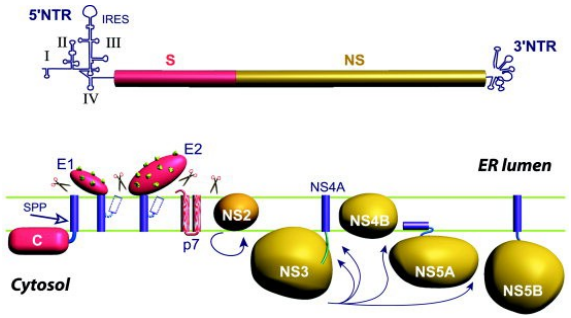
How to optimize current therapy of non G1 patients: Genotype 3



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PHC, 13.01.2014

UNIVERSITÉ PARIS DESCARTES

AFEF
ASSOCIATION FRANÇAISE POUR L'ETUDE DU FOIE

ANRS France REcherche Nord & sud Sida-hiv Hépatites
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CENTRE DE RECHERCHE

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

Disclosures

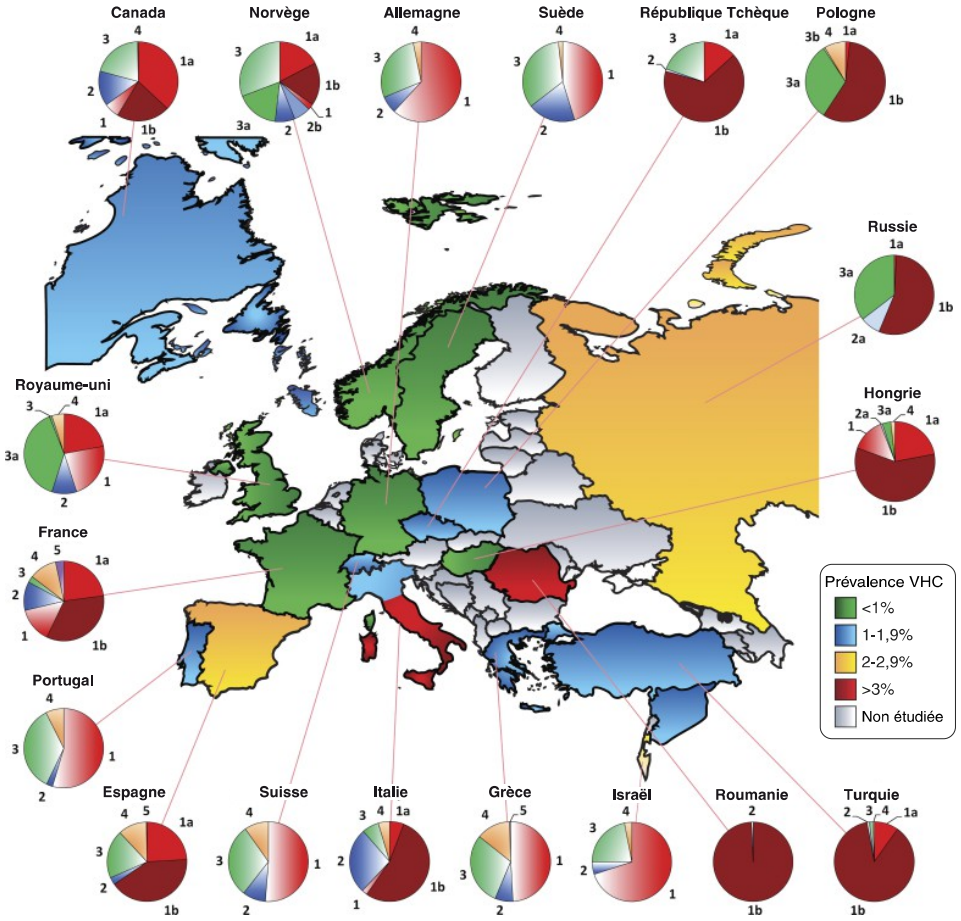
I have financial relationship(s) within the last 12 months relevant to my presentation with:

Consulting: Bristol-Myers Squibb, Boehringer Ingelheim, MSD, Roche, Janssen, Novartis, Sanofi, Glaxo Smith Kline and Gilead

Grant/Research Support: Bristol-Myers Squibb, Gilead, Roche and MSD

Genotype 3 in Europe & Israël

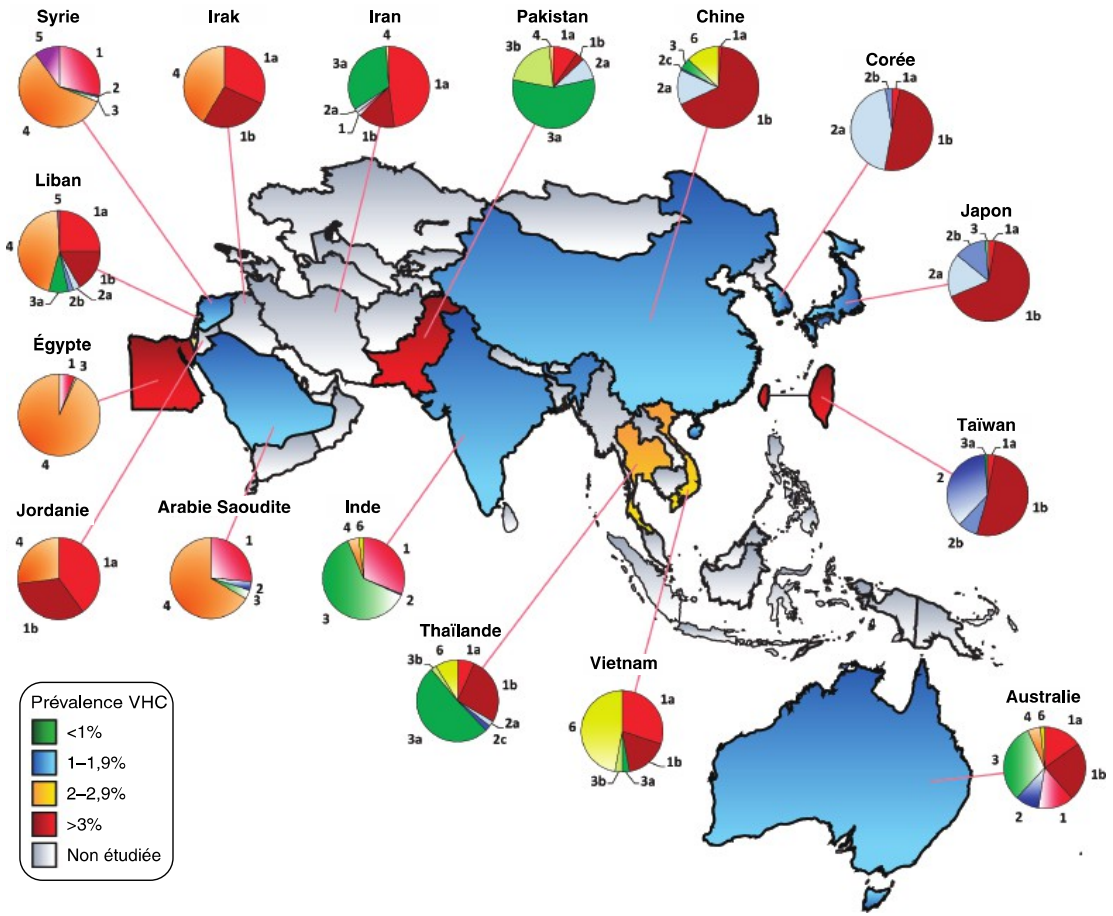
A changing prevalence according to areas



Cornberg M, et al. Liver International 2011;31(Suppl 2):30-60; Cozzolongo R, et al. Am J Gastroenterol 2009

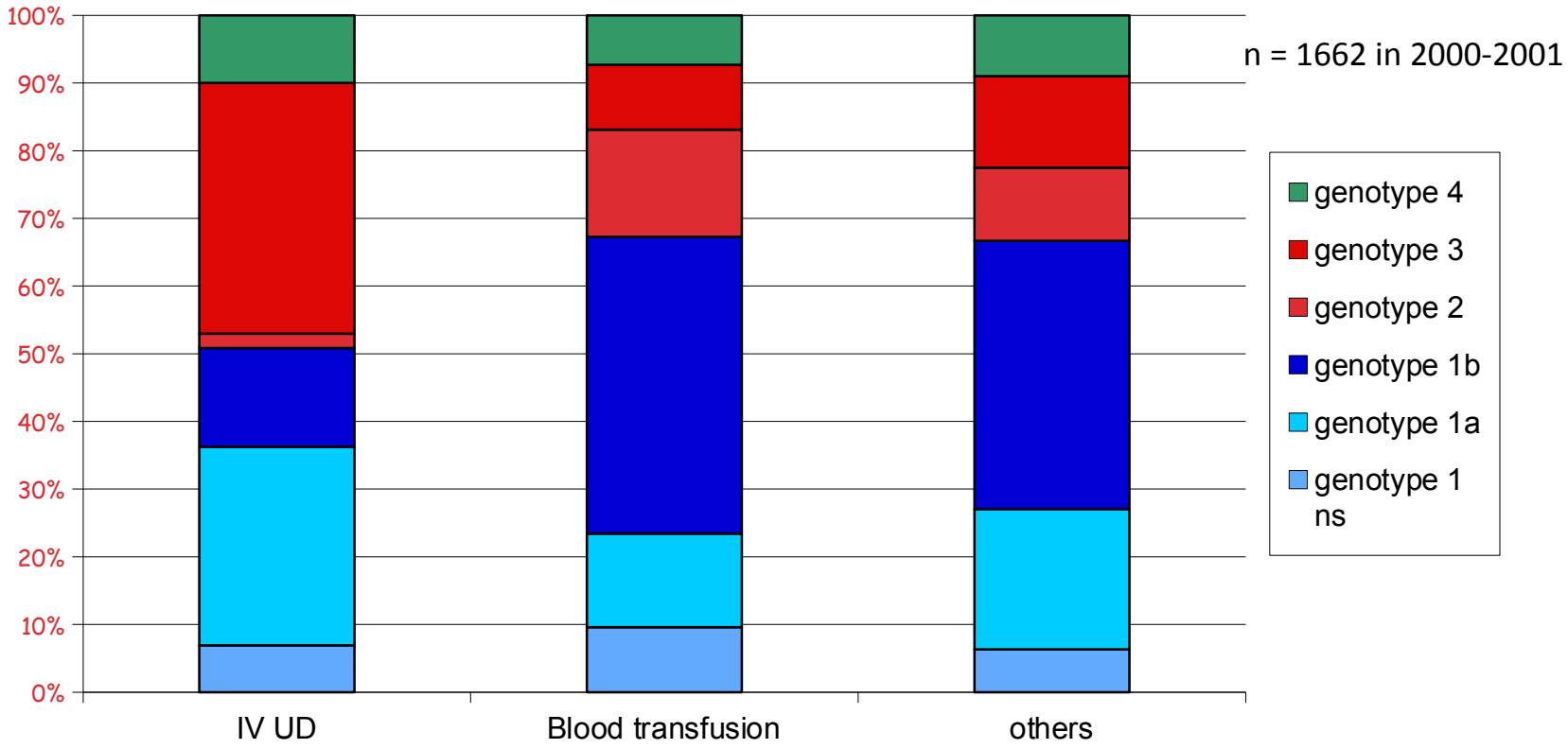
Genotype 3 in Asia, Australia and Egypt

A changing prevalence according to areas



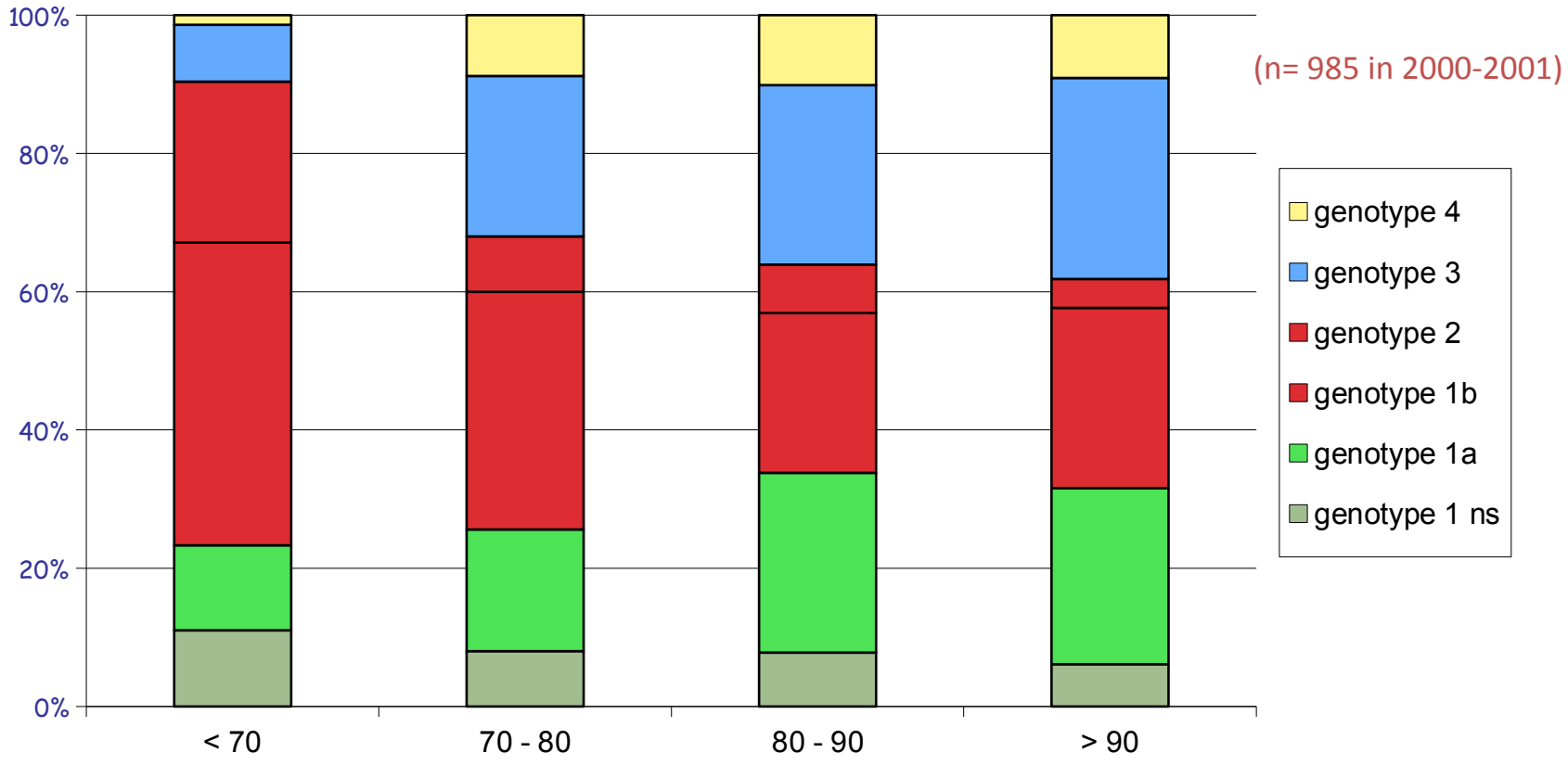
Sievert W, et al. Liver International 31 Suppl 2:61 -80

Genotype 3
Prevalence according to source of infection



C Payan et al, J Viral Hepatitis 2005

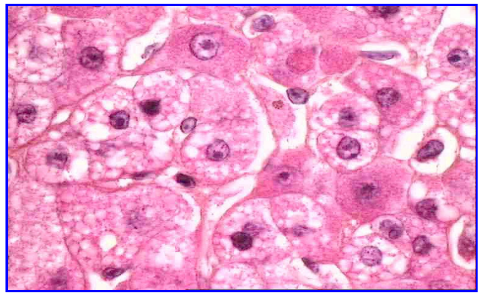
Genotype 3
Changing relative prevalence over time

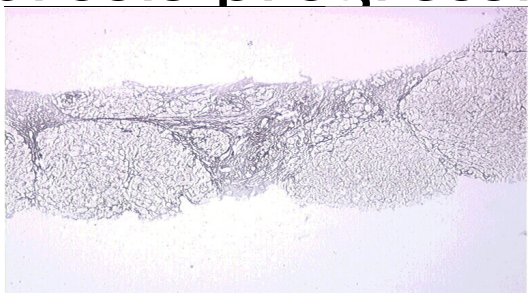


Pol et al. Gastroenterology 1995; C Payan et al, J Viral Hepatitis 2005

Genotype 3

Steatosis and more rapid fibrosis progression

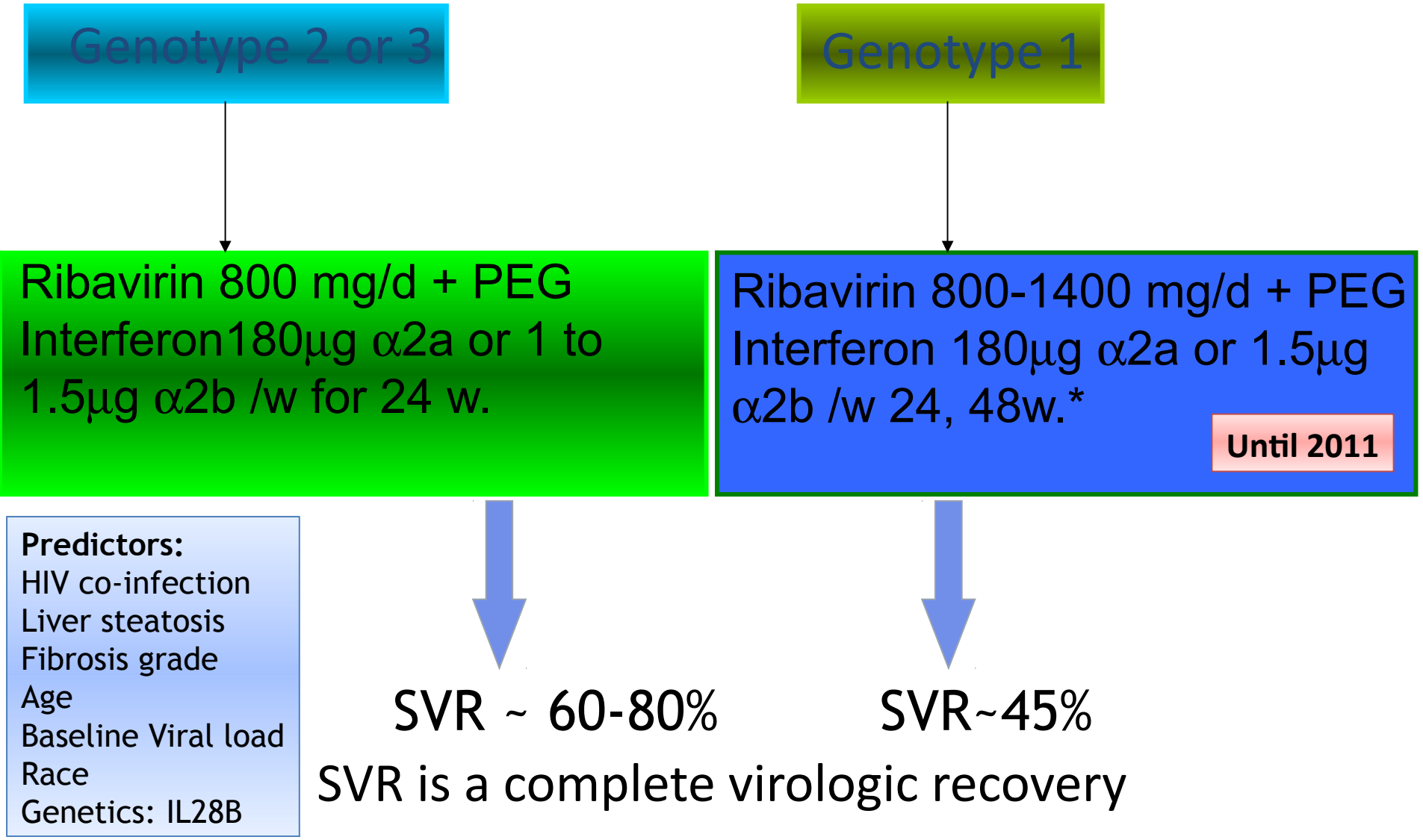




IL28B bad treatment-outcome allele is good for fibrosis

Bochud PY et al. J Hepatol 2009; Hepatol 2011

Treatment of chronic hepatitis C



SVR is a complete virologic recovery

*According to baseline viral load and fibrosis, rapid and early viral kinetics

EASL guidelines 2011

Treatment of chronic hepatitis C

Genotype 2 or 3

Ribavirin 800 mg/d
Interferon180µg α2
1.5µg α2b /w for 24

e 1

-1400 mg/d + PEG
0µg α2a or 1.5µg
w.*

Until 2011

Predictors:
HIV co-infection
Liver steatosis
Fibrosis grade
Age
Baseline Viral load
Race
Genetics: IL28B

S

SVR

overy

Genotype 2 or 3
Genotype 1
Genotype 4

*According to baseline viral load and fibrosis, rapid and early viral kinetics

EASL guidelines 2011

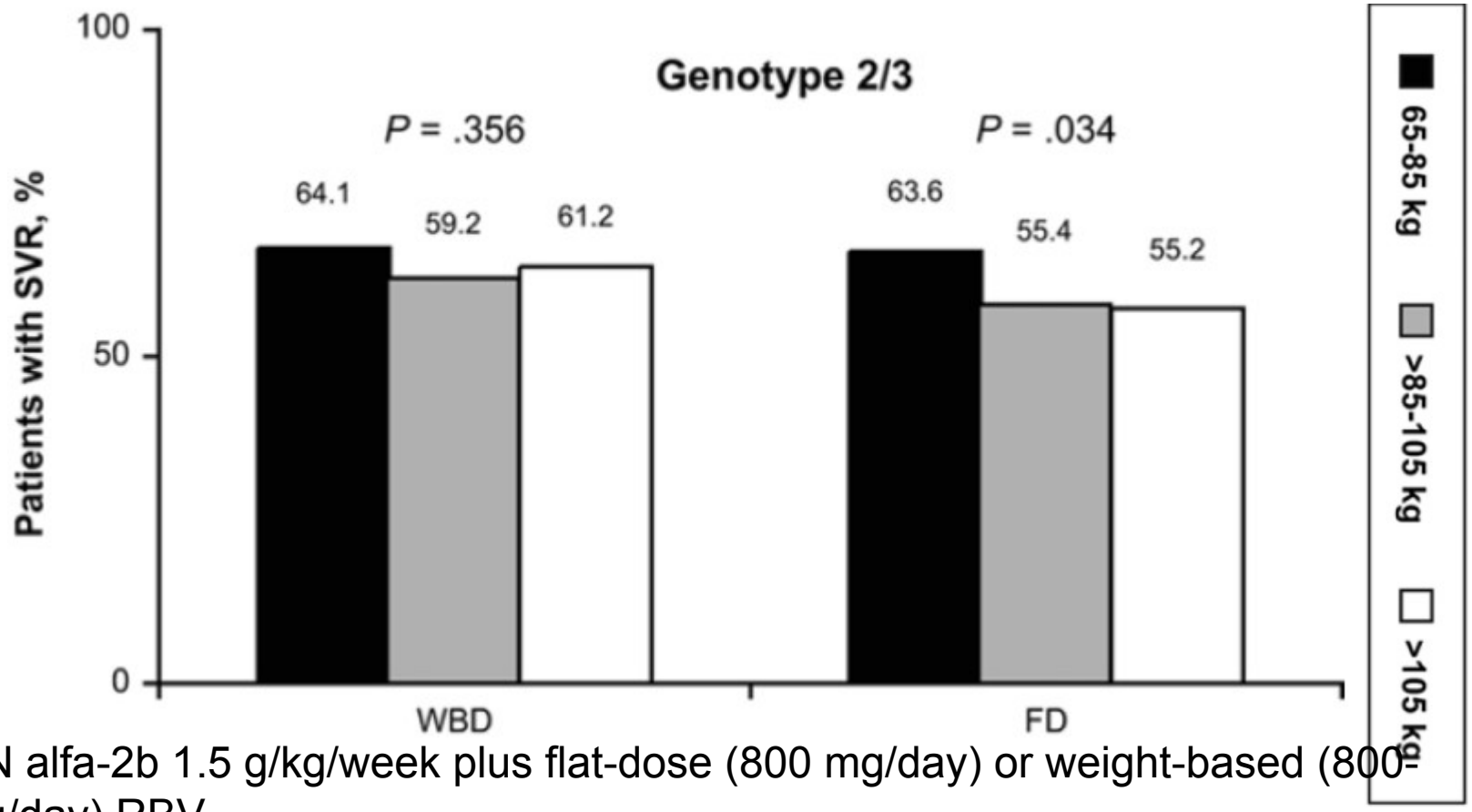
Treatment of HCV Genotype 3

A 24 week-course is enough

Jacobson IM et al. Hepatology 2007

Treatment of HCV Genotype 3

No need for weight-based RBV dosing

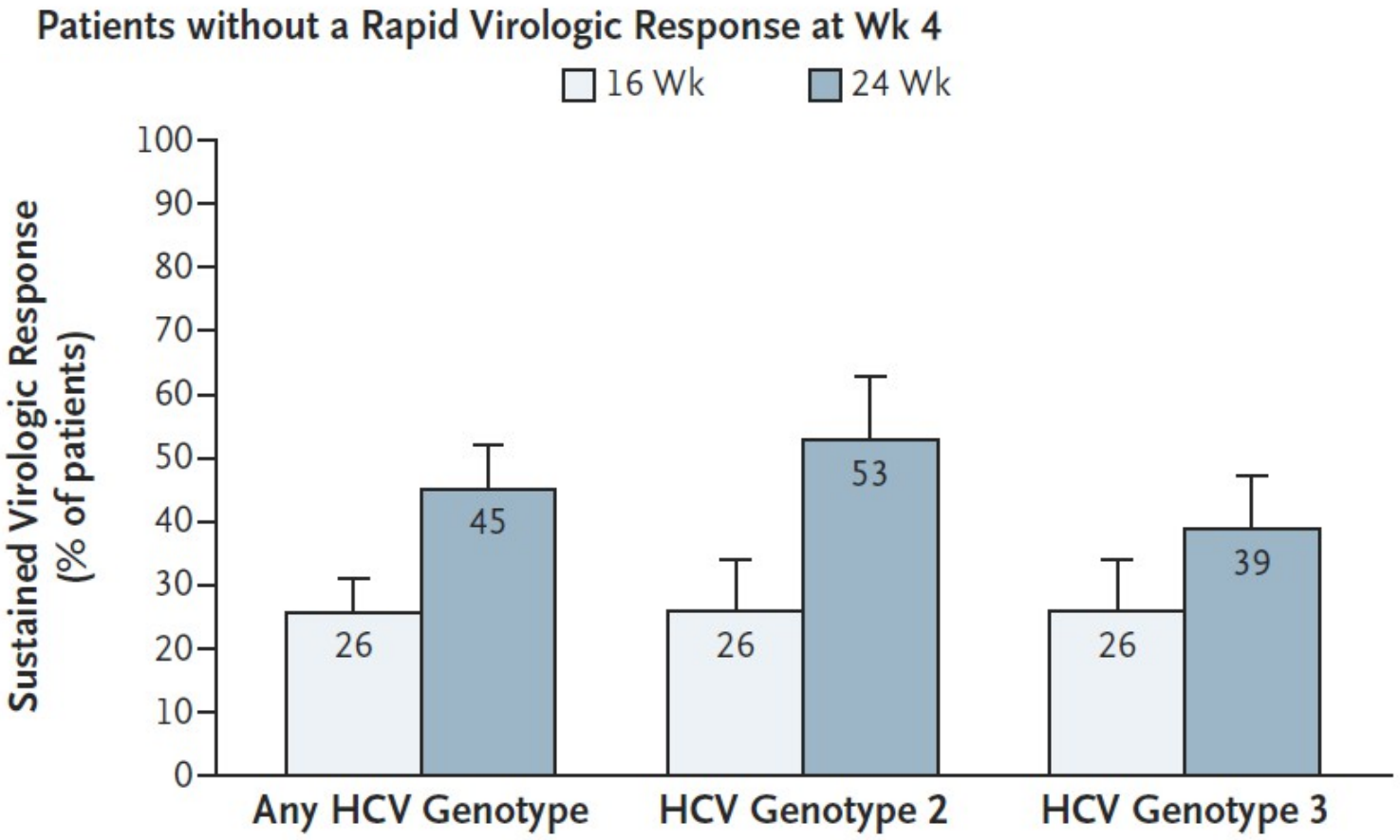


PEG-IFN alfa-2b 1.5 g/kg/week plus flat-dose (800 mg/day) or weight-based (800-1400 mg/day) RBV

Jacobson IM et al. Hepatology 2007

Treatment of HCV Genotype 3

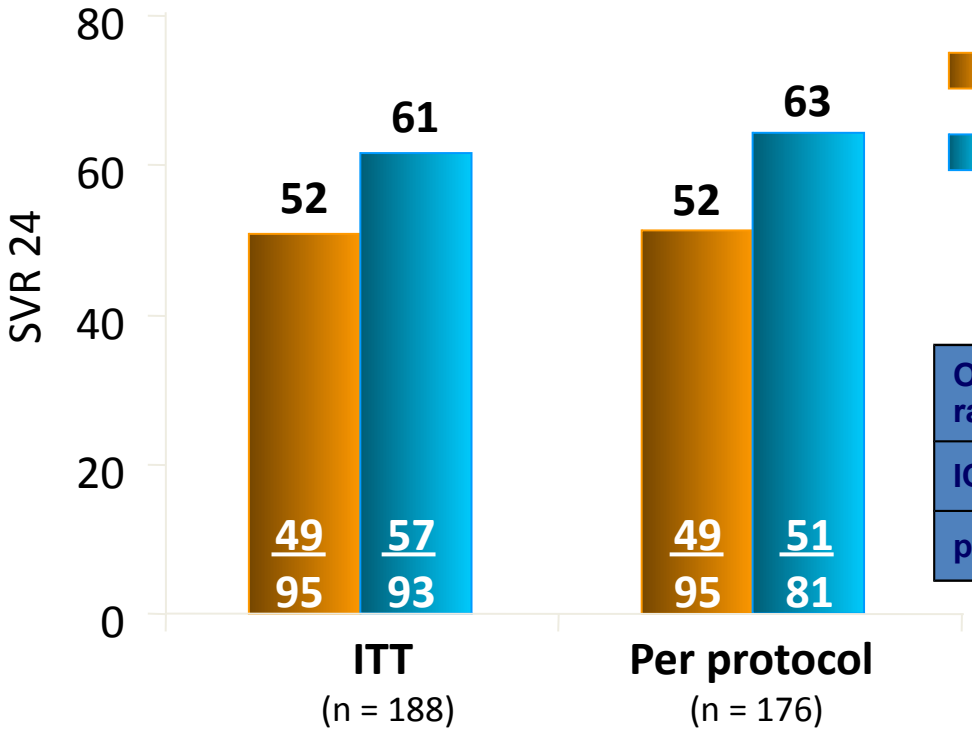
Modification of treatment duration



Schiffman M et al., New Engl J Med 2007

Treatment of HCV Genotype 3

N-CORE study: 24 vs 48 weeks in G2/3 without RVR

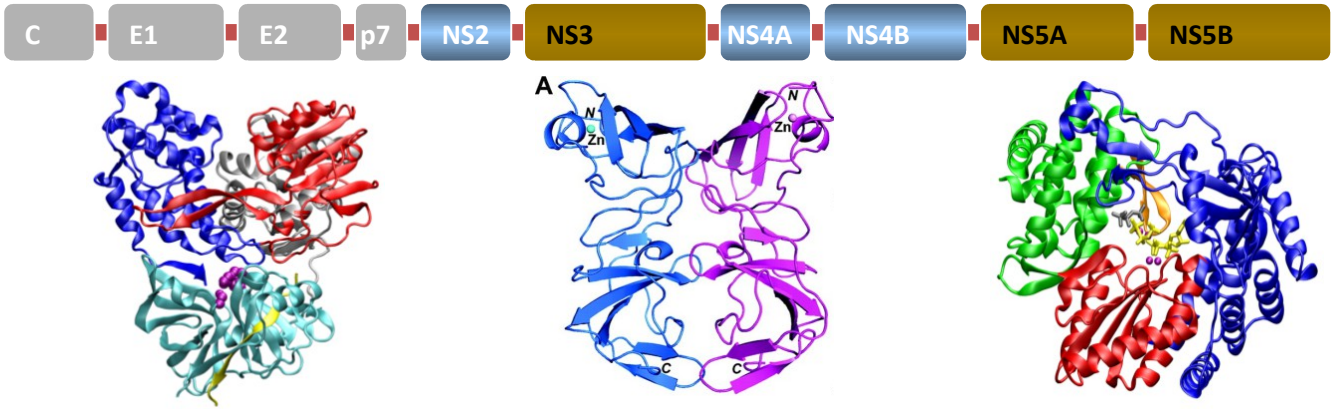


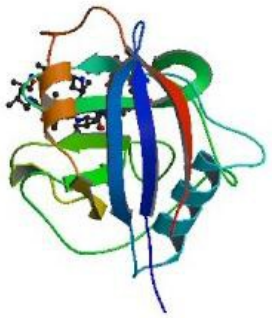
Odds ratio	0.68	0.63
IC 95 %	0.38-1.21	0.35-1.16
p	0.1934	0.1461

Cheinquer H, et al. AASLD 2012, Abs. 156

Understanding of HCV life cycle revealed several potential innovative drug targets

Viral targets | **Host targets**





NS3

The NS3/4A serine protease is essential for post-translational processing of HCV polyproteins1

Boceprevir
Telaprevir
ABT-450/r, ACH-1625
Asunaprevir, TMC-435
(Simeprevir), BI-201335
Danoprevir/r, GS-9451
MK-5172

NS5A

Multifunctional membrane-associated phosphoprotein essential component of the HCV-RNA replication complex2,3

Daclatasvir
GS-5885
ABT-267
PPI-668

NS5B

NS5B is an HCV-specific, RNA-dependent RNA polymerase1

<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

Cyclophilin A

Host protein involved in HCV replication through interaction with NS5A and the HCV polymerase4

Alisporivir**
SCY-635

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

Treatment of HCV Genotype 3

2012 2017 2020 > 2020

PEG-IFN – RBV

DAAs

IFN-containing regimens

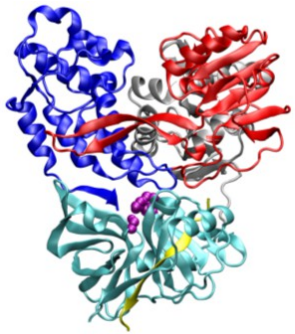
DAAs Combinations (PI/Pol I/NS5A Inh) +/_ RBV…

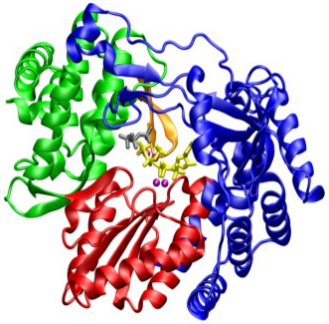
IFN-free regimens

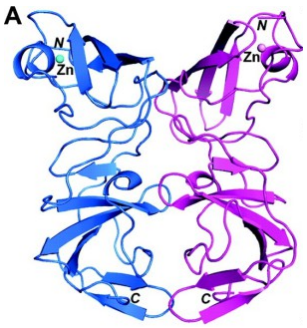
Dual
Triple
Quad therapy

Cyclophyllin inhibitors

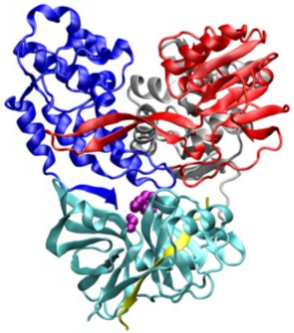
In clinical trials since 2011
Expected in 2014-2015

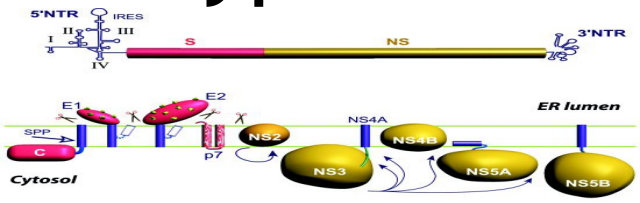




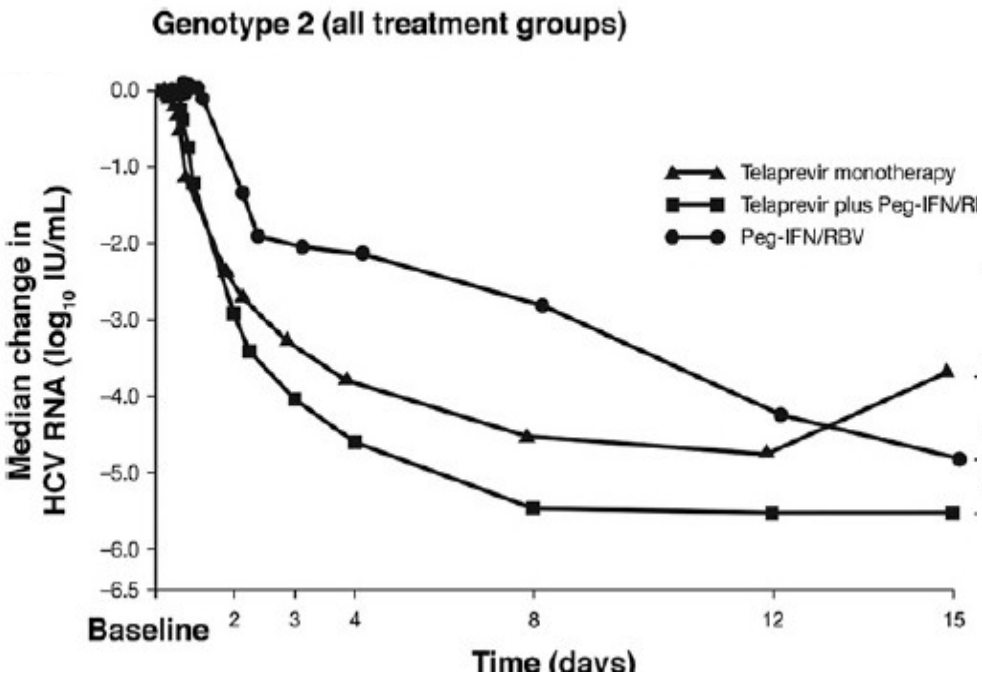


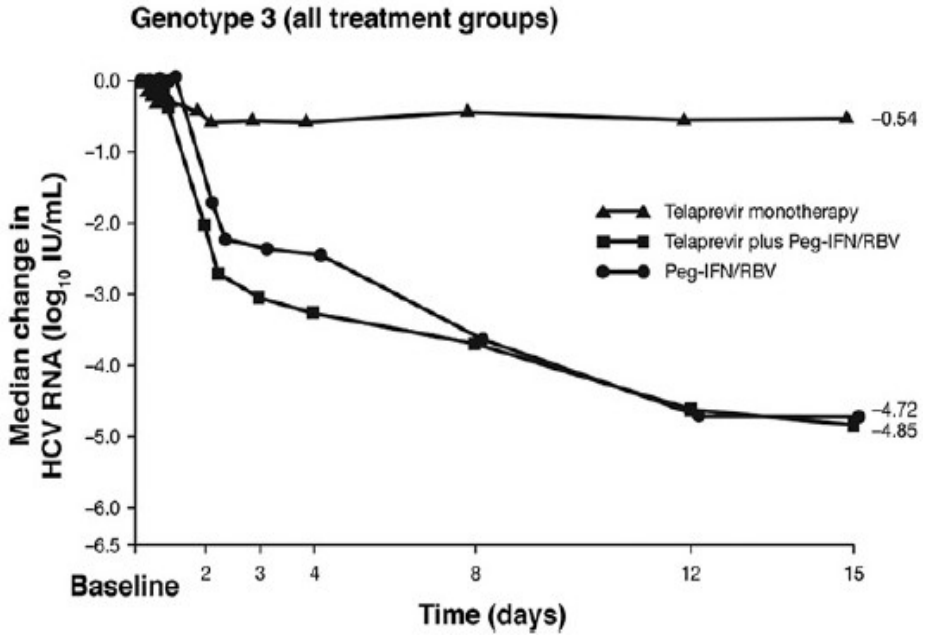
Treatment of HCV Genotype 3 DAAs





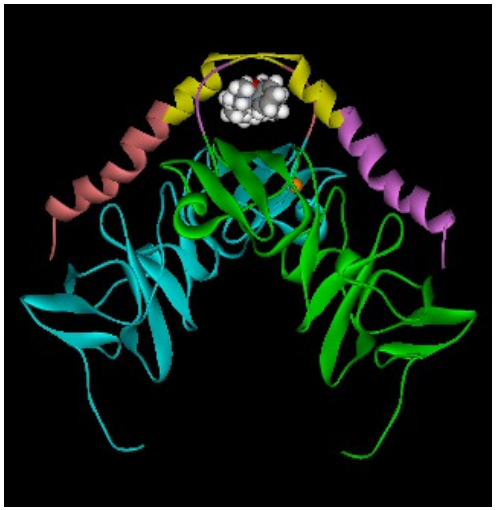
2 weeks Telaprevir monotherapy reduces G2- but not G3-viral load

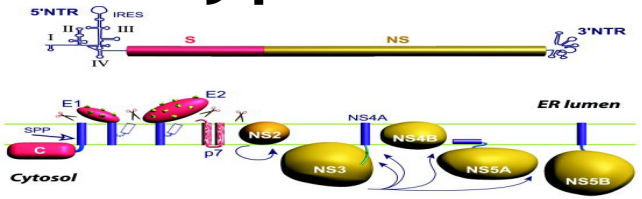




Foster GR et al., Gastroenterology 2011

Treatment of HCV Genotype 3 DAAs





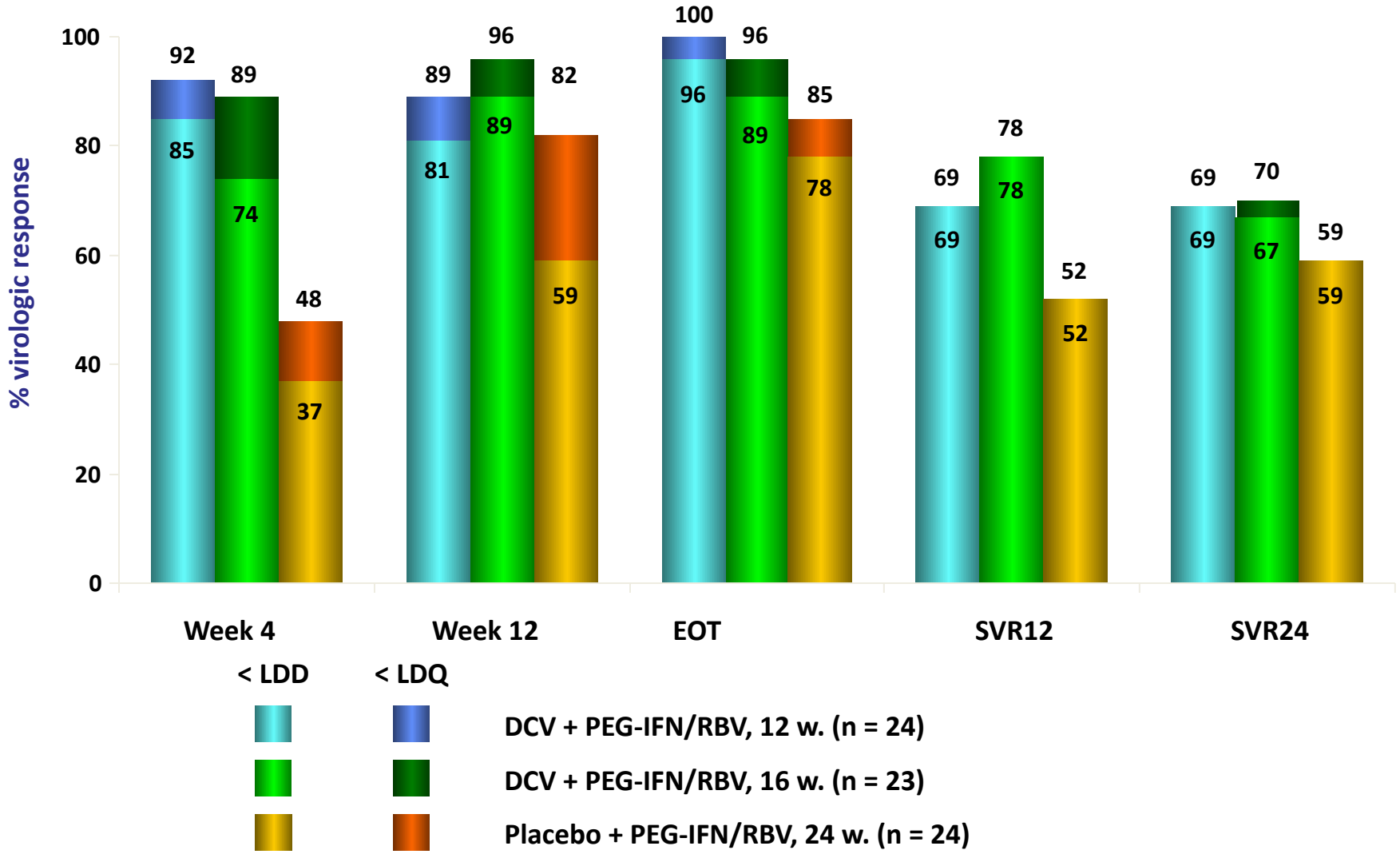
Daclatasvir is a highly potent (picomolar EC50) and selective HCV-NS5A inhibitor with broad genotypic coverage

HCV Replicon or Virus Genotype	EC50 pM
1a	50
1b	9
2a (JFH)	63
2a (JFH virus)	12
3a (chimera)	127
4a (chimera)	12
5a (chimera)	33

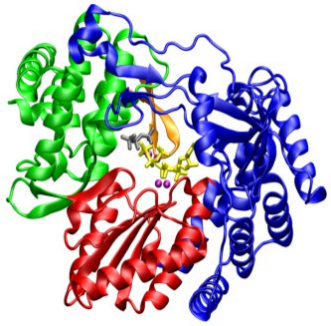
1Gao M, *et al. Nature* 2010;465:96-100; 2Fridell RA, *et al. J Virol* 2011;85:7312-7320.

Treatment of HCV Genotype 3

COMMAND 2/3 trial : PEG-IFN + RBV (PR) + daclatasvir versus PR

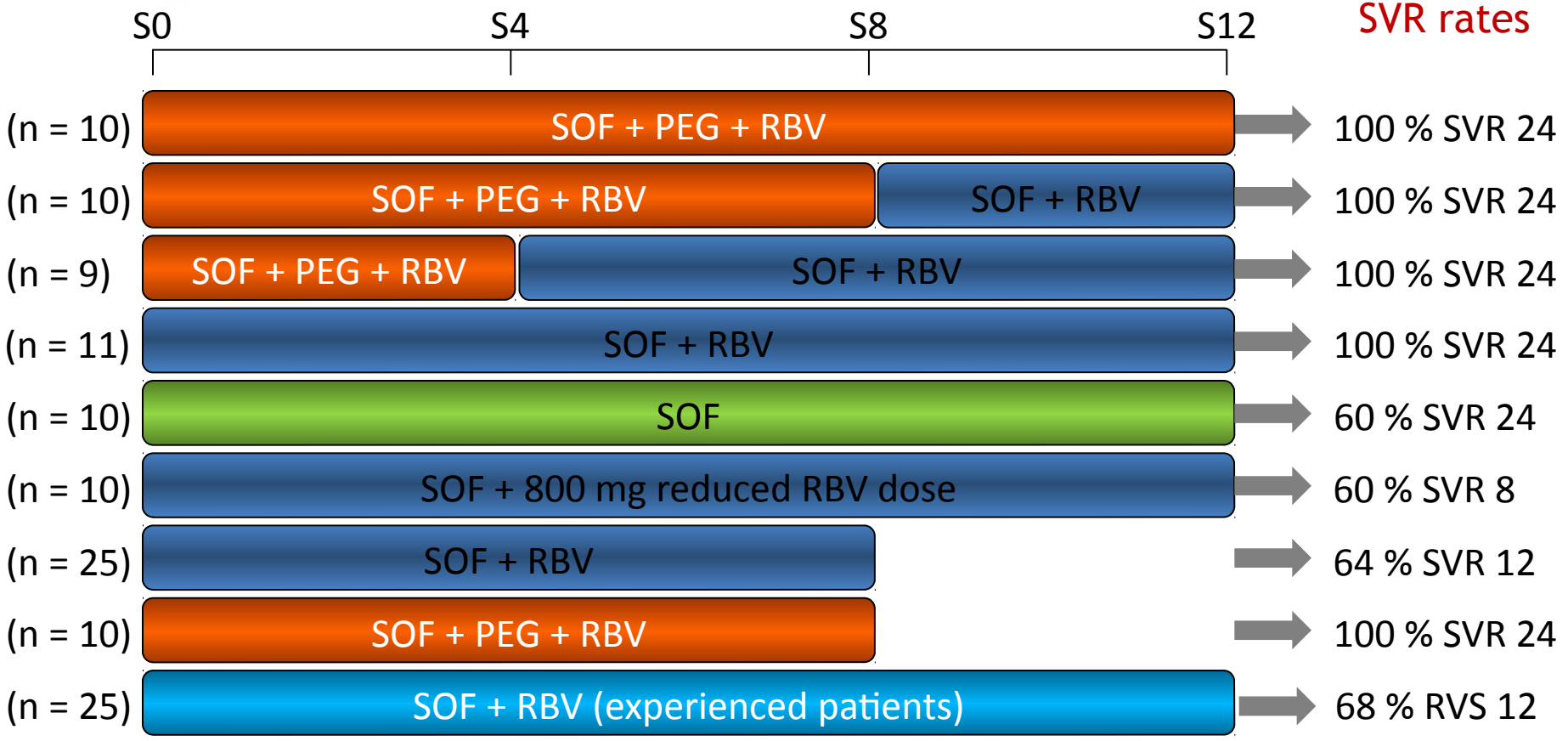


Dore G et al. EASL 2013, Abs. 1418



Treatment of HCV Genotype 3

)N study: genotypes 2/3

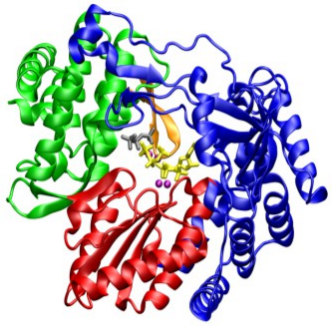


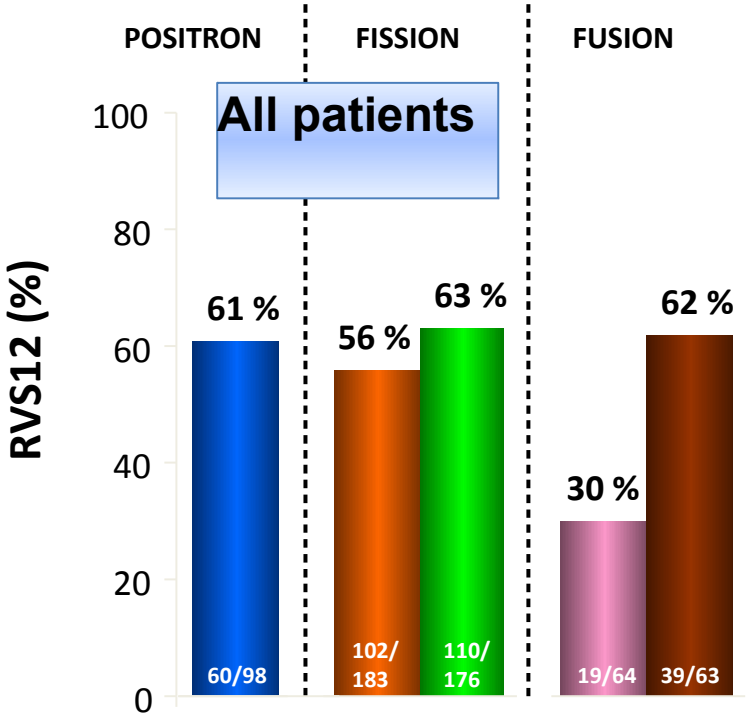
SOF : sofosbuvir
PEG : PEG IFN alfa
RBV : ribavirin

Gane E et al. NEJM 2013

Treatment of HCV Genotype 3

Sofosbuvir et RBV





POSITRON : SOF + RBV 12 w.

FISSION : SOF + RBV 12 w.

FISSION : PEG-IFNα-2a + RBV 24 w.

FUSION : SOF + RBV 12 w.

FUSION : SOF + RBV 16 w.

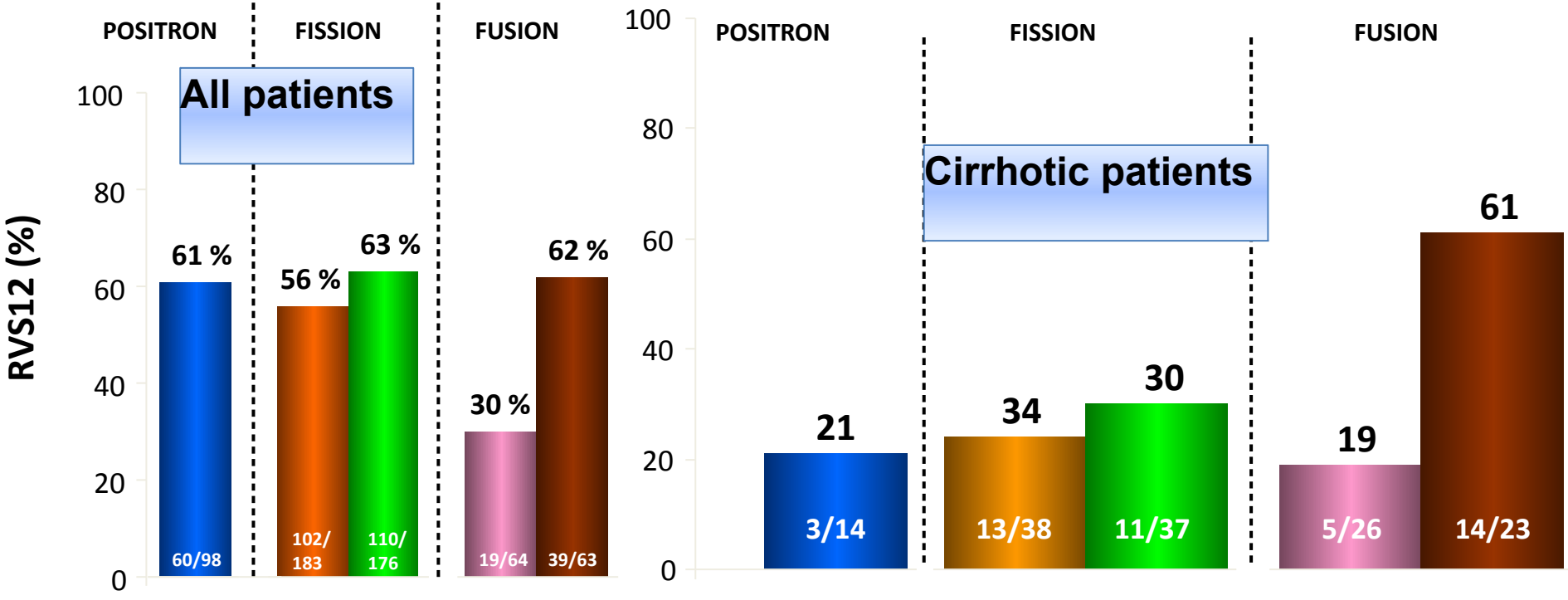
Gane E et al., EASL 2013, Abs. 5

Jacobson IM et al., EASL 2013, Abs. 61

Nelson D et al., EASL 2013, Abs. 6

Treatment of HCV Genotype 3

Sofosbuvir et RBV



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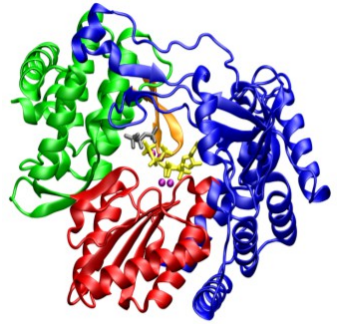
Gane E et al., EASL 2013, Abs. 5

Jacobson IM et al., EASL 2013, Abs. 61

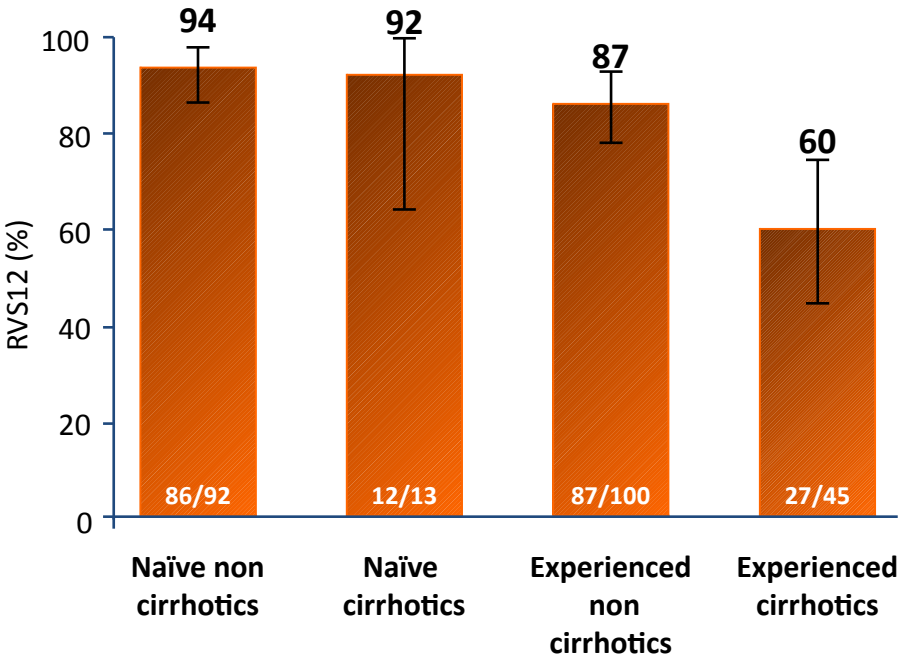
Nelson D et al., EASL 2013, Abs. 6

Treatment of HCV Genotype 3

Sofosbuvir and RBV: VALENCE trial



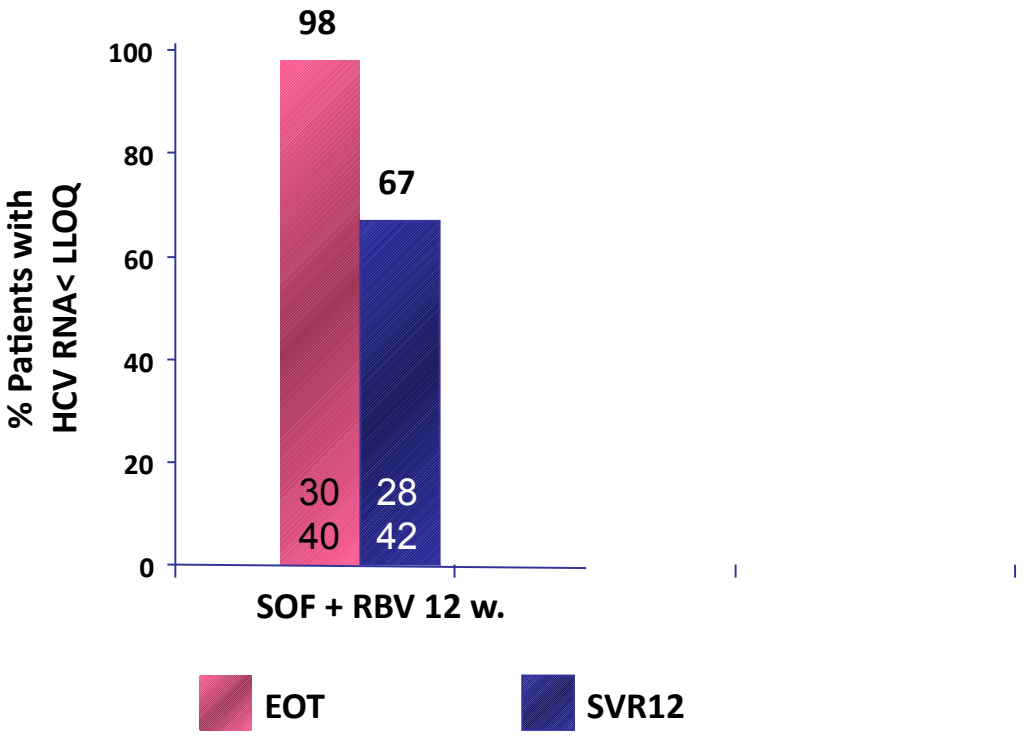
SVR12 in G3 patients treated 24 weeks



Zeuzem S et al. AASLD 2013, Abs. 1085

Treatment of HCV Genotype 3
Sofosbuvir and RBV in HIV co-infected: PHOTON 1

- Co-infected naïve patients
  - ARV : efavirenz, rilpirivine, PI/r, raltegravir + tenofovir/emtricitabine
- Patients without RVS:
  - Relapse: 29 % G3
  - No resistance



Sulkowski M et al. AASLD 2013, Abs. 212

Treatment of HCV Genotype 3
How to improve the SVR rate?

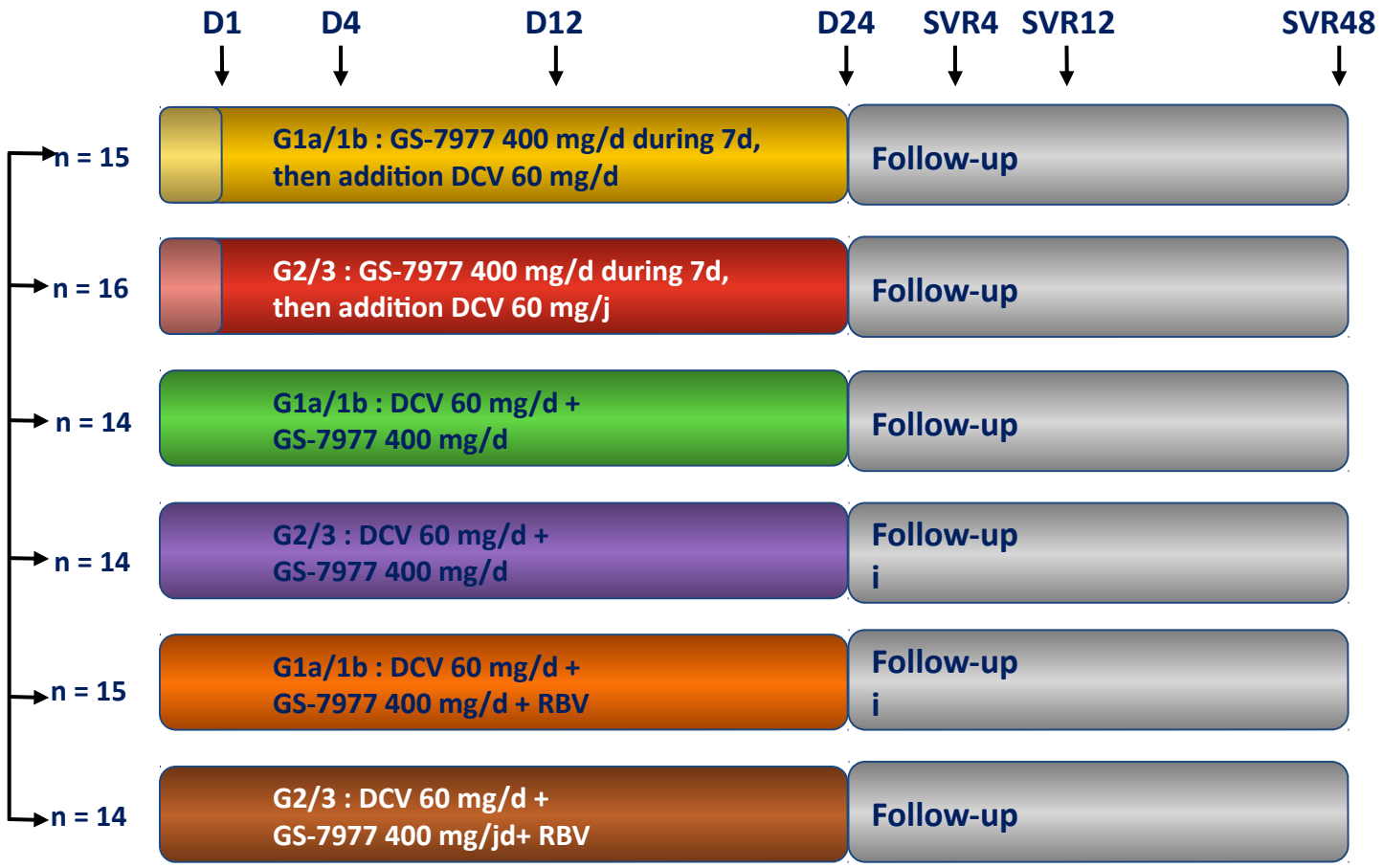
Genotype 1,2,4,5,6

Genotype 3

Treatment of HCV Genotype 3

Triple oral: SOF + DCV ± RBV

Phase 2a, naïve and non-cirrhotic G1, G2 et G3 patients



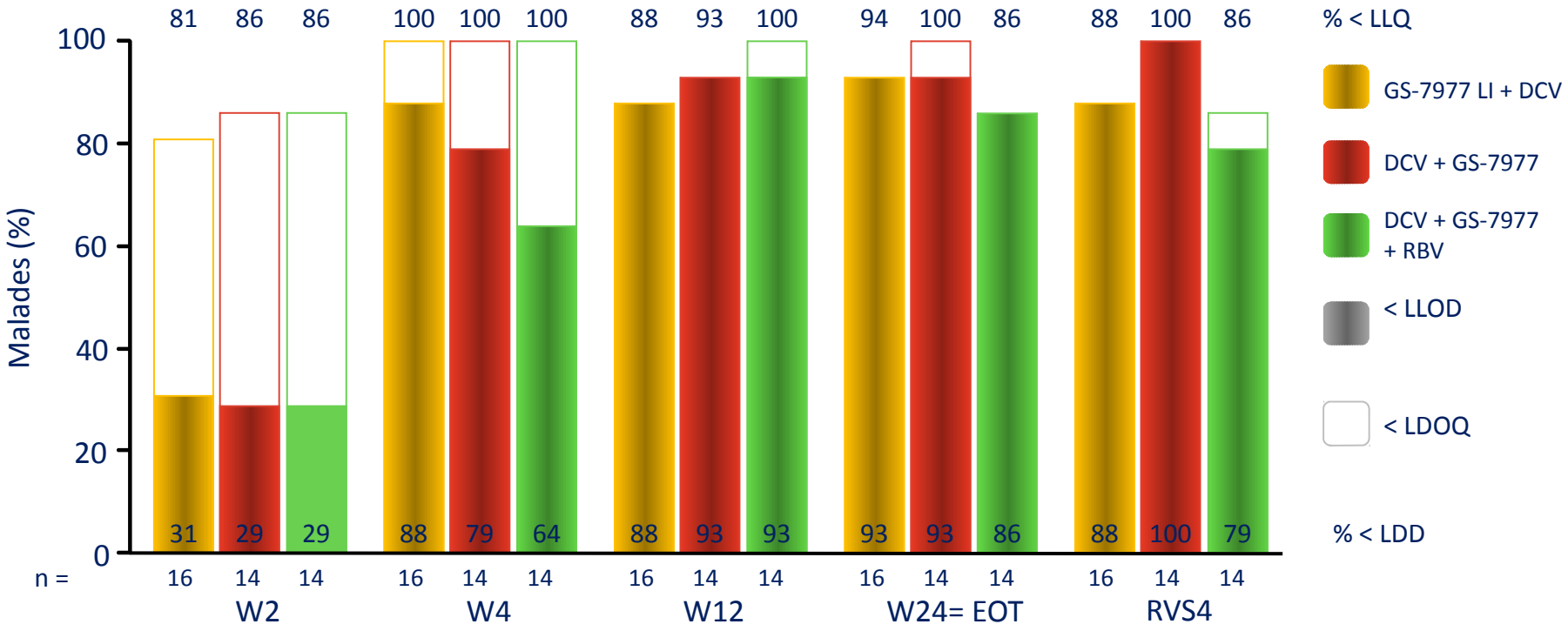
RBV : 1 000-1 200 mg/according to the weight for G1; 800 mg/d for G2/3

Sulkowski M et al. EASL 2012, Abs. 1422

Treatment of HCV Genotype 3

Triple oral: SOF + DCV ± RBV

Efficacy in genotypes 2/3

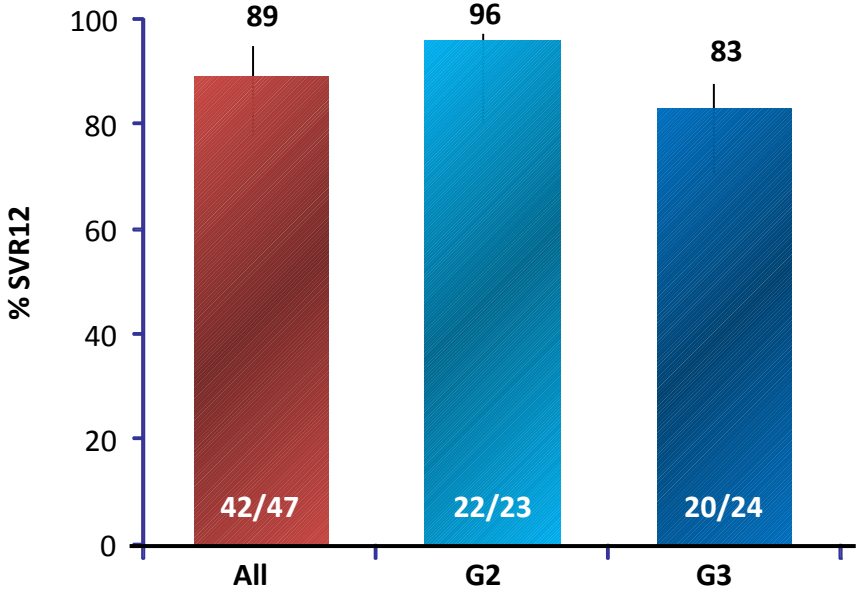


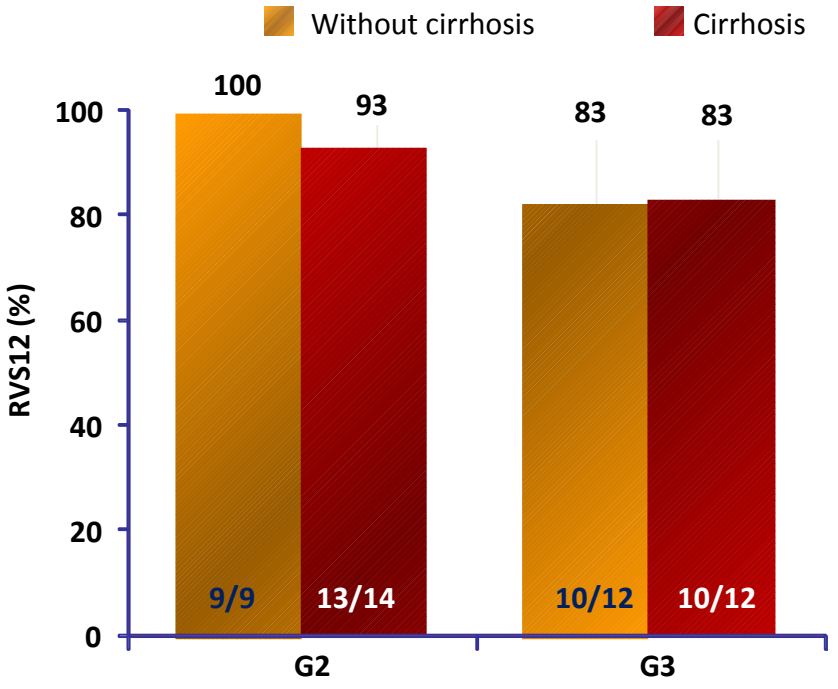
Sulkowski M et al. EASL 2012, Abs. 1422

Treatment of HCV Genotype 3

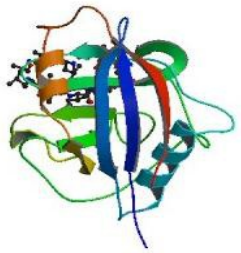
LONESTAR-2 trial: sofosbuvir + PEG-IFN/RBV in experienced G2/3 patients

- 47 patients (56 y, 68 % M, 51 % G3, 55 % cirrhosis, 36 % IL28B CC, 85 % relapsers or VB
  - SOF 400 mg/d + PEG-IFNα-2a 180 µg/w. + RBV 1 000-1 200 mg/d for 12 w.



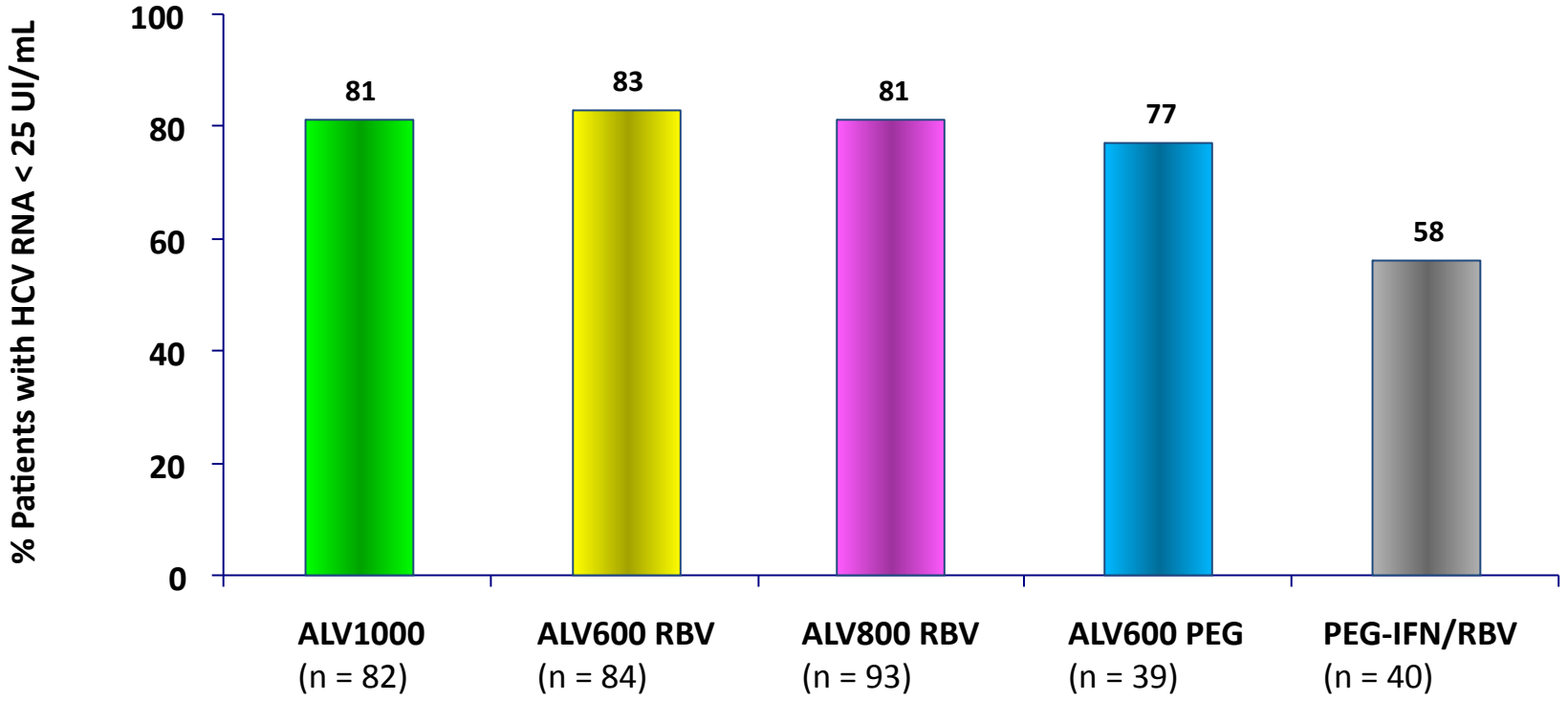


Lawitz E et al. AASLD 2013, Abs. LB4



Treatment of HCV Genotype 3

VITAL-1 : alisporivir + ribavirin in genotypes 2-3



ALV1000-alisporivir 1 000 mg QD; ALV600RBV-alisporivir 600 mg QD plus ribavirin; ALV800RBV-alisporivir 800 mg QD plus ribavirin; ALV600PEG-alisporivir 600 mg QD plus PEG-IFN

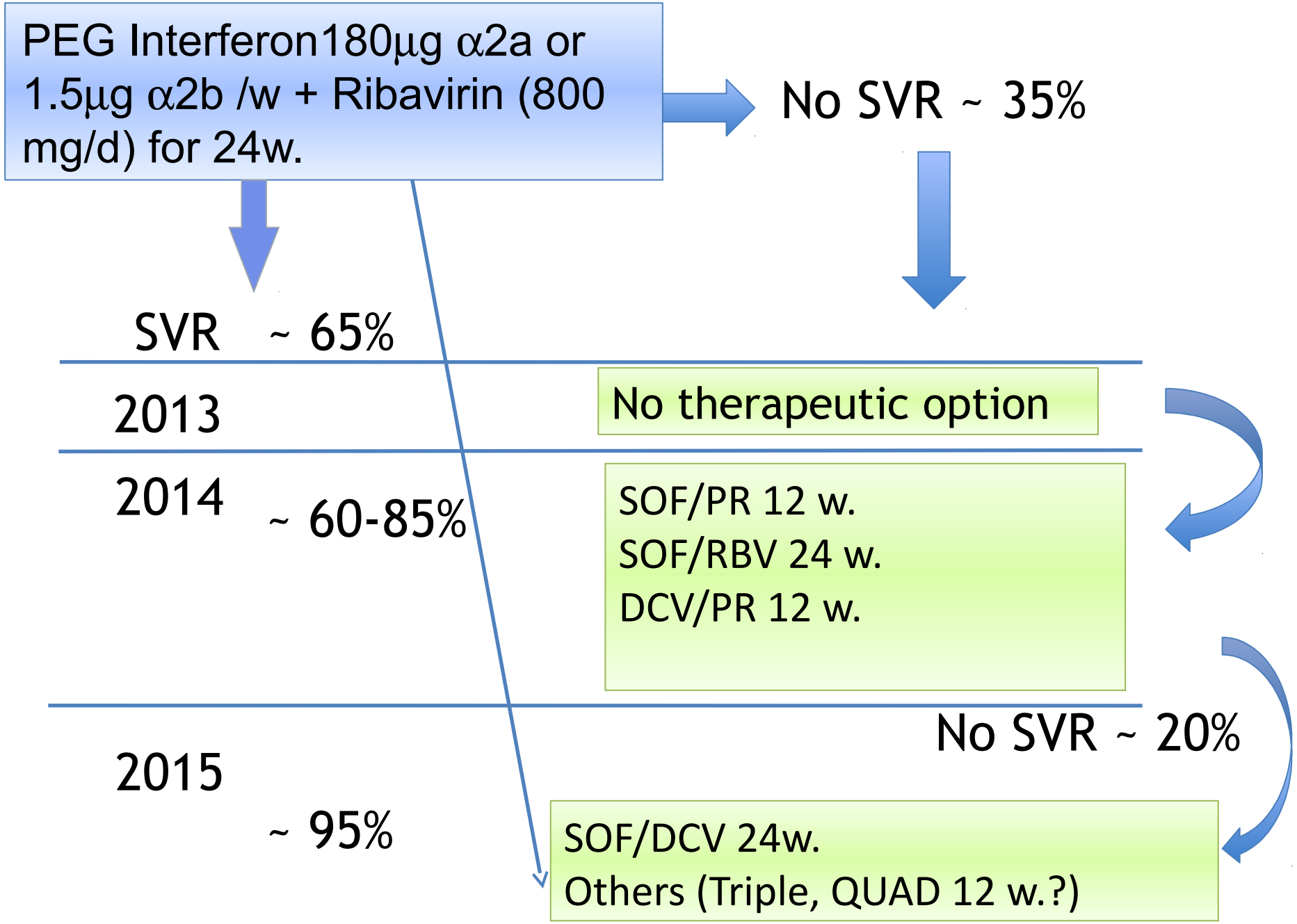
Pawlotsky JM et al. EASL 2012, Abs. 1405

HCV Genotype 3
Conclusions

- One third of patients are infected by a genotype 3

- Risk of more severe disease

- According to the availabilities of the drugs, the ability to pay…, therapeutic opportunities vary from PEG-RBV 24w., triple PEG-RBV/DCV or SOF 12w. to SOF/DCV or LDV 12-24w.


PEG Interferon180µg α2a or 1.5µg α2b /w + Ribavirin (800 mg/d) for 24w.
No SVR ~ 35%
SVR ~ 65%
2013
No therapeutic option
2014
~ 60-85%
SOF/PR 12 w.
SOF/RBV 24 w.
DCV/PR 12 w.
No SVR ~ 20%
2015
~ 95%
SOF/DCV 24w.
Others (Triple, QUAD 12 w.?)