UMC Utrecht

Viral and host factors predictive of sustained viral response

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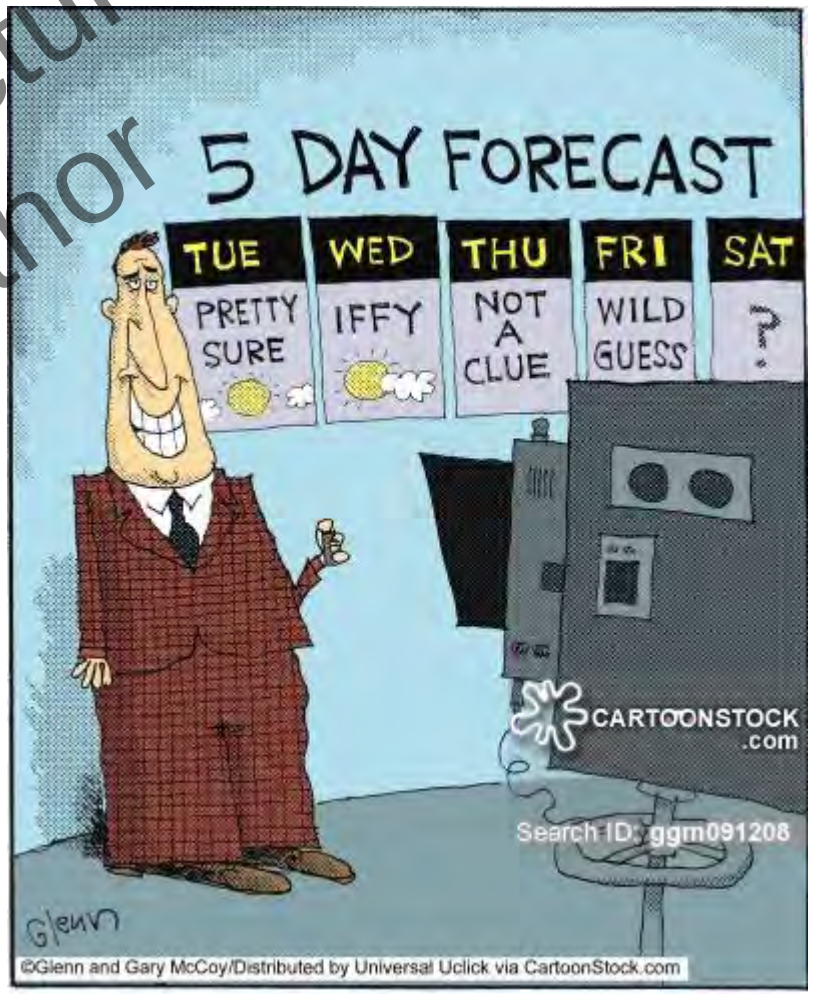
What's on the agenda

- interpretation of predictors in sustained viral response
- types of predictors
  - Host
  - Viral
- are there any predictors left?

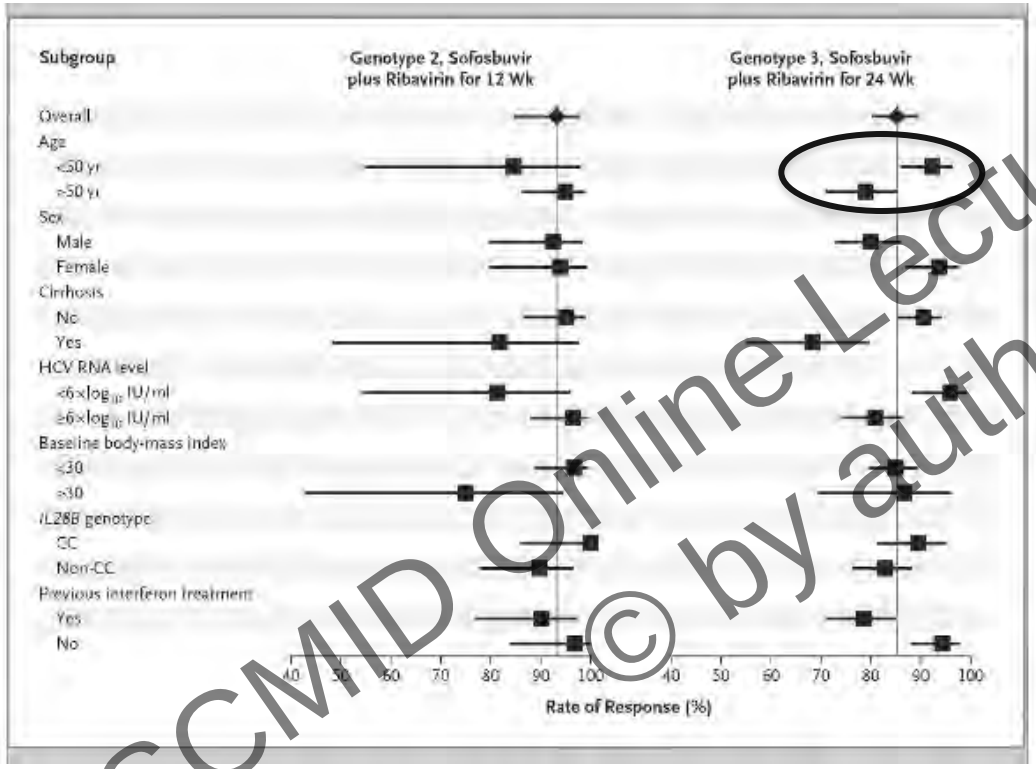
Predictor of response

- **predictor** - information that supports a probabilistic estimate of future events

Predictors tell you about groups not about individuals



A predictor can be statistically significant but clinically useless



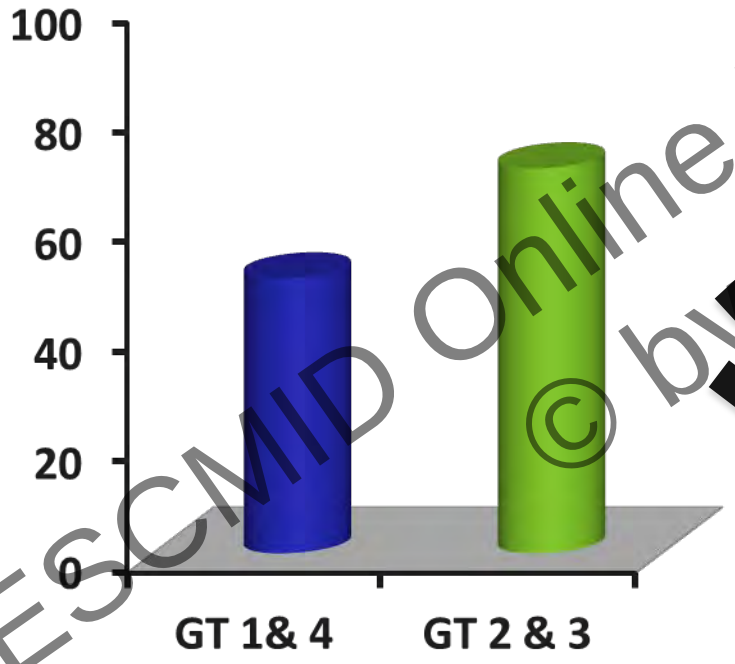
VALENCE-study:
Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3

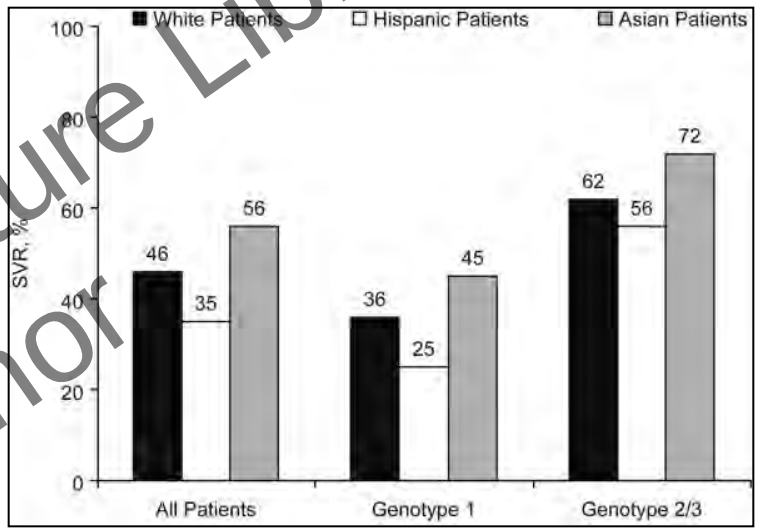
Table S5. Multivariate Logistic Regression in Identifying Factors Associated with SVR12 in Patients with HCV Genotype 3

Variable	Odds Ratio	95% CI	2-Sided P-Value
Age group (years): <50 vs ≥50)	2.823	(1.214, 6.566)	0.0160
Sex: Female vs Male	3.180	(1.217, 8.311)	0.0183
Cirrhosis: No vs Yes	3.462	(1.603, 7.476)	0.0016
Baseline HCV RNA (log_{10} IU/mL): <6 vs ≥6	4.231	(1.208, 14.812)	0.0241

Zeuzem et al. N Engl J Med 2014; 370:1993-2001May 22, 2014

Where did this urge for predictors come from





Severe adverse events profile
24 to 48 weeks treatment duration

Manns Lancet 2001; Fried N Eng J Med 2002; Hadzyannis Ann Intern Med 2004

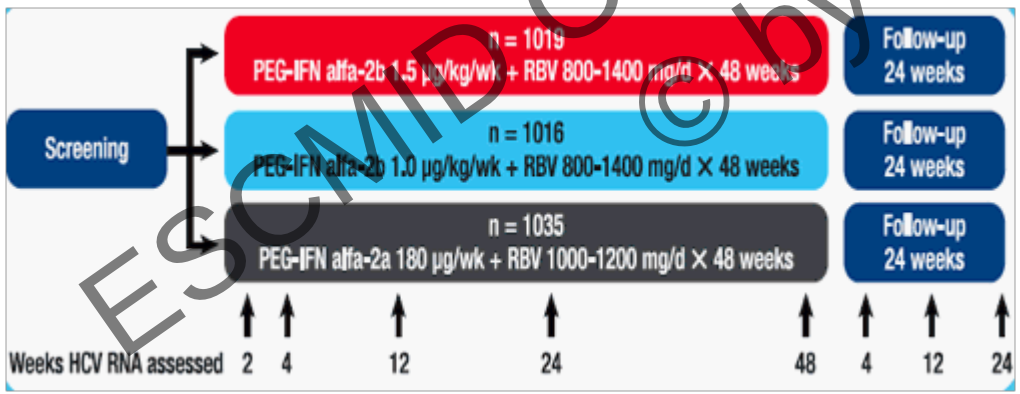
Host risk factors

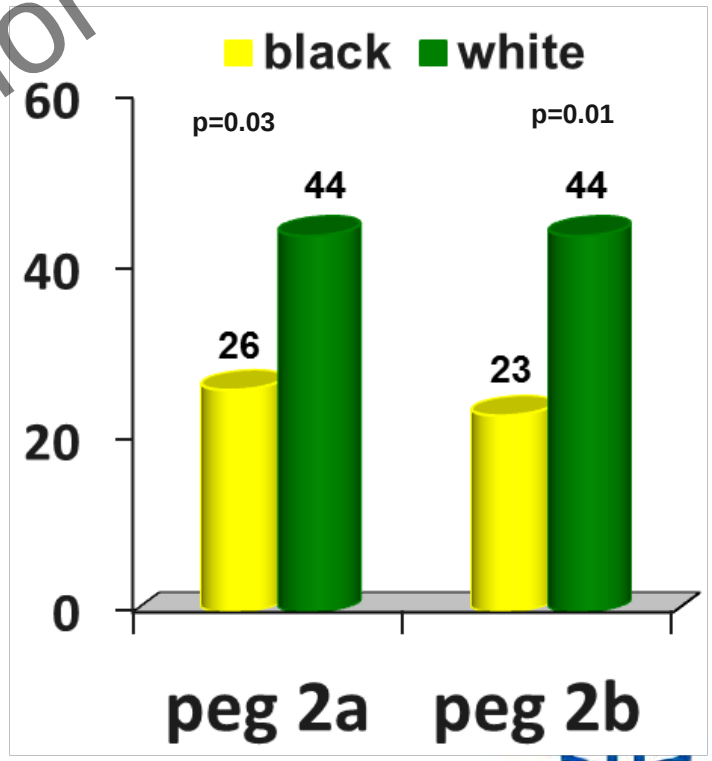
- Traditional
  - obesity, age, alcohol use, male/ female sex
- cirrhosis
- IL28B

So what about IL28B?

Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance

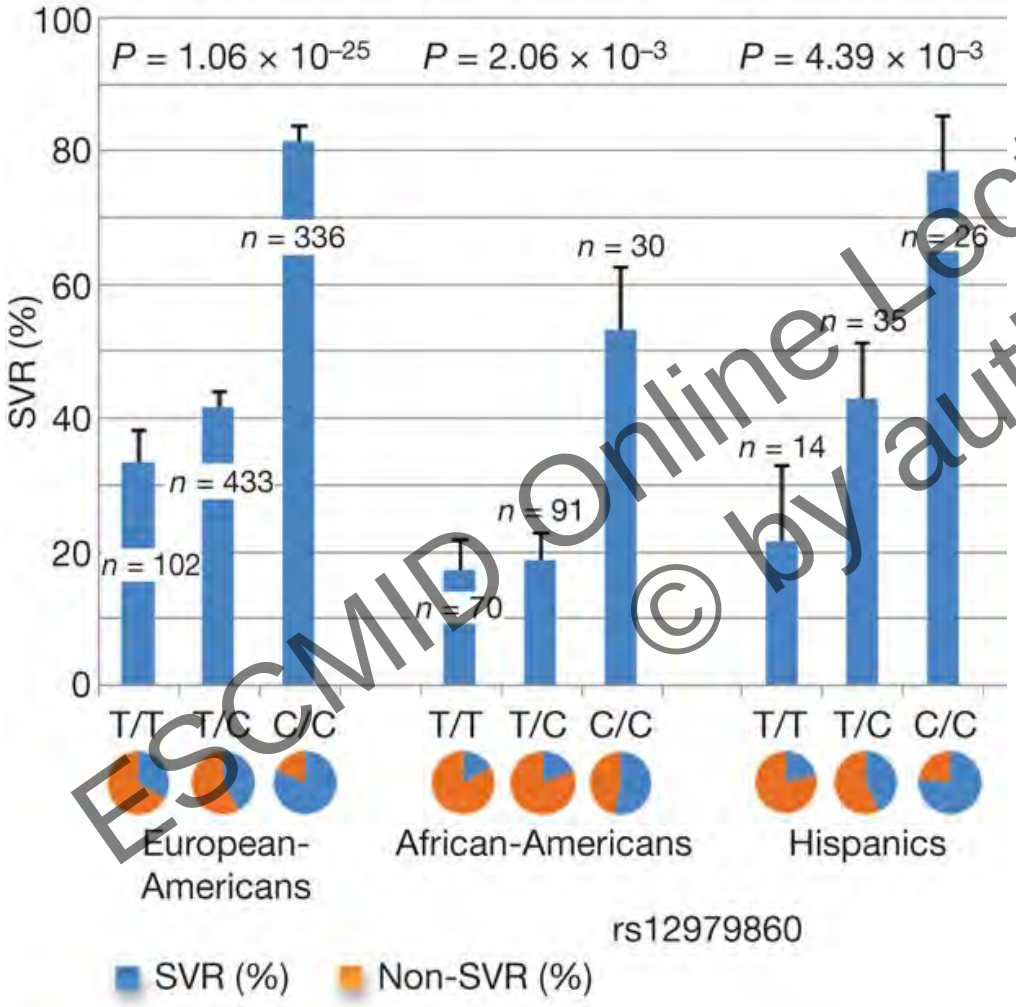
Dongliang Ge[1], Jacques Fellay[1], Alexander J. Thompson[2], Jason S. Simon[3], Kevin V. Shianna[1], Thomas J. Urban[1], Erin L. Heinzen[1], Ping Qiu[3], Arthur H. Bertelsen[3], Andrew J. Muir[2], Mark Sulkowski[4], John G. McHutchison[2] & David B. Goldstein[1]

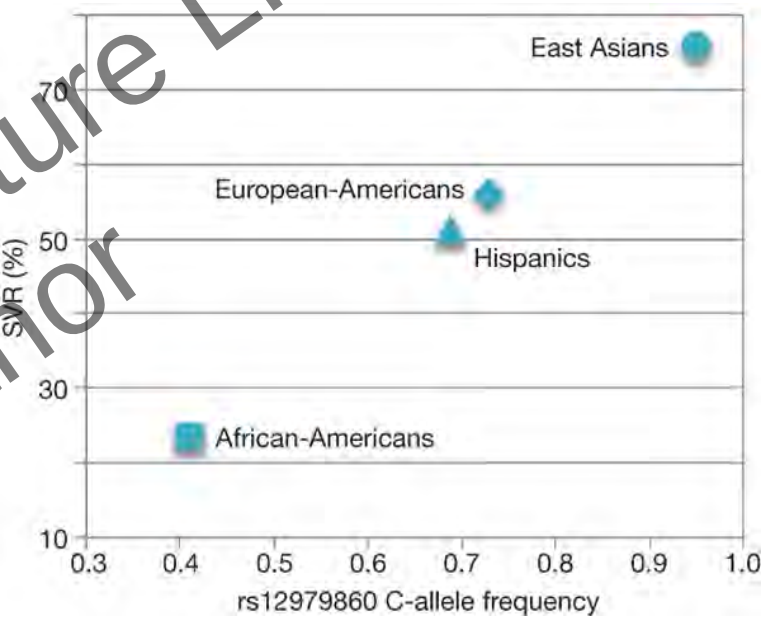




Ge et al. Nature 2009
McHutchison et al. New Engl J Med 2009

SVR with pegINF/RBV for GT 1 is dependent on host IL28B genotype





IL28B gene located on gene 19, including 2 SNP clossely linked (rs12979860 and rs8099917)

Ge et al. Nature 2009

Is there still a role for IL28B in the DAA-era?

- In pegIFN/ RBV combined with telaprevir of boceprevir its role is limited (abbreviated course of therapy in treatment naive; no role in treatment experienced)

Table 2 Retrospective analyses of the association between IL28B genotype and treatment response in the phase-3 registration studies of boceprevir (BOC) and telaprevir (TVR), in both treatment-naïve (SPRINT-2 [8], ADVANCE [9]) and treatment-experienced patients (RESPOND-2 [48], REALIZE [49])

				IL28B genotype (rs12979860)		
Drug	Study population	Outcome	Treatment arm	C/C *n* (%)	C/T *n* (%)	T/T *n* (%)
Boceprevir (BOC)	Treatment-naïve SPRINT-2 (n = 653/1048)	SVR	BOC-PR48*	44/55 (80%)	82/115 (71%)	26/44 (59%)
			BOC-PR RGT	63/77 (82%)	67/103 (65%)	23/42 (55%)
			PR control	50/64 (78%)	33/116 (28%)	10/37 (27%)
		Week 8 response*	Pooled BOC-PR patients	118/132 (89%)	158/304 (52%)	
	Treatment-experienced RESPOND-2 (n = 259/393)	SVR	BOC	17/22 (77%)	48/66 (73%)	13/18 (72%)
			BOC RGT	22/28 (79%)	38/62 (61%)	6/11 (55%)
			PR control	6/13 (46%)	5/29 (17%)	5/10 (50%)
		Week 8 response*	Pooled BOC patients	41/50 (82%)	80/156 (51%)	
Telaprevir (TVR)	Treatment-naïve ADVANCE (n = 454/1088)	SVR	T12	45/50 (90%)	48/68 (71%)	16/22 (73%)
			T8	38/45 (84%)	43/76 (57%)	19/32 (59%)
			PR control	35/55 (64%)	20/80 (25%)	6/26 (23%)
		eRVR**	T12	39/50 (78%)	39/68 (57%)	10/22 (45%)
	Treatment experienced REALIZE (n = 527/662) (overall)	SVR	Pooled TVR arms	60/76 (79%)	160/266 (60%)	49/80 (61%)
			PR control	5/17 (29%)	9/58 (16%)	4/30 (13%)
	Prior relapsers	SVR	All TVR patients	51/58 (88%)	100/117 (85%)	29/34 (85%)
			PR control	4/12 (33%)	6/30 (20%)	3/10 (30%)
	Prior partial responders	SVR	All TVR patients	5/8 (63%)	33/57 (58%)	10/14 (71%)
			PR control	1/5 (20%)	2/10 (20%)	0/5 (0%)
	Prior null responders	SVR	All TVR patients	4/10 (40%)	27/92 (29%)	10/32 (31%)
			PR control	0/0 (0%)	1/18 (6%)	1/15 (7%)

Holmes et al. J Viral Hep 2012

IL28B does not play a role in IFN-free regimens

ION-1/2, Afdhal et al.

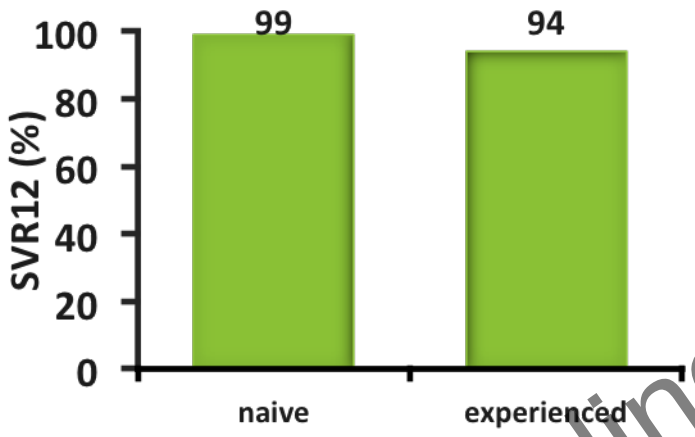


Table 2. Virologic Response Rates.

Response	Group 1 (N=19)		Group 2 (N=14)		Group 3 (N=17)	
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Rapid virologic response*	19/19†	100 (82–100)	13/14	93 (66–100)	15/17	88 (64–99)
Extended rapid virologic response‡	17/19	89 (67–99)	11/14	79 (49–95)	10/17	59 (33–82)
Response at week 12 of treatment	19/19†	100 (82–100)	13/14	93 (66–100)	11/17	65 (38–86)
Sustained viral response 12 wk after treatment§	18/19	95 (74–100)	13/14	93 (66–100)	8/17	47 (23–72)
Response to previous therapy						
Partial	—	—	—	—	5/10	50 (19–81)
Null	—	—	—	—	3/7	43 (10–82)
IL28 genotype						
CC	9/10	90 (56–100)	4/5	80 (28–99)	0/0	—
CT	7/7	100 (59–100)	7/7	100 (59–100)	6/12	50 (21–79)
TT	2/2	100 (16–100)	2/2	100 (16–100)	2/5	40 (5–85)

Poordad et al. NEJM 2014; 3D combi

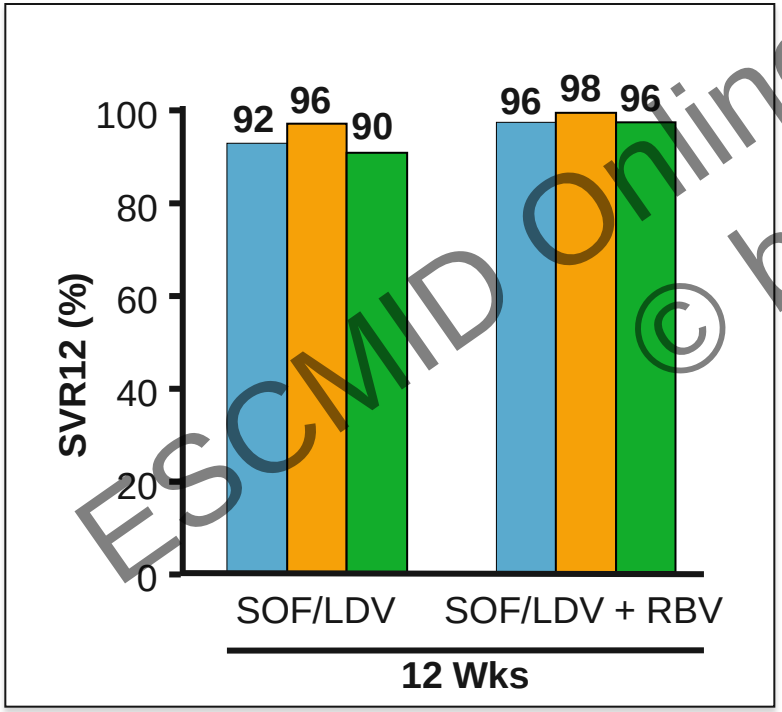
So what about cirrhosis?

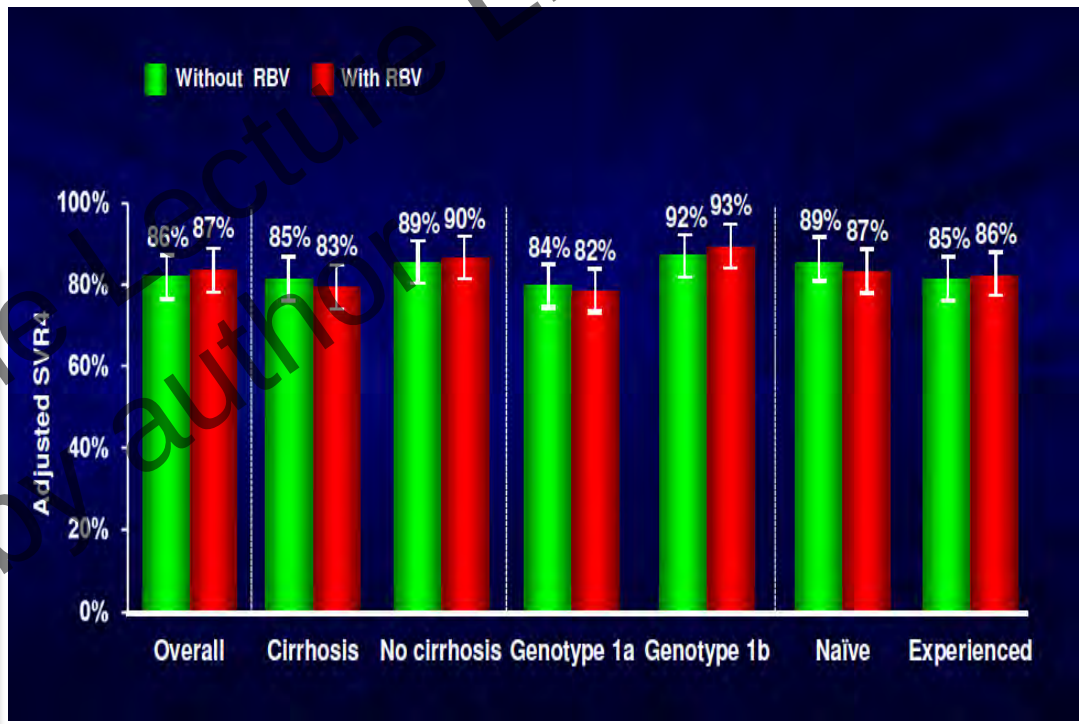
Cirrhosis no predictor for SVR in treatment naieve / experienced GT 1 patients

All pts (N = 513)

Tx-naive pts (n = 161)

Tx-experienced pts (n = 352)



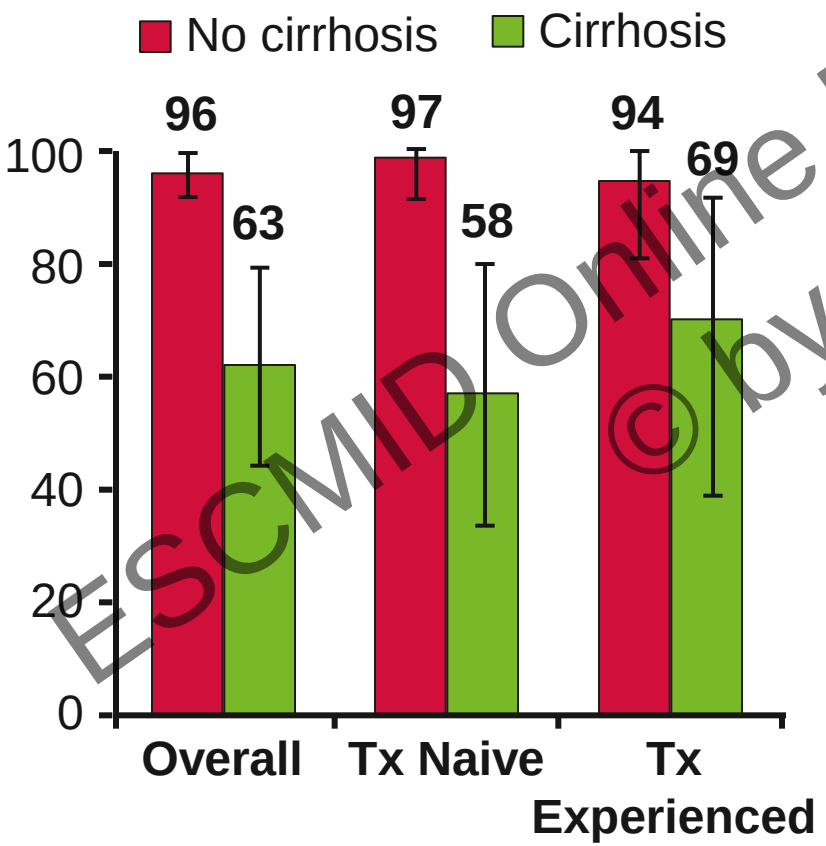


Compensated Cirrhosis Treated with Ledipasvir/Sofosbuvir

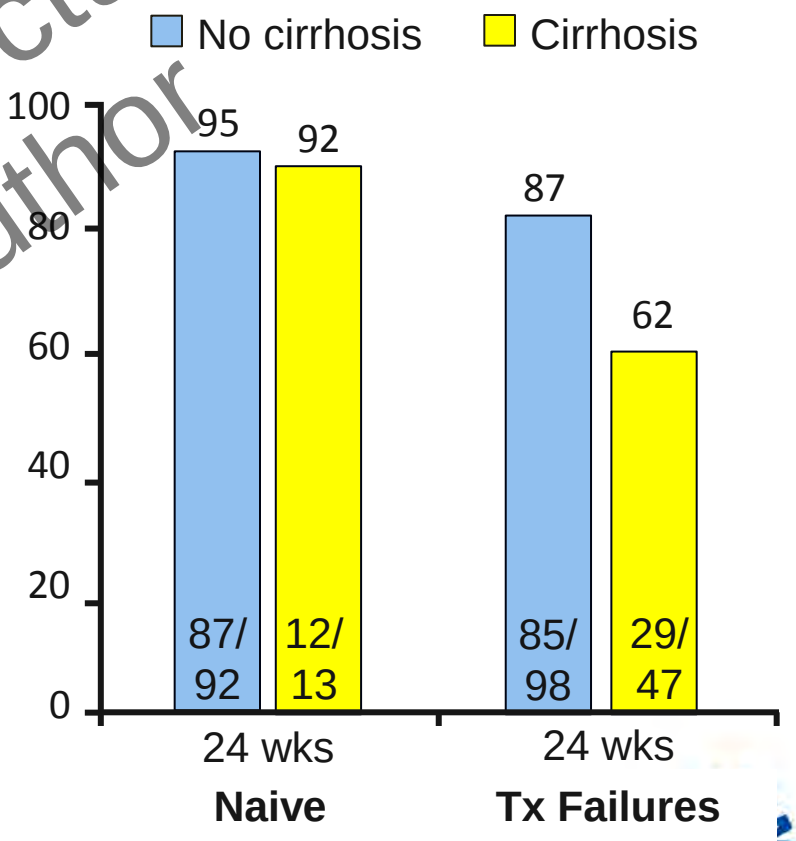
Bourliere M et al. AASLD 2014. abstract 82
Jensen DM et al. AASLD 2014. abstract 45

Combination of cirrhosis and previous treatment predictor of SVR in GT 3 patients

ALLY-3: DAC + SOF for 12 weeks in cirrhotic patients GT 3



VALENCE: SOF + RBV for 24 weeks in cirrhotic GT3 patients

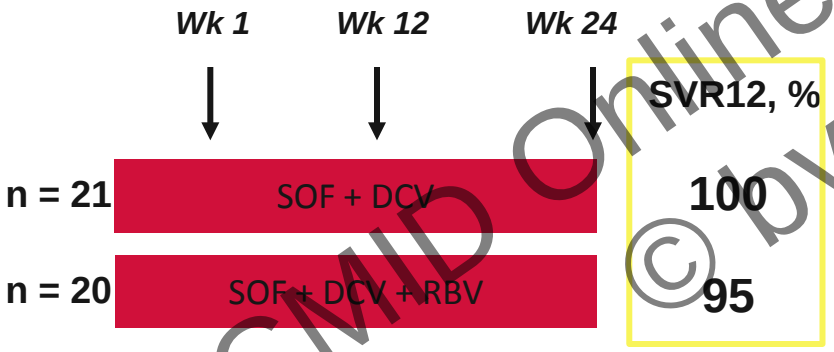


What about past treatment response?

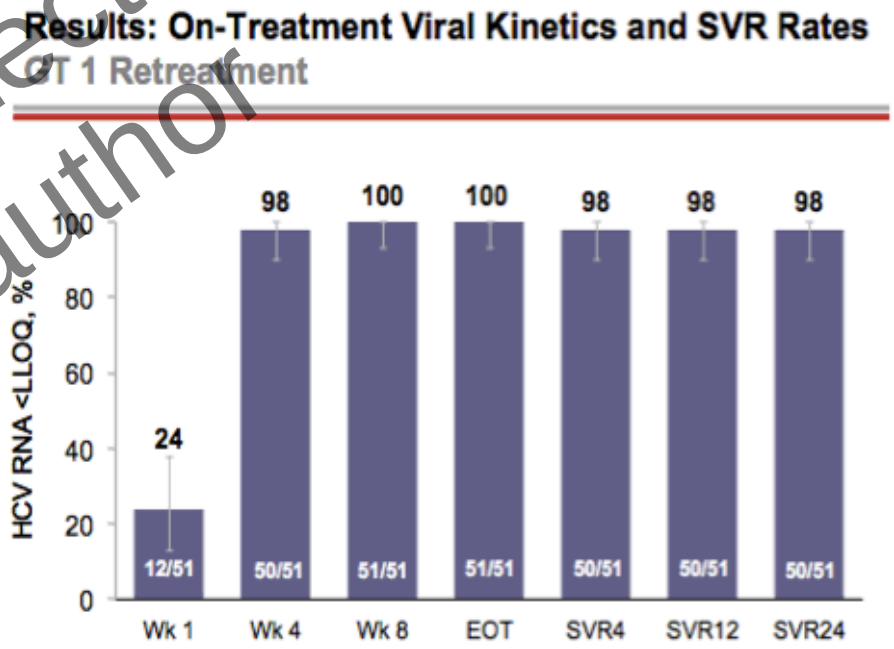
Is past treatment response a predictor for SVR?

PI-failures

(GT1 HCV TVR/BOC Treatment Failures)

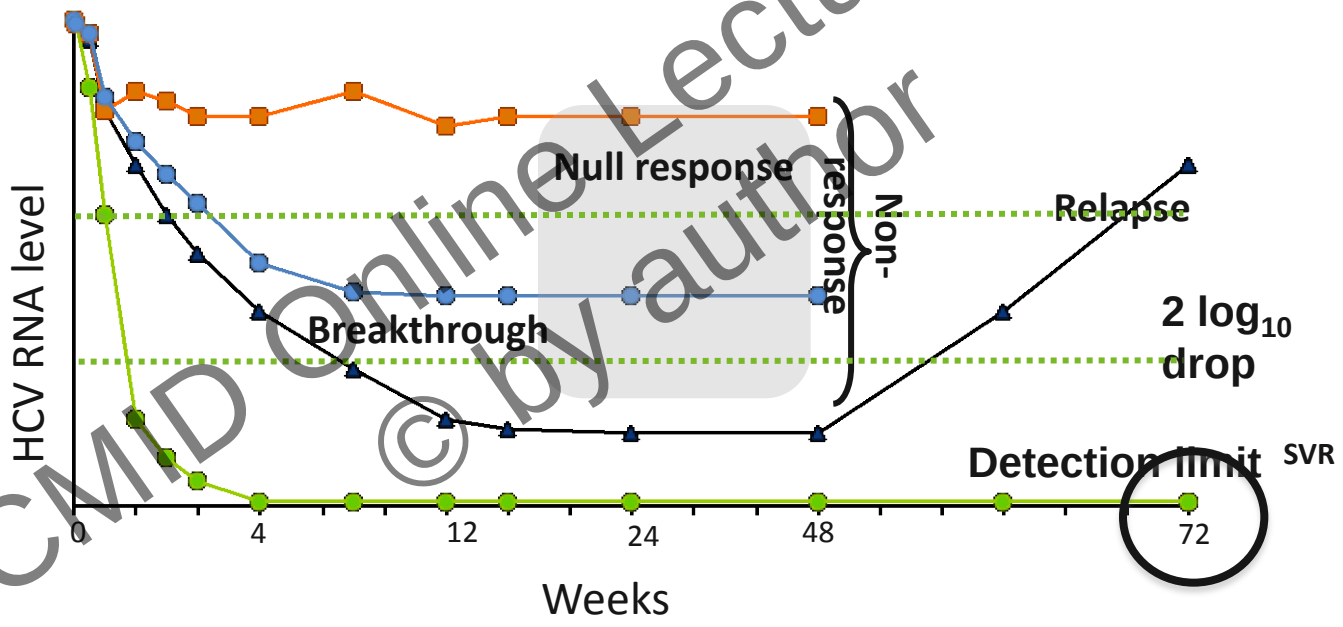


SOF-failure



Wyles et al. AASLD 2014
Sulkowski MS, et al. N Engl J Med. 2014;370:211-221.

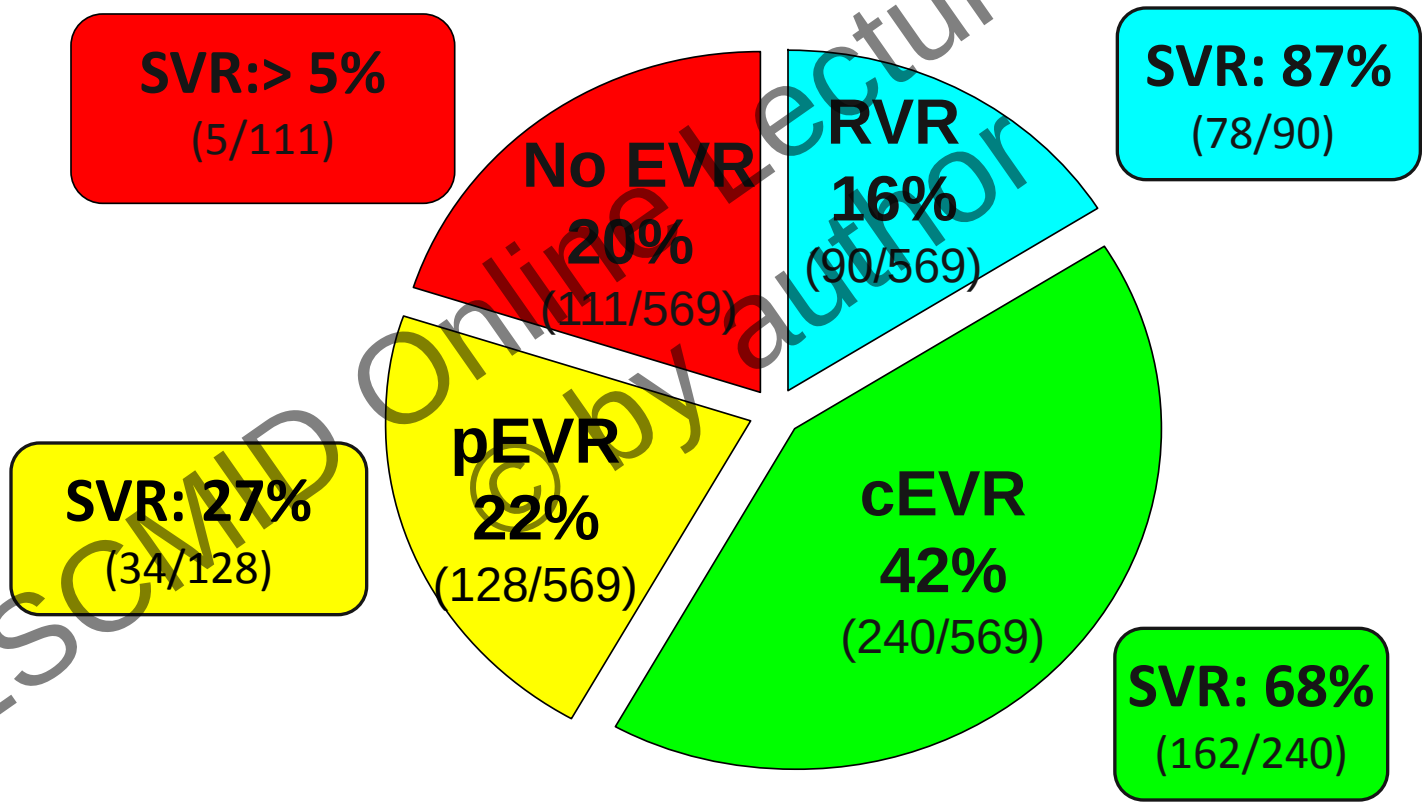
What about viral predictors?



Viral predictors of response

- traditional predictors
  - HCV viral load
  - HCV genotype
- HIV coinfection
- on treatment "viral kinetics"
  - achievement of RVR

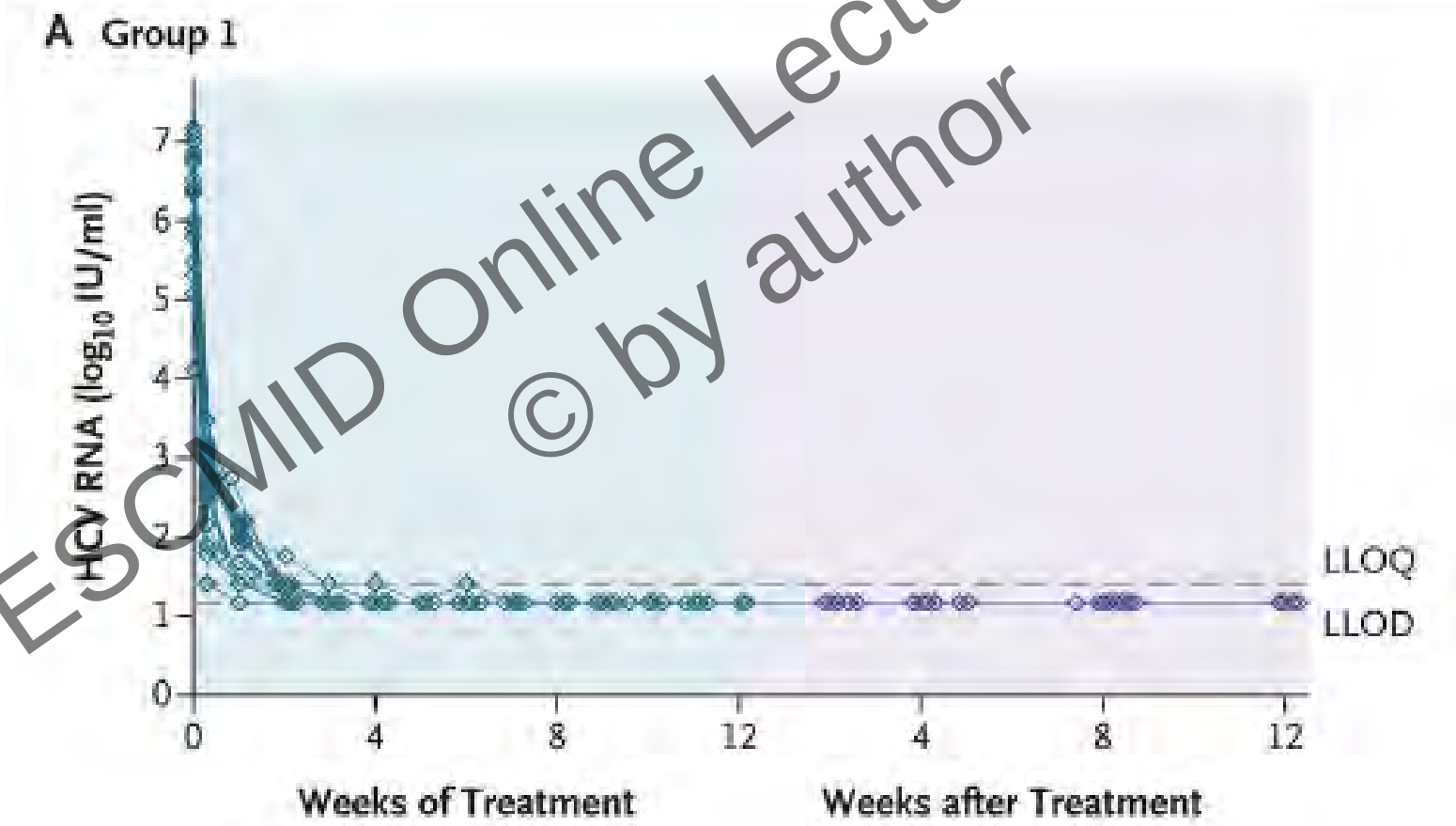
In pegIFN/ RBV era RVR was the most important predictor for SVR



Marcellin P, et al. 18th APASL 2008; Abstract FP022

In IFN-free treatment regimens HCV-RNA kinetics are no predictor for SVR anymore

phase 2a study with Paritaprevir/Ritonavir + Dasabuvir with RBV for 12 weeks



Utility of Hepatitis C Viral Load Monitoring On Directly Acting Antiviral Therapy

Sreetha Sidharthan[1], Anita Kohli[1], Zayani Sims[1], Amy Nelson[2,3], Anu Osinusi[4], Henry Masur[1], Shyam Kottilil[2,3]

[1]Critical Care Medicine Department, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, Maryland
[2]Institute of Human Virology, University of Maryland, Baltimore, Maryland
[3]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
[4]Gilead Sciences Inc., Foster City, California

Conclusions:

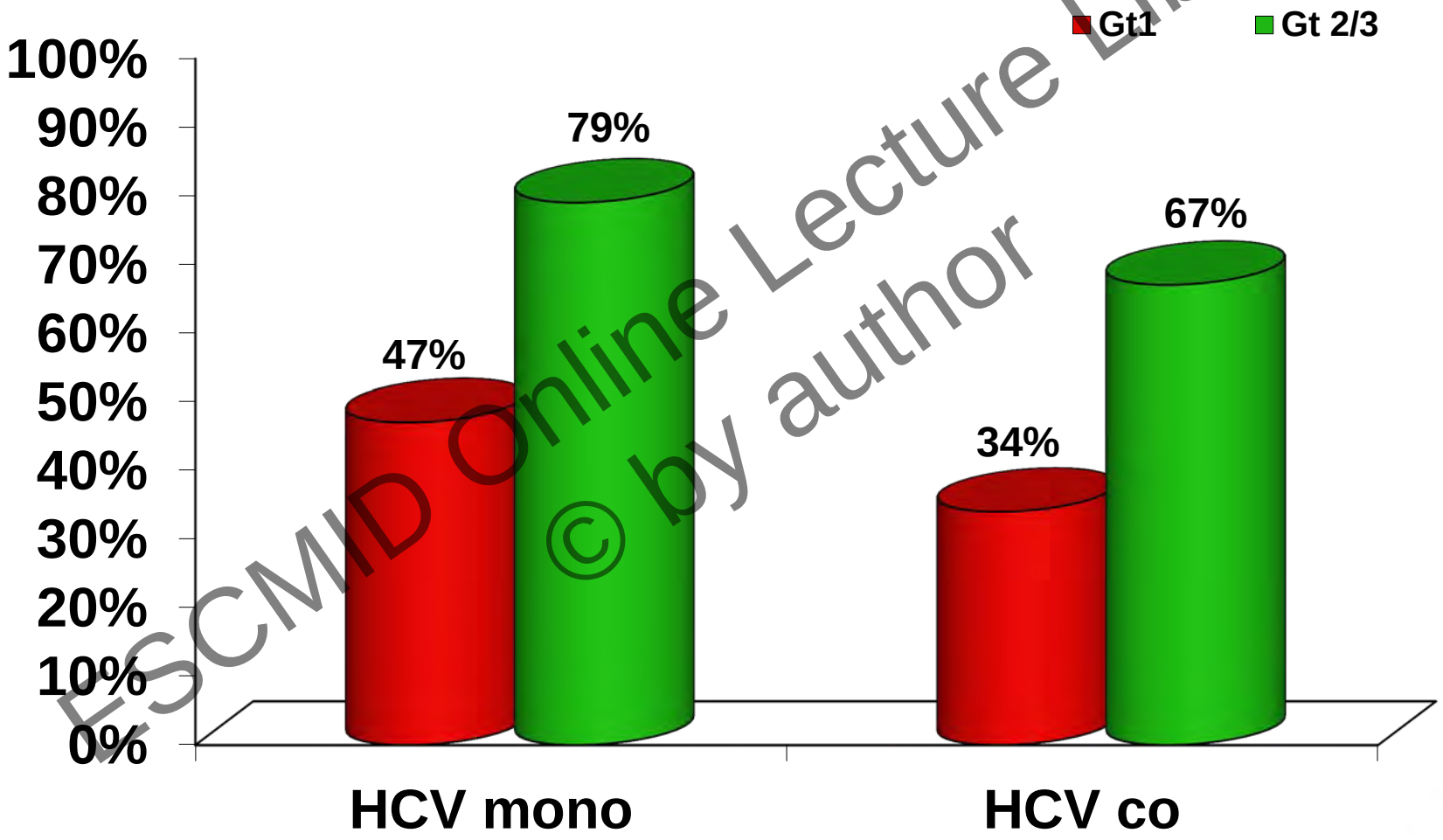
Contrary to past experience with interferon-containing treatments, low levels of quantifiable HCV RNA at EOT do not preclude treatment success.

Is HIV-coinfection still a predictor for SVR?

HCV

HIV/HCV

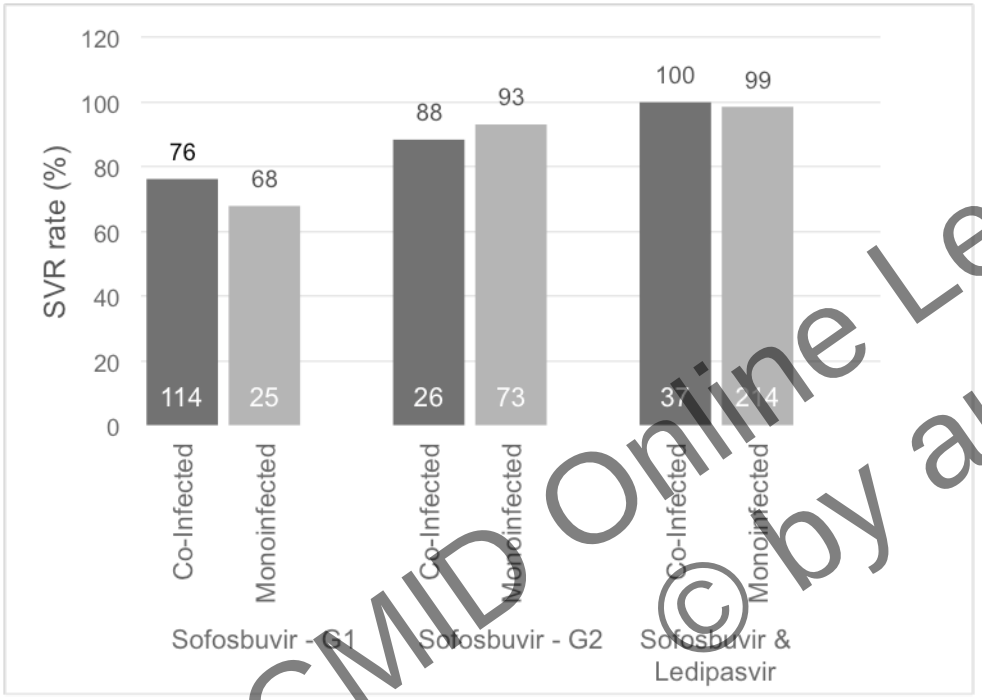
Difference in SVR between HCV mono- and HIV/HCV coinfection in the pegIFN/ RBV era

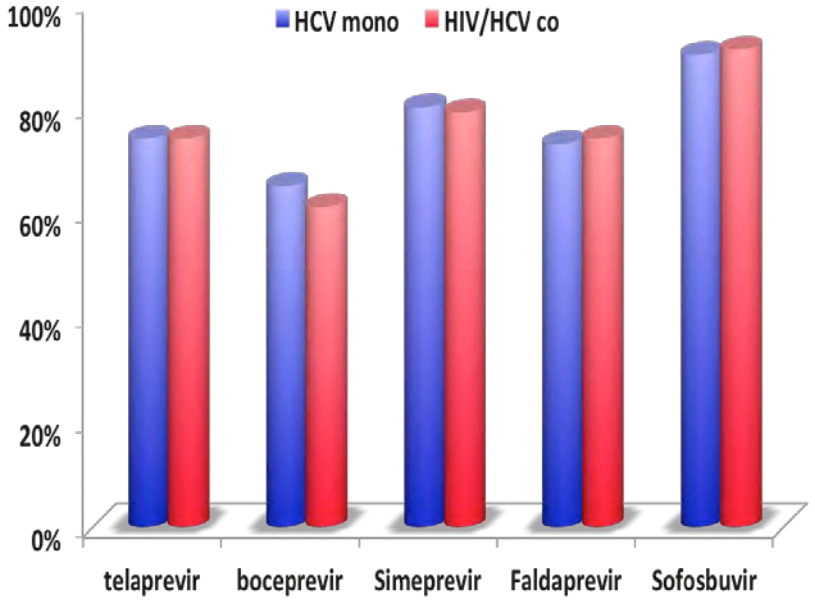


Manns Lancet 2001,
Fried N Eng J Med 2002,
Hadzyannis Ann Intern Med 2004
} HCV mono

Torriani et al. NEJM 2004
Carrat et al. JAMA 2004
Chung et al. NEJM 2004
Nunez et al. AIDS Res Hum Retroviruses 2007
} HCV co

SVR-rates between HCV mono- and HIV/HCV coinfected patients is identical





Arends et al. in preparation

EASL recommendation – april 2014

EASL
European Association for the Study of the Liver

Recommendations

Recommendations

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection **(Recommendation A1)**

In conclusion

- With increasing SVR rates to around 90%, the importance of SVR predictors is fading

- Past treatment response in combination with cirrhosis is the only and most important predictor for SVR in the IFN-free DAA era

- Previous important predictors like HCV-RNA, IL28B genotype, HIV-coinfection, HCV viral load and achievement of RVR are not relevant anymore

Questions?