IFN-free therapy for HCV infection: In search of Perfectovir

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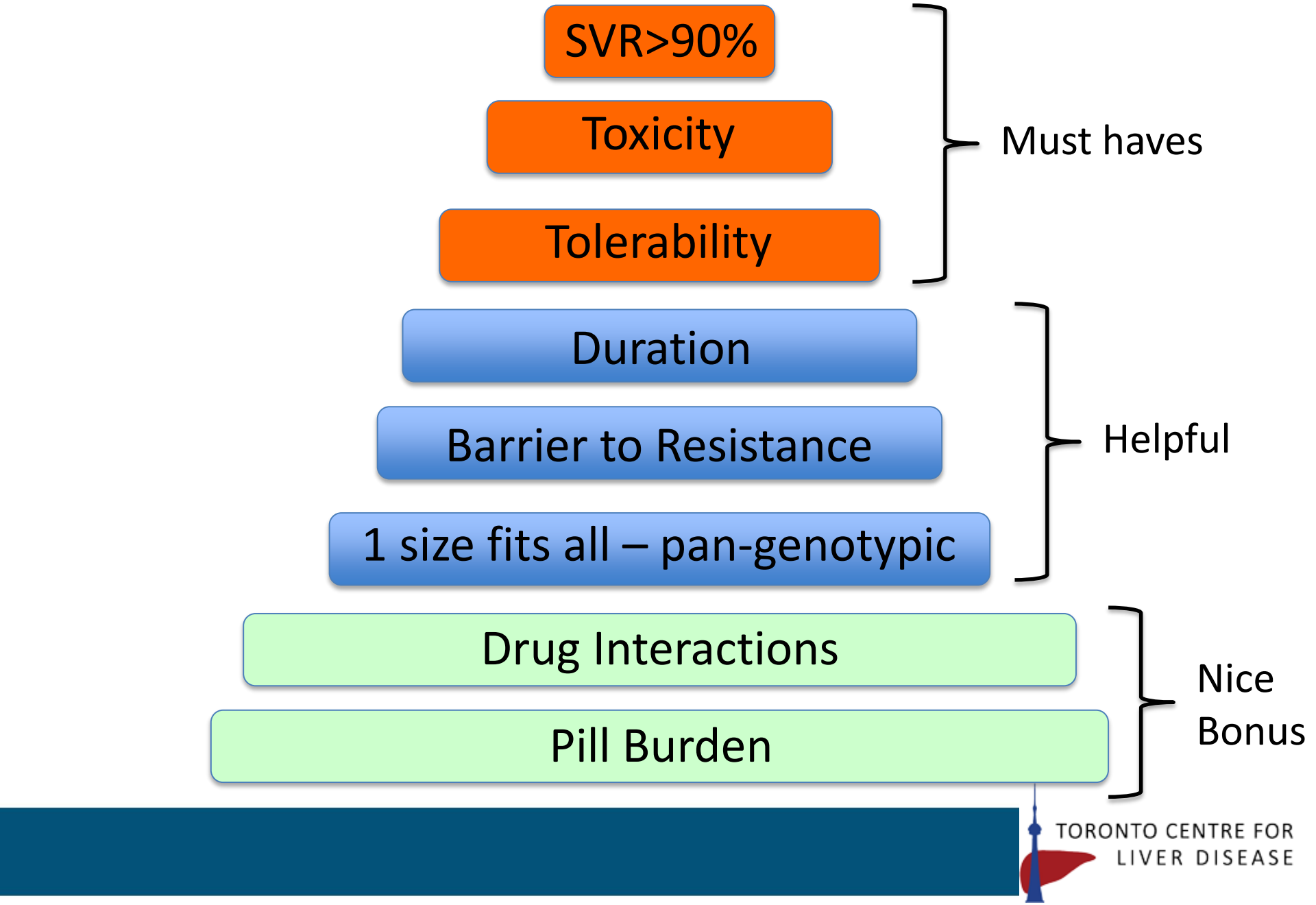
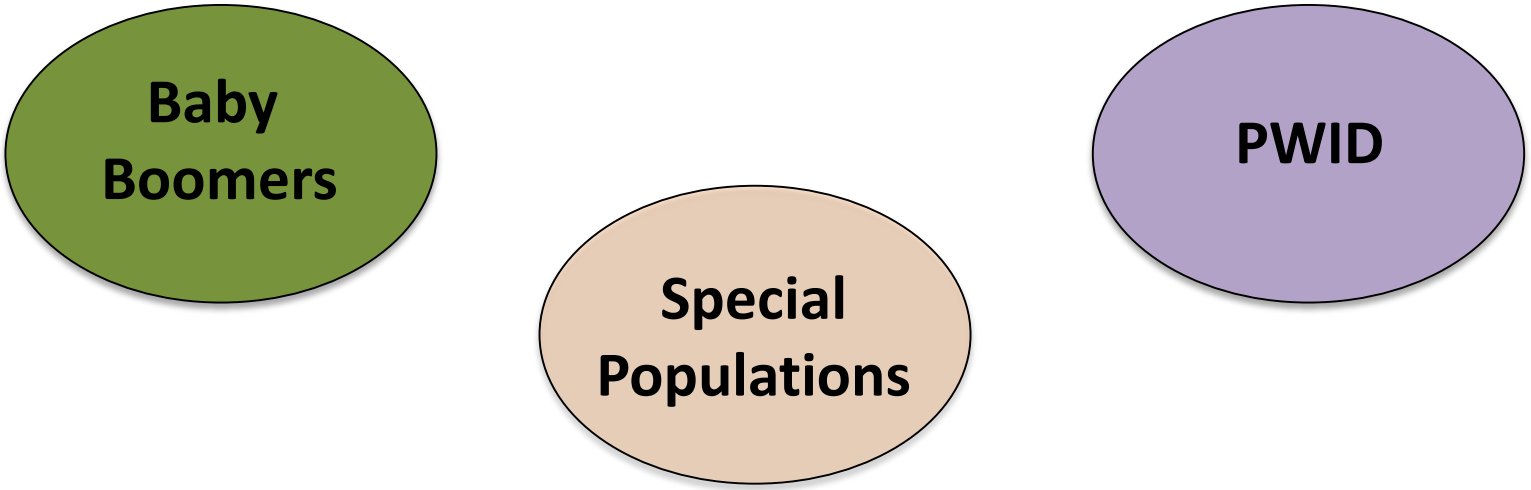
Outline

- What does ‘perfectovir’ look like?
  - Is it the same for all populations?
- Are we there yet?
  - A brief review of the data
- Areas for improvement
- The future


SVR>90%
Toxicity
Tolerability
Must haves
Duration
Barrier to Resistance
1 size fits all – pan-genotypic
Helpful
Drug Interactions
Pill Burden
Nice
Bonus

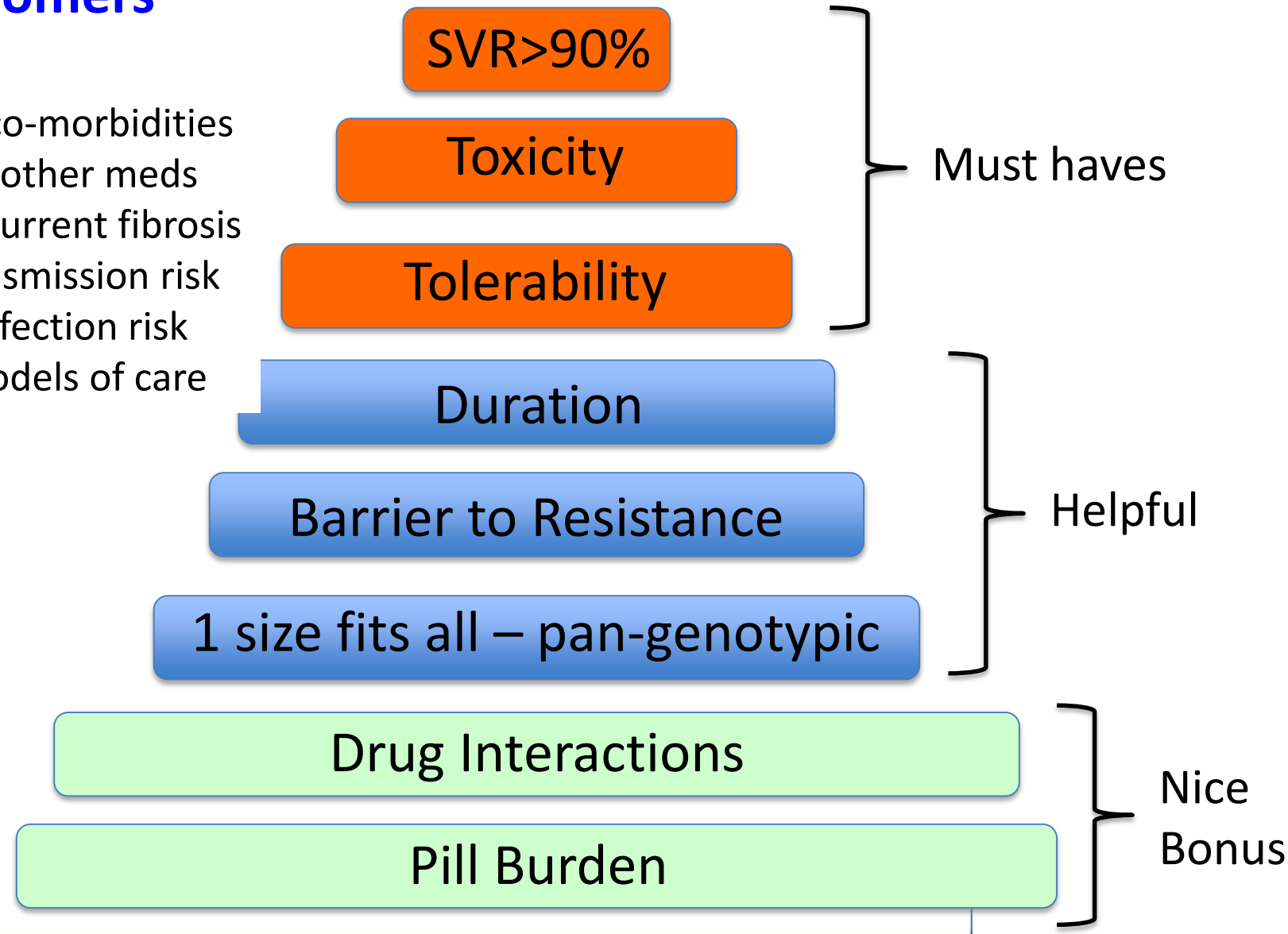
Do the priorities change for different populations?

- Yes and no
- Priorities likely the same
- Order of importance likely different



Baby Boomers

- Younger
- Few/no co-morbidities
- OST, few other meds
- Limited current fibrosis
- High transmission risk
- High reinfection risk
- Other models of care



The HCV Toolbox: Mix & Match

Nuc

High barrier to resistance

RBV

NS5A

NNI

PI

Modest barrier to resistance (esp to G1a)

Low barrier to resistance (esp to G1a)

Challenges

Treatment Duration

Genotype Subtype

Treatment History

Cirrhosis

Great options for G1
3 questions (or maybe just 2)

1. Does the patient have cirrhosis?
2. G1 subtype?
3. Naïve or experienced (and with what)?

Great options for G1

1. Does the patient have cirrhosis?

No → don't need to ask question 3 – regimens just about the same for naïve and experienced

No Cirrhosis	
1b	**1a**
Naïve/Experienced	**Naïve/Experienced**
SOF/DCV x 12w	SOF/DCV x 12w
SOF/LDV x (8-)12w	SOF/LDV x (8-)12w
PTV/r/OBV/DSV x 12w	PTV/r/OBV/DSV ***+ RBV*** x 12w
SOF/SIM x 12w	SOF/SIM x 12w

Great options for G1

1. Does the patient have cirrhosis?

Yes – now question 3 (naïve/experienced) matters and if experienced…with what i.e. Peg/RBV or Peg/RBV/PI or SOF/SIM?

Compensated Cirrhosis

1b

Naive	Experienced
SOF/DCV x 24w ± RBV	→ No change
SOF/LDV x 12w	→*"12w+RBV" or "24w"*
PTV/r/OBV/DSV x 12w	→ No change*
SOF/SIM x 24w	→ No change*

* Not to be used in past PI failures

1a

Naive	Experienced
SOF/DCV x 12w	→No change
SOF/LDV x 12w	→*"12w+RBV" or "24w"*
PTV/r/OBV/DSV + RBV x 12-24w	→ 24w nulls*
SOF/SIM x 24w if Q80K -	→ No change*

And if you fail the DAAs?

- Not so simple
- No clear evidence

Recommended regimen for patients in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed (including daclatasvir plus sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir plus dasabuvir).

For patients with minimal liver disease, deferral of treatment is recommended, pending availability of data.

Rating: Class IIb, Level C

For patients with cirrhosis or other patients who require retreatment urgently, testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below. Treatment duration of 24 weeks is recommended and, unless contraindicated, weight-based RBV should be added.

Rating: Class IIb, Level C

More on this later….

Summary SOF/ DCV

- **Highly effective**
  - Similar response (>97%) G1a or G1b
  - RBV unnecessary for non-cirrhotics
- **Duration**
  - **Duration and role of RBV unclear**
- **Safety**
  - Few AEs – headache, fatigue, mild GI
- **High barrier to resistance**
  - Retreatment with SOF-based regimen possible
- **Issues: Renal disease**

Summary PTV/r + OBV + DSV +/ RBV

- **Highly effective**
  - SVR 96% naïve/experienced
  - Similar G1a (95%) and G1b (98%)
- **Duration**
  - Similar efficacy & safety in cirrhosis (large dedicated trial)
  - 12 weeks adequate for all but **G1a cirrhotics** (null) → **24 wks**
- **Safety**
  - Placebo controlled – minimal toxicity (headache/fatigue/GI)
  - Mostly to do with RBV – not needed for G1b
- **Resistance**
  - Very few breakthroughs
  - Relapsers 2 or 3 class resistance
- **Issues: Pill burden, DDIs (minimal with OST), G1/4 only, resistance**

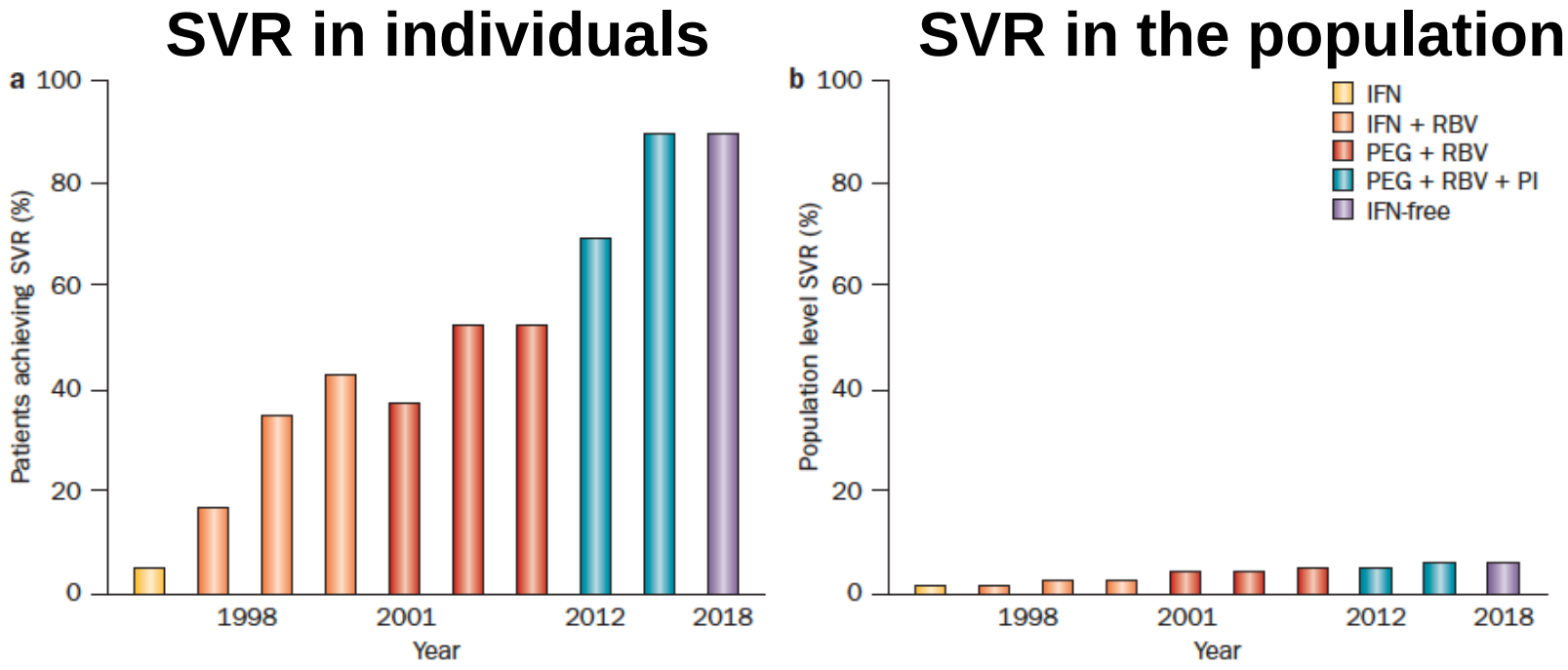
Summary SIM/SOF

- **Highly effective**
  - SVR>90% naïve/experienced
- **Duration**
  - 12 weeks very effective for non-cirrhotic
  - Unclear duration for cirrhotics, especially G1a → 24 weeks?
- **Safety**
  - Very safe – few additional AEs - Photosensitivity
- **Resistance**
  - Q80K important for G1a – especially with cirrhosis
  - Retreatment with SOF + NS5A-based regimen possible
- **Issues: G1 & (4) only, Q80K, duration, DDI (not with OST), renal**

Do we need more drugs?
Pretty close to perfectovir…

- No AEs ✓
- >95% SVR ✓
- IFN-free ✓
- ✓(?) RBV-free
- No DDIs ✓(?)
- ✓ 8-12 weeks
- 1 pill OD ✓
- Minimal/No Resistance ✓(?)

Treatment uptake more important than SVR rate



Improved access more important than improved therapy

Thomas Lancet 2010

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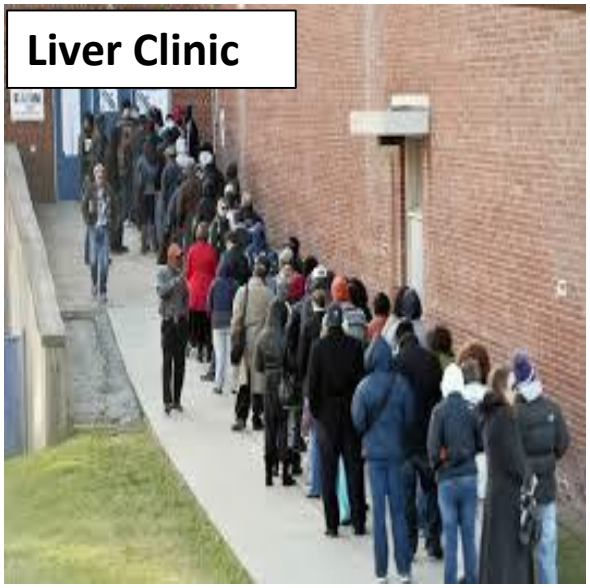
Would more drugs help?

- Likely
- Fill remaining gaps
- Competition
  - Brings down prices
  - Access to ‘imperfectovir’
- Increase the treater-pool

We can't treat everyone!



- Lack capacity even if we had access to the drugs
- We need to move out of specialty clinics
- Regimens still complicated…we need to simplify

Specific issues in PWID

- Uptake
- Adherence
- Treatment setting/model of care
- Regimens
- Retreatment
- Reinfection
- Transmission of resistant virus

Stay tuned…

Specific issues in PWID

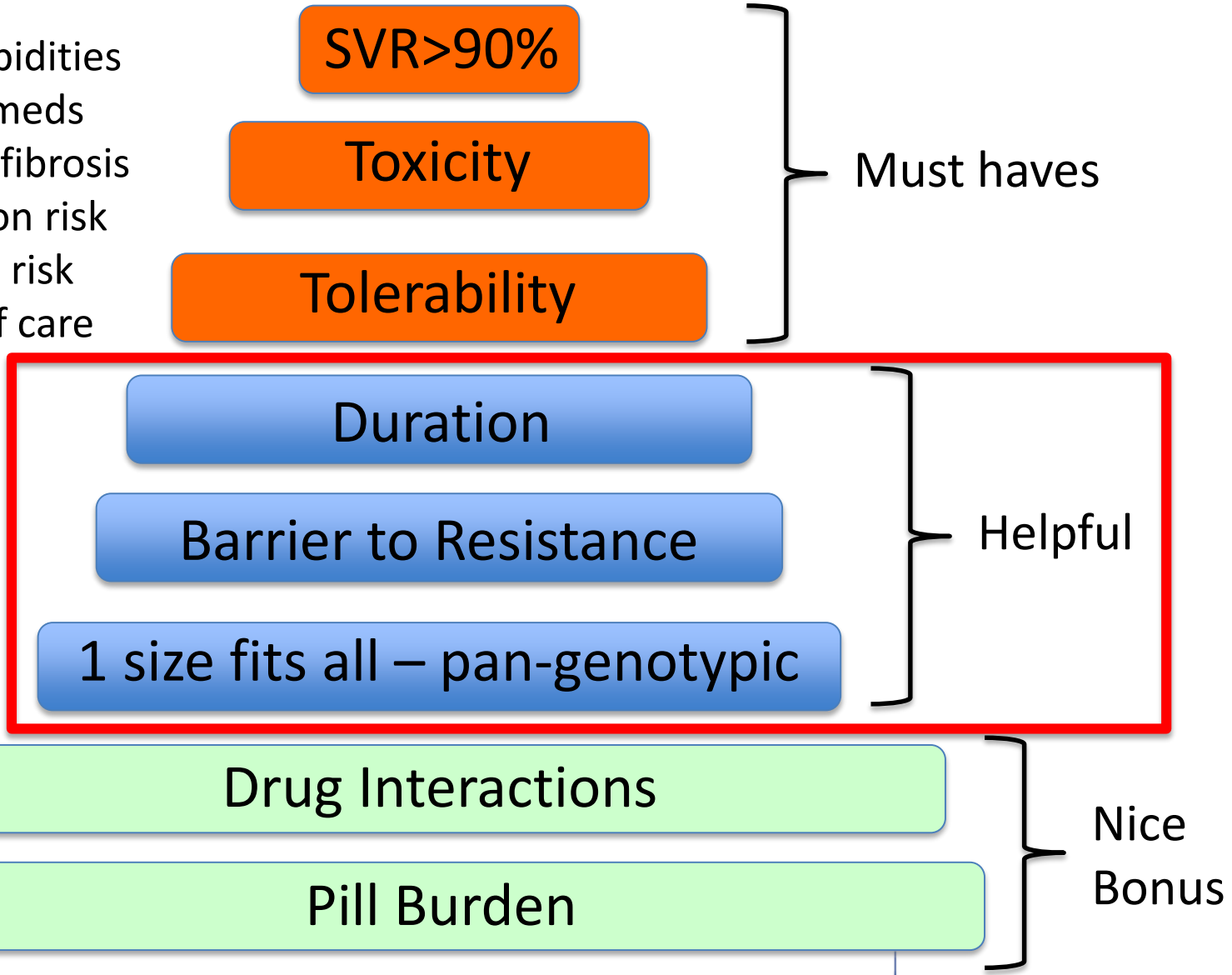
- Uptake
- Adherence
- Treatment setting/model of care
- **Regimens**
- **Retreatment**
- **Reinfection**
- **Transmission of resistant virus**

Regimens

- Specific populations
  - OST
  - PWID (active)
  - G3
- One size fits all
- Shorter duration

PWID

- Younger
- Few/no co-morbidities
- OST, few other meds
- Limited current fibrosis
- High transmission risk
- High reinfection risk
- Other models of care



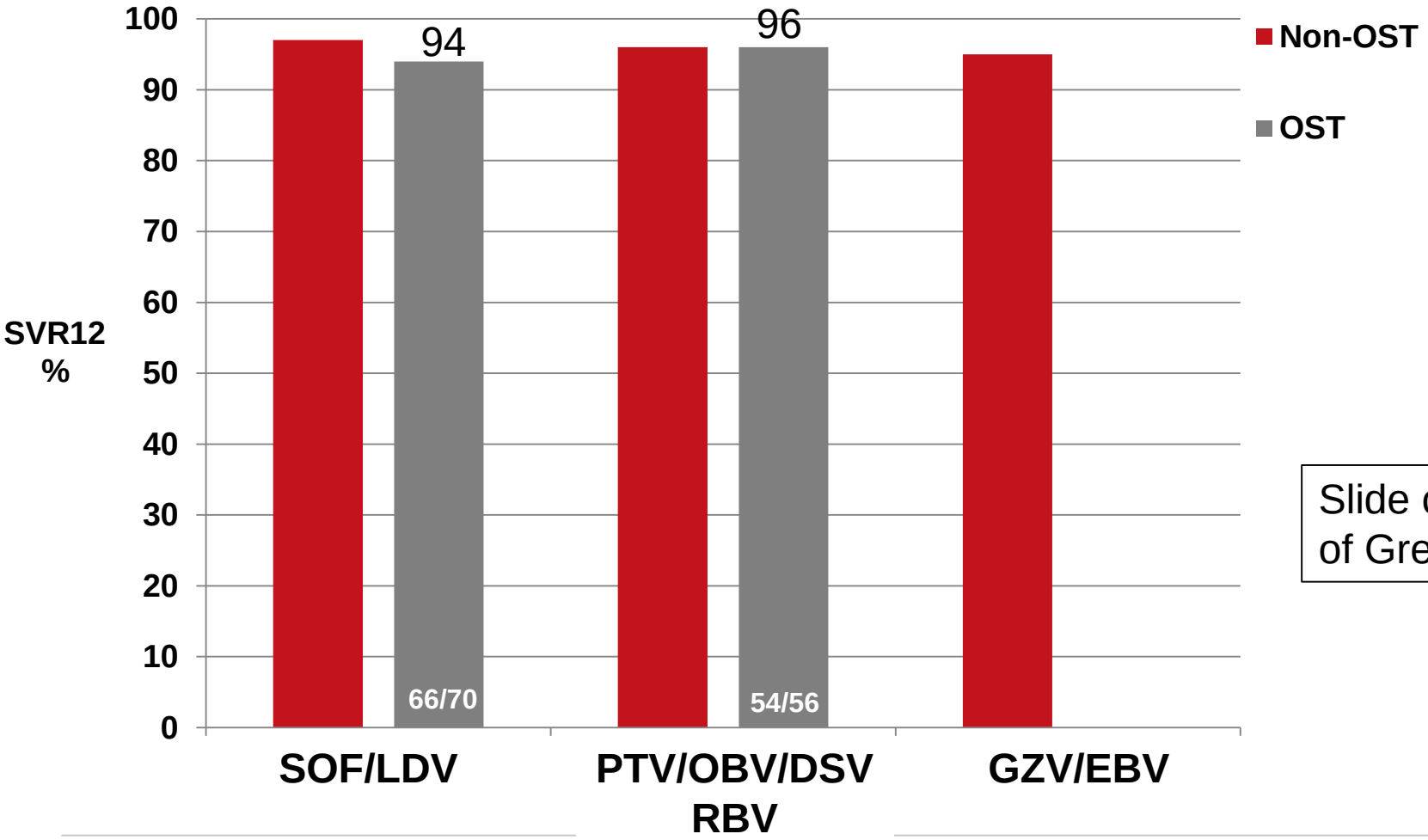
Current regimens for PWID

	PI/NS5A/NNI	NS5A/Nuc		PI/Nuc
	PVR/r/OBV/DSV	LDV/SOF	DCV/SOF	SIM/SOF
SVR>95%	✓✓✓	✓✓✓	✓✓(✓)	✓✓
AE profile	✓✓✓	✓✓✓	✓✓✓	✓✓
DDIs	✓	✓✓	✓✓✓	✓
Duration	✓✓	✓✓	✓✓	✓
Barrier to Resistance	✓✓	✓✓✓	✓✓✓	✓✓✓
Consequence of resistance	✓	✓✓	✓✓	✓✓✓
Genotype coverage	✓ (1,4)	✓✓ (1,4,5,6)	✓✓✓ (1-6)	✓ (1,4?)
One size fits all	-	✓	✓✓	-
Data in PWID	✓ (?)	✓(?)	✓(?)	✓(?)
Cost	✓✓	✓✓	✓	✓

Do we have data in PWID?

IFN-free DAA therapy: OST vs non-OST

GT1, treatment naïve, F0-4; 12 weeks duration

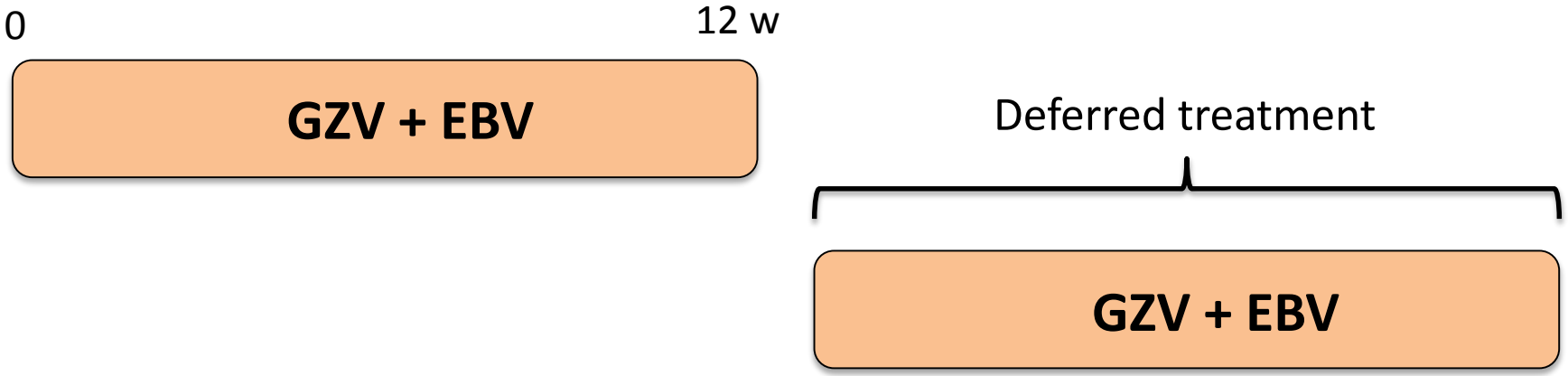


Slide courtesy of Greg Dore

Afdhal N, *NEJM* 2014; Feld J, *NEJM* 2014; Lalezari J, IAC 2015; Zeuzem S, ILC2015; Jacobson I, AASLD 2014

Grazoprevir (PI) + Elbasvir (NS5A) (CO-STAR)

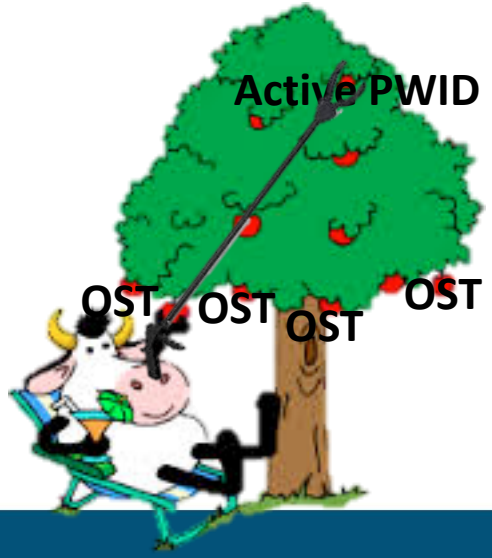
- Recent IDU
- In OST x 3 months with >80% attendance
- G1 only
  - Include HIV/HCV +/- cirrhosis



SVR data in 200 patients to be presented at AASLD 2015

Data in PWID

- Great to have OST studies
- But we need studies in people actively using drugs
- If TasP is going to work…we need to prove that treatment is safe and effective



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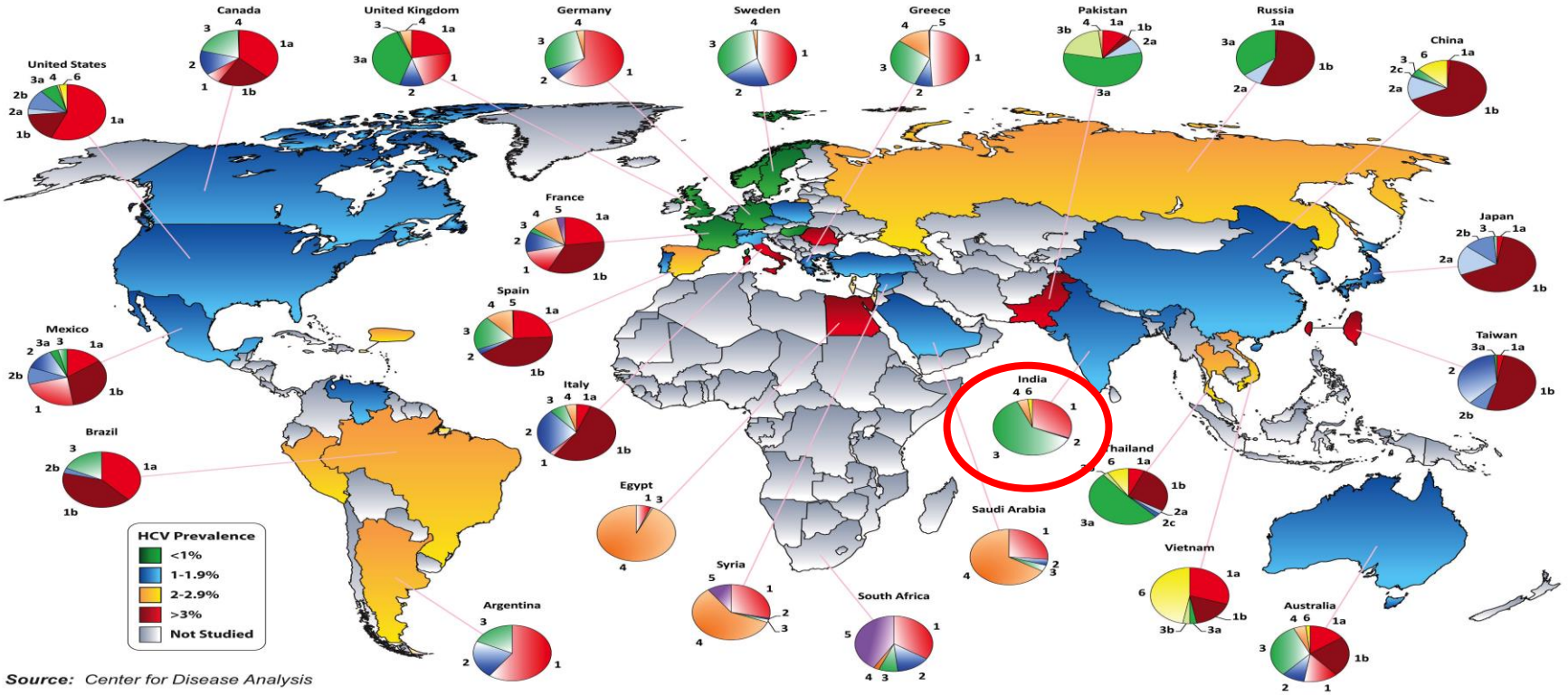
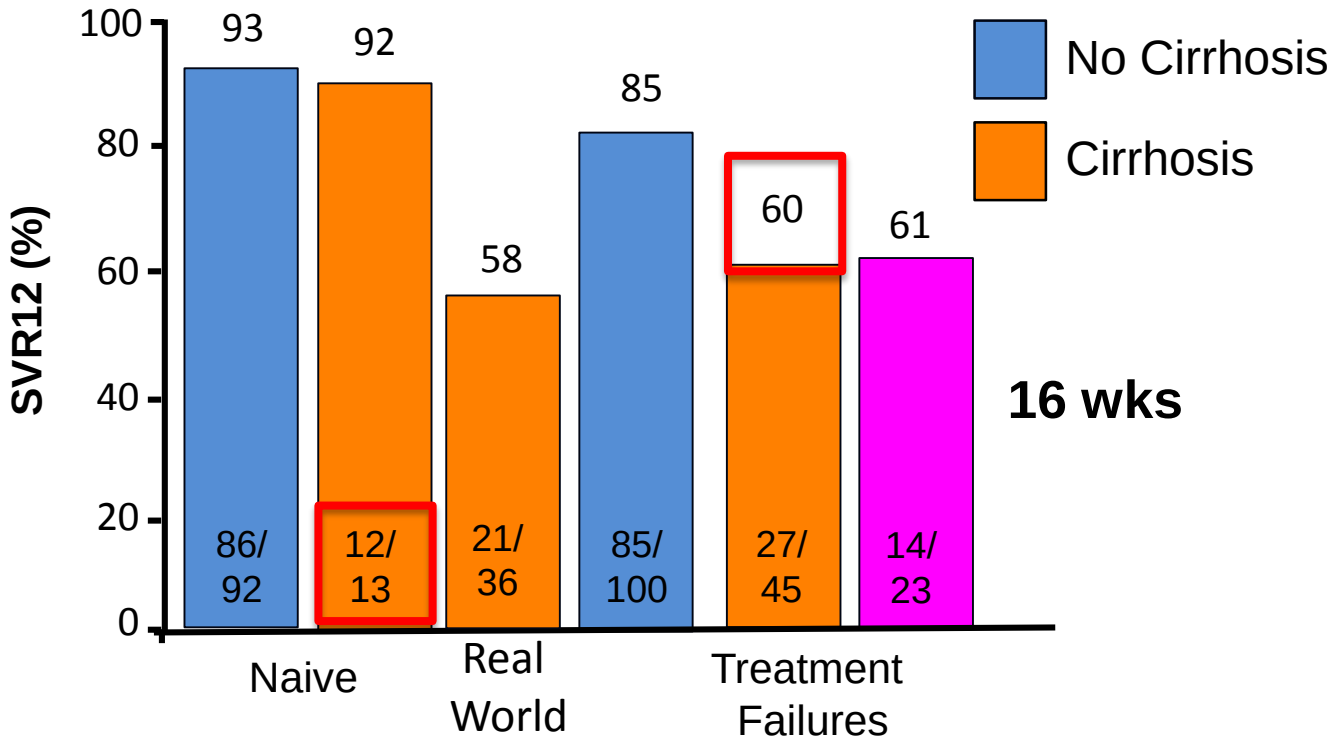
G3 – Still a challenge



- Concentrated South Asia & PWID
- More aggressive → progression to cirrhosis, HCC, steatogenic
- Current regimens sub-optimal – especially in cirrhosis

SOF/RBV

SOF + RBV x 24 wks for G3



- 24 weeks better for naives
- Cirrhosis still an issue

Zeuzem NEJM 2014
Feld et al in preparation

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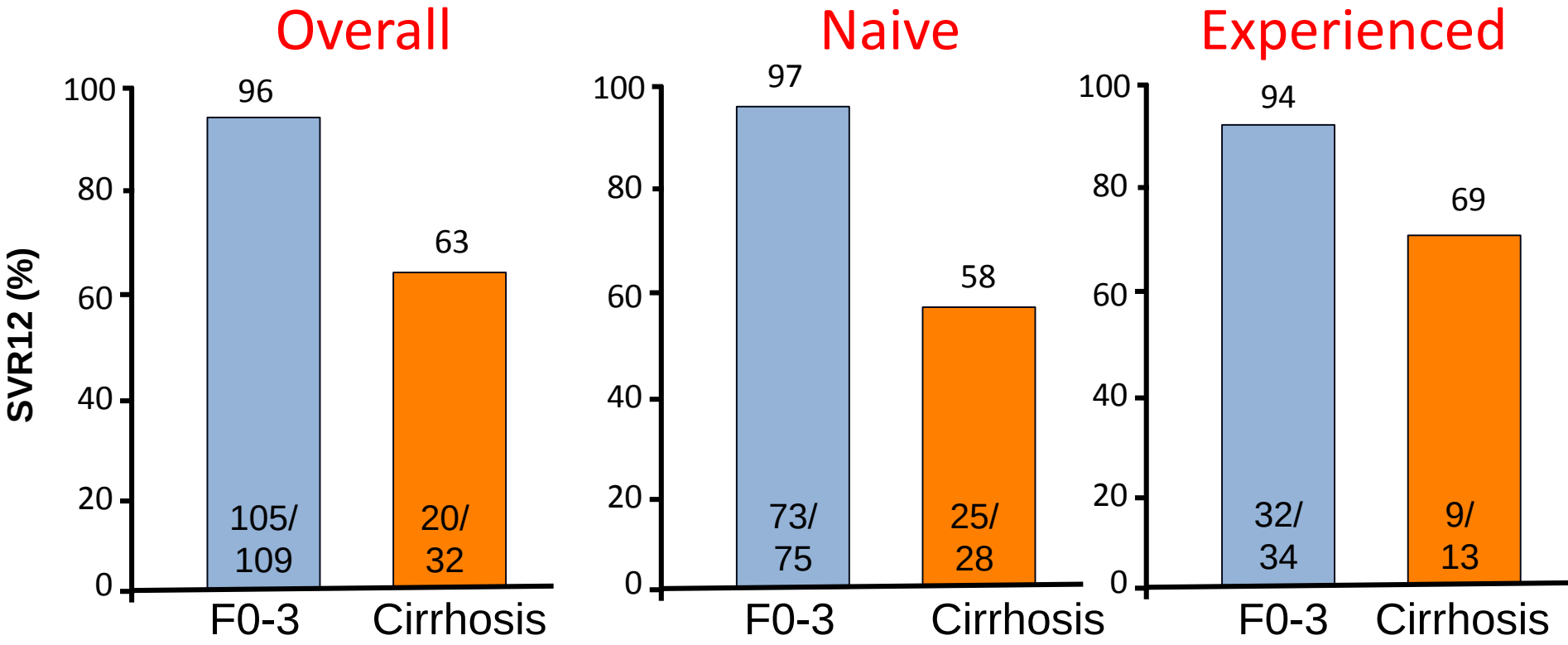
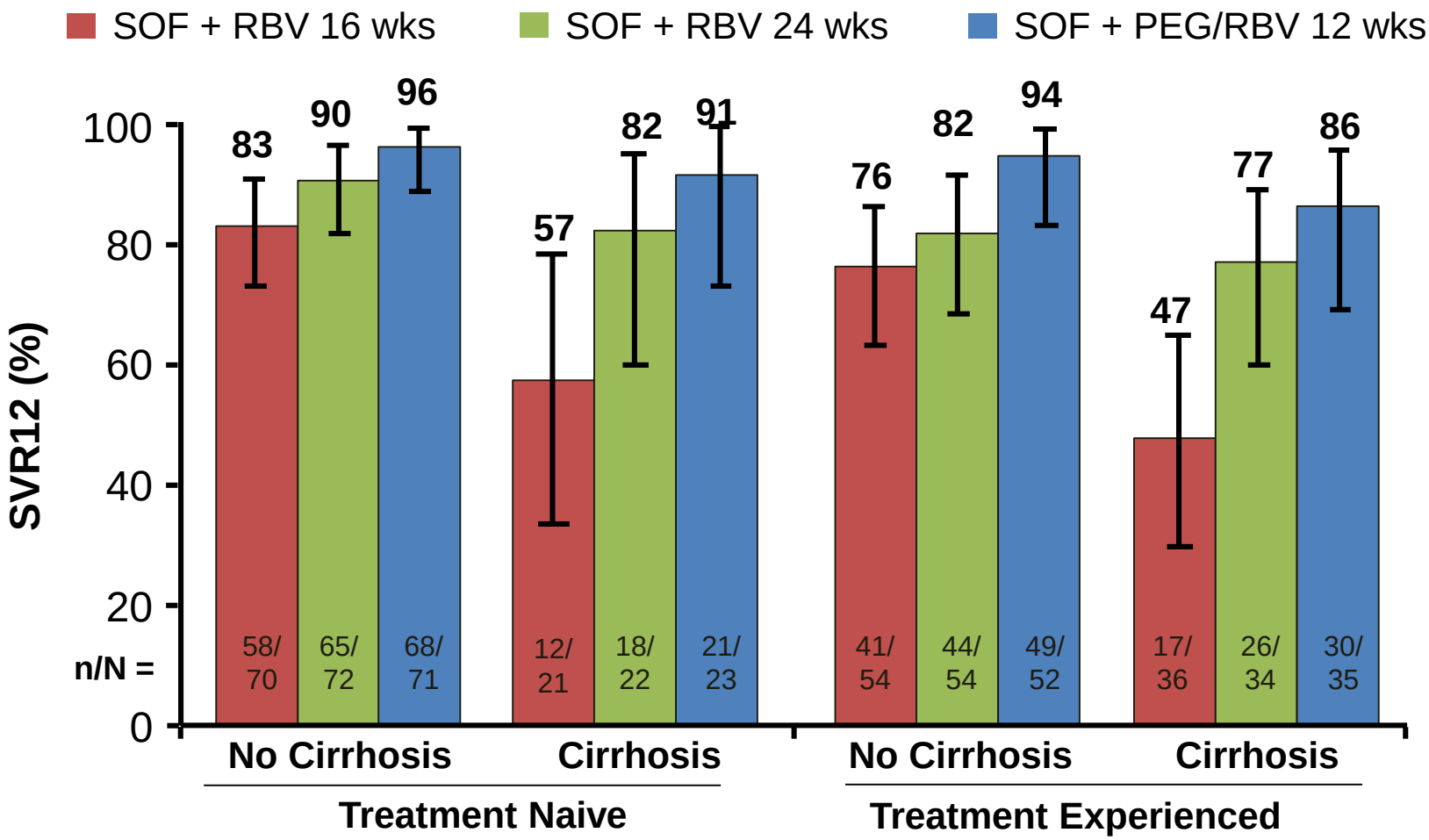
What about SOF/DCV?

SOF/DCV x 12 wks



- Great for G3 without cirrhosis (most PWID)
- Unfortunately, with cirrhosis…not the answer – at least not 12 wks

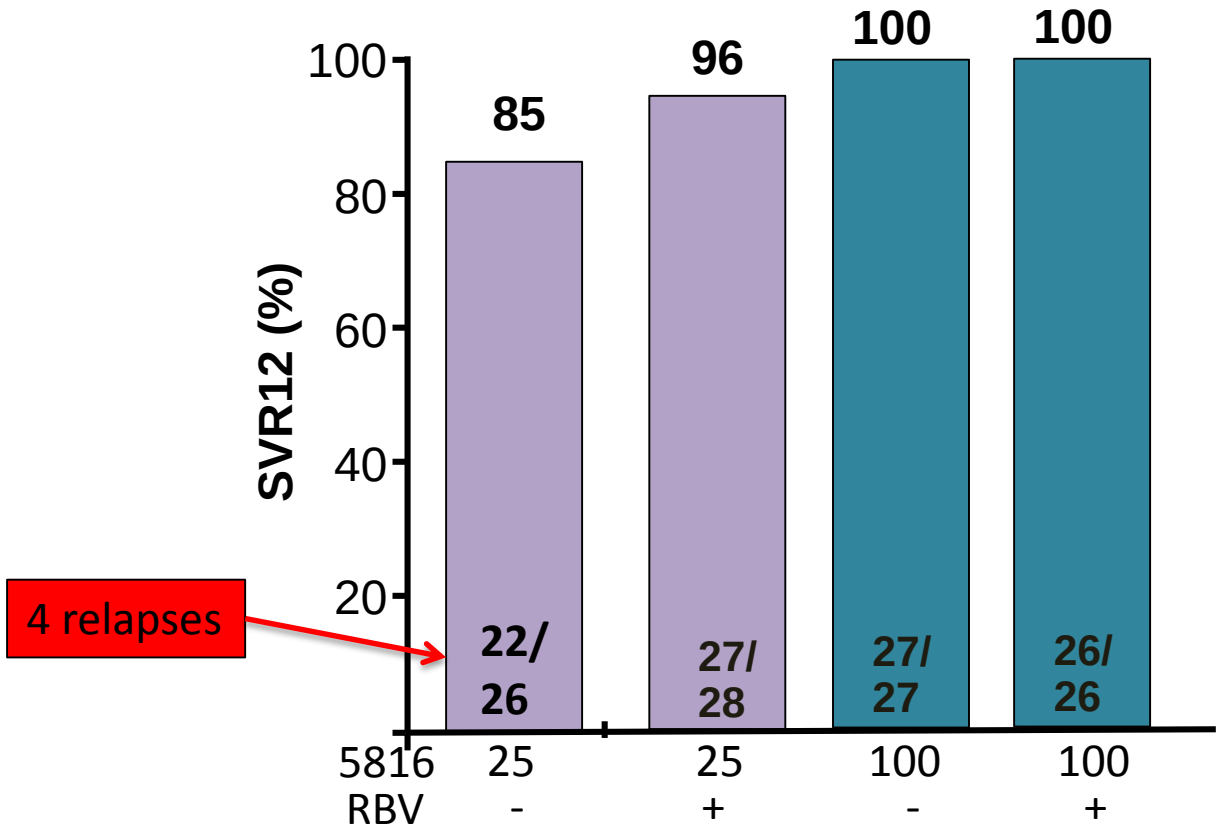
BOSON: SOF/RBV 16 vs 24 vs PEG/SOF/RBV x 12



- Clear advantage to Peg/RBV/SOF – especially in cirrhosis
- Only 1 trt-discontinuation – good safety…not a very popular choice

A new option

SOF + Velpatasvir (GS-5816) (NS5A) x 12 weeks TE G3 non-cirrhotic



Looks promising at higher dose without RBV

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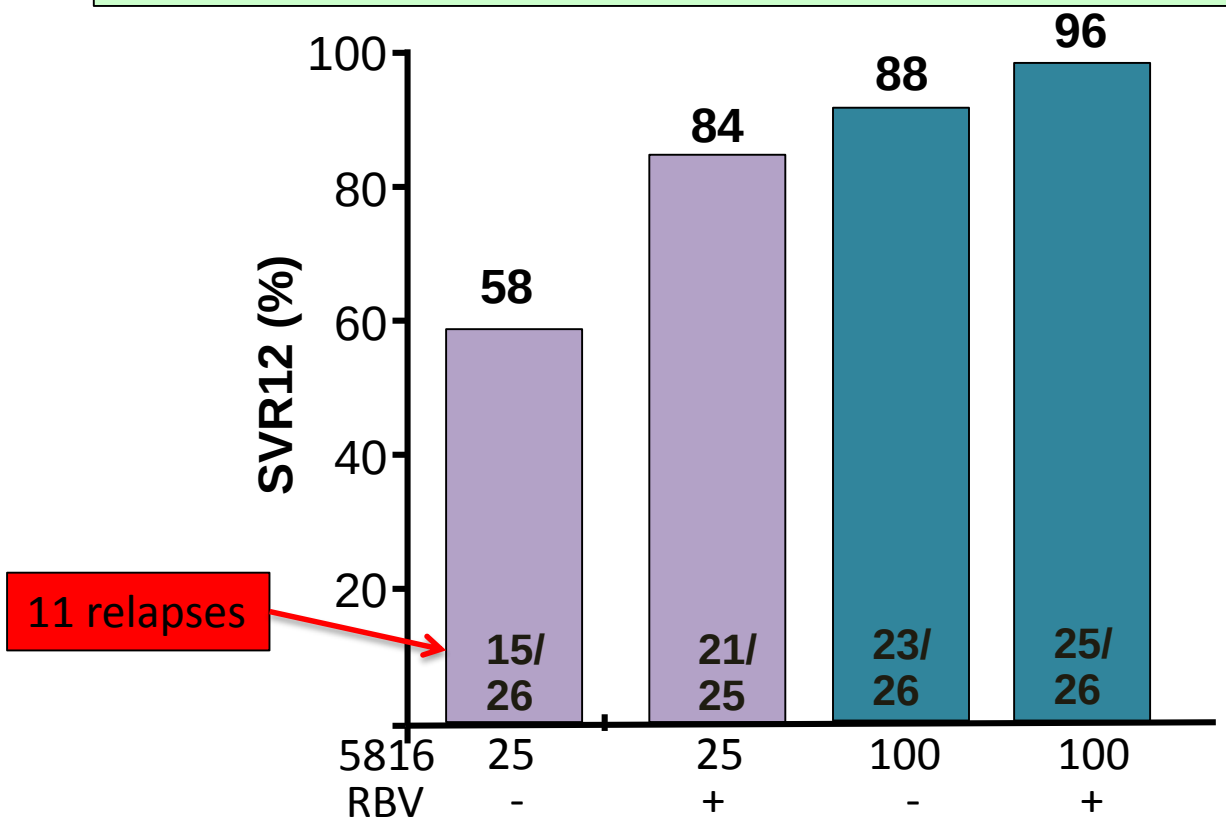
The real test

SOF + Velpatasvir (GS-5816) (NS5A) x 12 wks in
G3 treatment-experienced cirrhotics



In the experienced cirrhotics…RBV still required?

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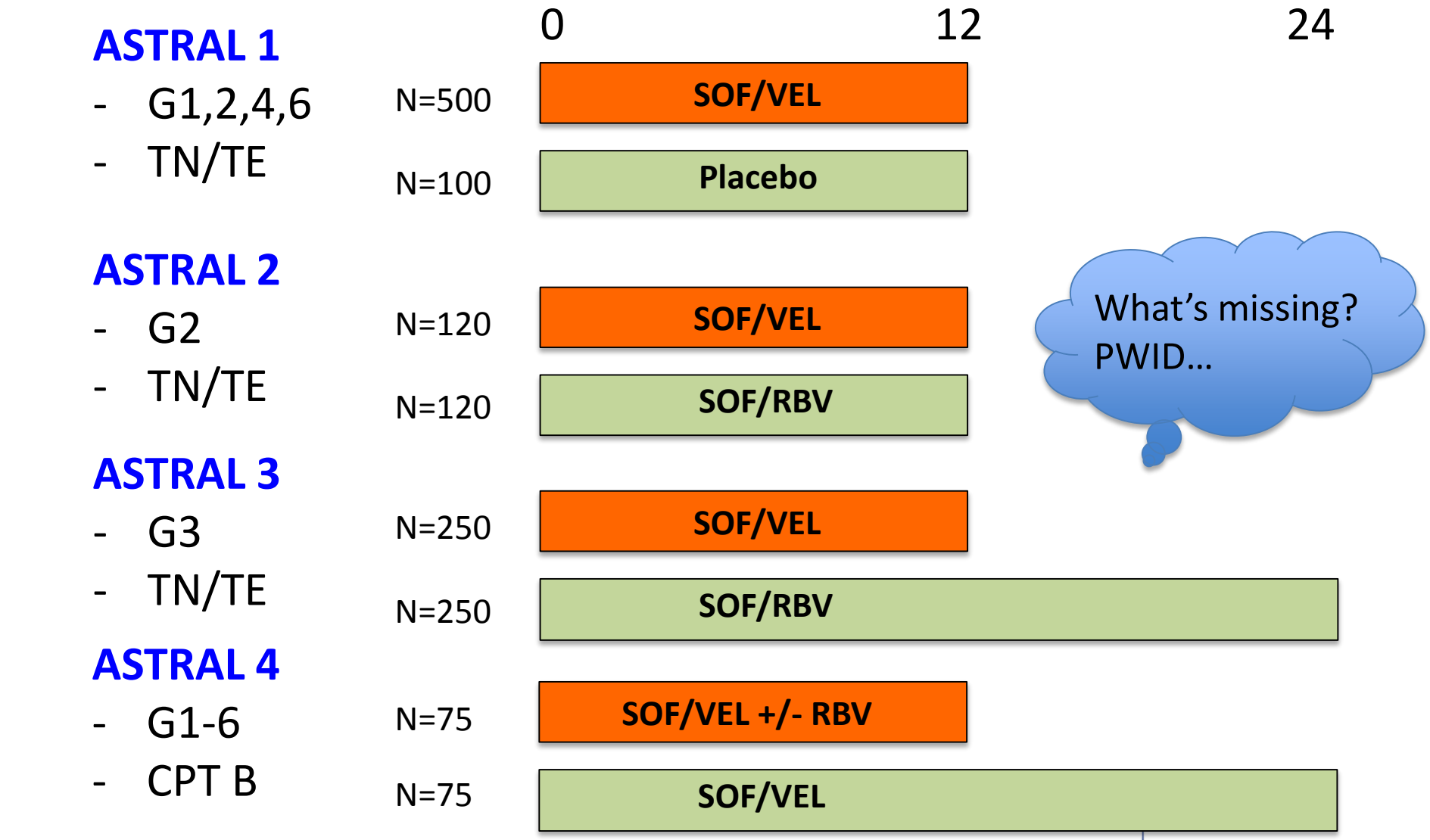
Effective beyond G3 – Ph 3 Trials



What's missing?
PWID…

Data at AASLD – press release looks VERY good!!

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Kirby Institute

UNSW AUSTRALIA

simplify

A phase II, open-label, multi-centre, international trial of sofosbuvir and GS-5816 for people with chronic hepatitis C virus infection and recent injection drug use

- SOF/VEL x 12 weeks
- Recent injection drug use (within 6 months)
- Genotypes 1 to 6
- International, multi-centre study to treat 100 people with goal of 90% SVR12
- Starting to enroll now…

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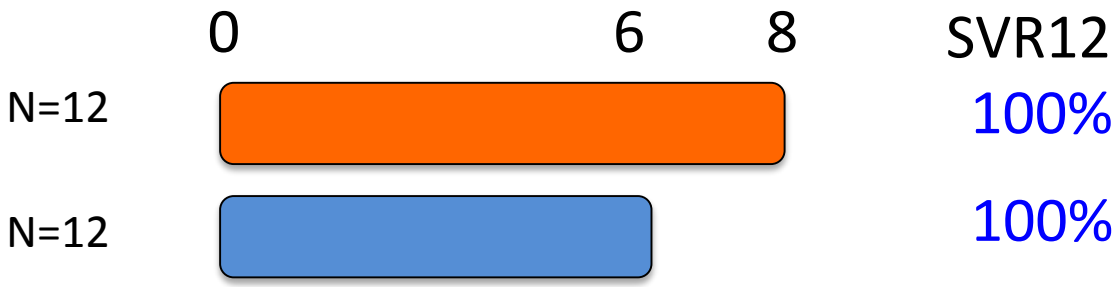
Everyone wants a pangenotypic regimen

- **Abbvie (G3?)**
  - ABT-493 (PI) + ABT-530 (NS5A)
- **Achillion/Janssen**
  - Sovaprevir (PI) + Odalasvir (ACH-3102) (NS5A) + ACH-3422 (Nuc)
- **Merck**
  - Grazoprevir (PI) + Elbasvir/8408 (NS5A) + MK-3682 (nuc)
- **Gilead**
  - SOF/Velpatasvir (5816) + GS-9857 (PI) or GS-9779 (NNI)

Early Data

Odalasvir (ACH-3102) (NS5A) + SOF (Nuc)
TN G1 non-cirrhotics



- Planning 4 week trial and expansion to other populations
- Likely to add PI – sovaprevir or simeprevir
- Long half-life of NS5A may allow for shorter treatment

Gane AASLD 2014, Achillion press release Feb 2015

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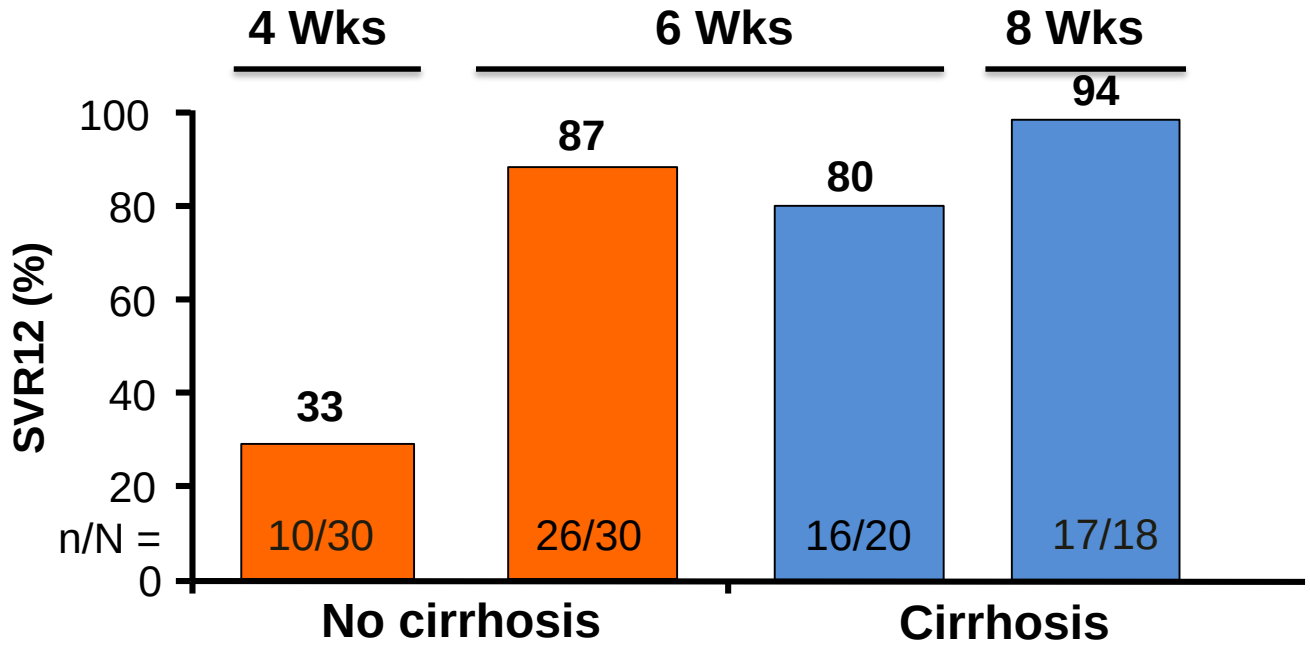
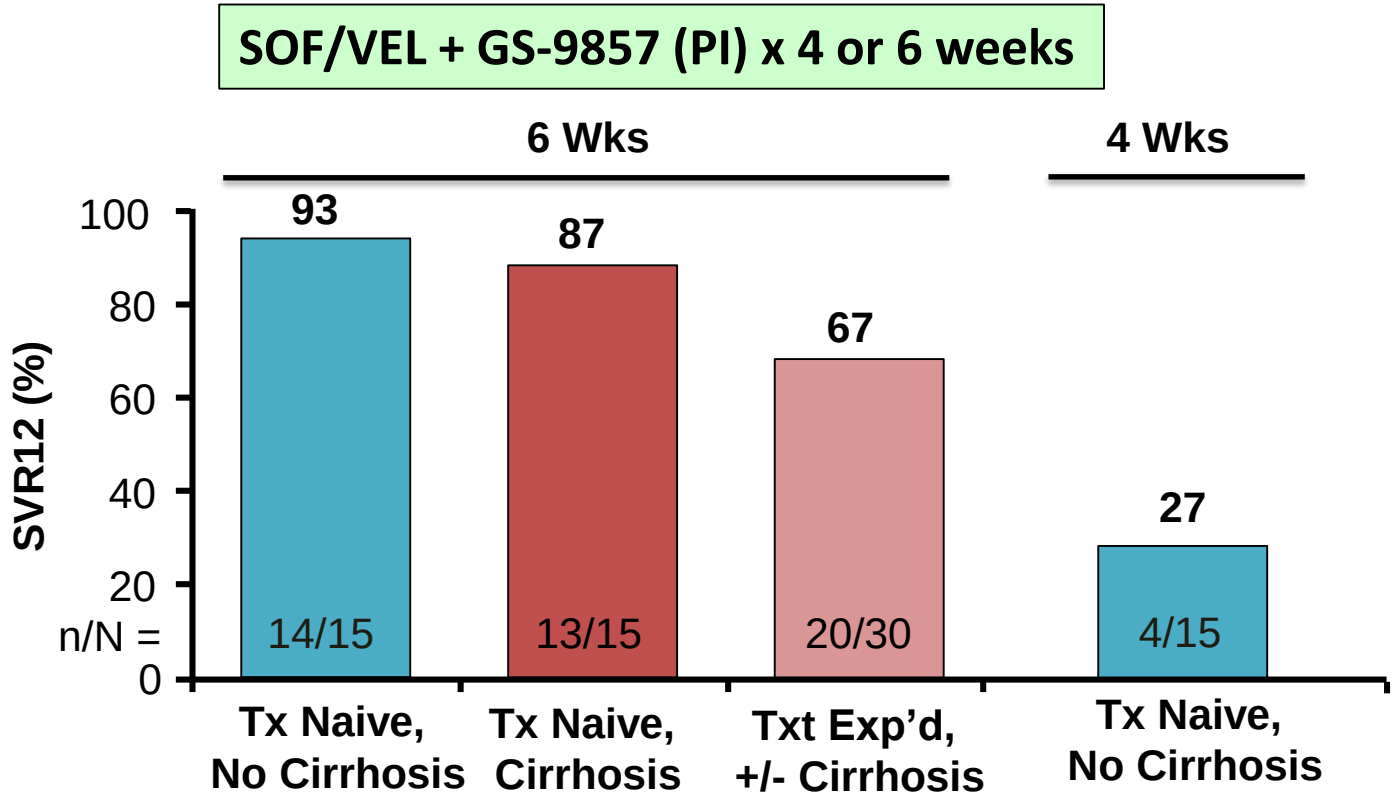
How short can we go?

Grazoprevir (PI) + Elbasvir (NS5A) + Sofosbuvir (Nuc) x 4 – 8 weeks in G1 with or without cirrhosis



- Very potent regimen → 4 weeks clearly inadequate

6 weeks seems to be the edge of the cliff…



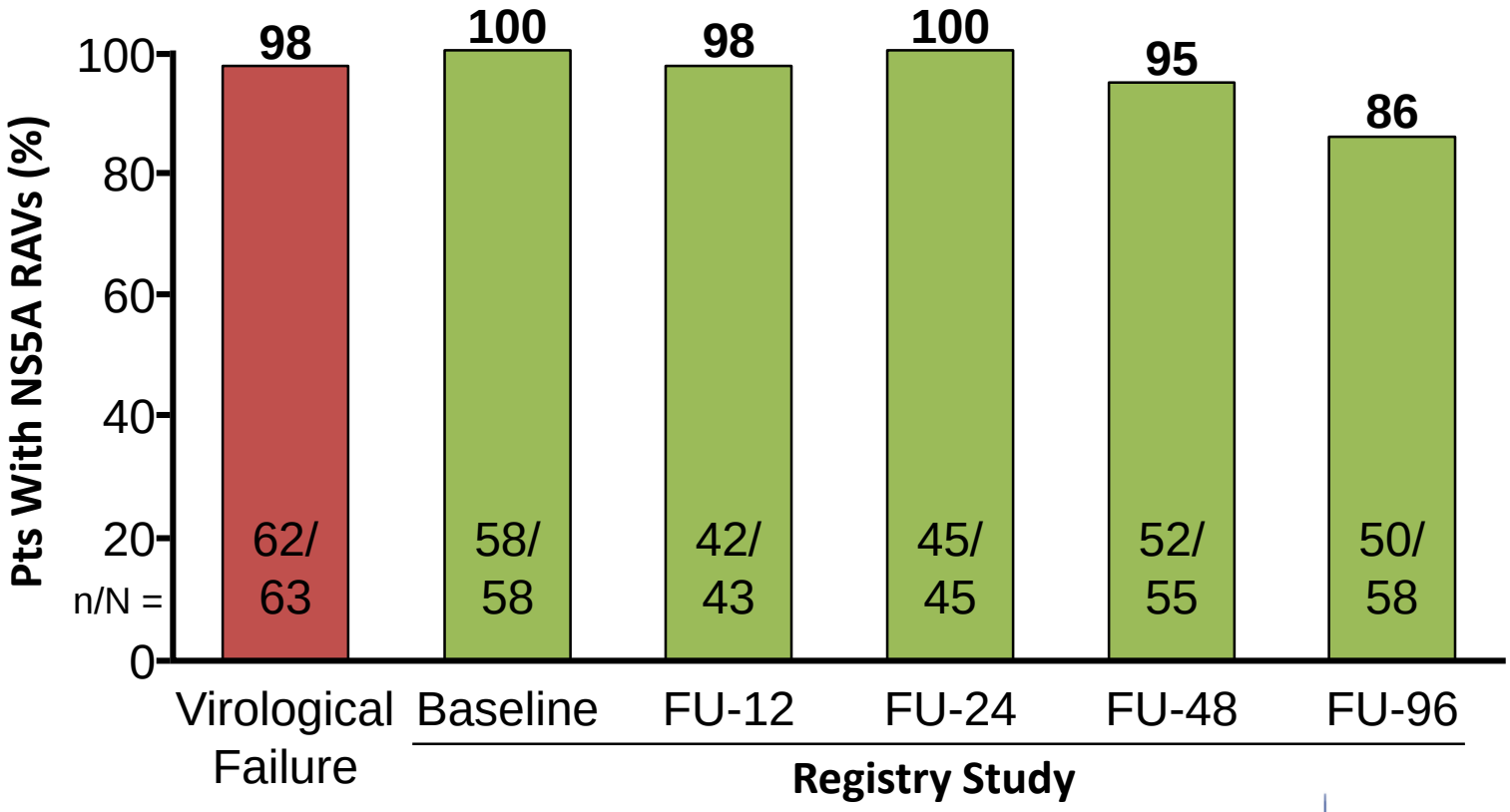
- Very potent regimen → 4 weeks clearly inadequate

Does duration matter?

- Yes and no
- Obviously shorter is better
  - Easier for patients
  - Easier for treaters
  - Cheaper (doesn't have to be…)
- But…only if truly does not increase relapse!
- Small decrements (2 weeks) probably not very important (except for cost)
- Until good retreatment options…be careful about push to shorten (even in trials!)

The risks of short therapy…resistance persists

Patients who failed LDV (NS5A) without SOF → follow-up off therapy



Dvory-Sobol H, et al. EASL 2015. Abstract O059.

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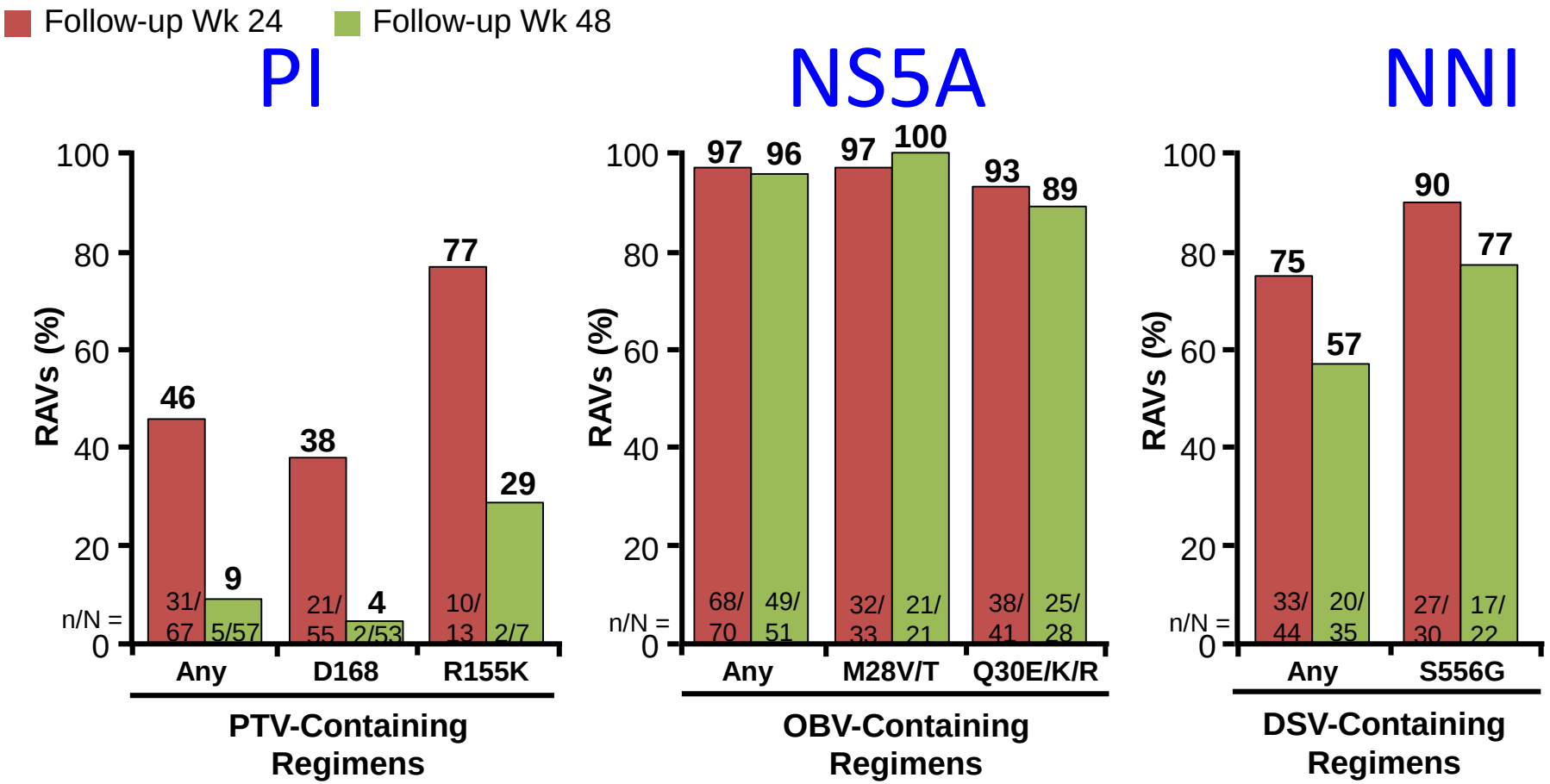
Not all resistance is the same…



RAVs Persistence: **NS5A>NNI>>PI>>>>Nuc**

Krishnan P. EASL 2015. Abstract O057.

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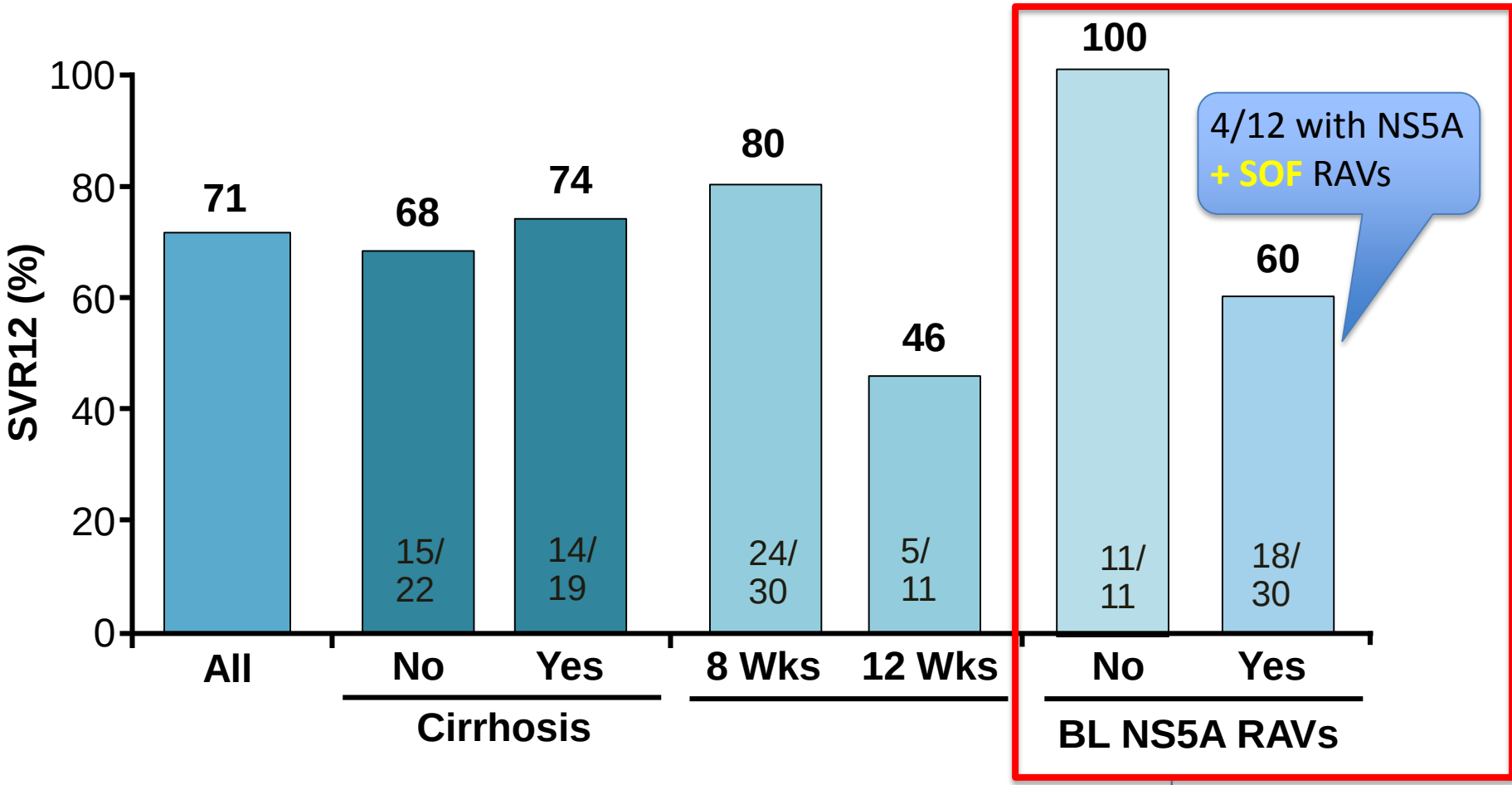
RAVS affect retreatment?

Retreatment of 41 SOF/LDV relapsers with SOF/LDV x 24 w



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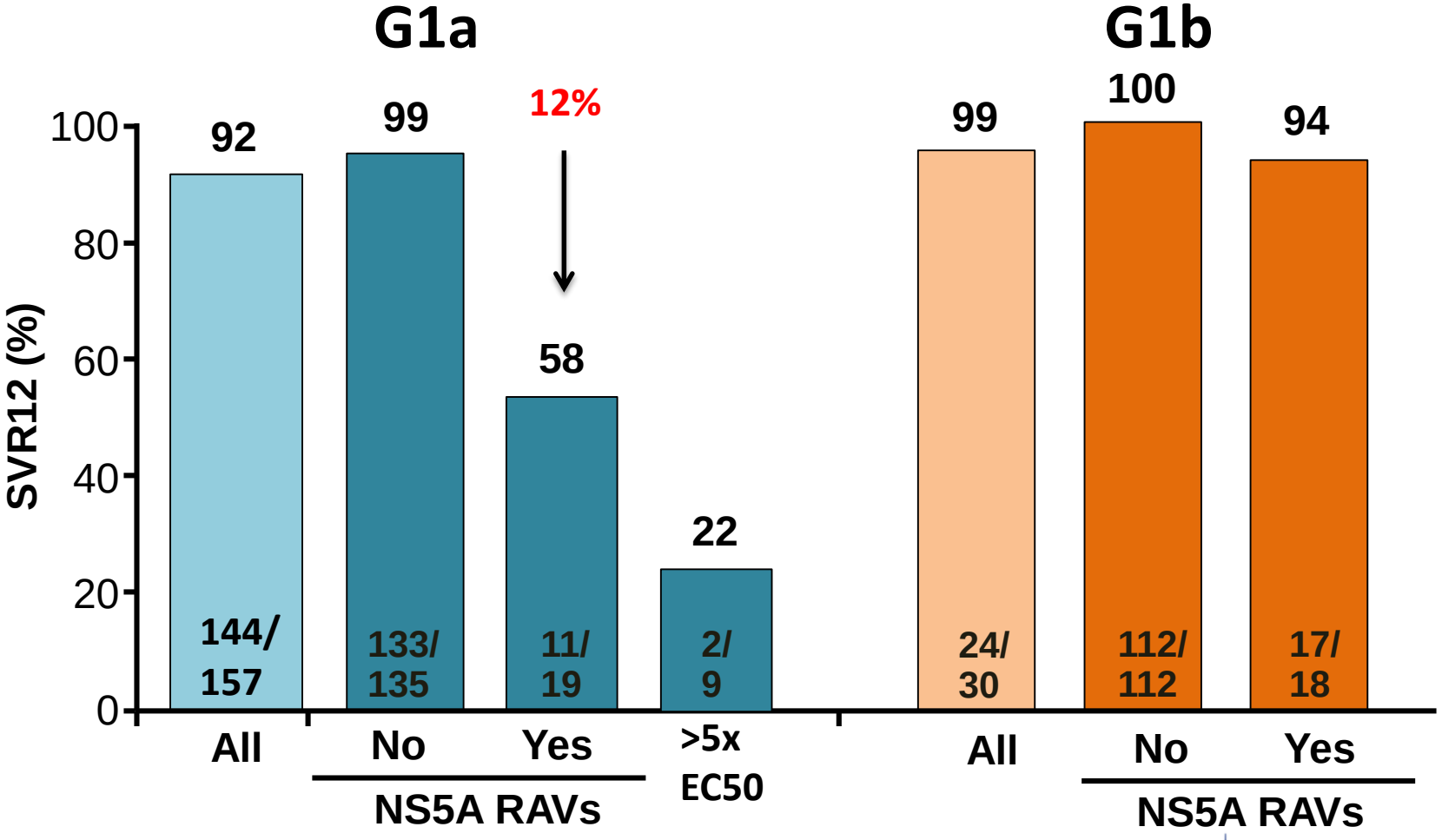
Baseline RAVs important for 1a

Grazoprevir (PI) + Elbasvir (NS5A) x 12 wk



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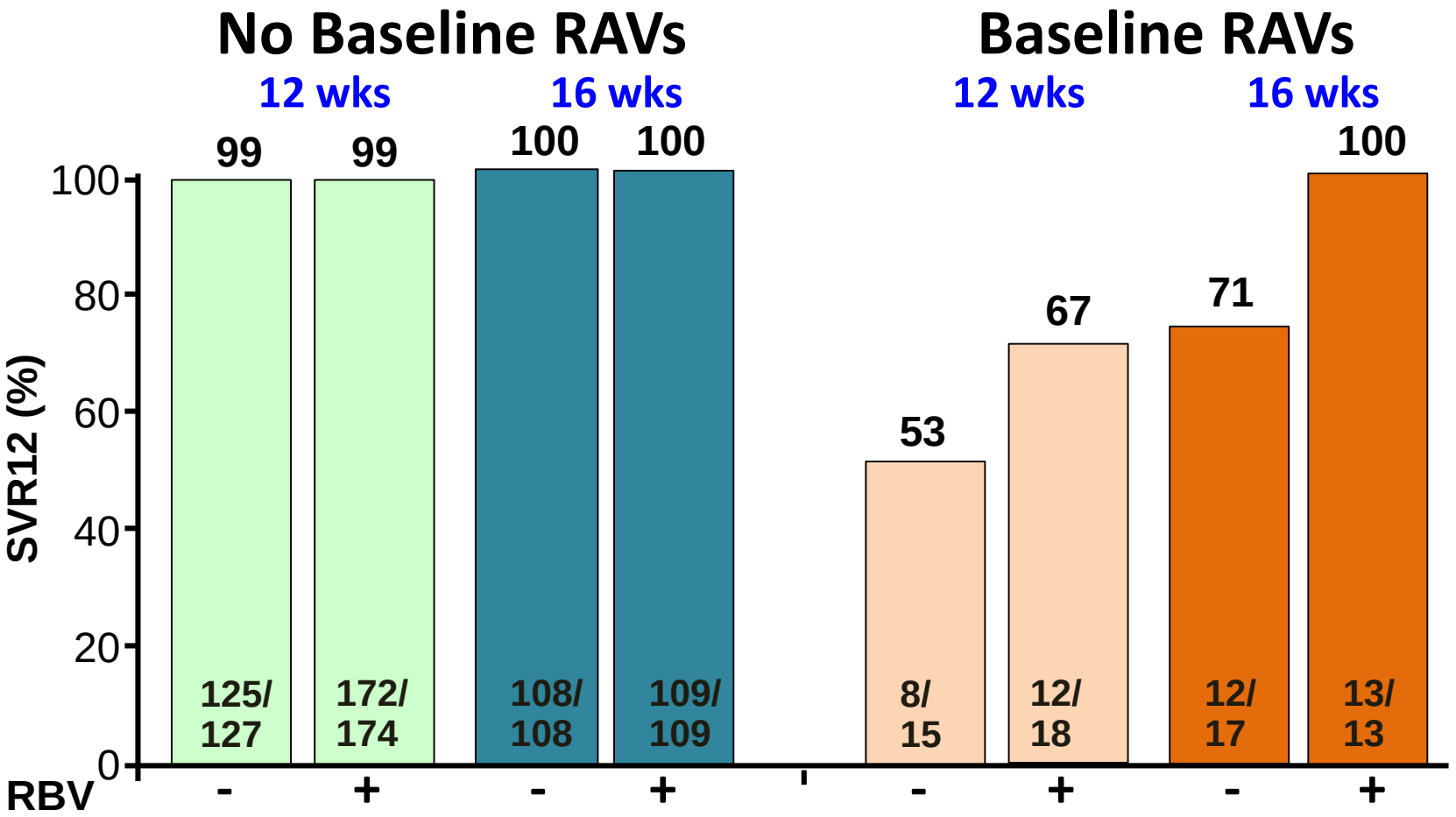
Overcoming RAVs (GZR/EBV)



Longer therapy or RBV overcomes RAVs…should we be testing?

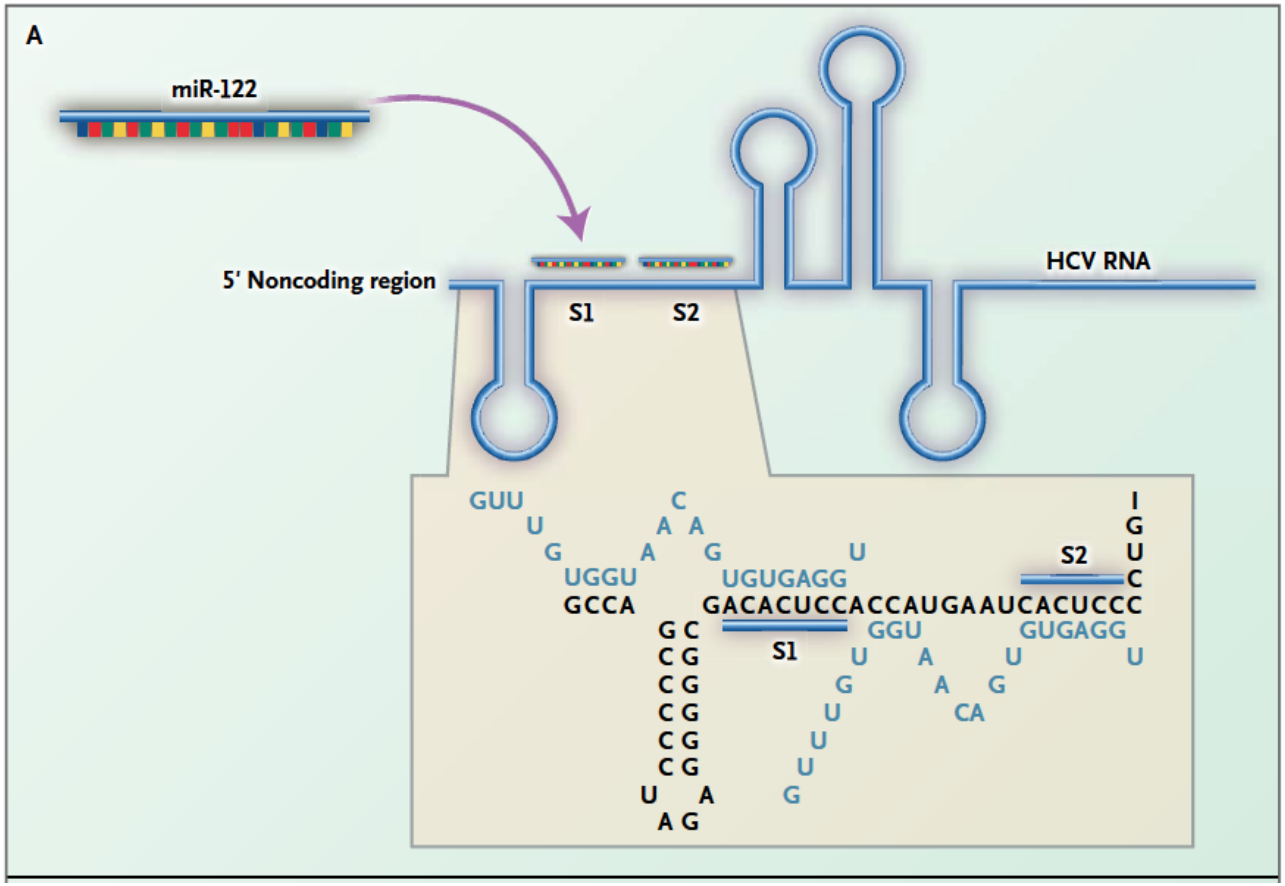
What does all this mean?

- If RAVs persist…

1. Need to get it right the first time
   - Salvage options may be limited (all contain NS5A)
   - Salvage options may not be permitted (payers)
   - Slight ‘over-treatment’ preferable to under-treatment
2. Concern of transmission of resistant virus
   - Should we be testing at baseline?
   - Necessary to alter therapy – longer, add RBV, change tx
   - Not likely useful for ‘old’ infections but may be important for new infections - PWID
   - Resistance testing costs less than the price of 1 pill
   - But…”complicates” therapy…limits treater-pool?
   - If we can simplify testing…it may be worthwhile

Is there another way forward?

miR122 – A host target



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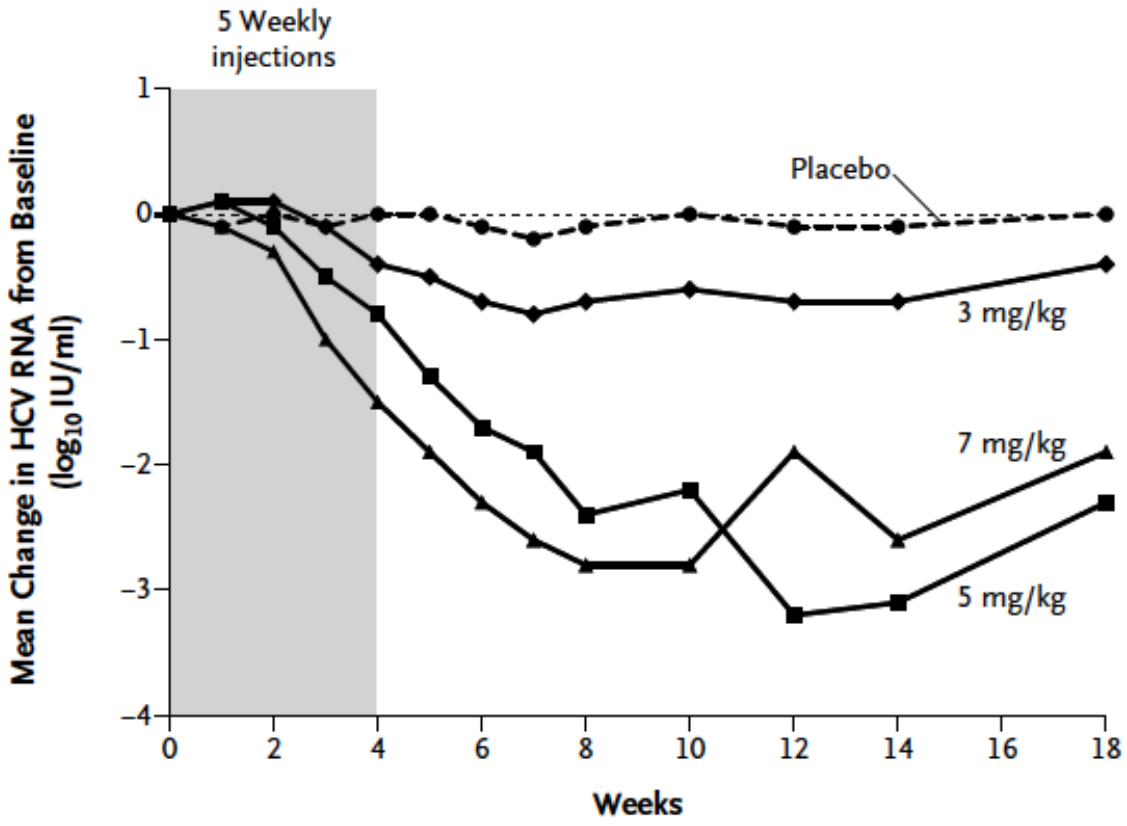
Miravirsen

Miravirsen SC injection weekly



Janssen NEJM 2013

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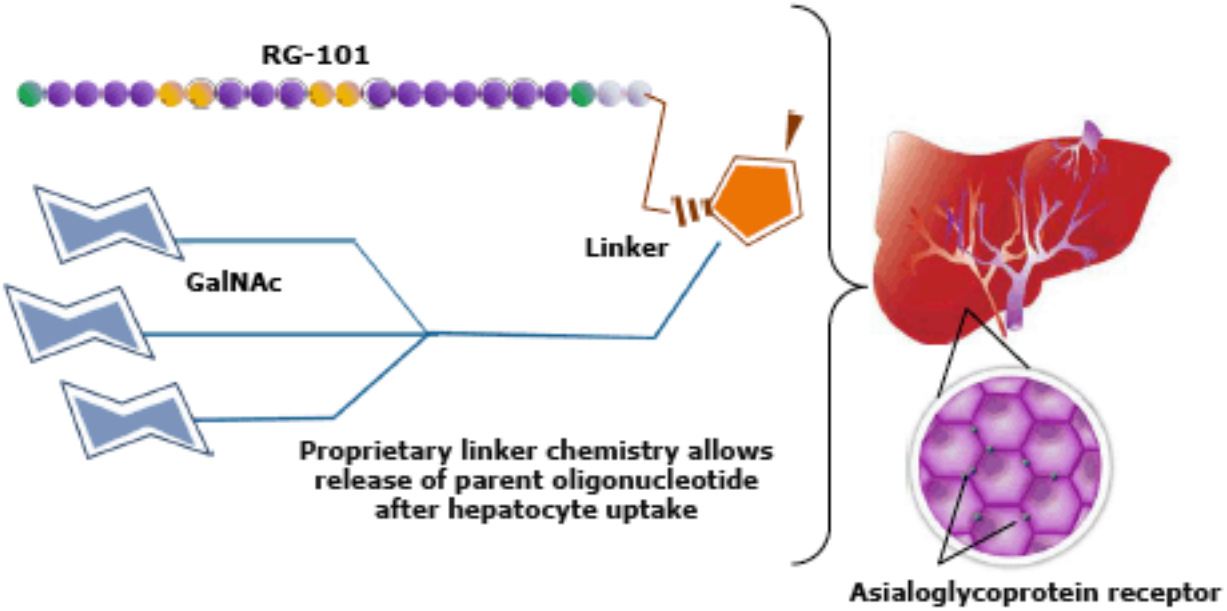
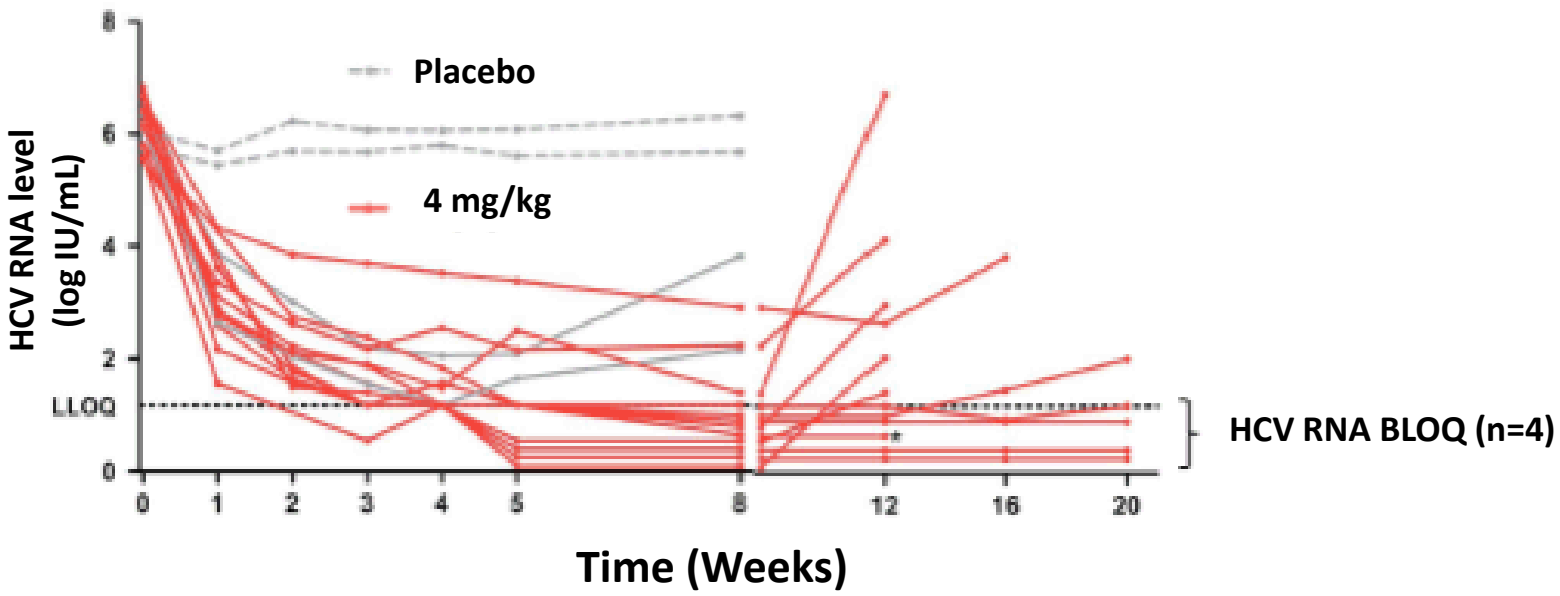
A better miR122 inhibitor



- Increases liver uptake
- Increased miR122 inhibition

Single injection

4 mg/kg
RG-101



- 9 of 12 patients with undetectable HCV RNA with single dose → 4 negative out to 20 weeks

Van der Ree EASL 2015

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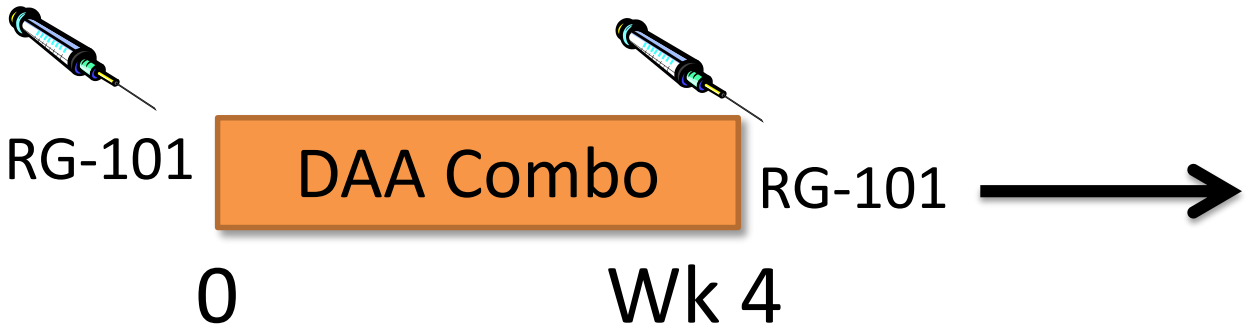
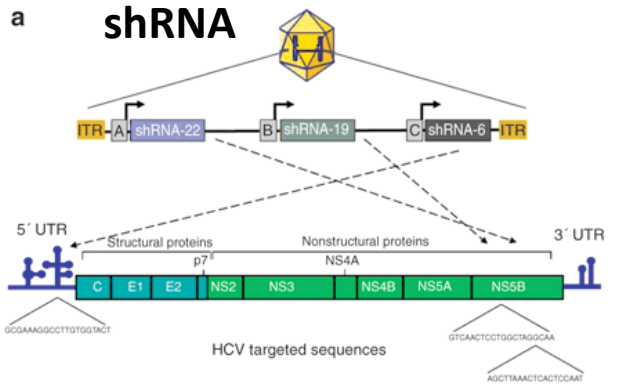
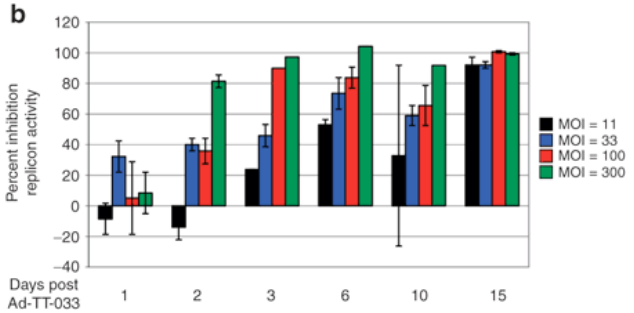
Aren't DAAs better than this?

- RG-101 alone
  - Unlikely – injections, response may be less universal
- As combination with DAAs
  - Long-acting → Could shorten therapy to 1 month
  - Very high barrier to resistance…?useful if adherence is an issue

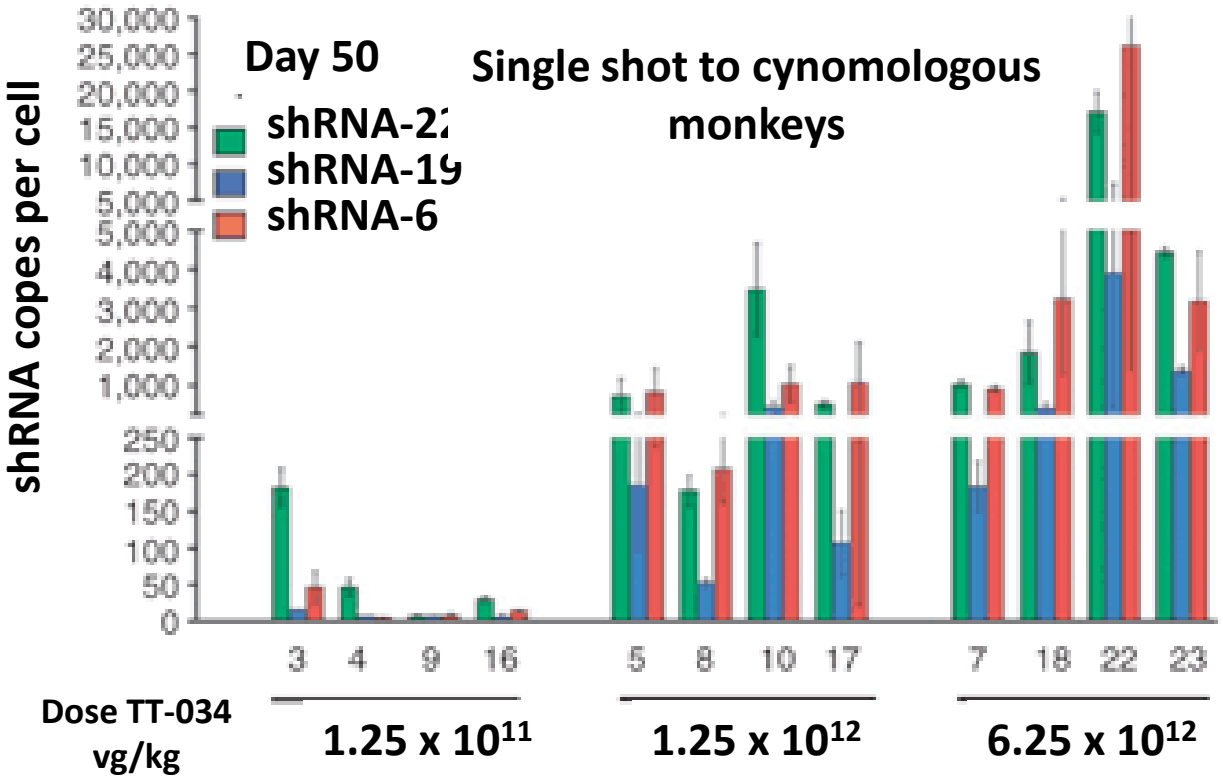


One injection for cure?





HCV Replicon



- 3 shRNAs targeting conserved regions of HCV
- Long-lasting expression (180 d) of all 3 shRNAs at levels needed to suppress replicon in non-human primates

Suhy Mol Ther 2012

TORONTO CENTRE FOR LIVER DISEASE

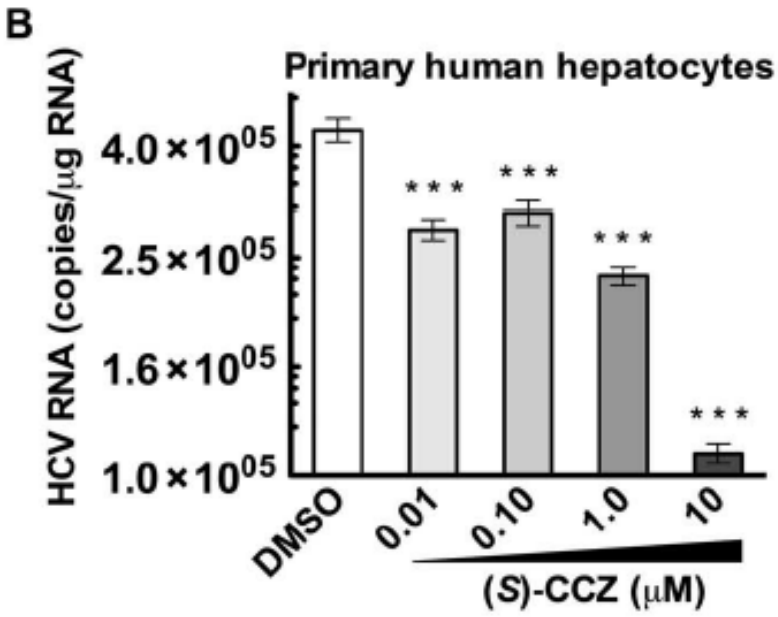
Summary

- Current therapy is highly effective
  - Arguably close to perfectovir
  - 'Perfectovir' may be slightly different for different populations
- For PWID population…still some work to do
  - Pangenotypic coverage – 1 size fits all (or most) – coming
  - Shorter duration (ideal, not critical)
  - Retreatment or treatment of 'newly acquired resistant HCV'
  - More studies – not just OST…active PWID → TasP
- May consider alternative approaches…host-targeting-agents
- The tools are here… (or almost here…) now we need to start using them

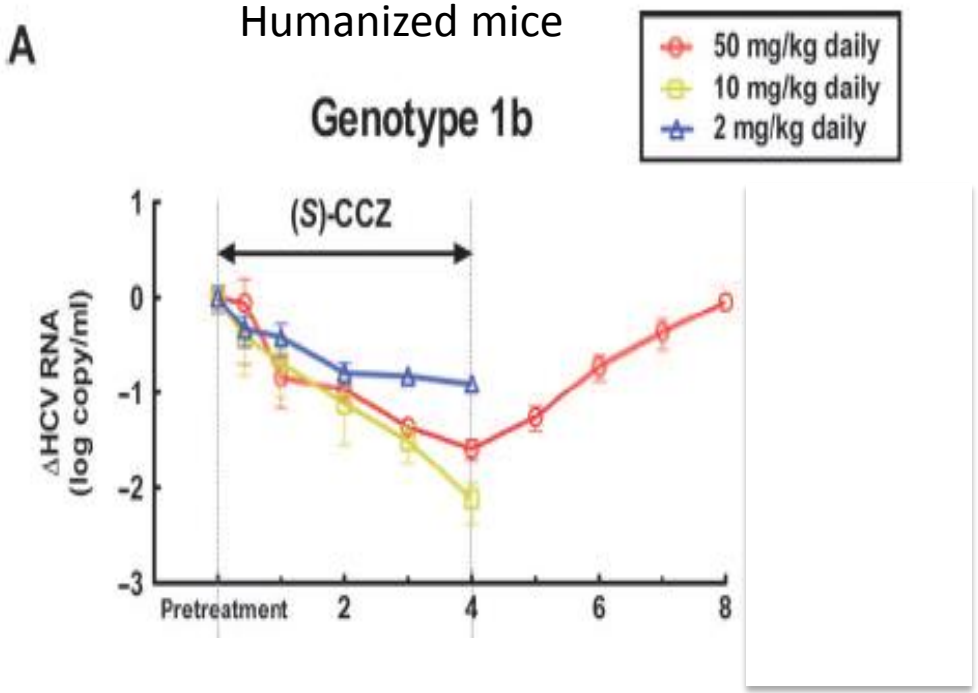
TORONTO CENTRE FOR
LIVER DISEASE

What about looking into the existing medicine cabinet?

Anti-histamine - chlorcyclazine



Humanized mice



- Costs pennies a day
- Could it be combined with suboptimal (cheap) DAAs?

He Sci Trans Med 2015

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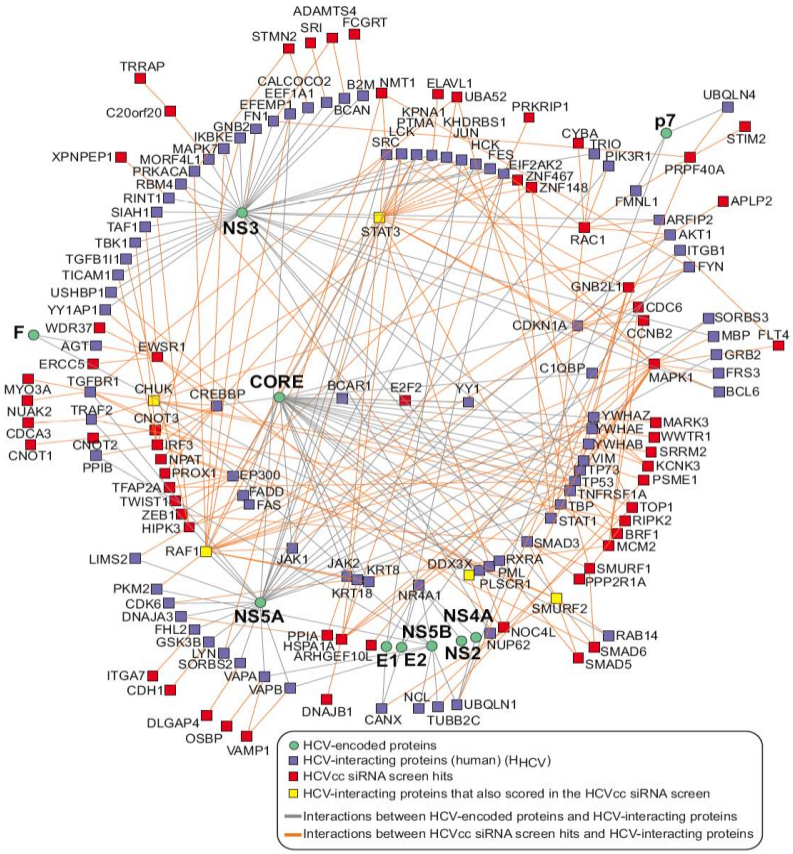
Many potential host targets



Li PNAS 2009

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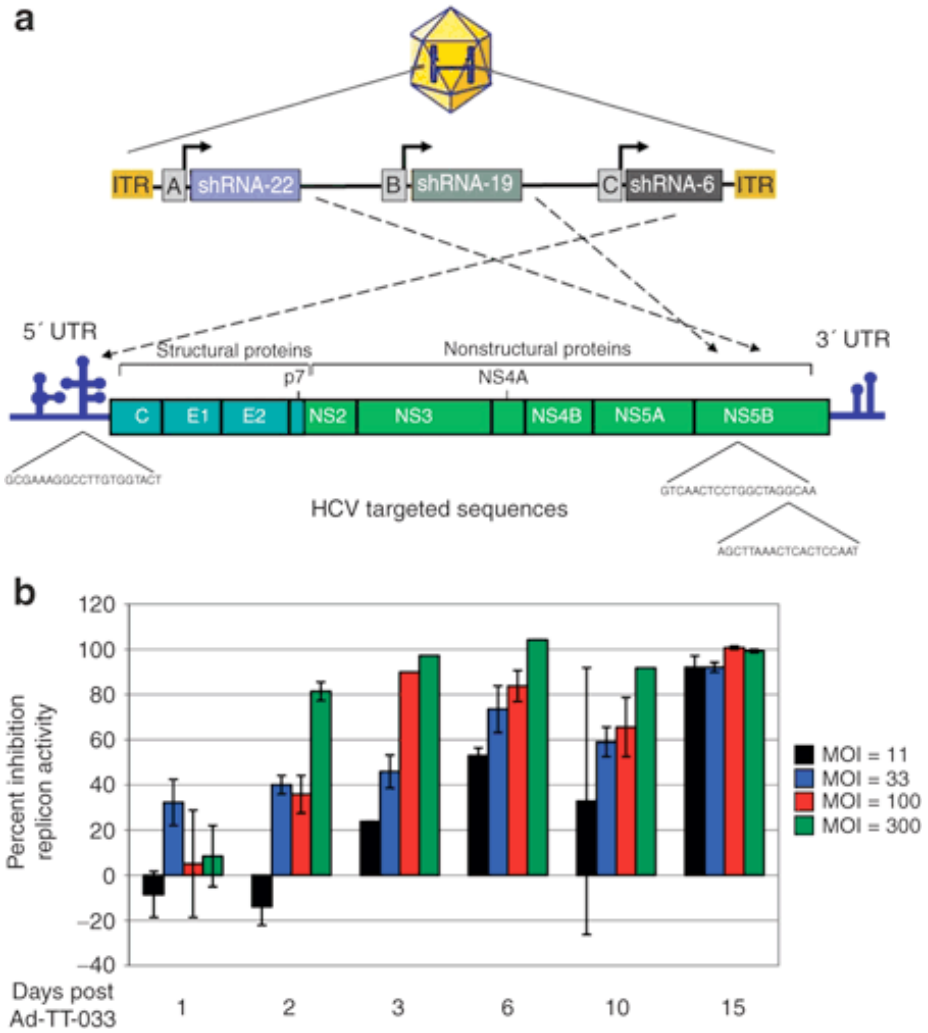
A single dose for cure?



- Multiple shRNAs targeting conserved sites in the virus
- Delivered via recombinant Adeno-associated virus (AAV)
- Inhibits HCV replicon

Suhy Mol Ther 2012

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Disclosures

- Research: Abbvie, BI, Gilead, Janssen, Merck

- Consulting: Abbvie, BI, BMS, Gilead, Janssen, Merck, Theravance