

# Individual Optimization of therapy

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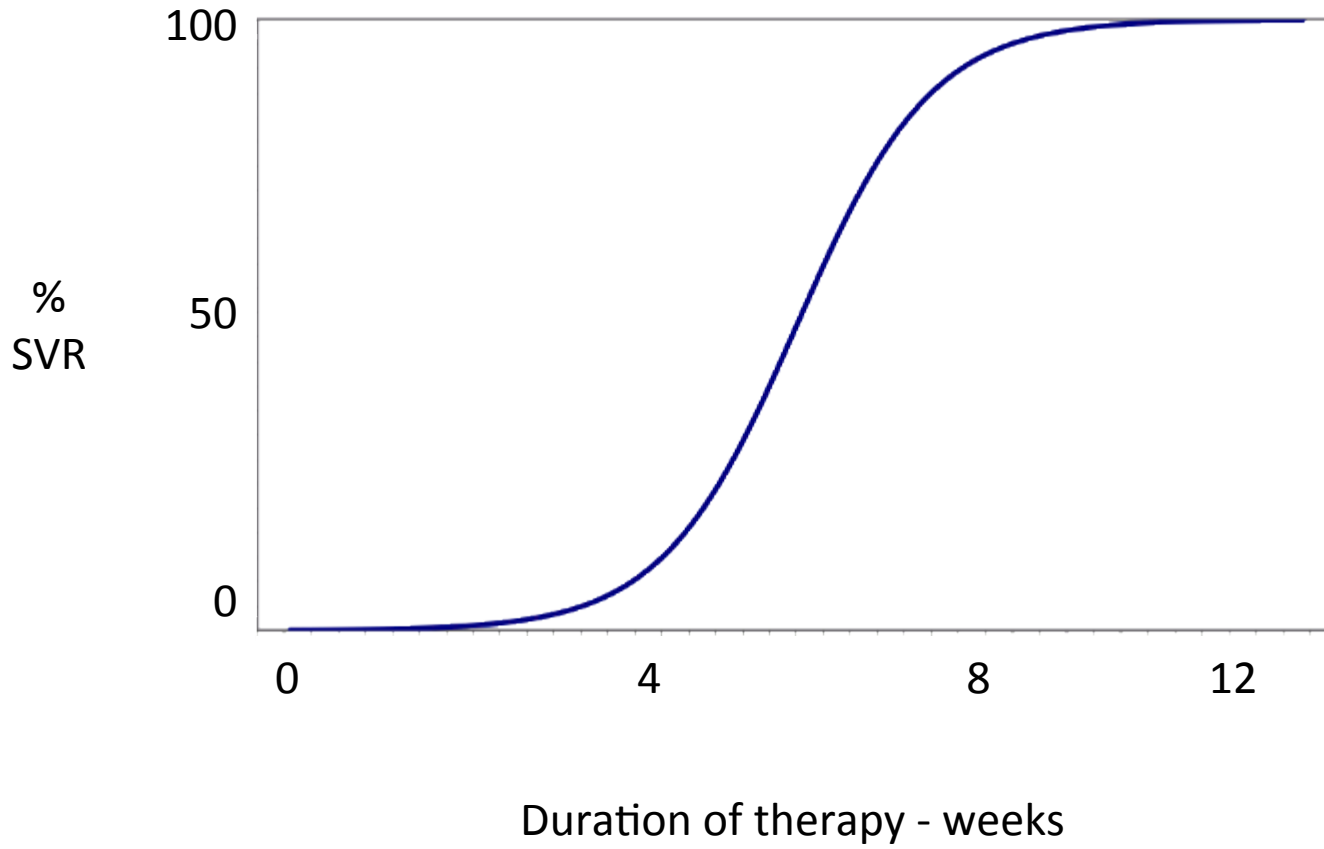
# Conflicts of Interest

- Speaker and consultancy fees received from
- AbbVie, BI, BMS, Gilead, Janssen, Roche, Merck, Novartis, Springbank, Achillion, Idenix

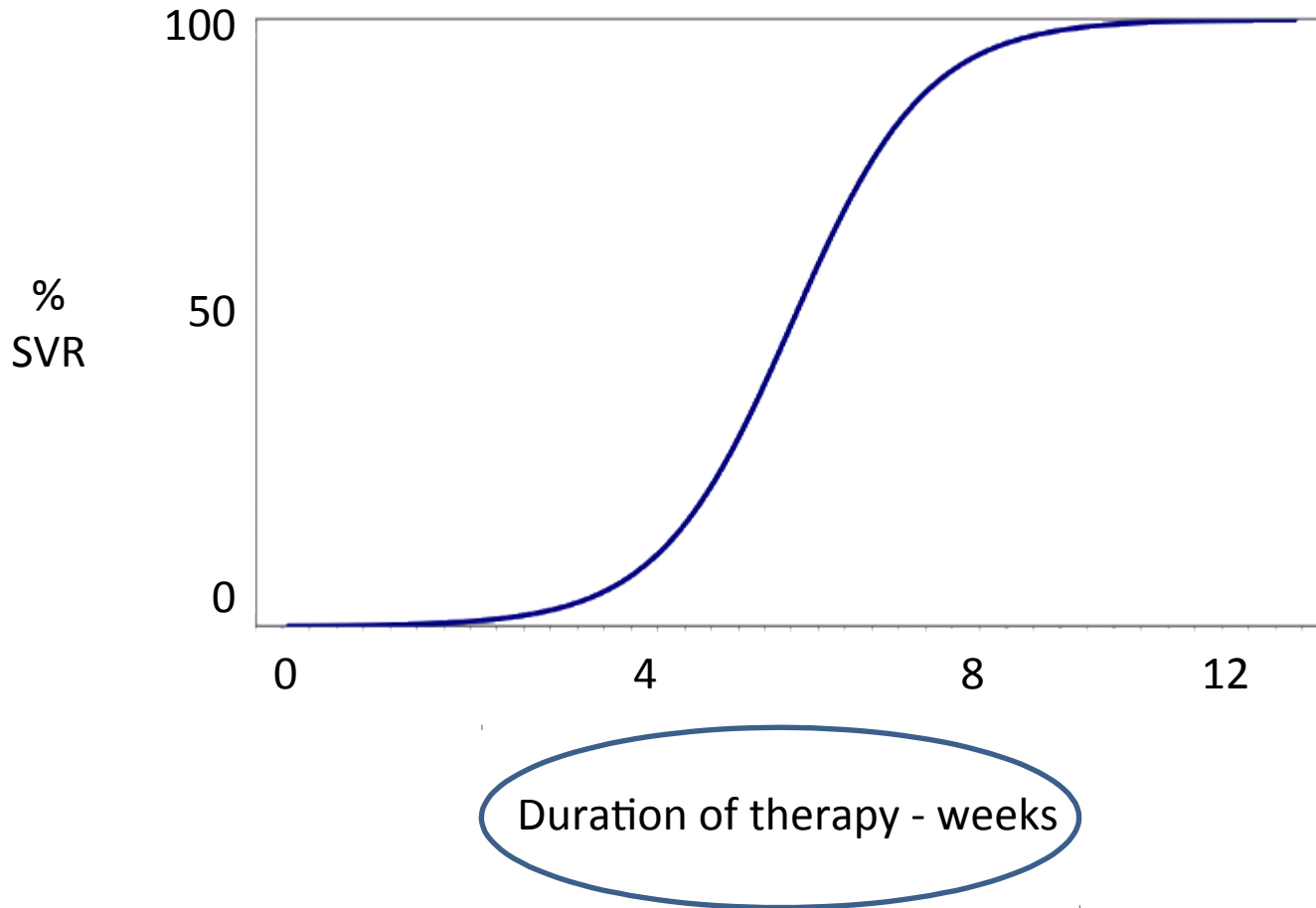
# Optimisation of Therapy

- The Theory
- The Practice
- The costs

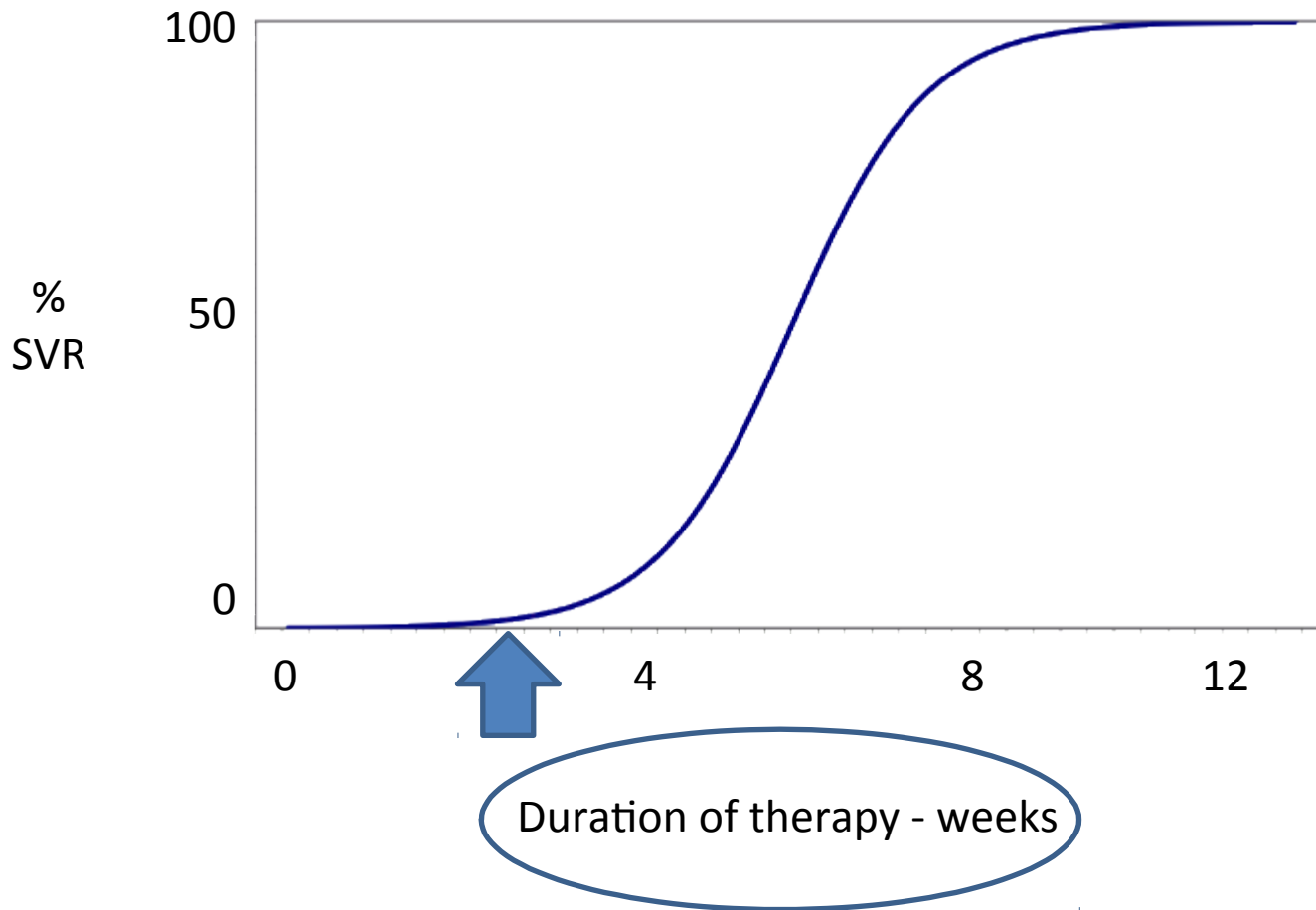
# Optimisation of therapy Theory



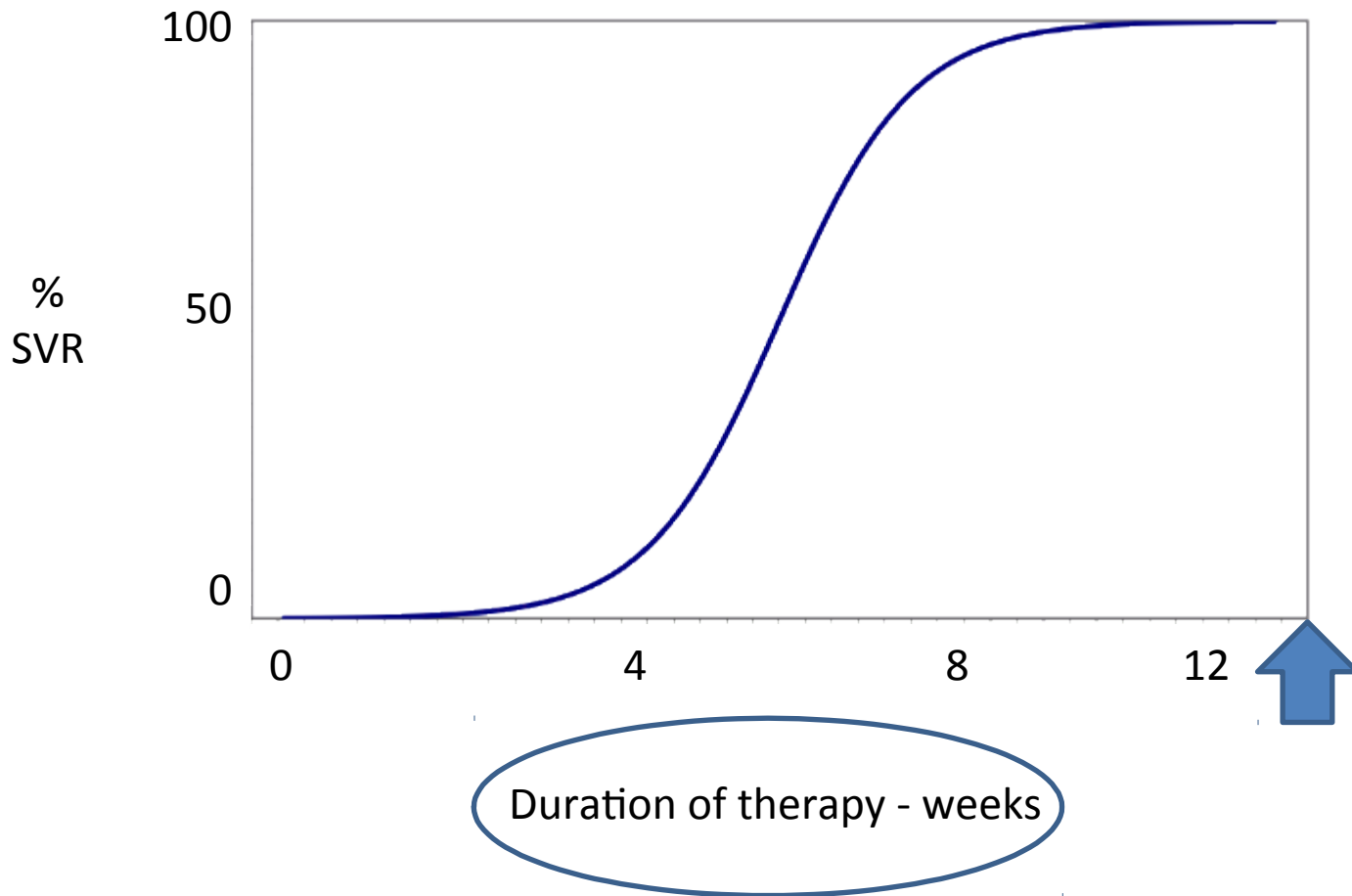
# Optimisation of therapy Theory



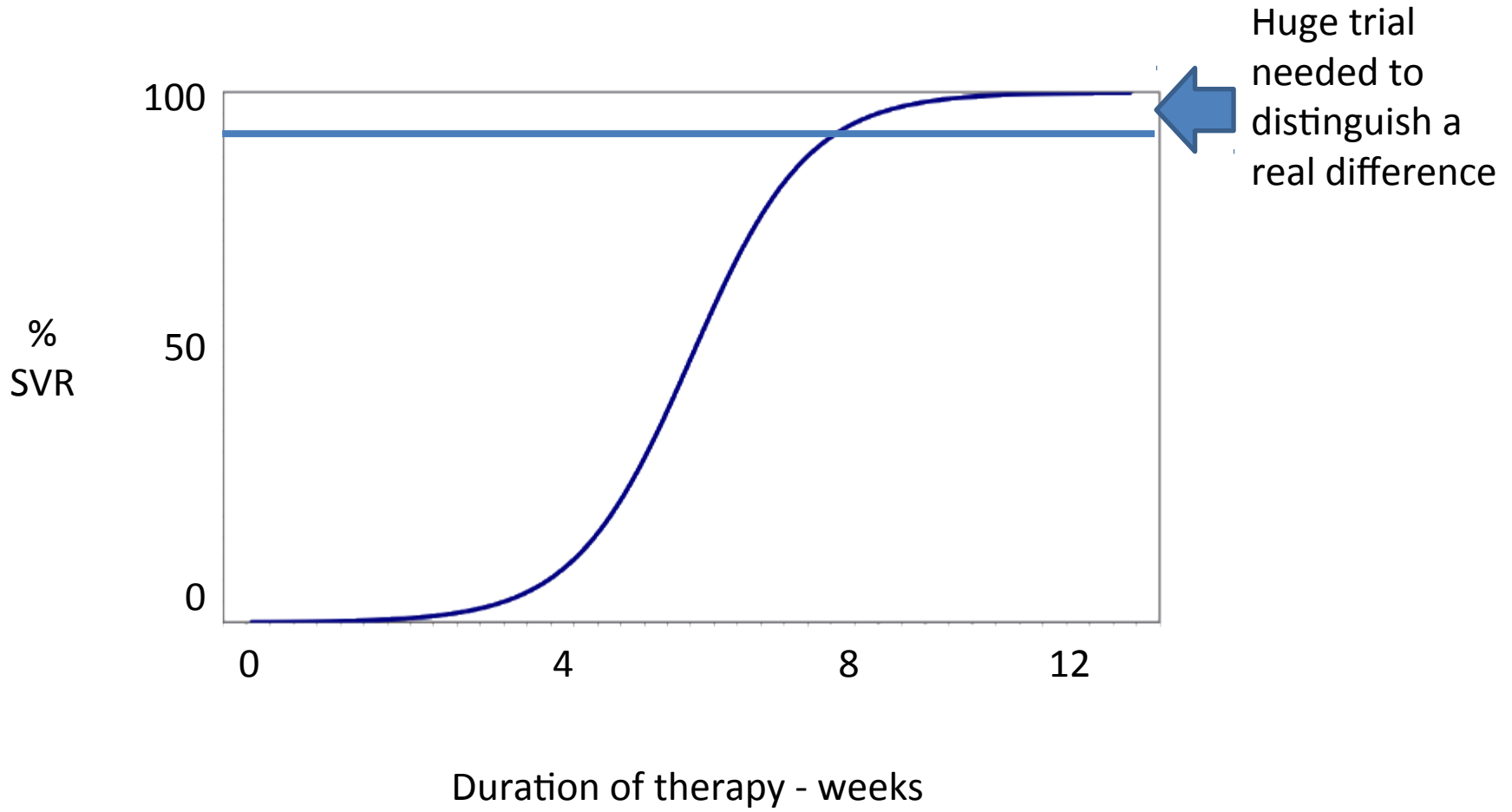
# Optimisation of therapy Theory



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# Optimisation of Therapy Theory





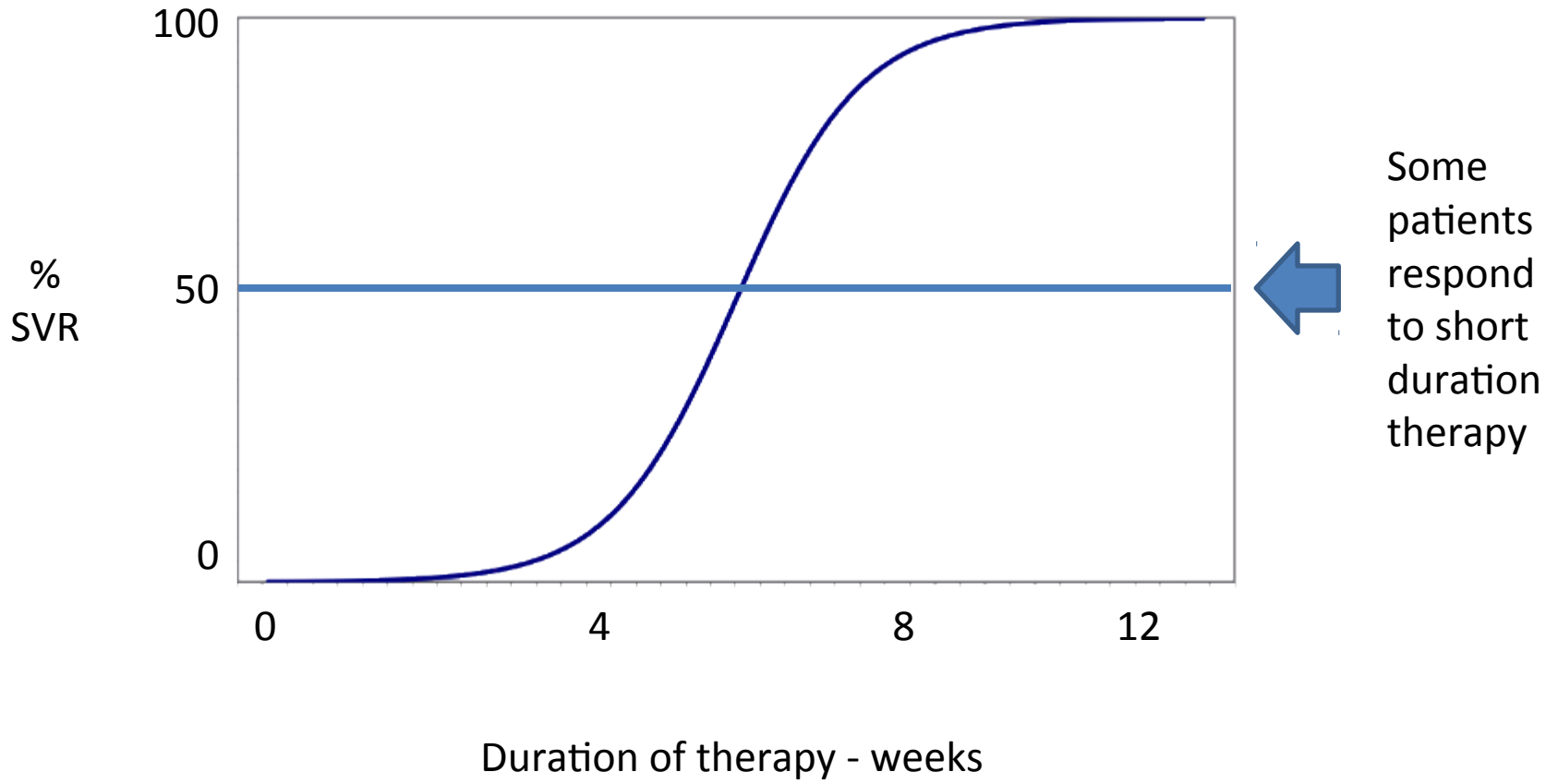
# Optimisation of Therapy Theory

- Shorter durations of therapy are cheaper

BUT

- They have a higher risk of relapse

# Optimisation of Therapy Theory



# Optimisation of Therapy Theory

- We could identify patients who will benefit from short duration therapy
- We can then treat them with short courses

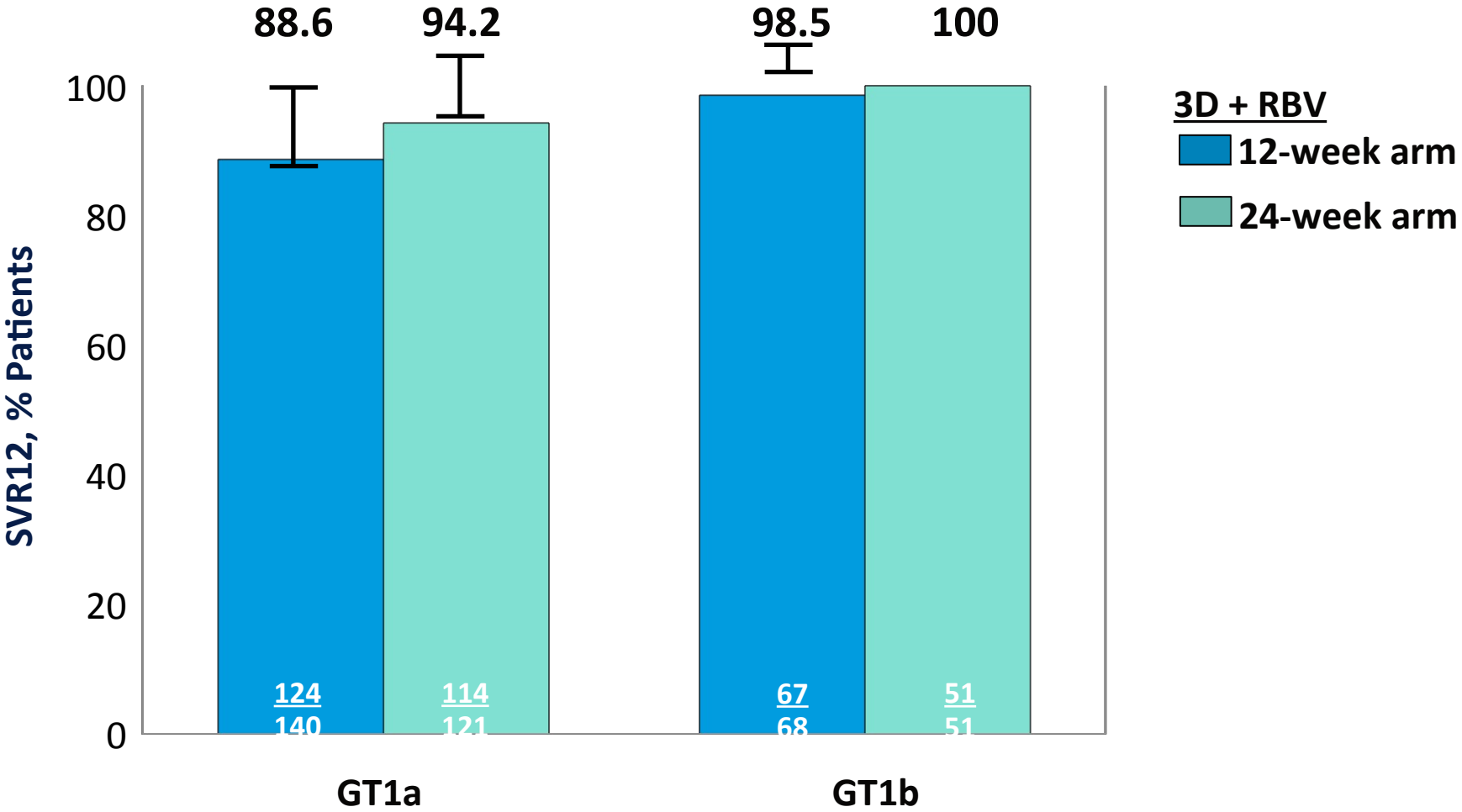
# Optimisation of Therapy Theory

- We could identify patients who will benefit from short duration therapy
- We can then treat them with short courses
- In theory this should save money...

# Optimisation of Therapy

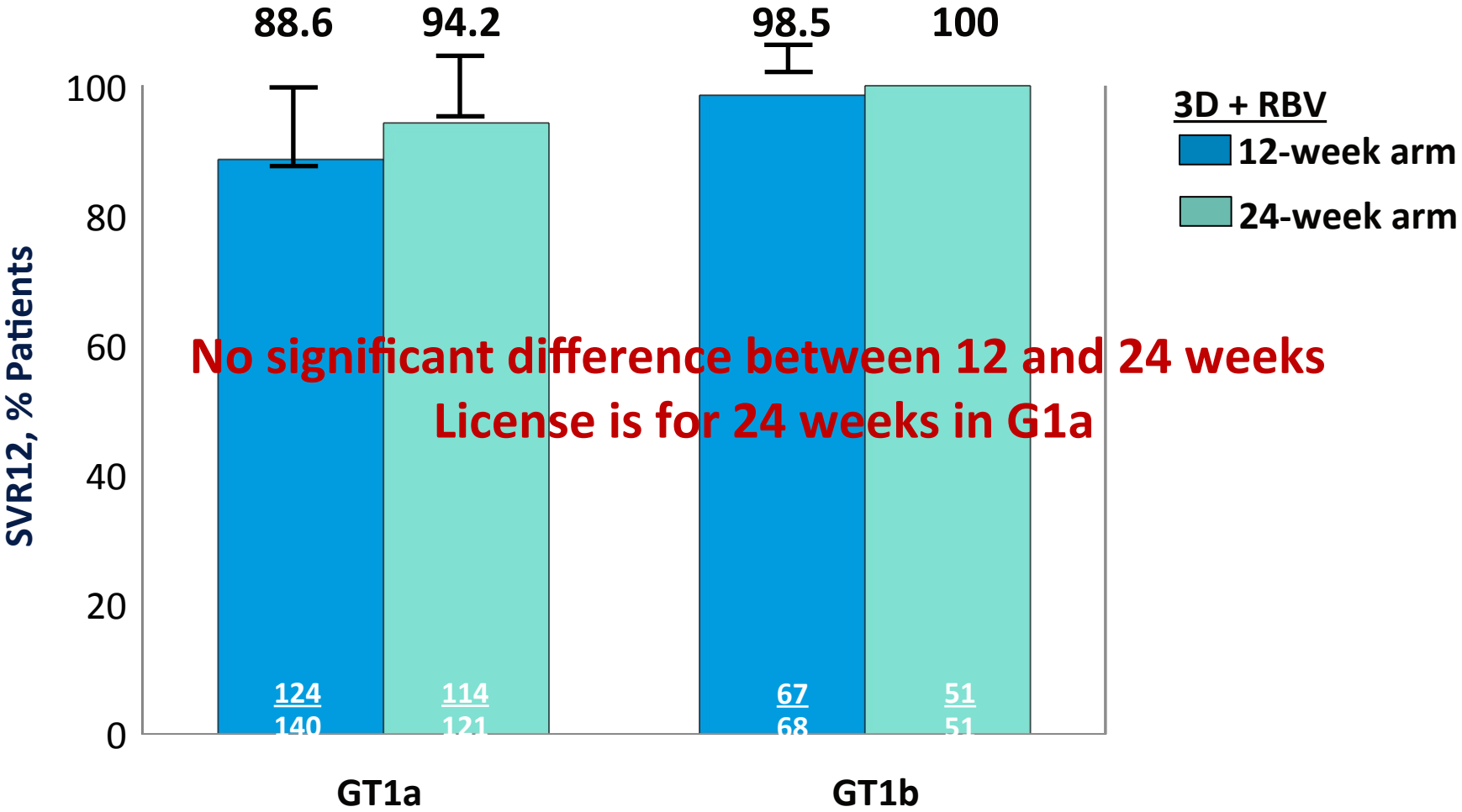
- The Theory
- **The Practice**
- The costs

# TURQUOISE-II: SVR12 rates in GT1 treatment-naive and experienced cirrhotic patients by HCV genotype



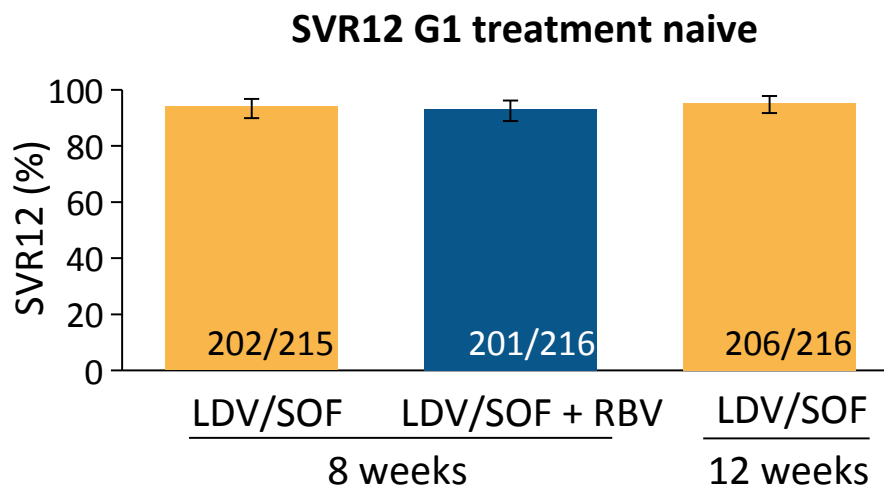
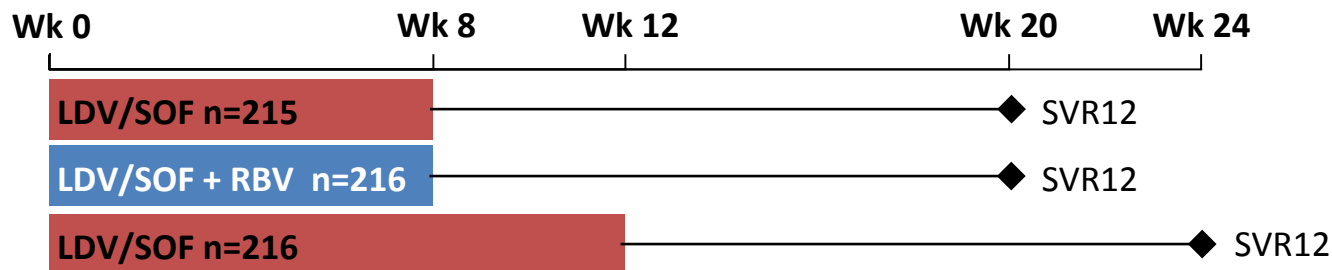
• Poordad F, et al. N Engl J Med 2014. Online DOI:10.1056/NEJMoa1402869.

# TURQUOISE-II: SVR12 rates in GT1 treatment-naive and experienced cirrhotic patients by HCV genotype



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# Sofosbuvir/ledipasvir ± RBV for 8 weeks vs 12 weeks in treatment-naive non-cirrhotic G1 HCV-infected patients



- 8 weeks without RBV not statistically inferior
- Without cirrhosis 8 weeks is the right duration

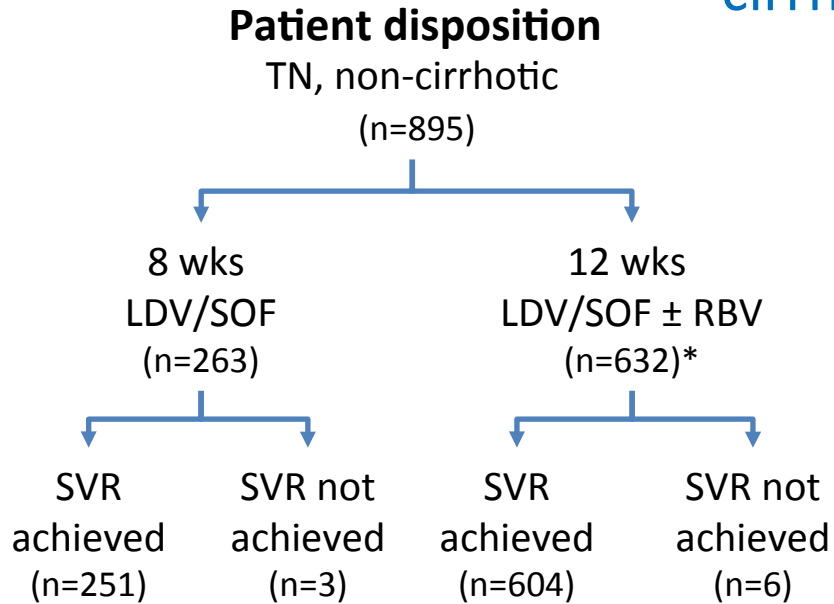


# Optimisation of Therapy

## The Practice

- Properly powered, prospective, randomised trial shows 8 weeks is equal to 12 weeks
- Is this widely used?

# Real-world experience from the TRIO Network: Effectiveness of 8- or 12-week LDV/SOF in treatment-naive, non-cirrhotic, G1

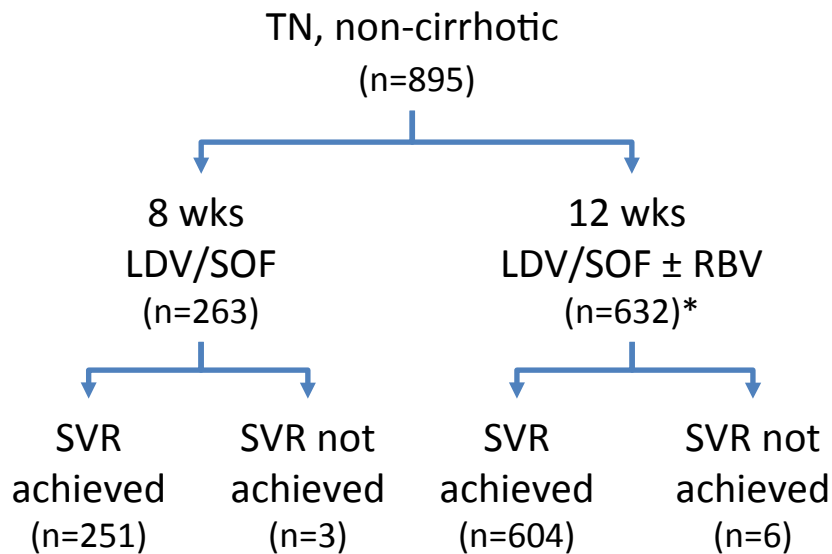


3 out of 4  
patients received  
the 'long'  
regimen

\*21 patients were on 12 weeks of LDV/SOF + RBV

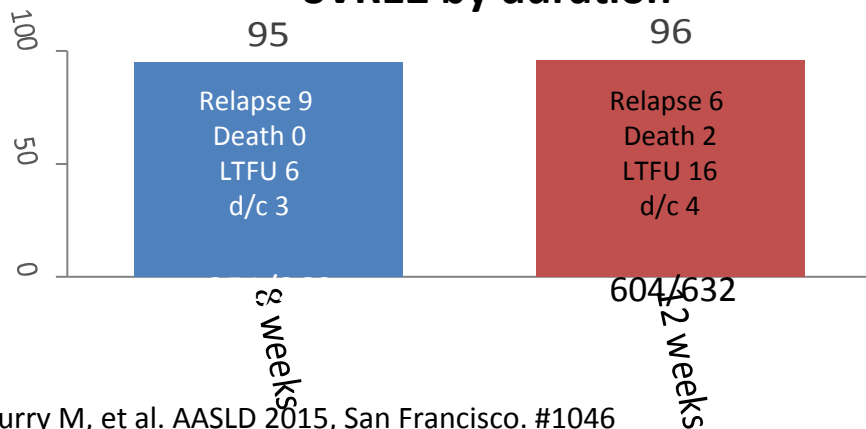
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## Patient disposition

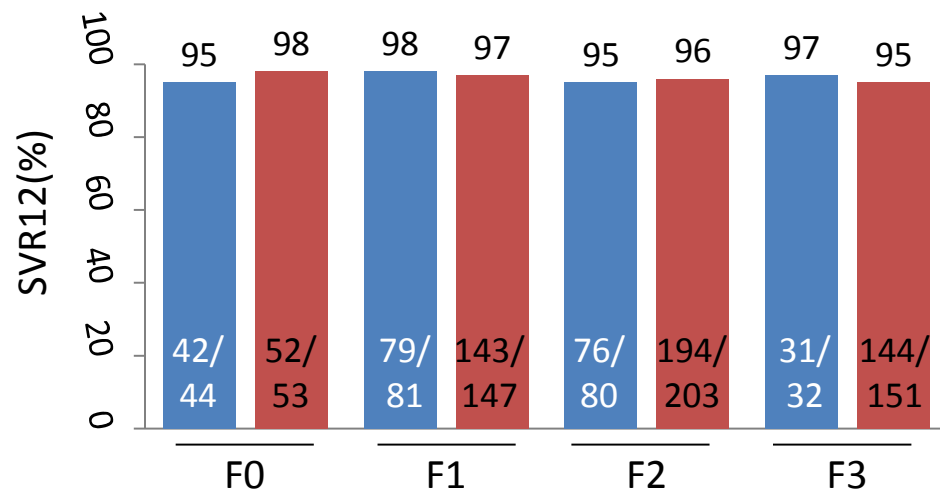


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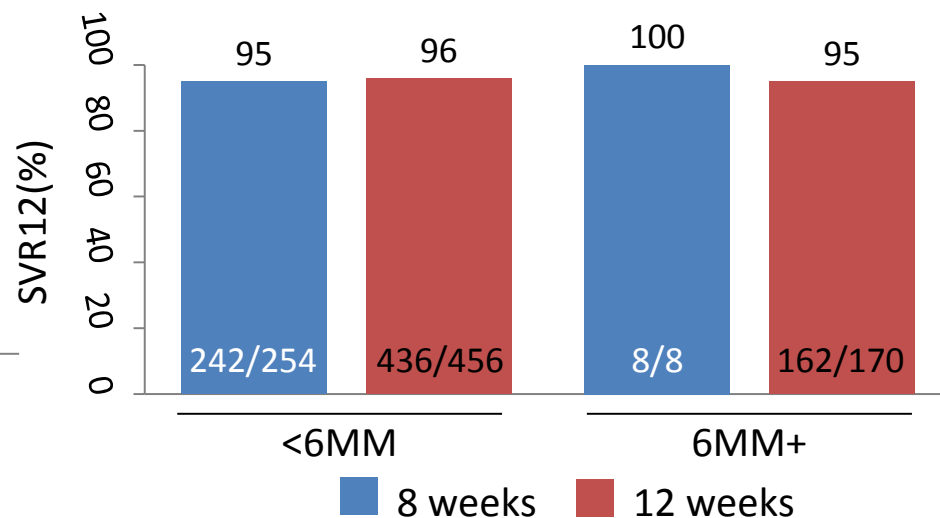
## SVR12 by duration



## SVR12 by fibrosis



## SVR12 by baseline viral load



# Optimisation of Therapy

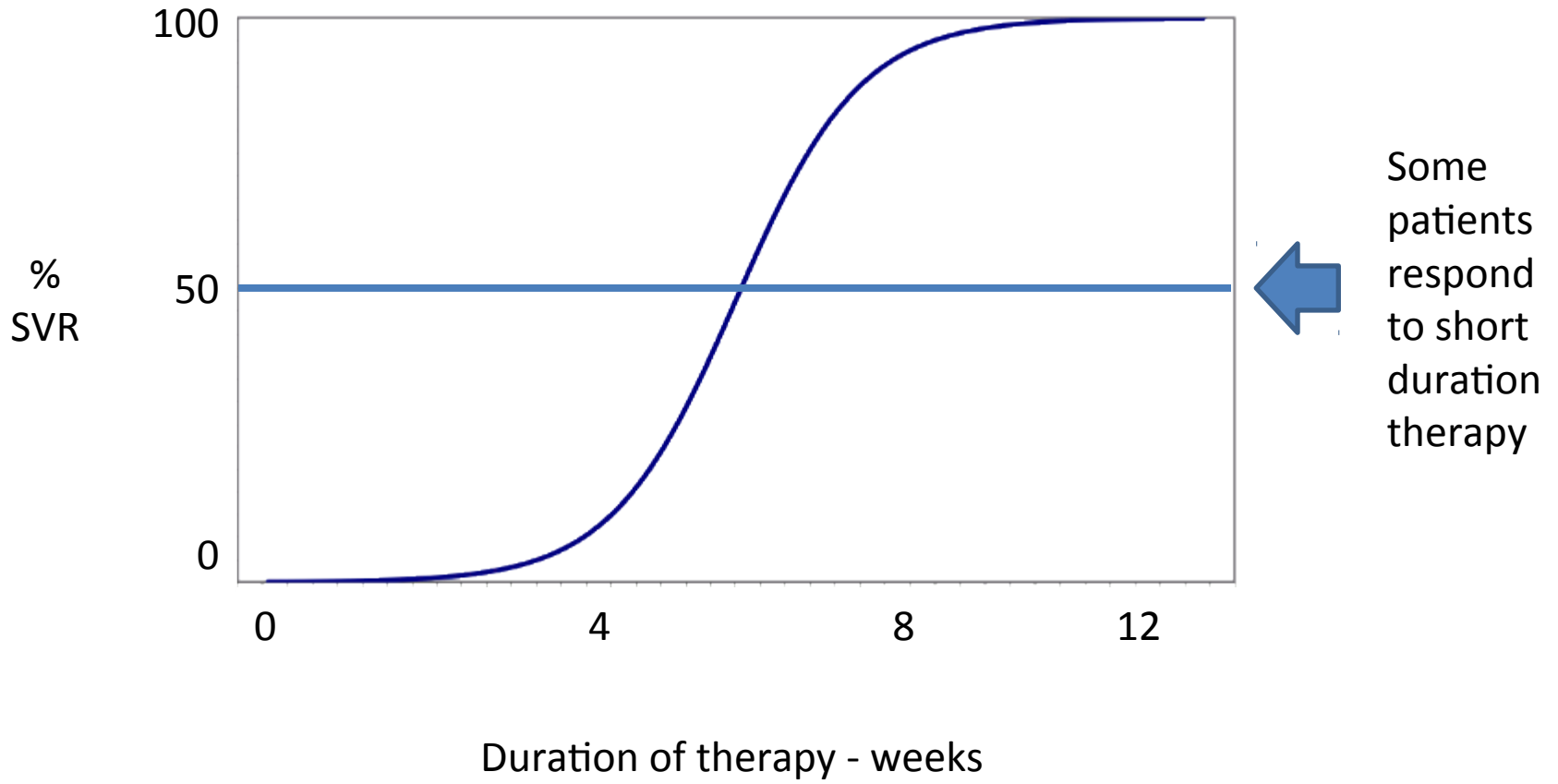
## The Practice

- Clinicians and patients are conservative
- They do not like to take risks
- Persuading people to use shorter durations will not be easy

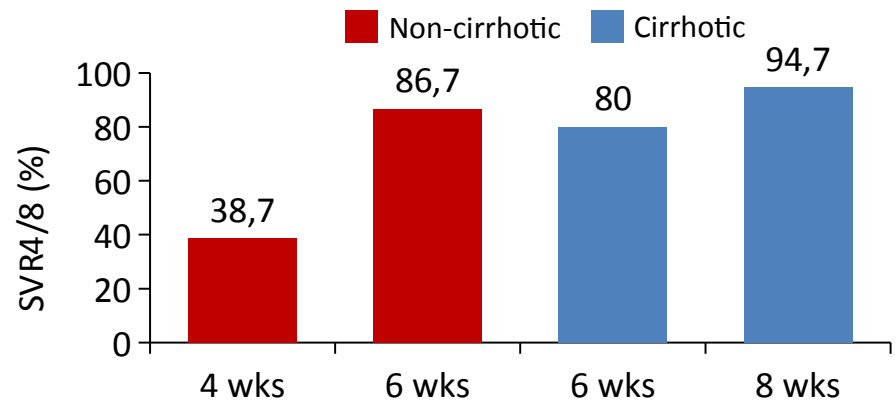
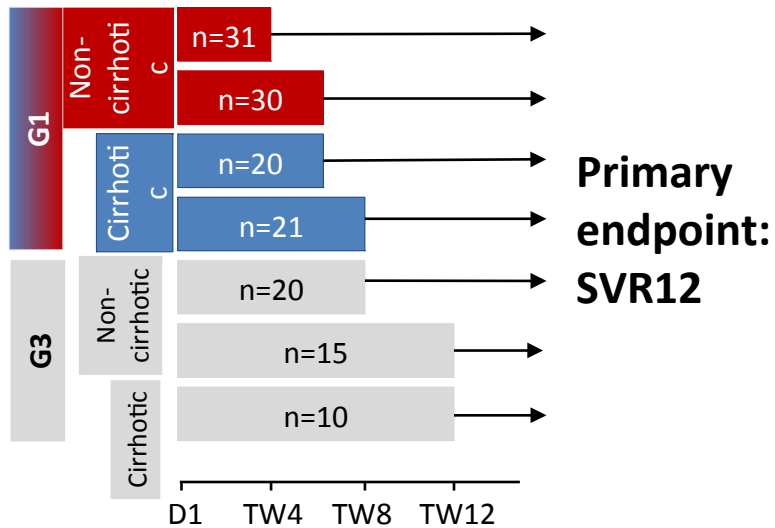
# Optimisation of Therapy

- What about shorter treatments?
- Can we find predictors of response to short duration therapy?

# Optimisation of Therapy Theory



# C-SWIFT: Grazoprevir)+ Elbasvir) + SOF in untreated G1 pts with/without cirrhosis, for 4, 6, or 8 weeks



# Short Duration Therapy



Some patients  
respond

Some patients  
don't respond



# Short Duration Therapy



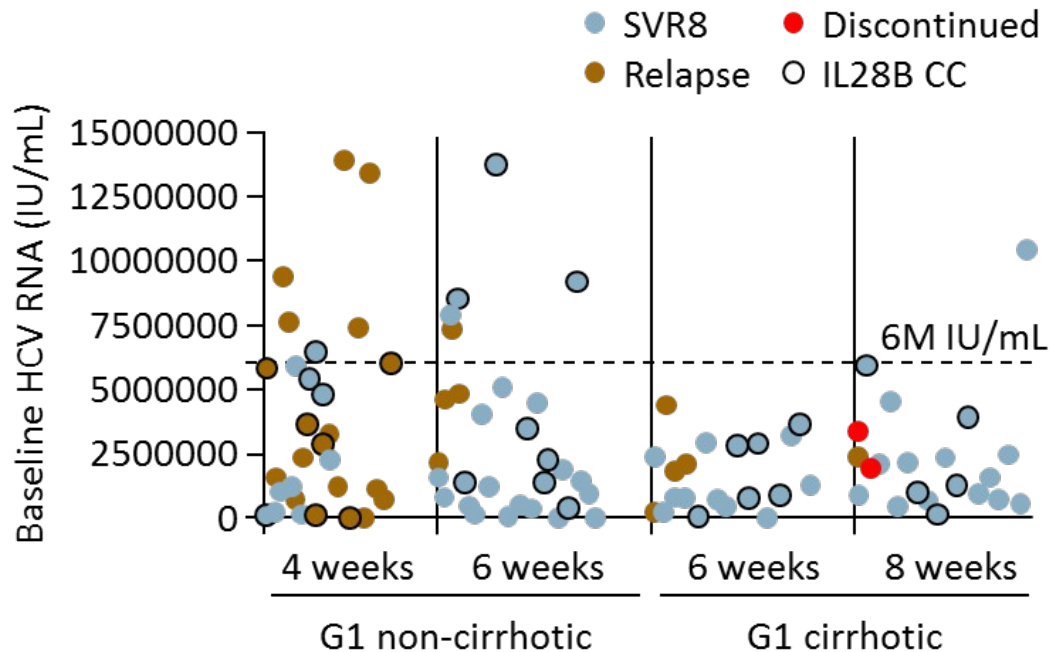
Some patients  
respond

Some patients  
don't respond

Can we predict who will respond and who won't?

# C-SWIFT: Grazoprevir)+ Elbasvir) + SOF in untreated G1 pts with/without cirrhosis, for 4, 6, or 8 weeks

## Impact of BL HCV RNA and IL28CC on SVR4/8



High viral load and non CC predictive of failure with 4-week duration

# Short Duration Therapy 'Response Guided Therapy'?

- With Peg/Riba response guided therapy was popular and effective
- With all oral regimes most patients are negative after 4 weeks

# Response Guided Therapy

## All-Oral Triple-DAA regimens

-  
-

Group / Tx regimen	RVR	SVR
<b>1:</b> SOF, LDV, ASV (n=12)	6/12	6/6
<b>2:</b> SOF, DCV, SMV (n=6)	6/6	6/6
<b>3:</b> SOF, DCV, ASV (n=8)	6/8	6/6

# Factors influencing SVR in English EAP

		Univariate		Multivariate	
		Odds ratio	95% CI	Odds ratio	95% CI
<b>Treatment</b>	Sof/DCV/Riba	Ref		Ref	
	Sof/LDV/Riba	0.9	0.5-1.7	2.7*	1.2-6.3
	Without Riba	2	0.8-5.0	9.0*	2.5-31.0
<b>Genotype</b>	Type 1	Ref		Ref	
	Type 3	5.1	2.6-10.1	10.3*	4.4-24.6
	Other	0.9	0.2-4.0	0.8	0.2-4.2
<b>Viraemic at 2 weeks?</b>	No	Ref		Ref	
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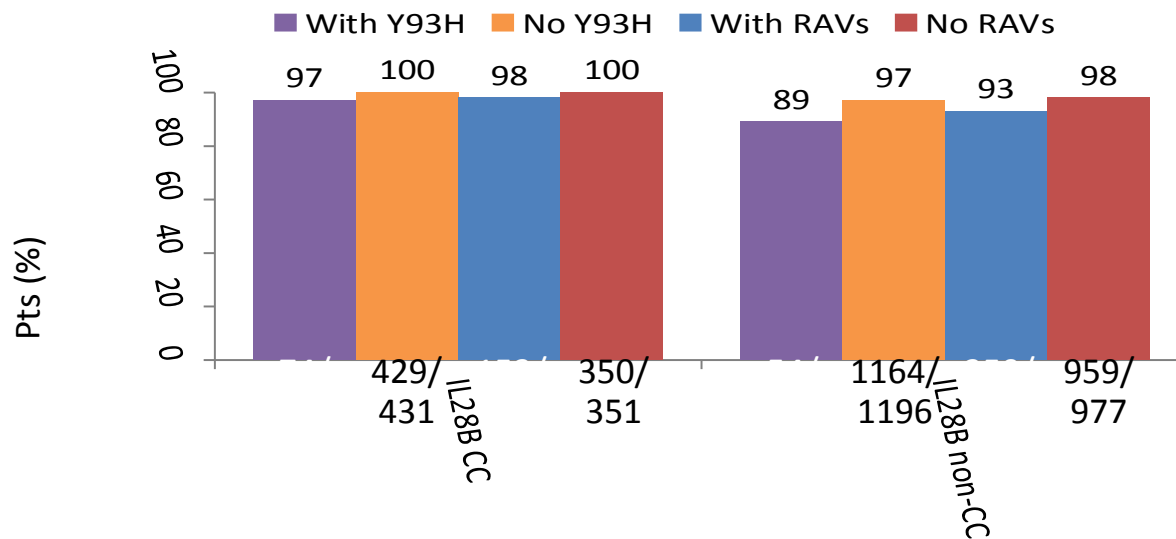
Trial of 24 vs 12 weeks sof/dac/riba in G3 slow responders under way

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# Resistance Associated Variants (RAVs) may reduce response

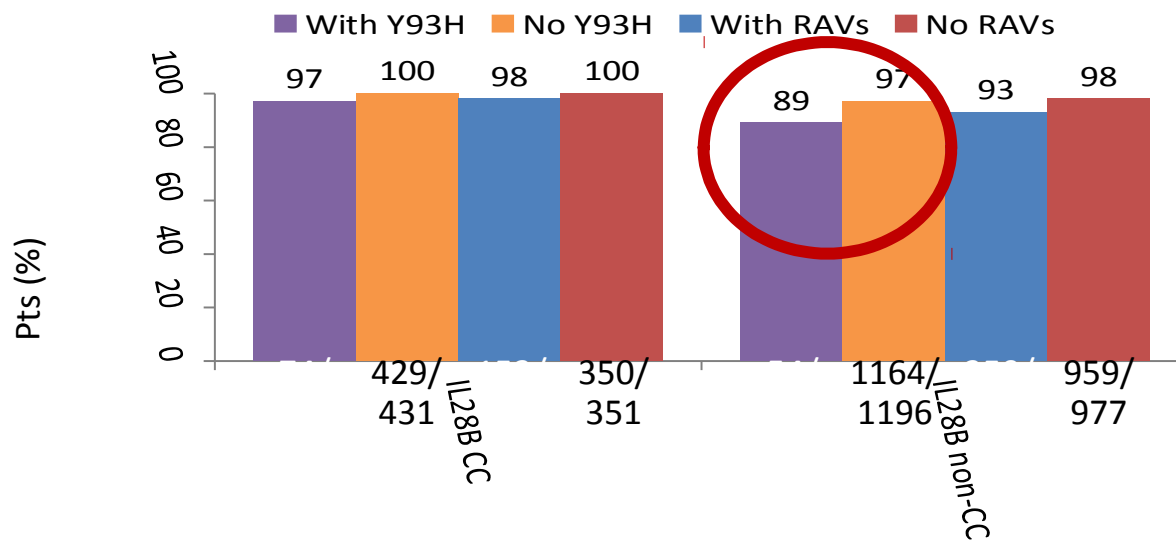
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# Resistance analyses (NS5A)

## Phase 2/3 studies of LDV/SOF ± RBV

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- 2144 G1 patients treated (51 (2.4%) no SVR)

### Deep sequencing at baseline

- NS5A RAVs in 16% → 92% SVR

### Deep sequencing at virologic failure (VF)

- NS5A RAVs in 38 (74.5%)

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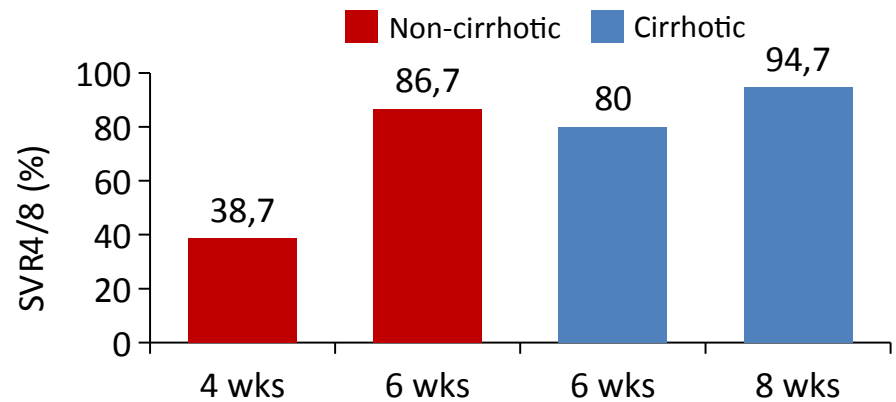
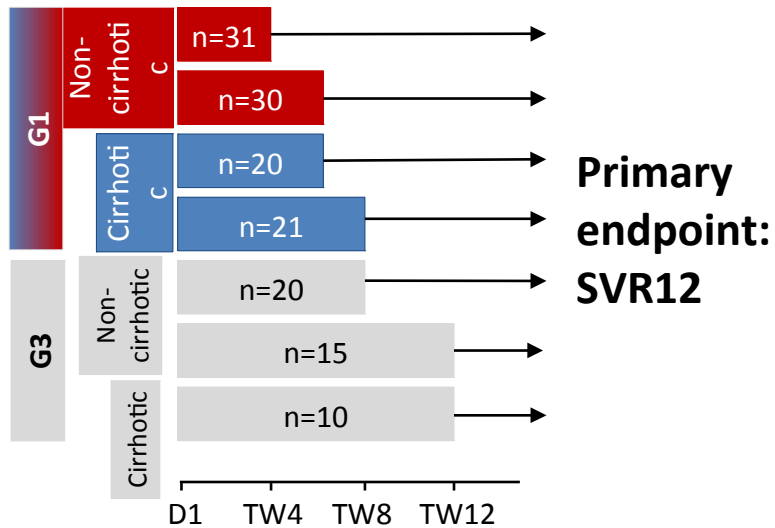
### Resistance analysis in patients with Virologic Failure

Variants	Subjects with NS5A RAVs n (%)		
	G1a (n=42)	G1b (n=9)	Total G1 (n=51)
<b>Present at BL</b>	19 (45.2)	3 (33.3)	22 (43.0)
<b>Present at VF</b>	30 (71.4)	8 (88.9)	38 (74.5)*

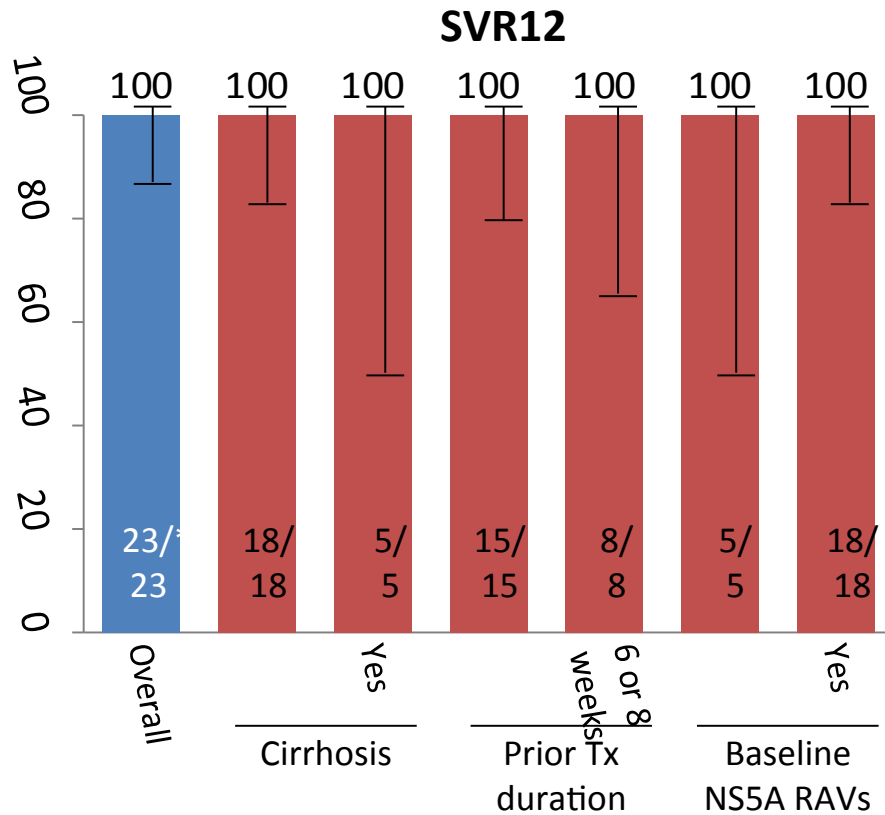
# RAVs

- Associated with failure
- More common post therapy in treatment failures
- Will short course therapy generate resistance?

# C-SWIFT: Grazoprevir)+ Elbasvir) + SOF in untreated G1 pts with/without cirrhosis, for 4, 6, or 8 weeks



# C-SWIFT retreatment : 12 weeks of EBR/GZR + SOF + RBV successfully treated G1-infected subjects who failed short-duration all-oral therapy



\*Excludes 2 patients LTFU at Day 3 and treatment Week 4

# RAVs

- Might be less problematic in patients treated with short courses

BUT

- Lengthy re-treatment needed



# Individual Optimisation of Therapy Theory

- Short course therapy with extended therapy for failures may be cost-effective
- Careful selection of patients will be critical
- Robust re-treatment regimens will be necessary
- Studies in the UK are on-going

# Individual Optimisation of Therapy Physicians Response?

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