Hepatitis C Treatment
How can we cure everyone, even the homeless?

Graham R Foster

Professor of Hepatology

Queen Mary University of London

Conflicts of Interest

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

HCV

- The disease and its impact
- Viro-babble
- The politics

HCV

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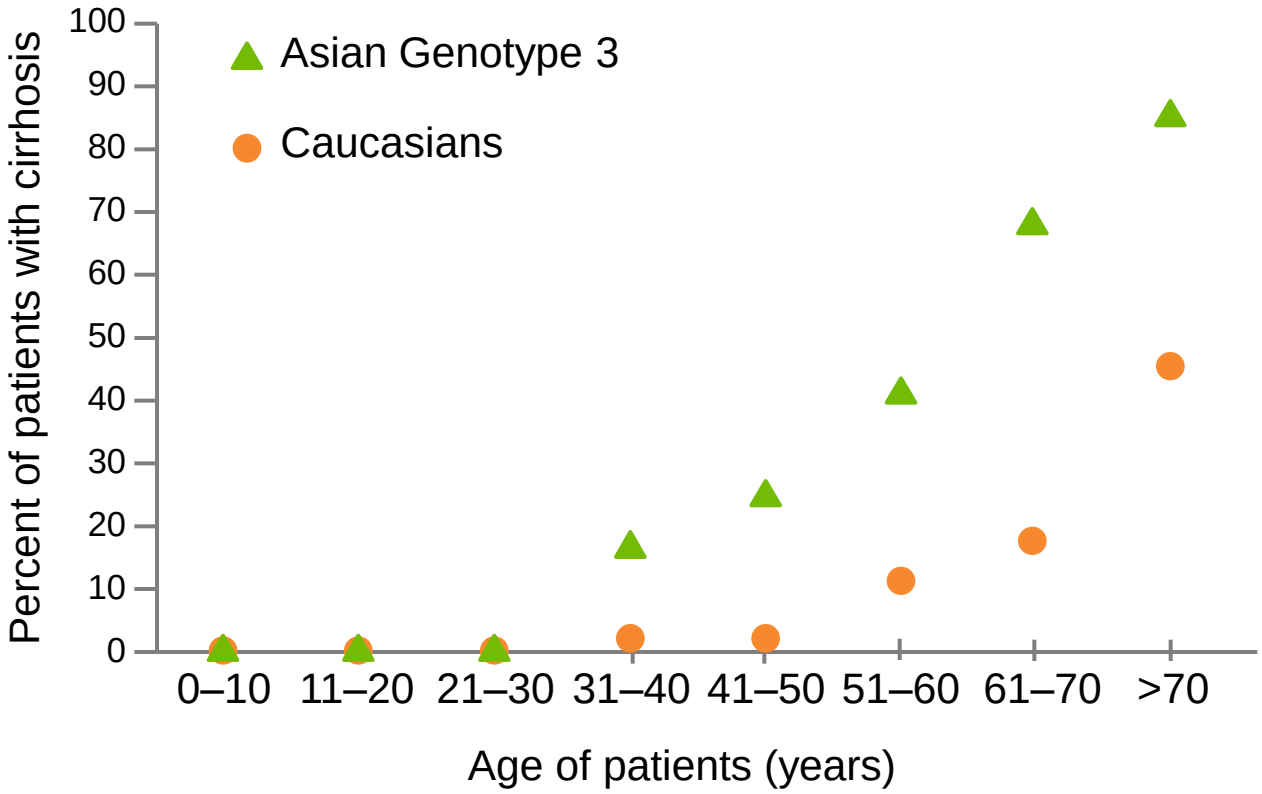
HCV causes slowly progressive liver fibrosis



Adapted from D'Souza. Clin Gastroenterol Hepatol 2005;3:910–17

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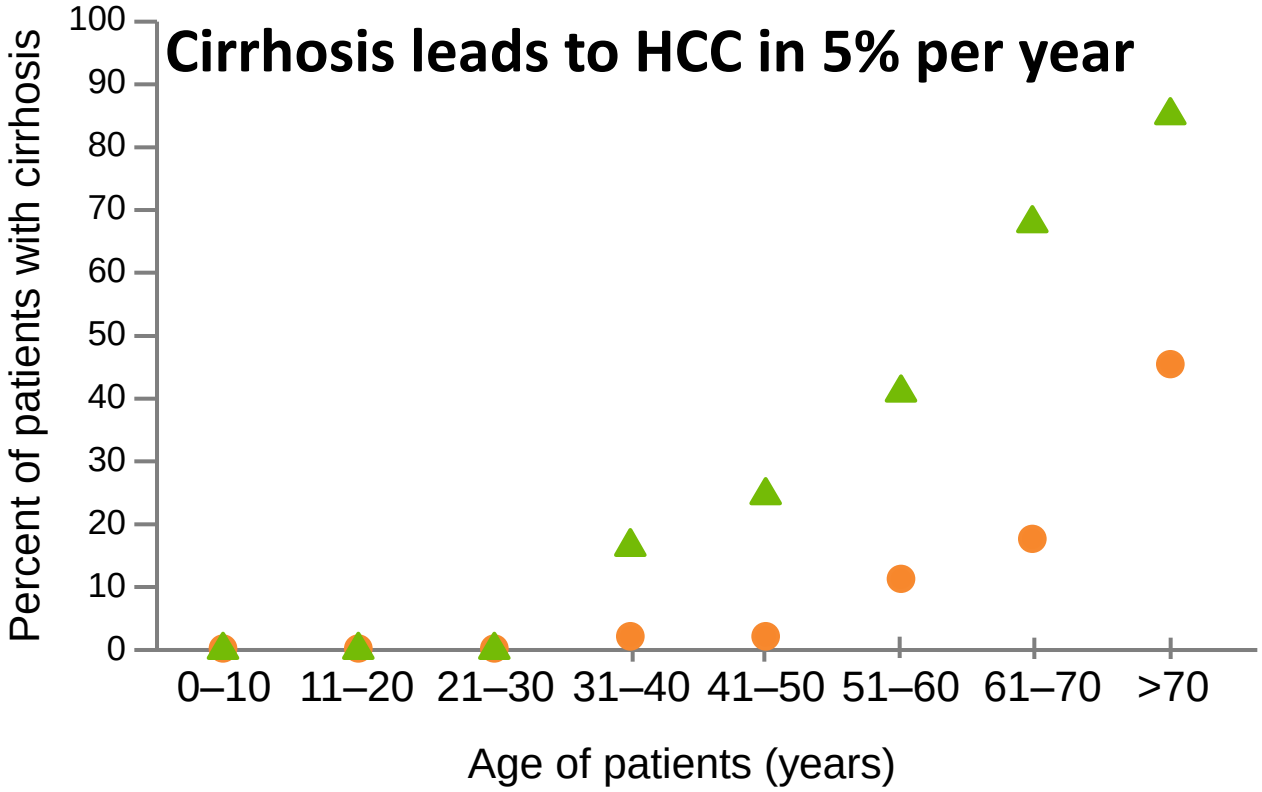

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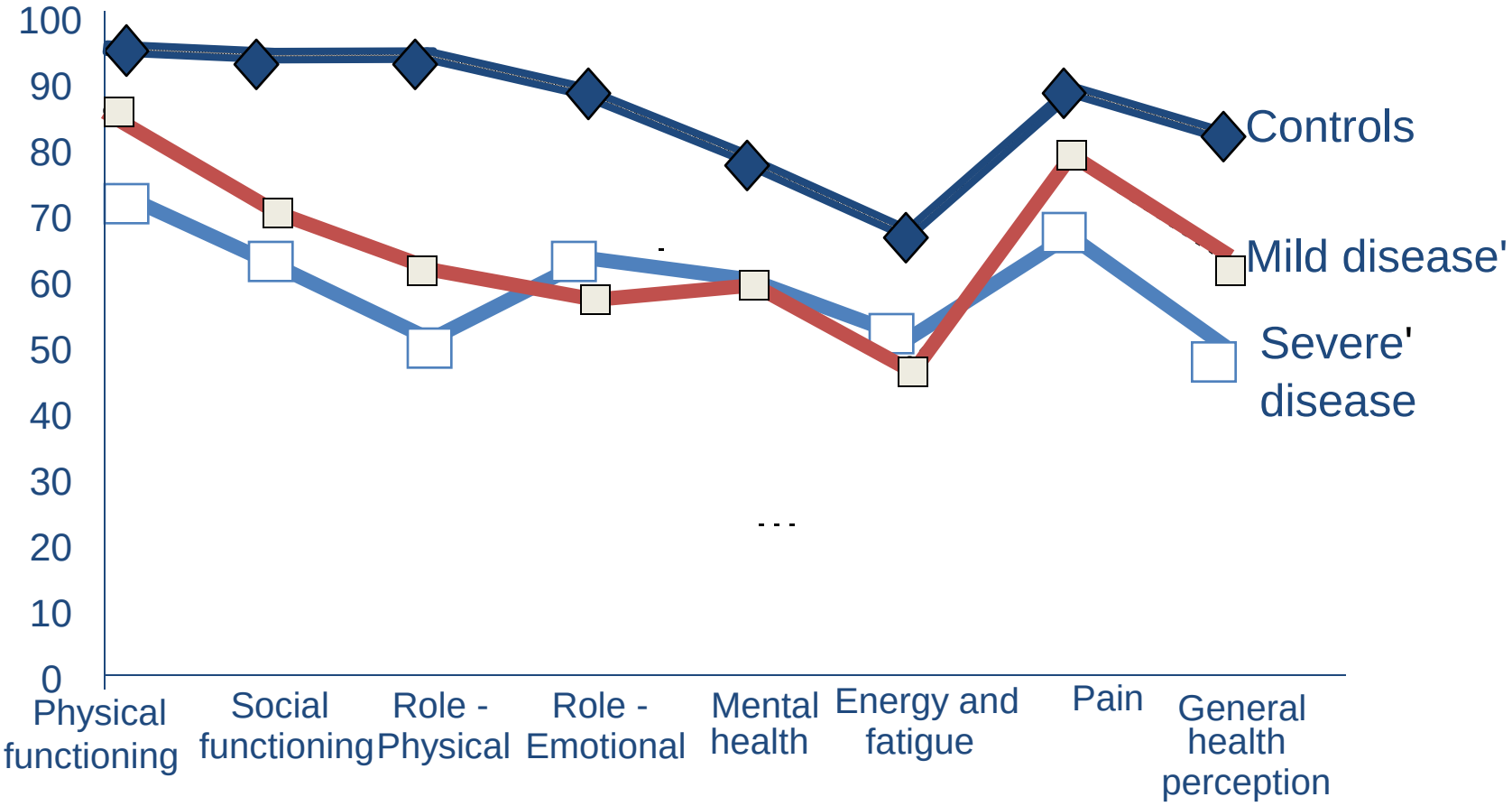
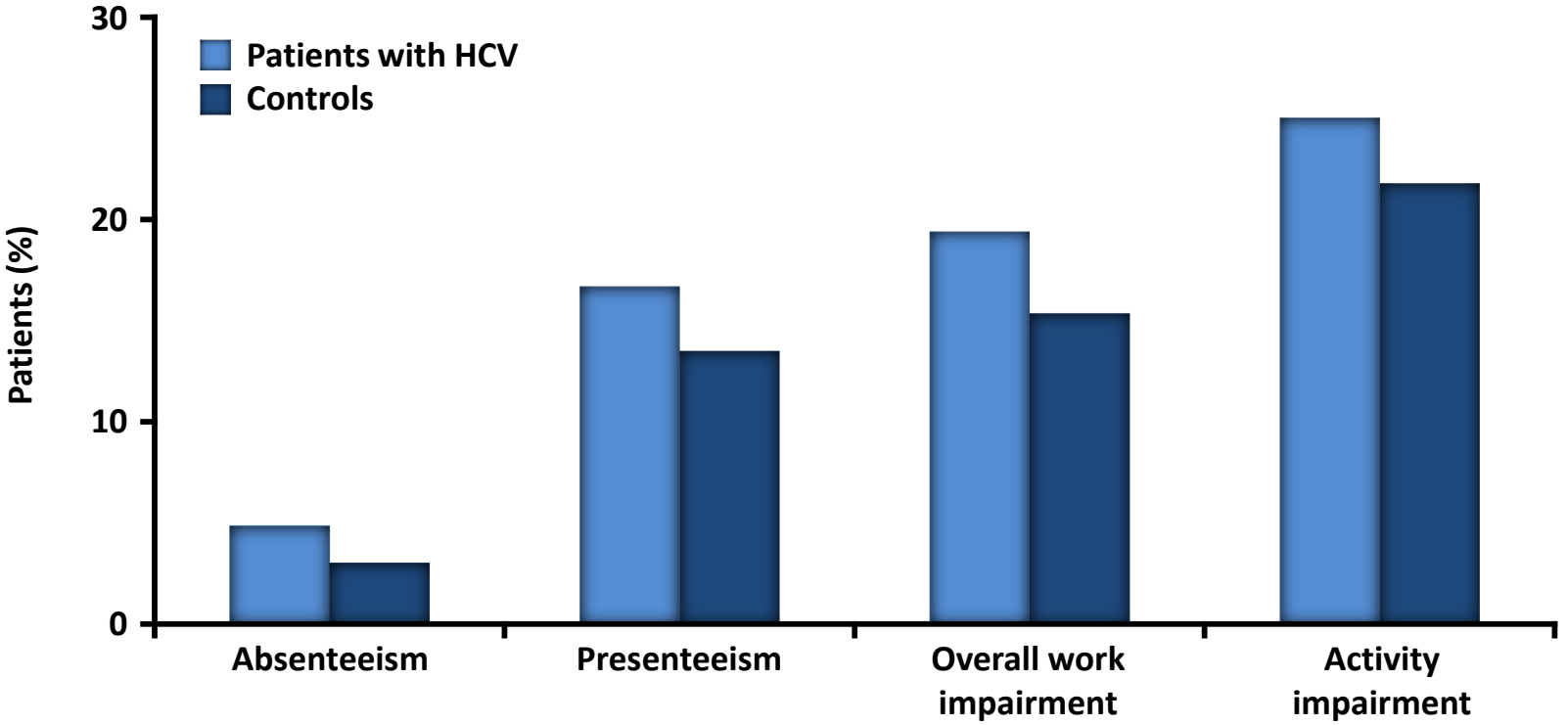
Patients with chronic HCV feel unwell



Foster et al Hepatology 1998

HCV has an impact on patient life now: the indirect economic costs of HCV



- Data from the 2009 US National Health and Wellness Survey showed patients with HCV were significantly less likely to be employed compared with controls ($p<0.0001$)[1]
- The presence of HCV in the EU population has been shown to significantly impact several domains of HRQL ($p<0.05$)[2]

1. DiBonaventura M, et al. J Med Econ 2011;14:253–61
2. DiBonaventura M, et al. Eur J Gastroenterol & Hepatol 2012;24:869–77

HCV

- Makes people sick
- Then it kills them

Where we started

- Have HCV – get a liver biopsy (not very nice)
- If very severe disease – die quietly (not very nice)
- If moderate disease – get up to 18 months injections and tablets for a 70% chance of a cure (not very nice)

Where we are today

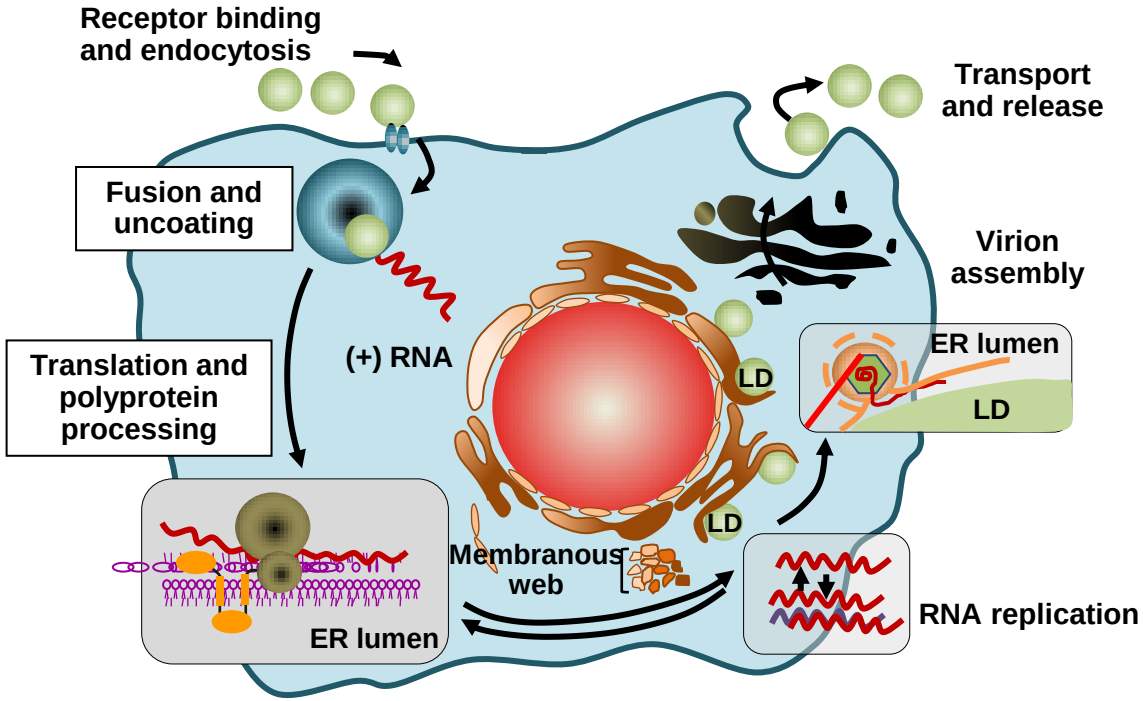
- Get a scan
- Take some tablets for a few weeks
- Get cured

(All very nice)

HCV

- The disease and its impact
- Viro-babble
- The politics

We now have highly efficacious DAAs that target different stages in the HCV lifecycle



Lindenbach BD, Rice CM. Nature 2005;436(Suppl):933–8;
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DAA: direct-acting antiviral agent; ER: endoplasmic reticulum; GT: genotype; IFN: interferon; LD: luminal domain; NA: nucleos(t)ide analogue; NS: non-structural protein; SVR: sustained virological response

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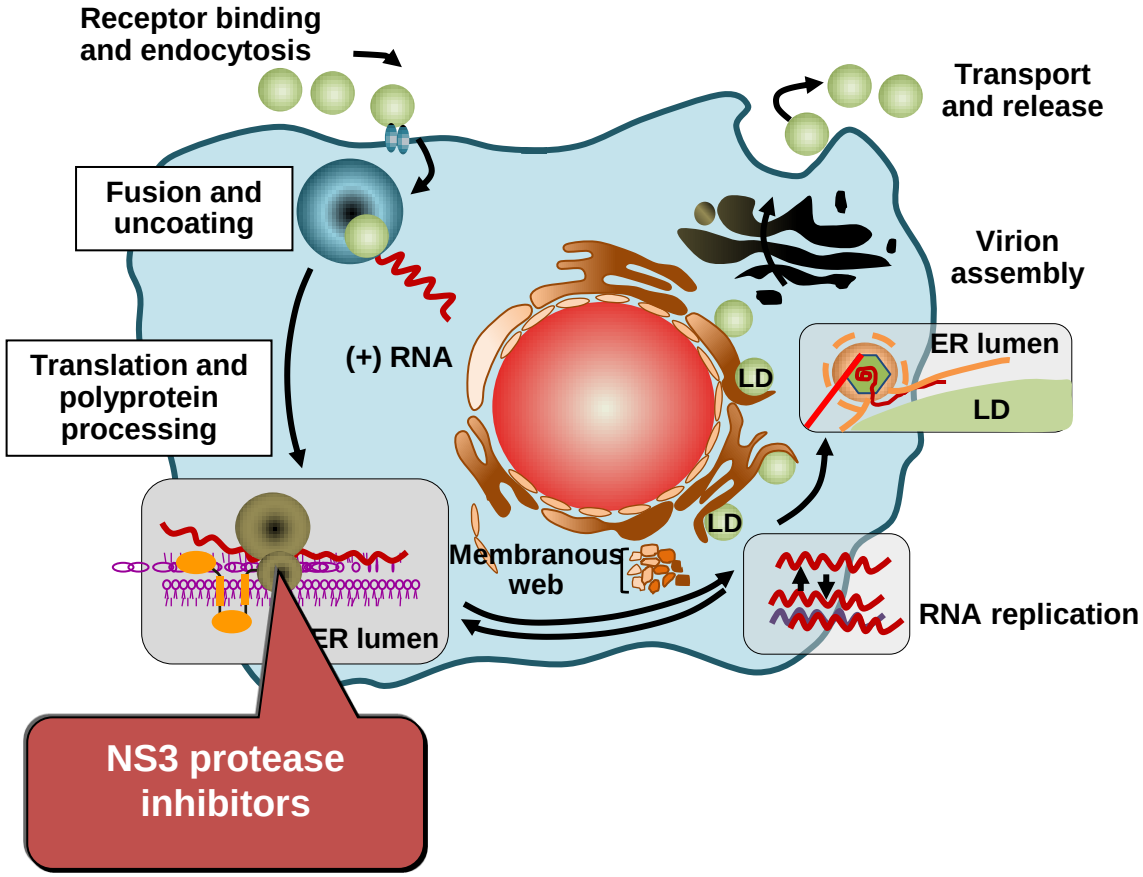

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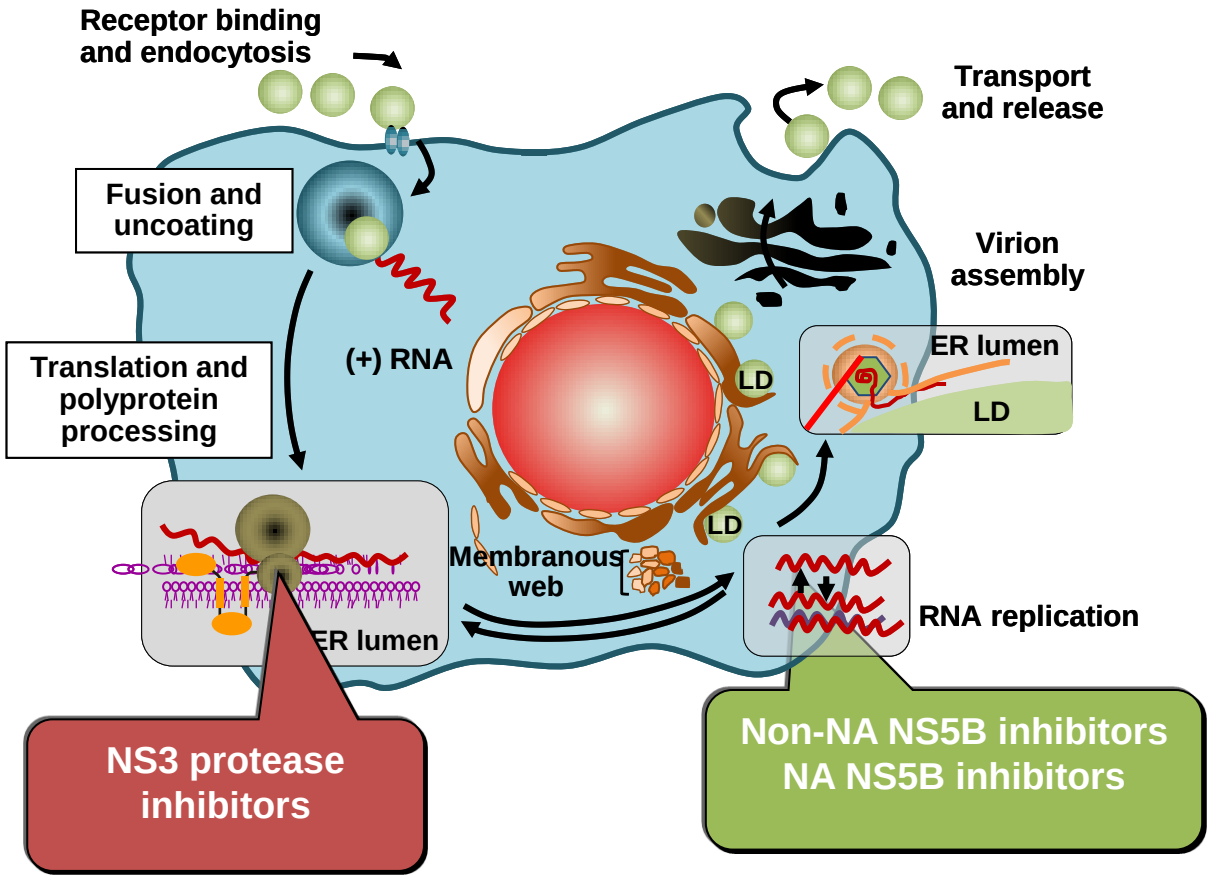

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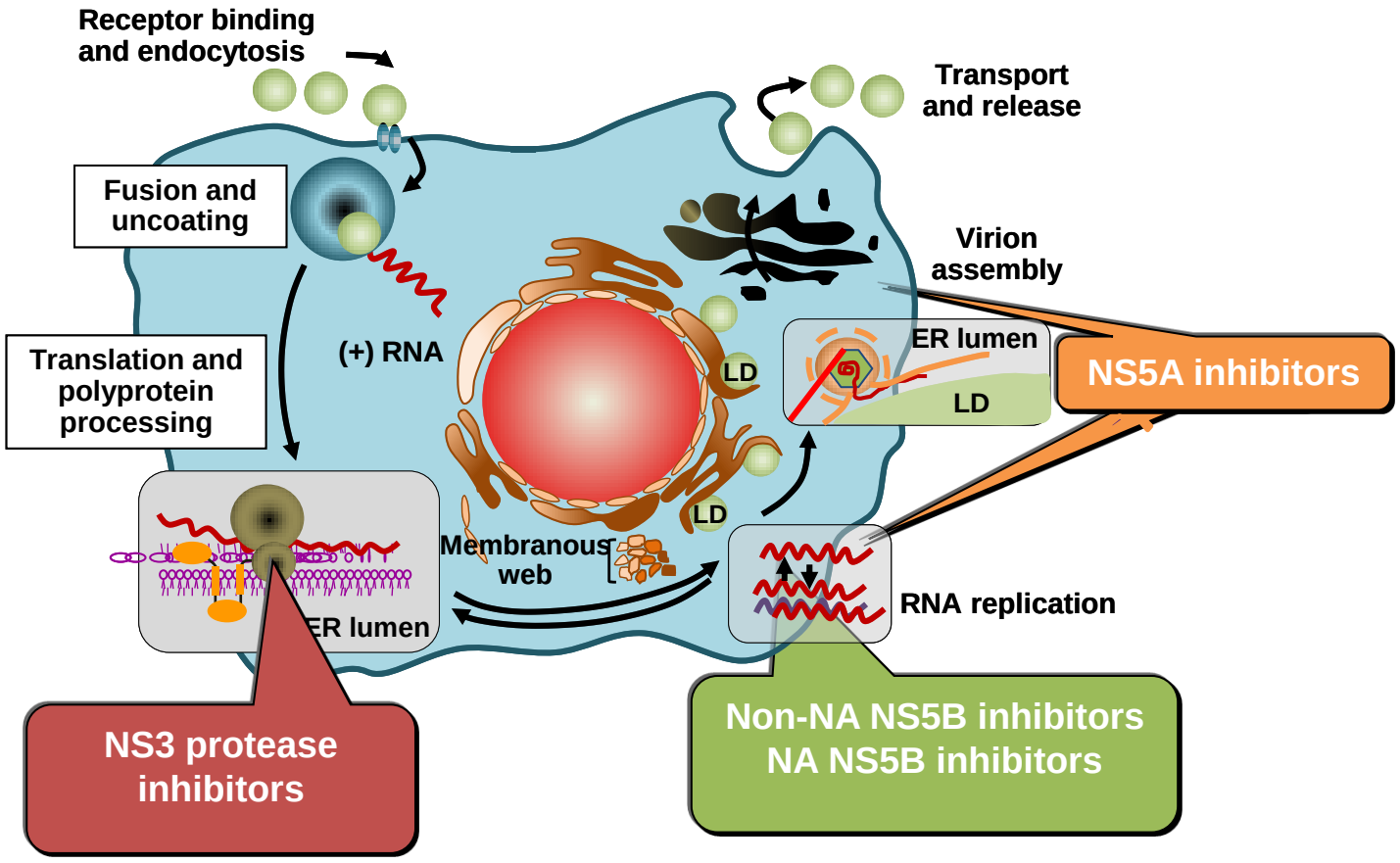

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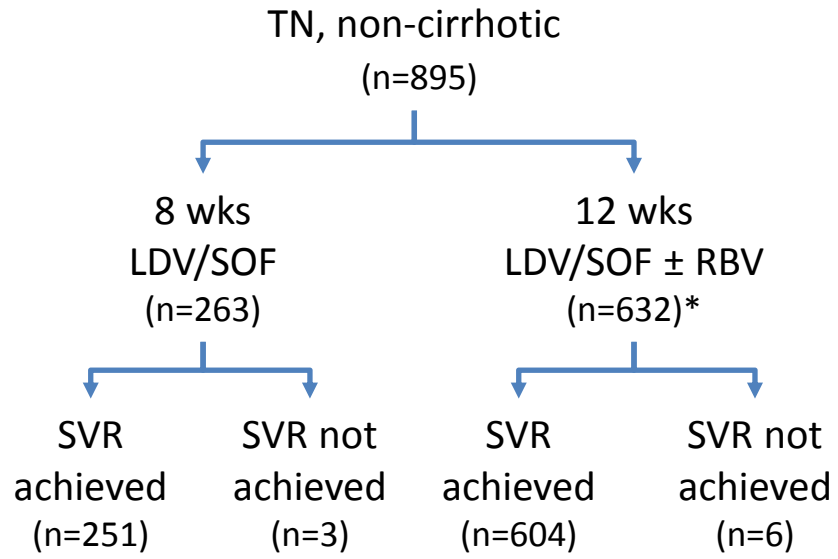
Genotype 1 without Interferon

- Two strategies emerging:-
- Sofosbuvir + anything
- Potent protease + 1 or 2 other drugs

Real-world experience from the TRIO Network:

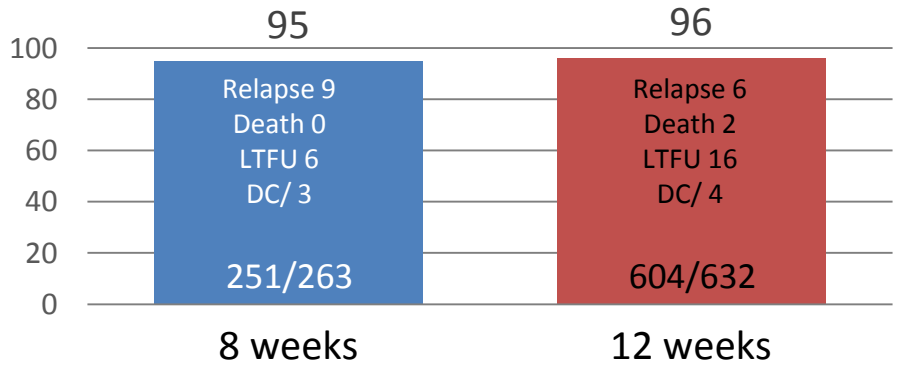
Effectiveness of 8 or 12 week LDV/SOF in treatment-naive patients with non-cirrhotic, G1 HCV

Patient disposition

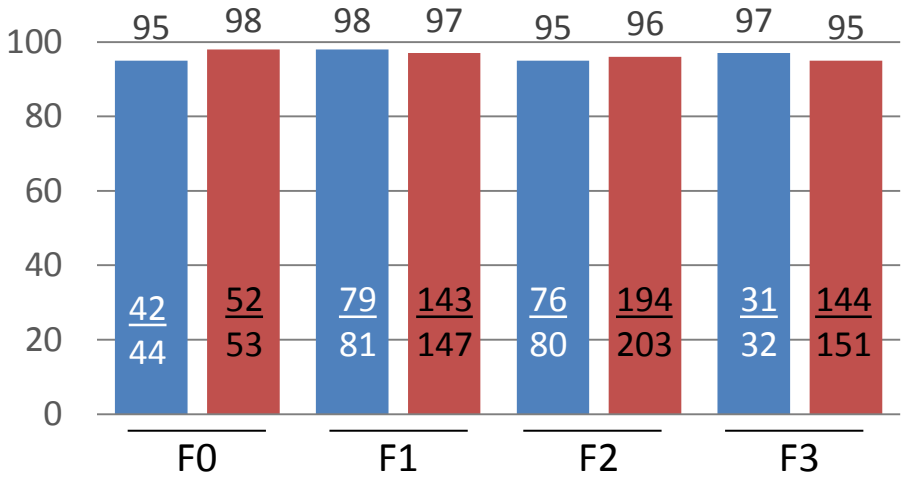


*21 Patients were on 12 weeks of LDV/SOF+RBV

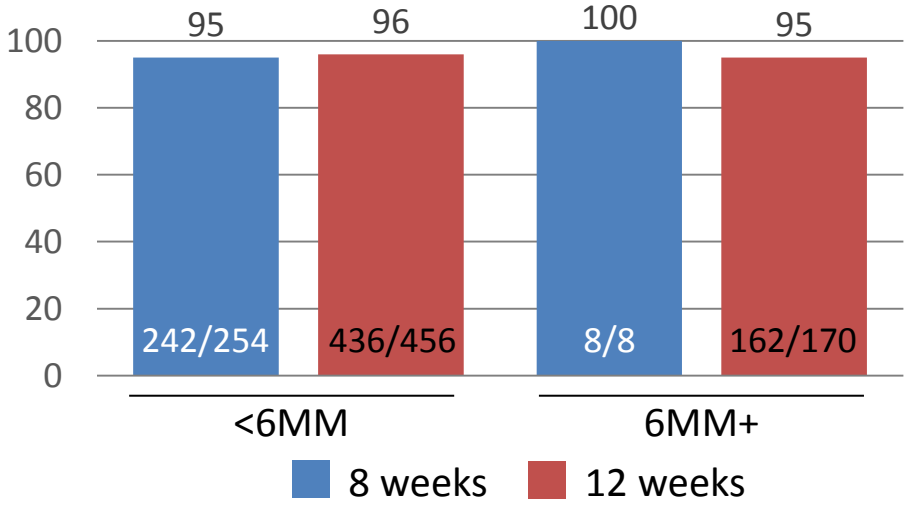
SVR12 by duration



SVR12 by fibrosis



SVR12 rates by baseline viral load



Curry M, et al. AASLD 2015, San Francisco. #1046

Sofosbuvir + Ledipasvir

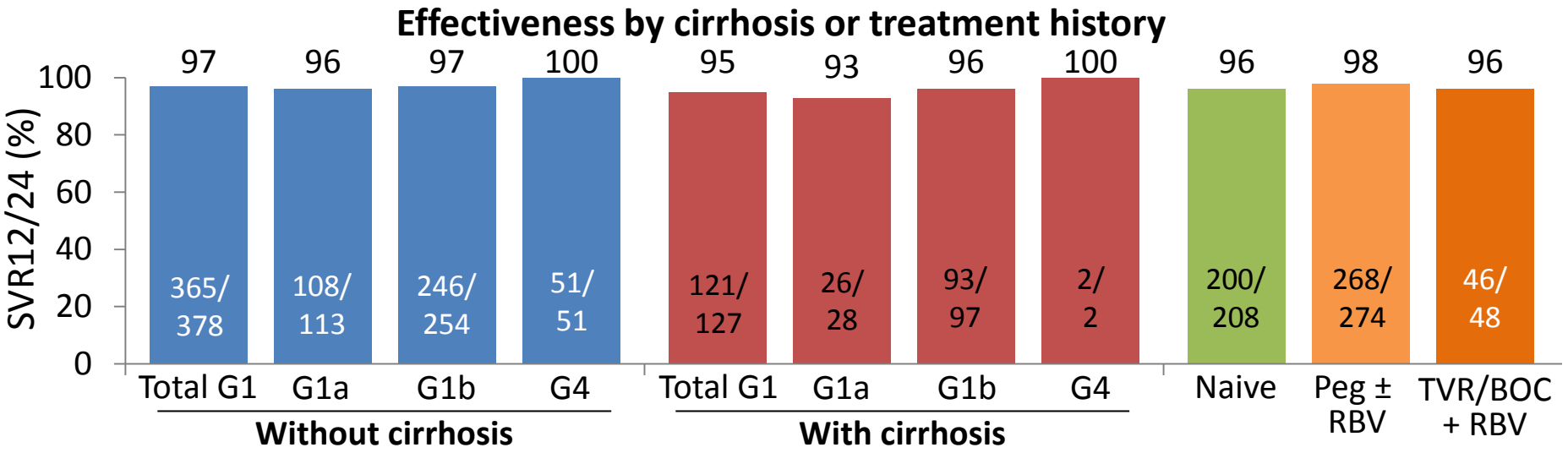
- A single tablet
- Cures most G1 in 8 weeks – side effect free
- Cures cirrhosis in 12 weeks

  (needs ribavirin, some side effects)

Genotype 1 without Interferon

- Two strategies emerging:-
- Sofosbuvir + anything
- Potent protease + 1 or 2 other drugs

Real-world safety and effectiveness of OBV/PTV/r with DSV and/or RBV in the **German hepatitis C Registry**



Safety, n (%)		2D/3D -RBV (n=436)	2D/3D + RBV (n=353)	2D/3D -RBV (n=44)	2D/3D + RBV (n=184)
Any AE		185 (42)	201 (57)	20 (45)	119 (65)
Any SAE		5 (1)	8 (2)	0	8 (4)
RBV dose mod.		-	26 (7)	-	18 (10)
Death		2 (0.5)	0	0	0
D/C due to AE		2 (0.5)	4 (1)	0	9 (5)
AEs in ≥5%of patients	Fatigue	80 (18)	97 (27)	8 (18)	58 (32)
	Pruritus	33 (8)	40 (11)	2 (5)	26 (14)
	Headache	35 (8)	35 (10)	5 (11)	16 (9)
	Insomnia	17 (4)	29 (8)	0	18 (10)
	Nausea	16 (4)	20 (6)	3 (7)	12 (7)
	Anemia	1 (0.2)	15 (4)	0	20 (11)

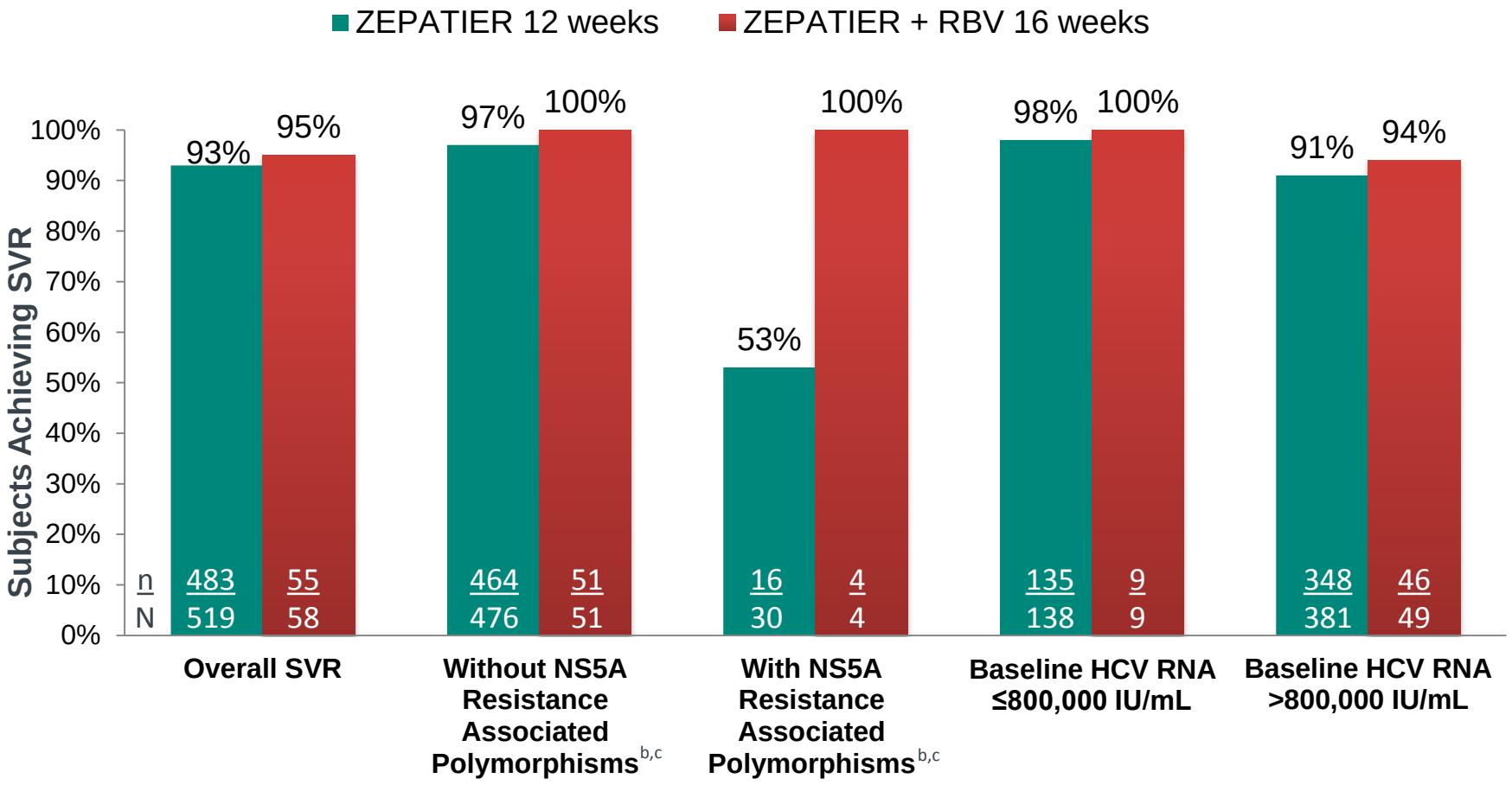
AbbVie Regimes

- For naïve 1a patients (+/- cirrhosis):-
  12 weeks ‘3D’ with ribavirin

- For naïve 1b patients (- cirrhosis)
  12 weeks ‘3D’ without ribavirin
  (add ribavirin for cirrhosis)

- For experienced patients with cirrhosis extend for 24 weeks in 1a non-responders

Elbasvir and grazoprevir: Pooled Efficacy in HCV GT1a Infected Patients



Genotype 1 – which drug?

- In the USA
- ‘The right drug for my patient is the one the insurance company will fund’ – Doug Dietrich

- In England
- The right drug is the ‘least acquisition cost’ option

Genotype 1 HCV

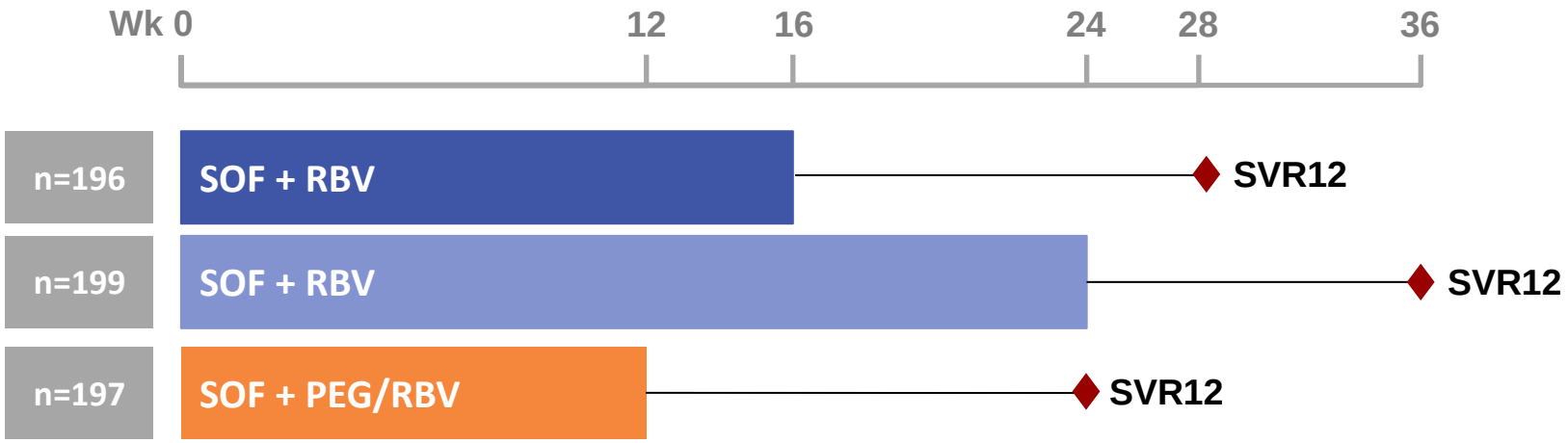
- Sorted!

Genotype 3
A tricky customer

Non-cirrhotic is easy to cure
(even cheap IFN/Riba works)

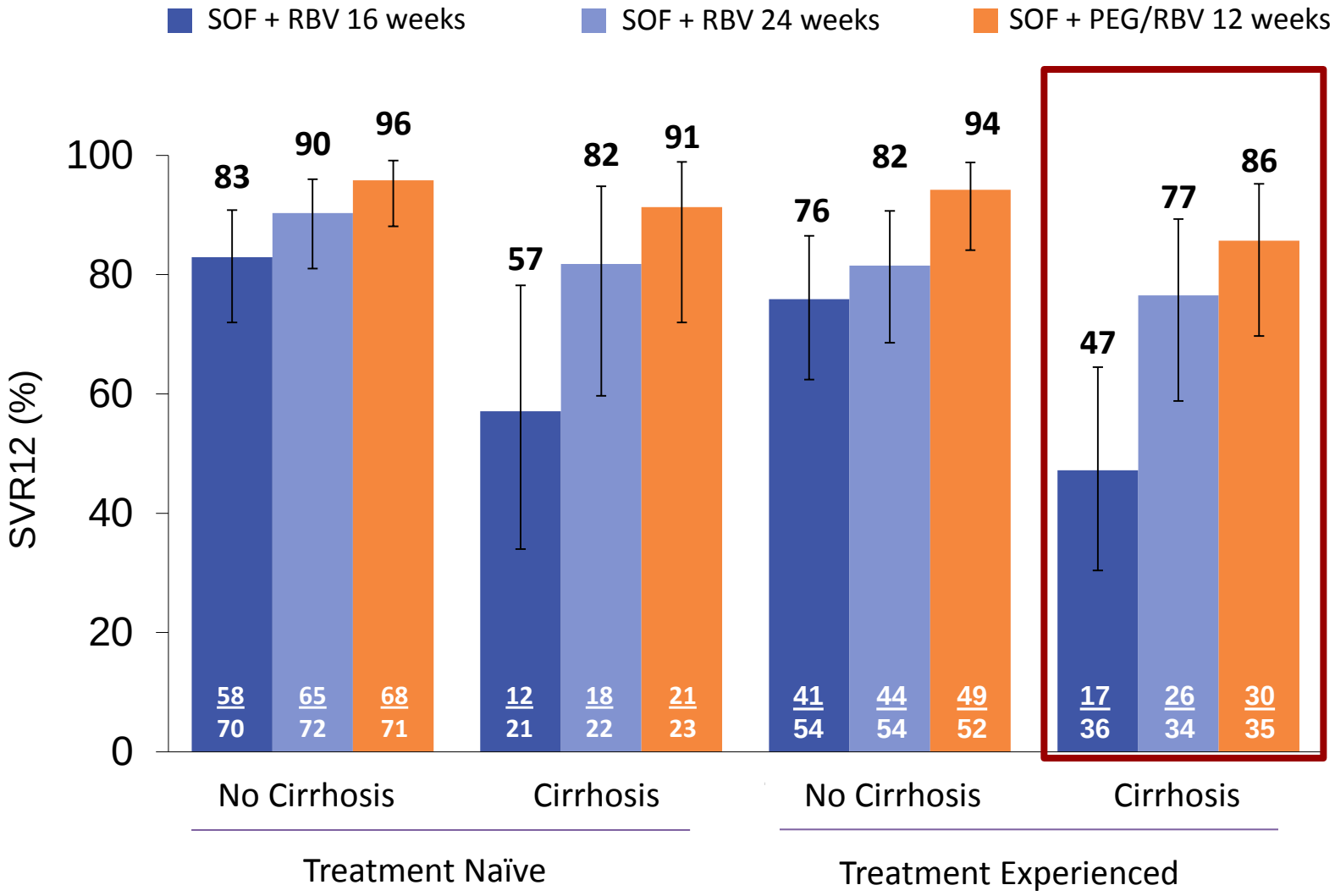
Cirrhotic is hard to cure

Treating Genotype 3 BOSON



- Multicenter study, open-label, randomized (1:1:1) study at 80 sites in UK, Australia, USA, Canada, and New Zealand
- GT 2 patients: treatment experienced (TE) with cirrhosis
- GT 3 patients: TE or treatment naïve (TN), with or without cirrhosis
- Stratification
  - Cirrhosis
  - HCV Genotype
  - Prior HCV treatment
- ♦ Platelets ≥60,000 cells/mm^3

SVR12 in GT 3
by Treatment History and Cirrhosis Status

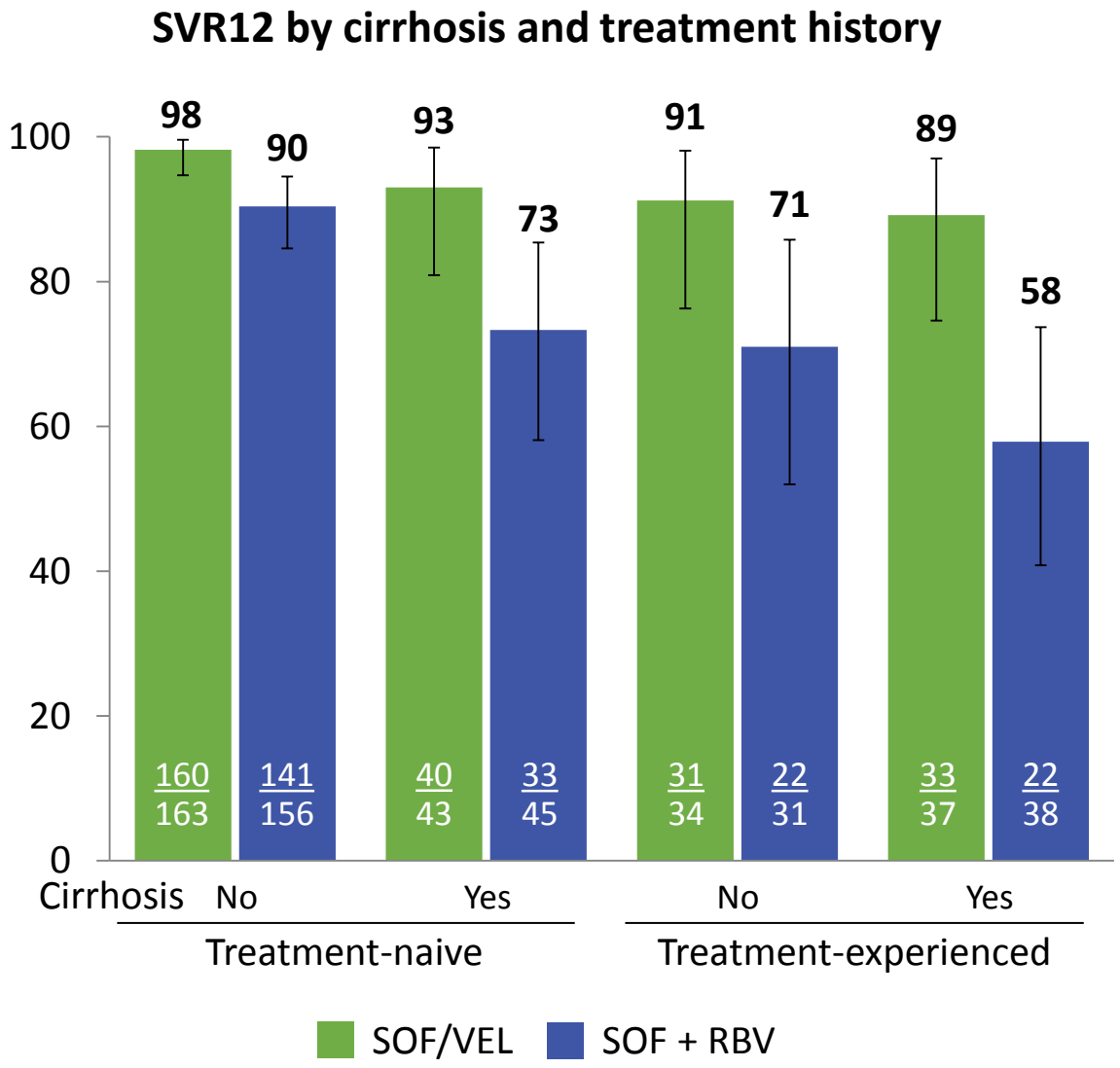


Genotype 3 – IFN based therapies

- Until recently the best we could offer Genotype 3 patients was interferon based treatment

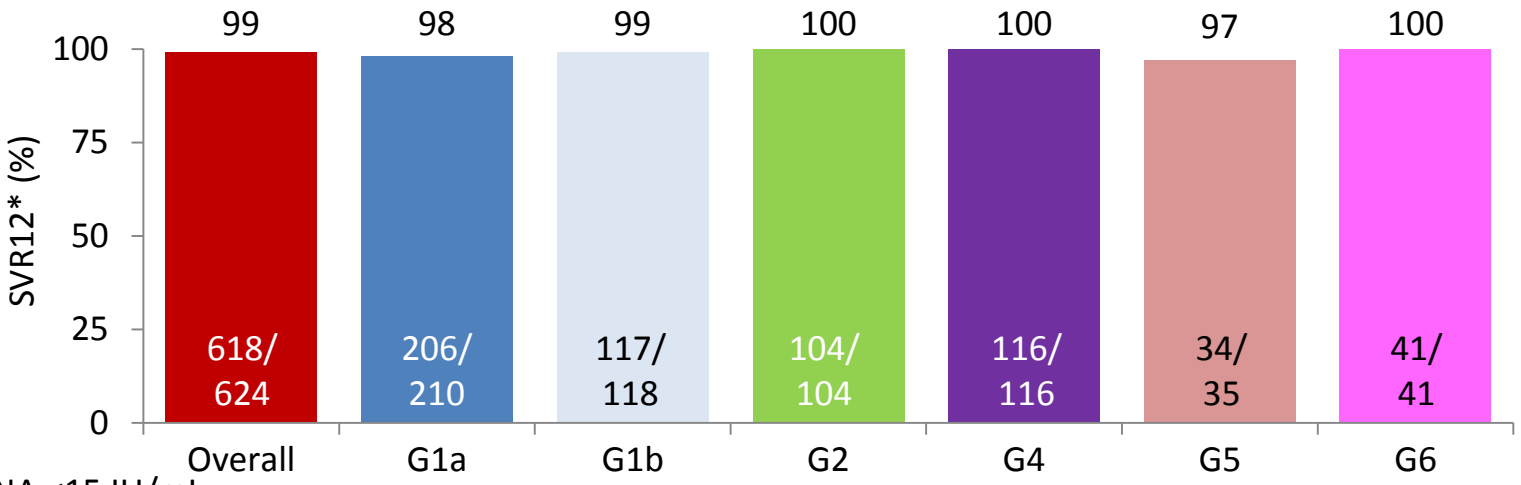
- Not any more!

ASTRAL-3 Phase 3 Study: SOF/VEL FDC for 12 weeks compared to SOF + RBV for 24 weeks in G3 HCV infected patients



Foster GR, et al. NEJM 2015

Phase 3 evaluation of SOF/VEL FDC for 12 weeks in Tx-naive and -experienced G1, 2, 4, 5, and 6 patients with and without cirrhosis: ASTRAL-1 study



*HCV RNA <15 IU/mL

- No pts in the PBO group had HCV RNA <15 IU/mL at any timepoint

Virologic failure, n (%)	
On-treatment failure	0
Post-treatment relapse	2 (<1)
Other reasons for classification as failure to achieve SVR 12, n (%)	
Lost to follow-up	2 (<1)
Withdrew consent	1 (<1)
Death	1 (<1)

Feld JJ, et al. AASLD 2015, San Francisco. #LB-2
Feld JJ, et al. N Engl J Med. 2015 Nov 16. [Epub ahead of print]

What is coming next?

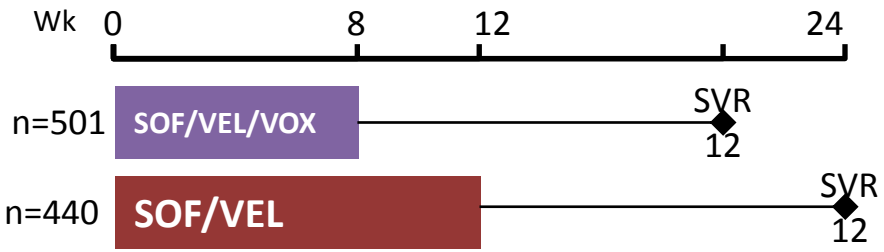
- We have great options available
- What can we expect in the future?

Two drugs good, three drugs better
Sofosbuvir based regimens

- Triple therapy with:-

- Nucleotide
- NS5A inhibitor
- Protease inhibitor

A randomized Phase 3 trial of SOF/VEL/VOX for 8 weeks compared to SOF/VEL for 12 weeks in DAA-naive G1–6 patients: The POLARIS-2 study



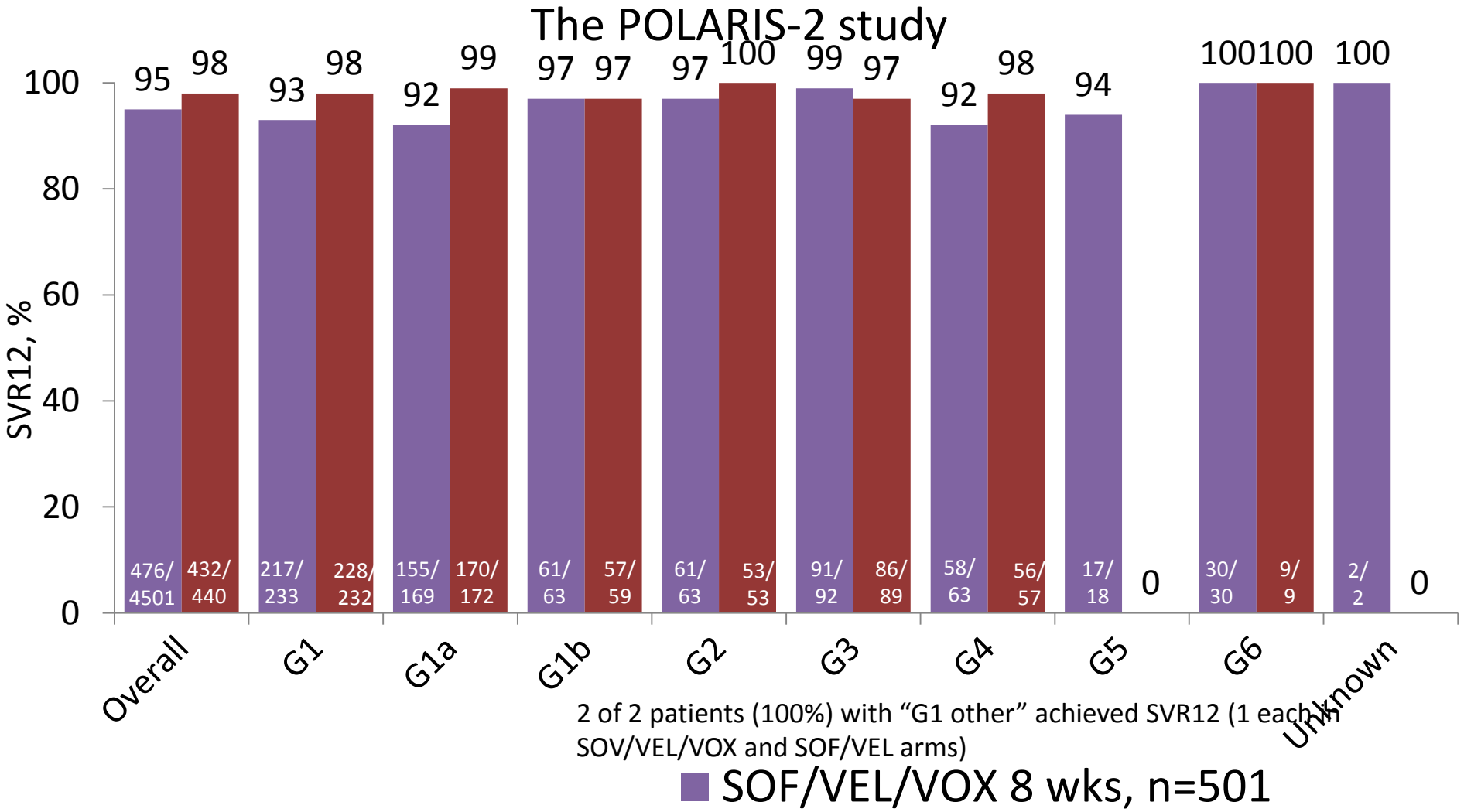
- G1–6 with and without compensated cirrhosis
- 1:1 randomization for G1–4 (other genotypes assigned to SOF/VEL/VOX)

Efficacy analysis: Non-inferiority of SOF/VEL/VOX to SOF/VEL with 5% margin

		SOF/VEL/VOX 8 weeks n=501	SOF/VEL 12 weeks n=440
Cirrhosis, n (%)		90 (18)	84 (19)
Genotype, n (%)	1a / 1b / Other	169 (34) / 63 (13) / 1 (<1)	172 (39) / 59 (13) / 1 (<1)
	2	63 (13)	53 (12)
	3	92 (18)	89 (20)
	4	63 (13)	57 (13)
	5 / 6 / Unknown	18 (4) / 30 (6) / 2 (<1)	0 / 9 (2) / 0
IFN experienced, n (%)		118 (24)	100 (23)

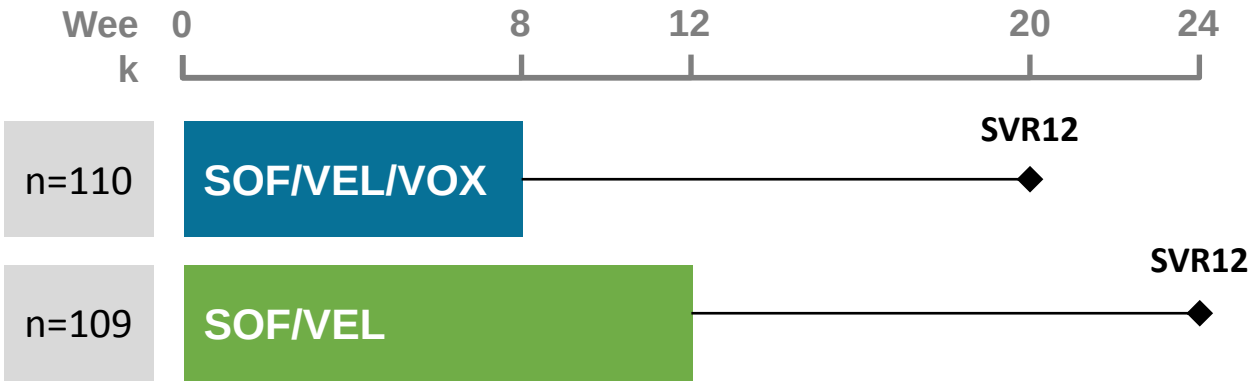
Jacobson IM, et al. AASLD 2016, Boston. #LB-12

A randomized Phase 3 trial of SOF/VEL/VOX for 8 weeks compared to SOF/VEL for 12 weeks in DAA-naive G1–6 patients:



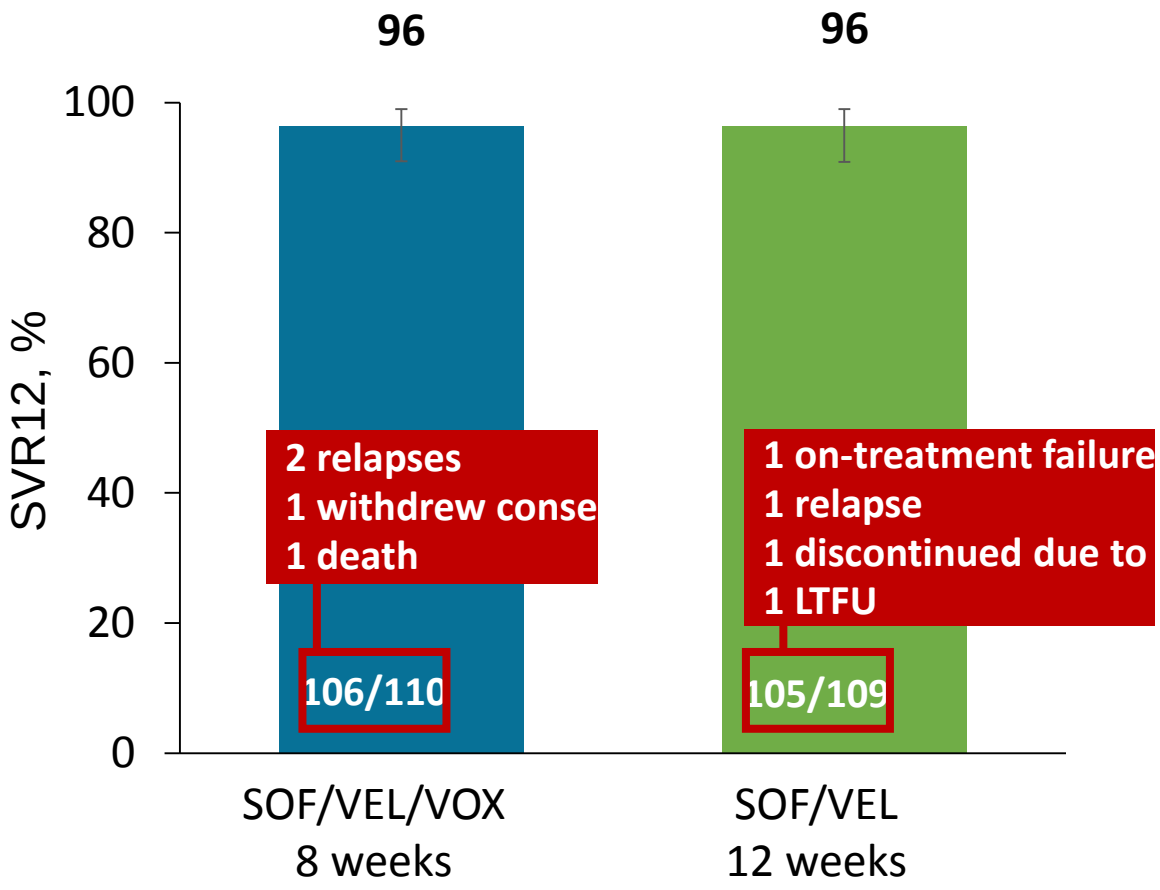
Jacobson IM, et al. AASLD 2016, Boston. #LB-12

Sof/Vel/Vox for G3
Polaris 3



- Open-label, randomized, active-comparator trial conducted at 84 sites (USA, Canada, France, Germany, UK, Australia, New Zealand)
- Patients with GT 3, all of whom had cirrhosis
- 1:1 randomization
  - Stratified by prior treatment experience (IFN experienced or naïve)

Results: SVR12



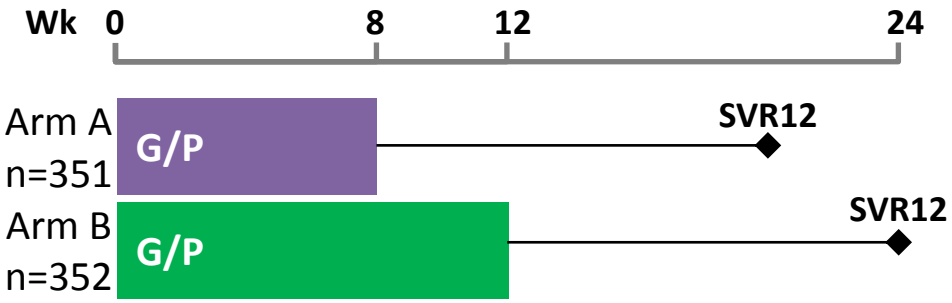
p <0.001 for superiority compared with prespecified 83% performance goal; error bars represent 95% confidence intervals.

Three drugs good, two drugs better
Non-nucleotide approach

- Dual therapy with:-

- Protease inhibitor
- NS5A inhibitor

ENDURANCE-1: Efficacy and safety of 8- vs 12-week treatment with Glecaprevir/Pibrentasvir in G1 patients



- Phase 3, randomized, multicenter, open-label study investigating 8- vs 12-week treatment with co-formulated GLE + PIB (G/P)
- G/P coformulated, dosed QD as 3x 100 mg/40 mg pills for total dose of 300 mg/120 mg
- Treatment-naive or -experienced G1 patients without cirrhosis and with or without HIV-1 coinfection

Zeuzem S, et al. AASLD 2016, Boston. #253

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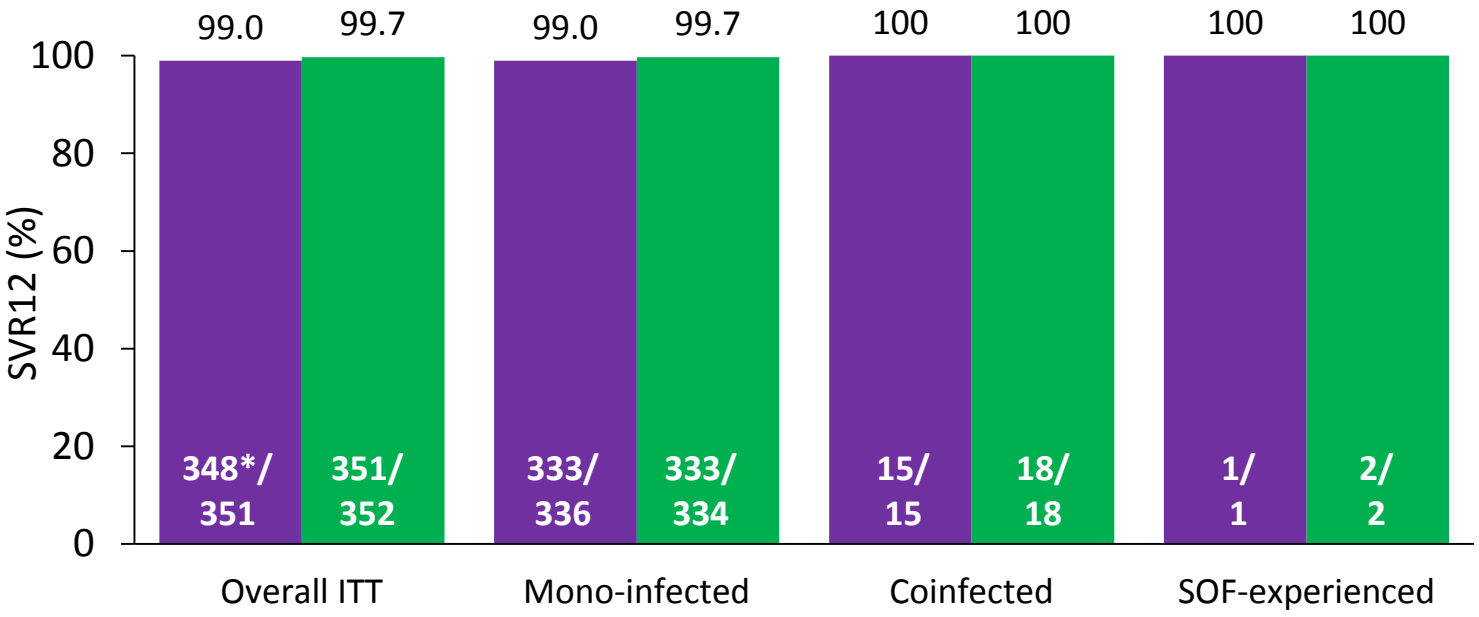


ITT population: All pts receiving study drug; none excluded

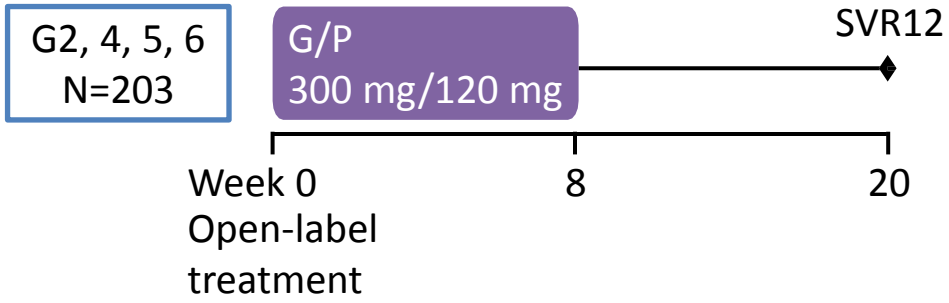
■ 8-wk

*1 pt in the 8-wk Tx arm experienced on-treatment virologic failure; 1 pt in the 8-wk tx arm d/c in Week 2 due to non-compliance; 2 pts, 1 in each tx arm, are missing SVR12 data

- All-oral, RBV-free G/P regimen can yield high SVR12 rates in 8 weeks for non-cirrhotic G1 patients, including those with HIV-1 coinfection

Zeuzem S, et al. AASLD 2016, Boston. #253

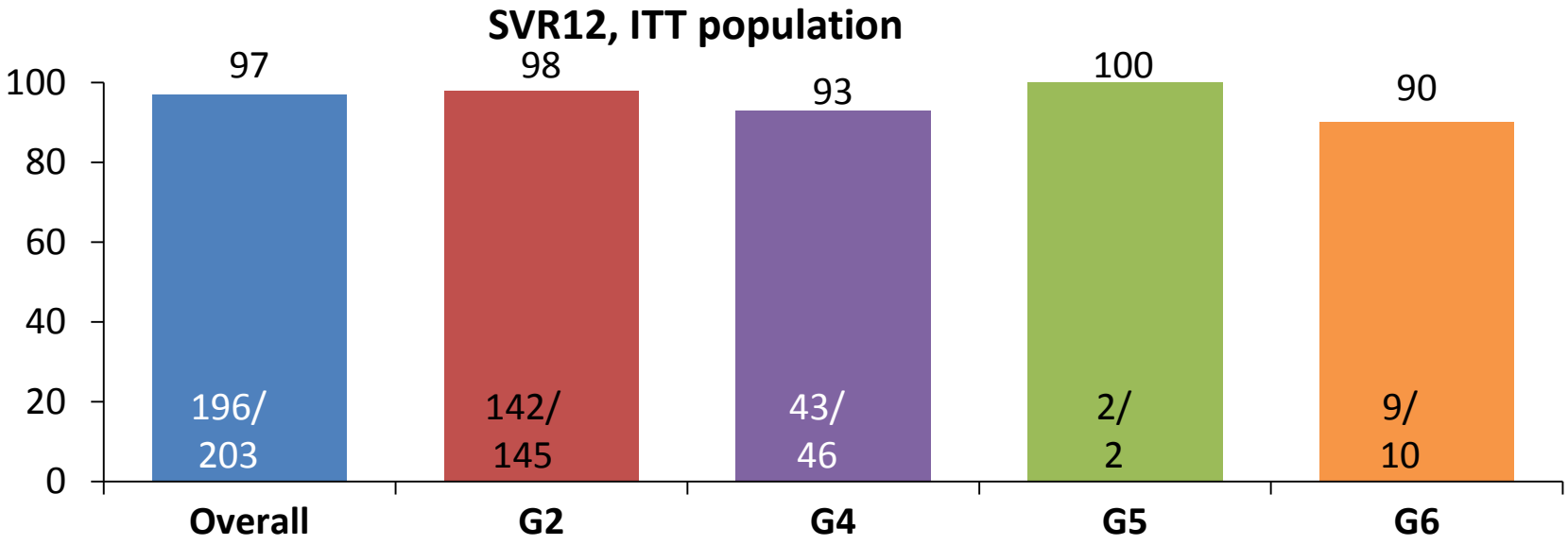
SURVEYOR-II, Glecaprevir/Pibrentasvir in G2, 4, 5, or 6 infection without cirrhosis



- Key inclusion criteria:
  - ≥18 years of age
  - BMI ≥18 kg/m^2
  - Chronic HCV G2, 4, 5, or 6 infection with HCV RNA >1000 IU/mL
  - Absence of cirrhosis documented by liver biopsy, transient elastography, or serum markers
  - HCV treatment-naive or treatment-experienced with IFN or pegIFN ± RBV or SOF + RBV ± pegIFN

Hassanein TI, et al. AASLD 2016, Boston. #LB-15

SURVEYOR-II, Glecaprevir/Pibrentasvir in G2, 4, 5, or 6 infection without cirrhosis

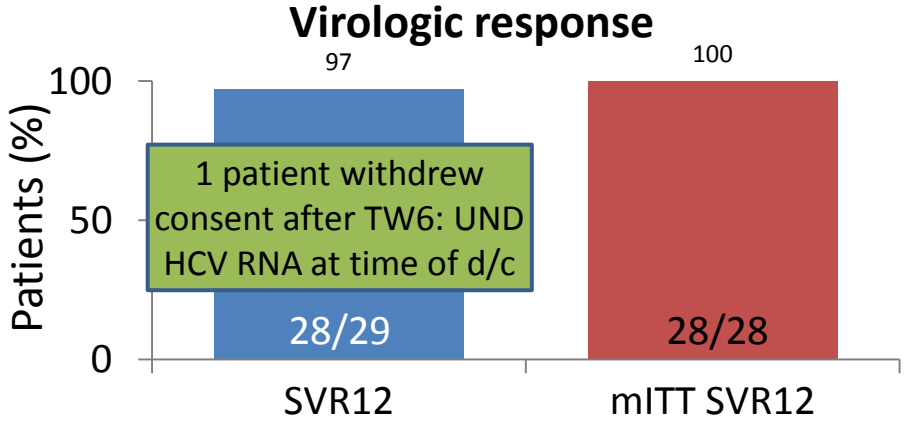


	Overall	G2	G4	G5	G6
Breakthrough	0	0	0	0	0
Relapse	2	2*	0	0	0
Discontinuation	2	1	1	0	0
Missing SVR12 data	3	0	2	0	1

- 8-week pan-genotypic regimen in easy-to-treat non-cirrhotic G2, 4, 5, 6 patients

Hassanein TI, et al. AASLD 2016, Boston. #LB-15

High SVR rates with ABT-493 + ABT-530 co-administered for 8 weeks in non-cirrhotic patients with HCV G3 infection

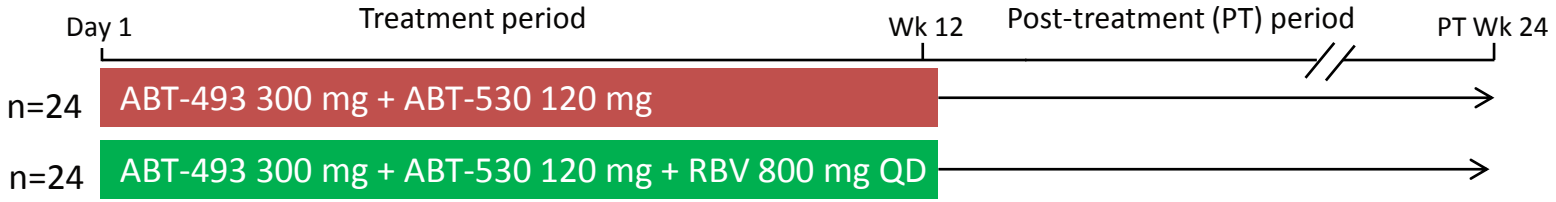


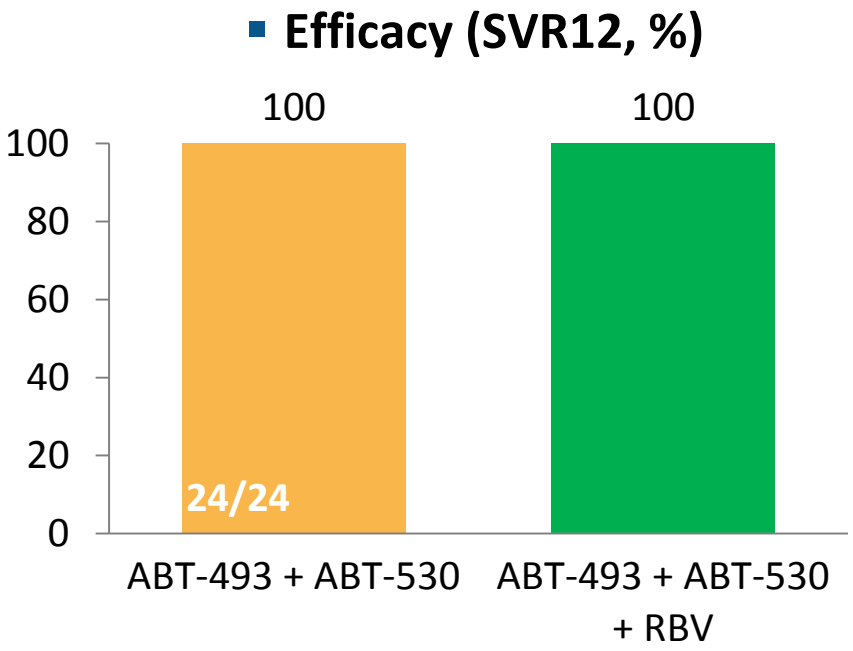
- No virologic failures
- No AEs leading to d/c, no SAEs
- Common AEs: Headache (17%), fatigue (10%), diarrhea (10%), insomnia (10%), oropharyngeal pain (10%), toothache (10%)
- No Grade ≥3 laboratory abnormalities

Muir AJ, et al. EASL 2016, Barcelona. PS098

ABT-493 and ABT-530 ± RBV in treatment-naive HCV G3 patients with cirrhosis

- **Aim:** Evaluate ABT-493 + ABT-530 in difficult-to-treat treatment-naive G3-infected patients with cirrhosis and assess whether RBV improves response rates (SURVEYOR-II)





Kwo P, et al. EASL 2016, Barcelona. #LB01

Next generation regimes

- Expected soon

- 2 or 3 drug 8 week regimens for all genotypes

- Sof/led OR G/P for G1
- Sof/vel/vox OR G/P for all others

HCV – a dead virus

- We can cure ALL patients with HCV with simple tablet based, side effect free regimens

HCV

- The disease and its impact
- Viro-babble
- The politics

HCV - Politics

- The drugs are expensive (but getting cheaper)
- NICE said ‘prioritise’ therapy
- NHSE set up treatment networks with treatment targets (run rates)

HCV - Politics

- The drugs are expensive (but getting cheaper)
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- NHSE set up treatment networks with treatment targets (run rates)

This year 10,016 next year 12,500

The Numbers

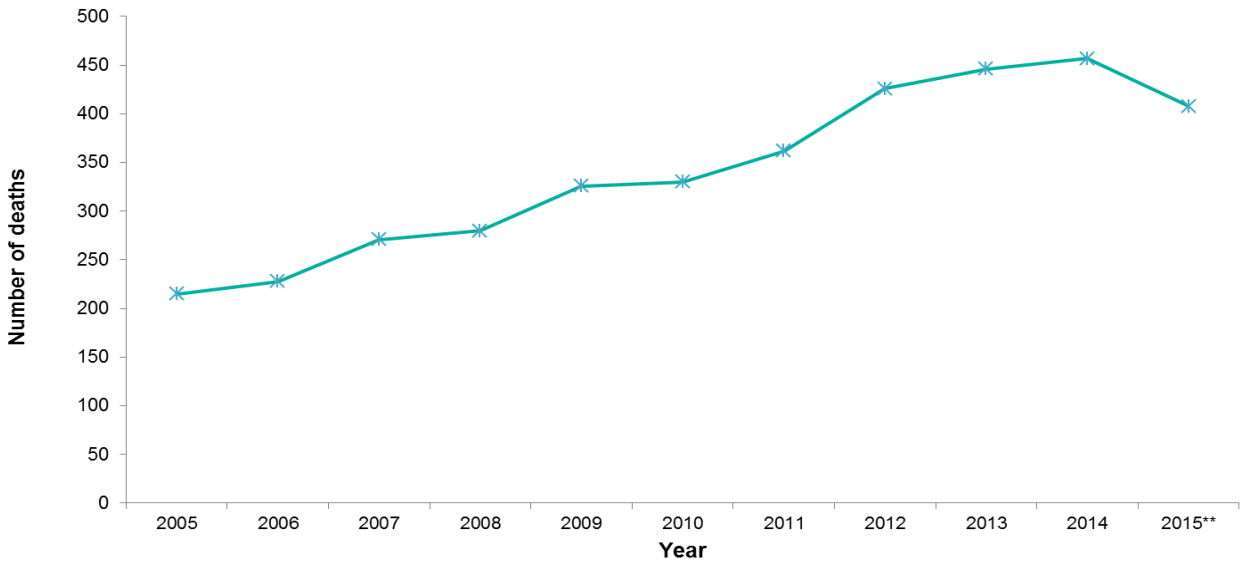
- 22 networks – 2 brand new to therapy
- Each network MUST have out-reach

- 100 treating hospitals

- 7206 patients treated (April-January)

Specialist Commissioning for HCV OUTCOME

Figure 5. Deaths from ESLD* or HCC in those with hepatitis C mentioned on the death certificate in the UK: 2005 to 2015

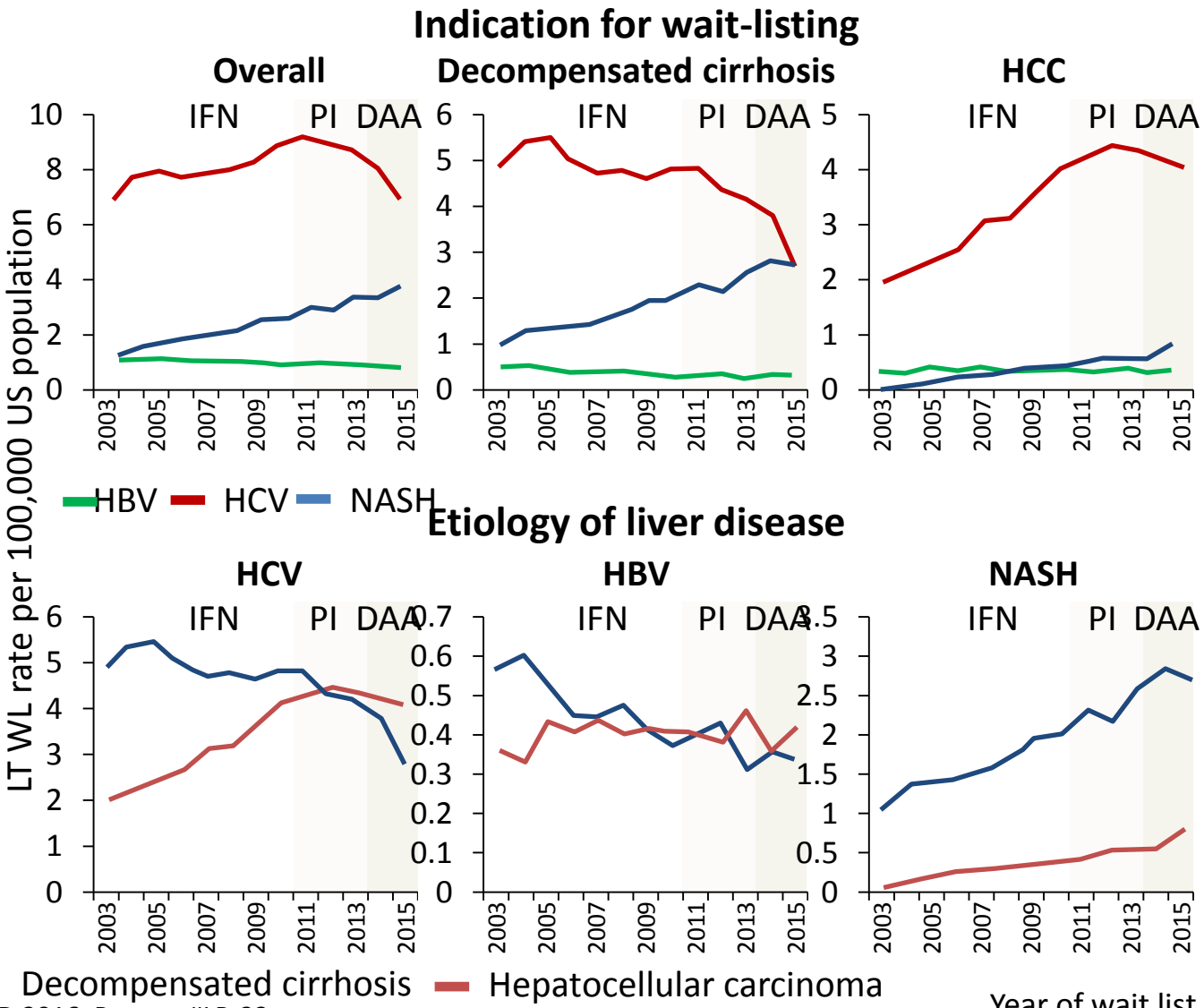


* Defined by codes or text entries for ascites, bleeding oesophageal varices, hepato-renal syndrome, hepatic encephalopathy or hepatic failure.
**2015 data for England and Wales is provisional and missing for Northern Ireland

Data source: Office for National Statistics for England and Wales; Deaths registration data as supplied by NISRA for Northern Ireland; Health Protection Scotland in association with the Information Services Division

Reduction in liver transplant wait-listing in the era of DAA therapy

Annual standardized incidence rates of LT wait-listing per 100,000 US population



Flemming JA, et al. AASLD 2016, Boston. #LB-23

The Numbers

- 22 networks – 2 brand new to therapy
- Each network MUST have out-reach

- 100 treating hospitals

- 7206 patients treated (April-January) need 10,000

  - We are running out of patients!

HCV Therapy 2017-18

- The ODNs have to find patients – they lose money if they fail
- Drug users, the homeless are ‘easy to find’
- Your ODNs will be begging for your patients

HCV Therapy 2017-18

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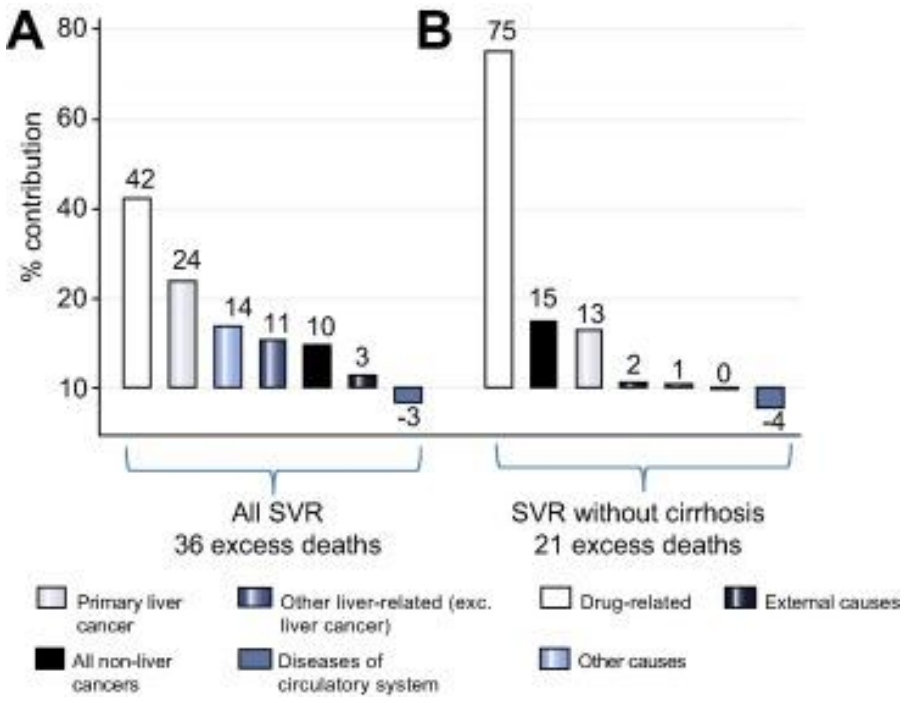
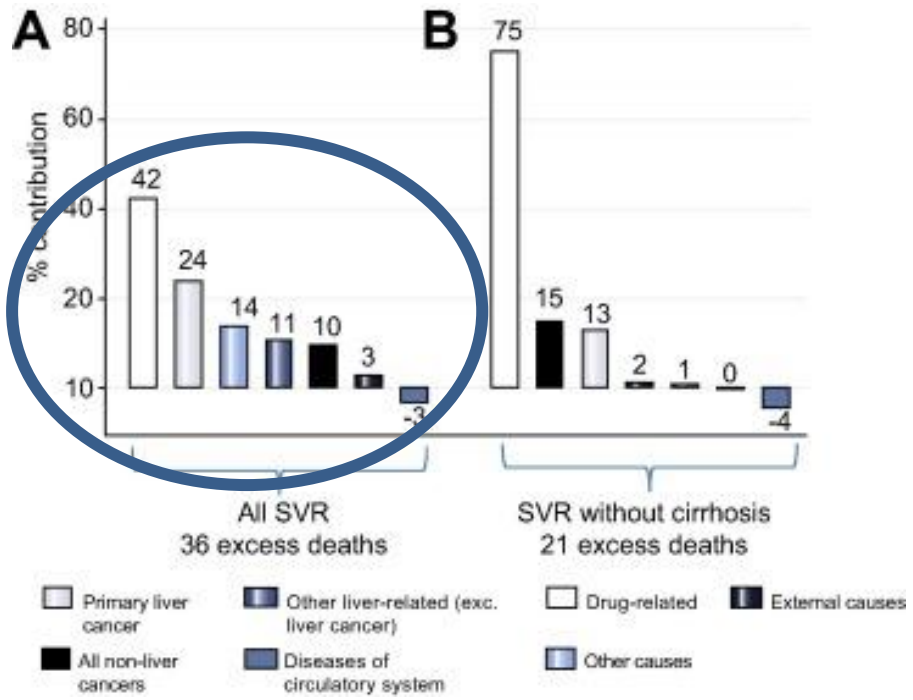
- BUT……..

HCV –Cure
How do people benefit?



Innes H et al Mortality in hepatitis C patients who achieve SVR J Hepatology 2016;66:19

HCV – Towards elimination
How do people benefit?



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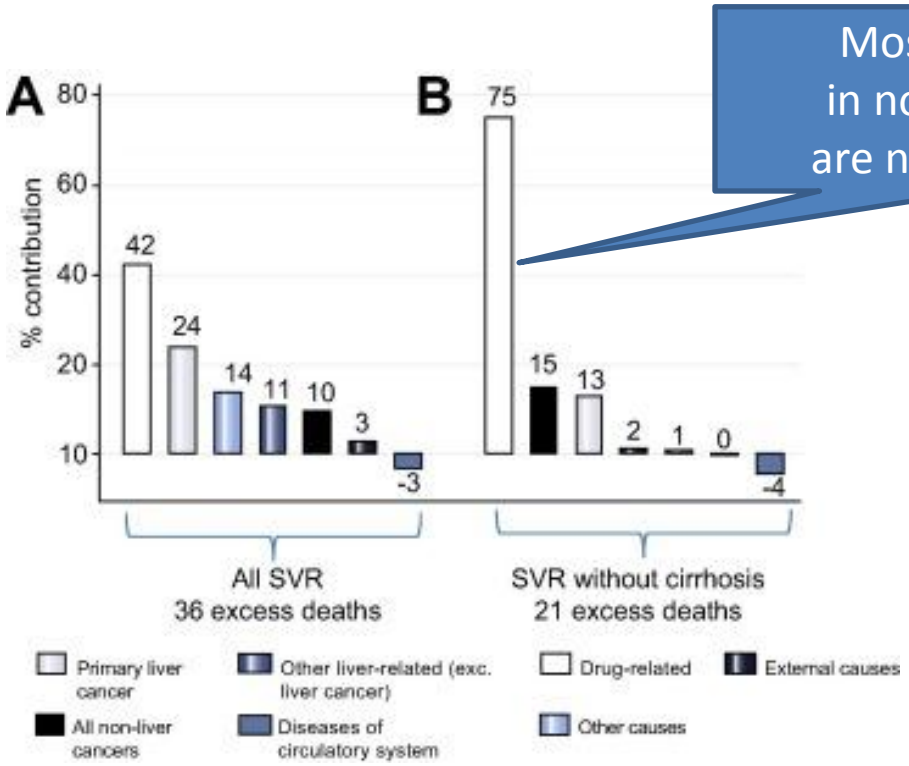

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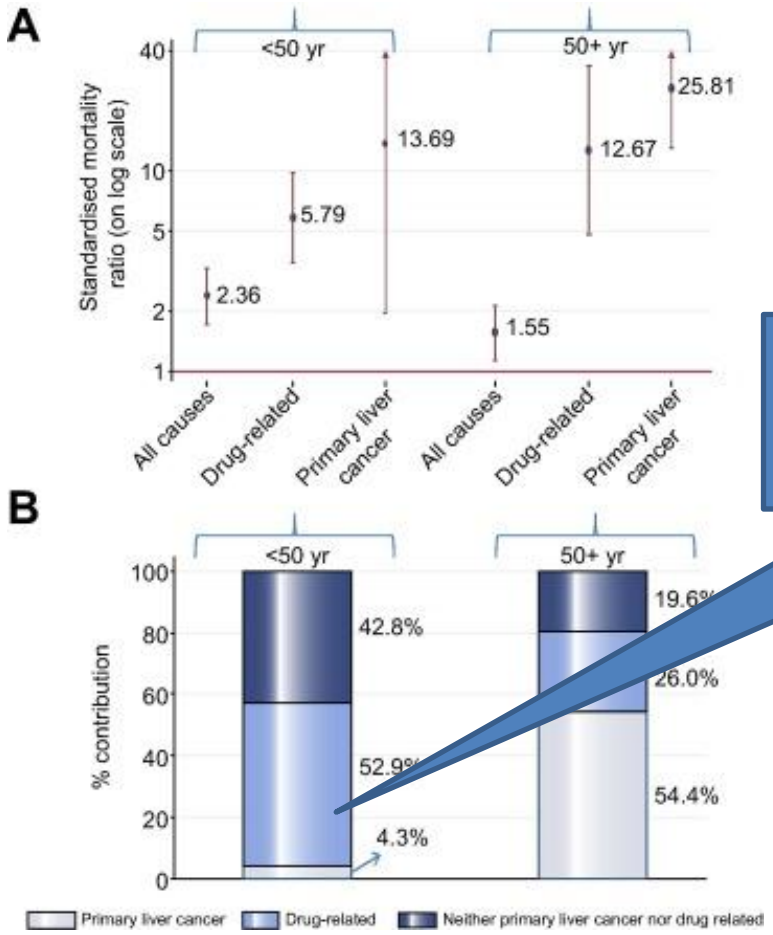


Most excess deaths
in young SVRs
are not related to HCV

Curing HCV in the young

- Curing young people with HCV does not return their life expectancy to normal

- (Without a control group we do not know the full benefits)

Curing HCV in the young

- Curing young people with HCV does not return their life expectancy to normal
- (Without a control group we do not know the full benefits)
- We need to take advantage of the ‘entry to care’ from HCV drugs

Hawthorne Effect

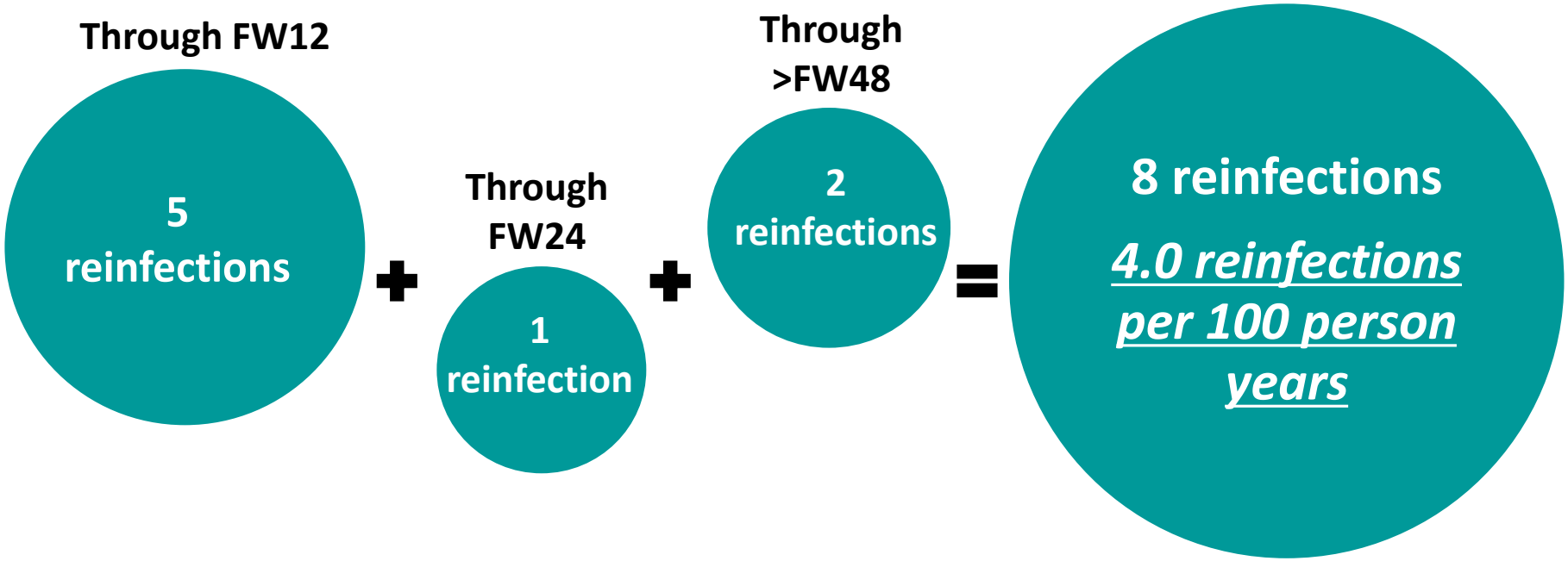
- Benefits of engaging with health care systems goes beyond the treated disease

HCV in Drug Users

- Therapy for HCV is very effective in drug users

- Re-infection is not a major issue
- (Provided needle exchange services etc are in place)

Incidence of reinfection



From End of Treatment Through Observation Visit 1		
• 8 reinfections	• 197.5 person years	• 4.0 reinfections per 100 person years (95% CI: 1.7, 8.0)
From End of Treatment Through Observation Visit 1 (Includes only those patients with persistent HCV RNA)		
• 5 reinfections	• 199.0 person years	• 2.5 reinfections per 100 person years (95% CI: 0.8, 5.9)

In summary

- We have fantastic curative therapies for HCV
- Treaters have massive financial incentives to find and treat patients

What to do now

- Contact your local HCV ODN lead and see how you can work together to treat your patients

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- Contact your local HCV ODN lead and see how you can work together to treat your patients

BUT

- Use this as an opportunity to engage and help

- A Hep C Free Death is not a good outcome