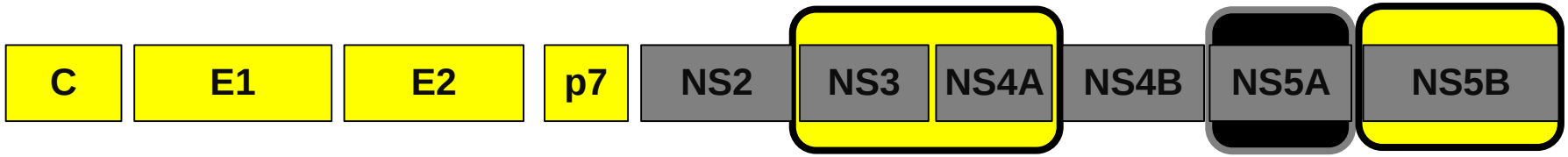
Direct-Acting Antiviral Agents: Key Characteristics



NS3/4A Protease Inhibitors (PI)

High potency

Limited genotypic coverage

Low barrier to resistance

NS5B Nucleos(t)ide Inhibitors (NI)

Intermediate potency

Pangenotypic coverage

High barrier to resistance

NS5A Inhibitors

High potency

Multigenotypic coverage

Low barrier to resistance

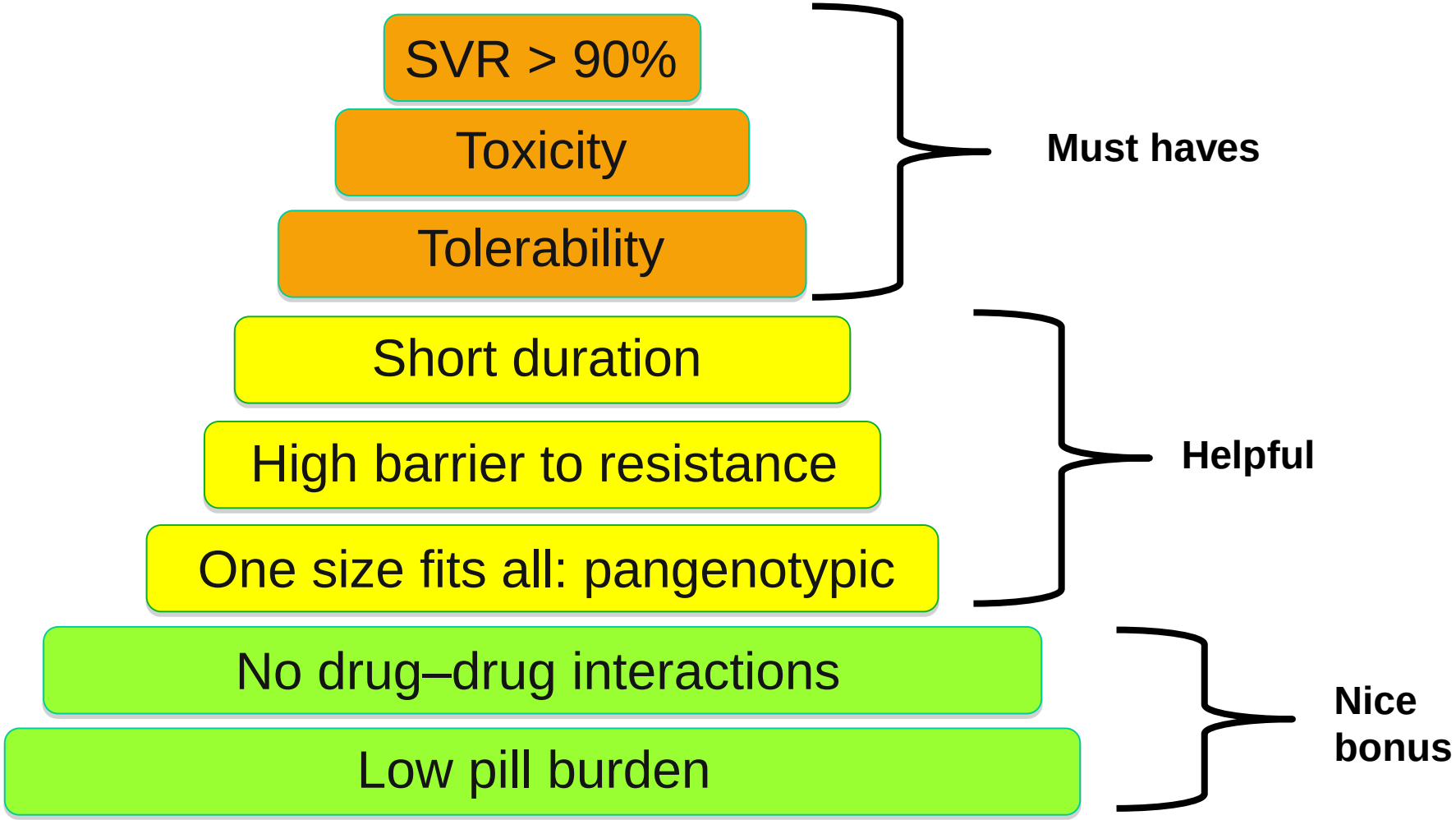
NS5B Nonnucleoside Inhibitors (NNI)

Intermediate potency

Limited genotypic coverage

Low barrier to resistance

Requirements for HCV therapy



SOC for Genotype 1

Treatment and Posology

PEG

RBV

Telaprevir

or

Boceprevir

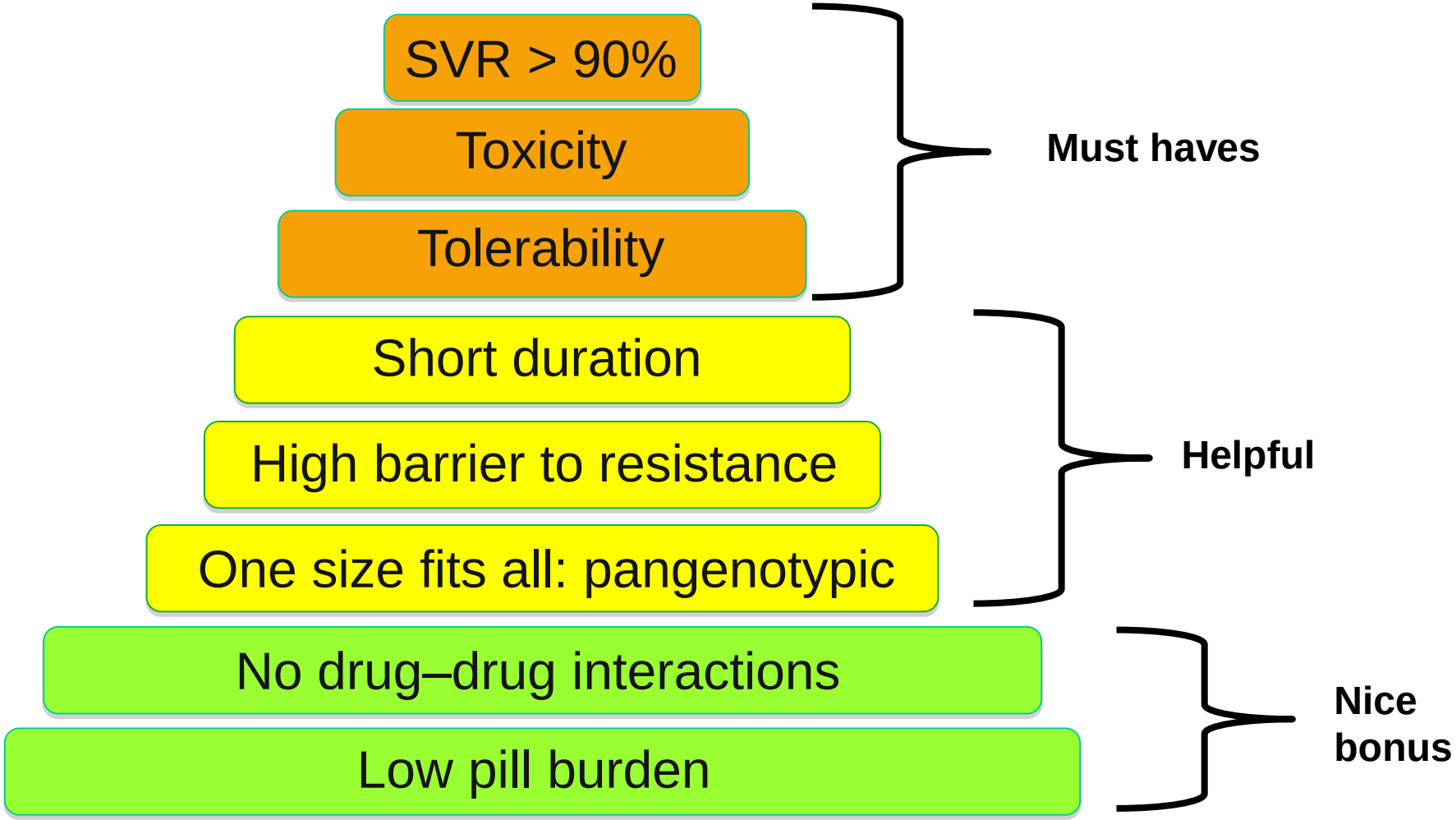
Drug-drug interactions

Drug	Dosing regimen	CYP metabolism	Non-CYP metabolism	P-gp Transporter
Telaprevir	Q8h Taken with food (20 g of fat)	**CYP 3A4:** ▪ Metabolised by ▪ Markedly Inhibits	–	▪ Substrate ▪ Inhibitor
Boceprevir	3 x daily Taken with food	**CYP 3A4**: ▪ Metabolised by ▪ Markedly Inhibits	AKR ▪ Metabolised by	▪ Substrate

:R: aldo-keto reductase; DAA: direct-acting antiviral
:h: every 8 hours; RTV: ritonavir; tid: three times daily

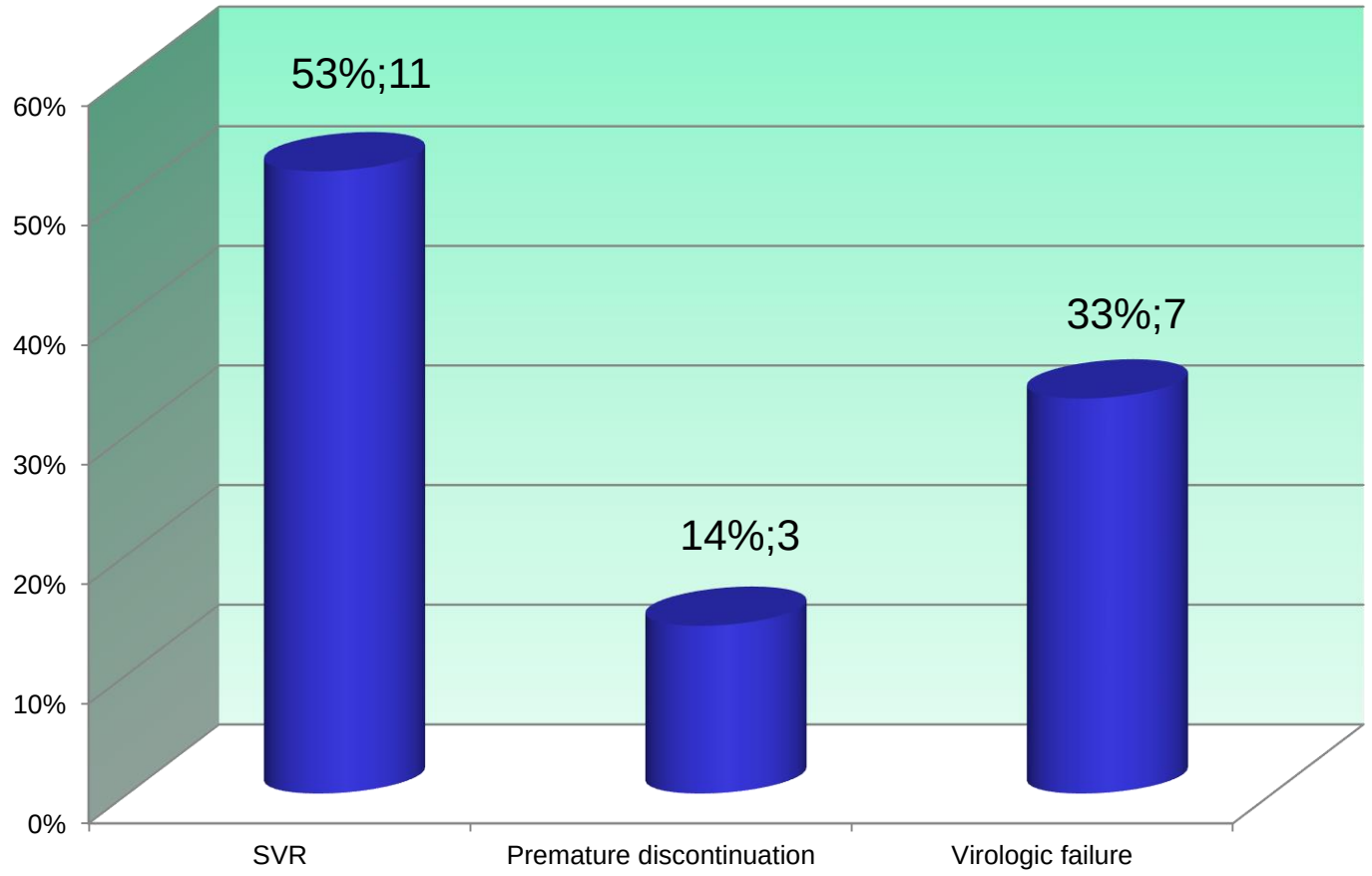
Telaprevir EU SmPC; Boceprevir EU SmPC
Kassera C, et al. CROI 2011. Abstract 118; Garg V, et al. CROI 2011. Abstract 629

Requirements for HCV therapy



Characteristics	TVR/BOC (n=21)
Mean age (range), yr	56 (46-70)
Male sex, n (%)	13 (62%)
Treatment history	
Treatment-naive	3
Treatment-experienced	18
Fibrosis	
F0-F1	0
F2	2
F3	5
F4	14
Child- Pugh score, n (%)	14 (67%)
A	14
B	0
C	0
MELD	
<10	14
10<13	0
≥13	0
HCV genotype 1 subtype, n(%)	
1a	4
1b	17
Others	0
Co-infection, n (%)	2 (10%)
HIV	2
HBV	0
HDV	0
HCV-RNA ≥800.000 IU/mL, n (%)	13 (62%)

Treatment virological response



Events	TVR/BOC (n=21)
Serious adverse event, n (%) Death, n (%) Grade 3/4 infection, n (%) Grade 3/4 hepatic decompensation, n (%) Grade 3/4 asthenia, n (%) Grade 3 rash, n (%)	13 (62%) 0 (0%) 0 (0%) 1 (5%) 12 (57%) 0 (0%)
Anaemia, n (%) Grade 2: 8.0<9.0 g/dL Grade 3/4: <8.0 g/dL Erythropoietin use Blood transfusion RBV dose reduction	17 (81%) 6 (29%) 1 (5%) 14 (67%) 7 (33%) 7 (33%)
Neutropenia, n (%)	1 (5%)
Thrombocytopenia, n (%)	0 (0%)

ANRS CO20-CUPIC: Week 16 analysis of safety and efficacy

- N=497/674 G1 Child A cirrhosis reached W16 of therapy
  - History of prior non-response
- Multivariate analysis: Baseline predictors severe complications
  - Plts ≤100,000/mm^3
  - Albumin <3.5 g/L
- Multivariate analysis: Baseline predictors anemia/transfusion
  - Female gender
  - No lead-in
  - Age ≥65 y
  - Low Hb

- High rates of anemia/SAEs
- Few RBV dose reductions
- High rates of viral response

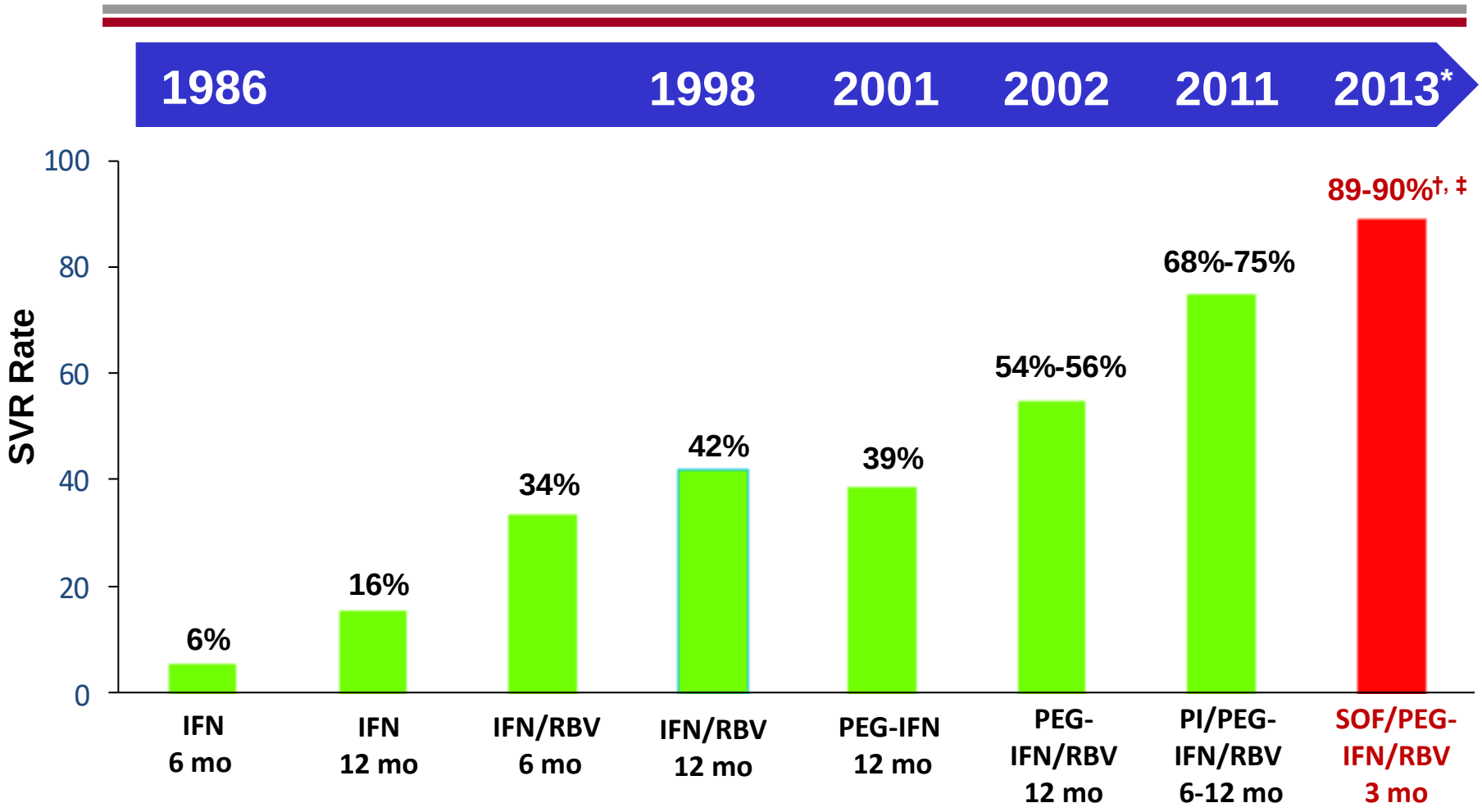
	TVR n=292	BOC n=205
SAEs	45%	32.7%
Discontinuation (SAEs)	14.7%	7.3%
Death	5	1
Infection (G3/4)	6.5%	2.4%
Hepatic decompensation	2%	2.9%
Anemia		
G2: 8.0 – <10.0 g/dL	18.8%	23.4%
G3/4: <8.0 g/dL	11.6%	4.4%
EPO use	53.8%	46.3%
Transfusion	16.1%	6.3%
RBV dose reduction	13%	10.7%
G4: <500/mm^3	2 (0.7%)	3.4%
Thrombopenia		
G3: 25000 – <50000/mm^3	9.6%	4.9%
Undetectable HCV RNA (PP/ITT)		
W4	58/55	3/2
W8	92/80	42/38
W12	93/79	64/55
W16	92/67	77/58

Hezode C, et al. AASLD 2012, Boston, #51

Risk-benefit (SAE / SVR 12)

Risk factors of SAE	Platelets count > 100.000/mmc	Platelets count < 100.000/mmc
Albumin > 35 g/L	SVR>>SAE	SVR>SAE
Albumin < 35 g/L	SVR>SAE	SAE>>SVR

SVR Rates in Patients With Genotype 1 HCV



***Year of publication of Phase 2 ATOMIC and Phase 3 NEUTRINO: Kowdley KV, et al. *Lancet*. 2013 Mar 14 [Epub ahead print]. Lawitz E, et al. *N Engl J Med.* 2013 Apr 23 [Epub ahead of print]. Lawitz E, et al. *N Engl J Med.* 2013 Apr 23 [Epub ahead of print].**
†SVR12 rate of 90% among patients in Group A (GT 1) in the Phase 2 ATOMIC trial (12 weeks of SOF+PEG-IFN+RBV)
‡SVR12 rate of 89% among GT 1 patients in the Phase 3 NEUTRINO trial (12 weeks of SOF+PEG-IFN+RBV)

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2012. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2011.

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SOFOSBUVIR

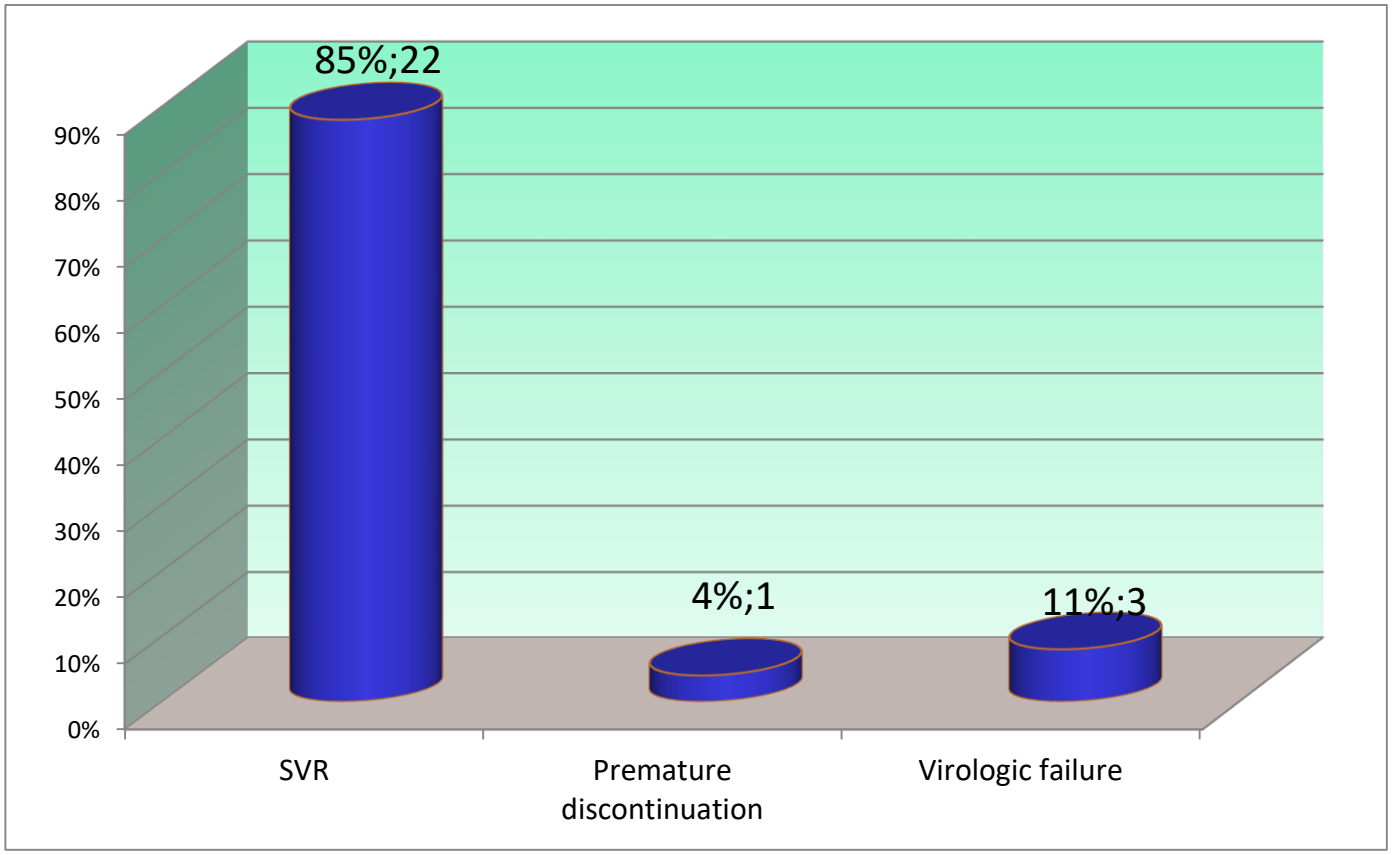
- Oral, once-daily nucleotide NS5B polymerase inhibitor
- Potent antiviral activity; pangenotypic
- High barrier to resistance
- Pharmacology profile
  - No significant drug interactions, including tacrolimus or cyclosporine
- Approved for combination treatment of HCV in following settings
  - GT1-4 HCV
  - HCC meeting Milan criteria; awaiting transplantation
  - HIV coinfection

SIMEPREVIR

- Oral, once-daily NS3 PI for G1-G4
- Improved adverse effect profile vs previous PIs: no anemia
- Fewer drug–drug interactions vs previous PIs: no meaningful drug–drug interactions with tacrolimus
- No data yet in CTP class B/C pts, but higher simeprevir exposure in CTP class B/C individuals without HCV infection makes dosing problematic
- Screening for Q80K in GT1a pts recommended

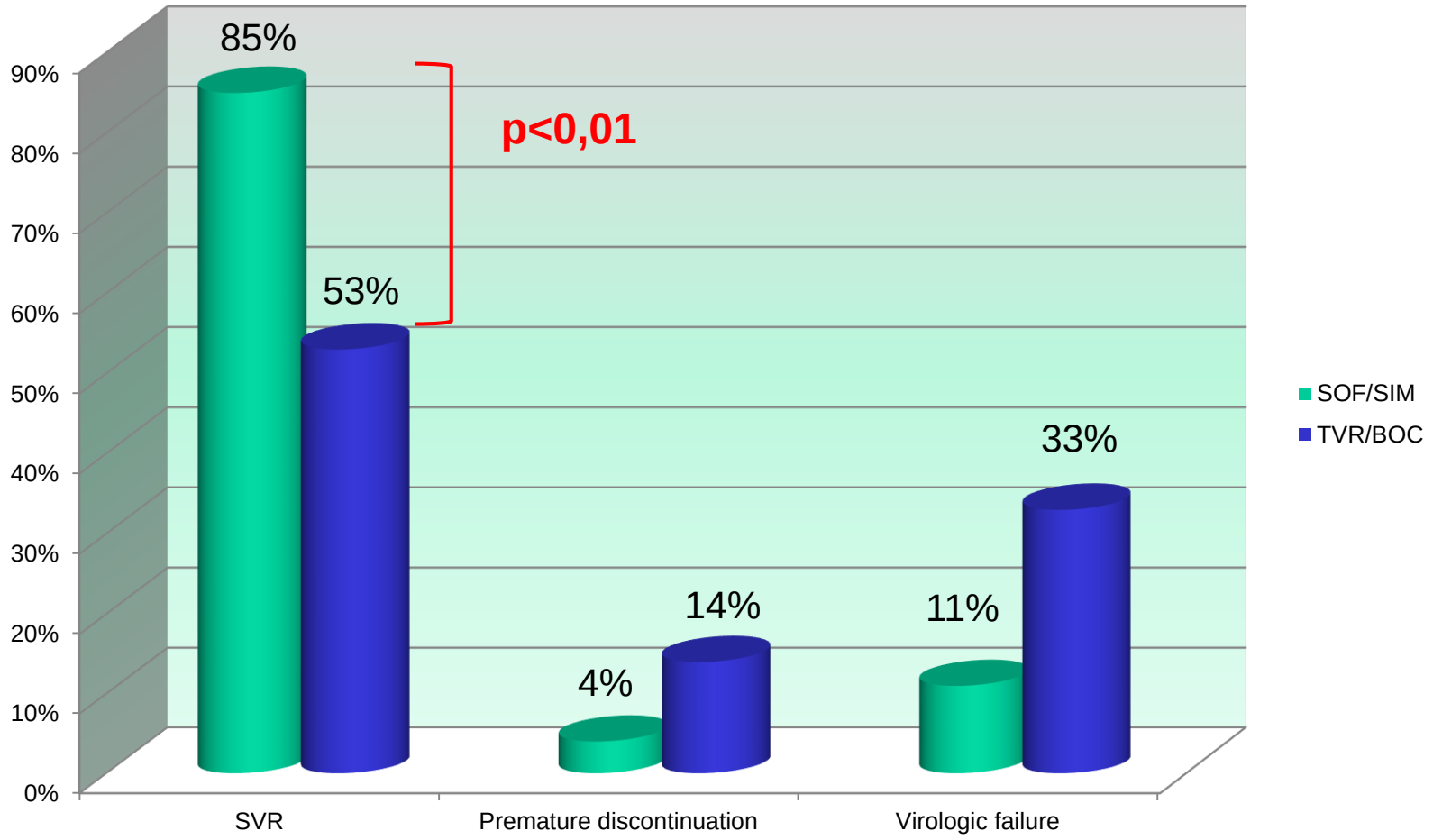
Characteristics	SIM/SOF (n=26)
Mean age (range), yr	61 (42-79)
Male sex, n (%)	16 (62%)
Treatment history Treatment-naive Treatment-experienced	 11 15
Fibrosis F0-F1 F2 F3 F4	 1 1 2 22
Child- Pugh score, n (%) A B C	22 (85%) 19 3 0
MELD <10 10<13 ≥13	 18 3 1
HCV genotype 1 subtype, n(%) 1a 1b Others	 5 21 0
Co-infection, n (%) HIV HBV HDV	0 (0%) 0 0 0
HCV-RNA ≥800.000 IU/mL, n (%)	15 (58%)

Treatment virological response



Events	SIM/SOF (n=26)
Serious adverse event, n (%) Death, n (%) Grade3/4 infection, n (%) Grade 3/4 hepatic decompensation, n (%) Grade 3/4 asthenia, n (%) Grade 3 rash, n (%)	1 (4%) 1 (4%) 0 (0%) 0 (0%) 0 (0%) 0 (0%)
Anaemia, n(%) Grade 2: 8.0<9.0 g/dL Grade 3/4: <8.0 g/dL Erythropoietin use Blood transfusion RBV dose reduction	5 (19%) 1 (4%) 0 (0%) 2 (8%) 0 (0%) 2 (8%)
Neutropenia, n (%)	0 (0%)
Thrombocytopenia, n (%)	0 (0%)

SOF/SIM vs TVR/BOC



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Drug	Prediction		Scored Mutations
Boceprevir	substitution on scored position		36V,170V
Paritaprevir	susceptible		none
Simeprevir	substitution on scored position		36V,170V
Telaprevir	possibly resistant		36V,170V,174S

Drug	Prediction		Scored Mutations
Boceprevir	resistant		36M,155K,174S
Telaprevir	resistant		36M,155K,174S
Simeprevir	resistant		155K

Drug	Prediction		Scored Mutations
Boceprevir	resistant		170A
Paritaprevir	susceptible		none
Simeprevir	substitution on scored position		170A
Telaprevir	possibly resistant		170A,174S

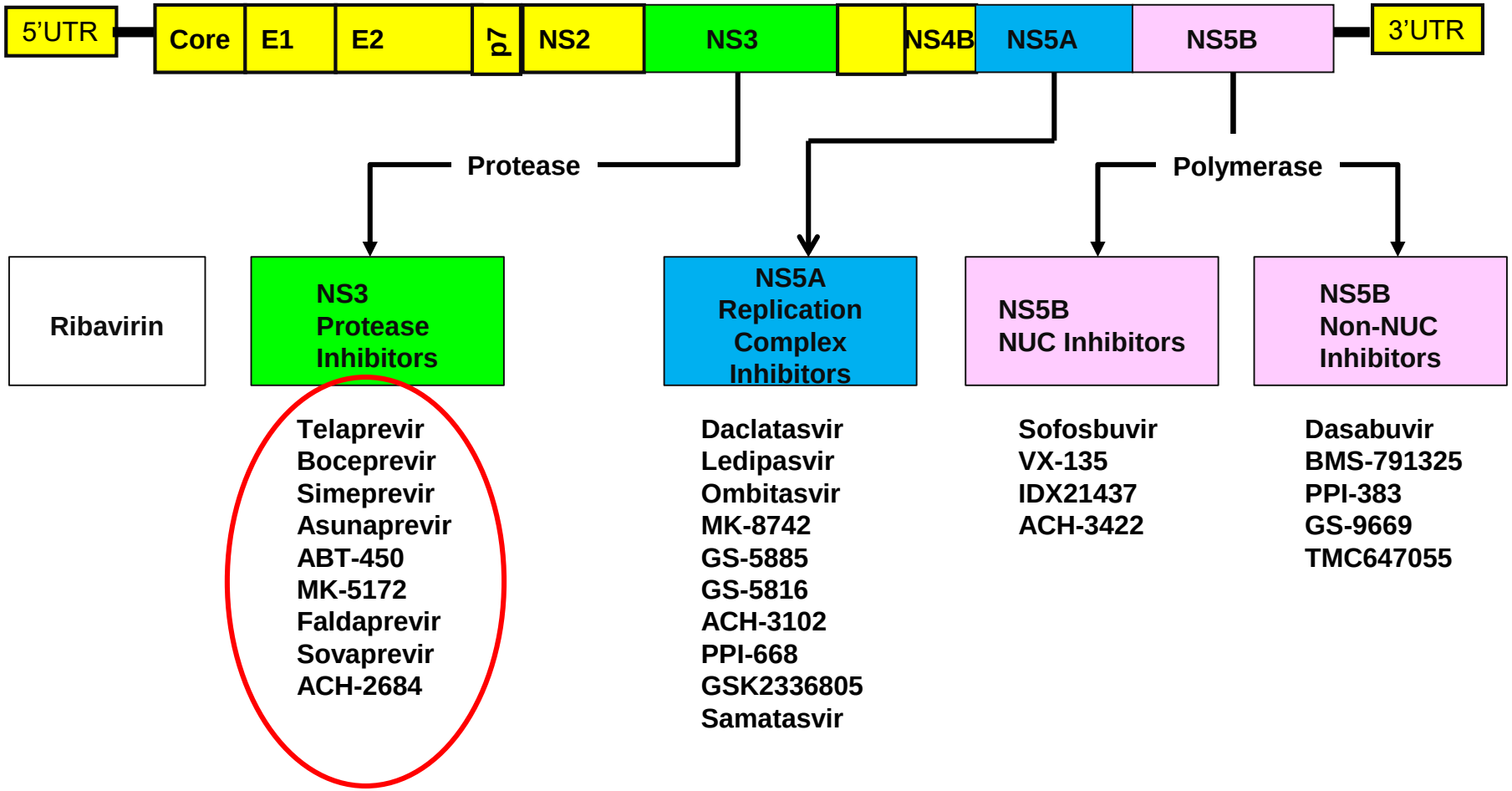
Treatment-Emergent Substitutions During PI-Based Therapy

- **Pooled analyses of subjects who had on-treatment failure or relapse during clinical trials with boceprevir or telaprevir**
  - **Patterns of treatment-emergent substitutions varied by subtype 1a vs 1b**
  - **Resistance most common among previous null responders and patients with subtype 1a**

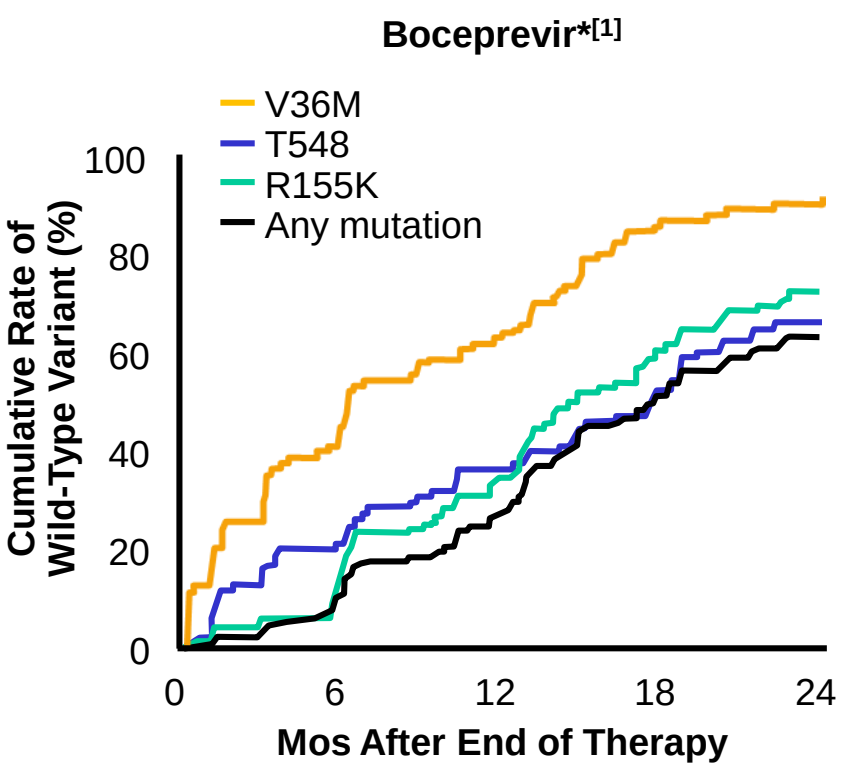
HCV Genotype 1 Subtype	Treatment-Emergent Substitutions	
	Telaprevir[1]	Boceprevir[2]
1a	V36M R155K Combination of V36M and R155K	V36M T54S R155K
1b	V36A T54A/S A156S/T	T54A/S V55A A156S I/V170A

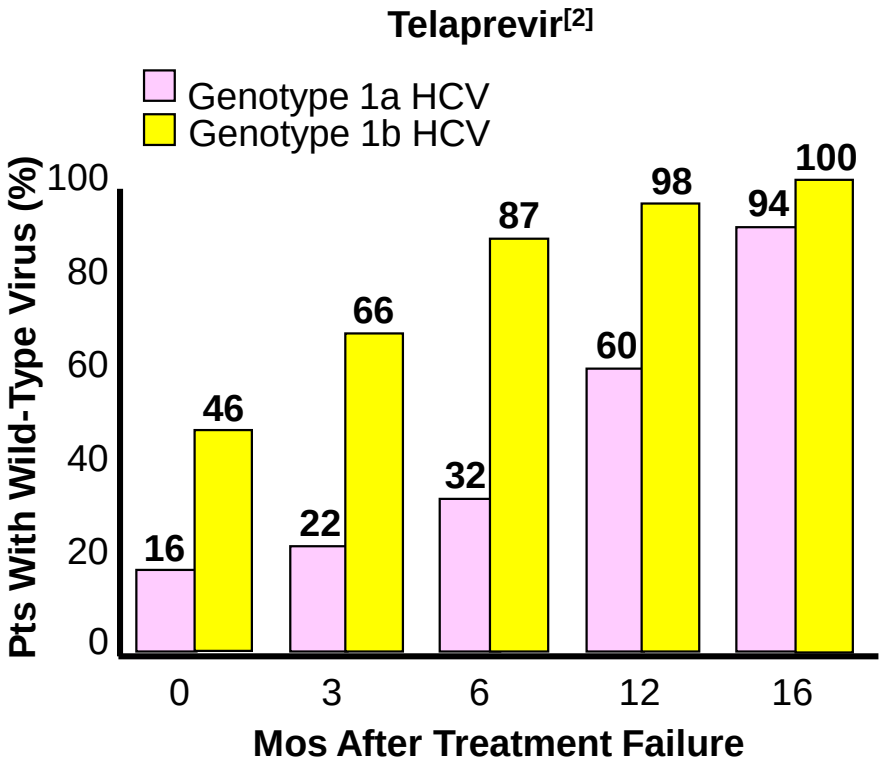
1. Telaprevir [package insert]. May 2011. 2. Boceprevir [package insert]. May 2011.

Direct-Acting Antiviral Agents



Loss of Detectable Resistance in Patients Stopping BOC or TVR + PegIFN/RBV



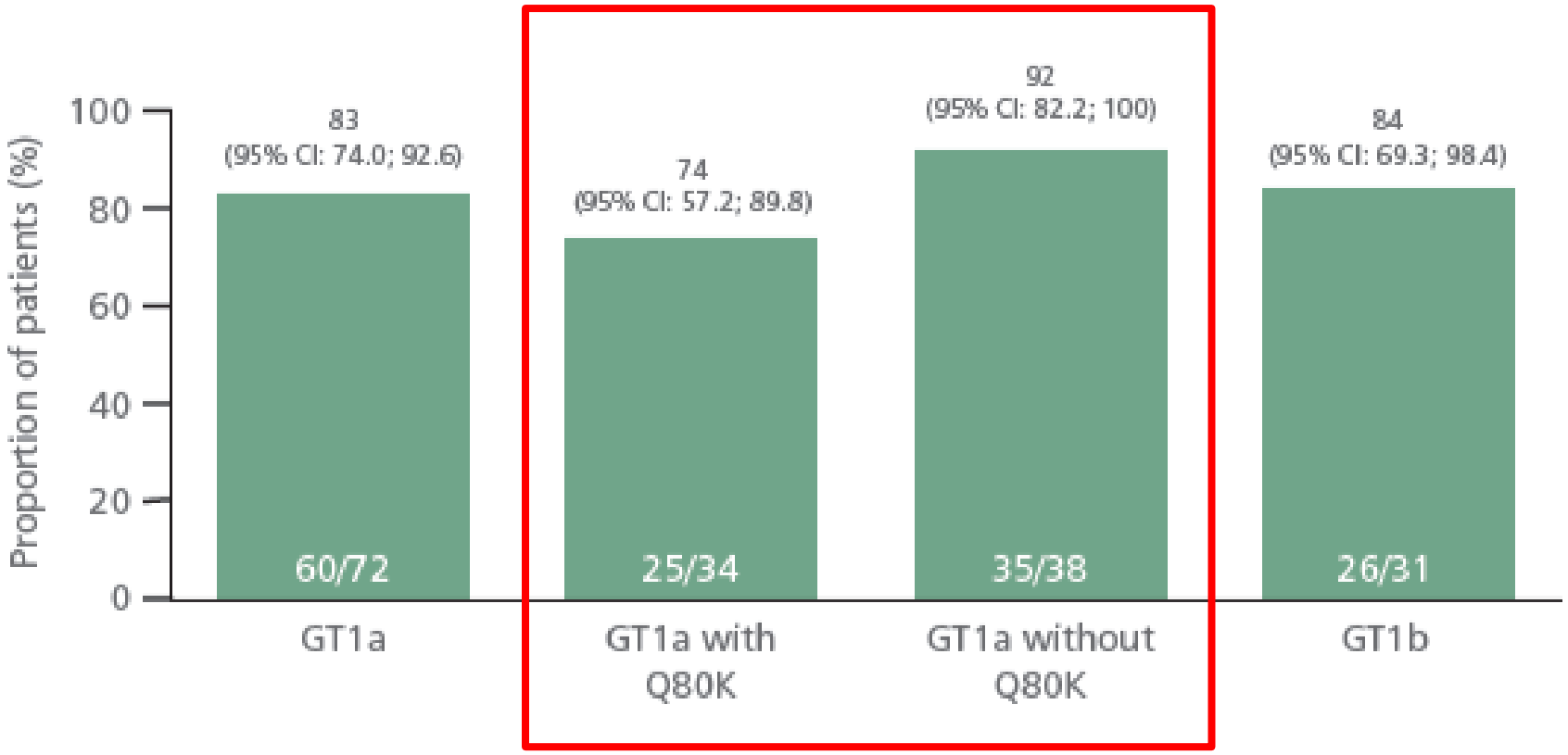


1. Vierling JM, et al. EASL 2010. Abstract 2016. 2. Sullivan J, et al. EASL 2011. Abstract 8.

SOFOSBUVIR

	Genotype activity	Resistance	Key resistance mutations
NS3 protease inhibitors	■ *First PI generation*: genotypes 1 (1b >1a) (Telaprevir & Boceprevir) ■ *Second wave and second PI generation*: across all but genotype 3 (D168Q) (**Simeprevir**, faldaprevir, vaniprevir, asunaprevir, sovaprevir, MK-5172, ACH-2684)	Low genetic barrier High cross-resistance	First PI generation: G1a: **R155K**, V36M G1b: V36M, T54A/S, A156T **Second wave and second PI generation:** F43S, Q80K, **R155K**, D168A/E/H/T/V
NS5 nucleos(t)ide analogues inhibitors	Across all genotypes **Sofosbuvir** displays less antiviral activity againts genotypes 3 (treatment duration 24 weeks of sofosbuvir+RBV).	High genetic barrier High cross-resistance	Sofosbuvir*: G1a: **S282T**+(I434M) G1b: S282T G2a: S282T+(T179A, M289L, I293L, M434T, and H479P) Mericitabine*: **S282T**+(K81R,S84S/P, I239L, A300F/L/C, A421V, and Y586C)
NS5B non-nucleoside analogues inhibitors	Genotypes 1 (1b>1a)	Low genetic barrier Overlapping resistance profile for NNI-site 3 and site 5 inhibitors (C316Y/N and Y448H)	NNI-site 1: A421V, P495L/S, V499A NNI-site 2: L419S, R422K, M423I/L/T NNI-site 3: C316Y/NS368T, Y448C/H, S556G NNI-site 5: C316Y/N, Y448C/H
NS5A inhibitors	■ **First NS5A generation:** genotypes 1-4 (1b>1a) (Daclatastivir, Ledipasvir, ABT-267) ■ **Second NS5A generation:** across all genotypes (MK-8742, ACH-3102, GS-5816, ABT-530)	Low genetic barrier High cross-resistance Improved genetic barrier	G1a: M28T, Q30E/R, L31F/M/V, Y93C/H/N G1b: L31F/M/V, Y93C/H/N

Lower SVR12 rates to Simeprevir among patients with G1a Q80K polymorphism at baseline



Lawitz E, et al. EASL 2015. Abstract

How common is Q80K?

Prevalence of Q80K and across different regions in simeprevir phase IIB/III studies

	All HCV GT	HCV GT1a	HCV GT1b
Overall	13.7%	29.5%	0.5%
Europe	6.1%	19.4%	0.3%
North America	34.4%	48.1%	0%
South America	3.3%	9.1%	0%

Lenz O et al. AASLD 2013. Abstract 1101

Will There Still Be a Role for IFN ± PI?

- *Easy to cure*
  - *IL28B* CC – high efficacy, short duration
  - Mild disease – option of IFN vs waiting for progression
- *Drug users - prisoners*
- *Co-infection HIV/HCV*

DAA and RAVs

- How Do We Best Manage Patients with RAVs?
- Should All Patients Have Baseline RAV Testing?
- How Long Before Retreating a Patient with RAVs?

The final challenge will be paying for…

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