British HIV Association
BHIVA

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Stanislas Pol	Speaker : GSK ; BMS ; Boehringer Ingelheim ; Janssen ; Gilead ; Roche ; MSD Grants : BMS ; Gilead ; Roche ; MSD Member of Advisory Board : GSK ; BMS ; Boehringer Ingelheim ; Janssen ; Gilead ; Roche ; MSD ; Abbott ; Novartis ; Sanofi
Date	**22 September 2012**

The impact of resistance in the management of HCV with DAAs

BHIVA
London,
3 October 2012

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Resistance associated variants (RAVs) to DAAs pre-exist

Antiviral potency and genetic barrier to resistance are both important

Resistance in the real life:

- definition and incidence
- impact of viral subtypes
-genetics of RAVs
- no impact of the lead in phase
- persistence of RAVs
- cross-resistance
- re-treatmentwithRAVs

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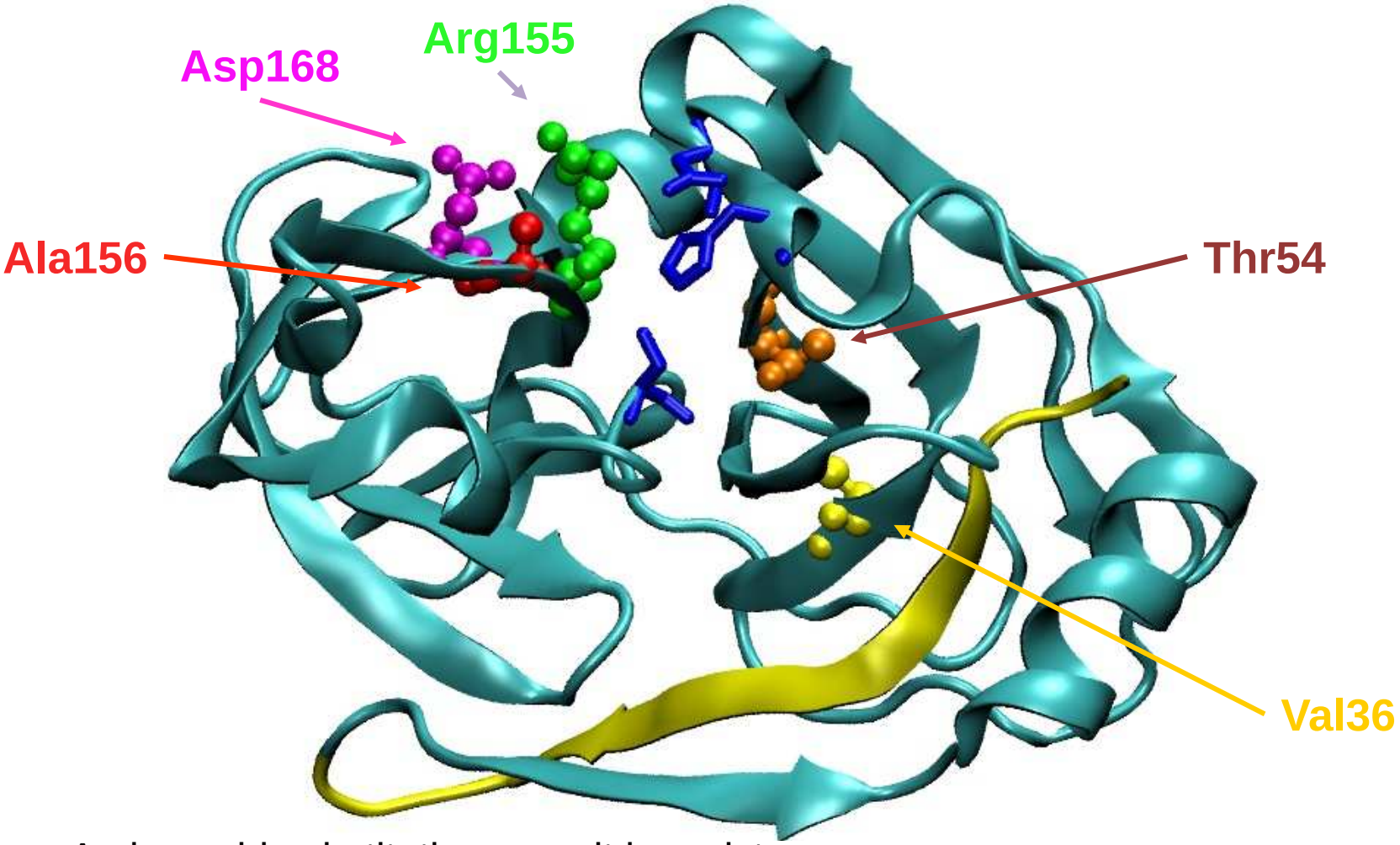
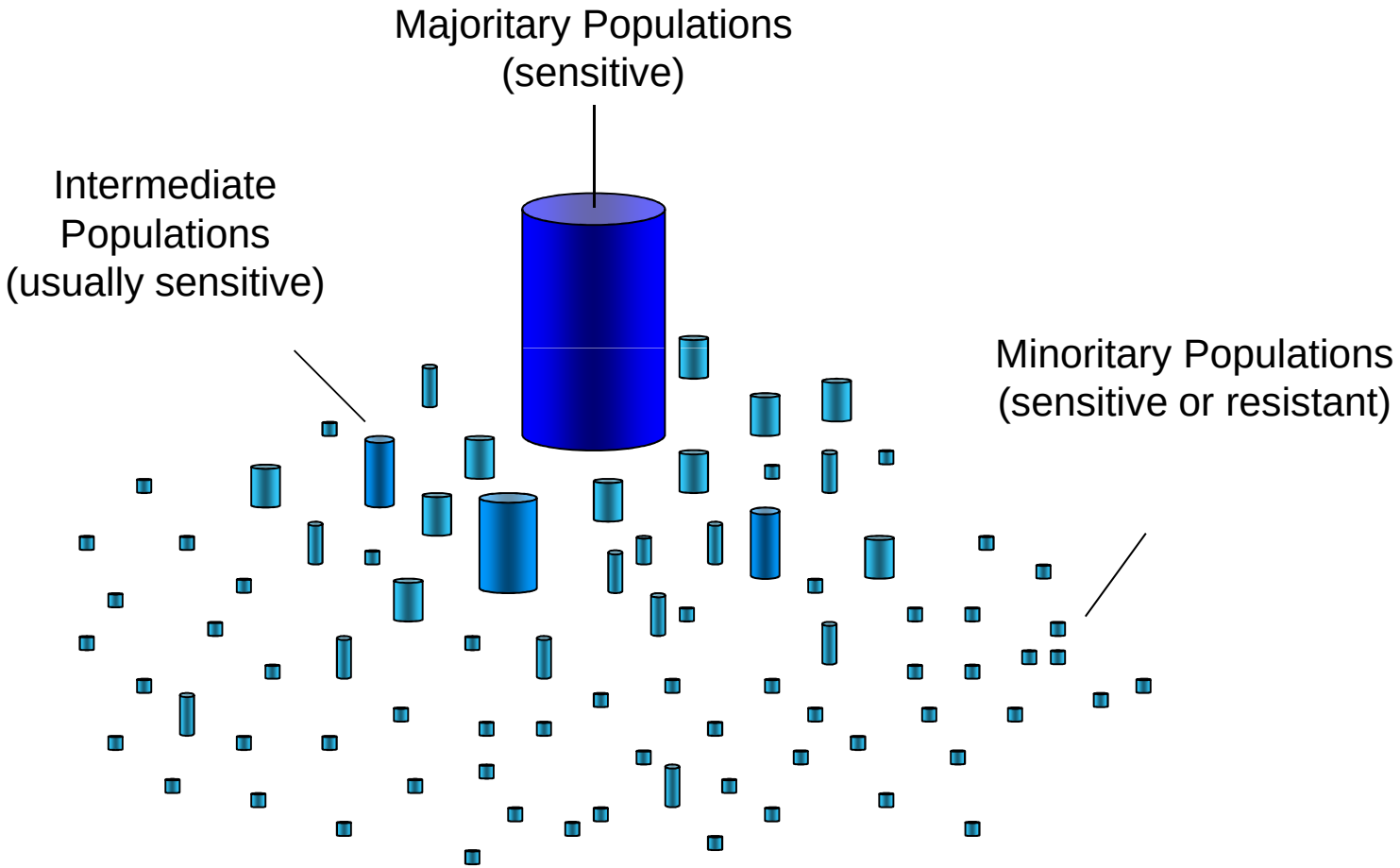


- Amino acid substitutions result in resistance

Pawlotsky JM, Ther Adv Gastroenterol 2009;2: 205-219

Resistance associated variants (RAVs) to DAAs pre-exist

Quasi-species distribution of HCV



Pawlotsky JM, Ther Adv Gastroenterol 2009;2: 205-219

Resistance associated variants (RAVs) to DAAs pre-exist: sensitivity of assays

Pt	IL28B geno-type*	Sub-type	Peg-IFN	RBV	TVR	Virologic Response	V36 A/M	T54 A/S	V55 A	Q80 R/K	R155 K/T/Q	A156 S/T/V	D168 A/V/T/H	I170 A/T
KHB	CT	1a				NR	–	90.0%	–	–	0.1%	0.4%	0.1%	0.5%
SF	CT	1a				NR	–	–	–	–	0.1%	1.1%	–	0.2%
LP	CT	1b				RR	–	–	–	–	0.5%	0.5%	–	0.2%
DT	TT	1b				RR	–	29.4%	–	–	–	1.3%	–	0.1%
SM	CT	1a				RR	–	–	–	–	0.1%	2.9%	0.1%	–
SG	CT	1b				RR	4.2%	–	–	–	0.1%	0.1%	0.1%	0.1%
PB	CT	1a				SVR	–	11.1%	–	0.7%	–	0.3%	–	0.3%
IM	CT	1a				SVR	–	–	–	–	0.1%	0.5%	0.1%	–
NT	CC	1a				SVR	–	–	–	–	0.6%	1.8%	–	–
HM	CC	1a				SVR	–	–	–	–	0.6%	–	–	0.1%
AZ	TT	1a				RR	–	–	100.0%	0.1%	6.0%	3.2%	0.1%	0.3%
VS	CT	1b				SVR	–	–	–	–	–	0.3%	–	0.1%
ES	CT	1b				SVR	–	–	–	–	0.2%	0.2%	–	0.8%
SC	TT	1b				NR	–	–	–	–	0.1%	0.2%	–	0.1%
NJ	CT	1b				SVR	–	–	–	–	0.4%	0.2%	0.1%	0.1%
AP	CT	1a				SVR	–	–	1.3%	0.5%	7.8%	0.2%	0.1%	0.1%
ML	CT	1a				SVR	–	47.4%	–	–	0.1%	0.4%	0.1%	0.1%
JK	CT	1b				SVR	–	20.0%	–	–	0.1%	0.4%	0.1%	0.1%

PROVE2 telaprevir study: PI resistance substitutions at baseline (UDPS sequencing; n=18)

*SNP rs12979860; cut-off: 0.1% according to statistical test based on Poisson's law

Chevaliez S, et al. J Hepatol 2011;54(Suppl. 1):S30

Resistance associated variants (RAVs) to DAAs pre-exist

Triple therapy with DCV + PR

- At baseline, polymorphisms at NS5A amino acid positions associated with resistance were observed in 13 of 36 patients treated with BMS-790052
- Overall, 11 patients treated with BMS-790052 met virologic failure criteria
  - Only 3 had baseline polymorphisms at positions associated with resistance (plus 1 lost to follow-up):
    - **GT 1a-NS5A:**-M28V, -H58P, -E62D
    - **GT 1b-NS5A:**-R30Q, -Q54H/N, -P58T/A/S, -Q62D/E, -A92E/V and -Y93H
  - Emerging resistance-associated variants detected in all patients who experienced viral breakthrough or relapse
    - **GT 1a-NS5A:** -Q30E/G, -Q30R-H58D, -Q30R/L31M, -L31M, and -L31M/Y93H
    - **GT1b-NS5A**:L28M-Y93H,P58A-Q62E-Y93H

Pol S et al. *Lancet ID* 201

Resistance associatedvariants (RAVs) to DAAspre-exist

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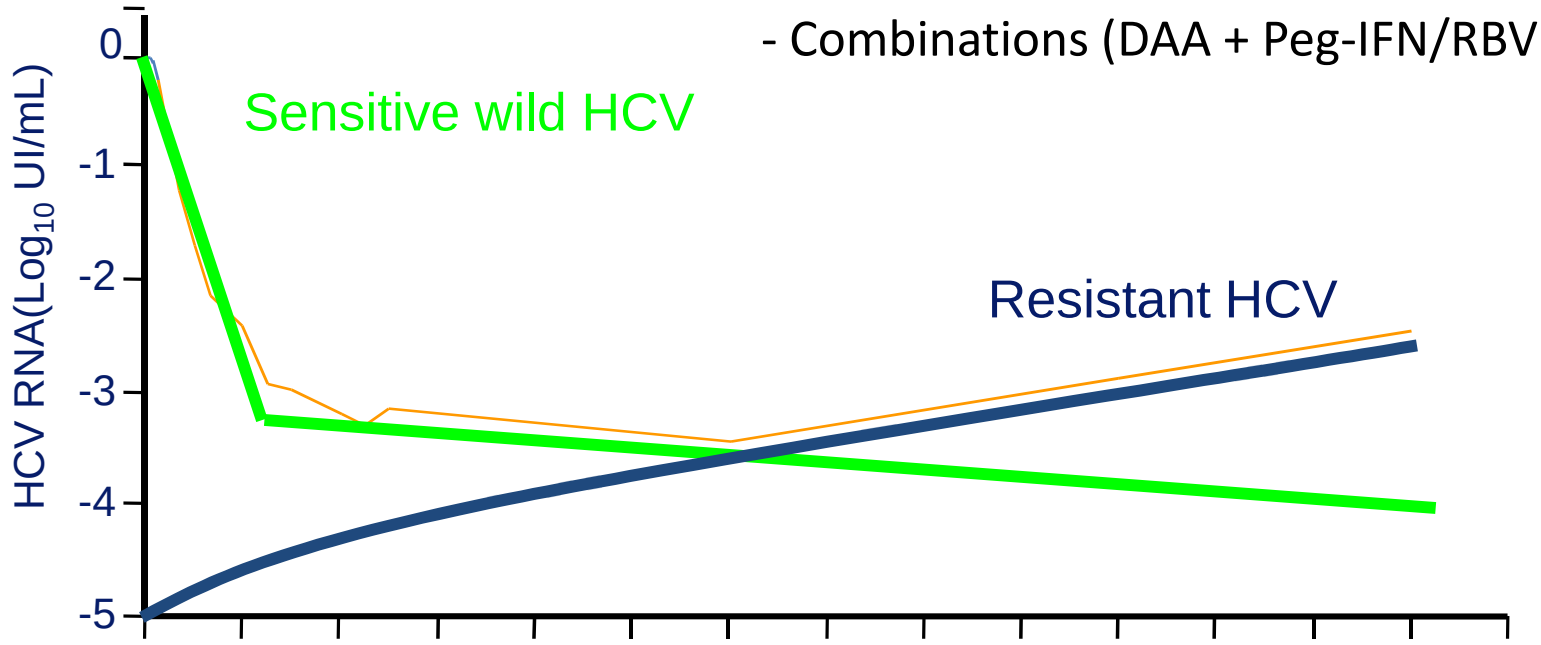
Antiviral potency and genetic barrier to resistance are both important

Virological

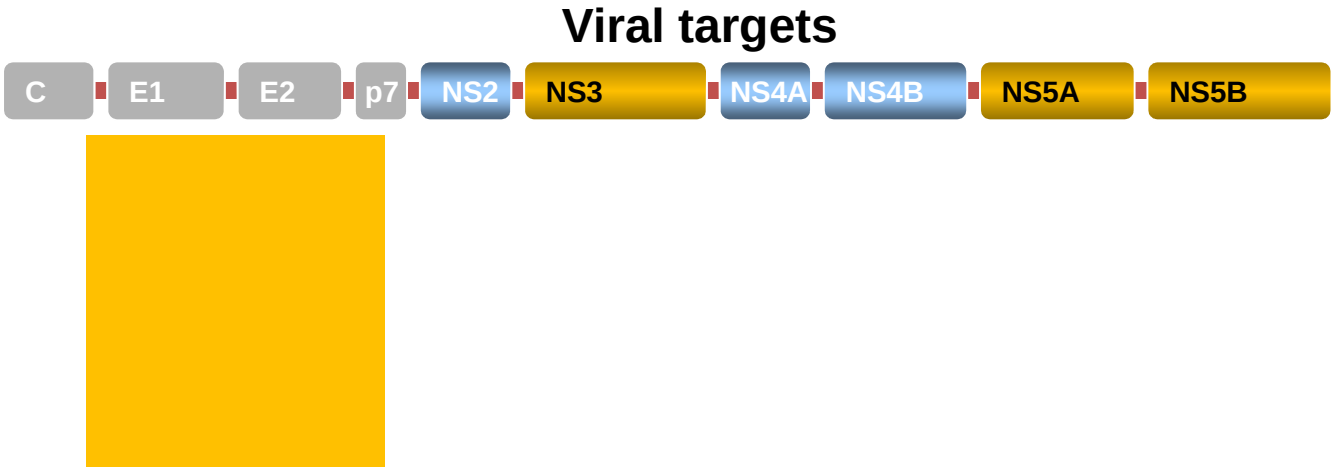
- Genetic Barrier
- Viral Fitness

Pharmacological

- Antiviral potency
- Pharmacokinetics
- Adherence/tolerability
- Combinations (DAA + Peg-IFN/RBV)



Antiviral potency and genetic barrier to resistance are both important



NS3	NS5A	NS5B	Cyclophilin A
The NS3/4A serine protease is essential for post-translational processing of HCV polyproteins[1]	Multifunctional membrane-associated phosphoprotein essential component of the HCV-RNA replication complex[2,3]	NS5B is an HCV-specific, RNA-dependent RNA polymerase[1]	Host protein involved in HCV replication through interaction with NS5A and the HCV polymerase[4]
Boceprevir **Telaprevir** ABT-450/r,ACH-1625 Asunaprevir, TMC-435 (Simeprevir),BI-201335 Danoprevir/r,GS-9451 MK-5172	Daclatasvir GS-5885 ABT-267 PPI-668	<u>Nucleos(t)ide analogue</u> GS-7977,Mericitabine, IDX-184* <u>Non-nucleoside analogue</u> BI-207127,ABT-333 ABT-072,BMS-791325 Tegobuvir,Setrobuvir VX-222,Filibuvir	Alisporivir** SCY-635

Adapted from 1. PawlotskyJM, et al. *Gastroenterology*2007;132:1979–98; 2. TellinghuisenTL, et al. *Nature*2005;435:374–9; 3. Gish R &Meanwell NA. *Clin Liver Dis*.2011;15:627–39; 4. Coelmont L, et al. *PLoSOne*2010;5:e13678.

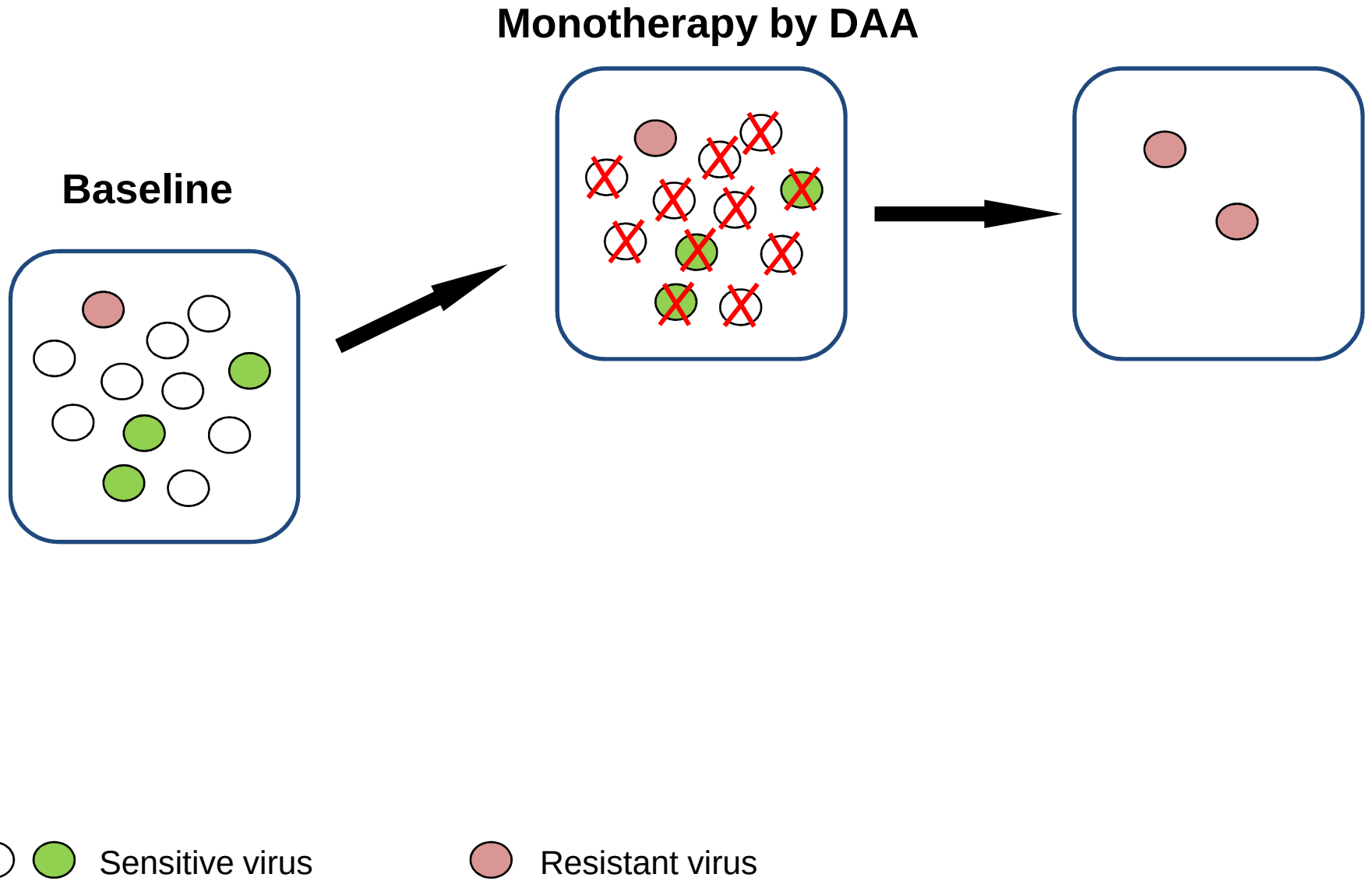
Antiviral potency and genetic barrier to resistance are both important

NS3/4A Protease Inhibitors	NS5A Replication Complex Inhibitor	NS5B Nucleos(t)ide Inhibitors	NS5B Non-nucleos(t)ide Inhibitors	Cyclophilin Inhibitors (HTA)
• Poor/no activity against GT3[1] • Low-to-medium barrier to resistance[1] • Extensive cross-resistance[1] • QD, BID or TID dosing • Potential for CYP-mediated DDIs[2,3]	• Picomolar activity against multiple GTs *in vitro*[4] • Low-to-medium barrier to resistance[1] • QD dosing[5,6] • Potential for CYP-mediated DDIs[7]	• Broad GT coverage[1] • High barrier to resistance[1] • QD or BID dosing[8] • Limited potential for CYP-mediated DDIs	• Most are GT/subtype specific[1] • Low barrier to resistance[1] • QD or BID dosing[8] • Limited potential for CYP-mediated DDIs[9]	• Broad GT coverage *in vitro*[1] • Limited resistance data available • BID/QD dosing[10] • Potential for CYP-mediated DDIs[9,11]

DDI=drug-drug interactions; HTA=host-targeted antiviral; GT=genotype

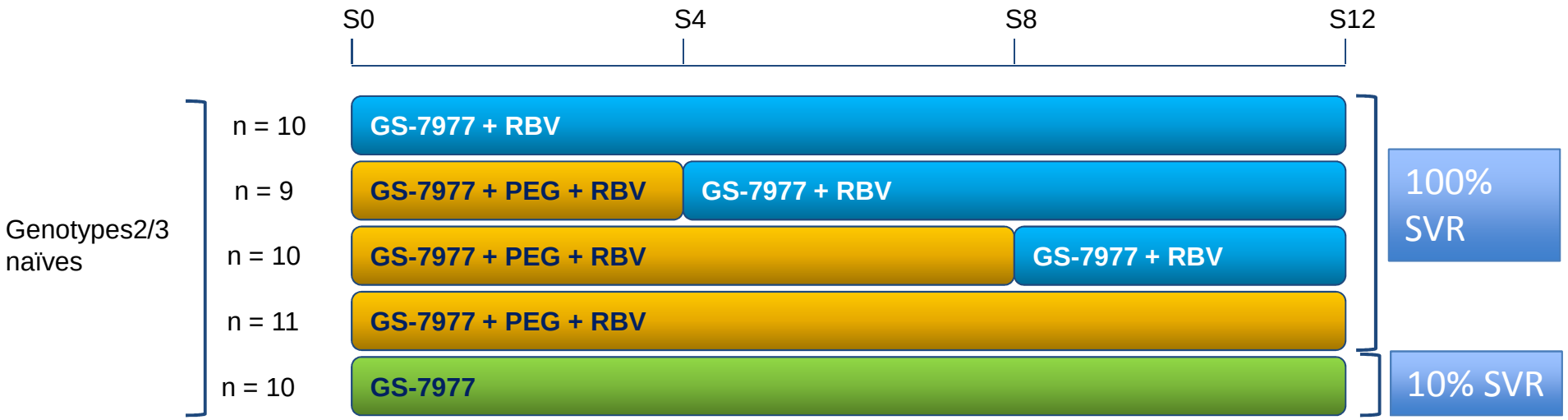
Created from 1.Sarrazin C, et al. *J Hepatol*. 2012;56:S88–S100; 2. Eley T, et al. AASLD 2011. Poster 381; 3. Sekar V, et al. EASL 2010, Poster 1076; 4. Gao M, et al. *Nature* 2010;465:96–100; 5. Pol S, et al. ICAAC 2011. Oral Presentation HI-376; 6. Lawitz EJ, et al. *J Hepatol*. 2012;Feb 4 [epub]; 7. Bifano M, et al. CROI 2012. Poster 618; 8. Poordad F, et al. *Am J Manag Care* 2011;17:S123–S130; 9. Seden K, et al. *J Antimicrob Chemother*. 2010;65:1079–1085; 10. Flisiak R, et al. EASL 2011. Oral 4; 11. Park S, et al. AASLD 2011. Abstract 364.

Antiviral potency and genetic barrier to resistance are both important



Antiviral potency and genetic barrier to resistance are both important

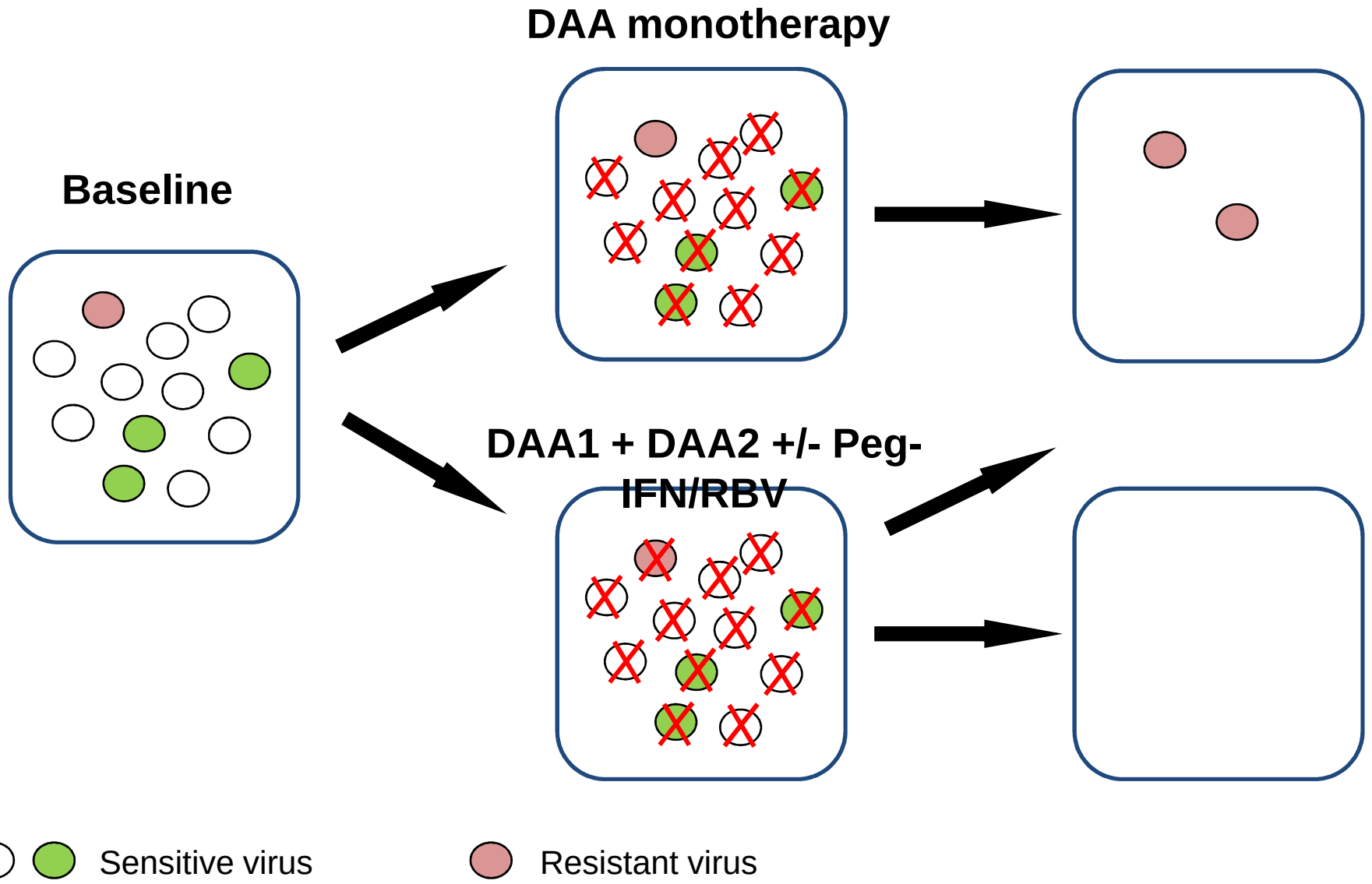
ELECTRON study



Gane EJ, EASL 2012, Abs. 1113

Antiviral potency and genetic barrier to resistance are both important

The genetic barrier to resistance is increased by combinations



Antiviral potency and genetic barrier to resistance are both important

Dual therapy with DCV + ASV in G1 null responders

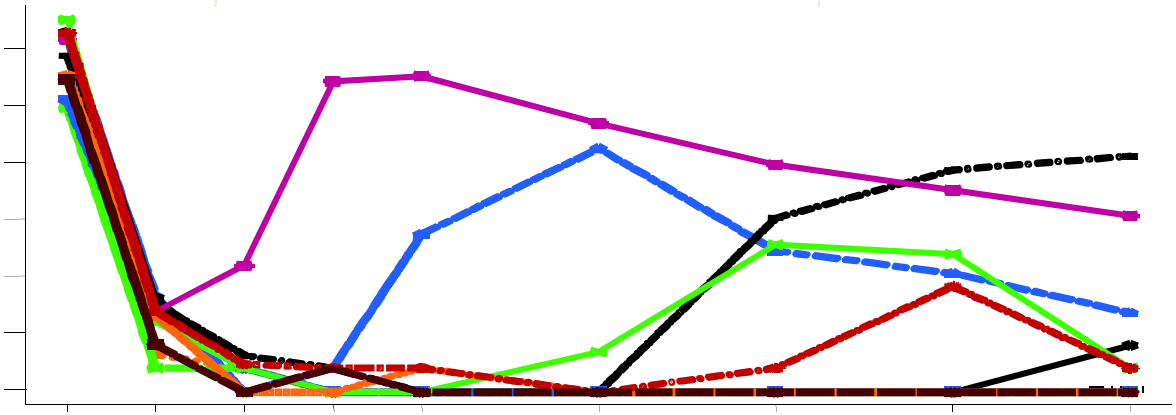
Group A

BMS-790052 (60 mg/d)
+
BMS-650032 (600 mg x 2/d)
(n = 11)

Post-treatment
Follow up: 48 weeks

24weeks of treatment

High rate of resistance in subtype 1a

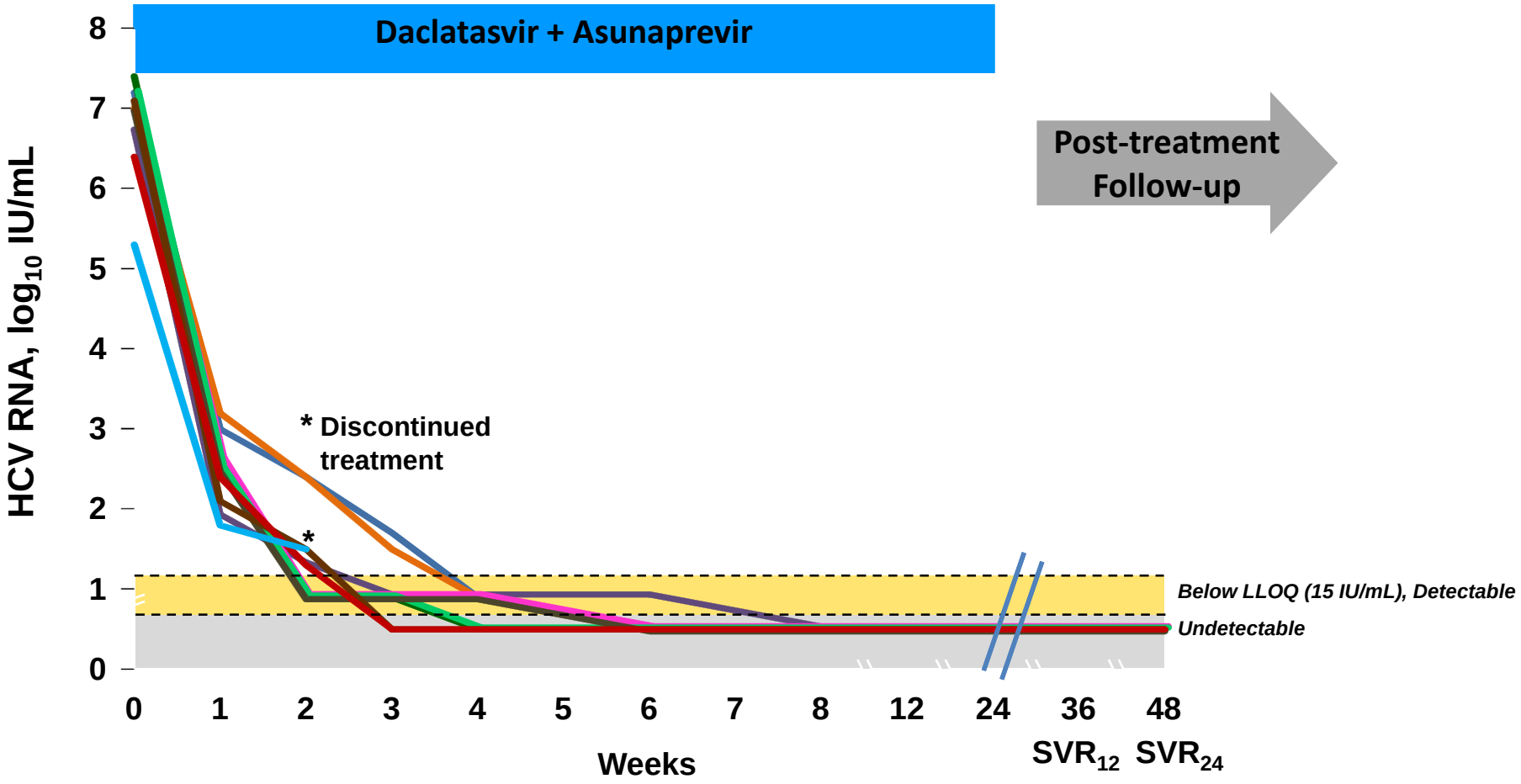


SVR24 = 36 %

Lok A.et al, NEJM 2012

Antiviral potency and gentic barrier to resistance are both important

Dual therapy with DCV + ASV in G1b null responders

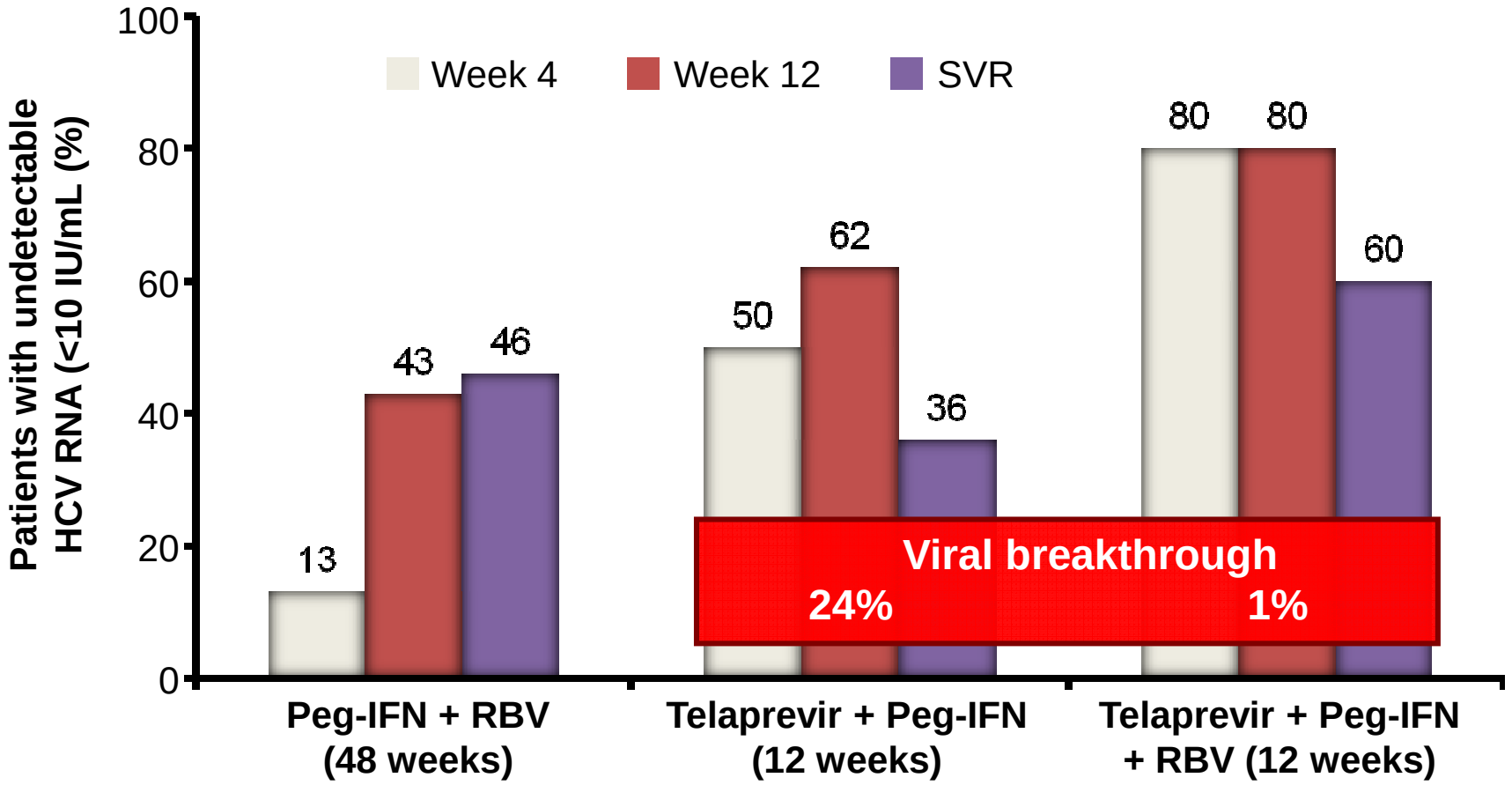


HCV RNA determined by Roche COBAS® TaqMan® HCV Auto assay (Roche Diagnostics KK, Tokyo, Japan), lower limit of quantitation (LLOQ)=15 IU/mL

Chayama K, et al. Hepatology 2012

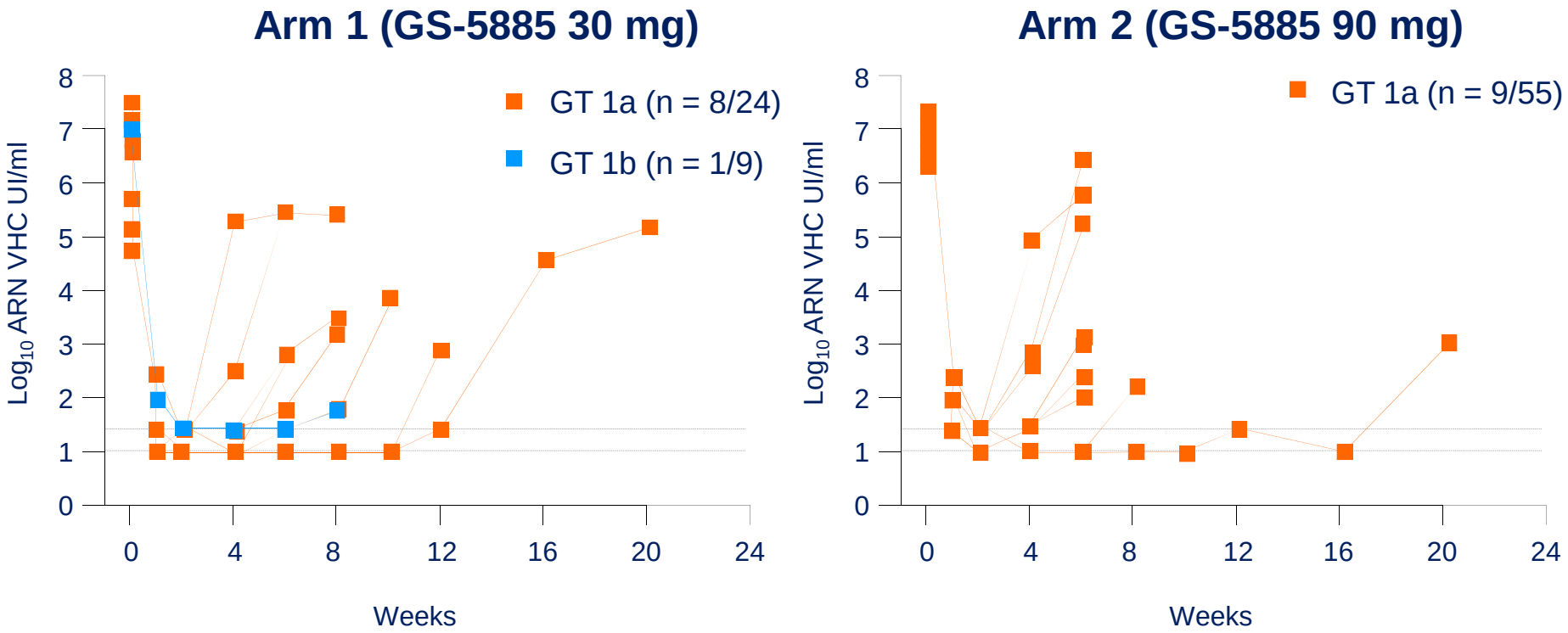
Antiviral potency and genetic barrier to resistance are both important

The genetic barrier to resistance is increased by combinations



Hézode C, et al. N Engl J Med 2009;360:1839–50

Oral Quad NS3/NS5A/NS5B inhibitors and ribavirin

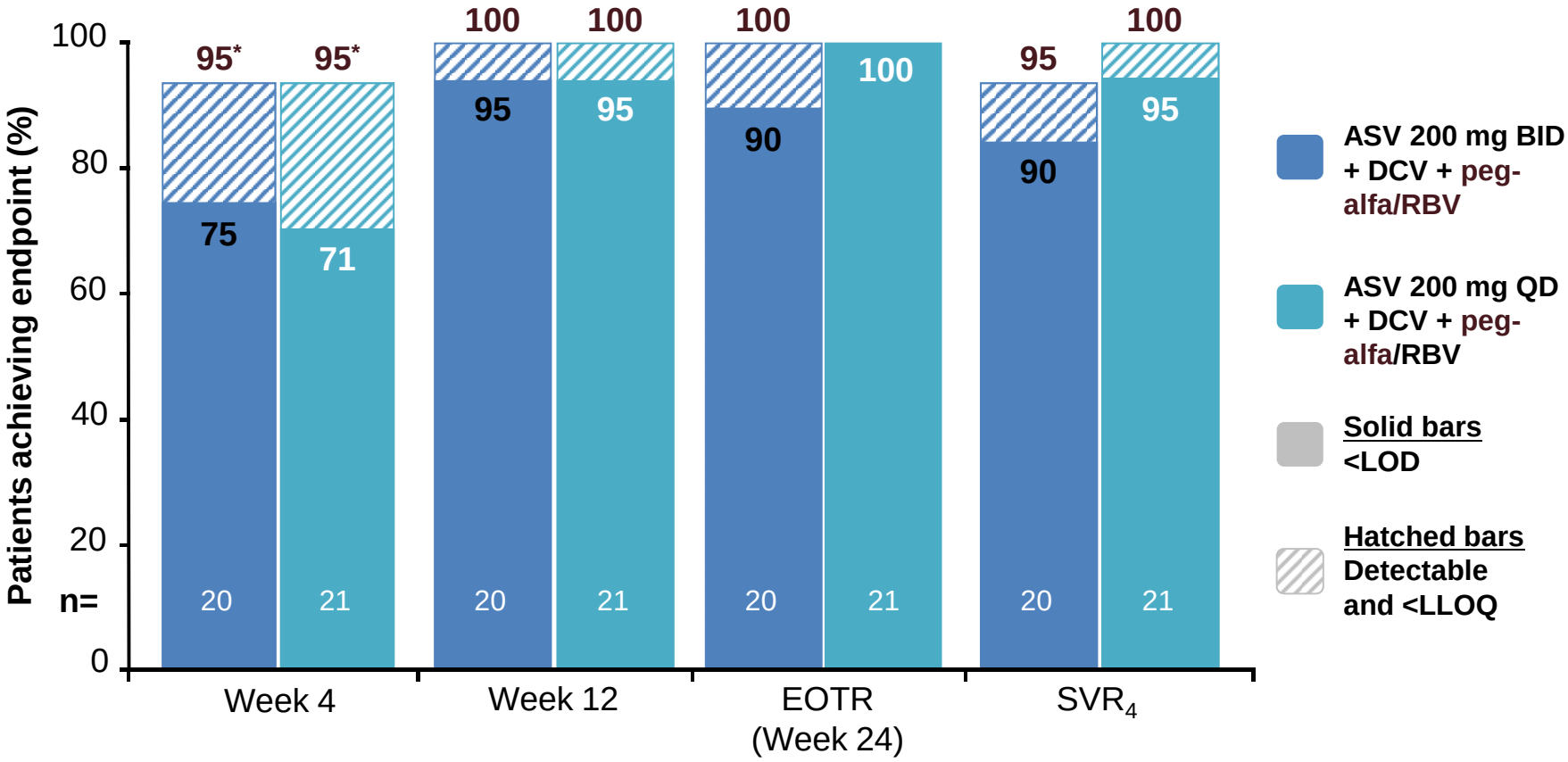


- Fair safety and high potency of this 12 weeks oral Quad
- Breakthrough occurred mainly in G1a

Sulkowski M, EASL 2012, Abs. 1421

Quad therapy with DCV + ASV + PR

Virological response rates



*1 patient with missing HCV-RNA measurement

1. ASV=asunaprevir; DCV=daclatasvir; EOTR=end-of-treatment response; LOD=lower limit of detection (~10 IU/mL); LLOQ=lower limit of quantitation (25 IU/mL); peg-alfa=pegylated interferon alfa-2a; RBV=ribavirin; SVR=sustained virological response

Adapted from Lok A, et al. EASL 2012. LB-1415.

Resistance associatedvariants (RAVs) to DAAspre-exist

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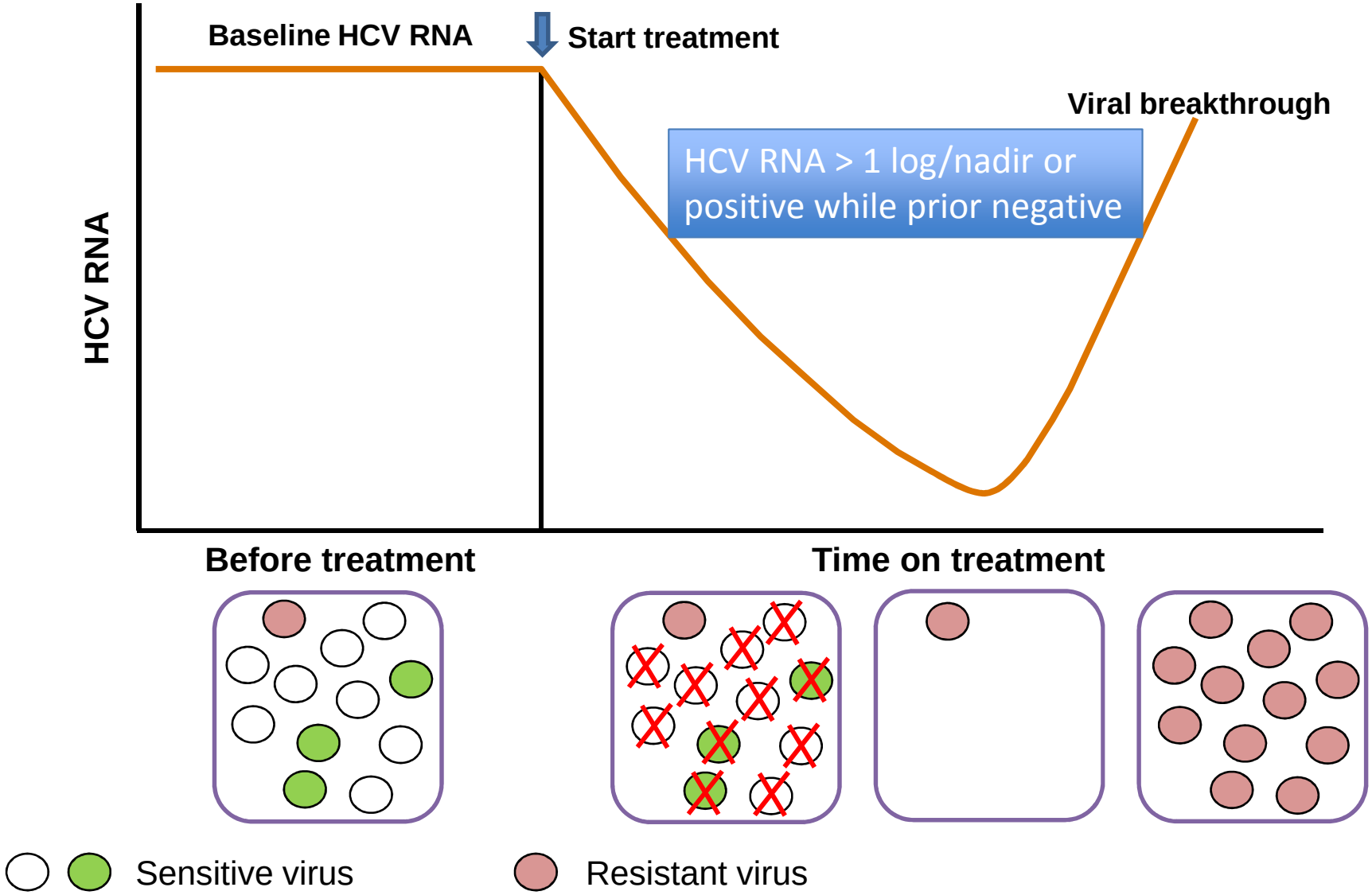
Regular monitoring of HCV RNA levels detects treatment failure and resistance

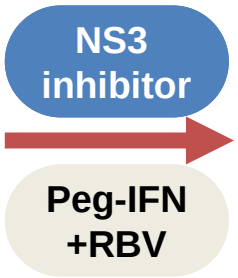


Incidence of resistance

Resistance emerges as a result of treatment failure

Wild-type virus

Resistant virus



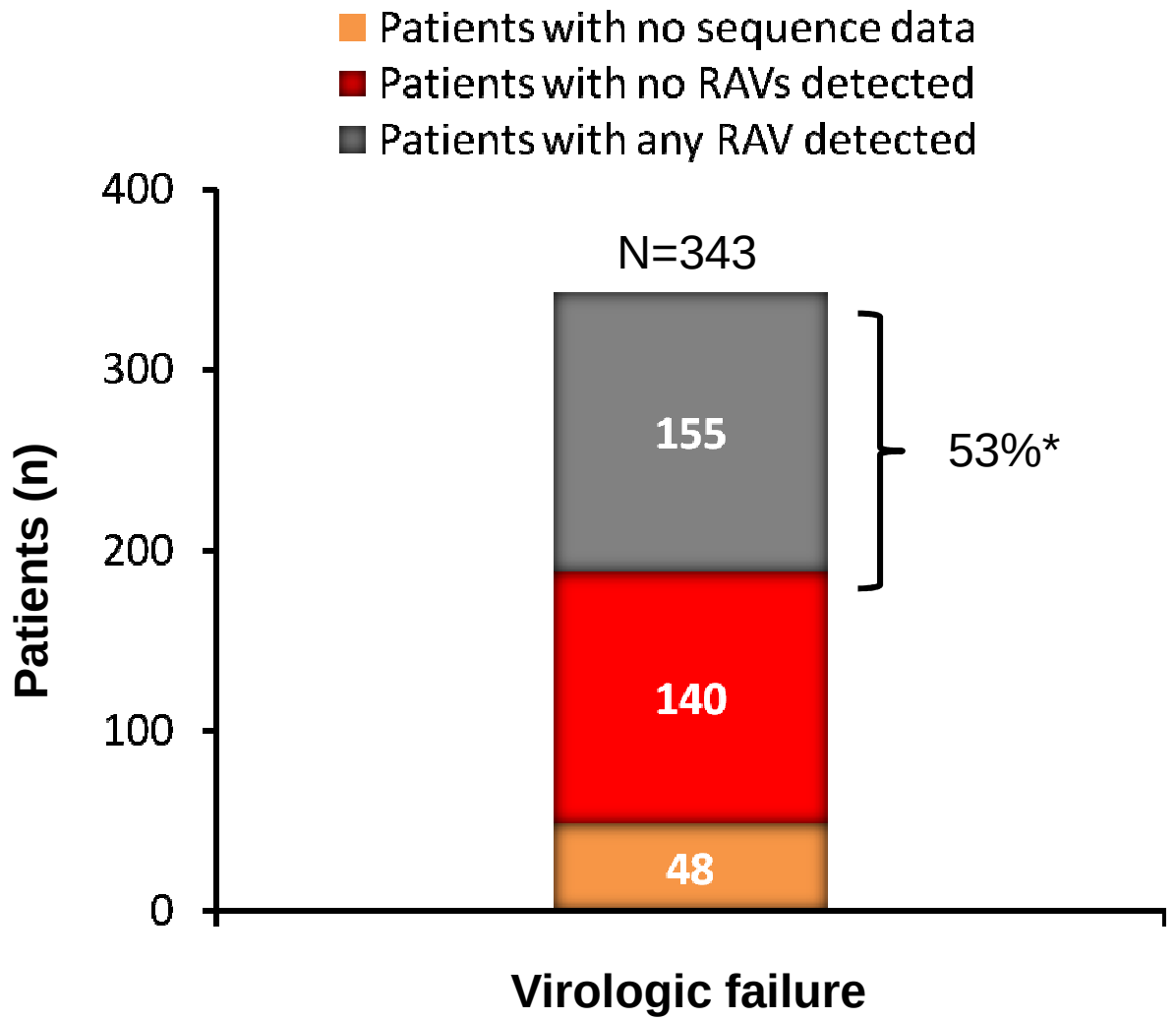
Treatment Failure: 30%

~15% discontinuations

~15% virologic failure
- **Never suppressed**
- **~5% breakthrough**
- **~10% relapse**

McHutchison JG, et al. N Engl J Med 2009;360:1827–38; Hézode C, et al. N Engl J Med 2009;360:1839–50; Kwo PY, et al. Lancet 2010; 376:705–16
Kieffer T, et al. Hepatology 2010;52(Suppl.):879A; Jacobson IM, et al.N Engl J Med 2011;364:2405–16
Sherman KE, et al. Hepatology 2010;52(Suppl.):401A; Poordad F, et al. N Engl J Med 2011;364:1195–206
Bacon BR, et al. N Engl J Med 2011;364:1207–17

Boceprevir Phase III trials: frequency of RAVs in non-SVR patients



*Denotes the percentage of patients with available resistance data
Data from patients that failed during or after boceprevir combination treatment within Phase III studies of treatment-naïve and -experienced patients (n=1057 enrolled)

Barnard RJ, et al. Hepatology 2011;54 (Suppl. S1):440A

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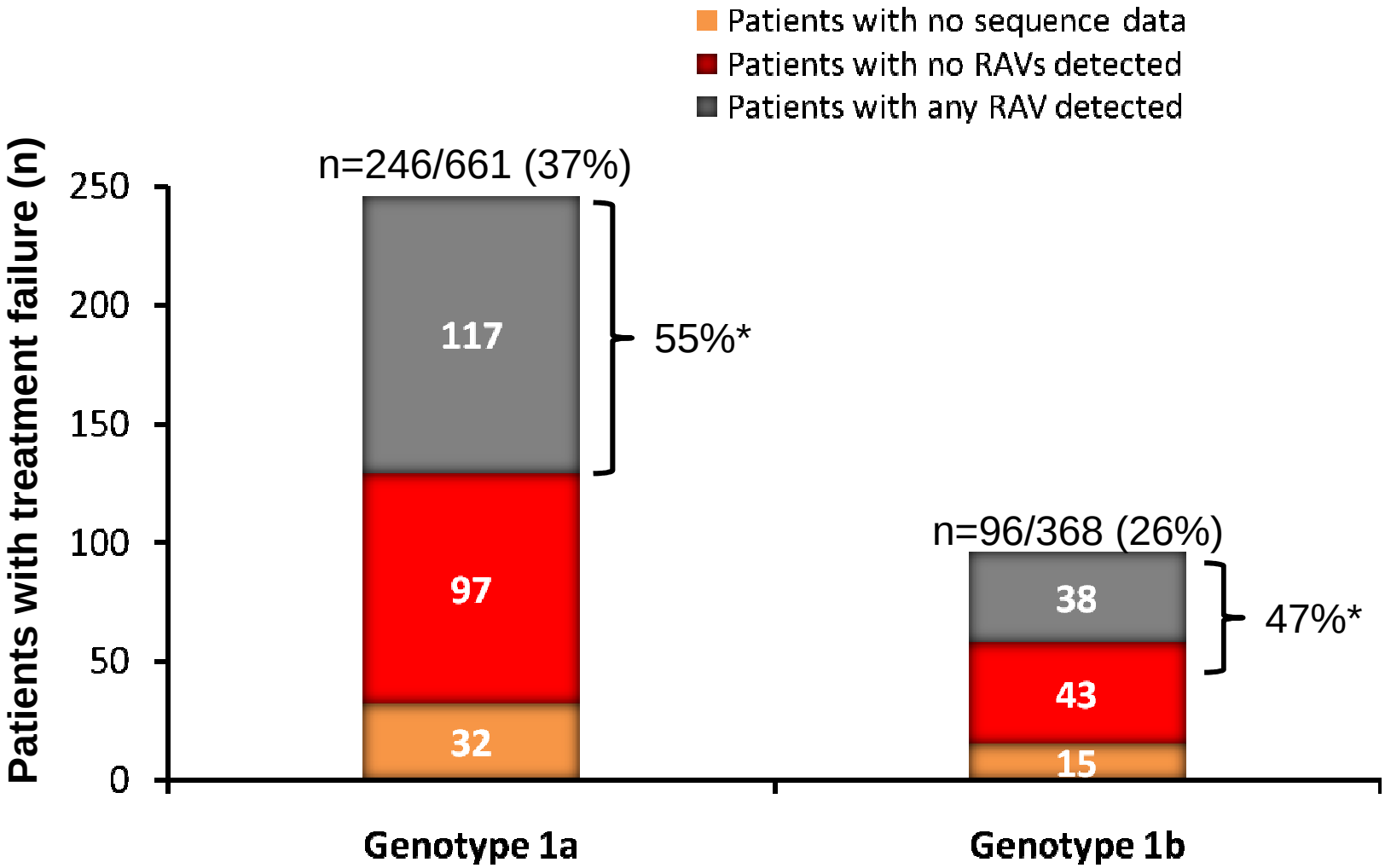
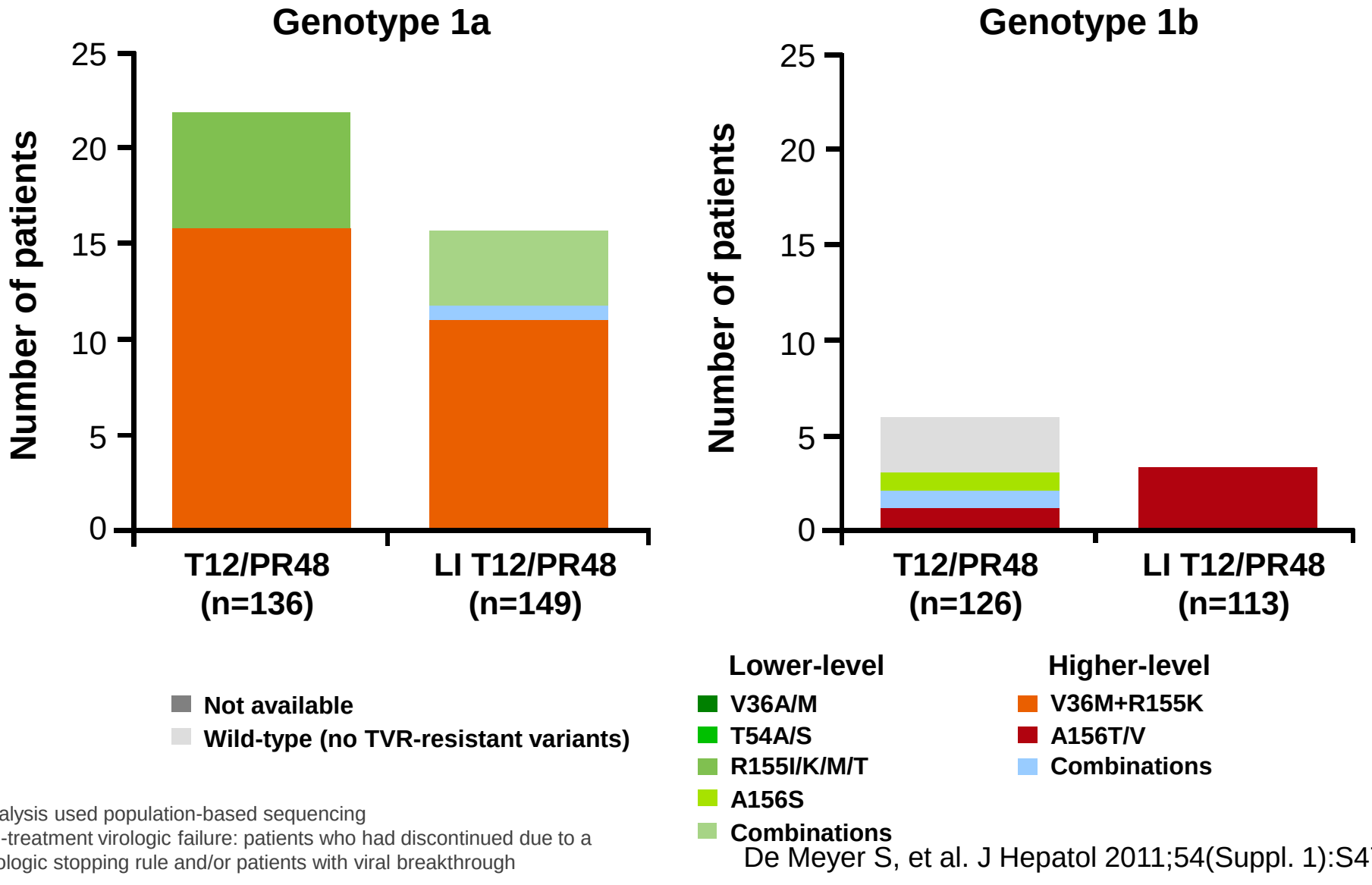
Boceprevir RAVs occurred more frequently in genotype 1a vs 1b HCV



Ogert RA, et al. Hepatology 2011;54 (Suppl. S1):794A

*Denotes the percentage of patients with available resistance data

Telaprevir RAVs occurred more frequently in genotype 1a vs 1b HCV (Realize)



Analysis used population-based sequencing
On-treatment virologic failure: patients who had discontinued due to a virologic stopping rule and/or patients with viral breakthrough

De Meyer S, et al. J Hepatol 2011;54(Suppl. 1):S475

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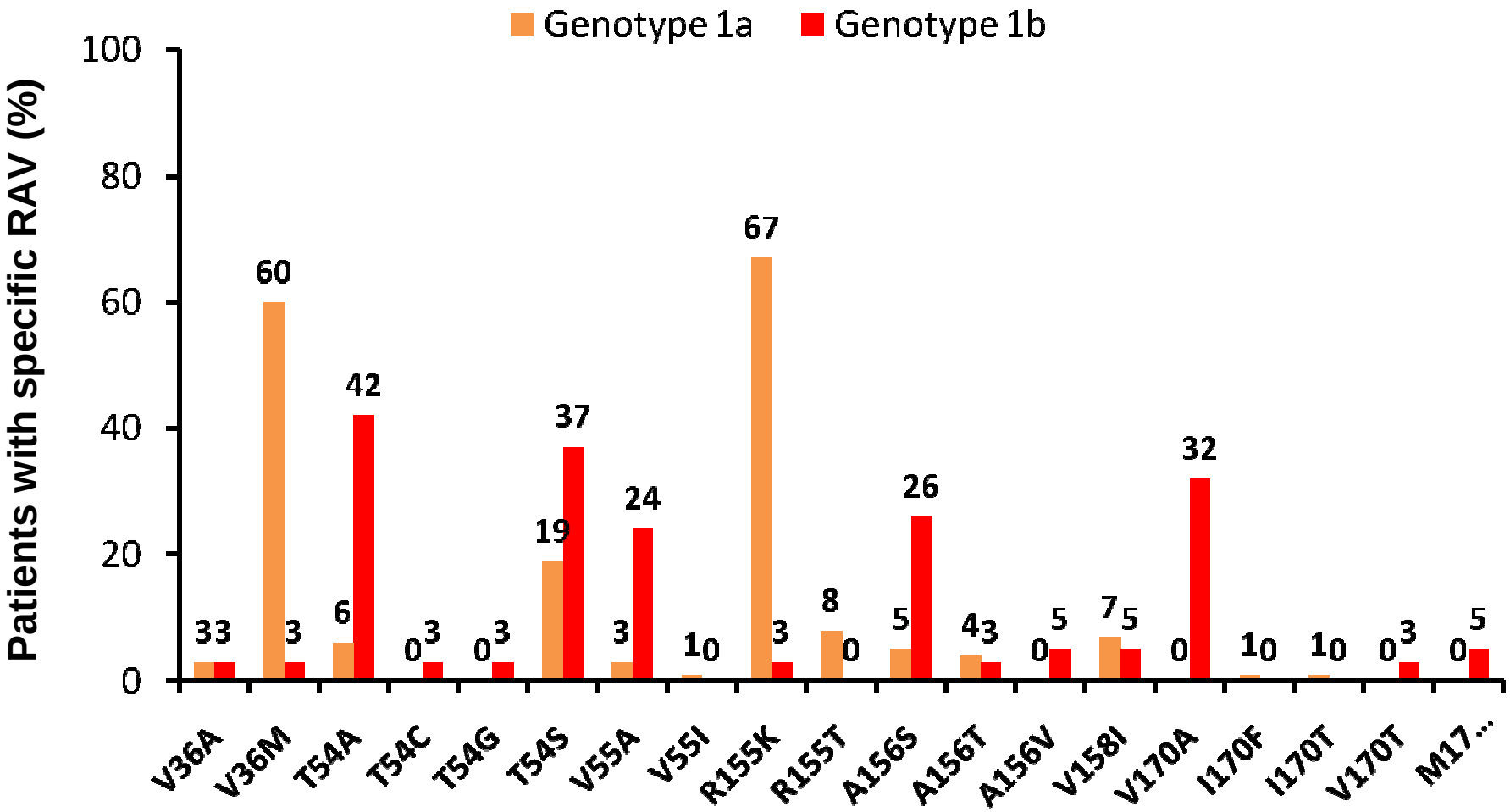
Frequency and distribution of boceprevir RAVs by genotype



Barnard RJO, et al. Hepatology 2011;54 (Suppl. S1):440A

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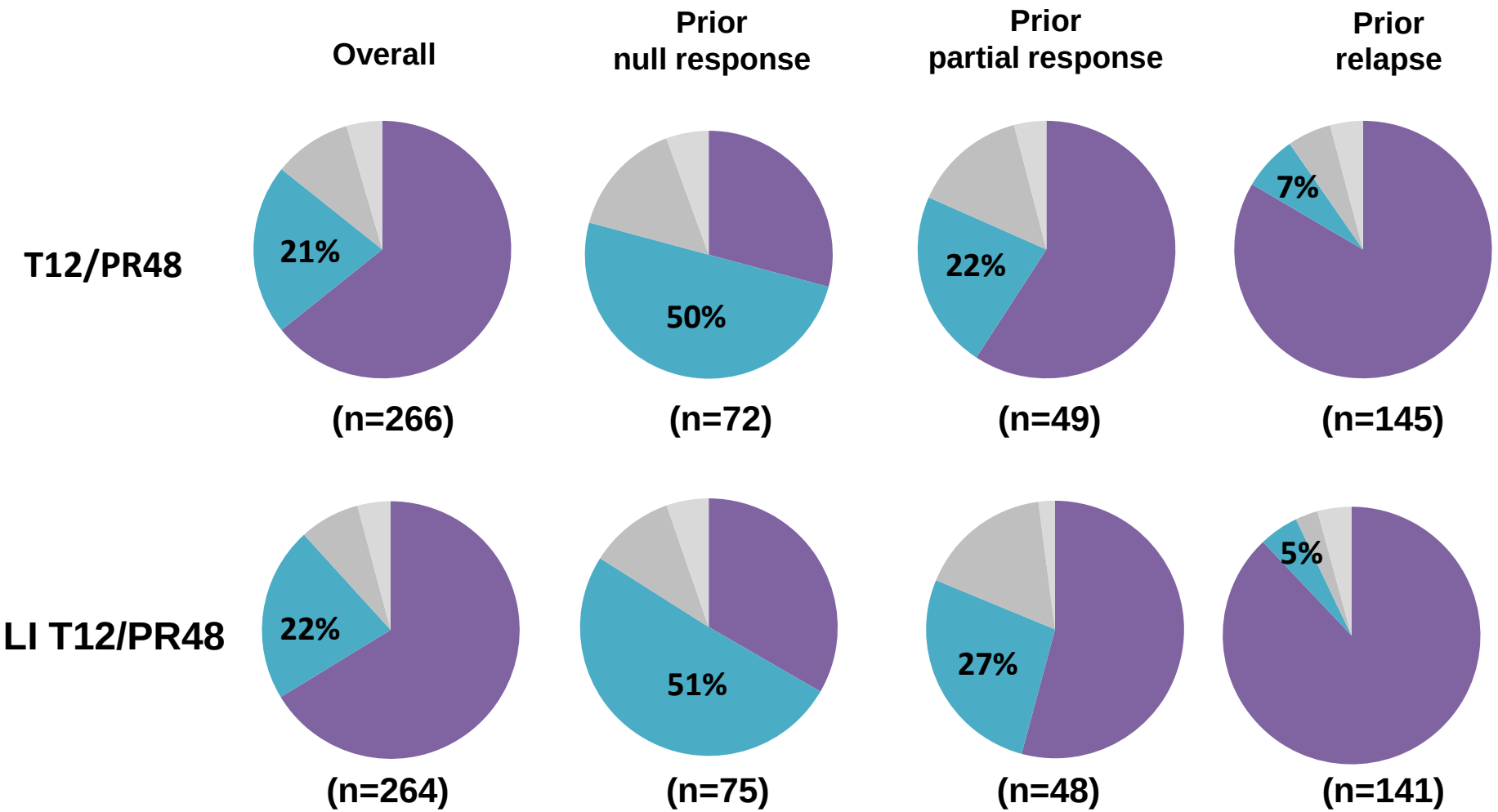
Realize: TVR-resistant variants at failure with or without a lead-in



De Meyer S, et al. Antivir Ther 2011;16(Suppl 1):A25

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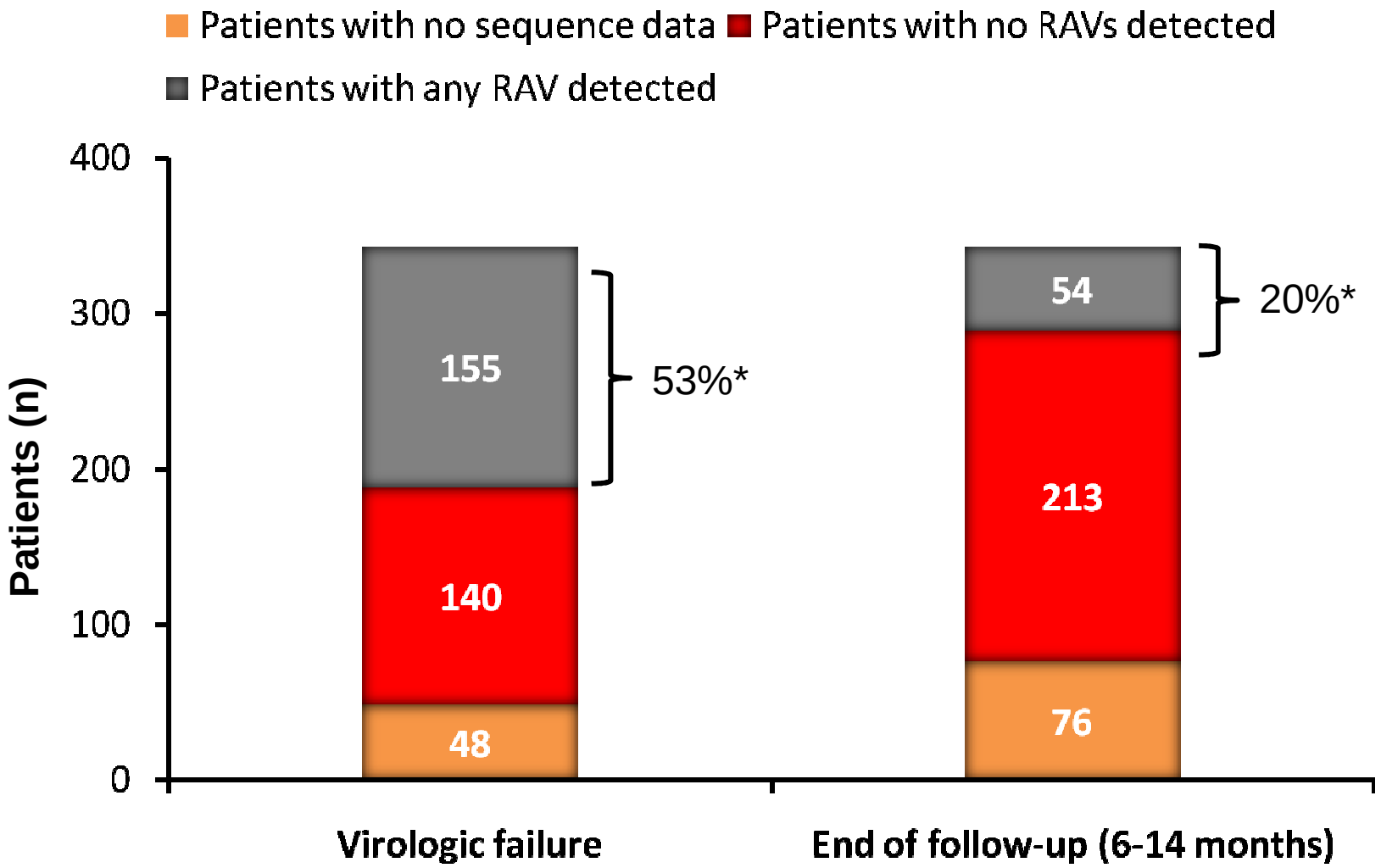
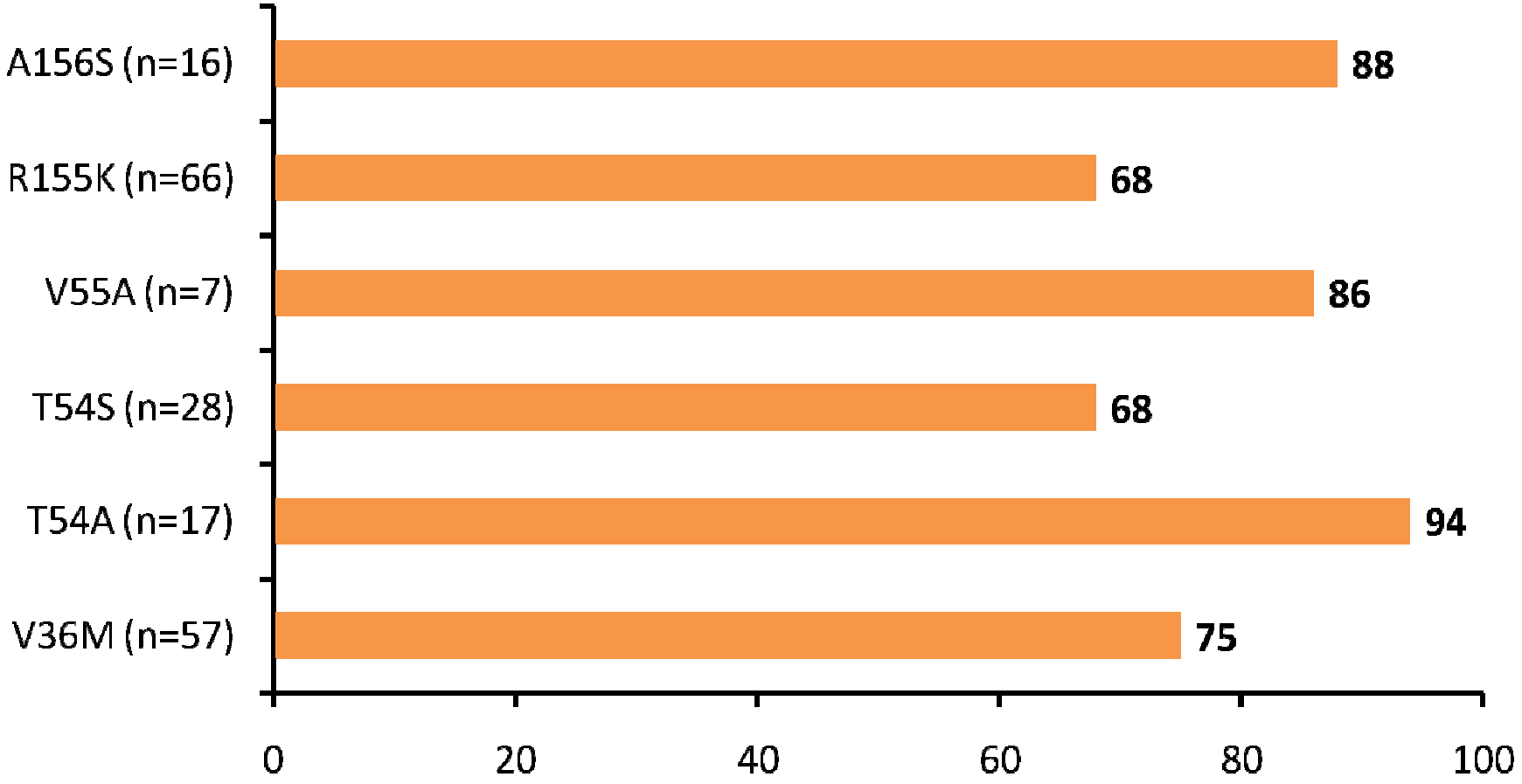
Boceprevir Phase III trials: follow-up of non-SVR patients with any detectable RAV



Barnard RJ, et al. Hepatology 2011;54 (Suppl. S1):440A

*Denotes the percentage of patients with available resistance data

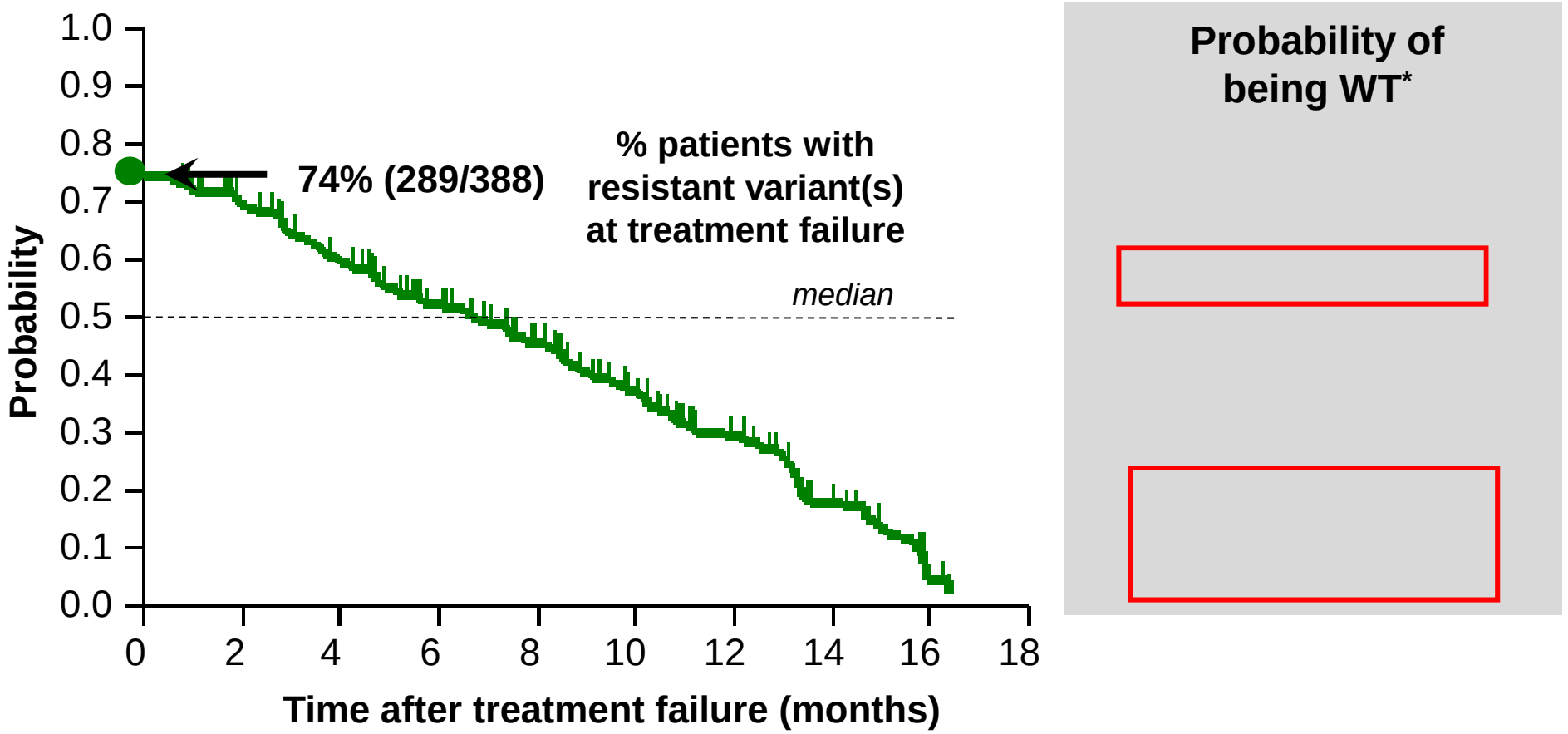
Boceprevir Phase III trials: detectability of most common RAVs* declines during follow-up



*In non-SVR patients with detectable RAVs at treatment failure in SPRINT-2 and RESPOND-2. As of latest follow-up time point (range 6–14 months)

Barnard RJ, et al. Hepatology 2011;54 (Suppl. S1):440A

Telaprevir Phase III trials: probability of RAVs being detected after treatment failure

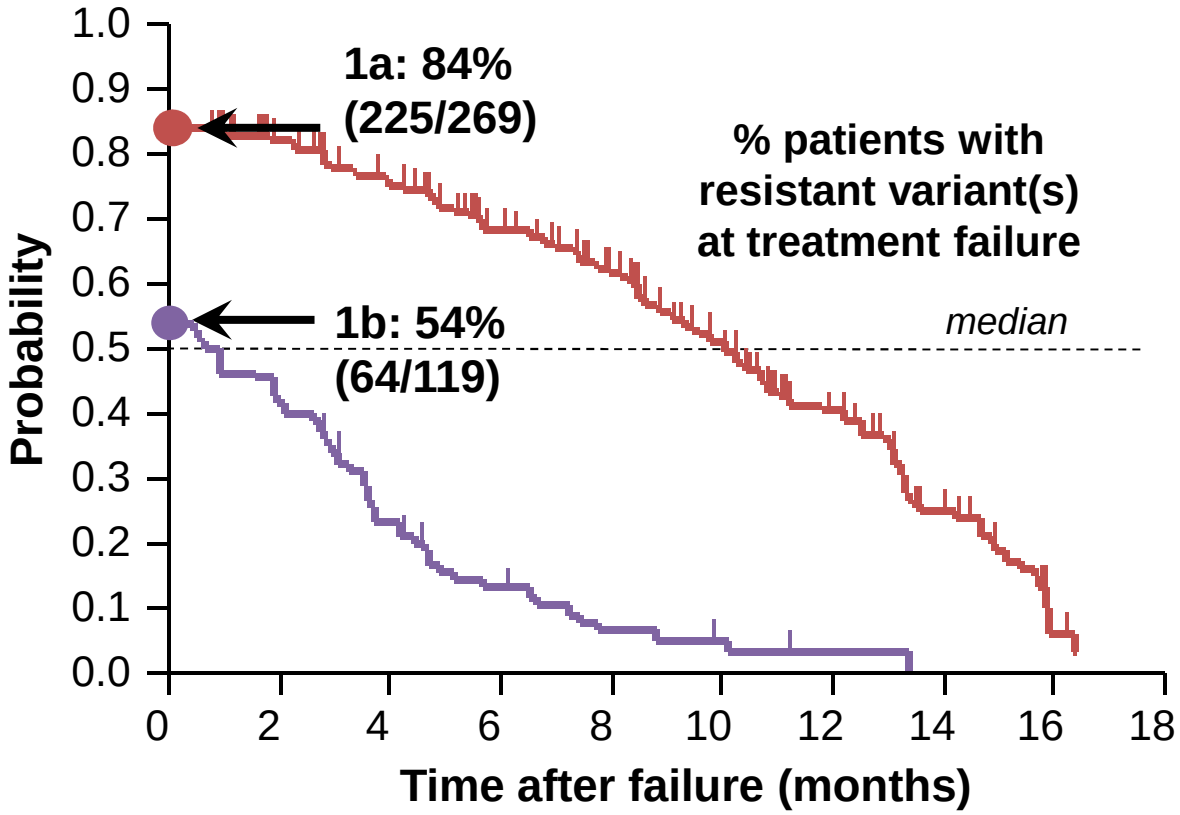


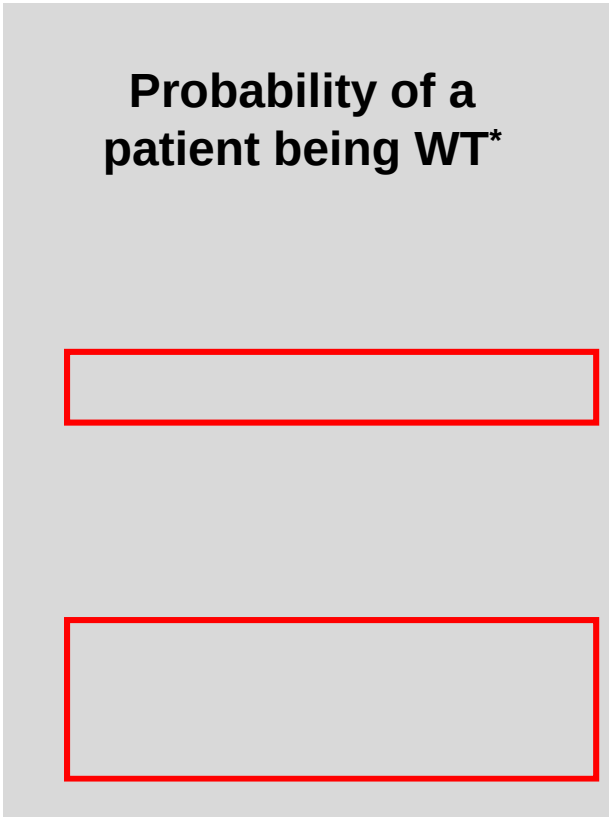
- Median time to WT by population sequencing: 7 months (95% CI: 5, 8)

*Based on Kaplan-Meier estimation using population sequencing; hash marks in plot indicate censored observations

Sullivan JC, et al. J Hepatol 2011;54(Suppl. 1):S4

Telaprevir Phase III trials: probability of RAVs being detected after treatment failure



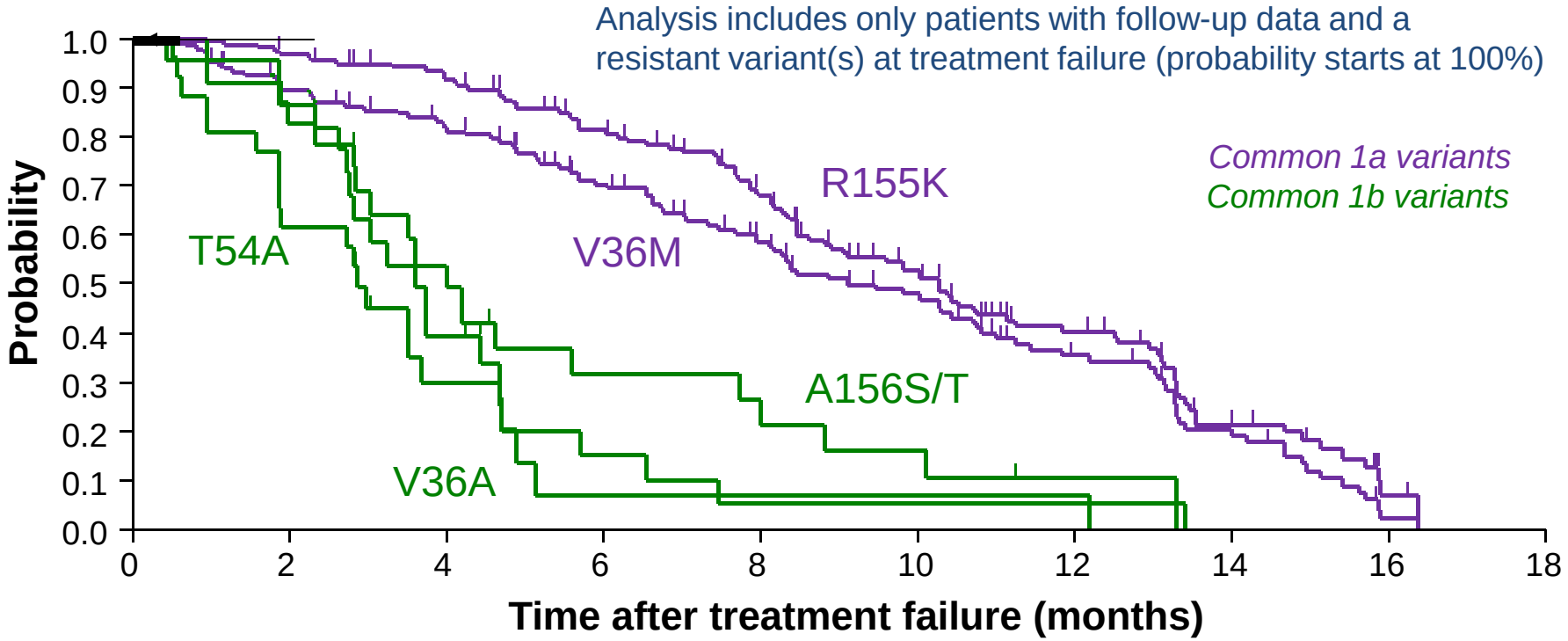


- Significant difference ($p<0.0001$) between genotype subtypes for the time to become wild-type by population sequencing (median, 95% CI)
  - 10 months (9,11) for genotype 1a, 0.8 months (0,2) for genotype 1b

*Based on Kaplan-Meier estimation using population sequencing; hash marks in plot indicate censored observations

Sullivan JC, et al. J Hepatol 2011;54(Suppl. 1):S4

Telaprevir Phase III trials: loss of resistant variants according to NS3 position



	V36M	R155K	V36A	T54A	A156S/T
Median months to loss (95% CI)	9 (8,11)	10 (9,11)	4 (3,4)	3 (2,4)	4 (3,6)

Sullivan JC, et al. J Hepatol 2011;54(Suppl. 1):S4

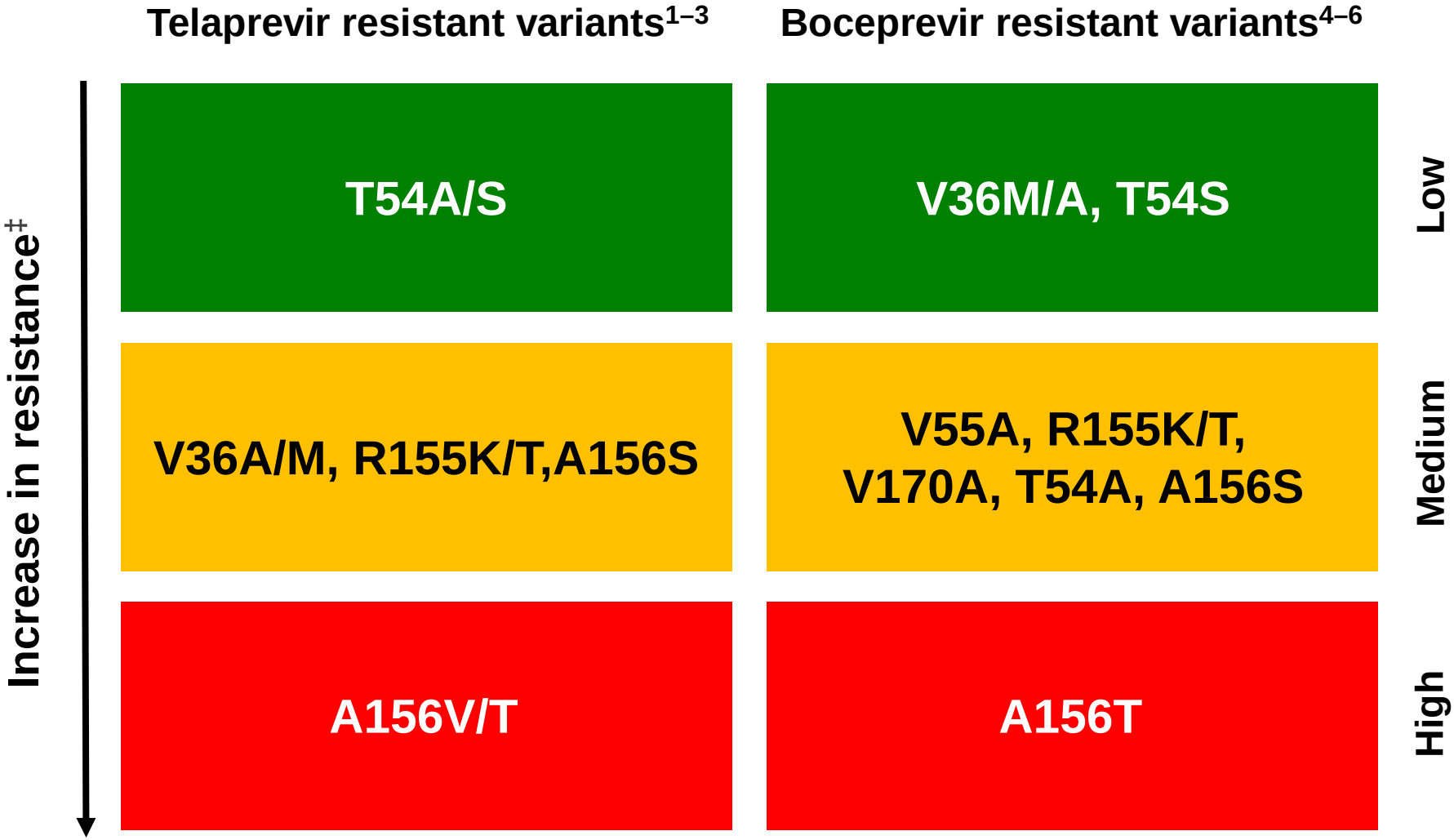
Resistance associatedvariants (RAVs) to DAAspre-exist

Antiviral potency and geneticbarrier to resistance are both important

Resistance in the real life:

- definition and incidence
- impact of viral subtypes
-genetics of RAVs
- no impact of the lead in phase
- persistence of RAVs
- cross-resistance
- re-treatmentwithRAVs

Single resistant variants associated with telaprevir and boceprevir*



*Double mutants have also been reported with telaprevir and boceprevir; ‡Measured by fold change in IC_{50} in the HCV replicon assay

1. Kieffer T, et al. Hepatology 2007;46:631–9
2. Kieffer T, et al. Hepatology 2010;52(Suppl.):879A; 3. De Meyer S, et al. J Hepatol 2011;54(Suppl. 1):S475
4. Susser S, et al. Hepatology 2009;50;1709–18; 5. Zeuzem S, et al. J Hepatol 2011;54(Suppl. 1):S4
6. Ogert RA, et al. Hepatology 2011;54 (Suppl. S1):794A

Lack of cross-resistance between Peg-IFN/RBV and DAAs

		DAA class							
Amino Acid	HCV Target	NS3 Linear	NS3 Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb	IFN	RBV
V36	NS3 Protease	R	S	S	S	S	S	S	S
T54		R	S	S	S	S	S	S	S
V55		R	S	S	S	S	S	S	S
V170		R	S	S	S	S	S	S	S
R155		R	R	S	S	S	S	S	S
A156		R	R	S	S	S	S	S	S
Q80		S	R	S	S	S	S	S	S
D168		S	R	S	S	S	S	S	S
M28	NS5A	S	S	R	S	S	S	S	S
Q30		S	S	R	S	S	S	S	S
L31		S	S	R	S	S	S	S	S
Y93		S	S	R	S	S	S	S	S
S282	NS5B	S	S	S	R	S	S	S	S
C316		S	S	S	S	R	S	S	S
M414		S	S	S	S	R	S	S	S
Y448		S	S	S	S	R	S	S	S
R422		S	S	S	S	S	R	S	S
M423		S	S	S	S	S	R	S	S
P495		S	S	S	S	S	R	S	S

R: resistant (>4-fold increase in EC_{50})
S: susceptible (<4-fold change in EC_{50})

Kieffer T, et al. J Antimicrob Chemother 2010;65:202–12
Gao M, et al. Nature 2010;465:96–100; Lagrace L, et al. Hepatology 2010;52(4 Suppl):1205A
Lenz O, et al. Hepatology 2010;52(4 Suppl):709A; Zeuzem S, et al. Hepatology 2010;52(4 Suppl):400A

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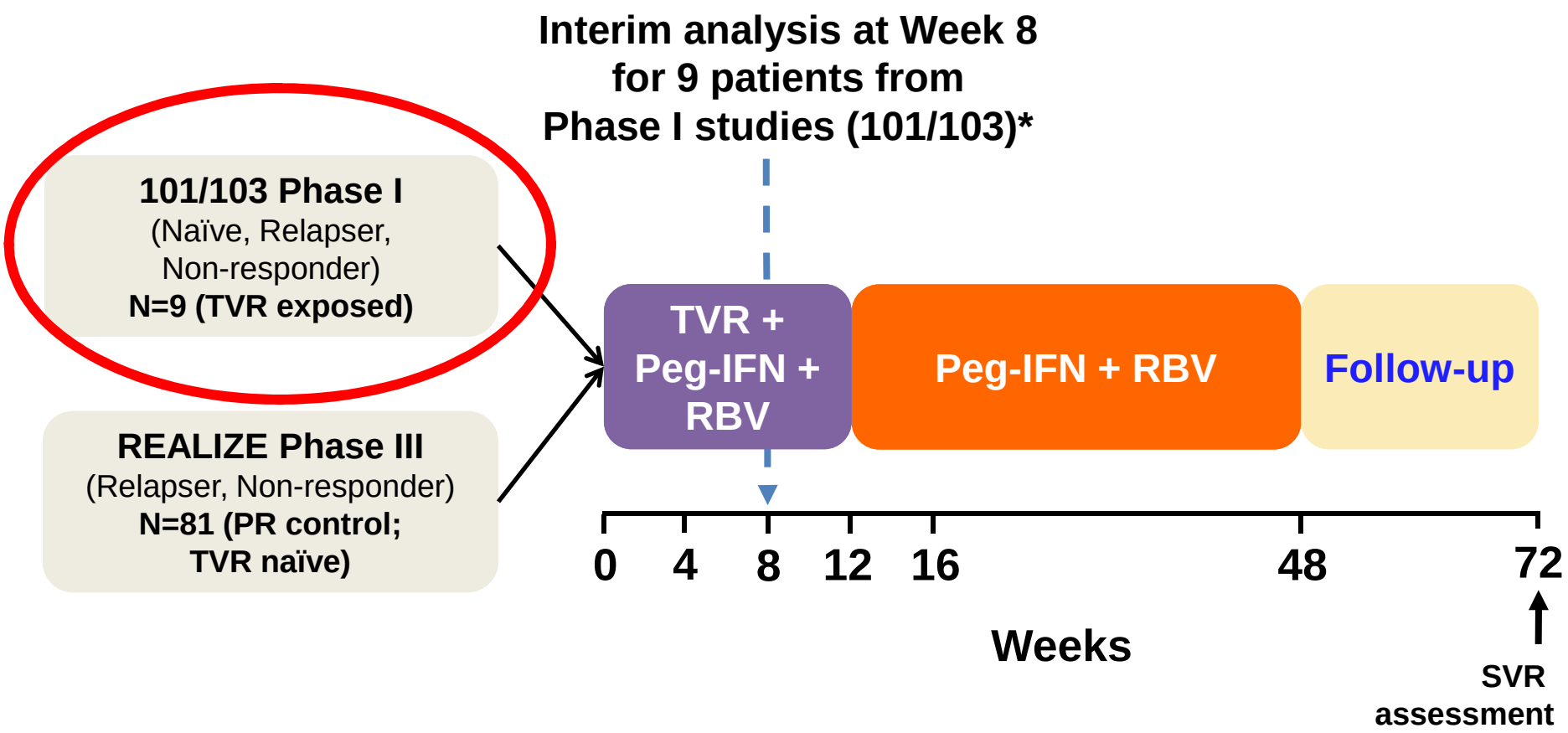
- re-treatment with RAVs

C219: Phase IIIb, open-label, roll-over study



*All 9 patients had completed Week 8 of treatment at the time of the analysis; Peg-IFN alfa-2a=180µg/week RBV=1000–1200 mg/day; TVR=750 mg every 8 hours; HCV RNA determined using Roche COBAS TaqMan® assay version 2.0 (lower limit of quantification [LOQ] 25 IU/mL, lower limit of detection [LOD] approximately 10 IU/mL)

Sarrazin C, et al. Hepatology 2011;54 (Suppl. S1):377A

C219: virologic response* to TVR-based treatment (previously TVR exposed)

Week	Responders, n (%)	
	<25 IU/mL HCV RNA	<25 IU/mL 'undetectable' HCV RNA
1	3 (33)	0
2	6 (67)	1 (11)
4	8 (89)	3 (33)
6	7 (78)	6 (67)
8	8 (89)	6 (67)

TVR-resistant variants during Phase I Studies 101 and 103: V36A/M+R155K/T/G (n=6); A156T/V (n=1); V36A+T54A (n=1); one patient with HCV RNA <100 IU/mL at end of treatment had wild-type virus during follow-up

No variants were detected by population sequencing before initiation of Study C219

Sarrazin C, et al. Hepatology 2011;54 (Suppl. S1):377A

*Week 8 interim analysis

The impact of resistance : conclusions

- Resistance associated variants (RAVs) to DAAs pre-exist

- Antiviral potency and genetic barrier to resistance are important to limit the occurrence of resistance

- Resistance is not frequent , depends on viral subtypes and may be by-passed by adapted combinations of DAAs

-Dual, Triple or Quad regimen should be tailored to the host- and virus-related factors (subtype, fibrosis, prior therapies and tolerance, co-morbidities, DDI): the best “à la carte” combination