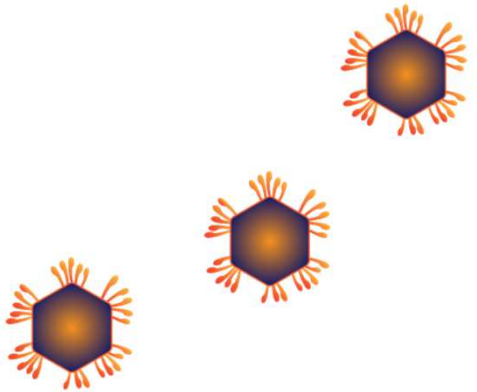


Hepatitis C for HIV doctors

Dr Chloe Orkin

Consultant Physician and Honorary Reader in HIV Medicine

Barts Health NHS Trust

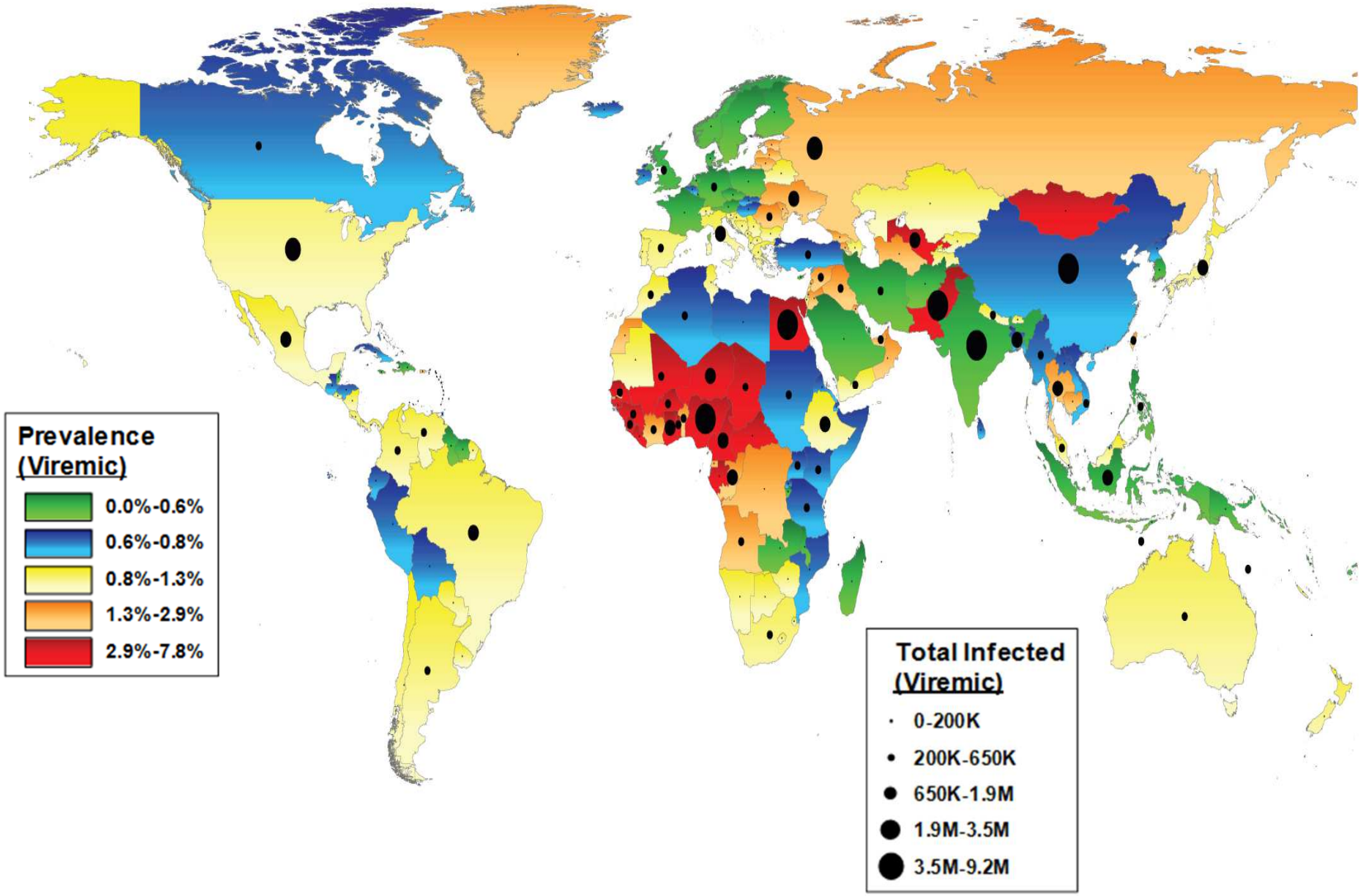
Disclosures

- **Disclosures: I have received honoraria, educational grants, travel scholarships and research grants from Gilead, MSD, BMS, Viiv, Janssen, J&J , BI and GSK**

Objectives

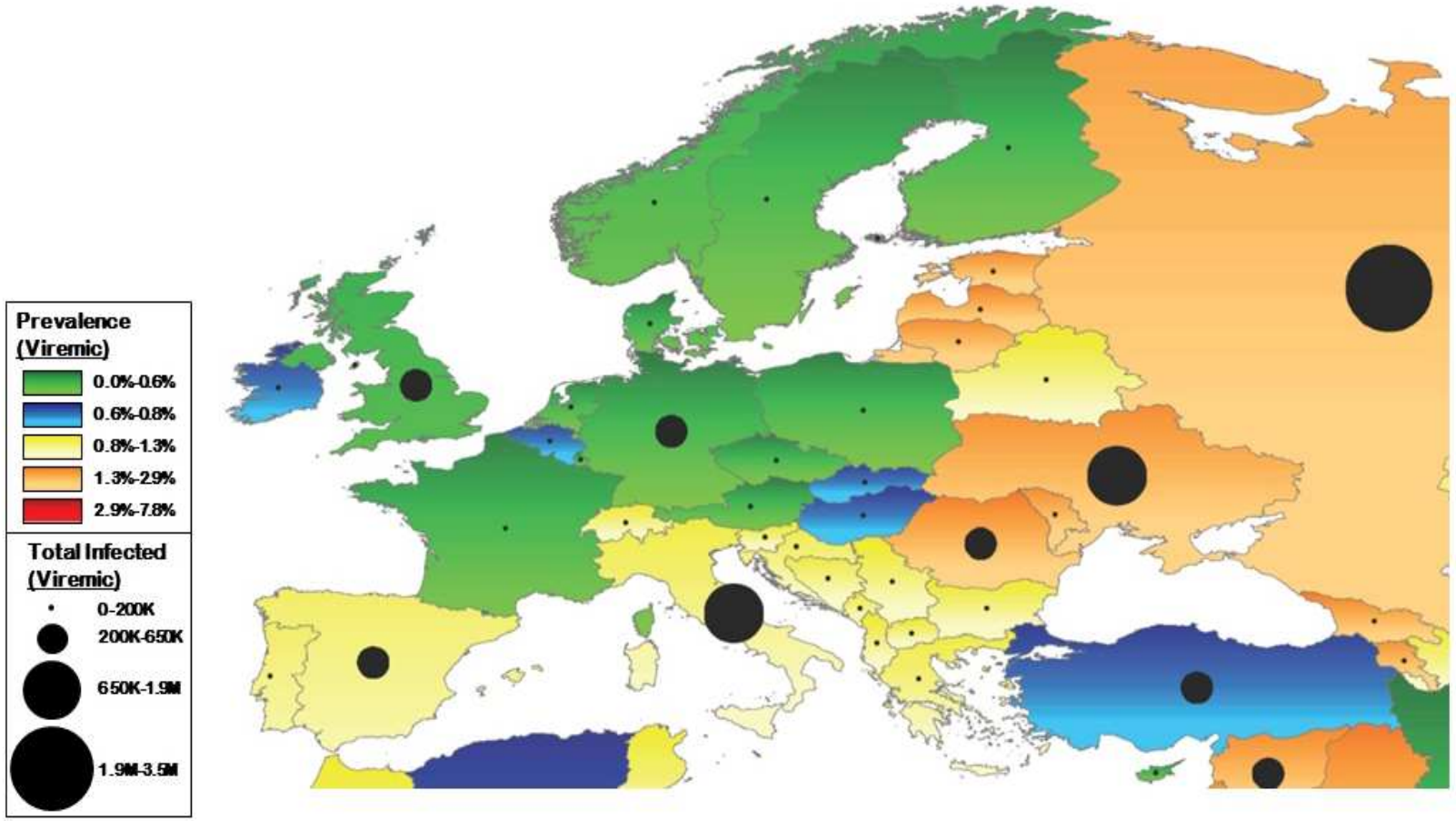
- The problem: epidemiology
- Why treat?
- Who to treat?
- Which drugs to use for which patients? (genotype, cirrhosis, ribavirin)
- How long to treat for?
- What about co-infection?
- Does resistance matter for HCV?
- What about acute HCV?
- What will this cost?

130–150 million people globally have chronic HCV infection, and 350,000 to 500,000 people die each year



Razavi H, Gower E, Estes C, Hindman S. Global HCV Genotypes. AASLD 2013; 2013 Nov 1-5; Washington, DC, United States.

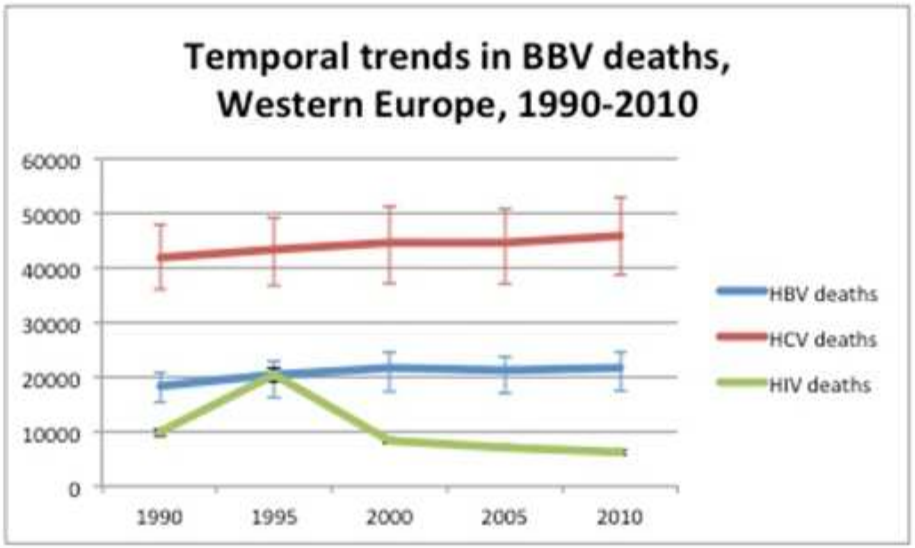
3.7 million RNA+ (viraemic) HCV infections in 2014 in the EU , 13.3 million HCV Ab+ in all Europe

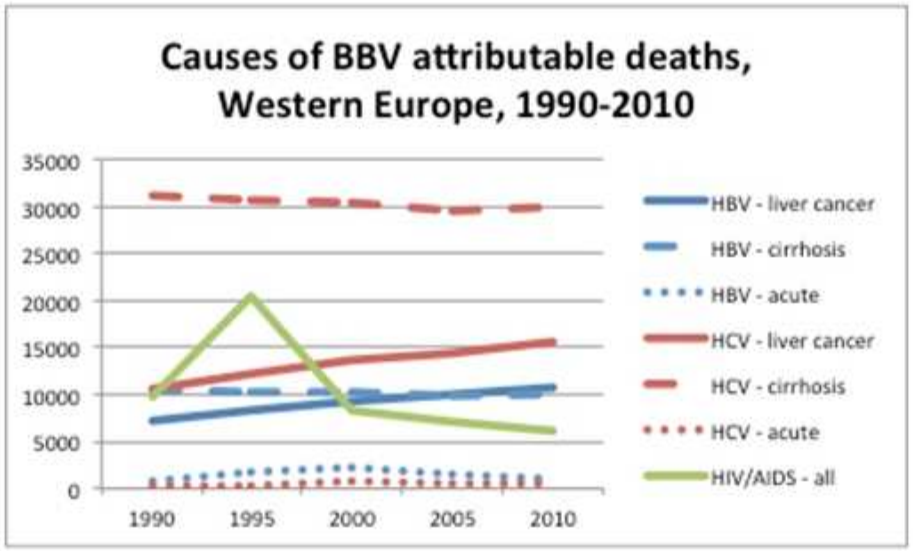


Gower et al J Hep 2014; 61 (Suppl 1):S45

Deaths attributable to HIV and Hepatitis in western Europe

- A relatively higher burden of HIV related mortality is observed to 1995, with subsequent decline from 2000 onwards
- HBV infection is a relatively lower contributor to mortality in Western Europe





GBD Study: Cowie et al J Hep 2014 ;60 (Suppl 1):O86

Objectives

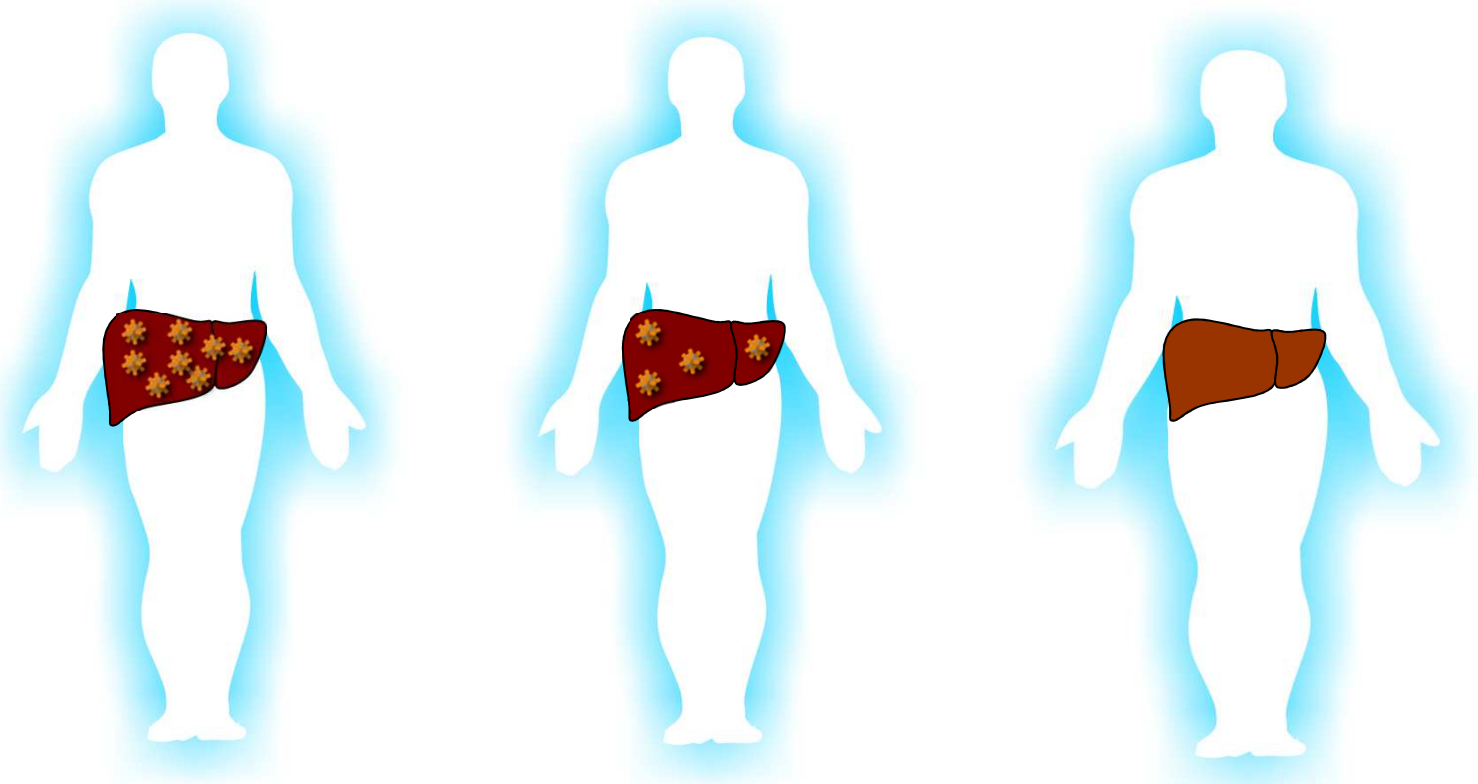
- The problem: epidemiology
- Why treat?
- Who to treat?
- Which drugs to use for which patients? (genotype, cirrhosis, ribavirin)
- How long to treat for?
- What about co-infection?
- Does resistance matter for HCV?
- What about acute HCV?
- What will this cost?

The goal: sustained virological response (SVR) to treatment

Achievement of SVR following completion of treatment = cure

SVR is associated with

- -70% reduction in Hepatocellular carcinoma
- -50% reduction in all-cause mortality

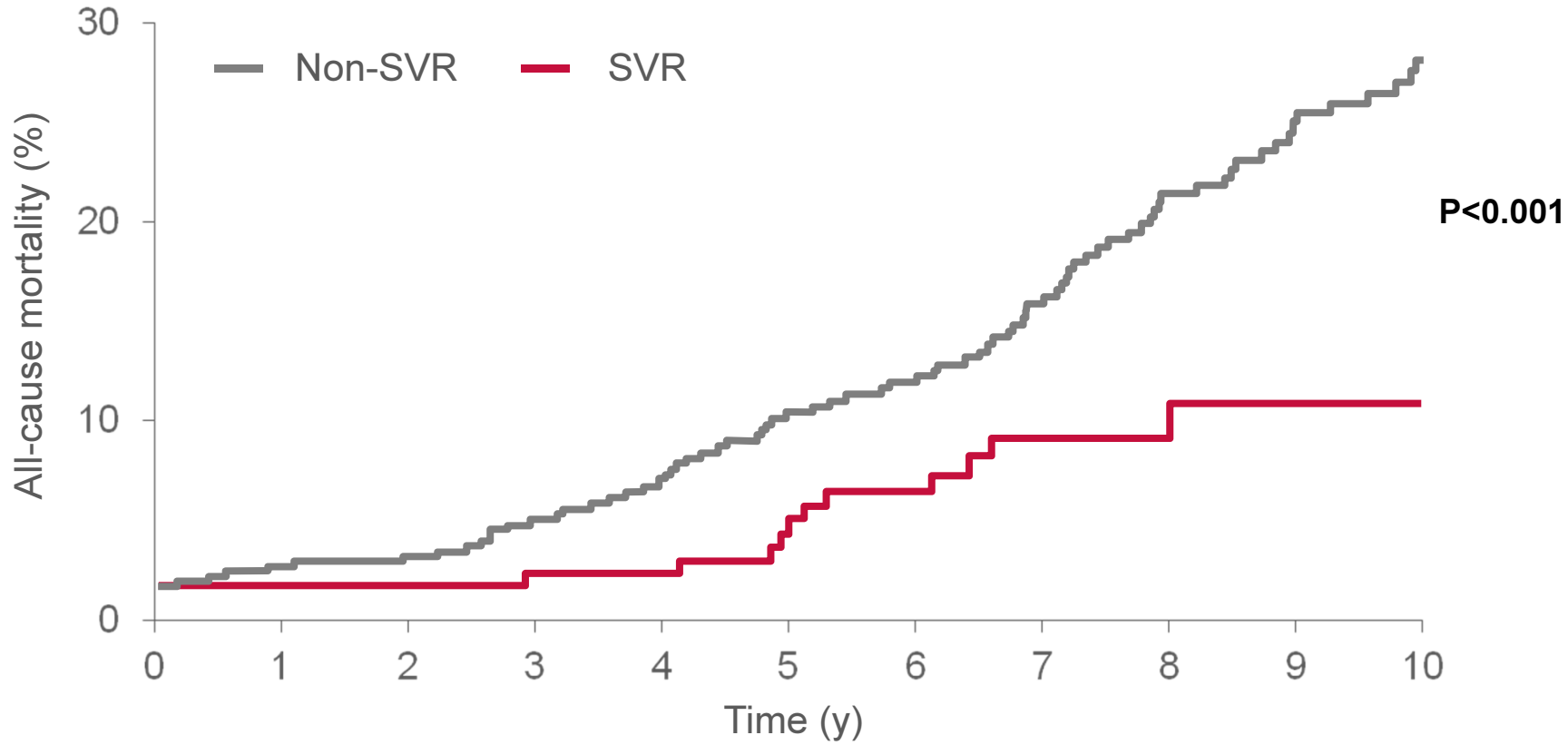


Acute Infection **Chronic Infection** **Cure**

Ghany M, et al. *Hepatol*. 2009. Asselah T, Marcellin P. *Liv Int.* 2012. Lok A-S. *N Engl J Med*. 2012

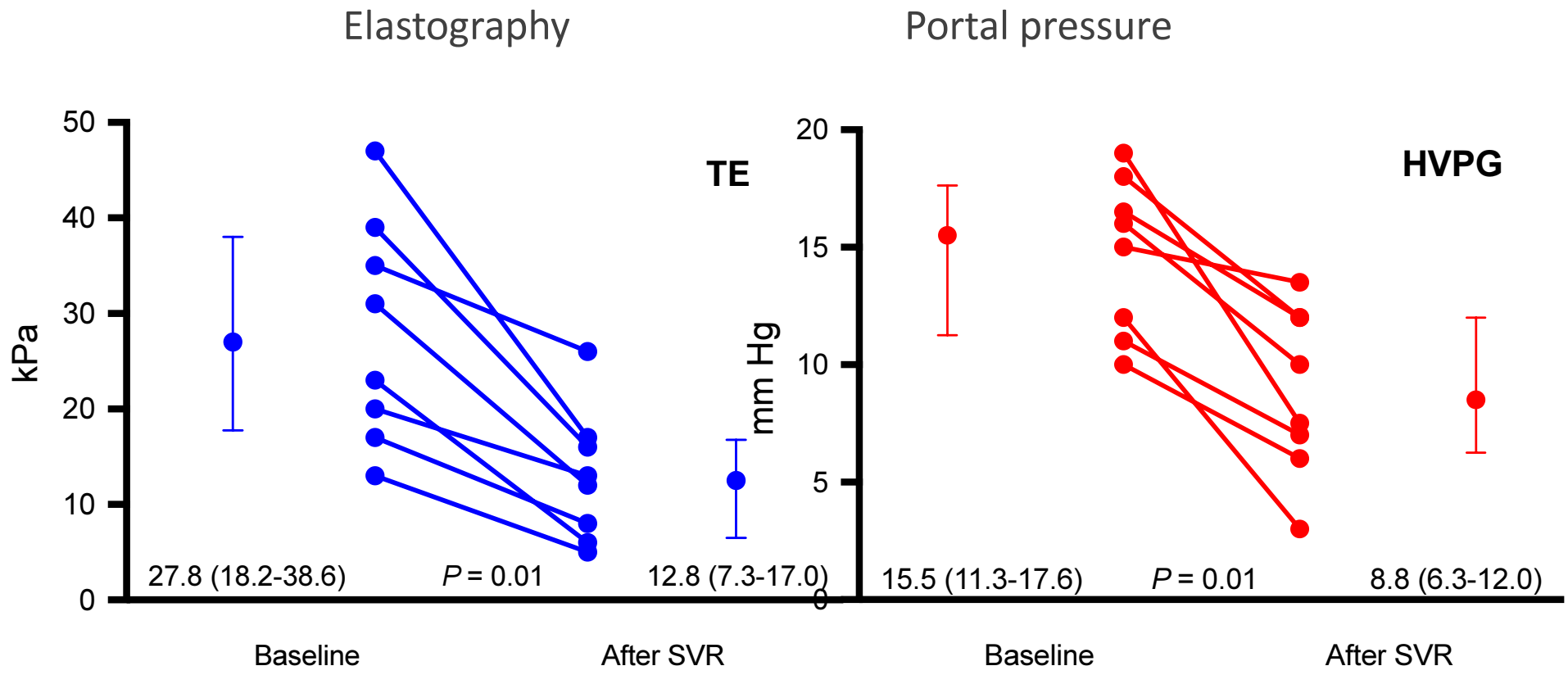
SVR reduces all-cause mortality

Long-term follow-up 230 advanced fibrosis/cirrhosis patients treated with IFN-based regimen (1990–2003)



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

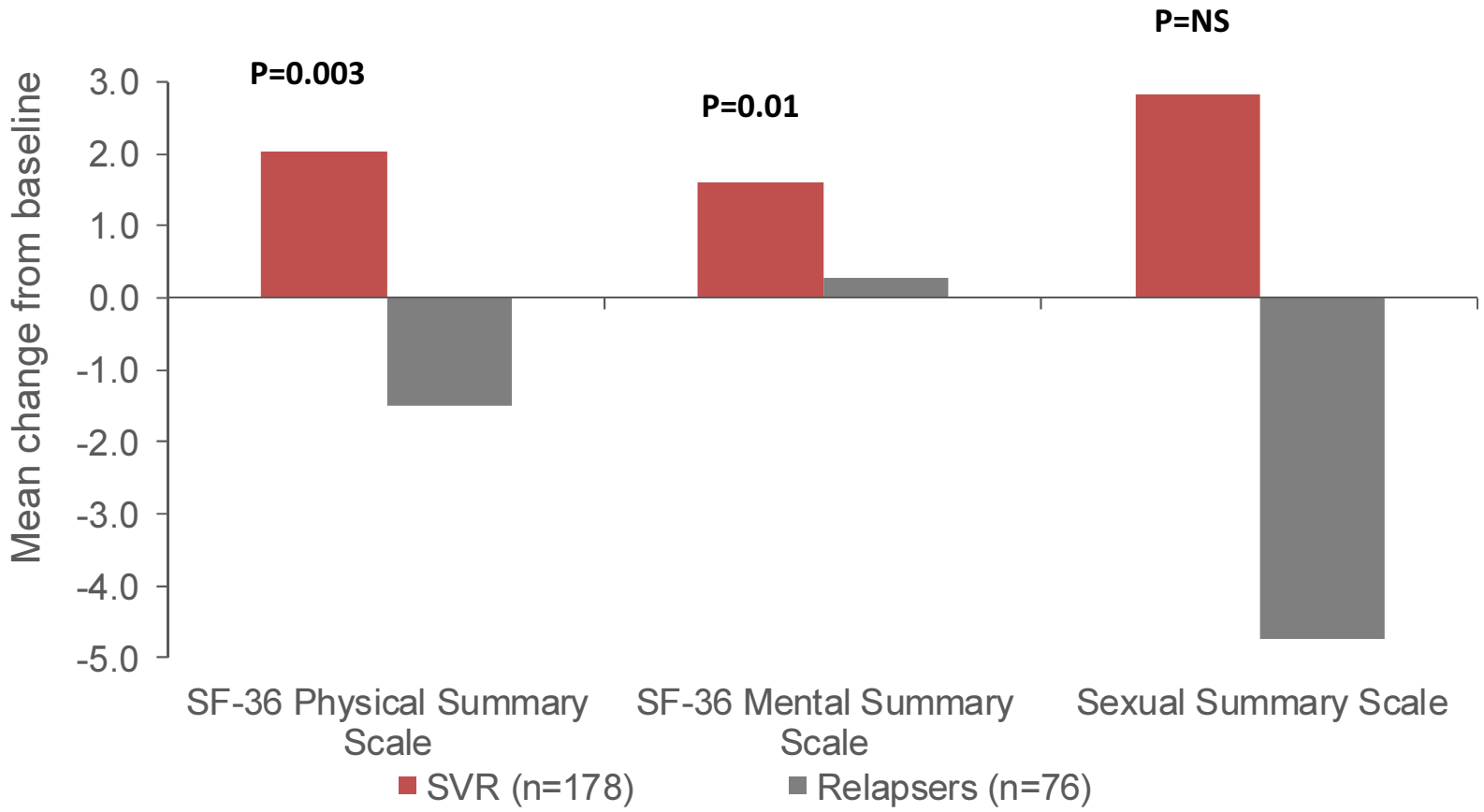
Liver stiffness and portal pressure decreases with HCV SVR in HIV+



Sánchez-Conde JAIDS in press 2015 #657

SVR is associated with improved health-related quality of life

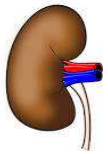
Patients with SVR had better physical & mental scores compared to baseline



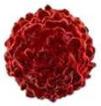
Bonkovsky HL, et al. J Hepatol 2007;46:420–31.

HRQoL: health-related quality of life; NS: not significant;
SF-36: short form 36

Non Hepatic complications of HCV


Renal disease (Chen 2014)

Cryoglobulinemia

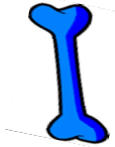

Lymphoproliferative disease (Feld 2013)

Insulin resistance (Hsu YC, 2014)

Vascular disease (CAD & CVA) (Maria 2014)

Cognitive impairment

Skin disease including porphyria cutanea tarda


Bone Disease (Lo Re 2014)

American Association for the Study of Liver Diseases

AASLD

Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

"Successful hepatitis C treatment results in sustained virologic response (SVR), which is tantamount to virologic cure, and, as such, is expected to benefit nearly all chronically infected persons."

Goal of treatment

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.

Rating: Class I, Level A

Recommended regimens for HIV/HCV-coinfected individuals.

HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections).

Rating: Class I, Level B

AASLD/IDSA HCV Guidelines; www.hcvguidelines.org

Objectives

- The problem: epidemiology
- Why treat?
- Who to treat?
- Which drugs to use for which patients? (genotype, cirrhosis, ribavirin)
- How long to treat for?
- What about co-infection?
- Does resistance matter for HCV?
- What about acute HCV?
- What will this cost?

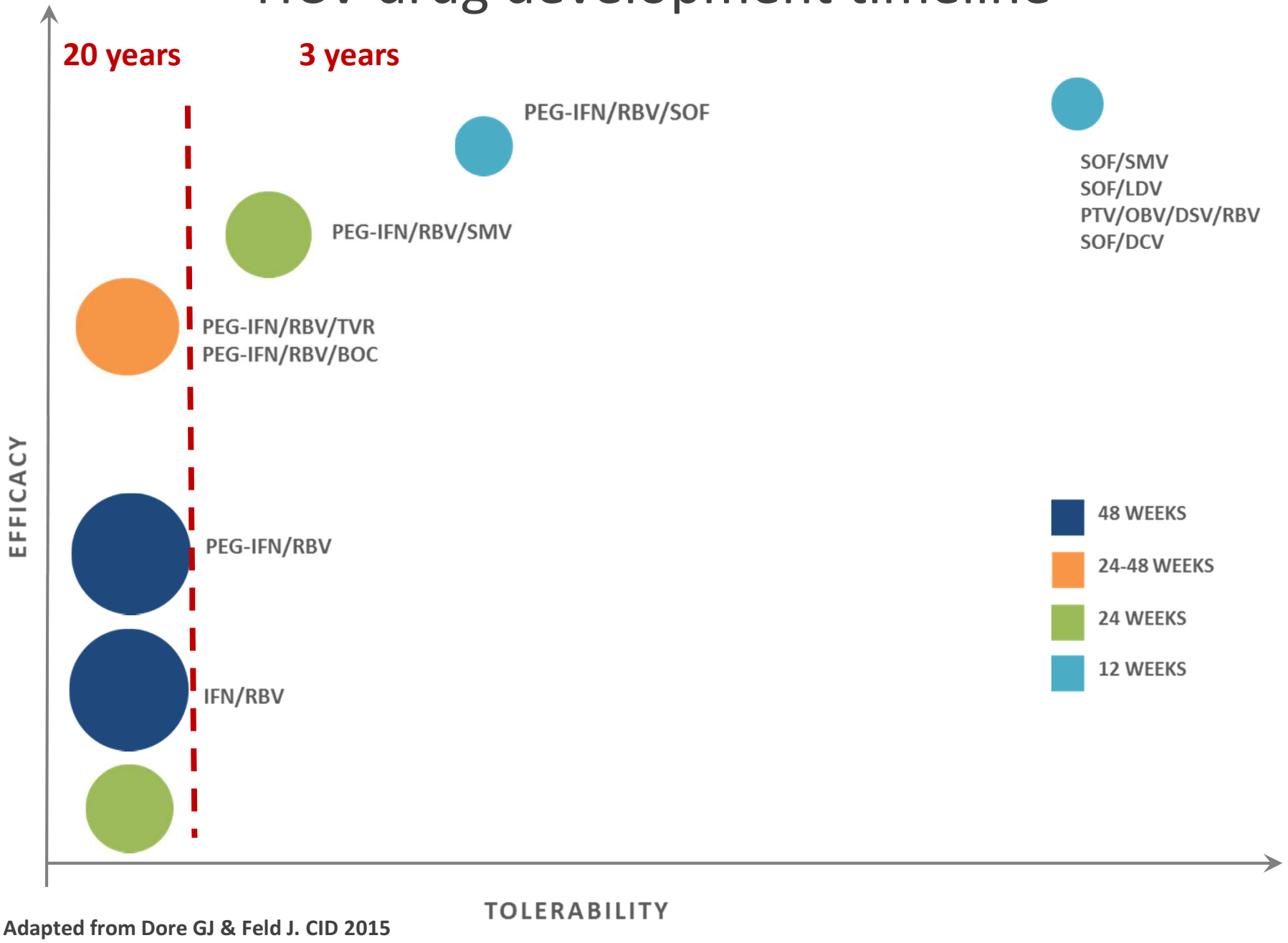
Spectrum treated thus far with directly-acting agents (DAA's)?

- Treat patients in need across the extremes of the spectrum:
  - IFN-free for IFN-ineligible patients
  - Advanced cirrhosis and to prevent post-transplant recurrence
  - Mild disease Treatment
  - TASP

* Cure is defined as SVR

Adapted Slide courtesy of Graham Foster

HCV drug development timeline



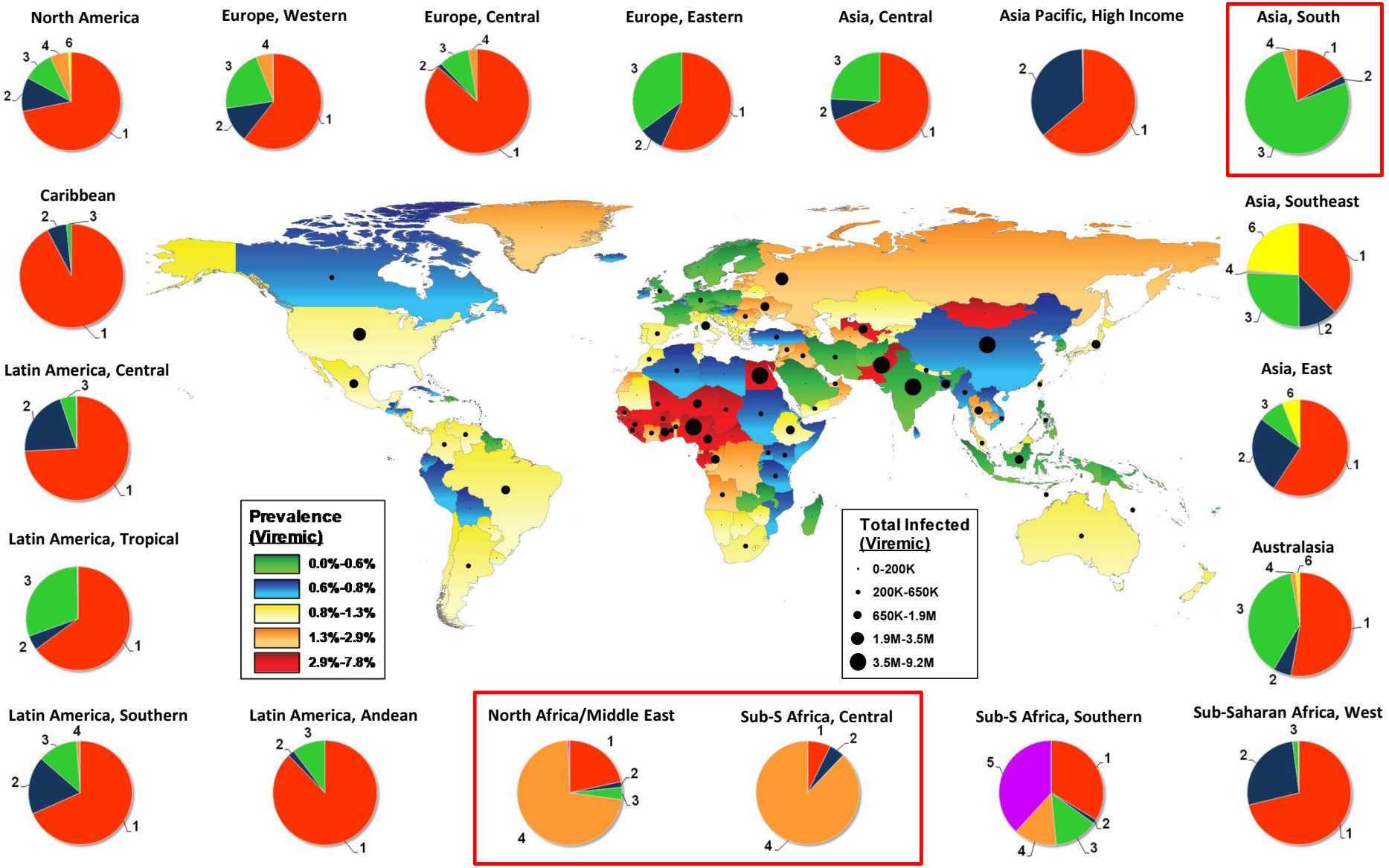
Adapted from Dore GJ & Feld J. CID 2015

HCV New Drugs= all oral DAA's

Peg-IFN

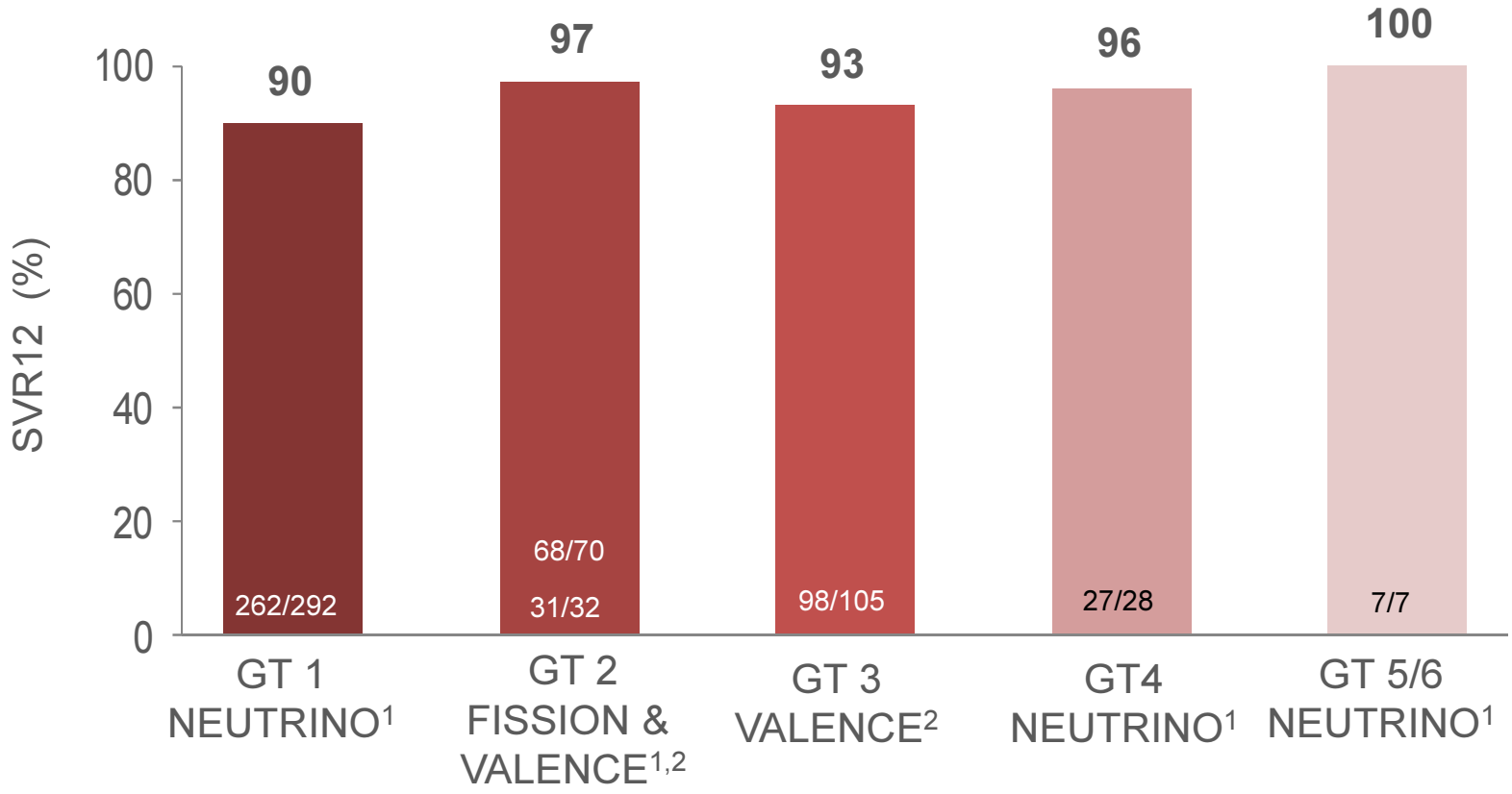
Ribavirin

GT (Genotype) differs in different parts of the world



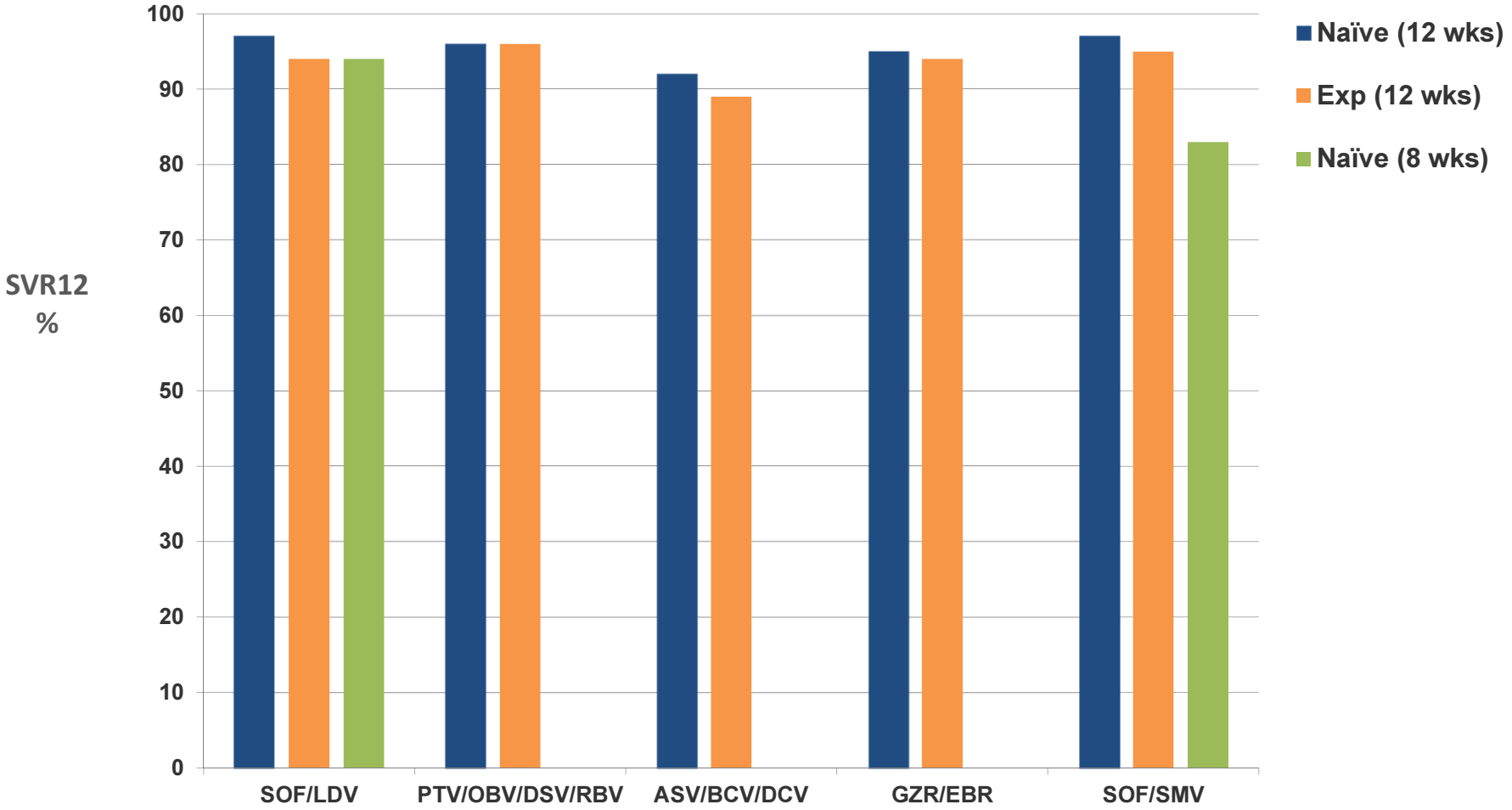
Razavi H, Gower E, Estes C, Hindman S. Global HCV Genotypes. AASLD 2013; 2013 Nov 1-5; Washington, DC, United States.

>90% SVR12 across **treatment-naïve**
GT 1, 2, 3, 4, 5, 6



1. Lawitz E, et al. N Engl J Med 2013;368:1878–87;
2. Zeuzem S, et al. AASLD 2013. Poster #1085.

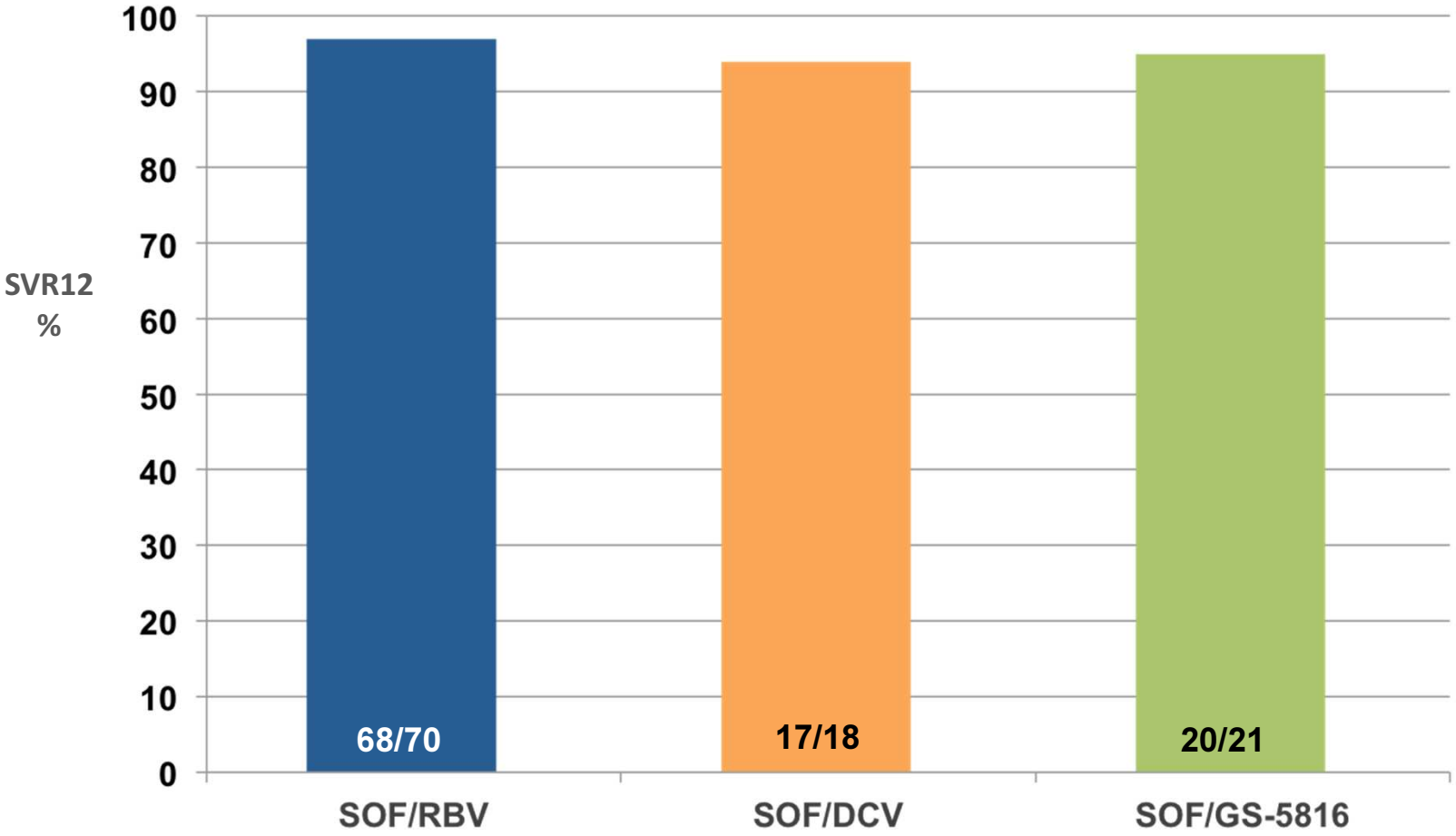
PEG-IFN-FREE DAA THERAPY: GT1 REGIMENS



Zeuzem, NEJM 2014; Afdhal, NEJM 2014; Kowdley, NEJM 2014; Feld, NEJM 2014; Poordad, AASLD 2014; Zeuzum, ILC 2015; Kwo, ILC 2015

PEG-IFN-FREE DAA THERAPY: GT2 REGIMENS

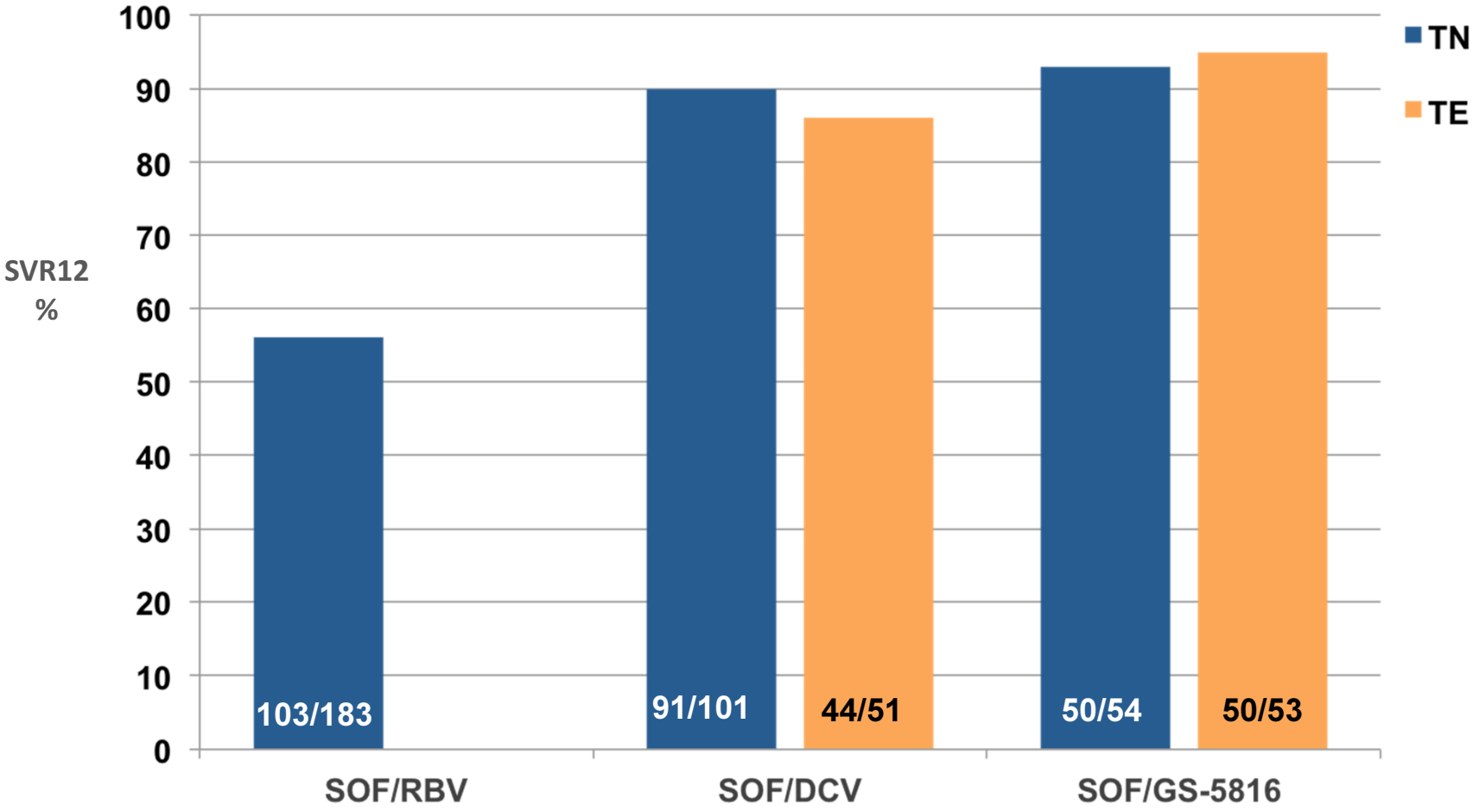
Treatment naïve and experienced on 12 wks therapy



Lawitz E, et al. NEJM 2013; Everson G et al. ILC 2014; Wyles D et al. CROI 2015; Poordad F et al. ILC 2015

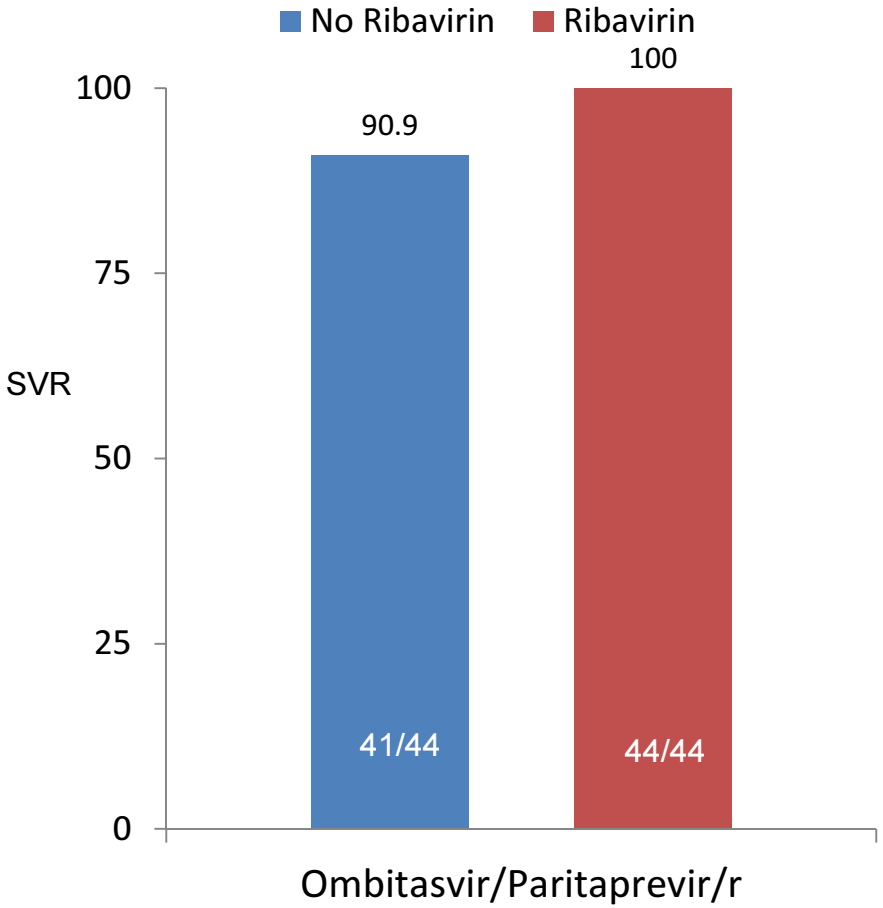
PEG-IFN-FREE DAA THERAPY: GT3 REGIMENS

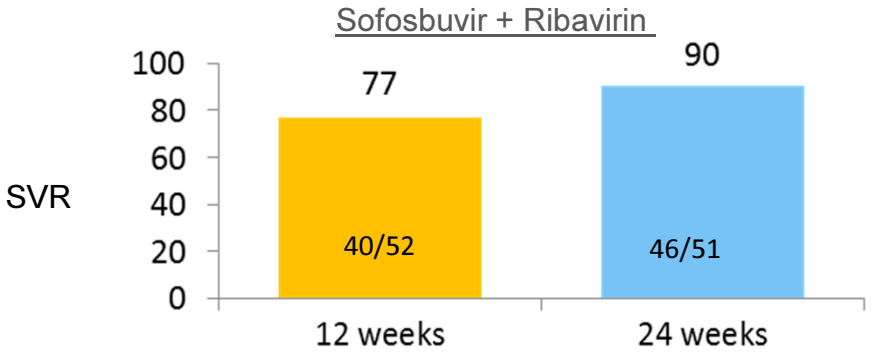
Treatment naïve and experienced , 12 wks treatment



Lawitz E, *NEJM* 2013; Nelson DR, *Hepatology* 2015; Everson G, ILC2014; Pianko S, AASLD 2014

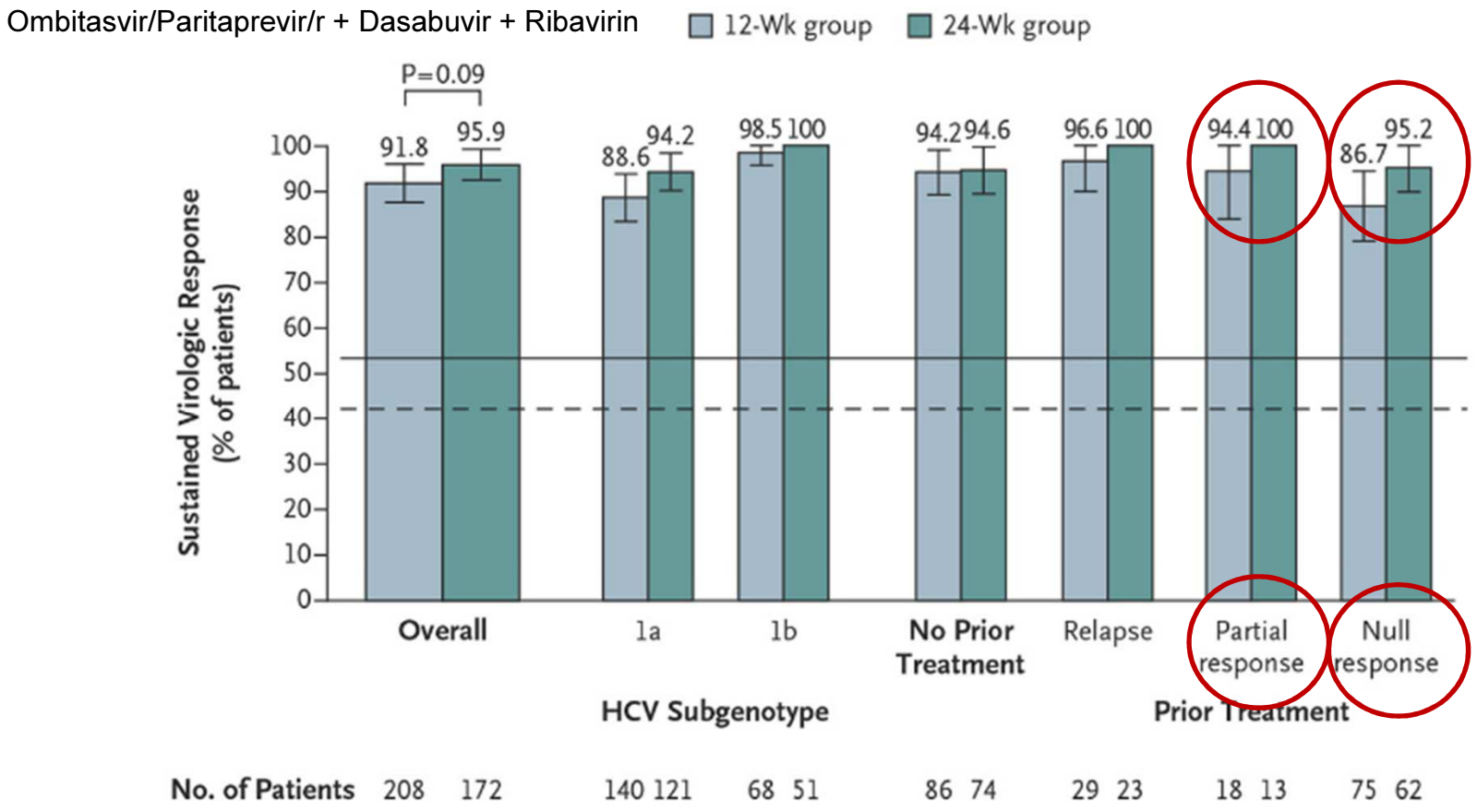
PEG-IFN-free DAA therapy: GT4 regimens





Kapoor AASLD 2014; Pol AASLD 2014; Hassanenein J Hepatol 2015; Esmat AASLD 2014; Lenz J Hepatol 2013

HCV cure may take longer in prior non-responders

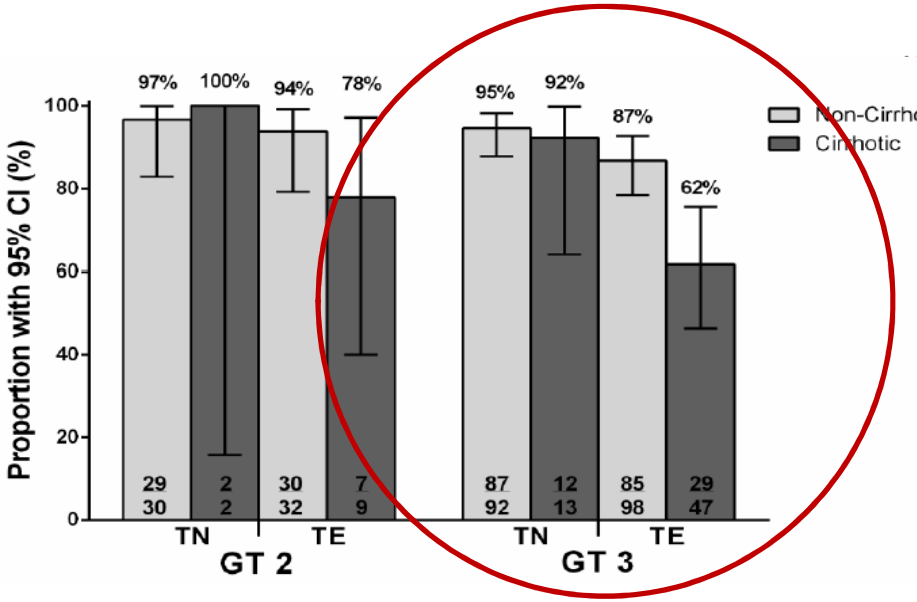


HCV relapse rate : 12 week group [12 of 203 patients, for a rate of 5.9% (95% CI, 2.7 to 9.2)] versus 24 week group [1 of 164 patients, for a rate of 0.6% (95% CI, 0 to 1.8)]

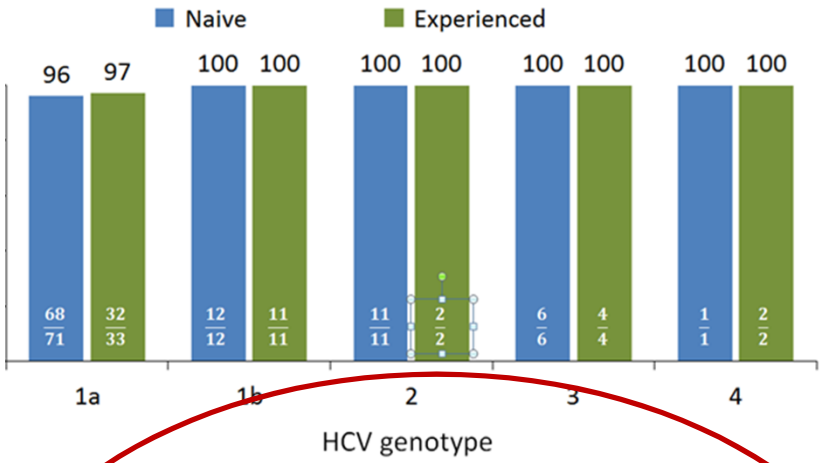
Poordad F, et al. *N Engl J Med*. 2014;370:1973-1982.

Cirrhosis affects treatment outcomes eg HCV genotype 3 infection

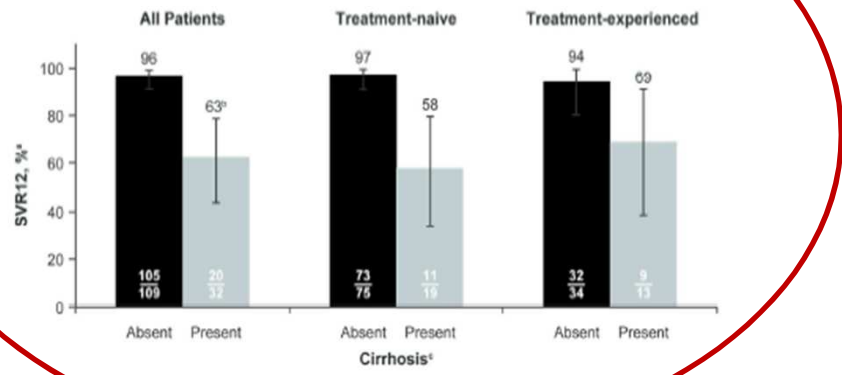
Sofosbuvir + Ribavirin for 24 weeks in persons with HCV genotype 2 or 3 infection



Daclatasvir + Sofosbuvir for 12 weeks in persons with HIV infection and HCV genotype 1, 2, 3, or 4 infection



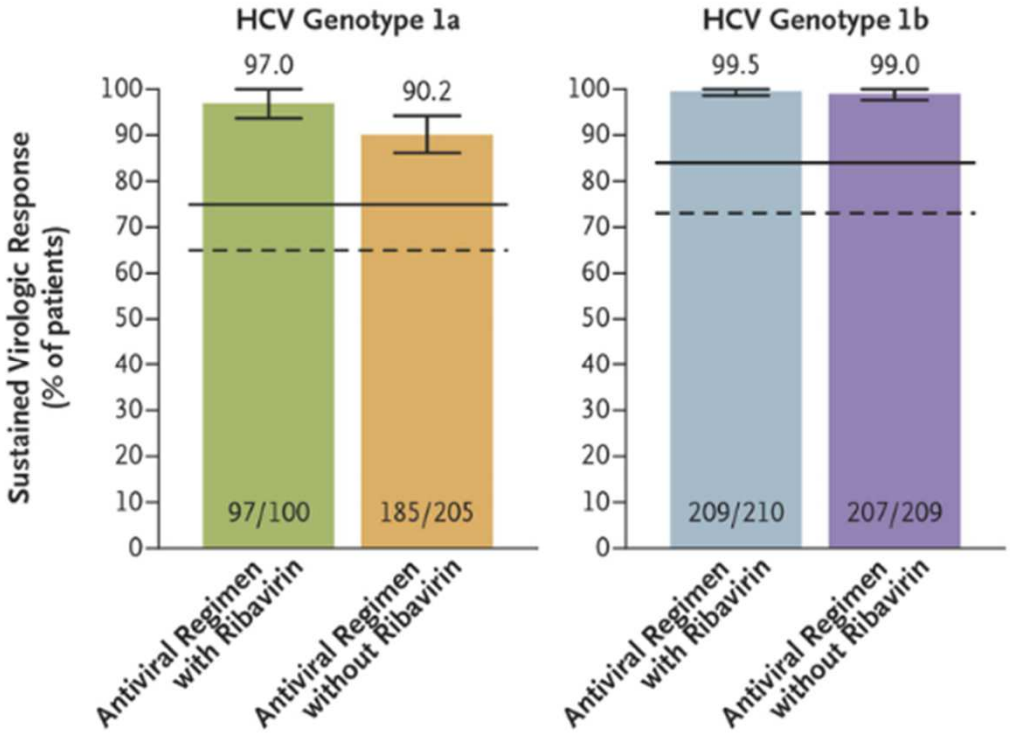
Daclatasvir + Sofosbuvir for 12 weeks in persons with HCV genotype 3 infection



Zeuzem NEJM 2014;
Wyles CROI 2015
Nelson Hepatology 2015

Ribavirin can prevent treatment failure

Ombitasvir/Paritaprevir + Dasabuvir with or with Ribavirin



Ferenci NEJM 2014

Summary: the ‘stress tests’ for regime efficacy

- Stress test for HIV treatment regimen :

  -performance in patients VL> 100,000c/ml

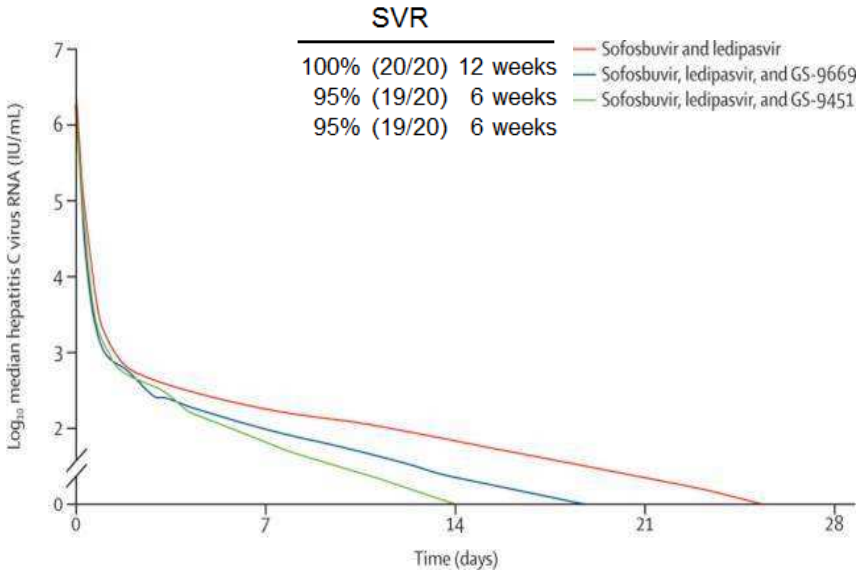
- Stress test for HCV treatment regimen:

  - performance in the following areas is key:
    - Cirrhotic patients
    - Treatment Experienced vs Treatment Naïve
    - Genotypes especially G3 TE/cirrhotic

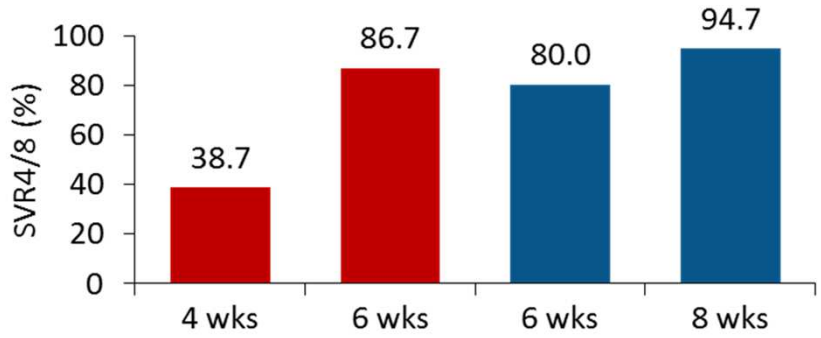
Shorter duration treatment under investigation but 4/52 is inadequate

6 weeks of Sofosbuvir/Ledipasvir +

GS-9669 or GS-9451 (nuc NS5B/NS5A + non-nuc NS5B or NS3)



4, 6 or 8 weeks of Grazoprevir/Elbasvir + Sofosbuvir persons with and without cirrhosis



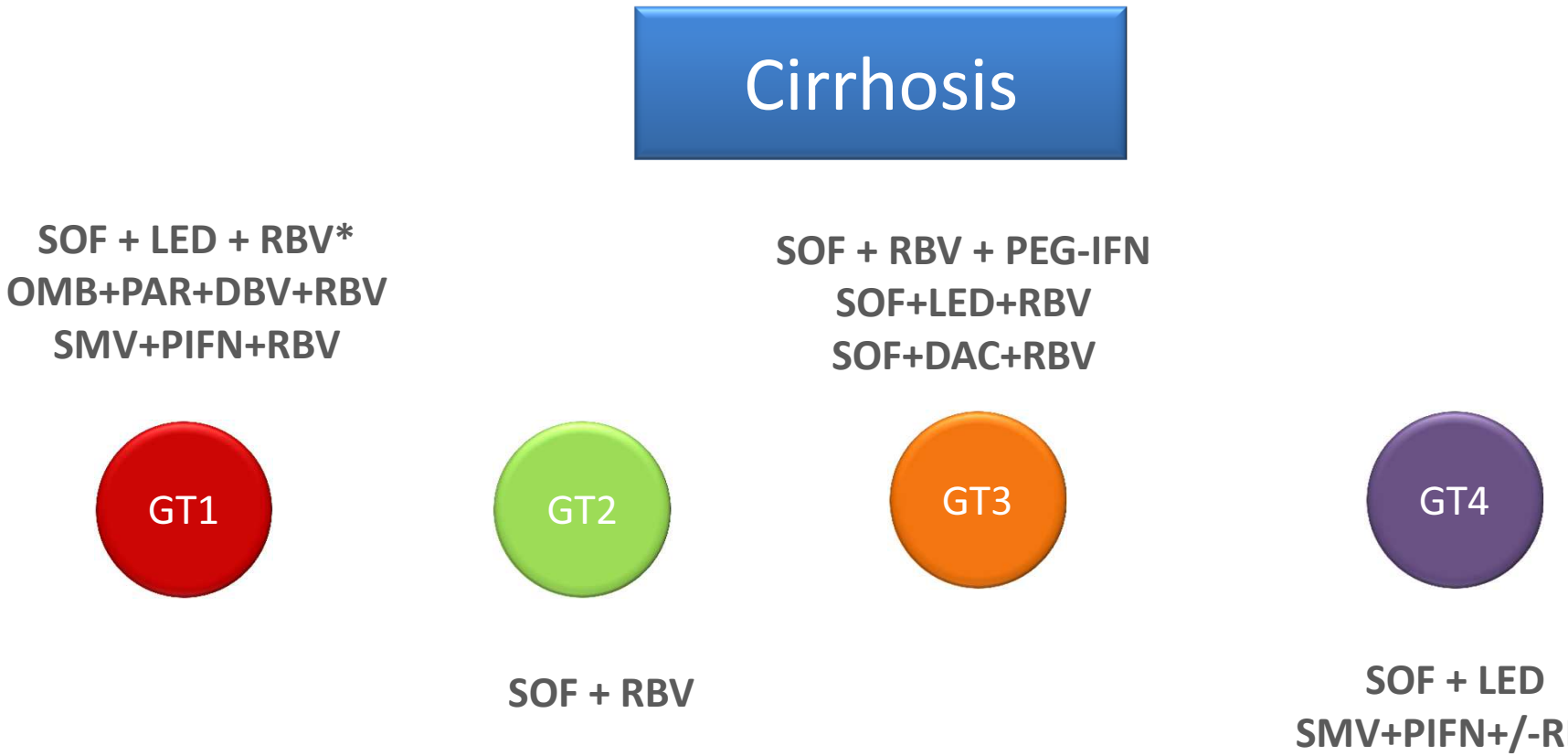
Breakthrough	**0**	**0**	**0**	**0**
Relapse				
All relapse	**19**	**4**	**4**	**1**
Relapse at FU4	**10**	**4**	**2**	**1**
Relapse at FU8	**9**	**0**	**2**	**0**

Kohli Lancet 2015

Lawitz AASLD 2014

NHS-England Approved Treatment now…12 weeks

Cirrhosis



EMA indication also allows for 24 weeks of therapy

Gilead Sciences Europe. SOVALDI (sofosbuvir), Summary of Product Characteristics, January 2014.

GT: genotype; PEG-IFN: pegylated interferon; RBV: ribavirin; SOF: sofosbuvir

HCV TREATMENT STRIVING FOR PERFECTION

- Efficacy (>95%)in TE, TN, cirrhosis
- Well tolerated
- Once daily dosing
- Pangenotypic
- Short duration (6-8 weeks)
- **Affordable**

Objectives

- The problem: epidemiology
- Why treat?
- Who to treat?
- Which drugs to use for which patients? (genotype, cirrhosis, ribavirin)
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- What about acute HCV?
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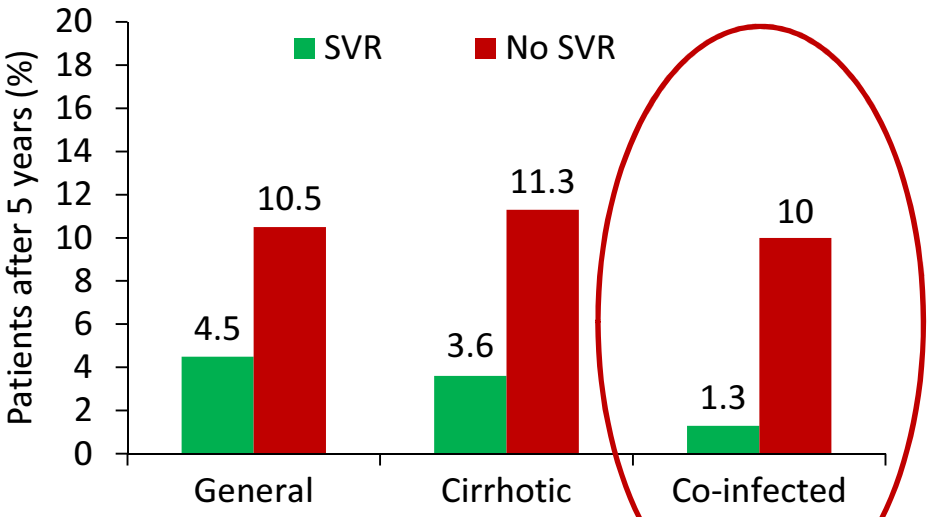
Effects of SVR on the risk of hepatocellular carcinoma and death

5-year risk of death (all-cause) by SVR

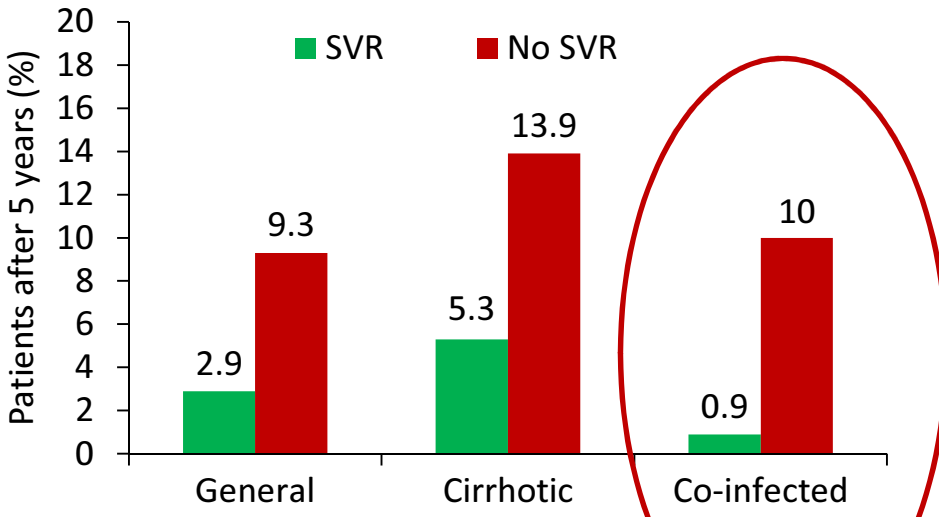


General: 18 studies
n=29,269
Avg. FU=4.6 years

Cirrhotic: 9 studies
n=2,734
Avg. FU=6.6 years

HIV/HCV: 5 studies
n=2,560
Avg. FU=5.1 years

5-year risk of hepatocellular carcinoma by SVR



General: 21 studies
n=12,496
Avg. FU=6.1 years

Cirrhotic: 18 studies
n=4,987
Avg. FU=6.6 years

HIV/HCV: 3 studies
n=2,085
Avg. FU=4.7 years

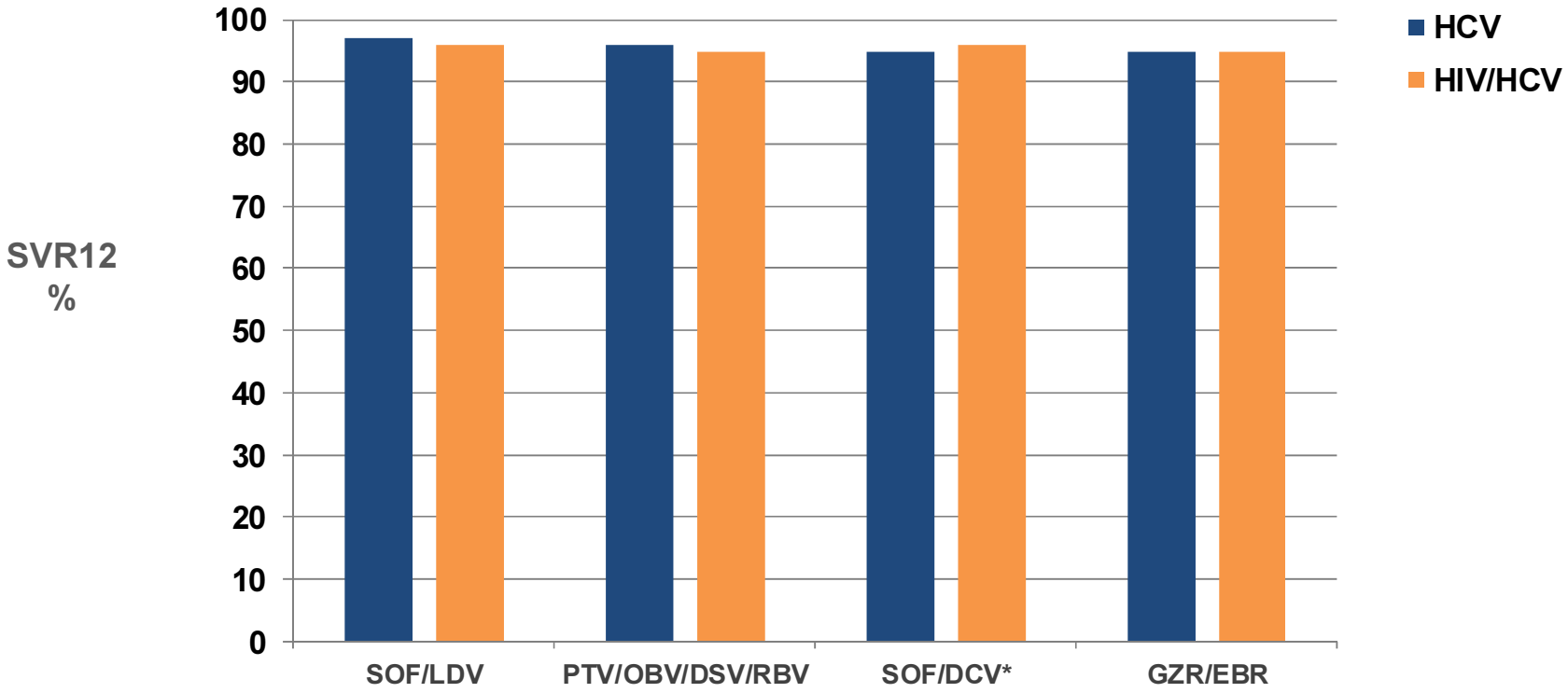
- Benefits may be offset by re-infection over 5 years
  - 0.9% in 'low-risk' persons
  - 8.2% in persons who inject drugs
  - 23.6% in persons coinfected with HIV

Hill AASLD 2014

Meta-analysis of 129 studies of 34,563 patients with HCV infection

PEG-IFN-FREE TRIAL DATA: HCV VS HIV/HCV

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



*HCV mono in post-transplant

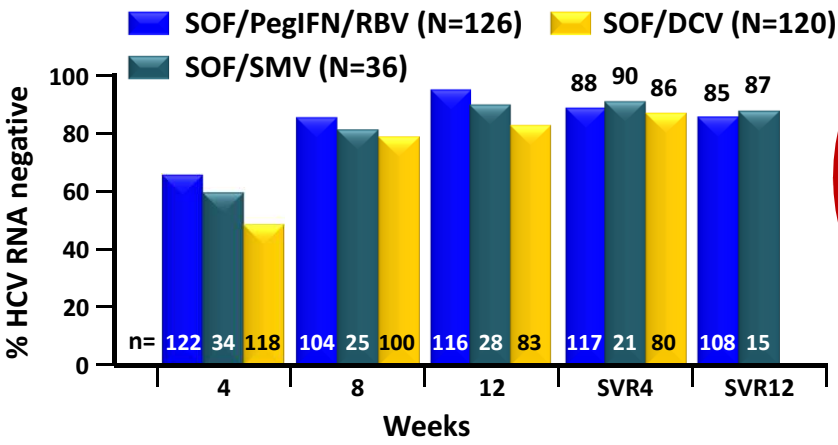
Afdhal, NEJM2014; Naggie, CROI2015; Feld, NEJM2014; Rockstroh, WAC2014; Wyles, CROI2015; Zeuzem, ILC2015; Rockstroh, ILC2015; Poordad, ILC2015

‘Real world’ HIV/HCV cohorts

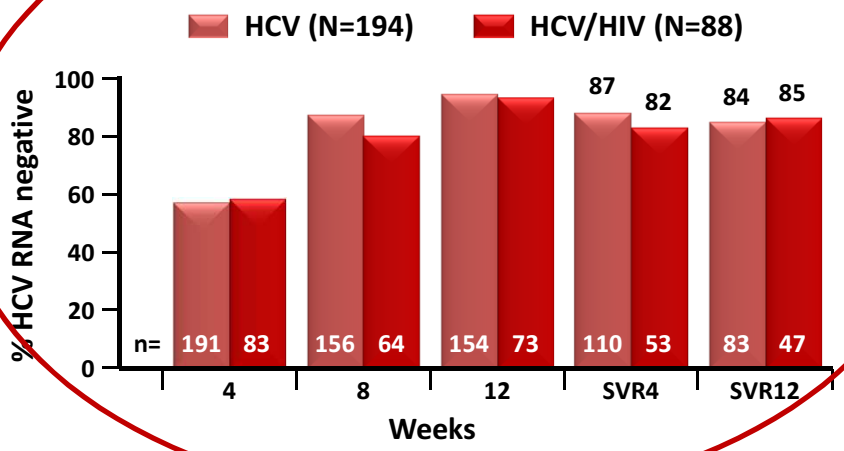
- GECOSO
- NORTH-WESTERN
- MOUNT SINAI
- BARTS HEALTH NHS TRUST
- PENNSYLVANIA

German cohort on sofosbuvir based therapy for HCV/HIV- & HCV-infection (GECOSO)

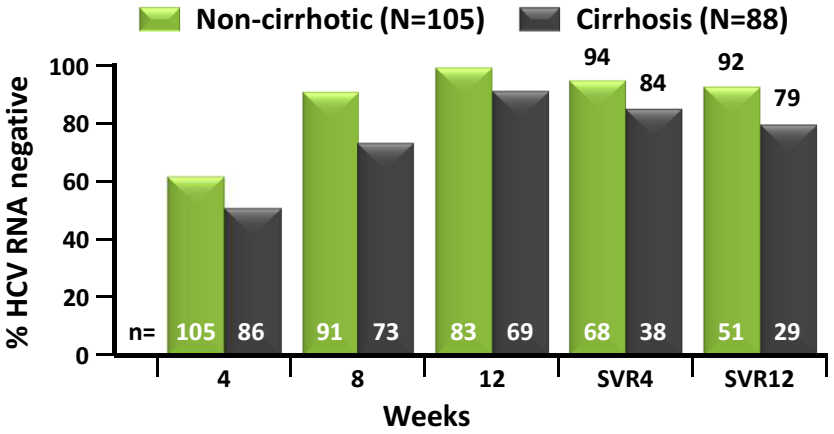
Viral response according to treatment regimen



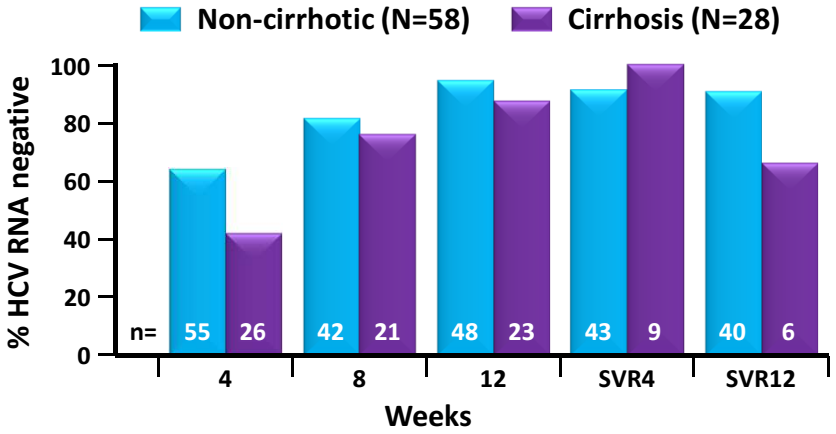
Viral response according to HIV status



Viral response according to liver cirrhosis (HCV)



Viral response according to liver cirrhosis (HCV/HIV)



Mauss S *et al*, Abstract 646, CROI Seattle 2015

Drug - Drug Interactions

GRZ/
EBV

3D/r

ASV

SMV

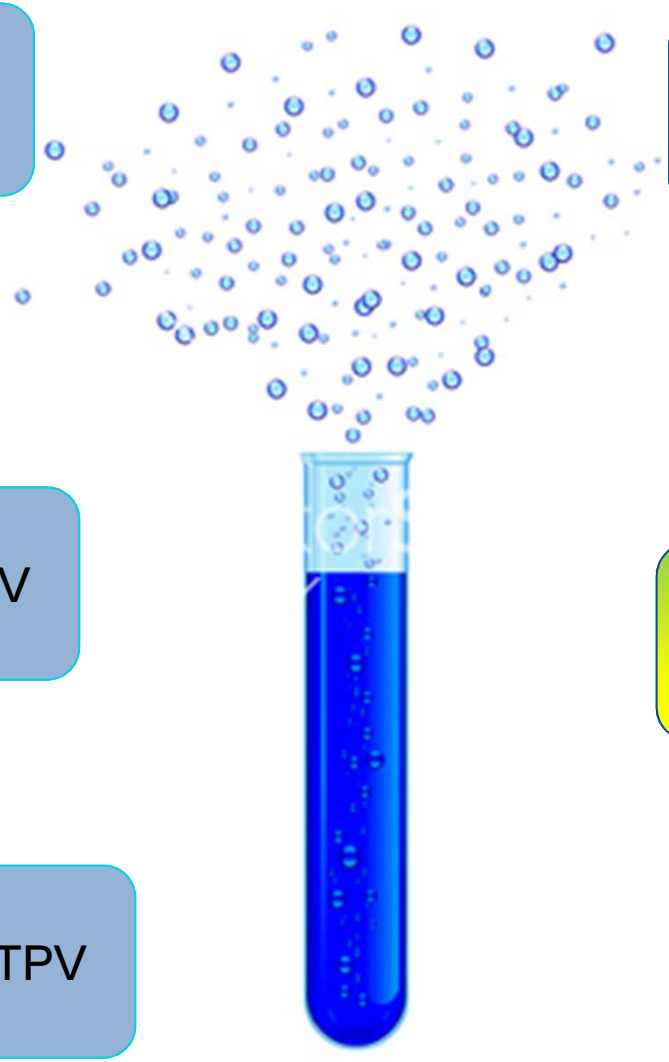
LDV

BOC

SOF

DCV

TPV



DRV/r

RAL

DTG

EFV

FTC

EVG

ATZ/r

TDF

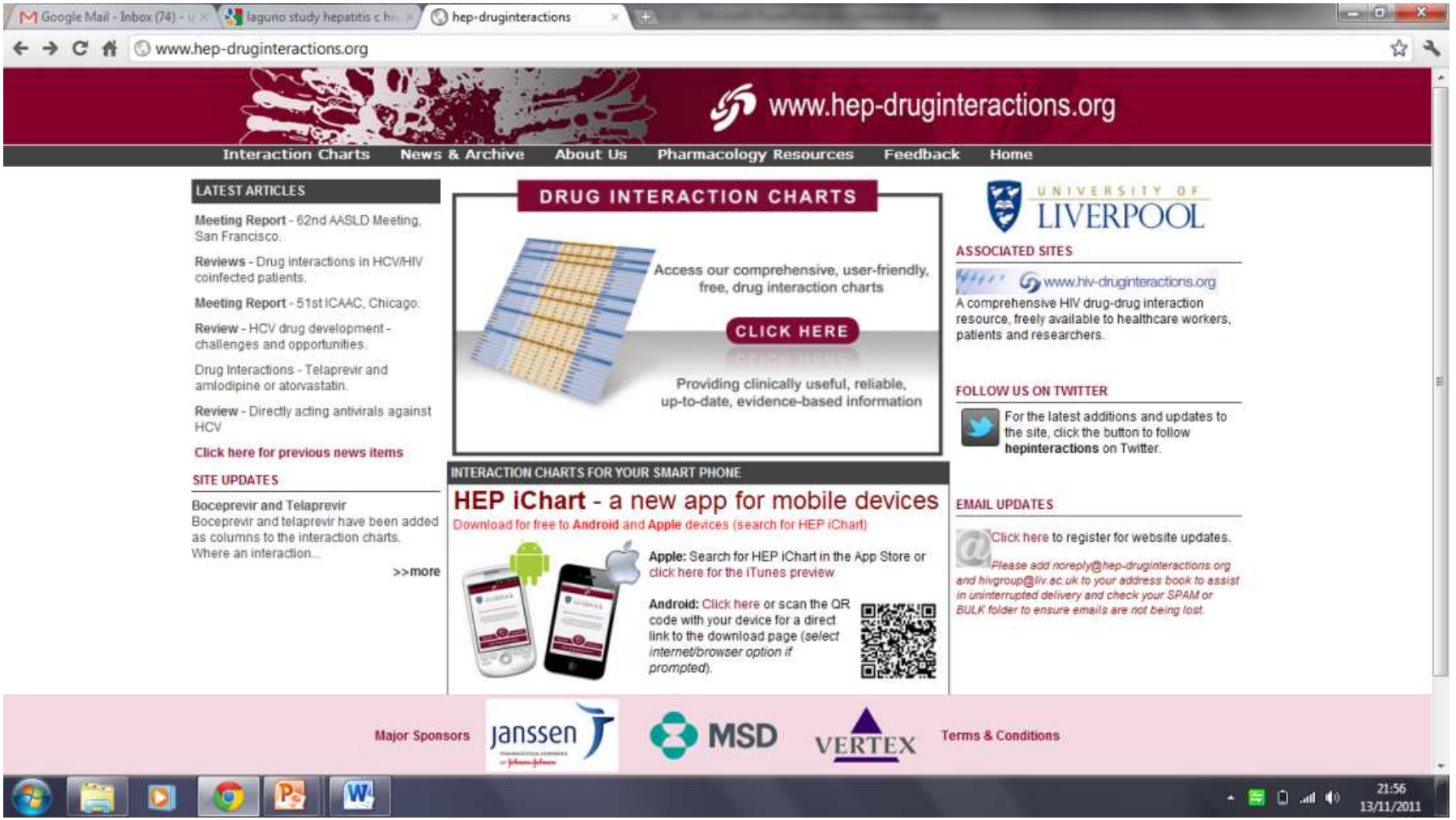
RPV

ABC

ETR

Hepatitis C – which ART

- Depends largely on drug-drug interactions…



Objectives

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Any role for routine baseline genotyping?

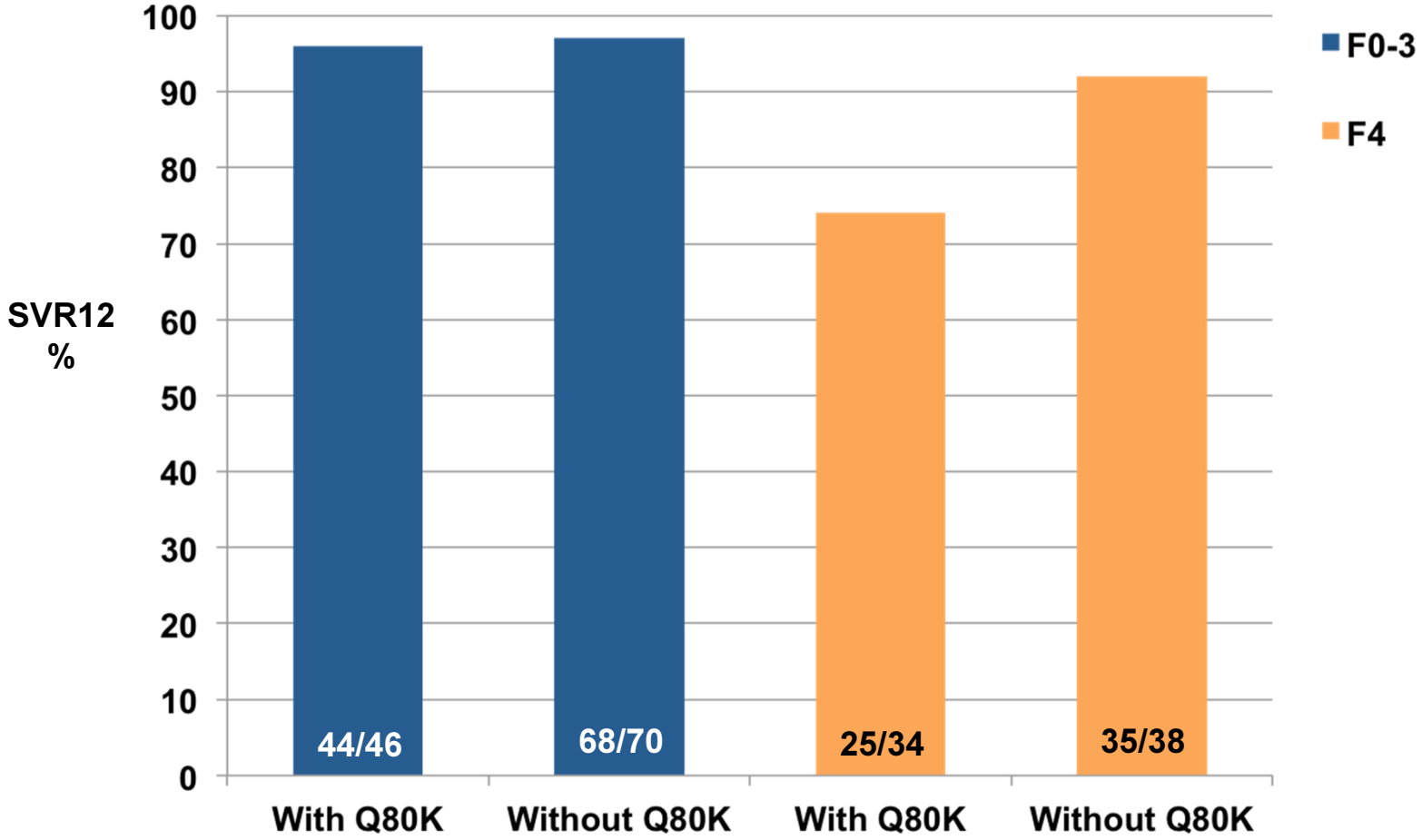
- EASL* Guidance = not recommended at baseline
- Except…

*European Association for the Study of the Liver

http://www.easl.eu/medias/cpg/HEPC-2015/Summary.pdf

SOFOSBUVIR/SIMEPREVIR

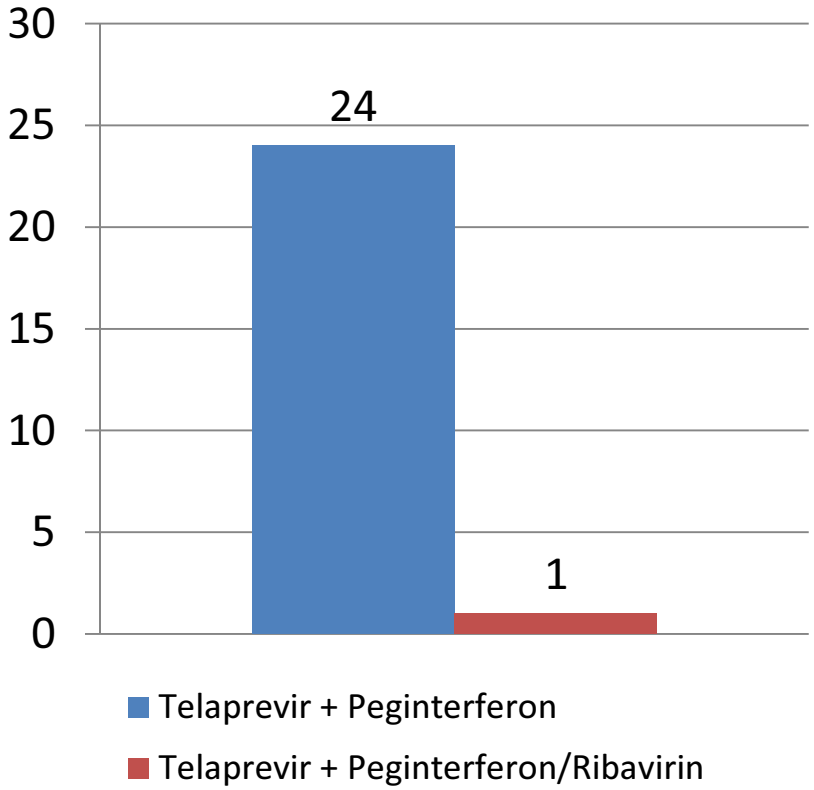
OPTIMIST-1&2: GT1, F0-3/F4, TN/TE, 12 wks



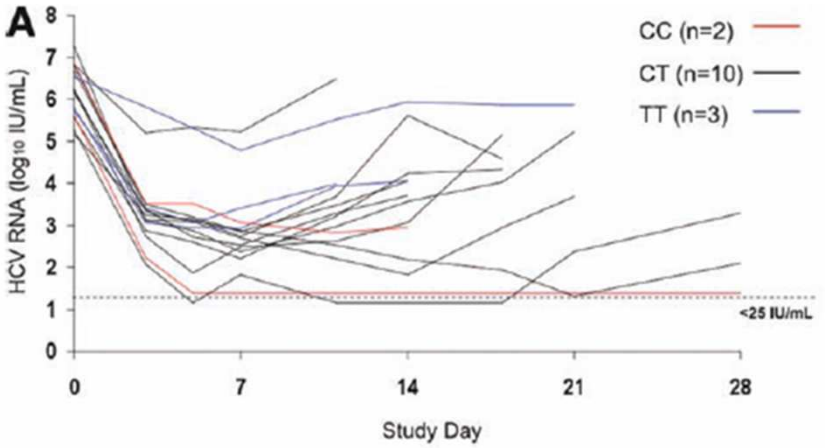
Kwo P, et al. ILC 2015; Lawitz E, et al. ILC 2015

Ribavirin prevents the emergence of resistance associated variants

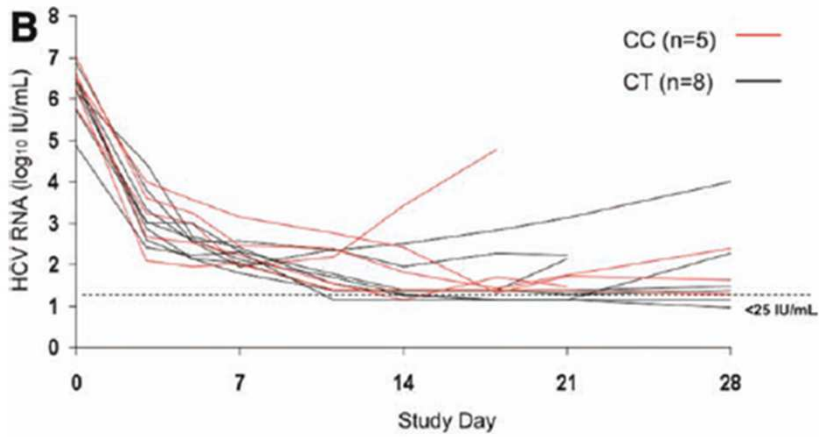
HCV breakthrough with or without ribavirin during telaprevir/peginterferon



Zeuzem Hepatology 2012
Hezode NEJM 2009



NS3 protease + non-nuc NS5B polymerase inhibitor +
No Ribavirin



NS3 protease + non-nuc NS5B polymerase inhibitor +
Ribavirin

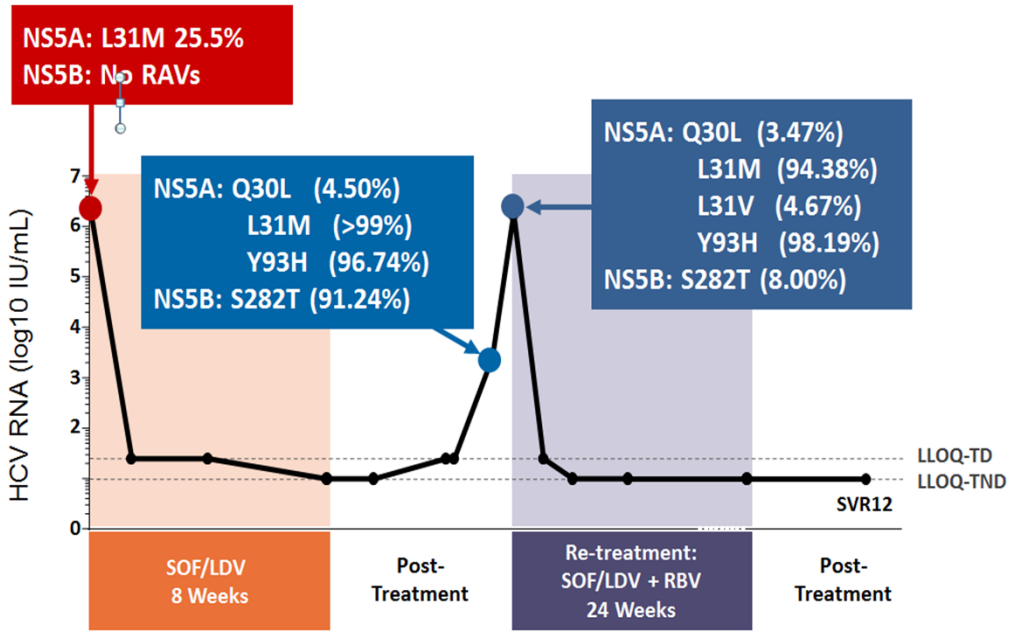
Impact of drug resistance in subsequent HCV treatment is uncertain

Resistance associated variants can occur at the time of virologic failure

- Ledipasvir/Sofosbuvir (n=37)
  - NS5A RAVs, n=23 (62%)
  - NS5B RAVs,
- Ombitasvir/Paritaprevir/r + dasabuvir (n=64, 58 G1a
- NS3 RAVs, n=55 (86%)
  - NS5A RAVs, n=47 (73%)
  - NS5B RAVs, n=40 of 57 (62%)
  - All three targets, n=30 of 58 (53%)

Successful retreatment of relapser (8/52) SOF/LDV

Retreated SOF/LDV +RBV for 24 weeks



Lawitz Lancet 2013
US prescribing information for each regimen

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BHIVA guidelines for Acute Hepatitis C

- Discuss benefits of early vs deferred treatment
- Treatment if no spontaneous clearance:
  - <2log drop in HCV RNA after 4 weeks
  - Any positive RNA at 12 weeks

- Make sure start treatment before 24 weeks....
  - If > 24 weeks post diagnosis then =chronic
- Rx
  - Peg-IFN & weight-based Ribavirin following stopping rules:
    - If RVR then for 24 weeks
    - If no RVR then 48 weeks
    - If no EVR then stop.... (futile)

TASP

HCV TREATMENT AS PREVENTION EVALUATION POTENTIAL GOAL OF ERADICATION

Potential Populations

- Community-based PWID
- Prisoners
- HIV+/HCV+ co-infected
- Antenatal
- Hospitalised

Adapted from Dore GJ

Objectives

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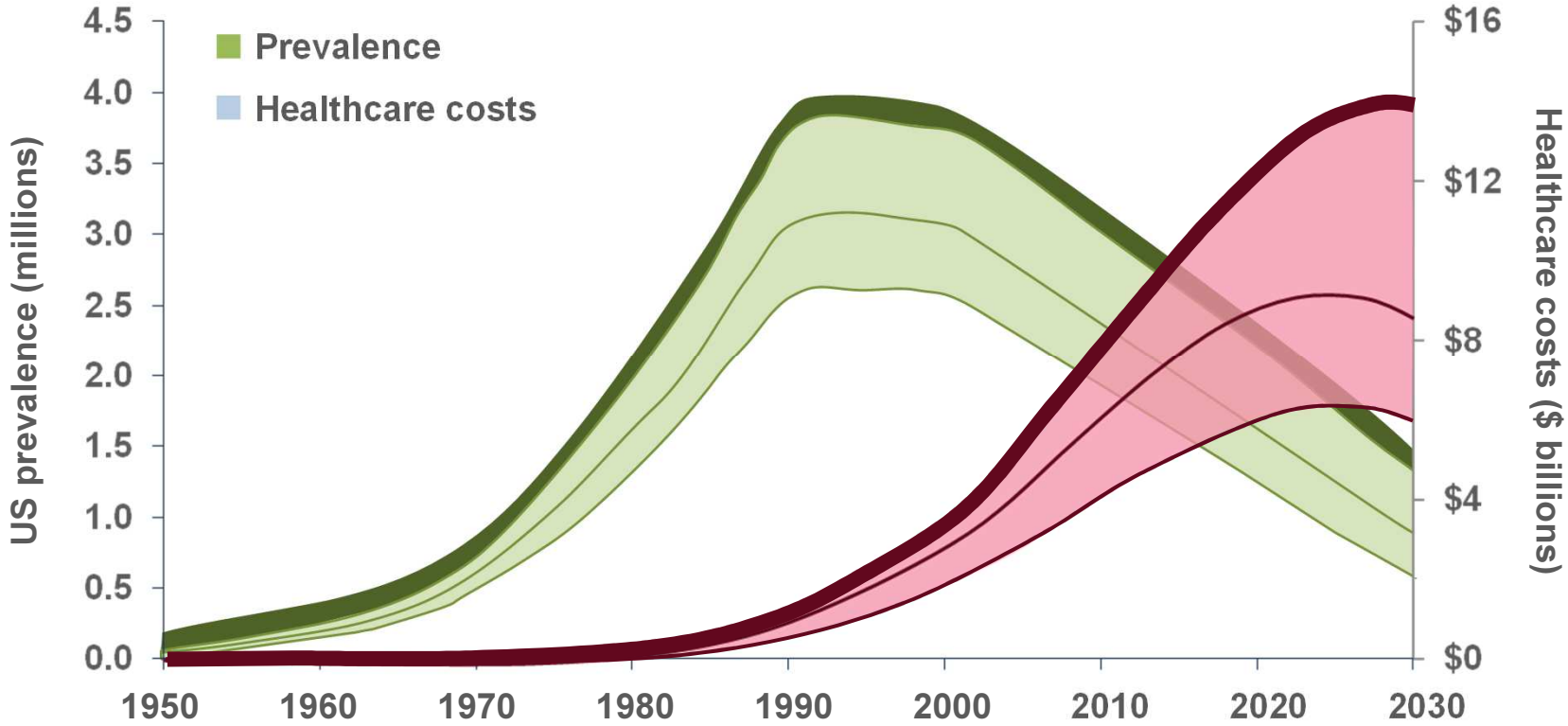
Healthcare costs are climbing due to patients progressing to more advanced liver disease



The HCV population is ageing
Serious liver disease associated with HCV will have a greater healthcare system impact as the infected population ages

Razavi H, et al. Hepatology 2013;57:2164–70.

Cost-effectiveness of HCV treatment

- HCV treatment is cost effective
  - Less than $50,000
  - Varies depending upon base assumptions (% in various stages, progression rate of fibrosis, reduction of QOL with HCV)
- Immediate treatment of moderate and advanced fibrosis appears to be cost-effective (>F1).
- Immediate treatment of patients with no fibrosis can be cost-effective, BUT at lower treatment costs

Liedner 2015

Our Response

Thanks to….

Barts Health NHS
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