Tackling Liver Disease Progress at last!

Graham R Foster
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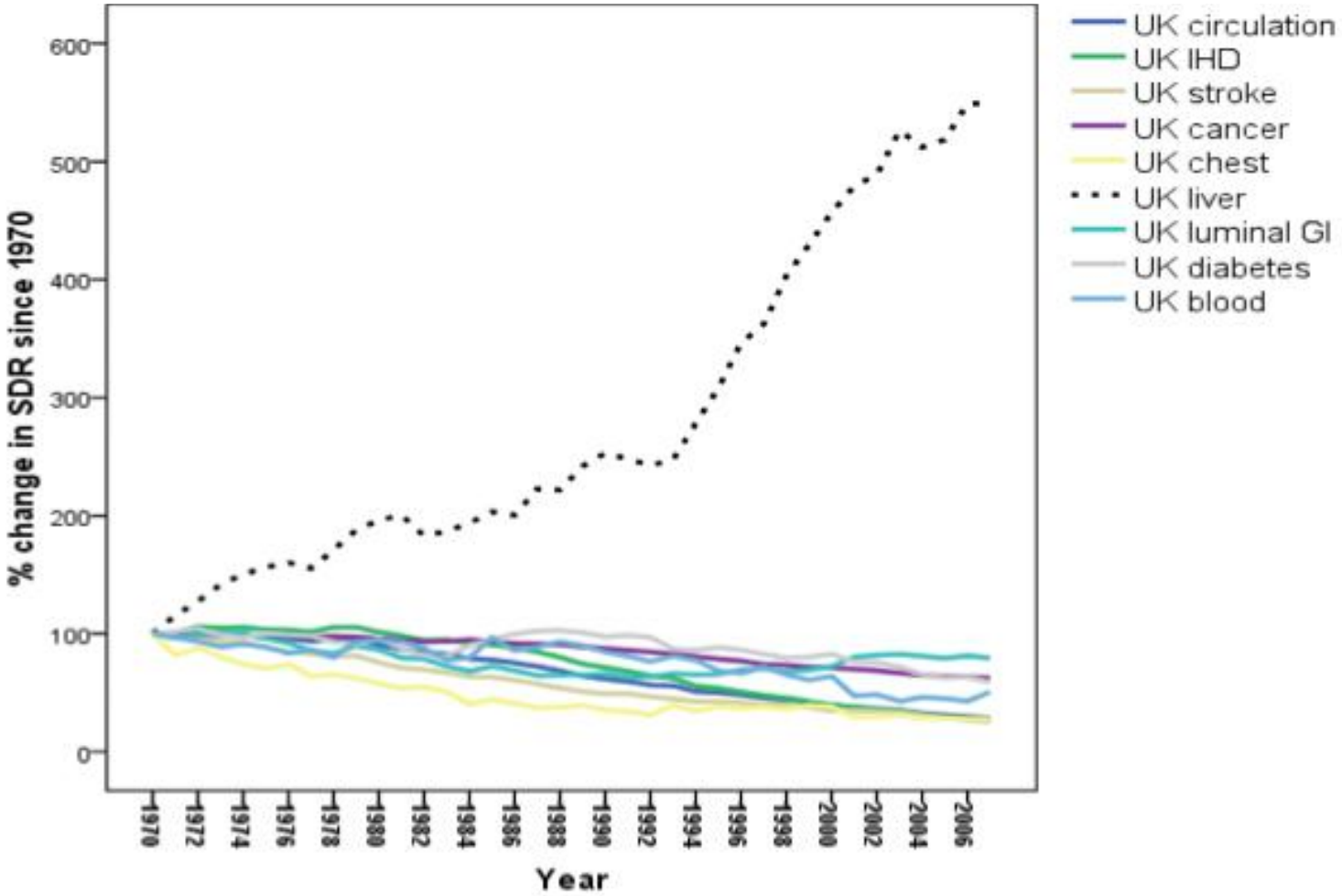
UK Standardised death rates (<65 years)



LIVER AND DIGESTIVE HEALTH -
UCLPartners

Liver Mortality in the UK

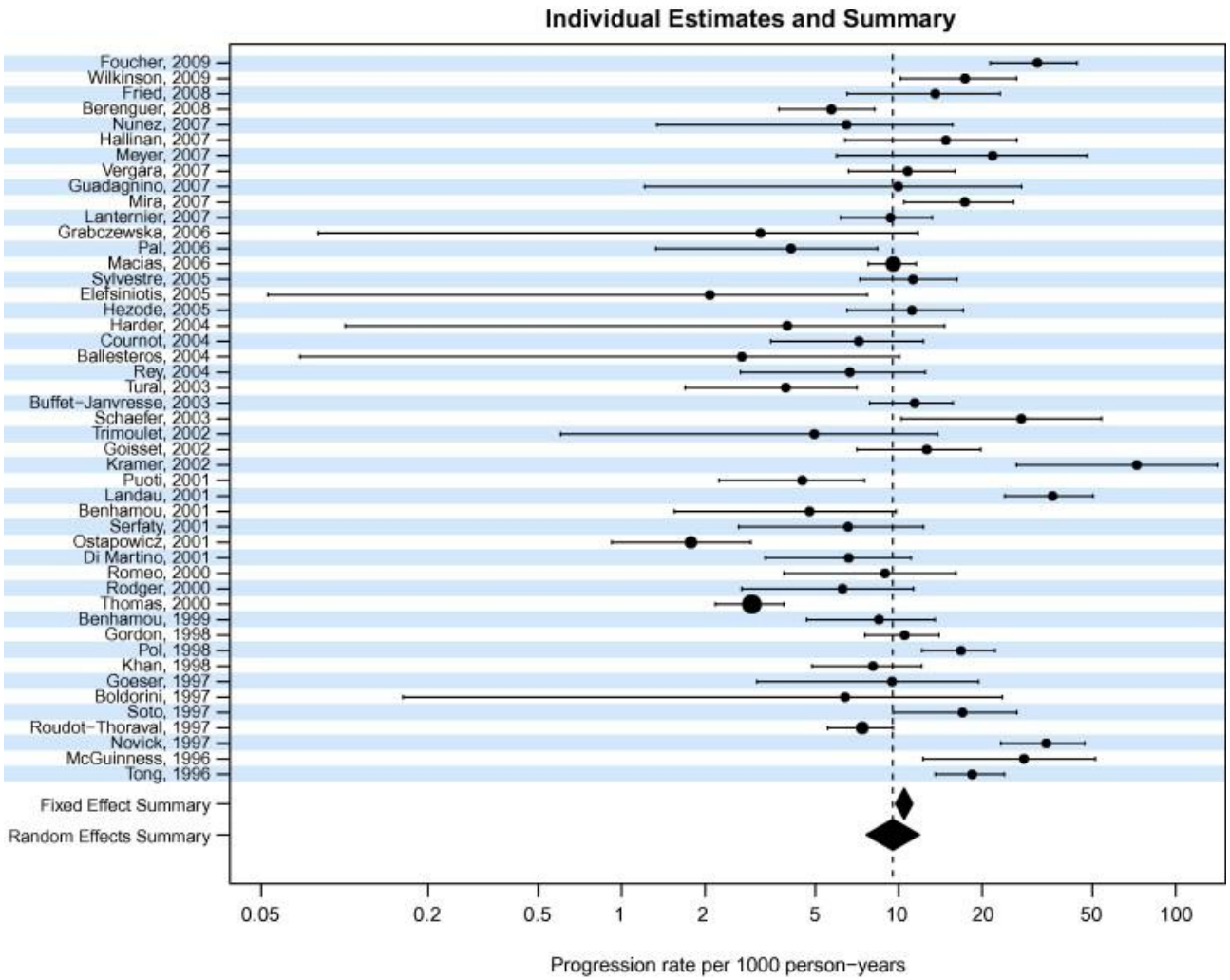
- A large proportion of liver mortality is due to alcohol (minimum pricing will fix this)

- There is a growing mortality from HCV

Impact of HCV in Injectors

- HCV places a large burden on injectors

HCV and Cirrhosis



Baptiste et al J Hep 2010

HCV and Cirrhosis

- 8.1 per 1000 patient years will develop cirrhosis
- 14.8% have cirrhosis after 20 years

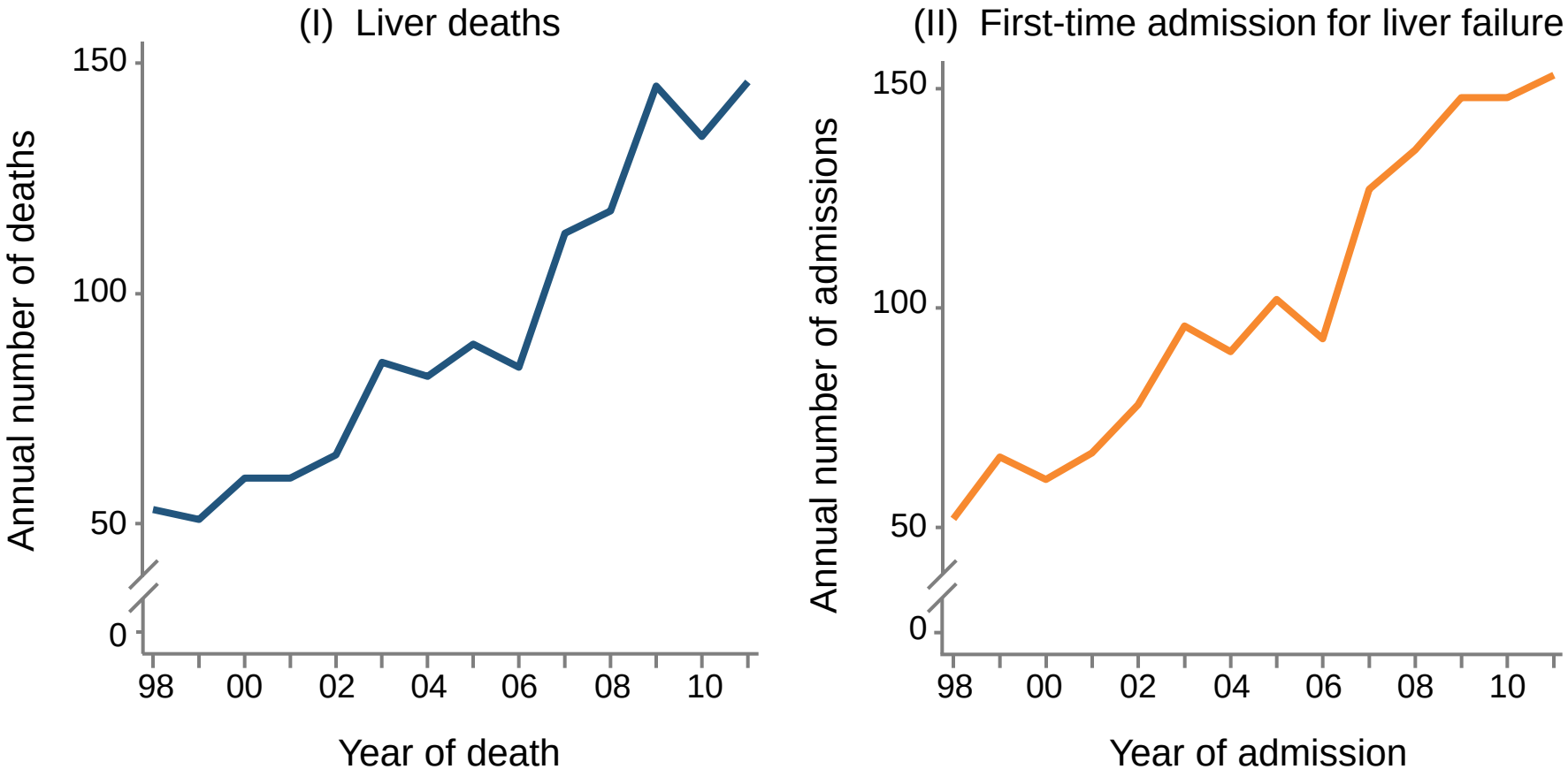
What happens when you have cirrhosis ?

- Annual rate of:-

- Death/transplantation = 4.58%
- Decompensation = 6.37%
- Liver cancer = 3.66%

Alazawi et al AP&T 2010

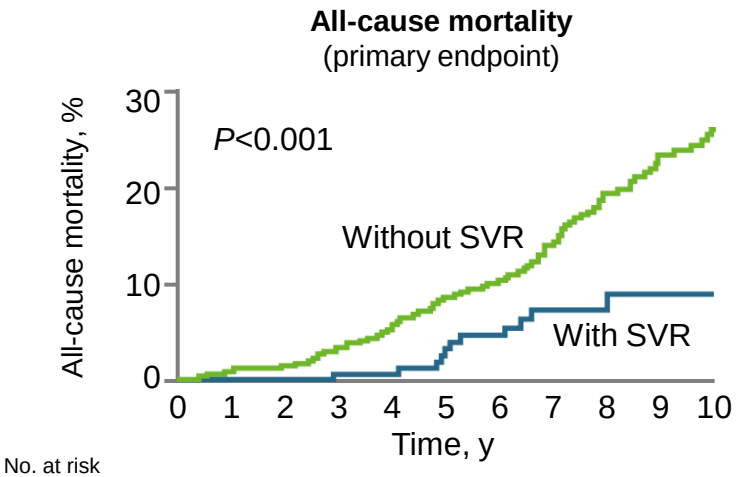
Liver deaths and first time liver failure among persons with HCV in Scotland, 1998–2011



Data on hospitalisations were obtained via record-linkage of Scotland's National Hepatitis C Diagnoses Database to the national database on hospital admissions

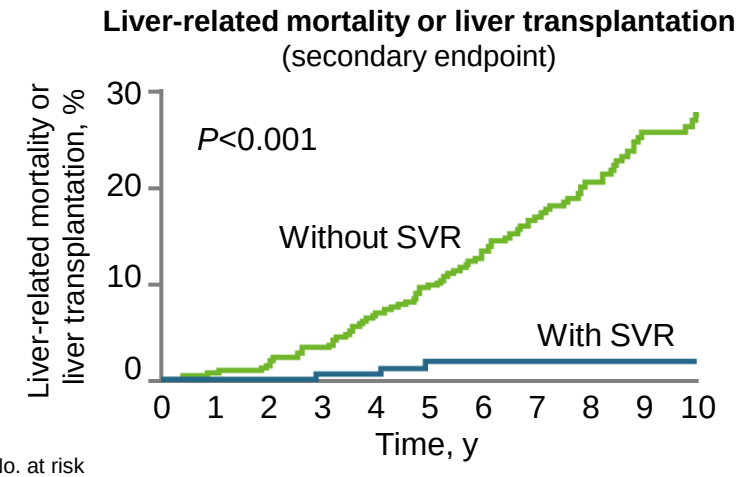
Adapted from Health Protection Agency Hepatitis C in the UK (2013)
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139502302

Effective treatment reduces the impact of cirrhosis



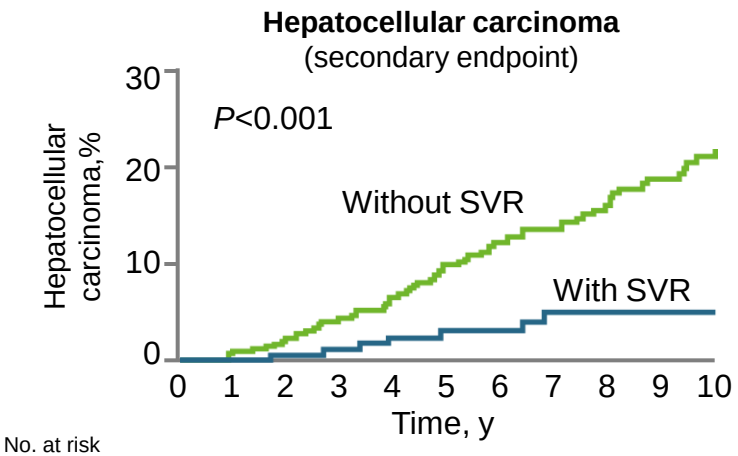
No. at risk

Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28



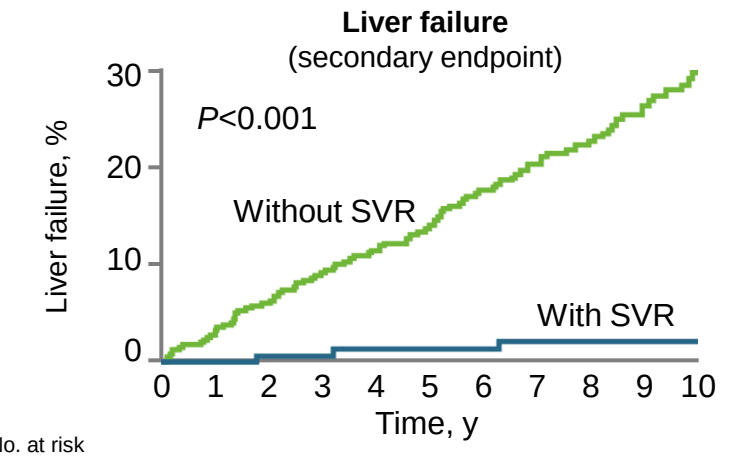
No. at risk

Without SVR	405	392	380	358	334	305	277	229	187	146	119
With SVR	192	181	168	162	155	144	125	88	56	40	28



No. at risk

Without SVR	405	390	375	349	326	294	269	229	191	151	122
With SVR	192	181	167	161	152	142	124	86	54	39	27



No. at risk

Without SVR	405	384	361	337	314	288	259	216	184	143	113
With SVR	192	180	166	160	152	141	123	88	56	40	28

International multicentre chart review of 530 patients with Ishak score 4–6 receiving INF-based therapy between 1990 & 2003

Adapted from van der Meer AJ et al. JAMA 2012;308:2584–93

Liver Mortality

- Mortality from HCV is rising rapidly
- Effective therapy aborts the epidemic

Liver Mortality

- Mortality from HCV is rising rapidly

- Effective therapy aborts the epidemic

- BUT –
- Current therapy is with interferon and ribavirin

Treating Hard to Reach Groups

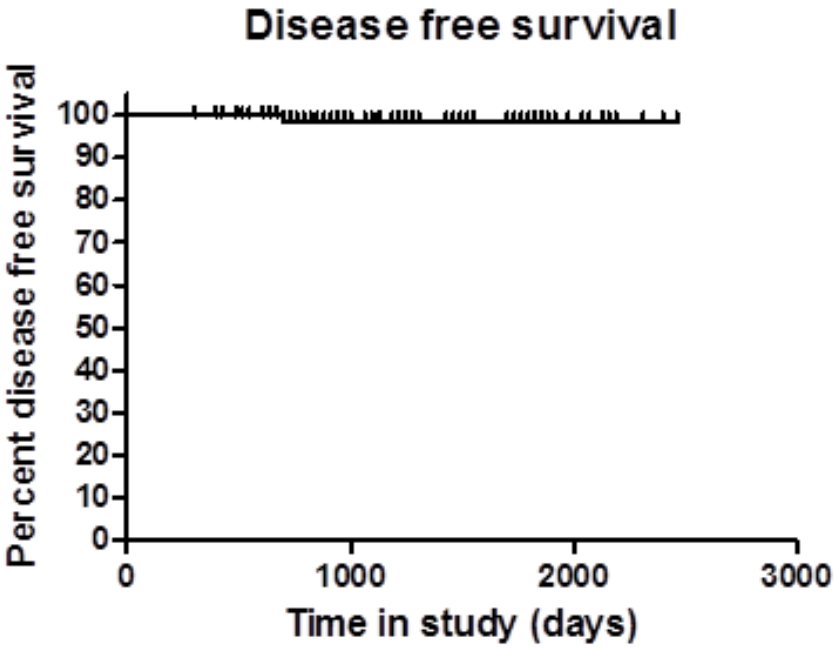
- Success is heavily influenced by nature of the clinic
- Clinical teams are very important

The East London Model

- Blood Borne Virus (BBV) Nurse led
- Hub and spoke model
  - 3 central Specialist Addiction Units
  - 10 outreach clinics
- Monthly consultant led clinic in SAU to decide on treatment

Disease free survival

- 55% (N=83) of patients achieved SVR
- 54% (N = 45) had repeat HCV RNA testing after completion of treatment
- One reinfection occurred 14 months after completed treatment



HCV in Hard to Reach Groups

- Therapy CAN be given
- People can be cured (and stay cured)

HCV in Injectors

- Therapy CAN be given
- People can be cured (and stay cured)
- BUT – what proportion are treated?

HCV in Hard to Reach Groups
Is there a better way?

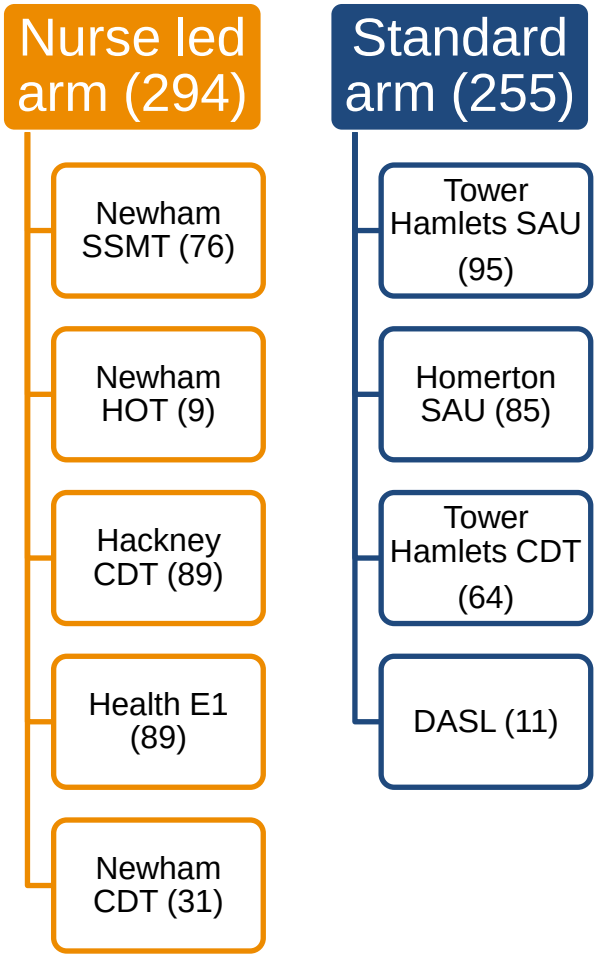
- At present therapy is supervised by doctors
- Nurses have day-to-day engagement with the patients
- Does nurse led care improve uptake?

Injecting drug users

- Randomised study of ‘nurse-led’ vs ‘standard therapy’ for active injectors

Kunkel J et al. Poster presented at BASL 2013

Cluster randomised trial: the clusters



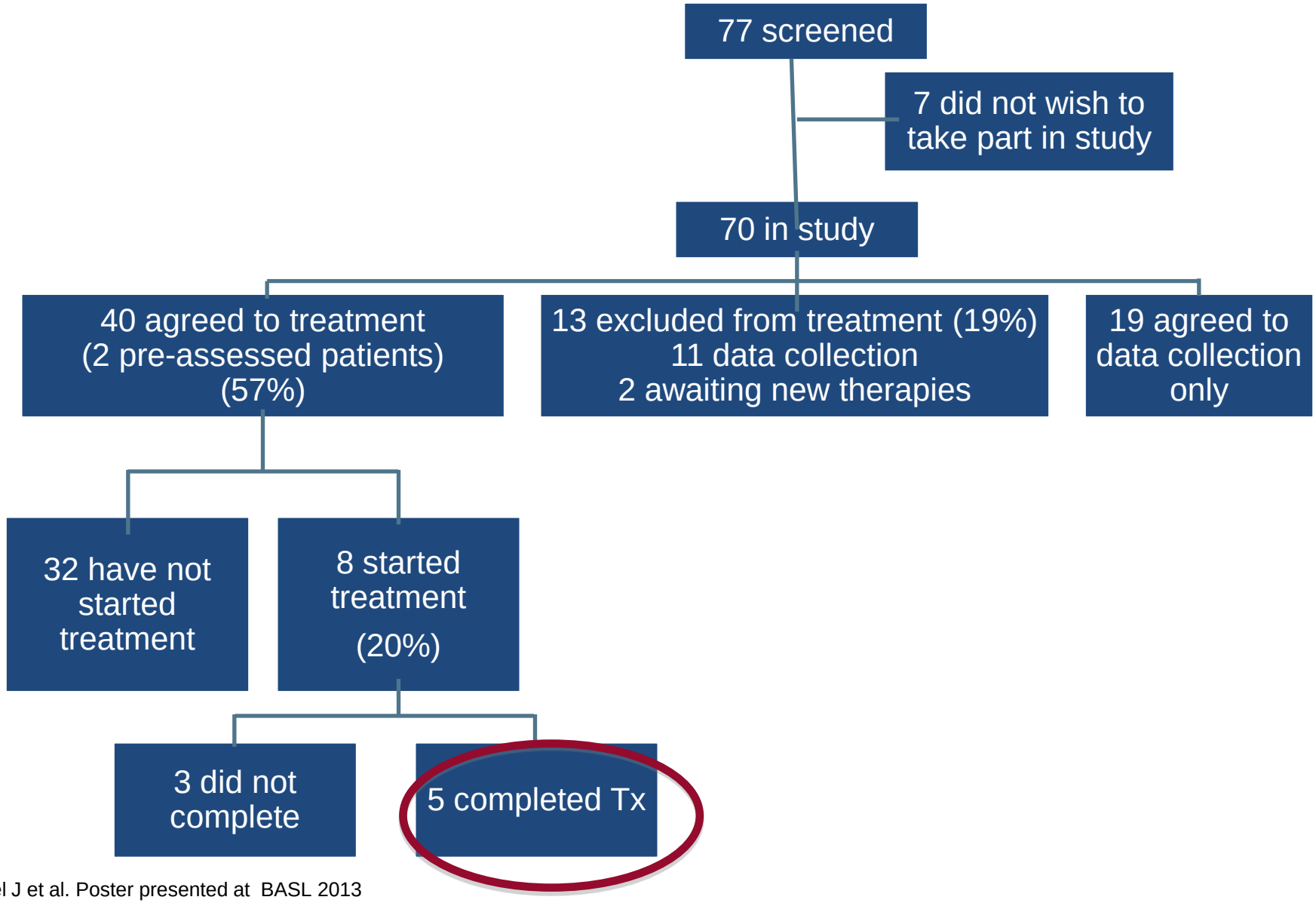
Kunkel J et al. Poster presented at BASL 2013; unpublished data provided by Prof Graham Foster

Exclusion criteria for nurse-led arm

- Those who wish to receive consultant-led care
- Cirrhosis of the liver – blood test, imaging or liver biopsy evidence
- Anaemia (low red cells) Haemoglobin <12
- Thrombocytopenia (low platelet count) <150
- Lymphopenia (low white cells)< 3
- Active infection of any kind including HIV or HBV co-infection
- Serious psychiatric disorders in the last 2 years
- Uncontrolled asthma, chronic obstructive pulmonary disease, ischaemic heart disease, renal failure, heart failure, serious neurological problems, active autoimmune disease, significant dermatological condition
- Pregnancy or participants who are planning to become pregnant during or up to 6 months after treatment

Kunkel J et al. Poster presented at BASL 2013; unpublished data provided by Prof Graham Foster

Results – SOC arm



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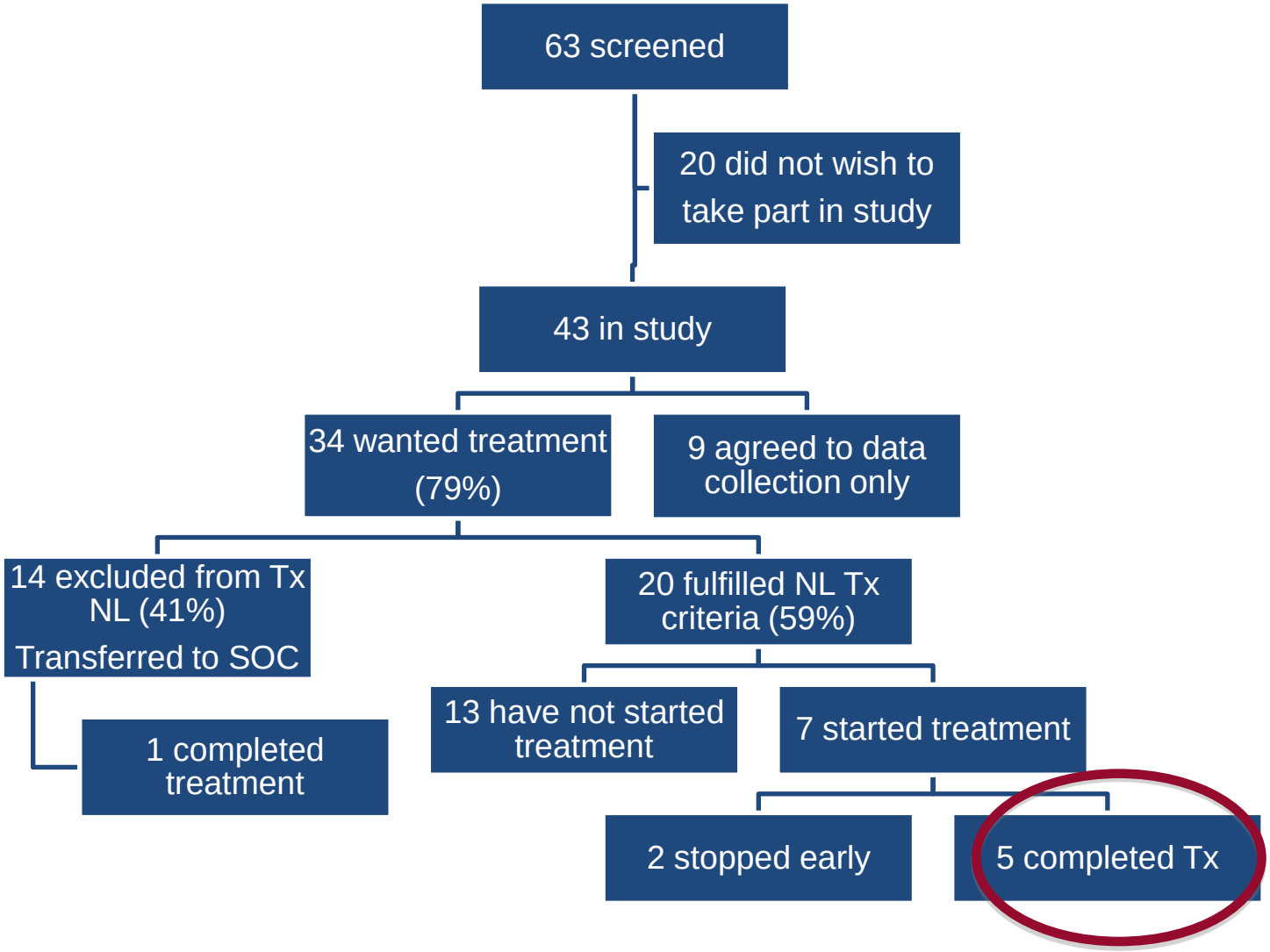

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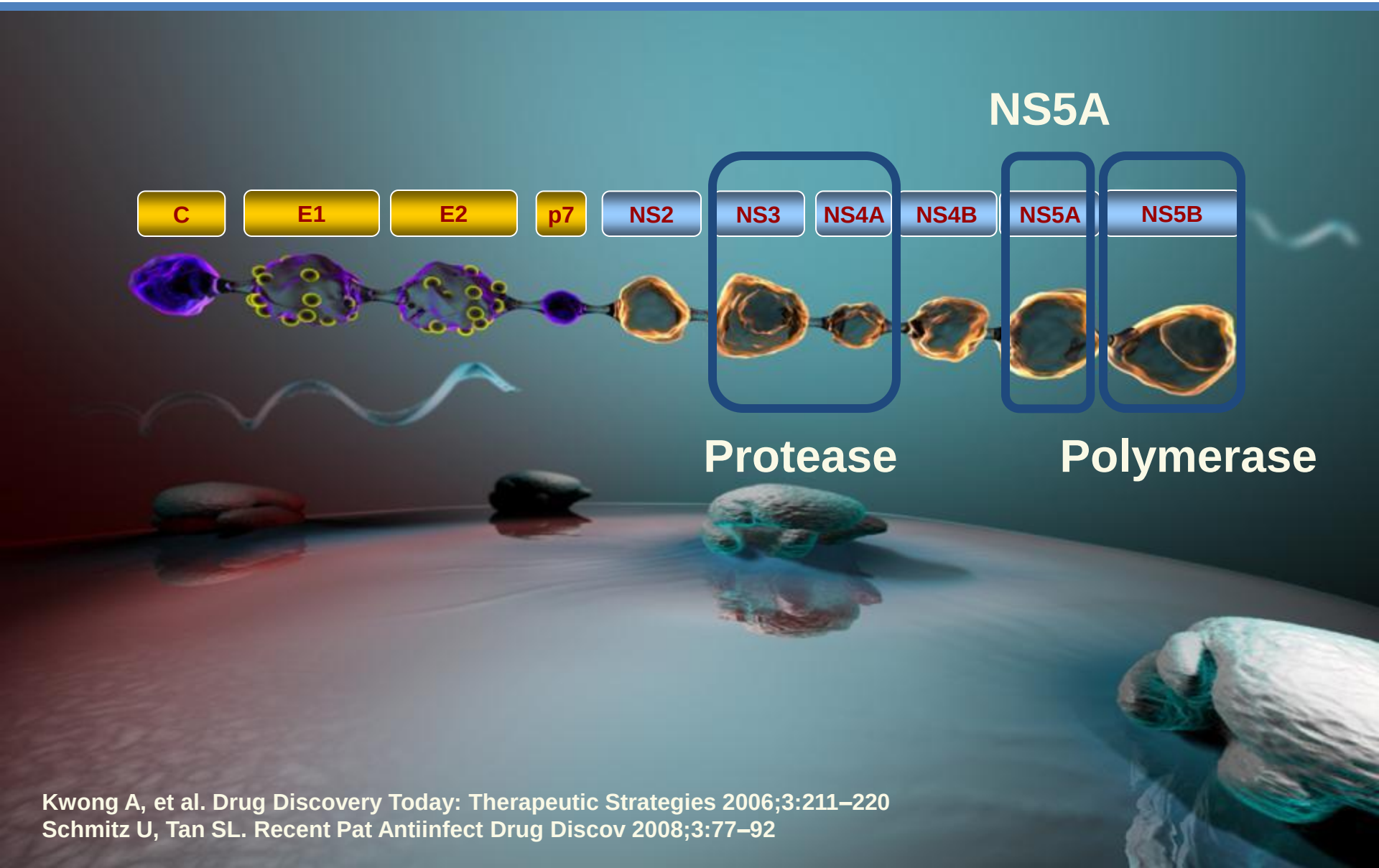
Accessing Hard to Reach Groups

- No matter how easy we make this – homeless injectors are not going to take interferon

- We need better drugs

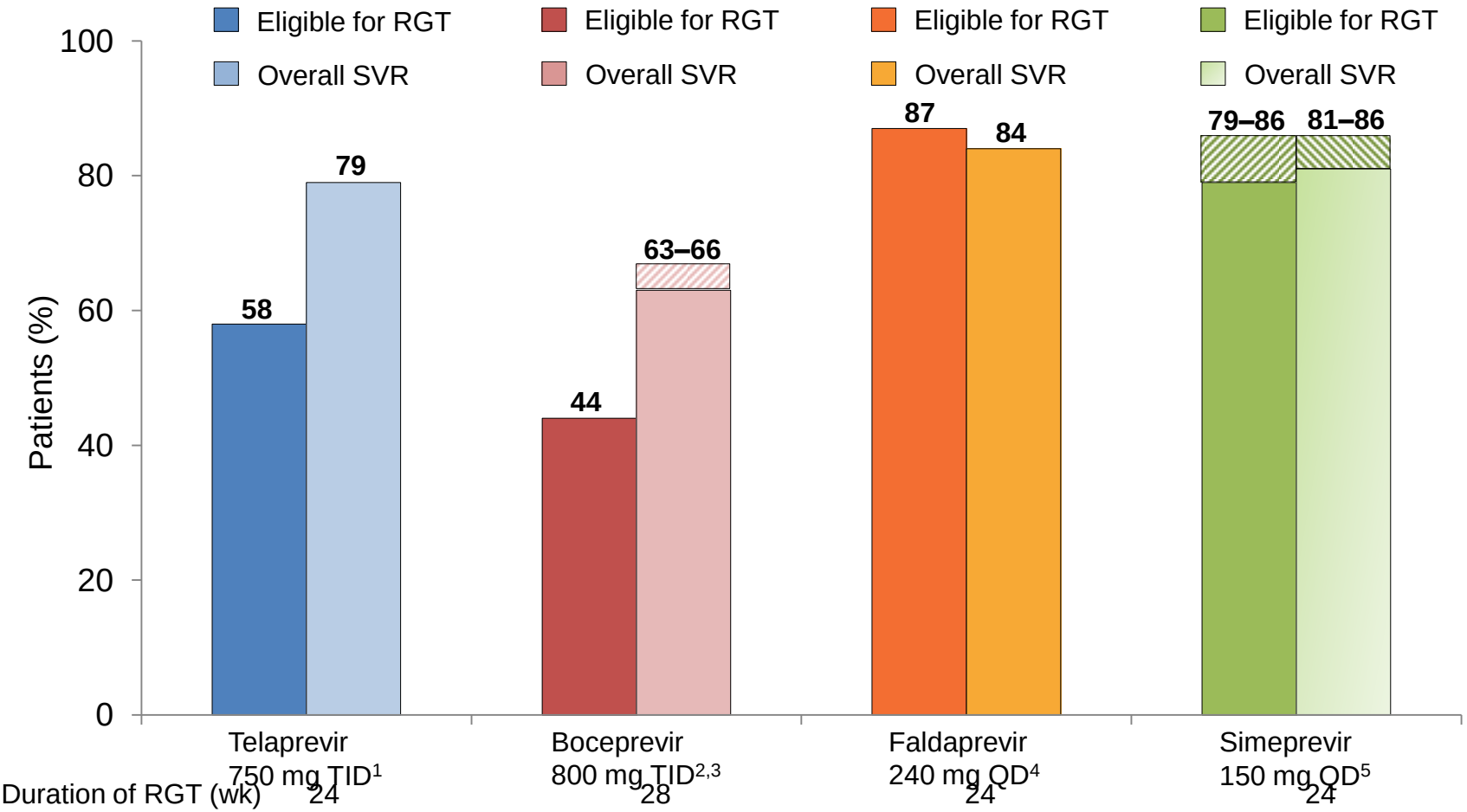
Specific targets for HCV treatment: protease, polymerase and NS5A inhibition



Kwong A, et al. Drug Discovery Today: Therapeutic Strategies 2006;3:211–220
Schmitz U, Tan SL. Recent Pat Antiinfect Drug Discov 2008;3:77–92

New Protease Inhibitors

New Protease Inhibitors (With Peg + Riba)



Results are for separate trials for each compound, not head-to-head studies, in treatment-naïve patients also receiving PegIFN/RBV
Hatched regions indicate ranges of results

QD, once daily; RGT, response-guided therapy; SVR, sustained virological response; TID, three times daily

1. Incivo EU SmPC 2011; 2. Victrelis EU SmPC 2011;
3. Poordad F, et al. N Engl J Med 2011;364:1195–1206;
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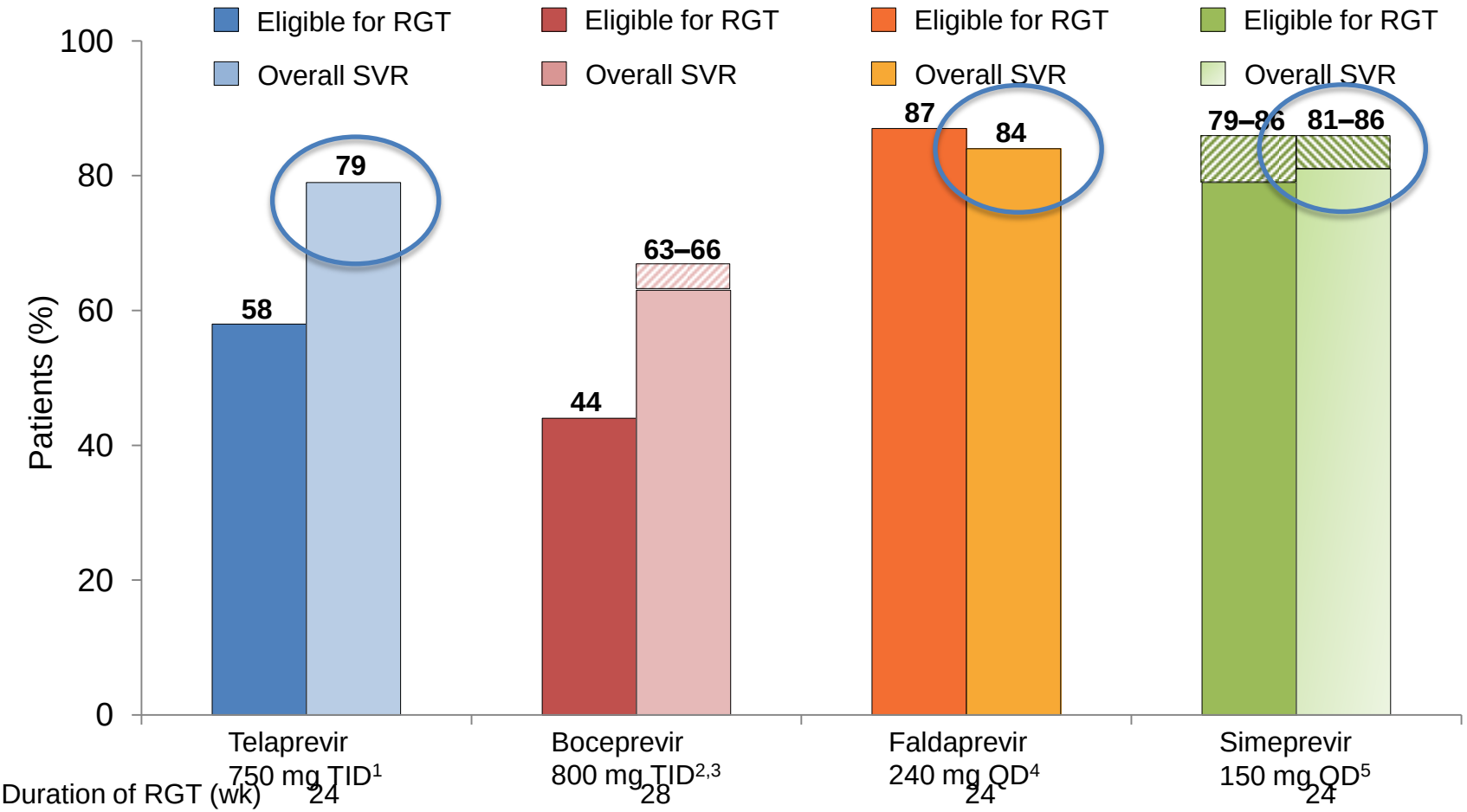

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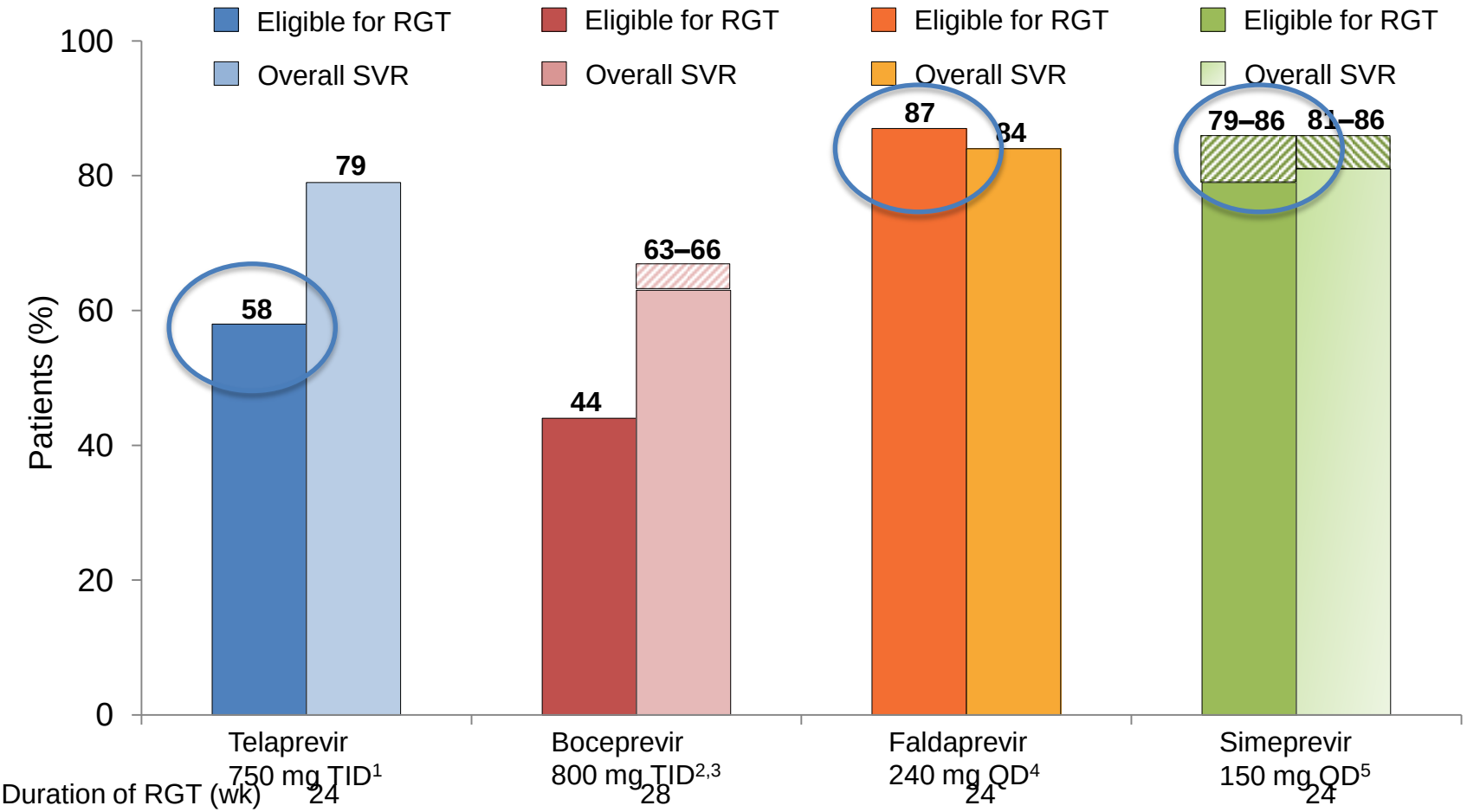

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New protease inhibitors

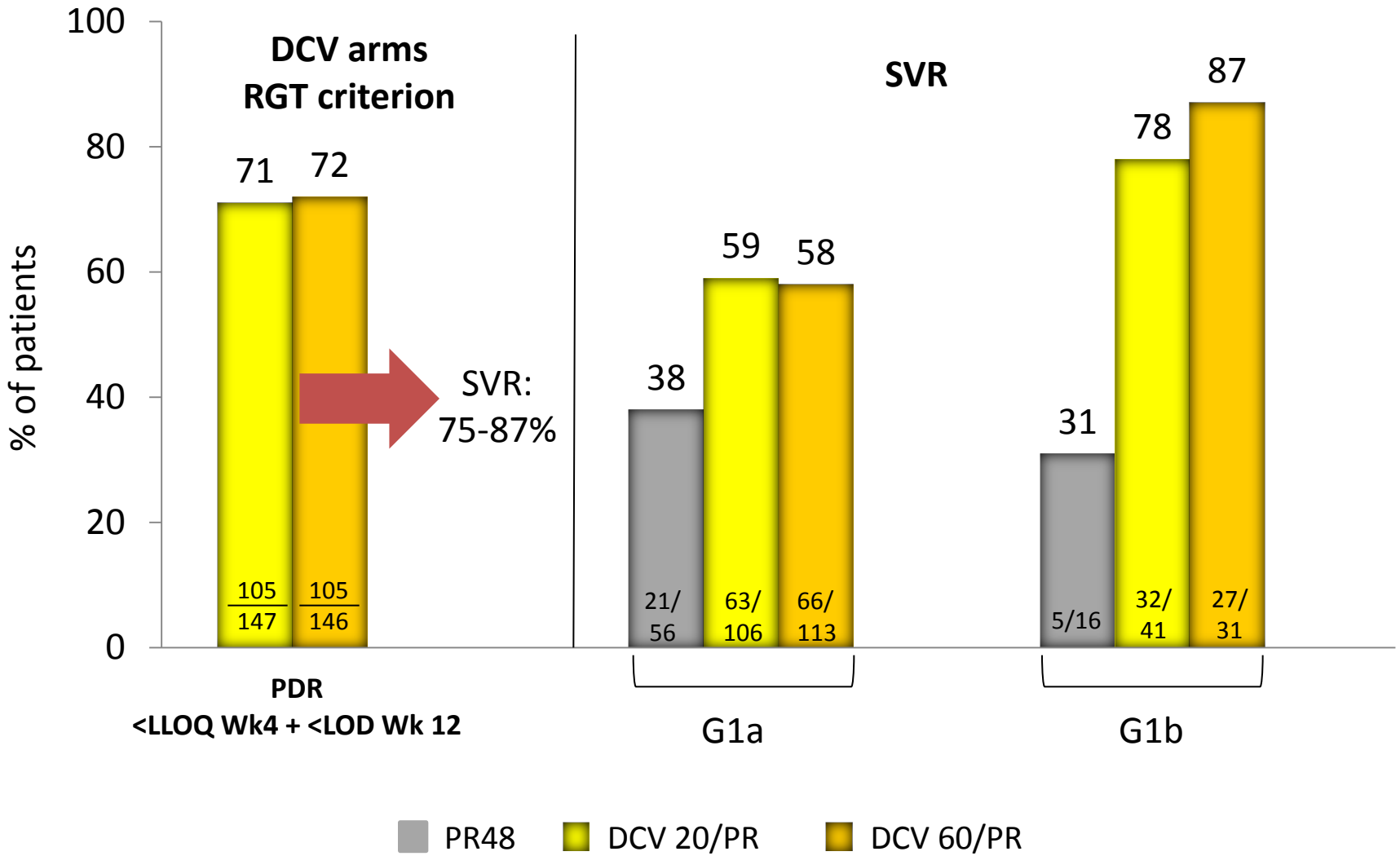
Restricted to the US viral strains

Still need interferon

(Not as good as they pretend they are)

NS5A Inhibitors

Daclatasvir + PR



PDR: protocol defined response

Hézode et al, AASLD 2012 (SVR 12 analysis), abstract 755; TVR EU SmPC

NS5A Inhibitors

Quirky

Large variation in efficacy

Good to work with

NS5B – Non Nucleotides

NS5B – Non Nucleotides

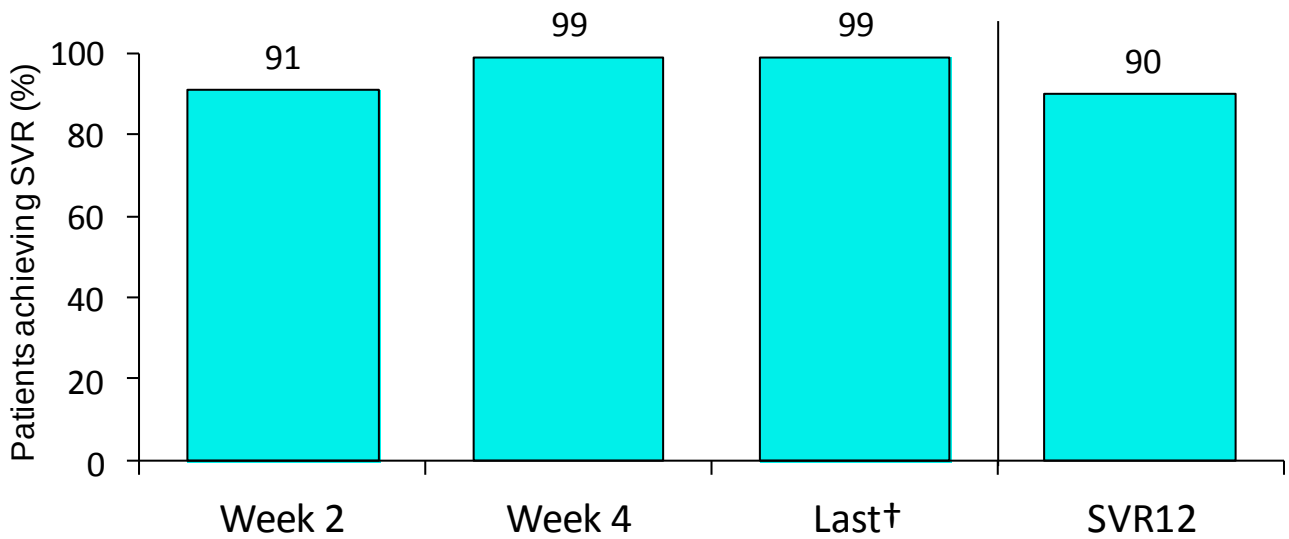
Very unpredictable

Generally G1 specific

Nucleotides

Sofosbuvir with PEG-IFN + RBV

- NEUTRINO Phase III trial
  - Sofosbuvir plus PEG-IFN + RBV* for **12 weeks**
  - Treatment naïve, GT1 (89%), 4, 5 or 6 (N=327)
    - 17% had compensated cirrhosis
  - Primary endpoint: SVR12



*Dose administered according to body weight
†Last observed measurement

Lawitz et al. N Eng J Med 2013;368:1878–87

Nucleotides

Fast
Effective
Cures all strains
Side effect free

(Too good to be true)

Interferon Regimes

6-12 months

- PI + Peg Riba
- Old PI (dirty, but cheap)
- New PI (clean, but expensive, ‘quirky’)

3 months

- Sofosbuvir - + Peg Riba

  Expensive

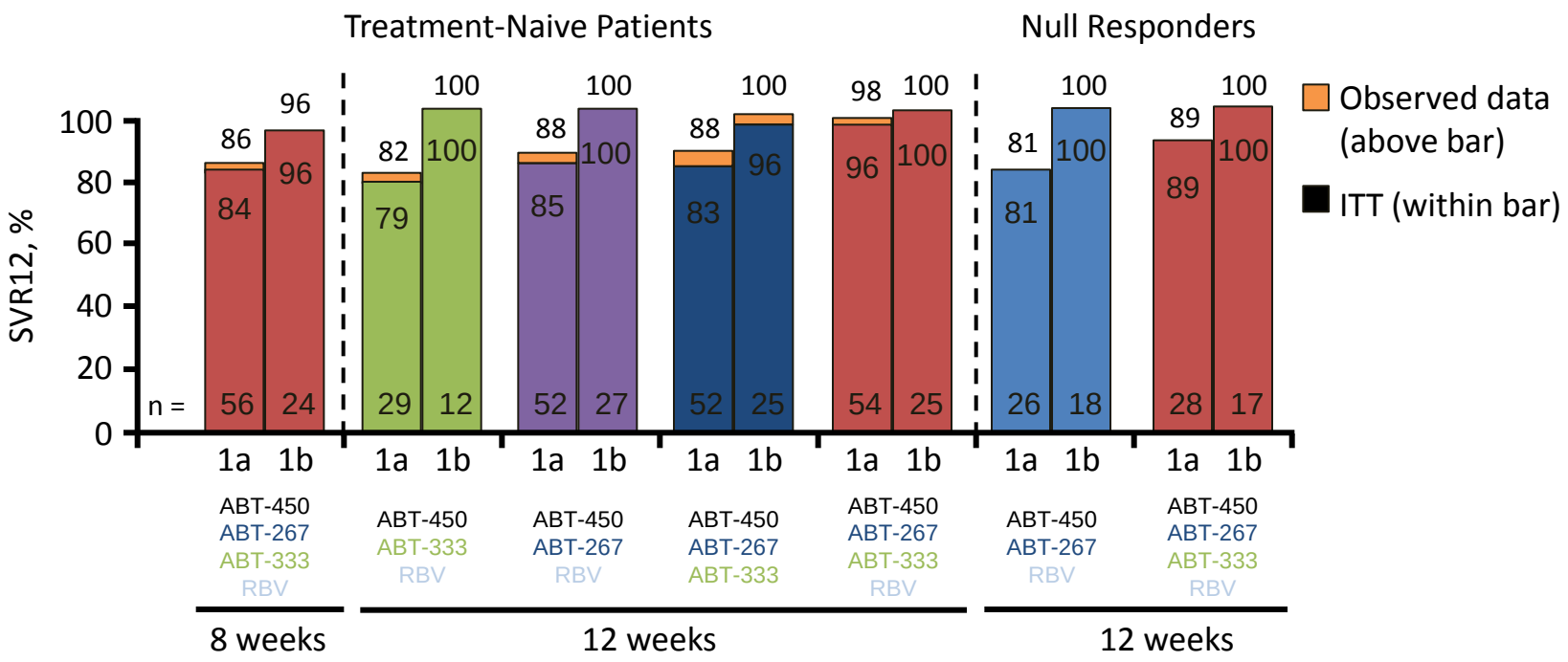
What about interferon free?

- Interferon is horrid - can we go to interferon free?

How about the A Team?

AVIATOR: SVR12 Rates With ABT-450/RTV, ABT-267, ABT-333, and RBV

- SVR12 rates higher in pts with HCV GT1b, but also high in pts with HCV GT1a
  - 12-wk regimen with all 3 DAAs + RBV produced highest SVR12 rates
- No drug-related SAEs reported; 2 pts discontinued tx due to drug-related AEs



Kowdley K, et al. AASLD 2012. Abstract LB-1.

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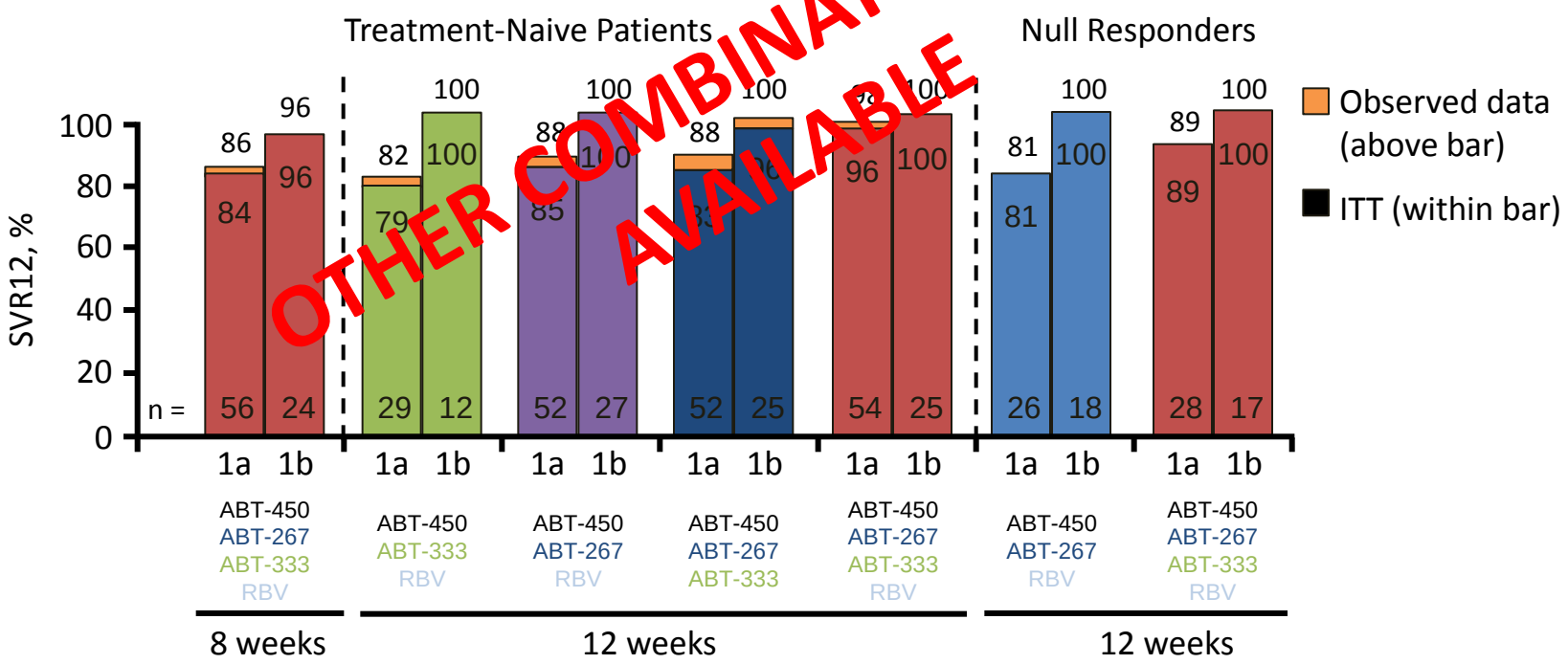


Kowdley K, et al. AASLD 2012. Abstract LB-1.

What about the alternatives?

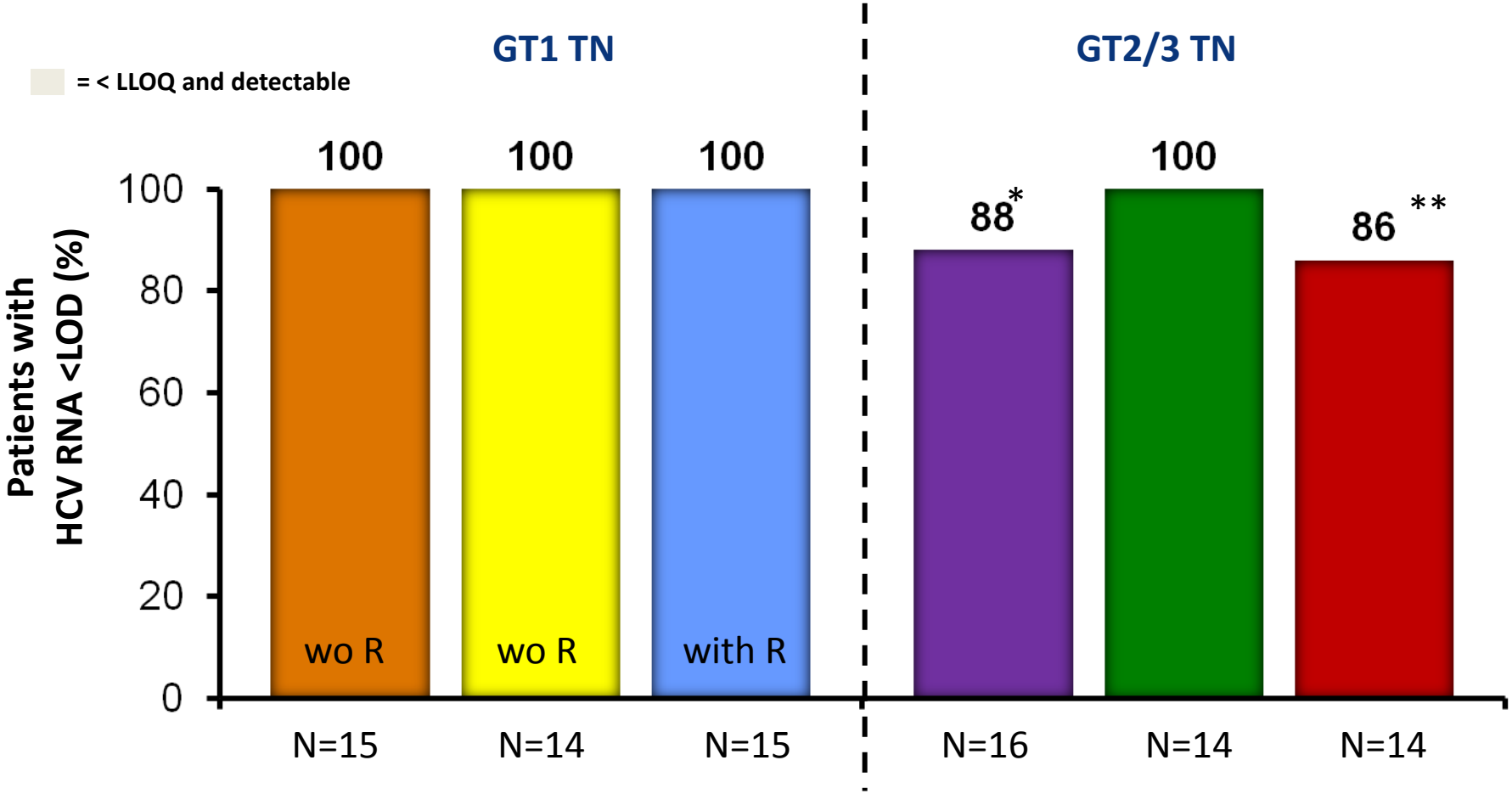
Sofosbuvir + Ribavirin 24 weeks

Cures 68% of tough patients

(Kottilil – JAMA 2013)

Does Superman need a friend

Sofosbuvir +DCV for 24 weeks



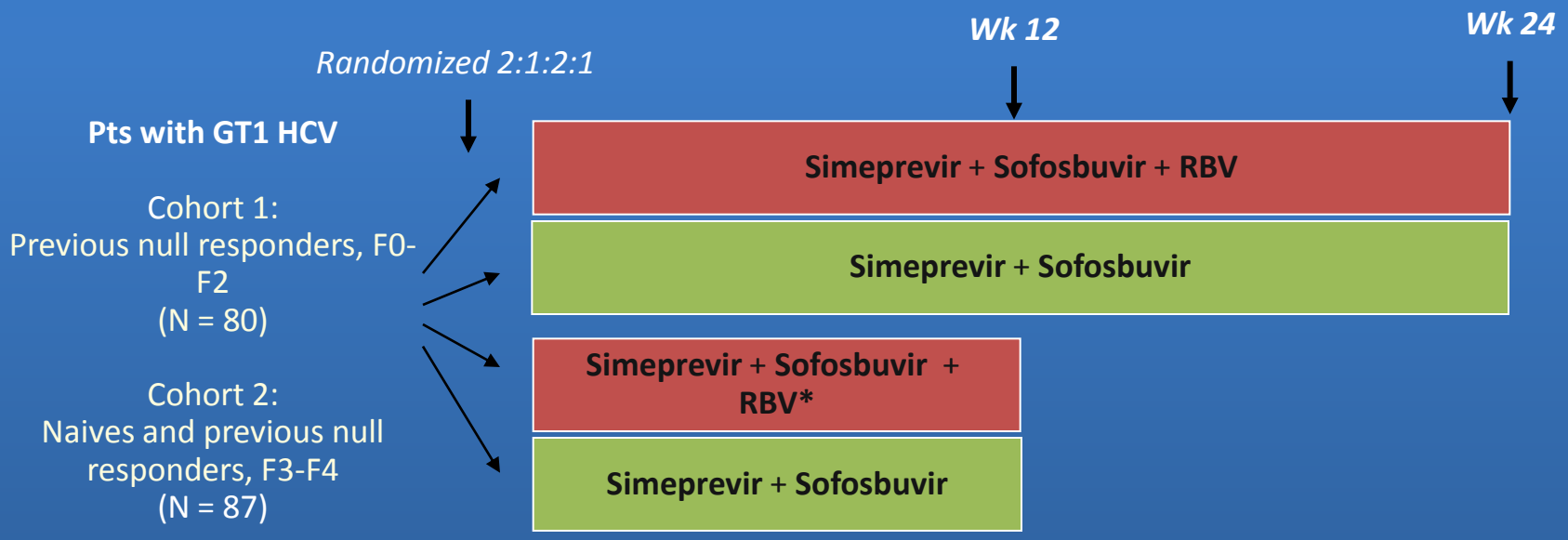
*1 patient required addition of peg-IFN/RBV, 1 patient with relapse at Week4
**2 patients lost to follow-up (following Week 12 and 24 visits)

Sulkowski M, et al. AASLD 2012, LB-2

Does Superman need a friend

COSMOS: Simeprevir + Sofosbuvir ± RBV in GT1 HCV Pts

- Planned interim analysis of phase IIa randomized study
- 2 cohorts with same study design; evaluating impact of duration and RBV
- Primary endpoint: SVR12

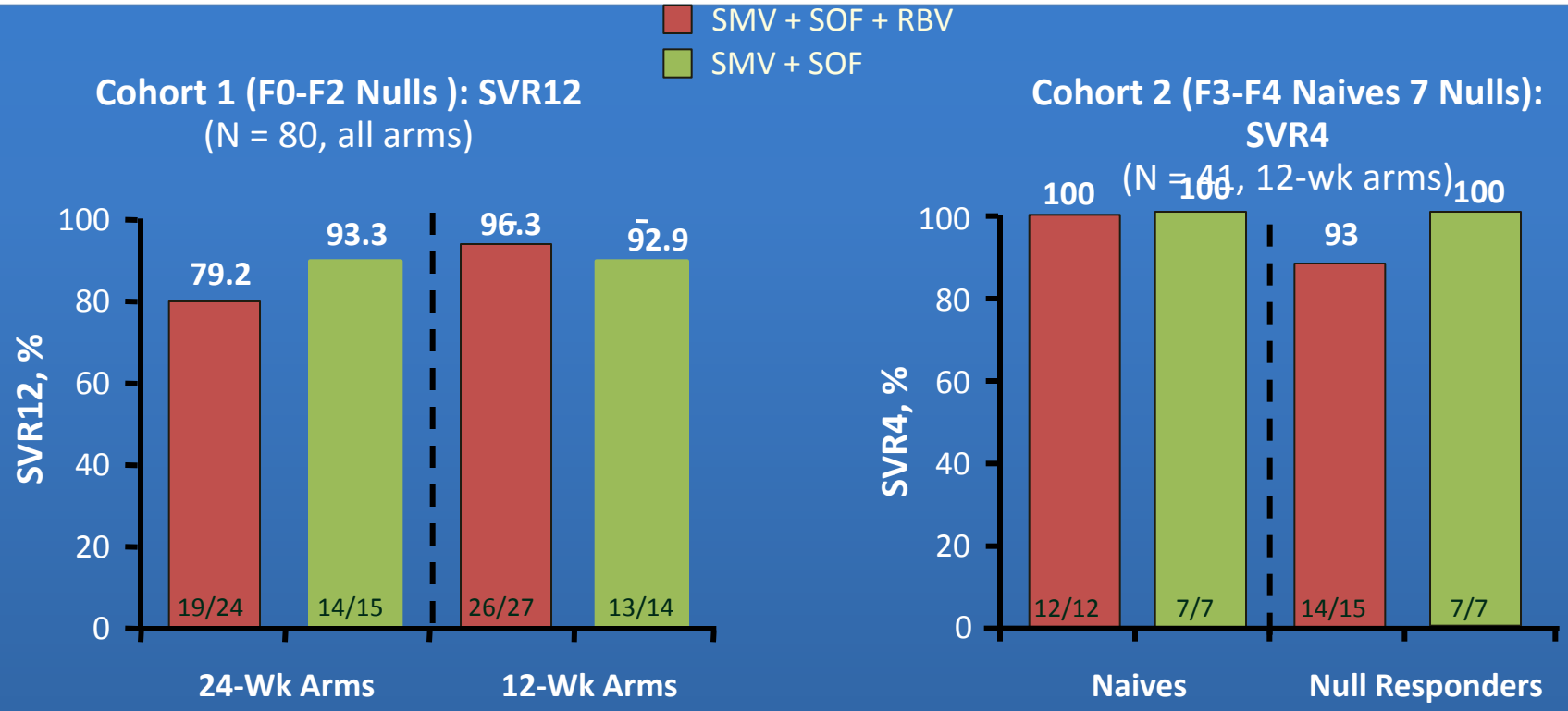


Simeprevir 150 mg QD; Sofosbuvir 400 mg QD; RBV 1000 or 1200 mg/day BID.

Jacobson I, et al. AASLD 2013. Abstract LB-3.

COSMOS: SVR12 in F0-F2 Pts (All Arms) and SVR4 in F3-F4 Pts (12-Wk Arms Only)

- AEs (anemia and indirect bilirubin increases) largely confined to RBV arms



Jacobson I, et al. AASLD 2013. Abstract LB-3.

Sofosbuvir +

- Sofosbuvir + ‘anything potent’ for 12 weeks looks wonderful

- Sofosbuvir + Ledipasvir (NS5A) = ~100%
- Sofosbuvir + Simeprevir (NS3) = ~100%

Sofosbuvir +

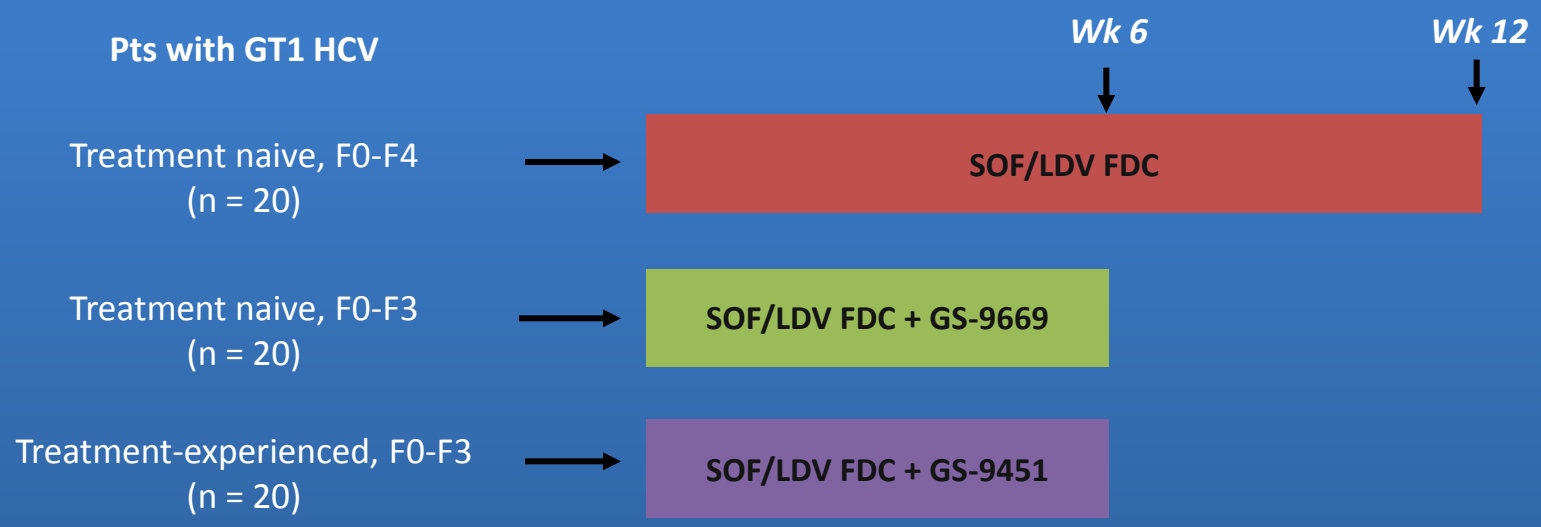
- Sofosbuvir + ‘anything potent’ for 12 weeks looks wonderful

- Sofosbuvir + Ledipasvir (NS5A) = ~100%
- Sofosbuvir + Simeprevir (NS3) = ~100%

- Can we shorten further?

SYNERGY: Sofosbuvir/Ledipasvir FDC ± GS-9669 (Non Nuc) or GS-9541 (PI) in GT1 HCV Pts

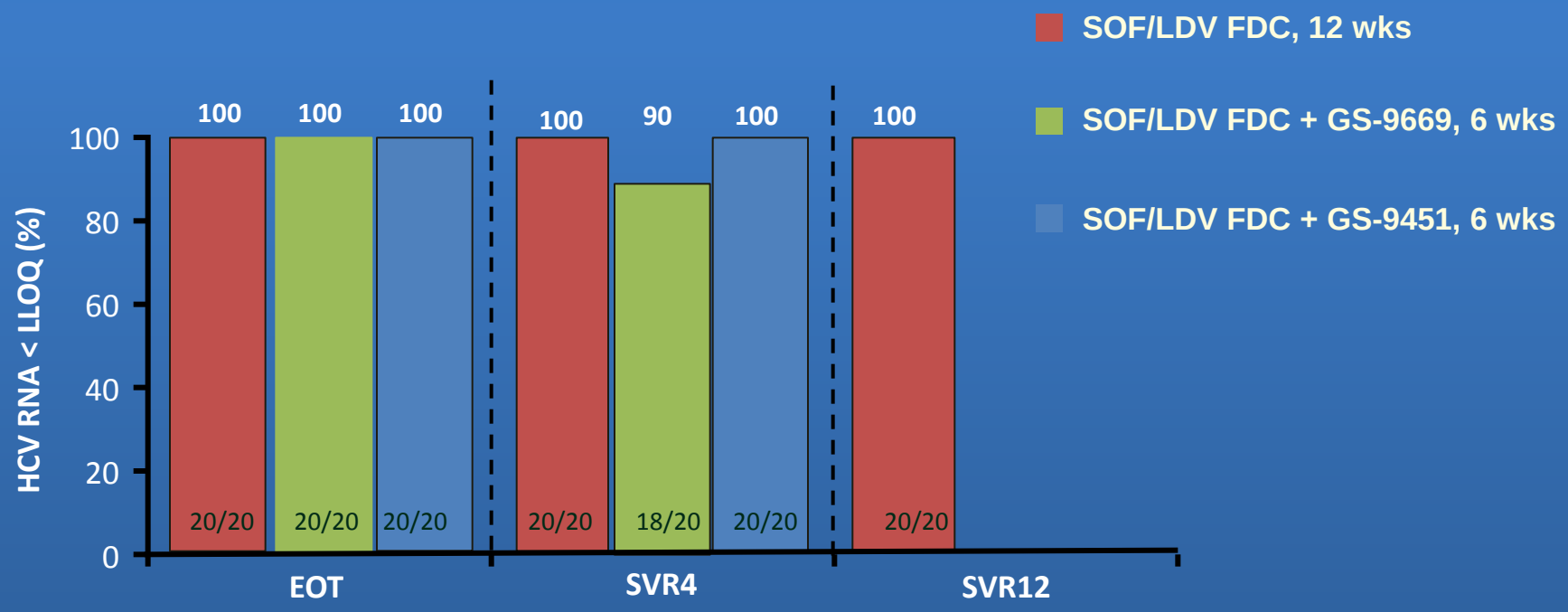
- NIAID nonrandomized parallel-arm phase II trial
- Primary endpoint: SVR12



Sofosbuvir 400 mg QD; ledipasvir 90 mg QD; GS-9669 500 mg QD; GS-9451 80 mg QD.

Kohli A, et al. AASLD 2013. Abstract LB-8.

SYNERGY: High Response Rates With 6-Week Triple-Drug Regimens



Kohli A, et al. AASLD 2013. Abstract LB-8.

Genotype 1
Interferon Free

- Sofosbuvir containing regimes look very, very good
- 12 weeks is the standard but triple therapy may allow shorter therapies
- AbVie have a fantastic triple 12 week regime

HCV of Other Genotypes

- Genotype 2 and 3 HCV is now under attack
- Very promising regimes due soon

HCV in Difficult to Reach People

- New drug regimes offer cures without tears
- Short, easy to manage regimes are highly effective

HCV in Difficult to Reach People

- We can cure everyone with HCV
- Now we need to get on with it