

Update on chronic hepatitis C treatment: current trends, new challenges, what next?

Matti Maimets

12.06.2015

Disclosure

- this presentation is sponsored by Gilead Sciences

Science April 21, 1989

Isolation of a cDNA Clone Derived from a Blood-Borne **Non-A, Non-B** Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY,
DANIEL W. BRADLEY, MICHAEL HOUGHTON

A random-primed complementary DNA library was constructed from plasma containing the uncharacterized non-A, non-B hepatitis (NANBH) agent and screened with serum from a patient diagnosed with NANBH. A complementary DNA clone was isolated that was shown to encode an antigen associated specifically with NANBH infections. This clone is not derived from host DNA but from an RNA molecule present in NANBH infections that consists of at least 10,000 nucleotides and that is positive-stranded with respect to the encoded NANBH antigen. These data indicate that this clone is derived from the genome of the NANBH agent and are consistent with the agent being similar to the togaviridae or flaviviridae. This molecular approach should be of great value in the isolation and characterization of other unidentified infectious agents.

The Fathers



Figure 3 The HCV team (from left to right; M. Houghton, Q-L Choo, G. Kuo and D. Bradley).

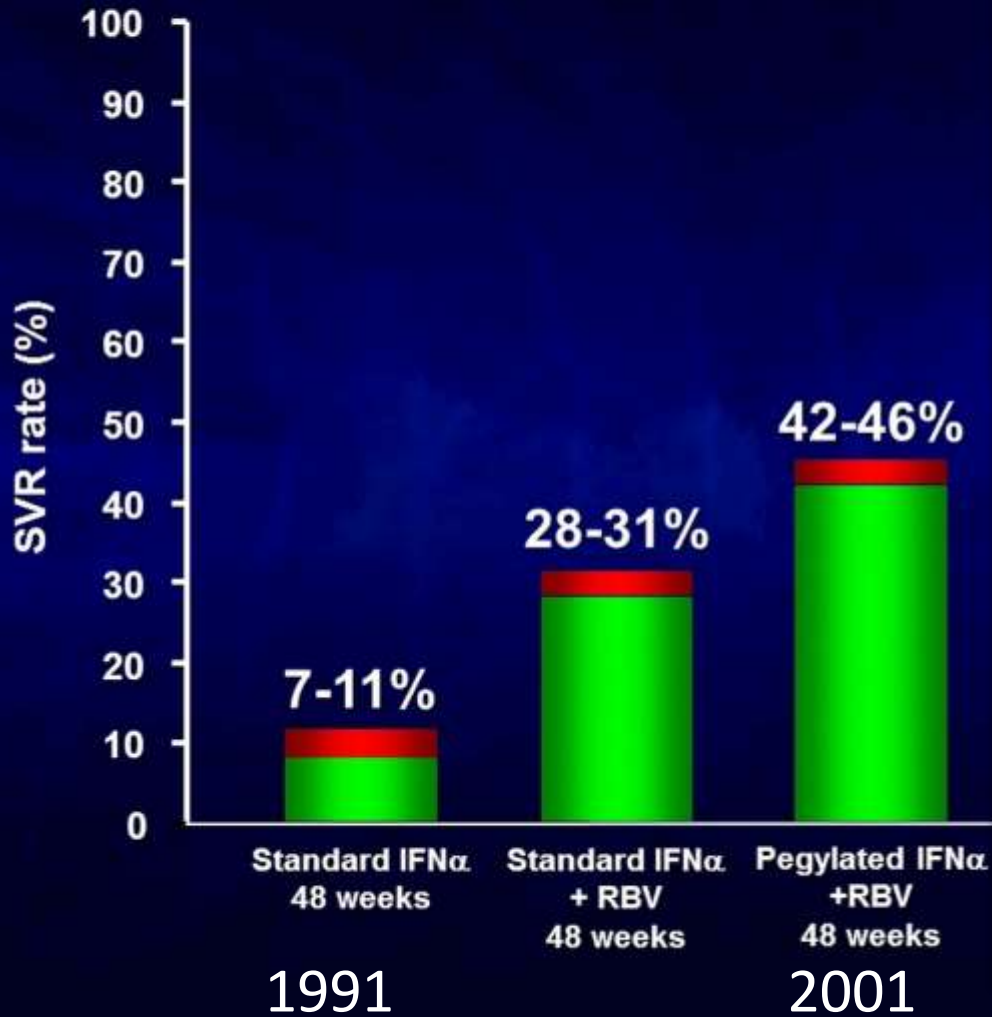
Houghton Nature Med 2000;6:1084

First Treatment Attempts

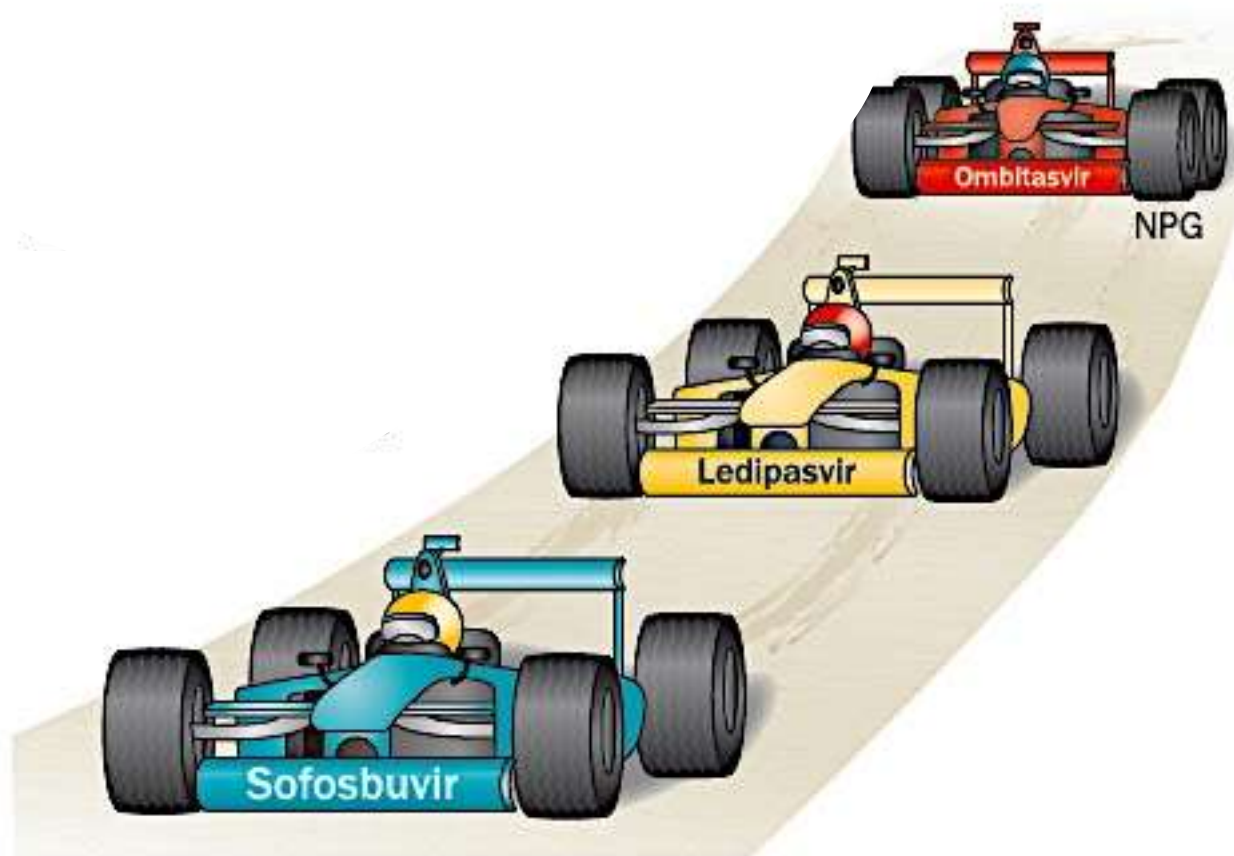
Interferon for chronic non-A, non-B hepatitis

- **1984 – 86**
- 10 patients
- ALT levels fell to normal in 8, remained normal in 5

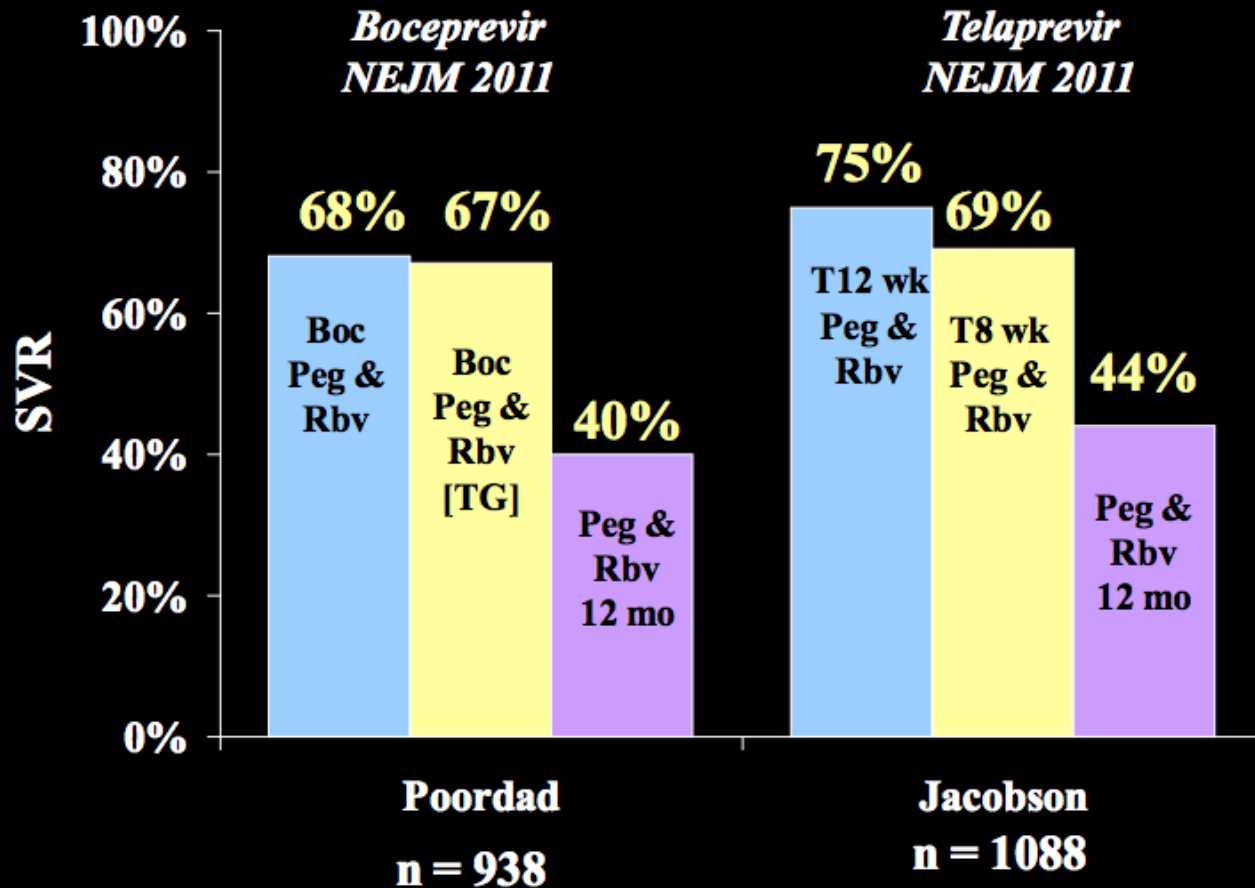
HCV Genotype 1 Therapy



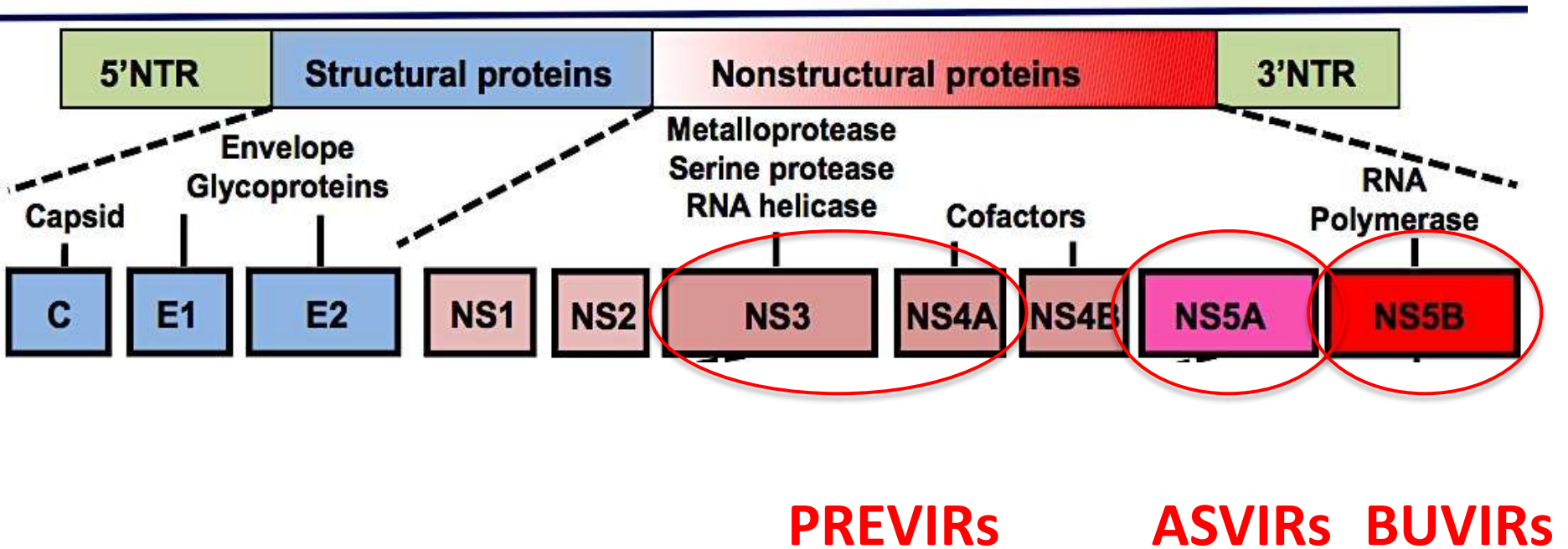
2010: The Directly Acting Antivirals (DAAs)



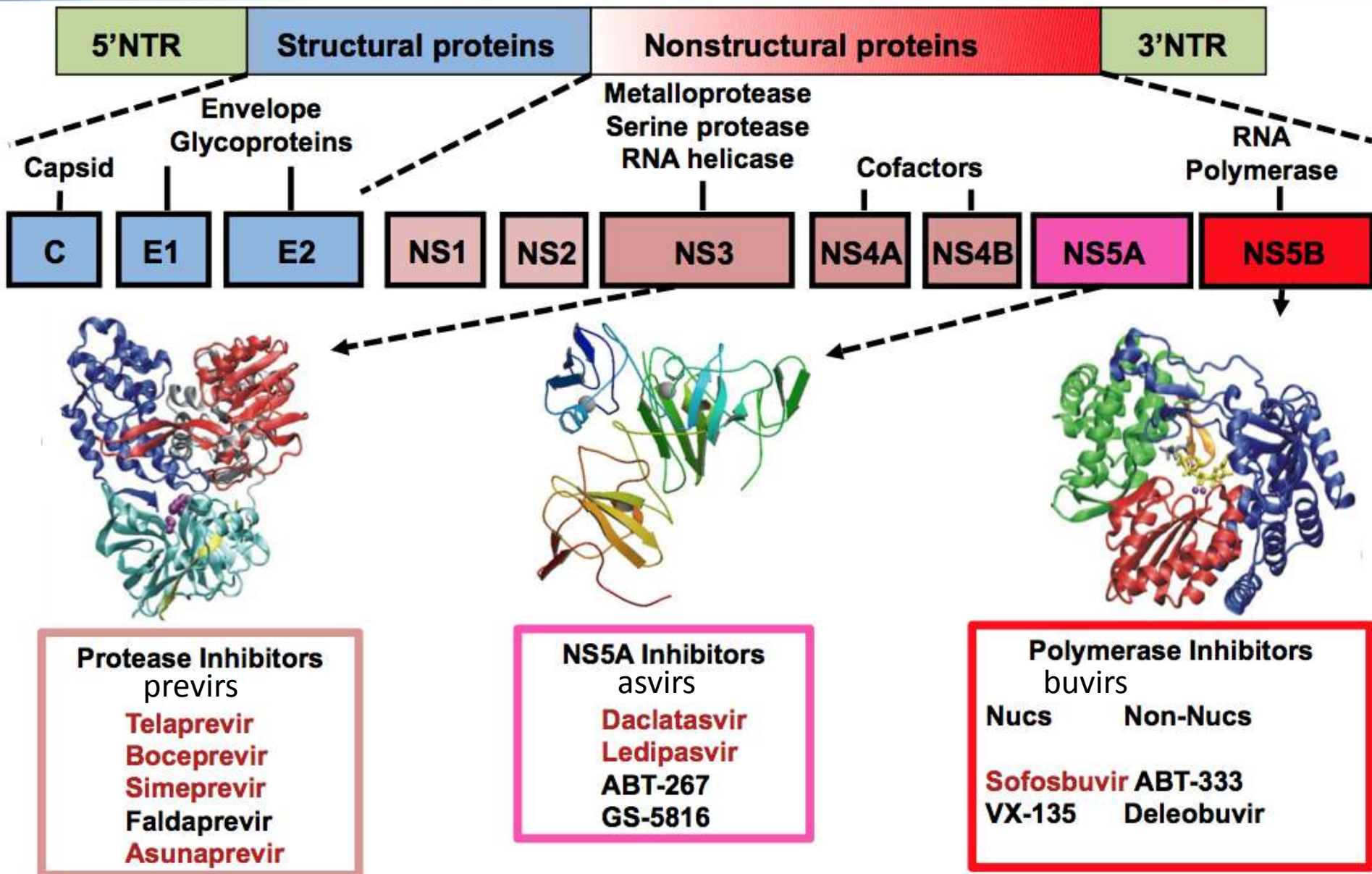
Two HCV Protease Inhibitors Efficacy in Chronic Hepatitis C, genotype 1



The DAAs



Direct acting antivirals



DAAs currently approved

2013-2014

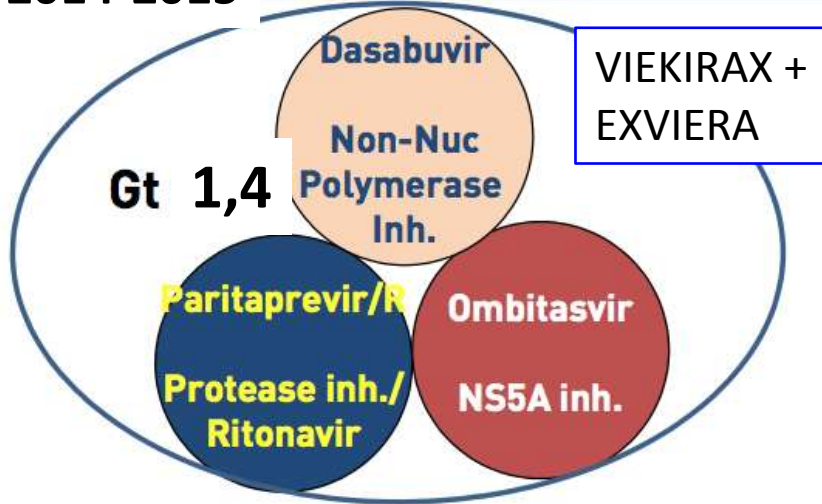


Triple therapy with PEG IFN and ribavirin

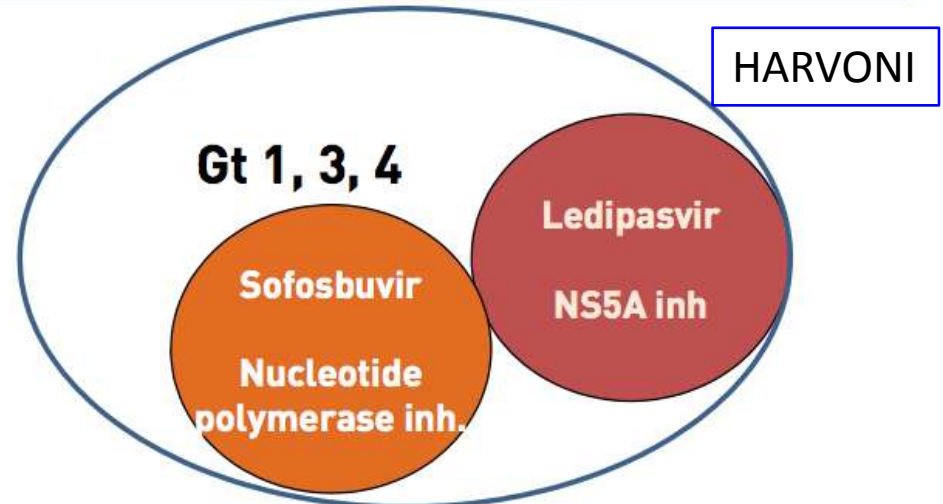
SOF and ribavirin, no IFN

of two DAAs \pm ribavirin

2014-2015



Fixed dose combination of three DAAs \pm ribavirin



Fixed dose combination of two DAAs \pm ribavirin.

Current access to second-generation DAAs in the European region

SMV
SOF

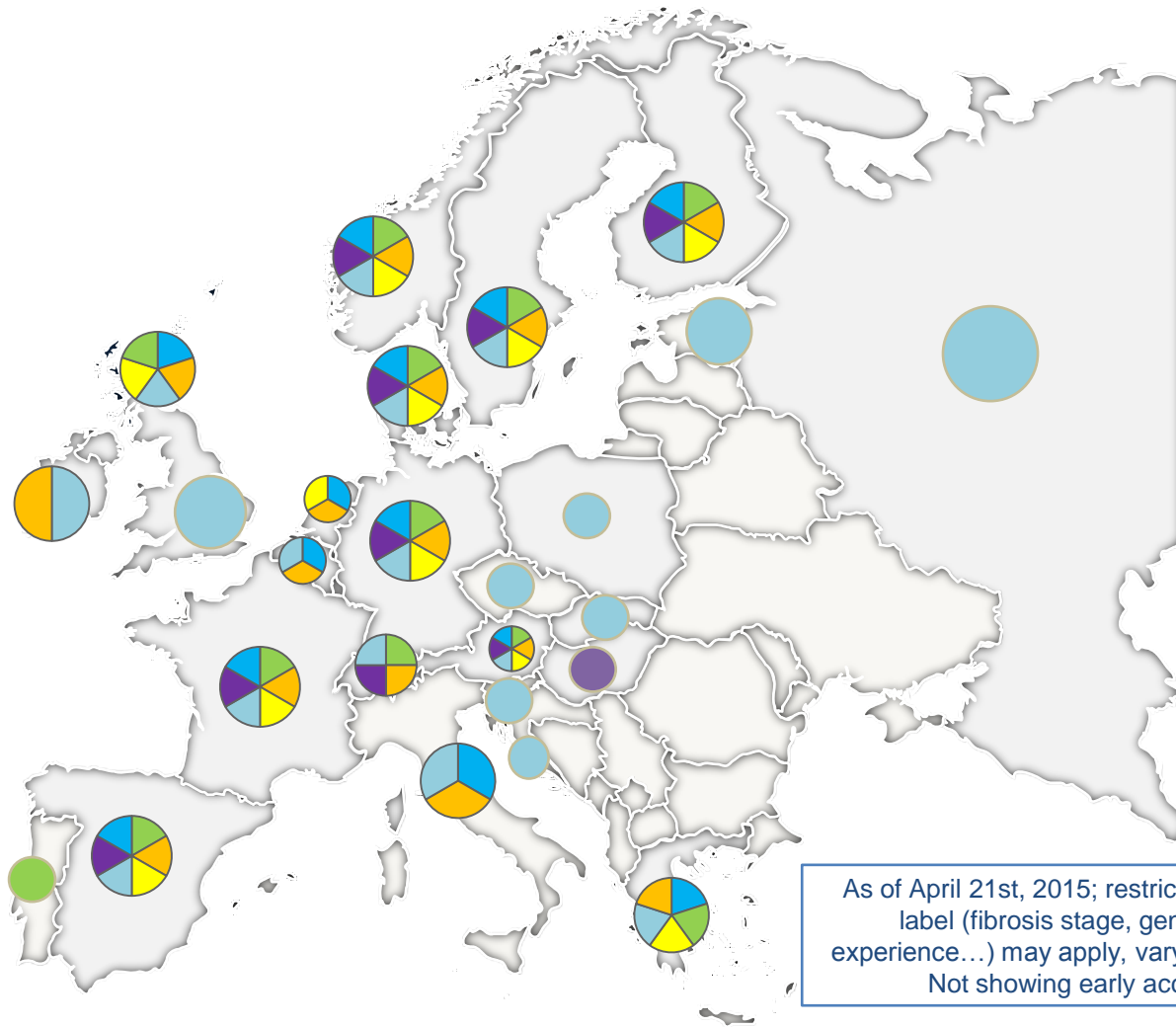
SMV
PR

SOF

SOF/
LDV

DCV

3D/r



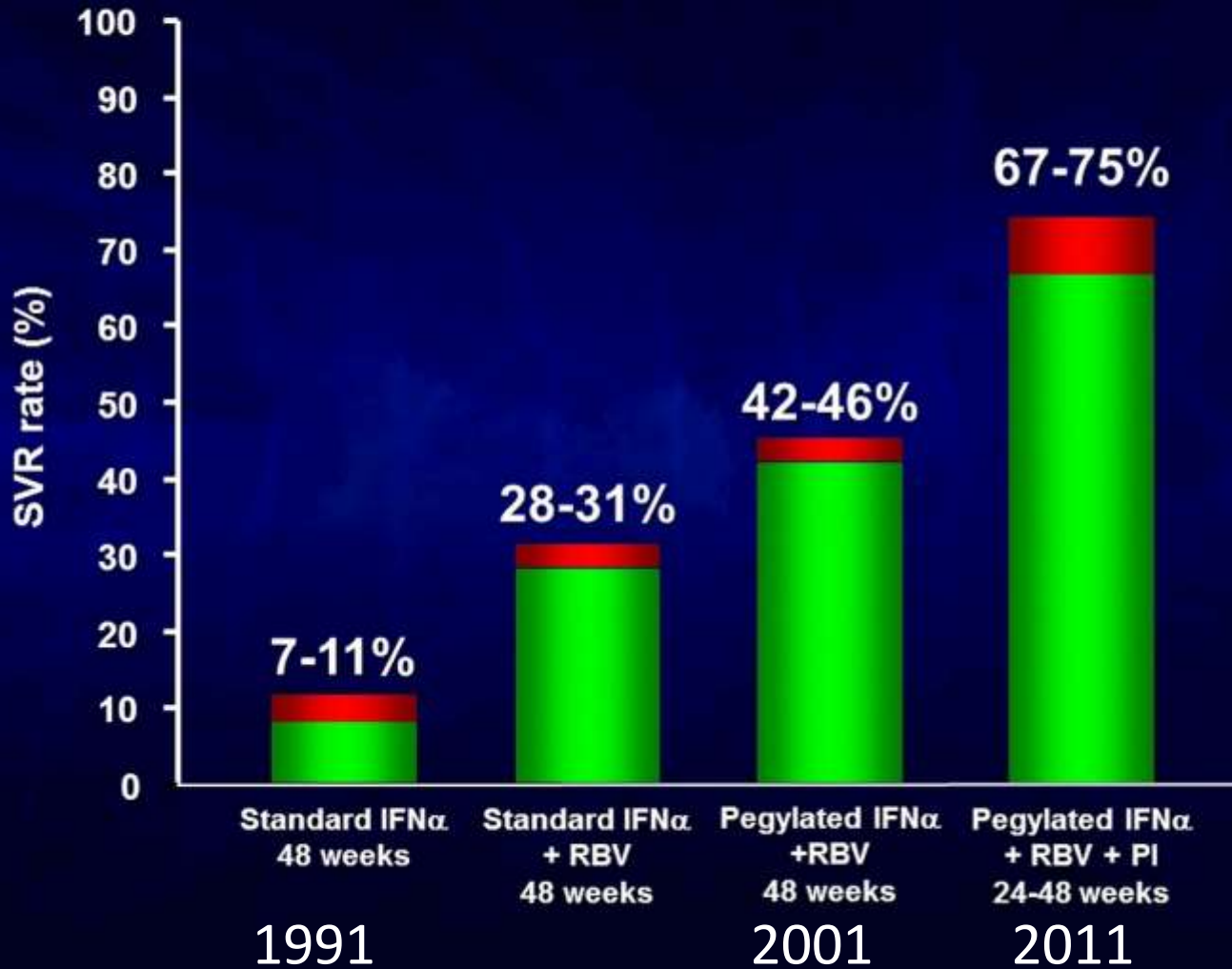
As of April 21st, 2015; restrictions compared to EU label (fibrosis stage, genotype, treatment experience...) may apply, varying country by country
Not showing early access programs

The DAA regimens

- **first-generation PI + PEG/RBV-based**
 - TLV + PEG/RBV
 - BOC + PEG/RBV
- **second-generation PI + PEG/RBV-based**
 - SOF + PEG/RBV
 - SMV + PEG/RBV
- **interferon free DAA combinations \pm RBV**

First-generation PI + PEG/RBV based regimens

HCV Genotype 1 Therapy



Adverse Events

- skin rash (TVR)
- anaemia
- leukopenia
- thrombopenia

Estonian NPP 2013

- 22 patients, 10 N, 12 M, G1b
- VL 5000 – 5 M
- **F 1-2: 3, F 3: 15, F 4: 4**
- SVR24: 13/17 **76%**

Estonian NPP 2013

- adverse events 20/22
- skin: 10/22
- anaemia: 9/22
- **stopped AE 1/22**
- **manageable, but not without effort**



Viešosios įstaigos Vilniaus universiteto ligoninės
Santariskių klinikų filialas

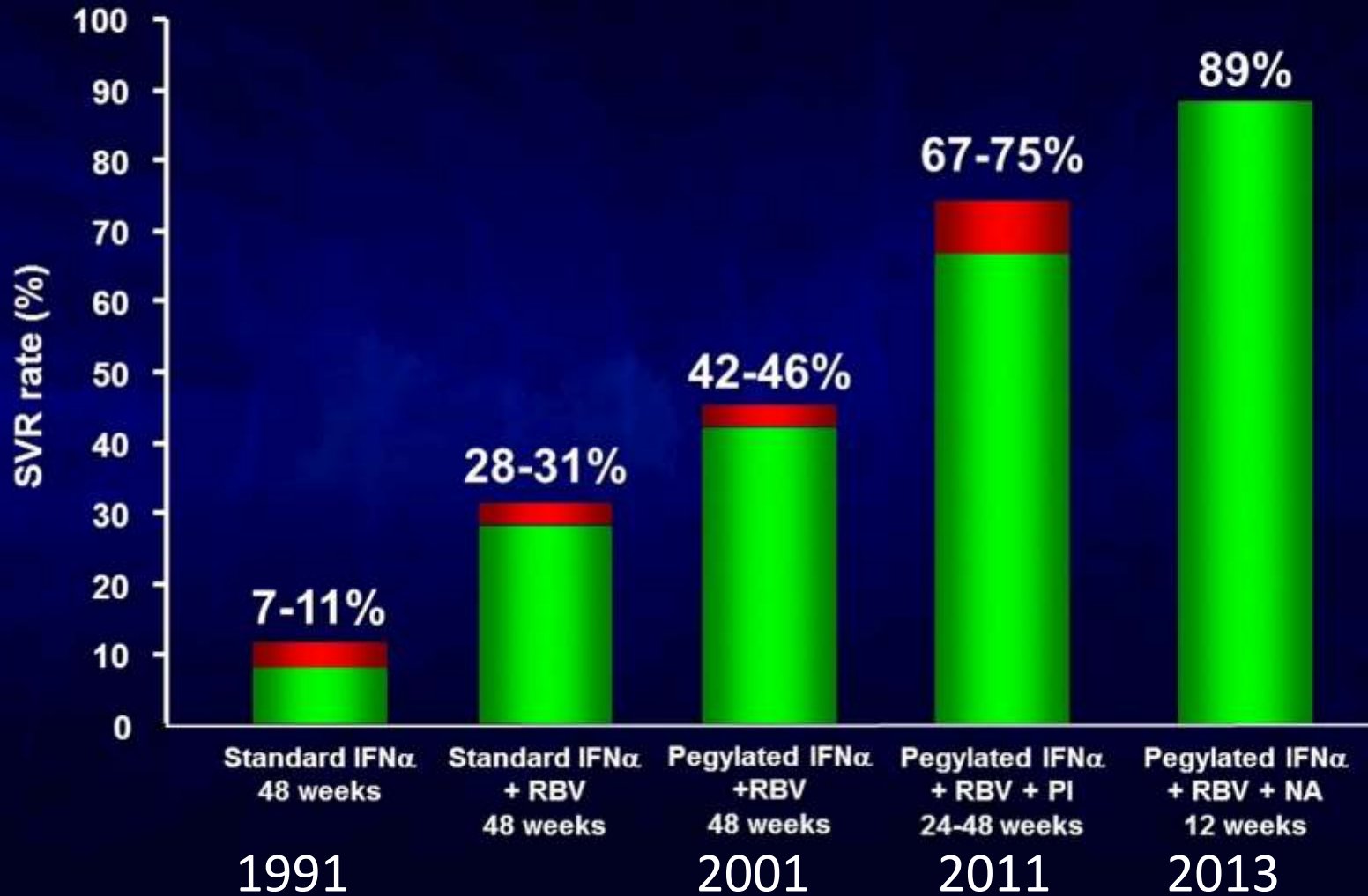
Overview of HCV treatment outcomes during DAA's early access program in Lithuania

Ligita Jančorienė
Vilnius University Hospital Santariskiu klinikos
Center of Infectious Diseases

2014-03-08

Sofosbuvir or Simeprevir + PEG/RBV based regimens

HCV Genotype 1 Therapy



Sofosbuvir + PR

N Eng J Med 2013;368

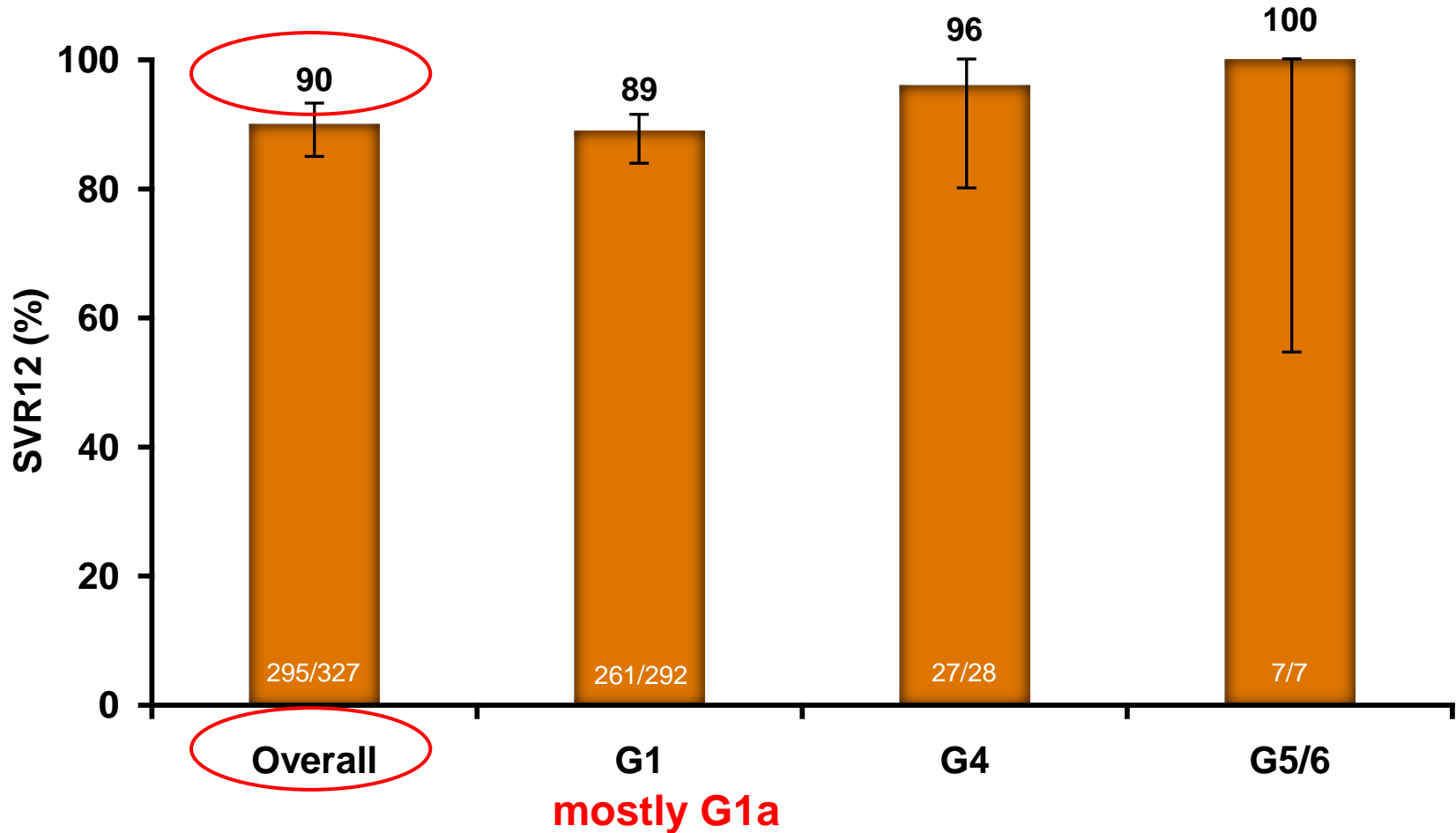
NEUTRINO STUDY

ORIGINAL ARTICLE

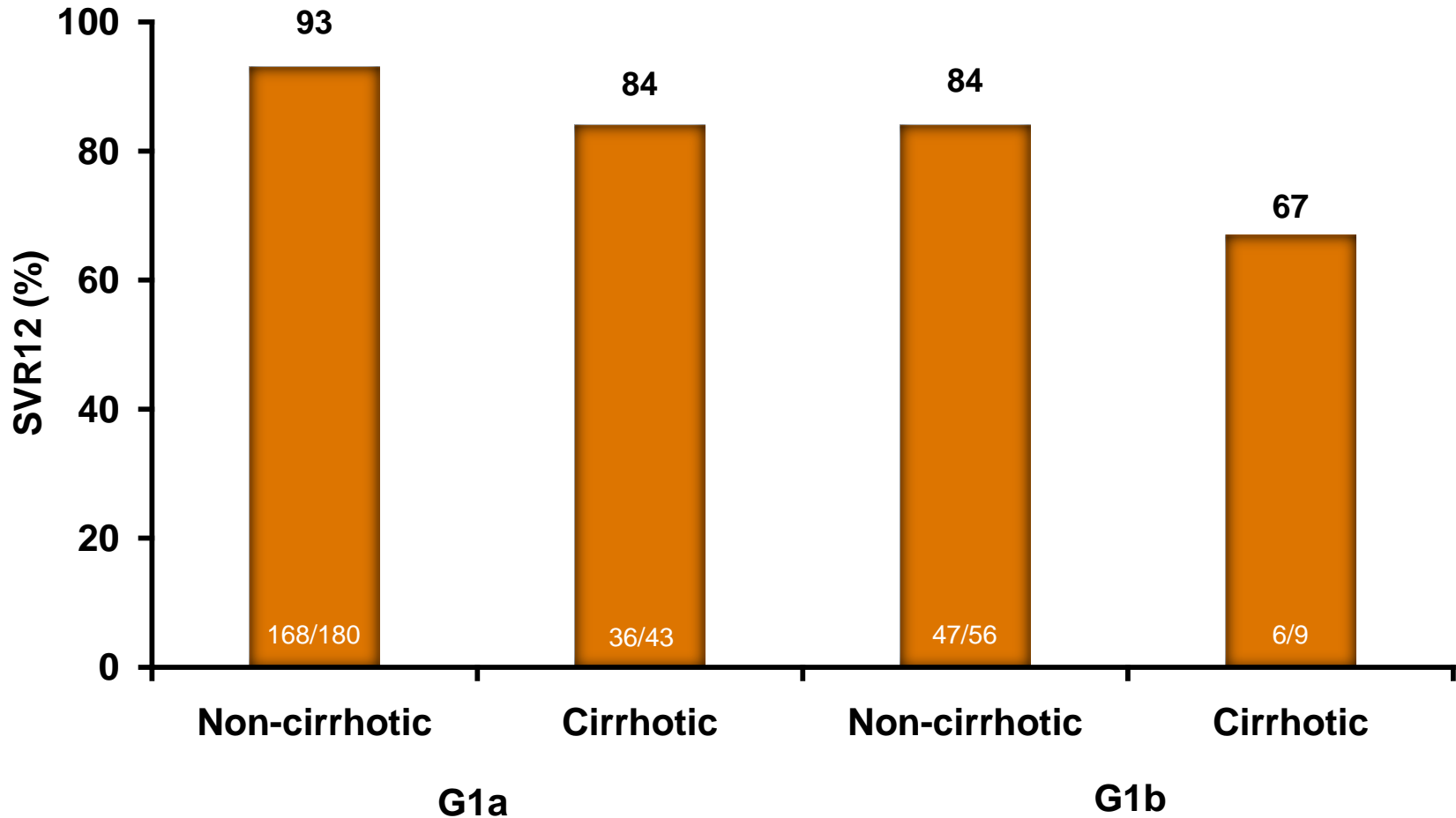
Sofosbuvir for Previously Untreated Chronic
Hepatitis C Infection

Eric Lawitz, M.D., Alessandra Mangia, M.D., David Wyles, M.D.,
Maribel Rodriguez-Torres, M.D., Tarek Hassanein, M.D., Stuart C. Gordon, M.D.,
Michael Schultz, M.D., Ph.D., Mitchell N. Davis, D.O., Zeid Kayali, M.D.,
K. Rajender Reddy, M.D., Ira M. Jacobson, M.D., Kris V. Kowdley, M.D.,
Lisa Nyberg, M.D., G. Mani Subramanian, M.D., Ph.D., Robert H. Hyland, D.Phil.,
Sarah Arterburn, M.S., Deyuan Jiang, Ph.D., John McNally, Ph.D.,
Diana Brainard, M.D., William T. Symonds, Pharm.D.,
John G. McHutchison, M.D., Aasim M. Sheikh, M.D.,
Zobair Younossi, M.D., M.P.H., and Edward J. Gane, M.D.*

SOF + PR 12 weeks (NEUTRINO): SVR12 rates by HCV genotype in treatment-naïve patients



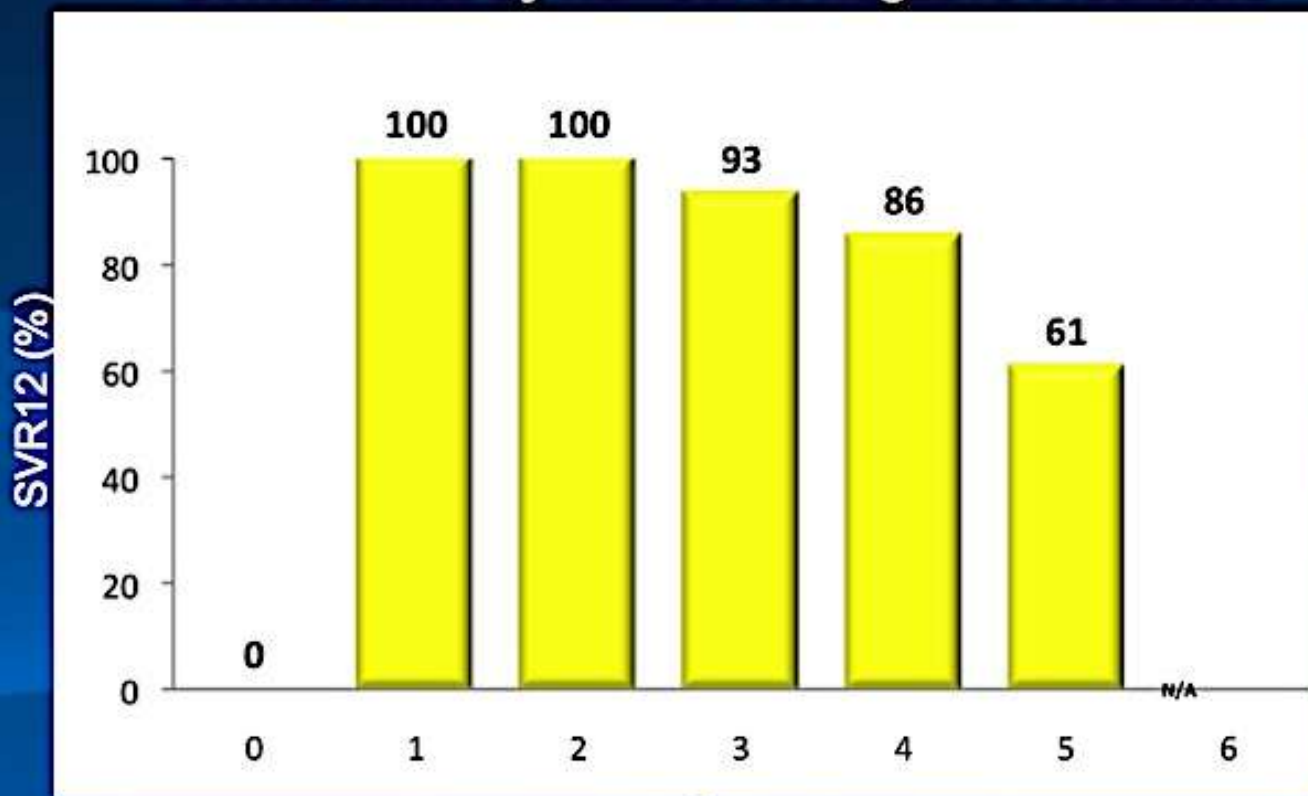
SOF + PR 12 weeks: impact of **cirrhosis status** and G1 subtype on efficacy in treatment-naïve patients (NEUTRINO)



SVR rates of SOF + PR among patients with multiple negative predictive factors (ATOMIC, NEUTRINO)

Negative predictors: cirrhosis, IL289B non-CC, RNA > 800 000, BW < 75, male gender

SVR12 Rates by Number of Negative Predictors



Simeprevir + PR

Lancet 2014,384:403 & 414



Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial

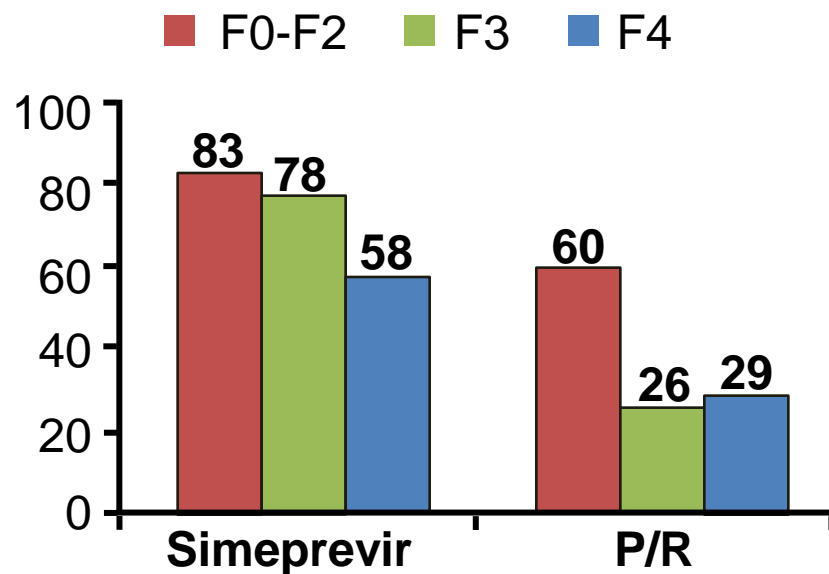
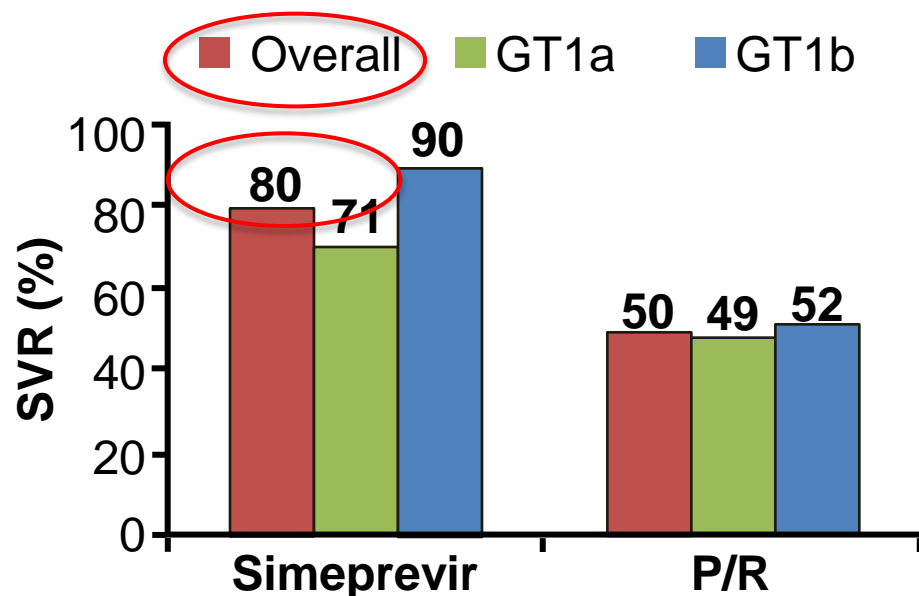
Ira M Jacobson, Gregory J Dore, Graham R Foster, Michael W Fried, Monica Radu, Vladimir V Rafalsky, Larysa Moroz, Antonio Craxi,



Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial

Michael Manns, Patrick Marcellin, Fred Poordad, Evaldo Stanislau Affonso de Araujo, Maria Buti, Yves Horsmans, Ewa Janczewska, Federico Villamil, Jane Scott, Monika Peeters, Oliver Lenz, Sivi Ouwerkerk-Mahadevan, Guy De La Rosa, Ronald Kalmeijer, Rekha Sinha, Maria Beumont-Mauviel

Simeprevir + P/R: Phase III QUEST-1: Impact of **Subtype** & **Fibrosis Stage** in GT1



- SVR: GT1b > GT1a
- SVR is lowest for patients with GT1a and baseline Q80K mutation
- SVR: F0-F2 > F4

Safety: The Major Advantage

| Regimen | Trial | HCV genotype/ population | N | F4 (%) | Grade 3–4 AE (%) | SAEs | D/C due to AEs(%) | Notable AEs* |
|---------------------------------|----------------------------------|-----------------------------|-----|-----------|------------------------|-------------|----------------------------|--|
| SMV + PR¹ | Pooled analysis Phase 2b/3 | G1 TN & TE | 924 | 11 | 31 | 5.5% | 4 | Increased bilirubin, rash |
| SOF + PR² | Neutrino | G1, 4-6 TN | 327 | 17 | 15 | 1% | 2 | Fatigue, headache, anemia, nausea, rash |

*Occurring more frequently vs PR except SOF/PR: most frequently reported AE in NEUTRINO. Lack of control arm did not allow identification of AEs occurring more frequently when SOF is added to PR
D/C: discontinuations; TN: treatment naïve; TE: treatment experienced

1. Manns M, et al. Hep DART 2013. Poster 57
2. Lawitz E, et al. N Engl J Med 2013;368:1878–87
3. Hézode C, et al. AASLD 2012. Poster 755

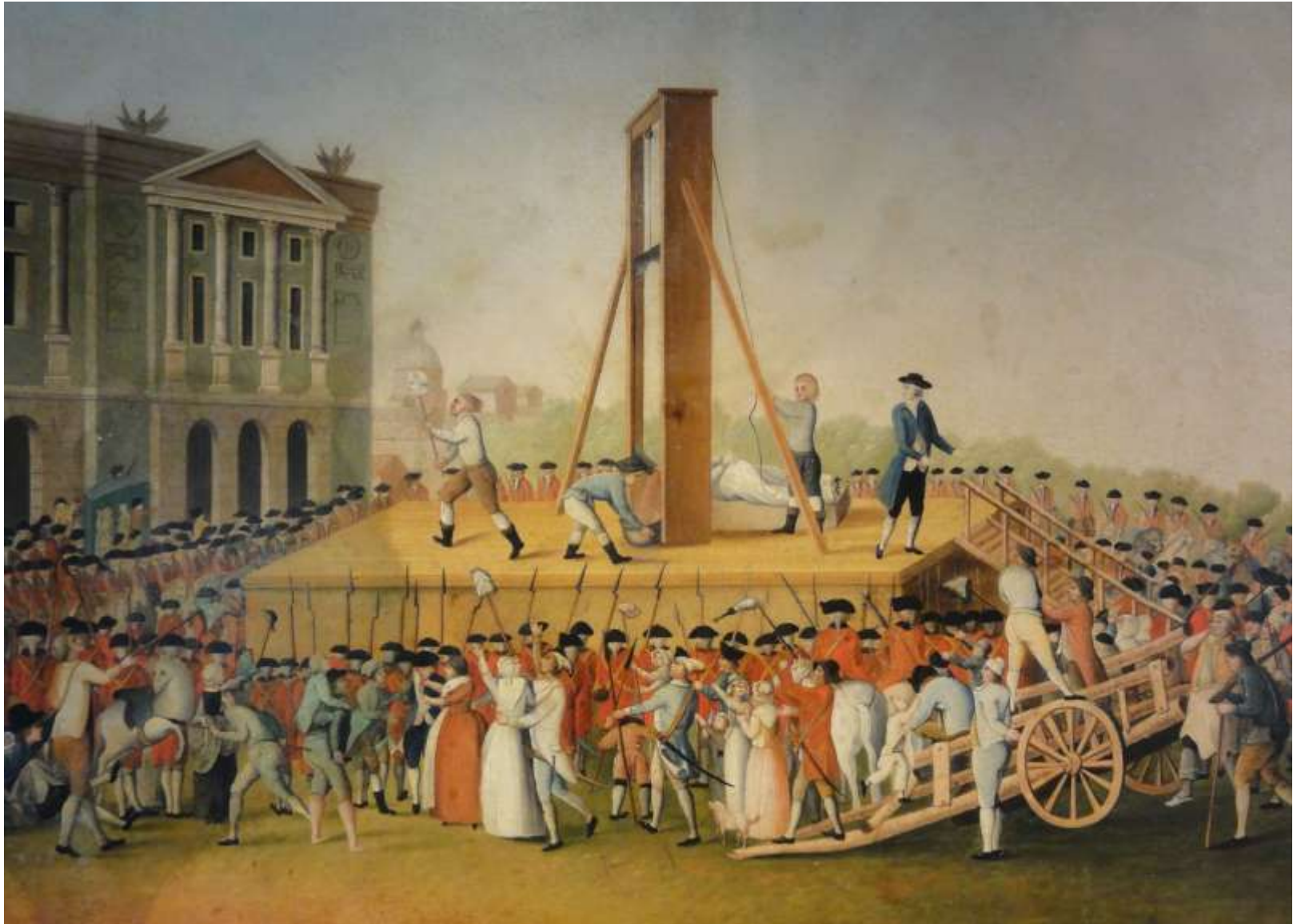
What did these studies show

- 12W SOF + PR overall SVR12 90%
- 12W SMV + 24(48)W PR G1b SVR12 85%
- SVR depends on
 - genotype 1b > 1a
 - fibrosis stage, cirrhosis
 - race
 - BMI
 - HCV RNA IU/ml
 - IL28 subgroup
- safety is not an issue

2014: The Revolution

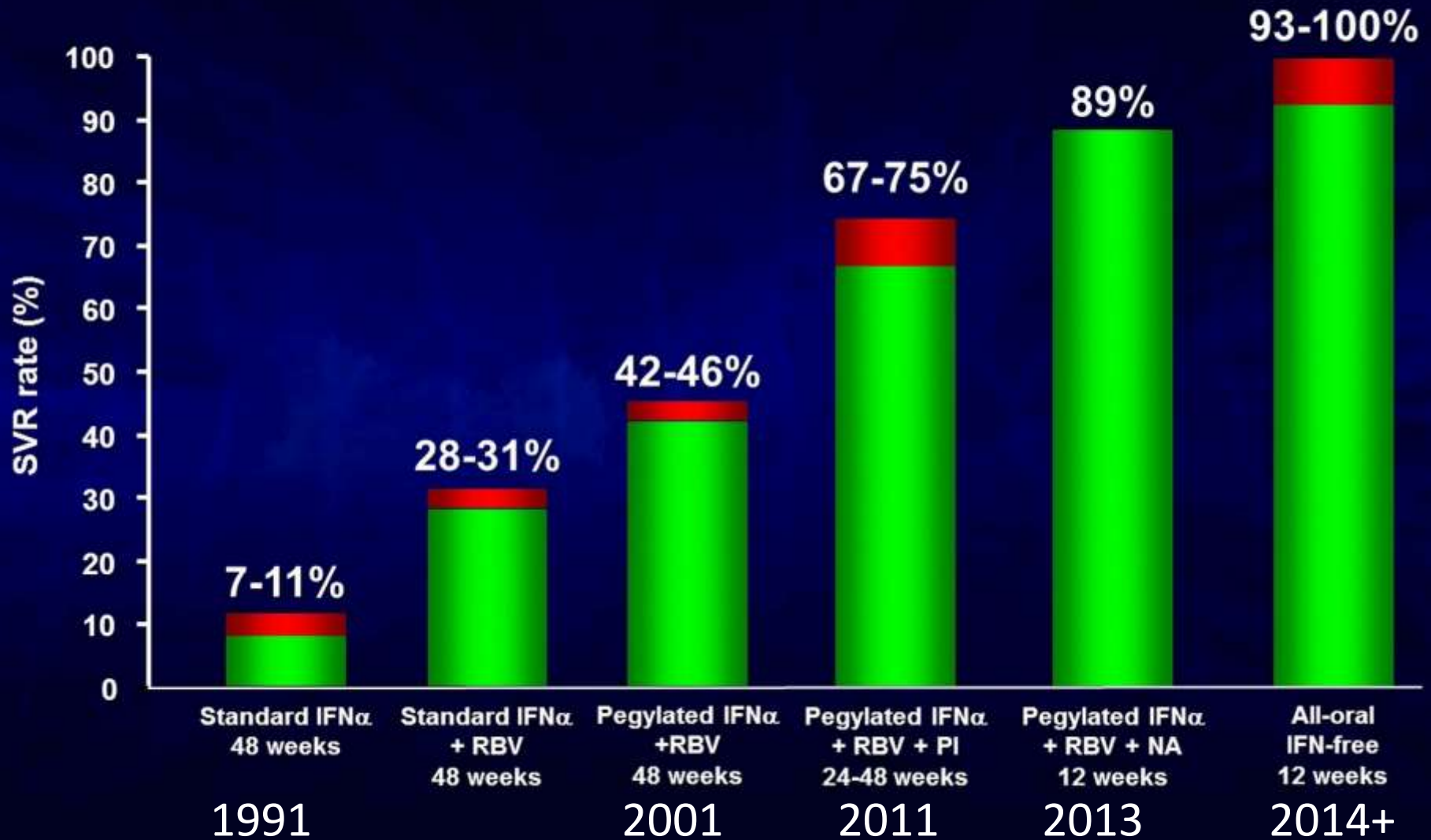
Interferon free

DAA combinations ± Ribavirin





HCV Genotype 1 Therapy



NEJM
Journal Watch

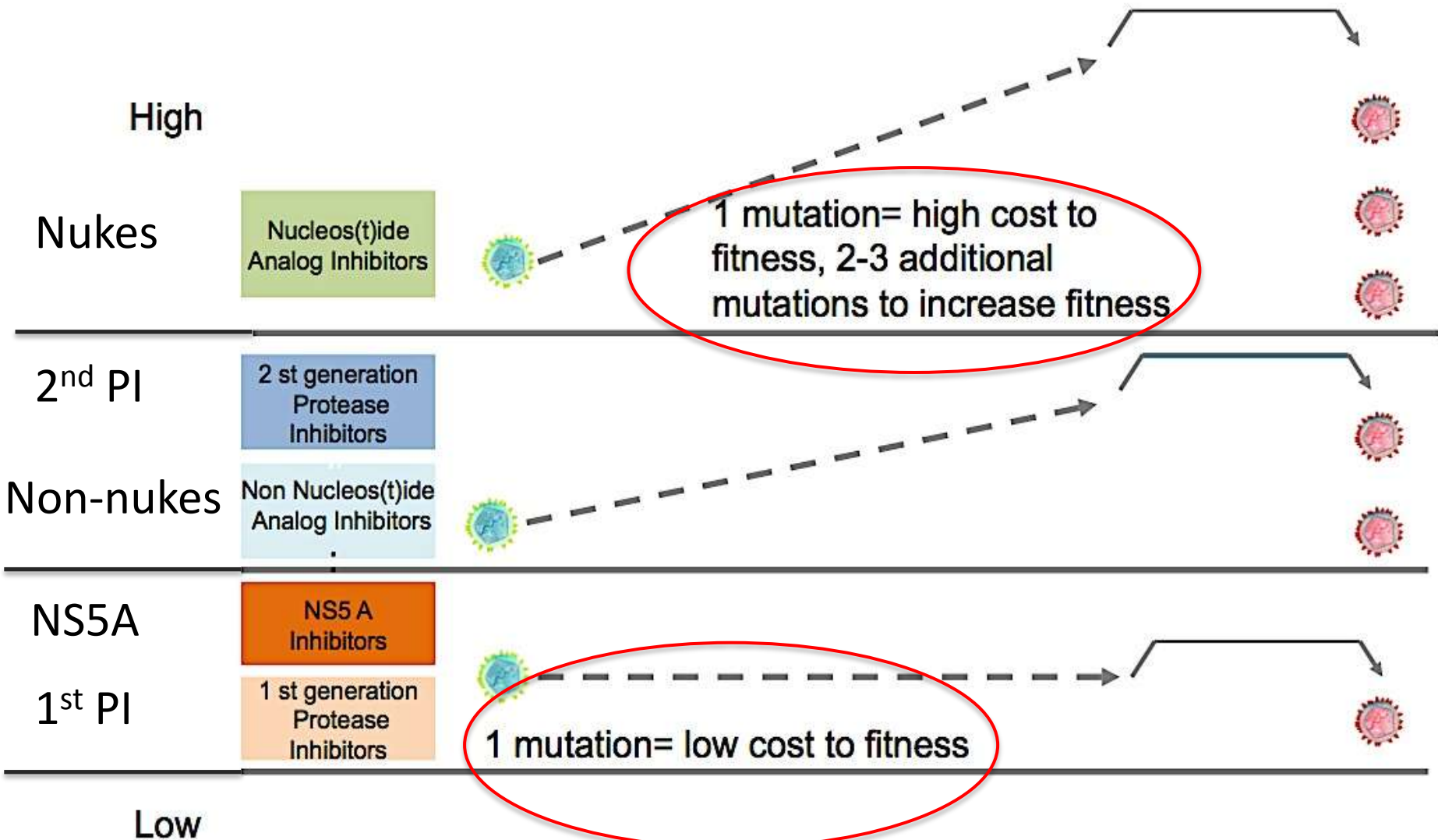
December 14th, 2014

2014 Top Stories in HIV Medicine

the most dramatic advance in treatment of an infectious disease since the discovery of penicillin

Which DAAs Can Be Combined

Genetic barrier for HCV direct acting antivirals

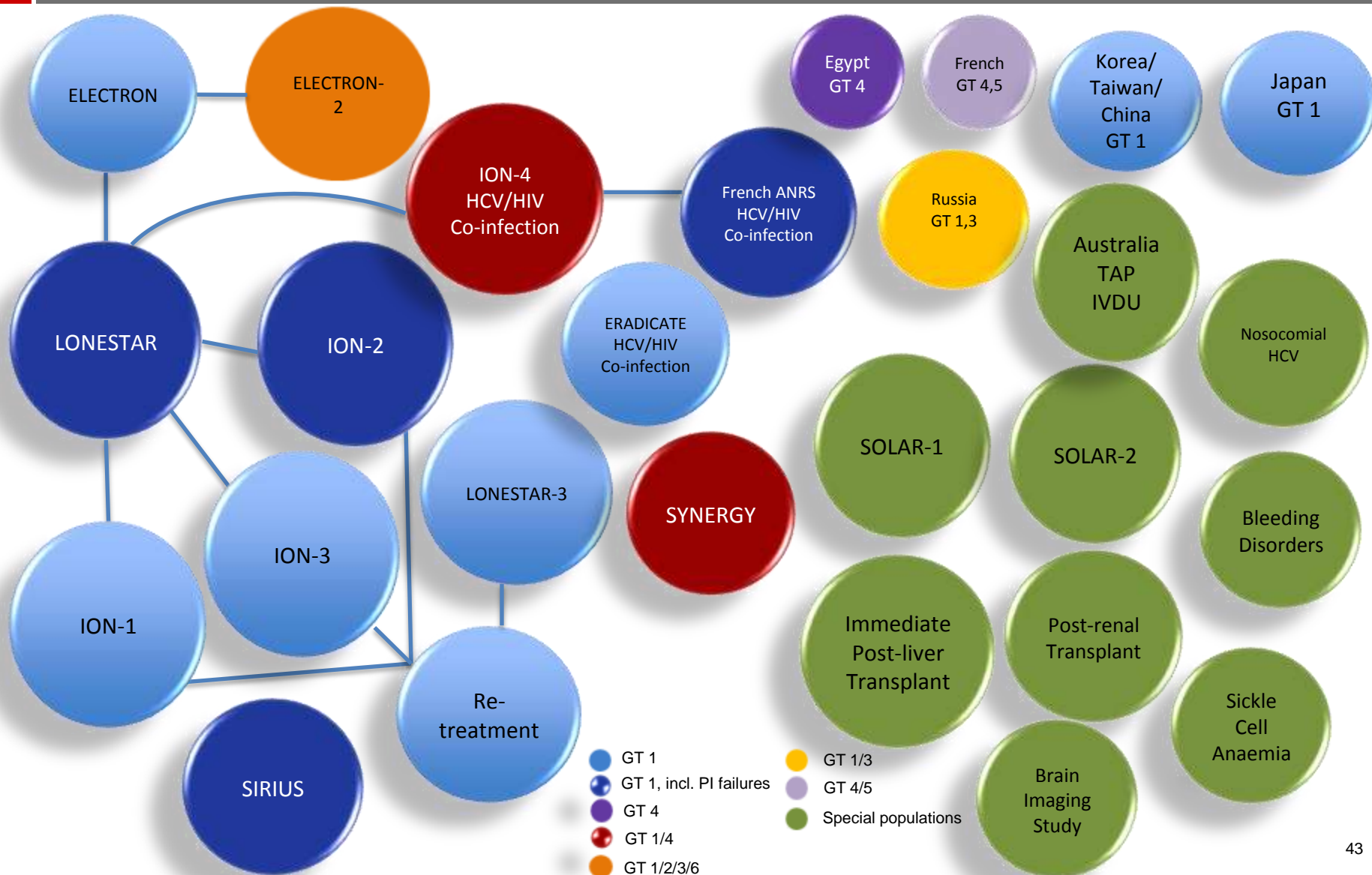


J Med Virology *early online*

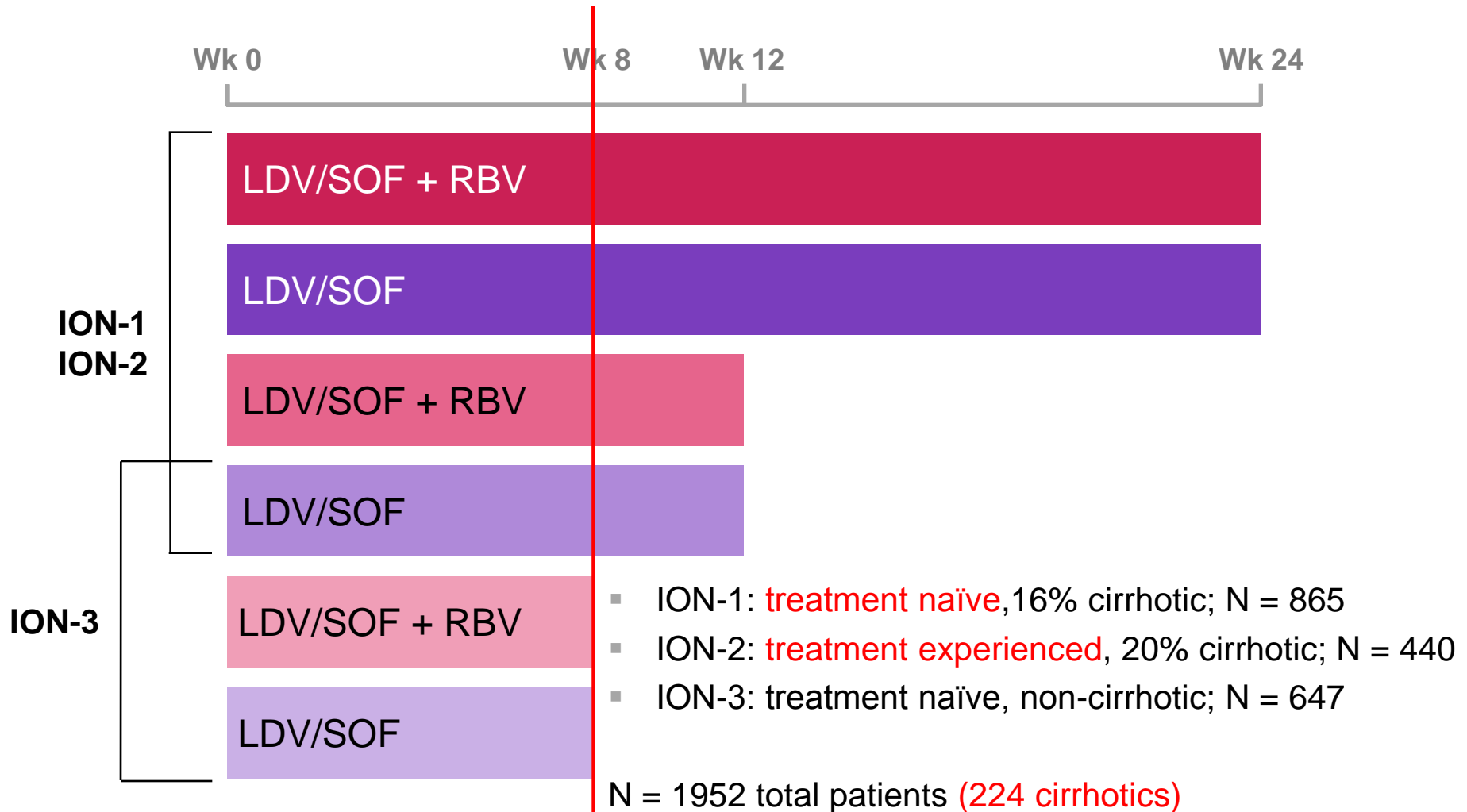
- Satoshi Yoshimi e.a. **Long term persistence of NS5A inhibitor-resistant hepatitis C virus in patients who failed daclatasvir and asunaprevir therapy**
- NS5A-L31M and -Y93H variants
- persisted as **dominant strains** until post-treatment **week 170**.

Studies of interferon free DAA combinations \pm Ribavirin

LDV/SOF Clinical Development Program

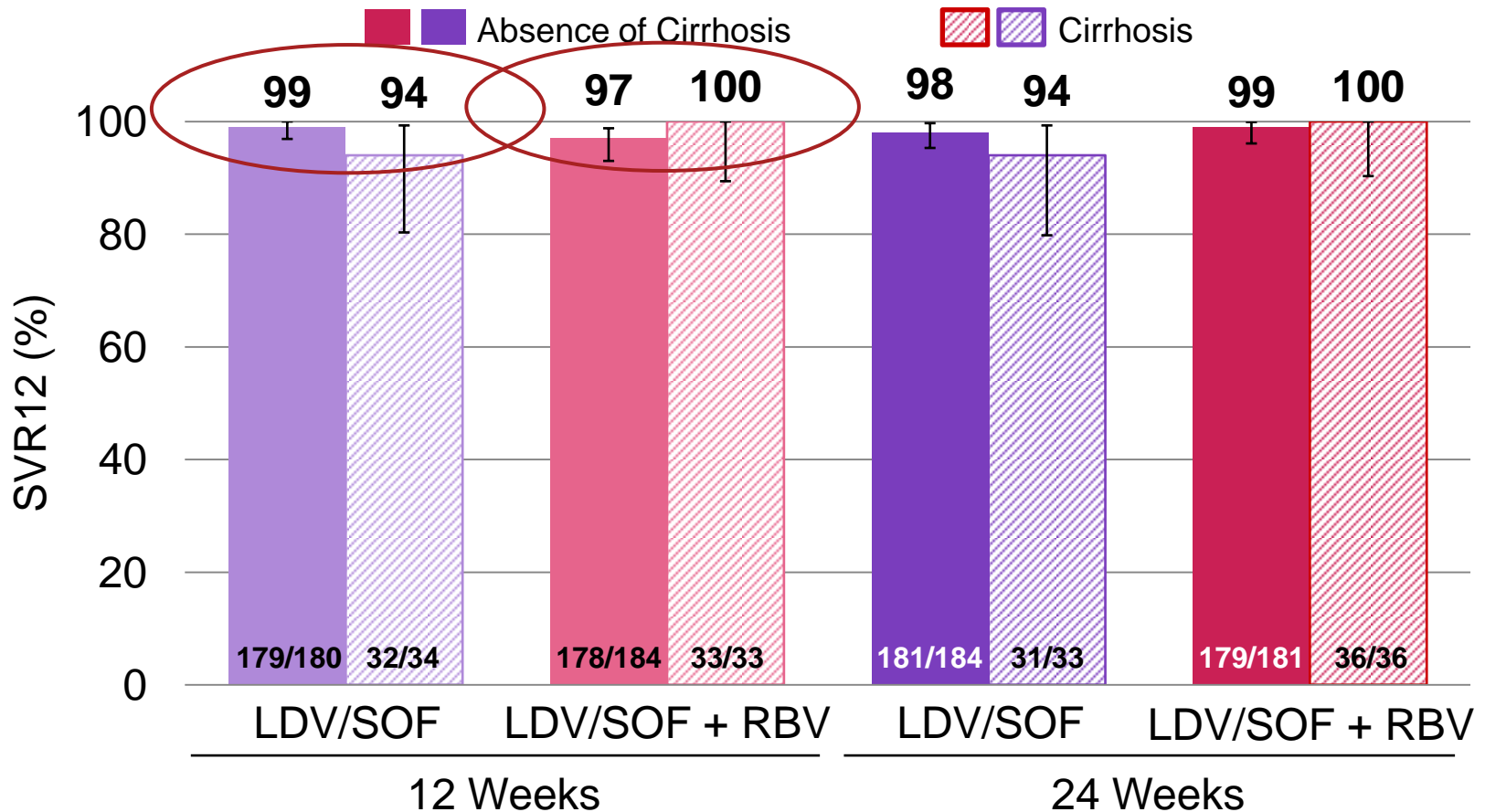


LDV/SOF Phase 3 Program (ION-1, ION-2, ION-3)



Afdhal N, et al. *N Engl J Med* 2014; 370:1889-1898;
 Afdhal N, et al. *N Engl J Med* 2014;370:1483-1493;
 Kowdley K, et al. *N Engl J Med* 2014;370:1879-1888

SVR12 by Presence of Cirrhosis (ITT)



- 97% (132/136) cirrhotic patients achieved SVR12
 - 2 patients were lost to follow-up; 2 patients relapsed

Error bars represent 95% confidence intervals

Large body of evidence shows IFN-free therapy new combinations are highly effective in GT 1

Summary of 8 N Engl J Med studies on IFN-free therapy in GT 1 published in 2014

| Trial | Regimen |
|--------------|-----------------------|
| ION-1 | LDV/SOF ± RBV |
| ION-2 | LDV/SOF ± RBV |
| ION-3 | LDV/SOF ± RBV |
| SAPPHIRE-I | PAR/r/OMB + DAS + RBV |
| SAPPHIRE-II | PAR/r/OMB + DAS + RBV |
| PEARL-III | PAR/r/OMB + DAS ± RBV |
| PEARL-IV | PAR/r/OMB + DAS ± RBV |
| TURQUOISE-II | PAR/r/OMB + DAS + RBV |

SVR (%)

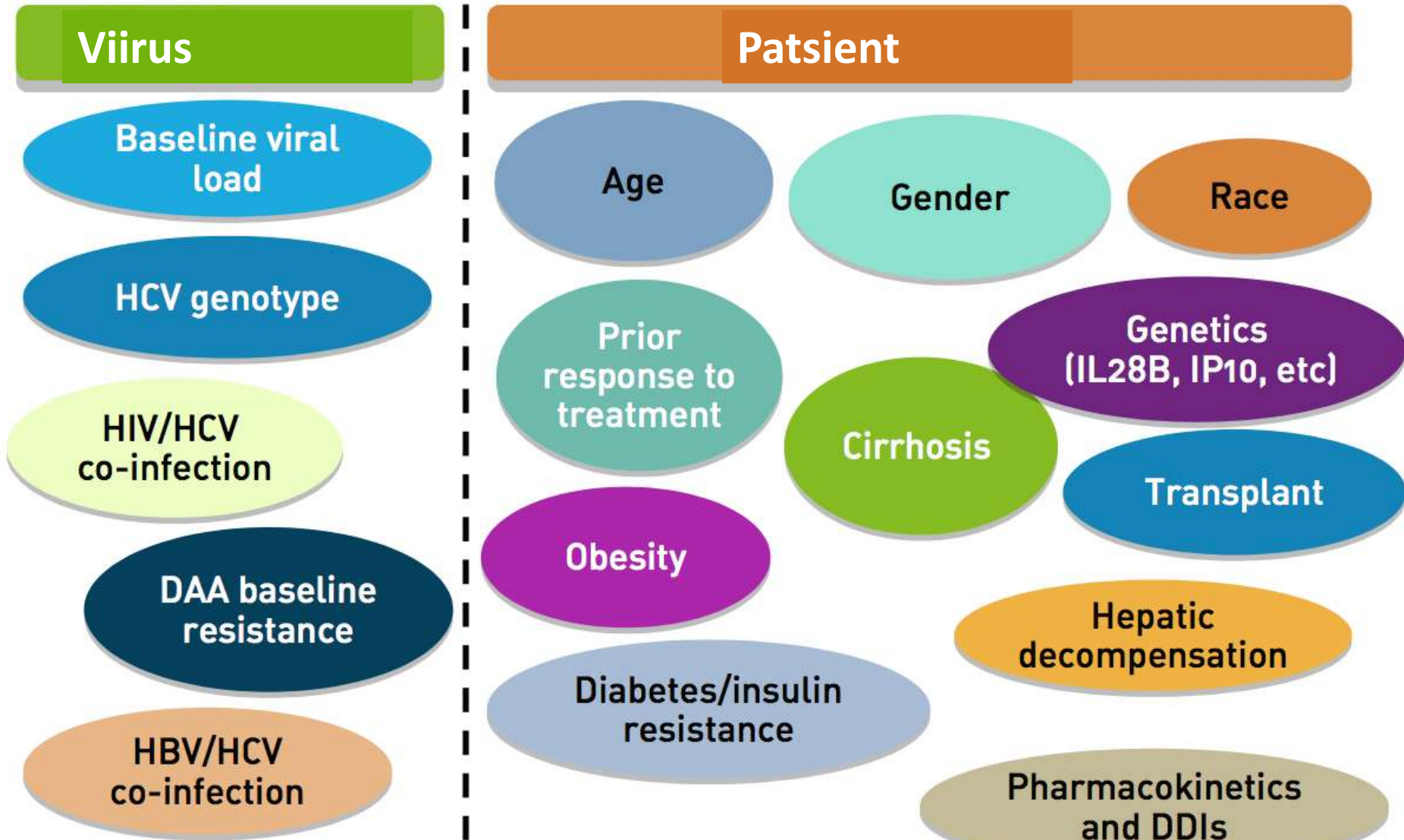


Short, well-tolerated treatment regimens 8–24 weeks
Included treatment-naïve and -experienced patients
and cirrhotics

NB: Summary of 8 heterogeneous Phase 3 studies

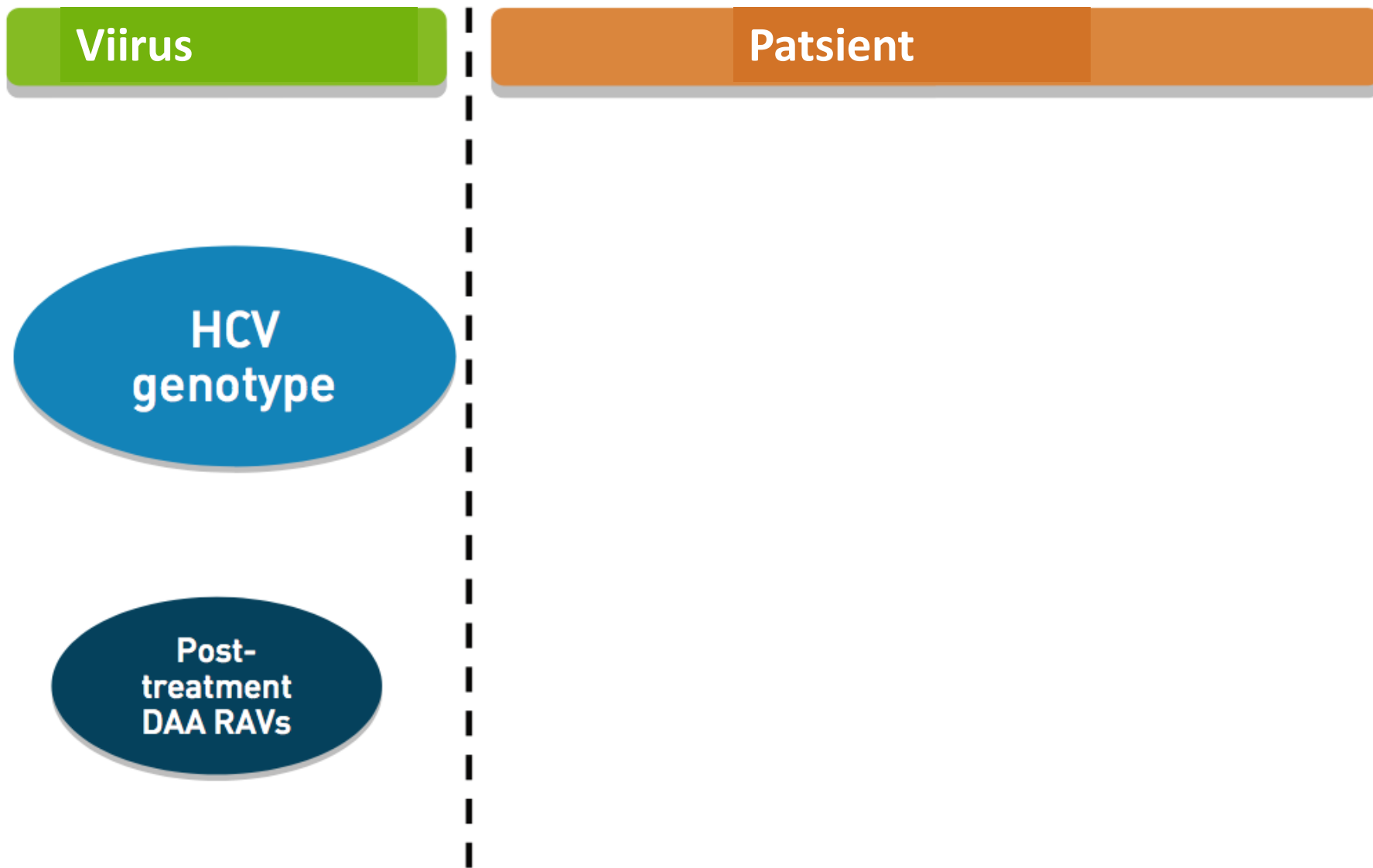
What did these studies show

Factors impacting response to HCV treatment: before 2015



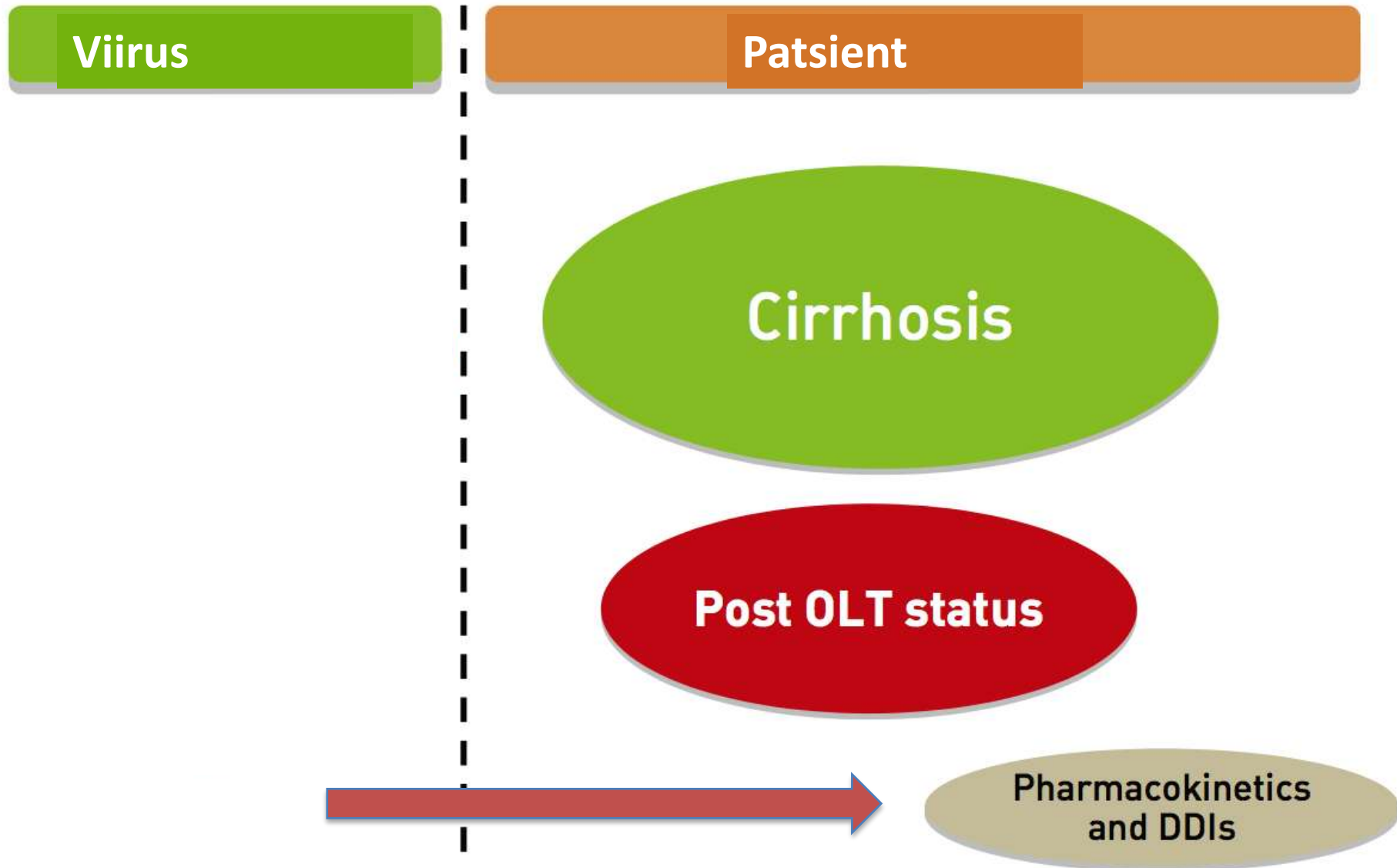


Factors impacting response to HCV treatment: after 2015



RAV, resistance associated variant (ravieelne quasispecies, Q80K)

Factors impacting response to HCV treatment: after 2015



RAV, resistance associated variant (ravieelne quasispecies, Q80K)

DDId

Potential for significant adverse interactions in patients on HCV therapy

Other Infections

Hypertension

Erectile dysfunction

Diabetes

Opioid dependency

Hepatitis

Hyperlipidemia

TB

Malignancies

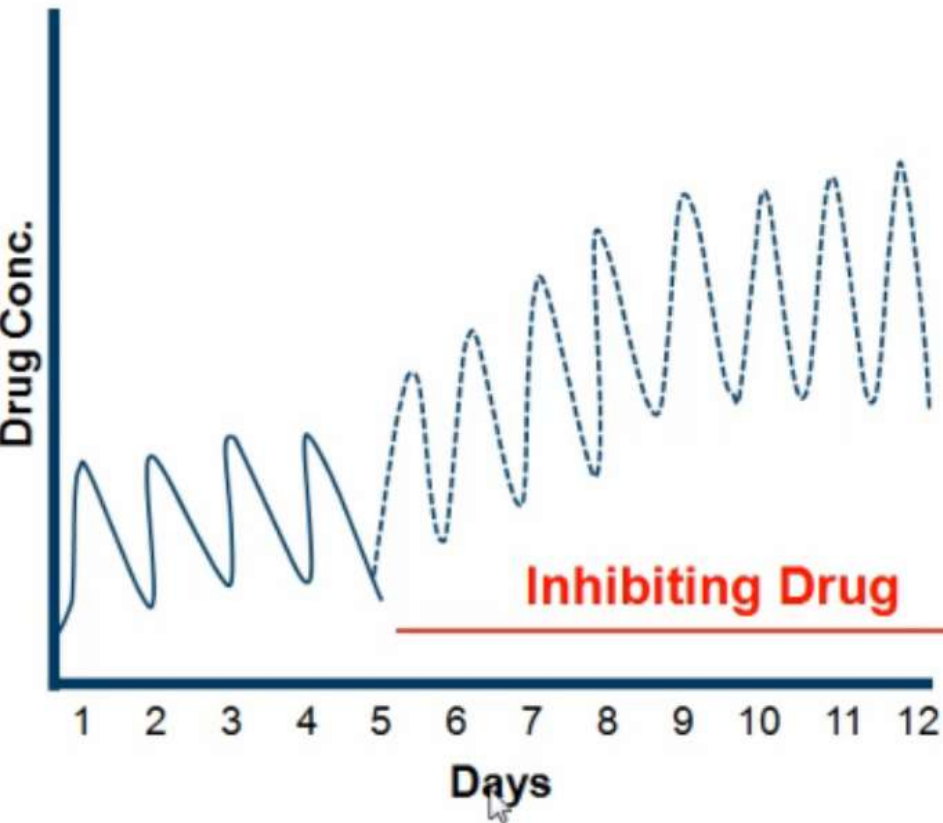
Neuro-psychiatric illnesses

Transplantation

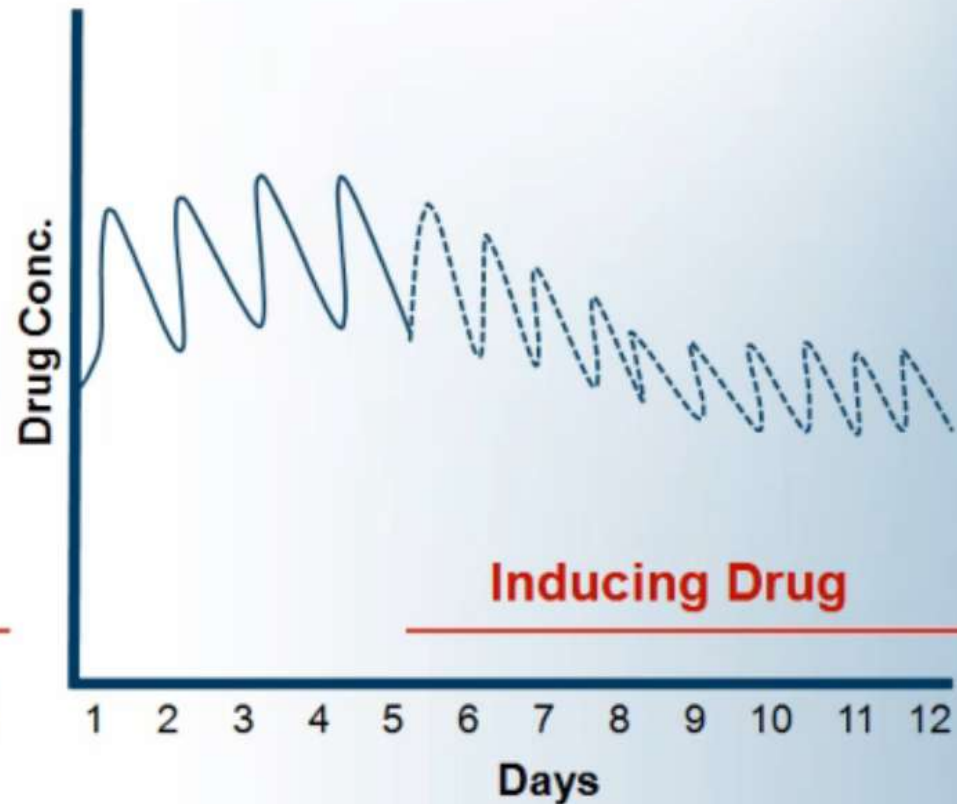
Importance of Enzyme Inhibition and Induction



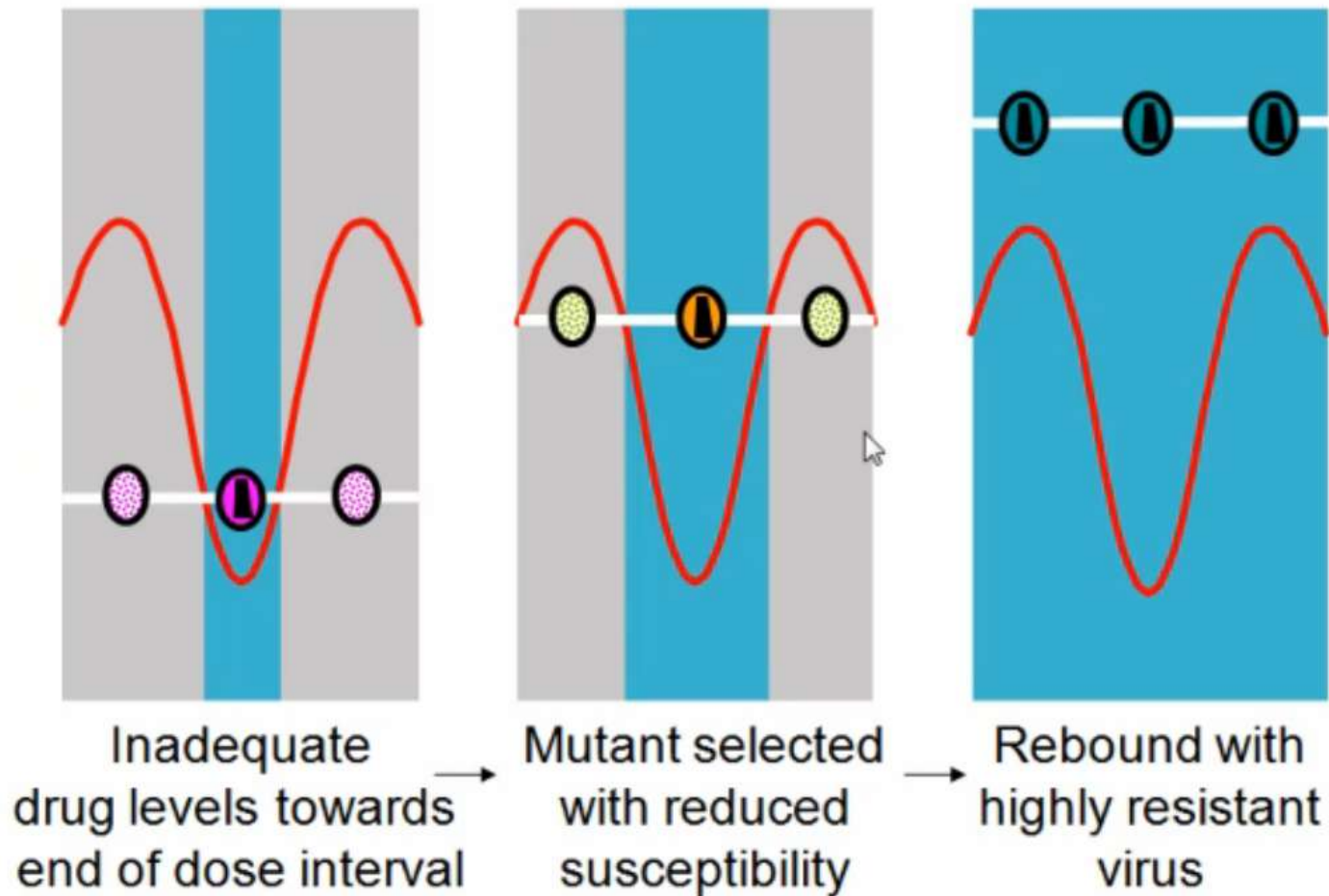
Enzyme Inhibition



Enzyme Induction



The problem of inadequate drug levels is critical in antiviral therapy.



<http://www.hep-druginteractions.org/>



UNIVERSITY OF
LIVERPOOL



DRUG INTERACTION CHARTS



Access our comprehensive, user-friendly,
free, drug interaction charts

CLICK HERE

Providing clinically useful, reliable,
up-to-date, evidence-based information



Guidelines 2015 G1,2,3

ELSEVIER

JOURNAL OF HEPATOLOGY

**EASL Recommendations
on Treatment of Hepatitis C 2015**

In Press, Corrected Proof, Available online 21 April 2015

http://www.hcvguidelines.org/

AMERICAN ASSOCIATION FOR
THE STUDY OF LIVER DISEASES



Recommendations for Testing, Managing, and Treating Hepatitis C



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Refresh

Background of the Hepatitis C Guidance

New direct-acting oral agents capable of curing hepatitis C virus (HCV) infection have

Treatment Indications

- **All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, should be considered for therapy**

Treatment Prioritization

| Treatment priority | Patient group |
|---------------------------------|--|
| Treatment should be prioritized | <ul style="list-style-type: none">. Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis. Patients with HIV coinfection. Patients with HBV coinfection. Patients with an indication for liver transplantation. Patients with HCV recurrence after liver transplantation. Patients with clinically significant extra-hepatic manifestations. Patients with debilitating fatigue. Individuals at risk of transmitting HCV |
| Treatment is justified | <ul style="list-style-type: none">. Patients with moderate fibrosis (F2) |
| Treatment can be deferred | <ul style="list-style-type: none">. Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations |
| Treatment is not recommended | <ul style="list-style-type: none">. Patients with limited life expectancy due to non-liver related comorbidities |

G1, no or compensated cirrhosis

| | AASLD/IDSA 2015 | EASL 2015 |
|------------------------------------|----------------------------------|------------------------------------|
| BOC/TVR + PEG/RBV | NR | NR, <i>it is possible, however</i> |
| SOF/RBV | NR | NR |
| SOF/PEG/RBV | NR | 12W |
| SIM/PEG/RBV naive, relaps | NR | 12/24W |
| SIM/PEG/RBV partials, nulls | NR | 12/48W |
| LDV/SOF naive | 12W | 8W, 12W, 12W + RBV |
| LDV/SOF nulls | 24W or 12W + RBV | 24W + RBV |
| SIM/SOF | 24W ± RBV | 24W or 12W + RBV |
| DCV/SOF | - | 24W or 12W + RBV |
| OBT/PTV/r/DSV | G1a: 24W + RBV G1b: 12W + RBV | G1a: 24W + RBV G1b: 12W + RBV |

G1, decompensated cirrhosis

| | AASLD/IDSA 2015 | EASL 2015 |
|--------------------------|------------------|------------------|
| BOC/TVR + PEG/RBV | NR | NR |
| SOF/RBV | NR | NR |
| SOF/PEG/RBV | NR | NR |
| SIM/PEG/RBV | NR | NR |
| LDV/SOF | 24W or 12W + RBV | 24W or 12W + RBV |
| SIM/SOF | NR | NR |
| DCV/SOF | - | 24W or 12W + RBV |
| OBT/PTV/r/DSV | NR | NR |

G2 & 3, no or compensated cirrhosis

G2

| | AASLD/IDSA 2015 | EASL 2015 |
|--------------------|-------------------------|-----------|
| SOF/RBV | 12 – 16W | 12W |
| SOF/PEG/RBV | 12W (PEG/RBV relapsers) | 12W |
| DCV/SOF | - | 12W |

G3

| | AASLD/IDSA 2015 | EASL 2015 |
|--------------------|-----------------|--------------|
| SOF/RBV | 24W | 24W (naives) |
| SOF/PEG/RBV | 12W | 12W |
| DCV/SOF | - | 12W + RBV |

G2 & 3, decompensated cirrhosis

G2

| | AASLD/IDSA 2015 | EASL 2015 |
|--------------------|-----------------|------------------|
| SOF/RBV | 24 – 48W | 16 – 20W |
| SOF/PEG/RBV | NR | NR |
| DCV/SOF | - | 24W or 12W + RBV |

G3

| | AASLD/IDSA 2015 | EASL 2015 |
|--------------------|-----------------|------------------|
| SOF/RBV | 24 – 48W | NR |
| SOF/PEG/RBV | NR | NR |
| DCV/SOF | - | 24W or 12W + RBV |

What's next

HCV ravimid 2015

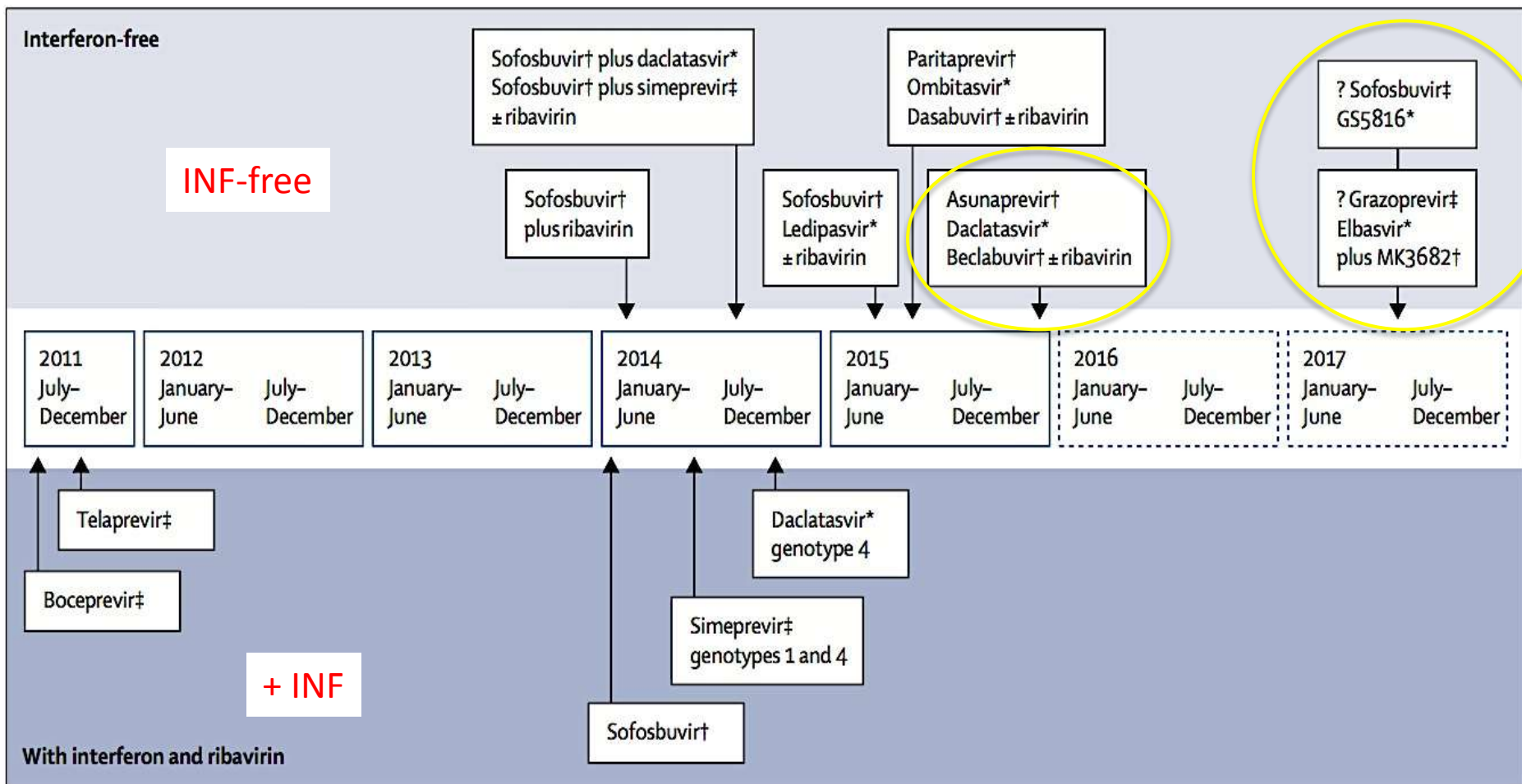


Figure 2: Treatment of HCV in 2015 (including protease, NS5B, and NS5A inhibitors that are approved or are about to be approved)

*NS5A inhibitor. †NS5B inhibitor. ‡Protease inhibitor.

Clin Infect Dis June 2015

INVITED ARTICLE

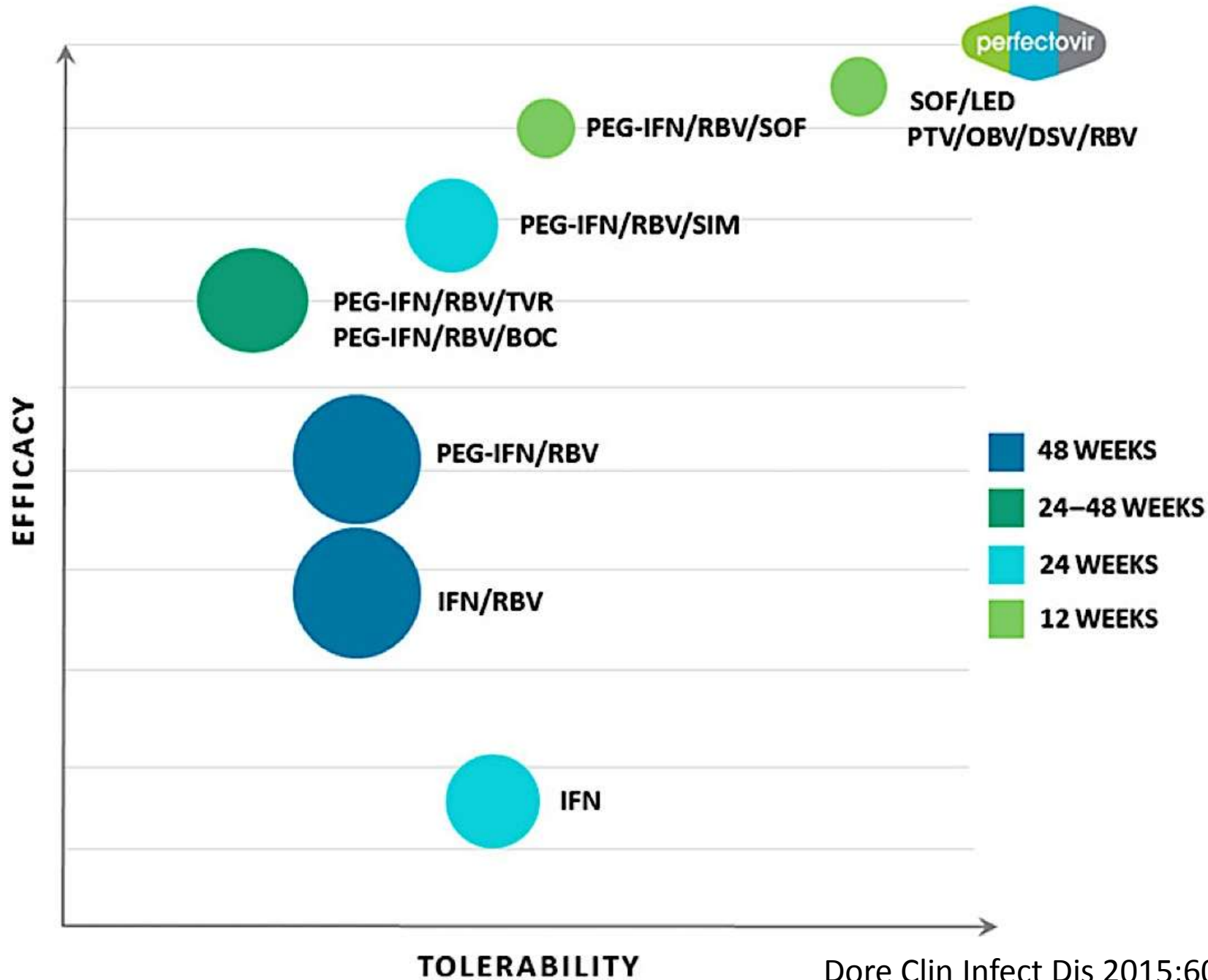
VIRAL HEPATITIS

Camilla S. Graham, Section Editor

Hepatitis C Virus Therapeutic Development: In Pursuit of “Perfectovir”

Gregory J. Dore^{1,2} and Jordan J. Feld³

¹Kirby Institute, University of New South Wales, and ²St Vincent’s Hospital, Sydney, Australia; and ³Toronto Centre for Liver Disease, Sandra Rotman Centre for Global Health, University of Toronto, Ontario, Canada



Perfectovir

- Extremely high treatment efficacy (>95%);
- Pangenotypic activity (ie, similar dosing and duration across genotypes);
 - Maintenance of high efficacy in decompensated cirrhosis and peritransplant settings;
 - Minimal toxicity;
 - Minimal HCV resistance;
 - Ease of dosing, preferably 1 tablet once daily;
 - Limited drug–drug interactions;
 - Short duration;
 - Affordability.

Challenges

Table 2. Strategies to Enhance Access to Interferon-Free Direct-Acting Antiviral Therapy

| Strategic Area | High-Income Countries |
|--|--|
| <u>Drug pricing</u> | Discounting for large-scale payers; amortization (costs spread over several years rather than upfront); pharmaceutical industry competition. |
| <u>Screening and diagnosis</u> | Public awareness campaigns; birth cohort screening; antenatal screening; subsidized or free HCV testing; integration of HCV screening within harm reduction and addiction medicine services; prison entry screening. |
| <u>Clinical assessment</u> | <u>Primary care practitioner education:</u> HCV testing algorithms incorporating automatic HCV RNA testing of antibody-positive individuals; enhanced access to noninvasive methods of fibrosis staging. |
| <u>Strategy development and public health advocacy</u> | <u>National HCV strategy development:</u> HCV testing and monitoring policies; treatment guidelines; World Hepatitis Day activities; partnerships with civil society. |



MIKE LUCKOVICH 2014

IT TOOK US 25 YEARS TO BRING HIM TO HIS KNEES... NOW LET'S FINISH HIM OFF!...

