
# *HCV eradication with direct acting antivirals (DAAs)?*

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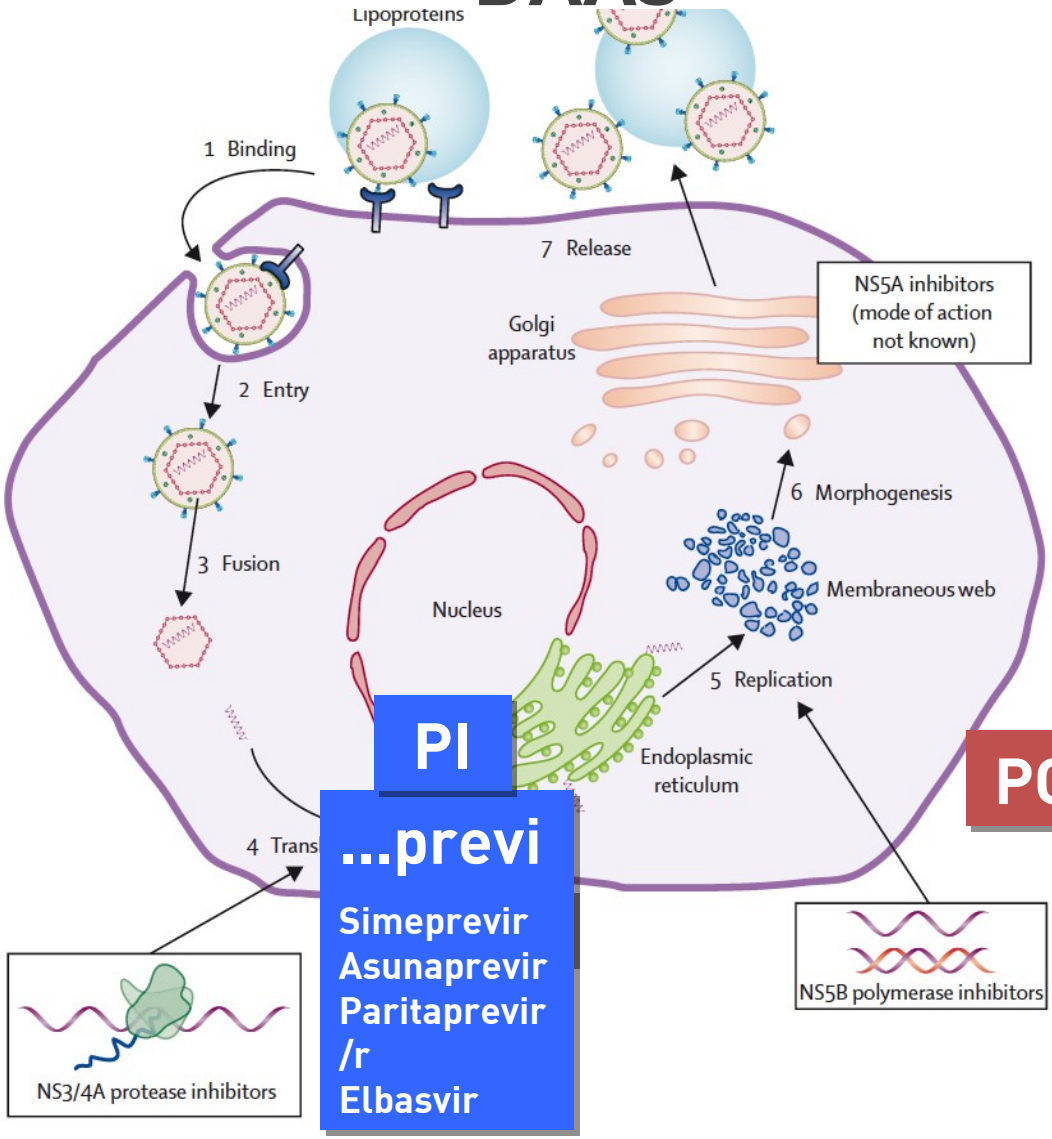
# HCV replicative cycle and main targets for DAAs




**NS5A**

**...asvir**

Daclatasvir
Ledipasvir
Ombitasvir
PPI-688
Elbasvir

**PI**

**...previ**

Simeprevir
Asunaprevir
Paritaprevir
/r
Elbasvir

**POL**

**NNI POL**

**...buvir**

Sofosbuvir
Dasabuvir
Beclabuvir
GS-9669

Modified from: Manns & Cornberg, Lancet Infectious Diseases 2013

# DAAs currently approved

**2013**

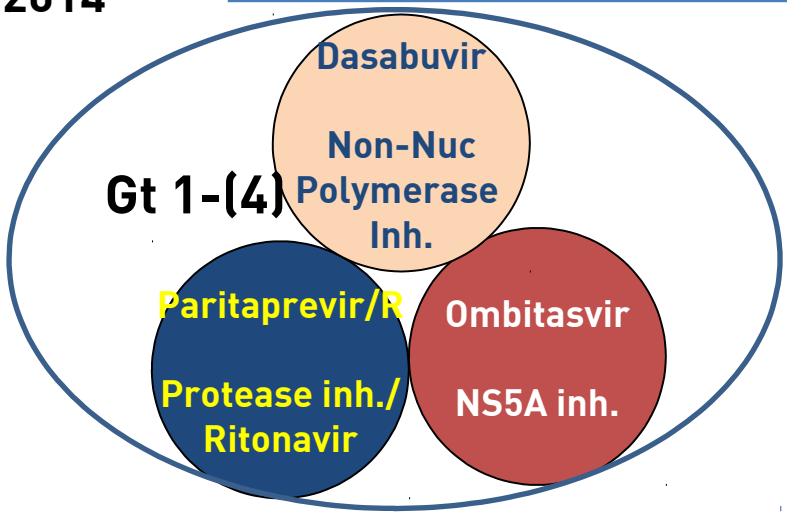
- **Sofosbuvir** — Nucleotide polymerase inh. All Gts (±3)
- **Simeprevir** — Protease inh. Gt 1, 4
- **Daclatasvir** — NS5A inh. Gt 1, 3, 4, 5, 6

**Triple therapy with PEG IFN and ribavirin**

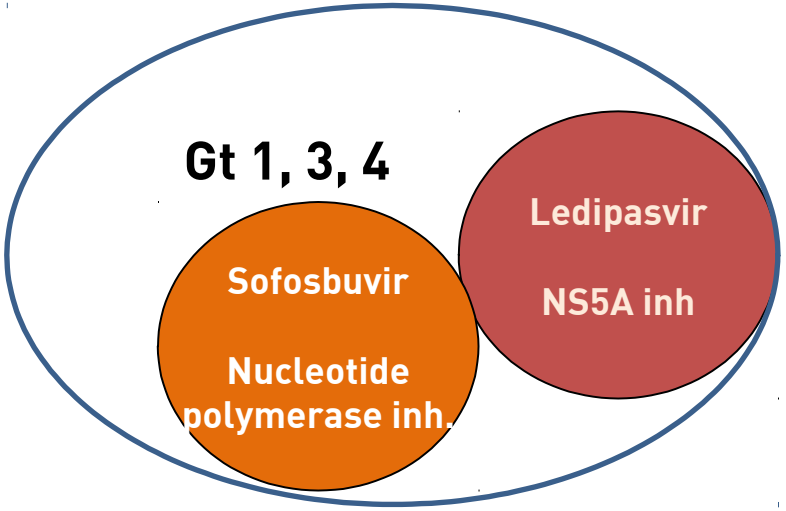
**SOF and ribavirin, no IFN**

**Off-label combination of two DAAs ± ribavirin**

**2014**




**Fixed dose combination of three DAAs ± ribavirin**

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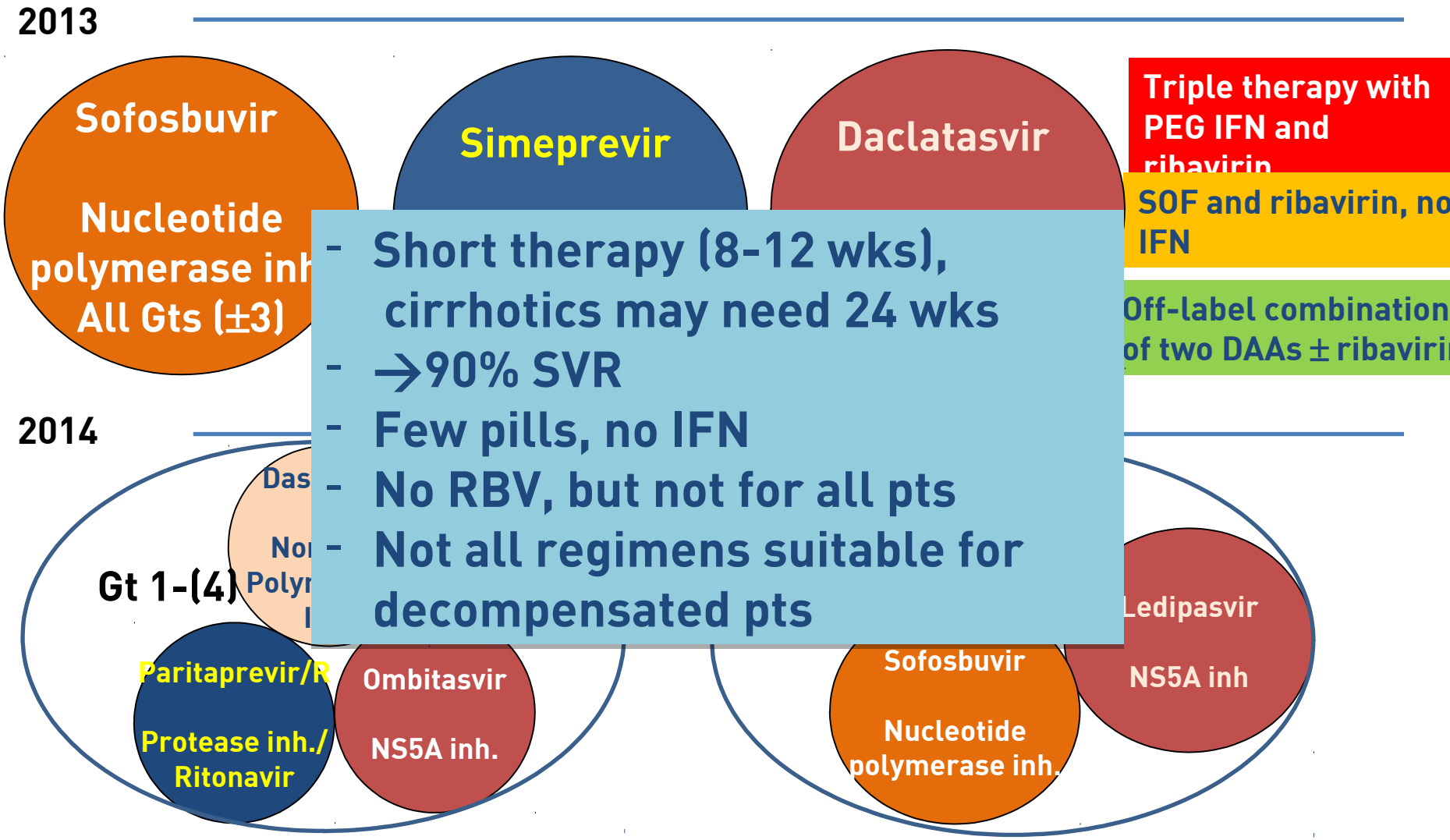

## Efficacy evaluation of different DAA-containing regimens

- **SOFOSBUVIR**
  - plus Ribavirin for HCV-2 (12 wks) *SVR 80-95%*
  - plus PEG-IFN / RBV for HCV-1, HCV-3, HCV-4 naive (12 wks) *SVR 80-92%*
  - plus Ribavirin (24 wks) for HCV-1 *SVR 50%, for* HCV-3, HCV-4 *SVR 70-80%*
  - plus Simeprevir (12 wks) for HCV-1 and HCV-4 *SVR → 90-95%*
- **SIMEPREVIR**
  - plus PEG-IFN/RBV for HCV-1 and HCV-4
    - P/R naive *SVR 75-80%*
    - P/R experienced *SVR 50-85%*
  - plus Sofosbuvir (12 wks) for HCV-1 and HCV-4 *SVR → 90-95%*
- **DACLATASVIR**
  - plus Sofosbuvir (12-24 wks) HCV-1 and HCV-4 *SVR → 90-95*

**Data on patients with F0 to F4 fibrosis (under-represented) and compensated disease**

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**overall**

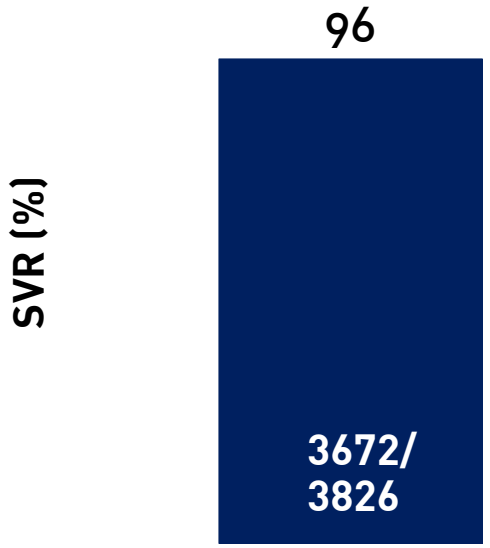
**IFN free off label combos perform better than TTs**

**Data on patients with F0 to F4 fibrosis (under-represented) and compensated disease**

# 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 |




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

**NB: Summary of 8 heterogeneous Phase 3 studies**

LDV, PAR/r, OMB and DAS are investigational agents and not approved for use in HCV by the EMA/FDA

Liang J, Ghany MG. N Engl J Med 2014;370:2040–7

DAS: dasabuvir; LDV: ledipasvir; OMB: ombitasvir; PAR: paritaprevir; r: ritonavir

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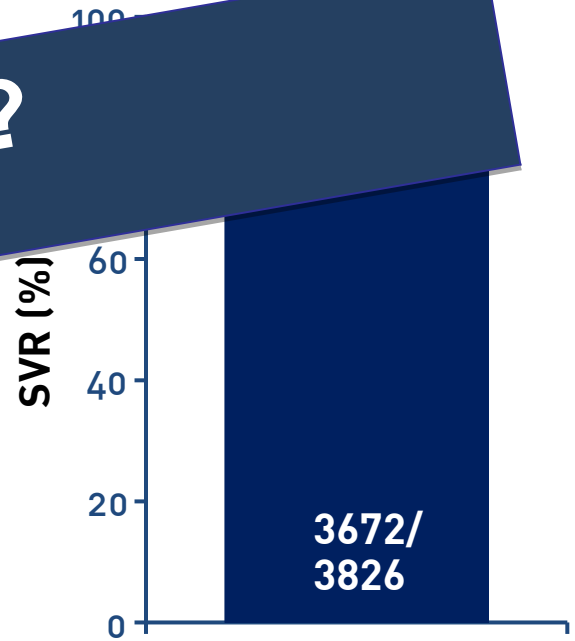
| | PAR/r/OMB + DAS + RBV |
| PEARL-III | PAR/r/OMB + DAS ± RBV |
| PEARL-IV | PAR/r/OMB + DAS ± RBV |
| TURQUOISE-II | PAR/r/OMB + DAS + RBV |

PERFECTOVIR ?
© J. Feld

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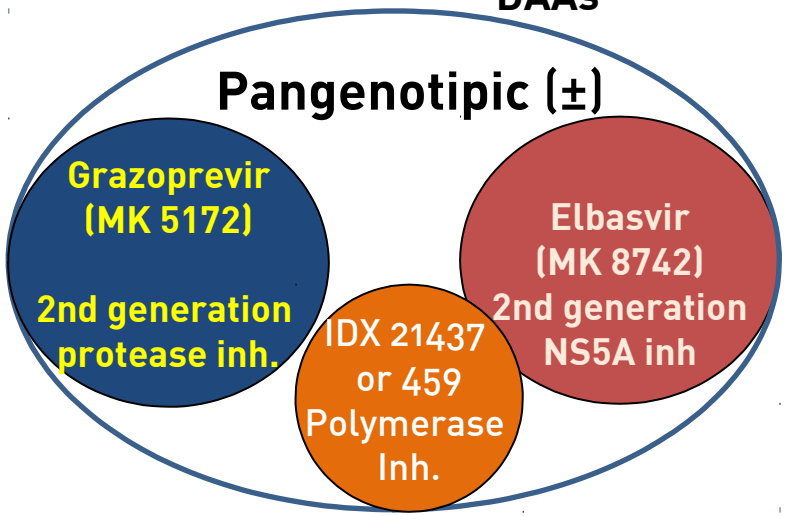
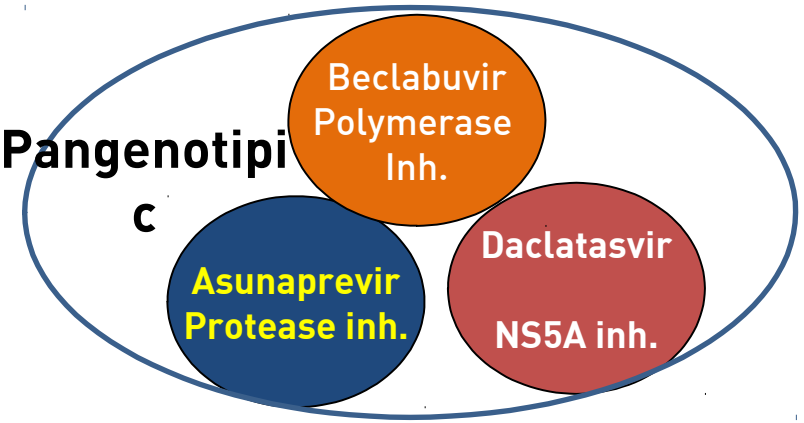
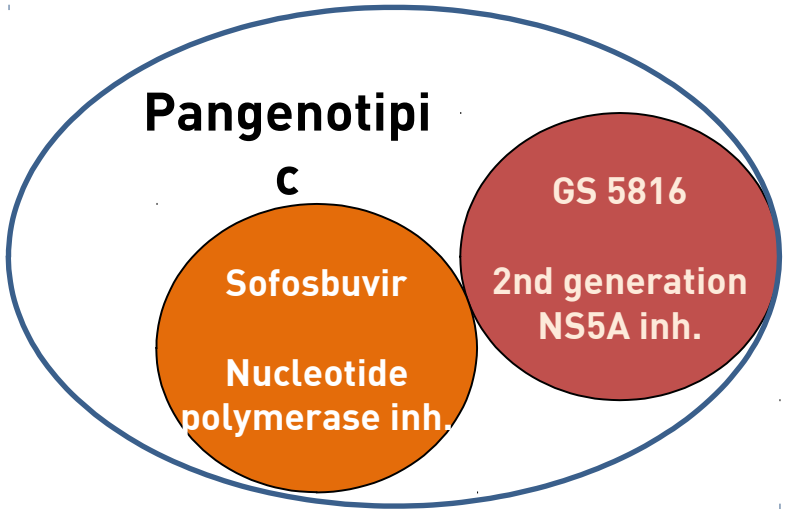
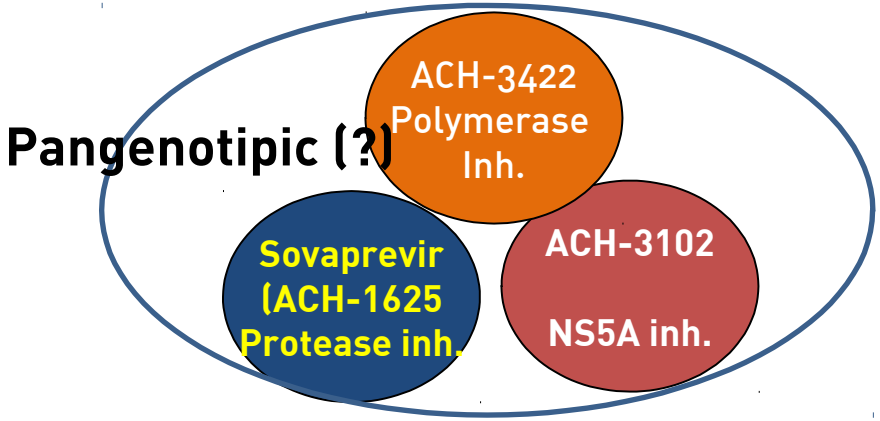
# Further DAA combos available within 2016-17

**Fixed dose combination of two or three DAAs**



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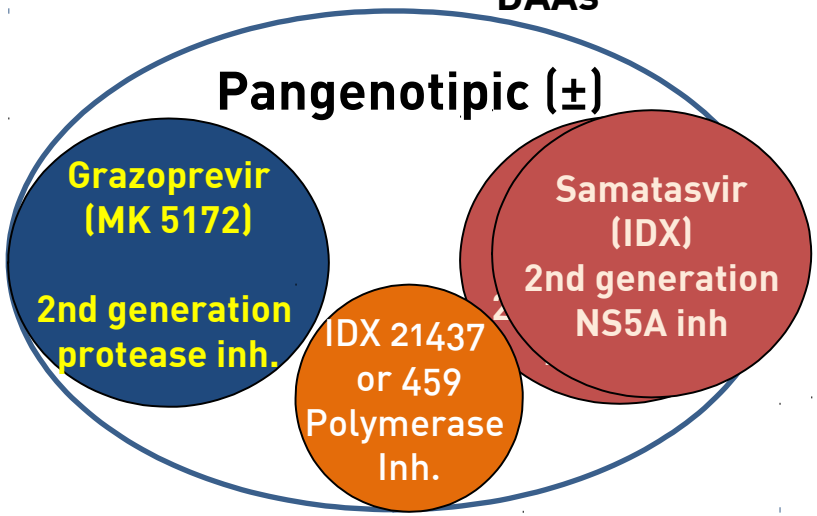


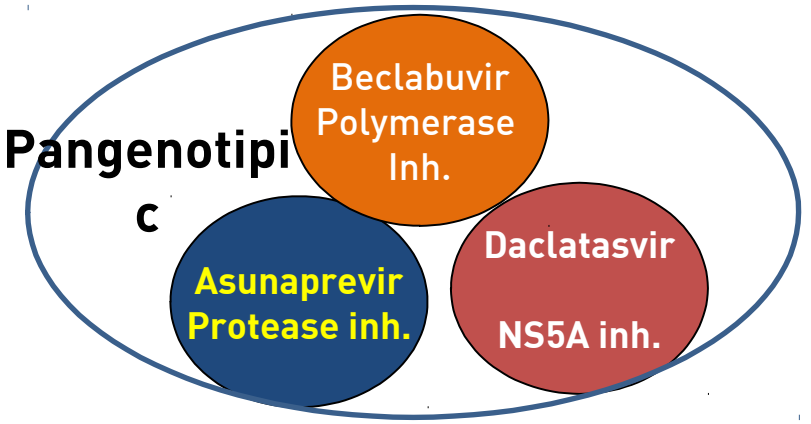


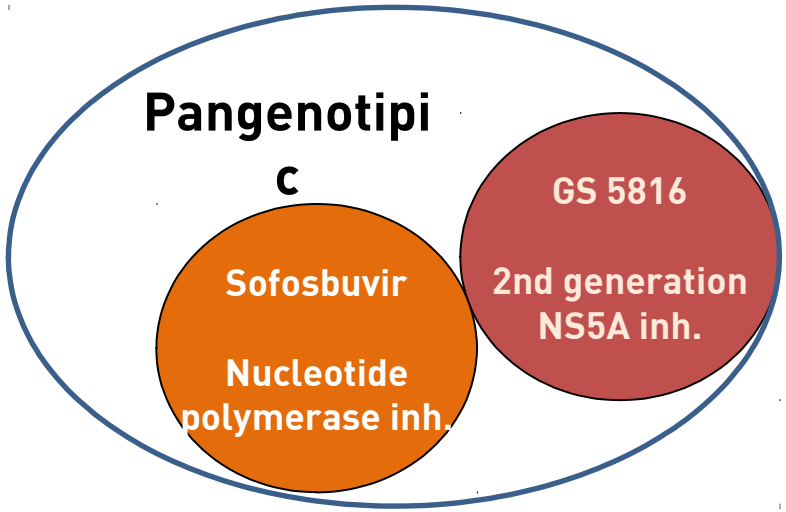


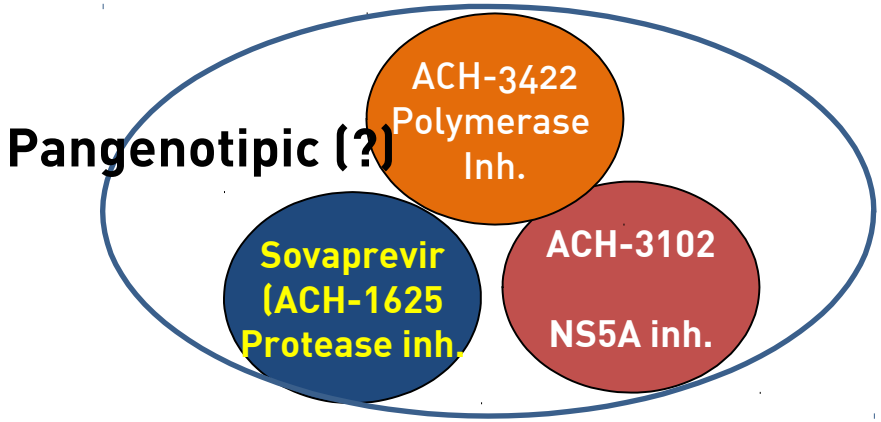

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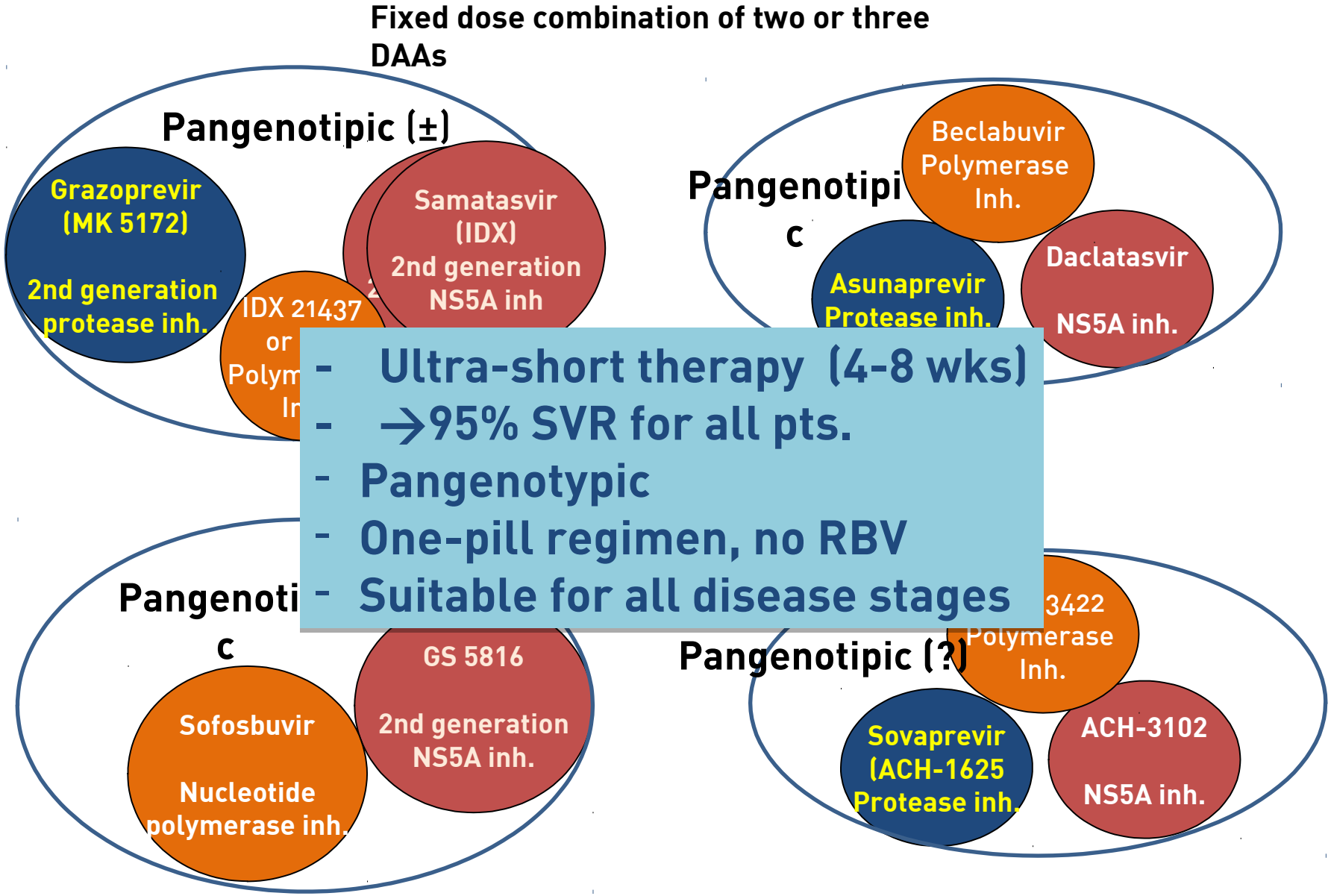
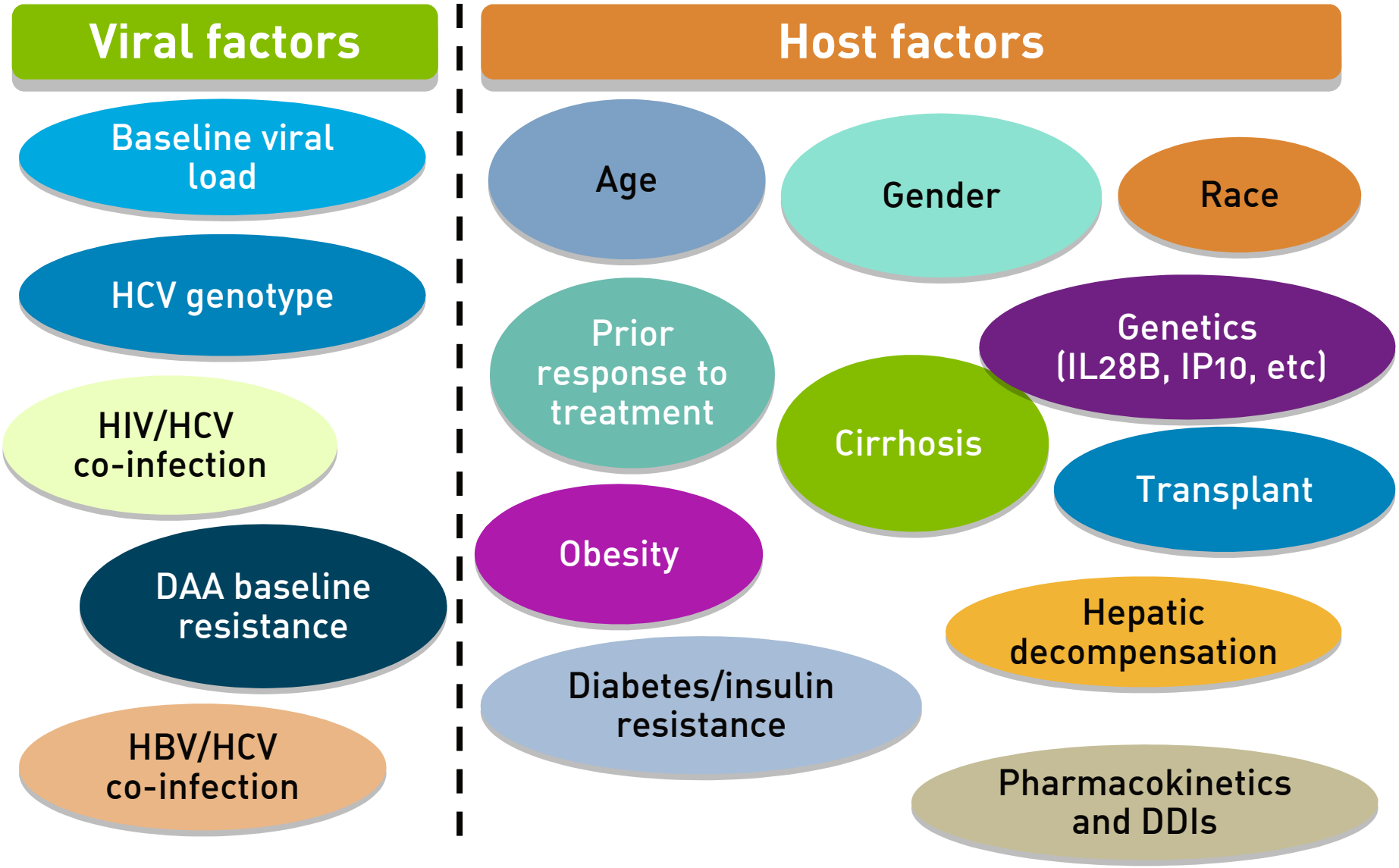


# Factors impacting response to HCV treatment: before 2015



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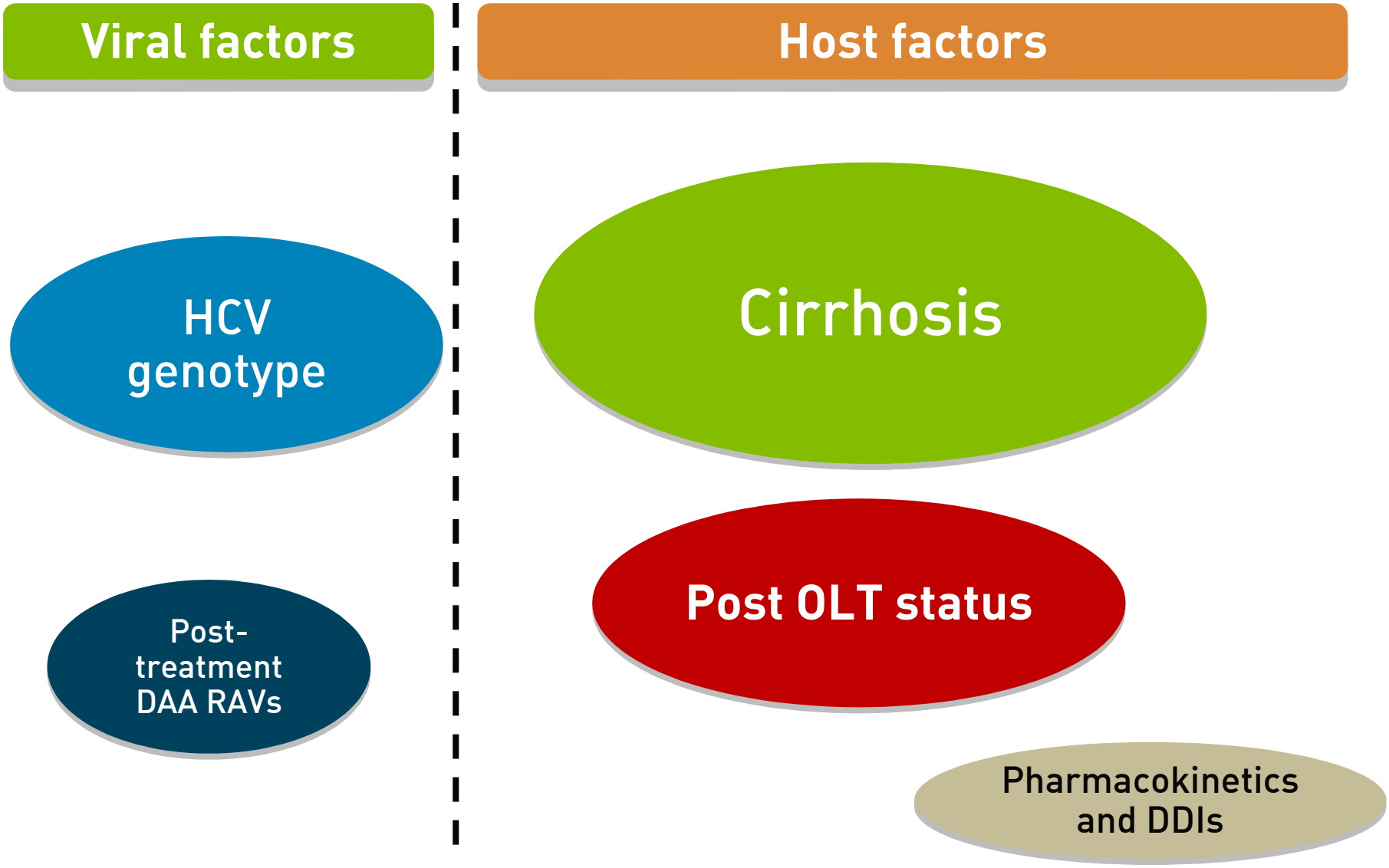


# Efficacy of SOF + SMV ± RBV in real-world settings

## HCV-TARGET
## Prospective Observational Cohort Study:

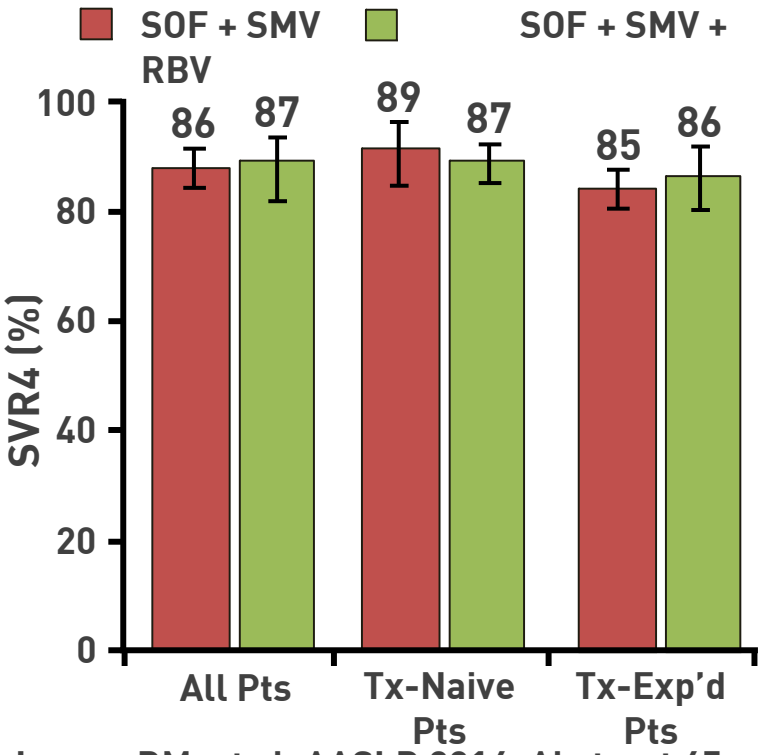
**2330 pts (51 US sites)**

**SOF + PR : 384**

**SOF + RBV : 667**

**SOF + SMV : 784**

**SOF + SMV + RBV : 228**



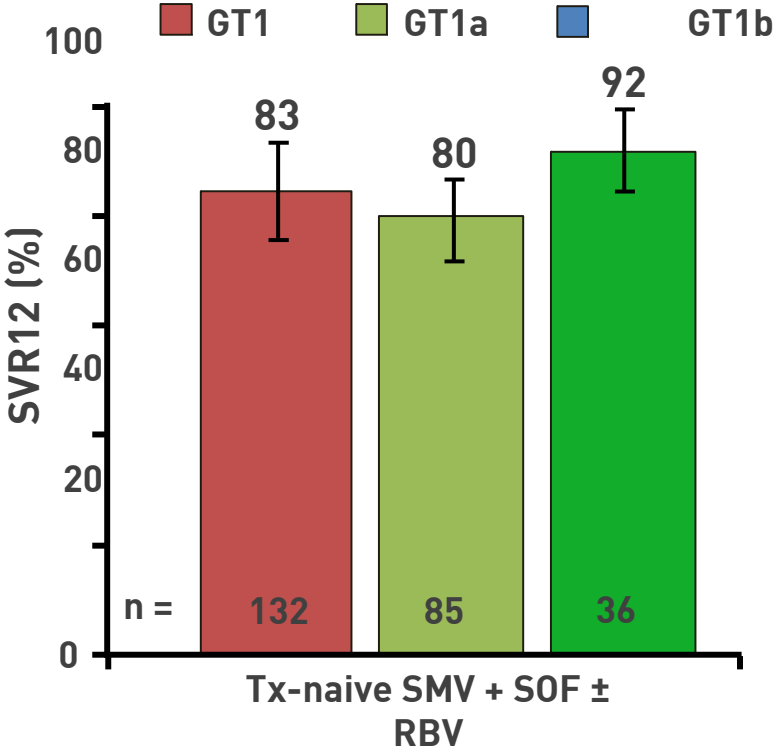

## TRIO
## Prospective Observational Cohort Study:

**955 pts enrolled**

**SOF + PR**

**SOF + RBV**

**SOF + SMV ± RBV**





1. Jensen DM, et al. AASLD 2014. Abstract 45.
2. 2. Dieterich D, et al. AASLD 2014. Abstract 46.

# HCV TARGET: analysis by subgroups

| *Adjusted* SVR4, %* | *Genotype 1 Patients Treated With SOF + SMV + RBV* | *Genotype 1 Patients Treated With SOF + SMV* |
|---|---|---|
| Overall | 87 | 86 |
| **Treatment history** | | |
| •Naive | 87 | 89 |
| •Experienced | 86 | 85 |
| **Genotype** | | |
| •1a | 82 | 84 |
| •1b | 93 | 92 |
| **Cirrhosis status** | | |
| •Noncirrhotic | 90 | 89 |
| •Cirrhotic | 83 | 85 |
| **Genotype and cirrhosis status** | | |
| •Genotype 1a noncirrhotic | 87 | 88 |
| •Genotype 1a cirrhotic | 80 | 82 |
| •Genotype 1b noncirrhotic | 94 | 93 |
| •Genotype 1b cirrhotic | 88 | 87 |

*Adjusted for cirrhosis status, genotype, previous treatment experience, previous decompensation, and previous triple therapy failure

Jensen DM, abs #45

# HCV TARGET: analysis by subgroups

| *Adjusted* SVR4, %* | *Genotype 1 Patients Treated With SOF + SMV + RBV* | *Genotype 1 Patients Treated With SOF + SMV* |
|---|---|---|
| Overall | 87 | |
| **Treatment history** | | |
| •Naive | | |
| •Ex | | |
| | | 92 |
| | 90 | 89 |
| Cirrhotic | 83 | 85 |
| **Genotype and cirrhosis status** | | |
| •Genotype 1a noncirrhotic | 87 | 88 |
| •Genotype 1a cirrhotic | 80 | 82 |
| •Genotype 1b noncirrhotic | 94 | 93 |
| •Genotype 1b cirrhotic | 88 | 87 |

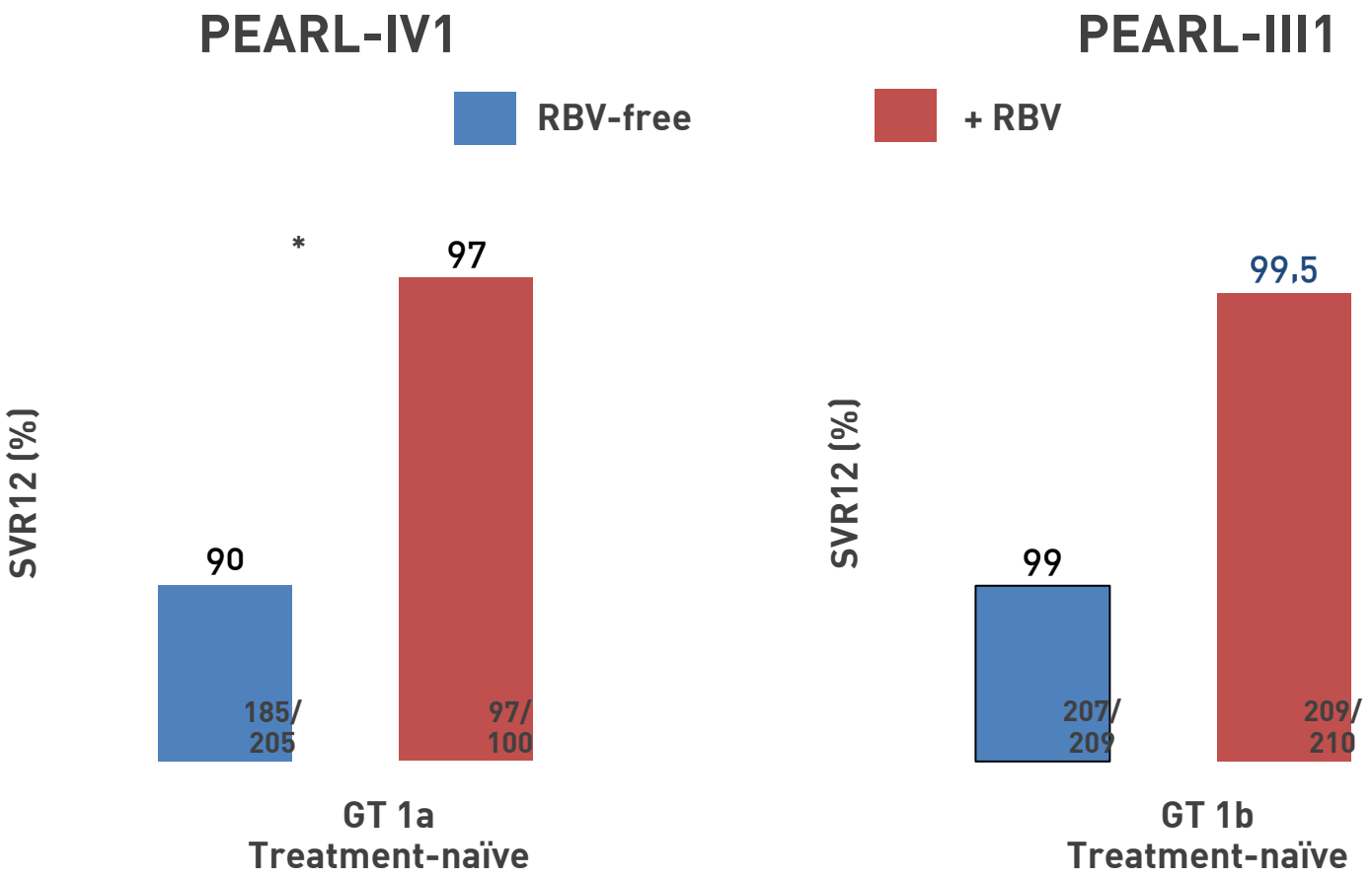
RBV not needed

GT1b performs better than GT1a

*Adjusted for cirrhosis status, genotype, previous treatment experience, previous decompensation, and previous triple therapy failure

Jensen DM, abs #45

# PTV/RTV/OMV + DSV + RBV in GT1




Ferenci P, et al. N Engl J Med 2014;370:1983–92.

*RBV-free arm did not meet non-inferiority vs RBV-containing arm;
Ombitasvir, paritaprevir, RTV + dasabuvir are not approved
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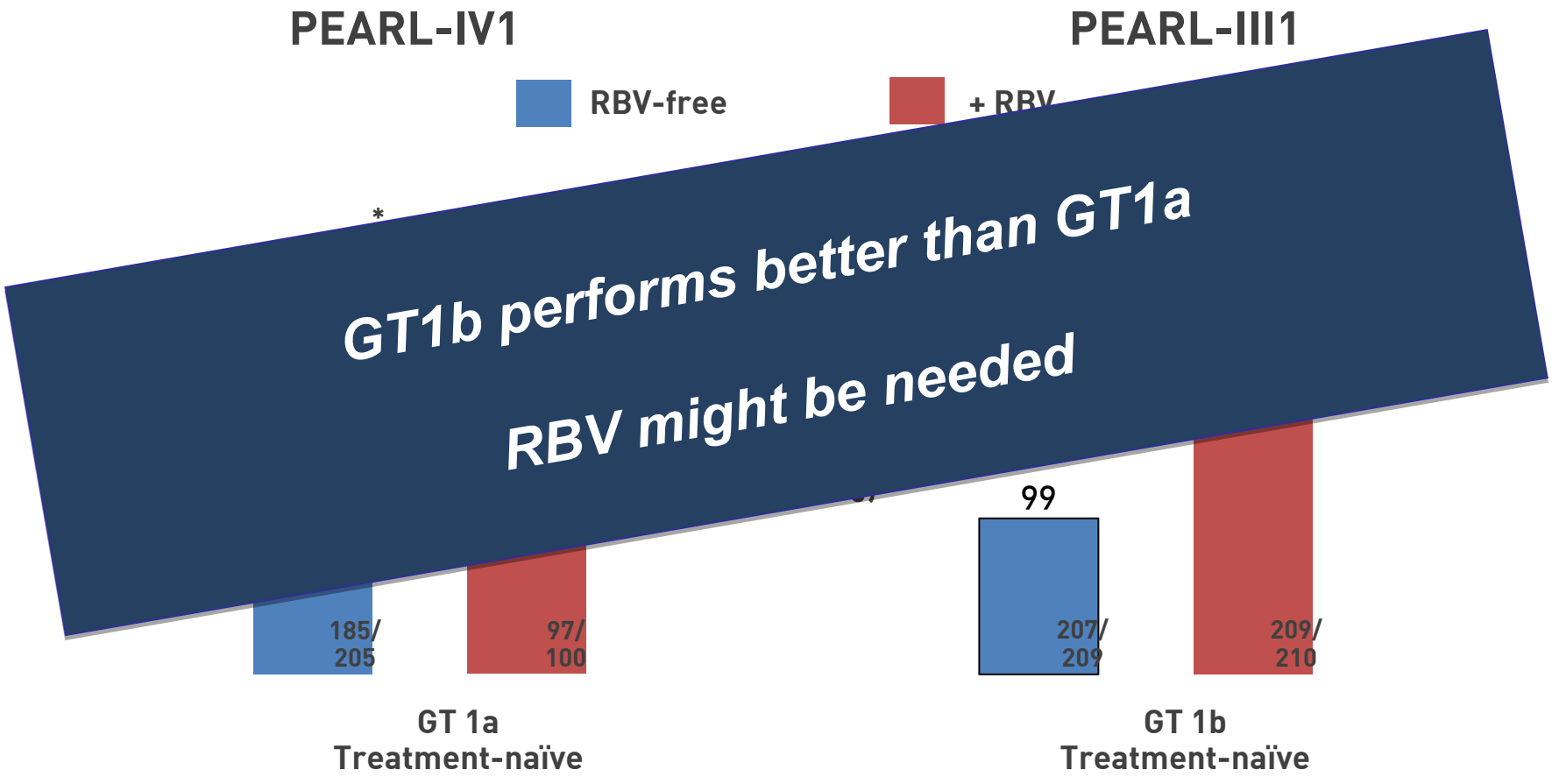


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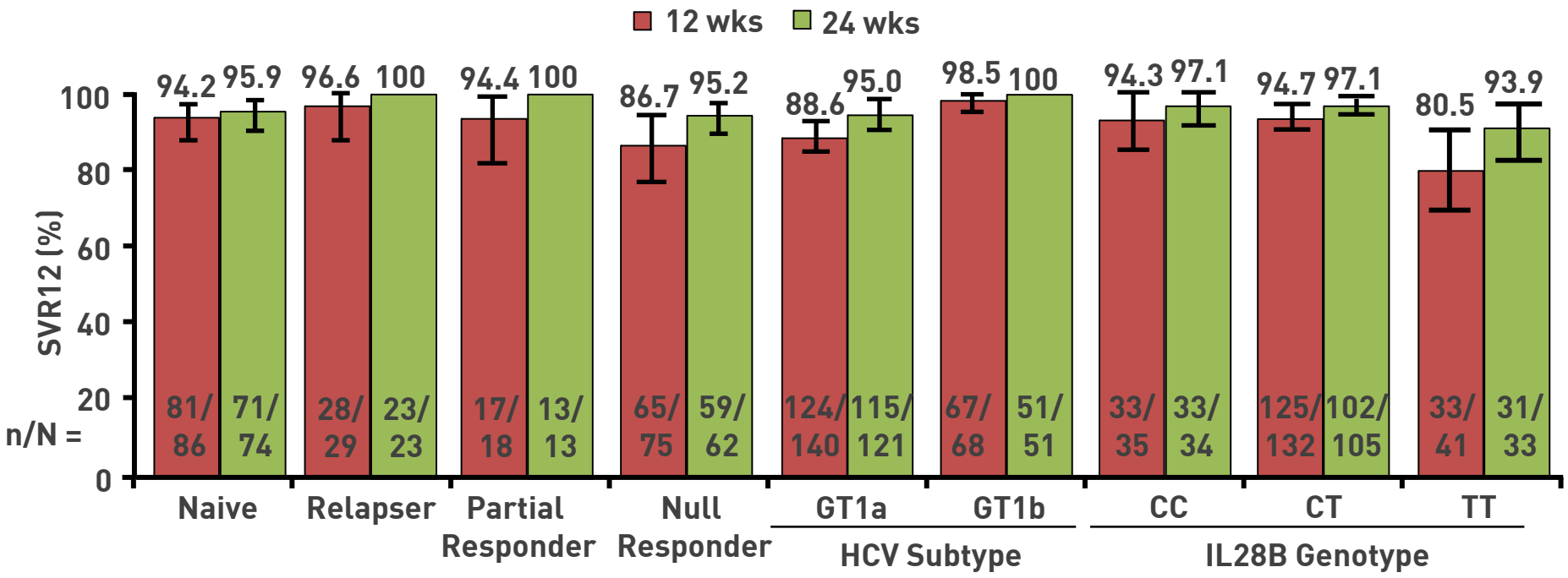
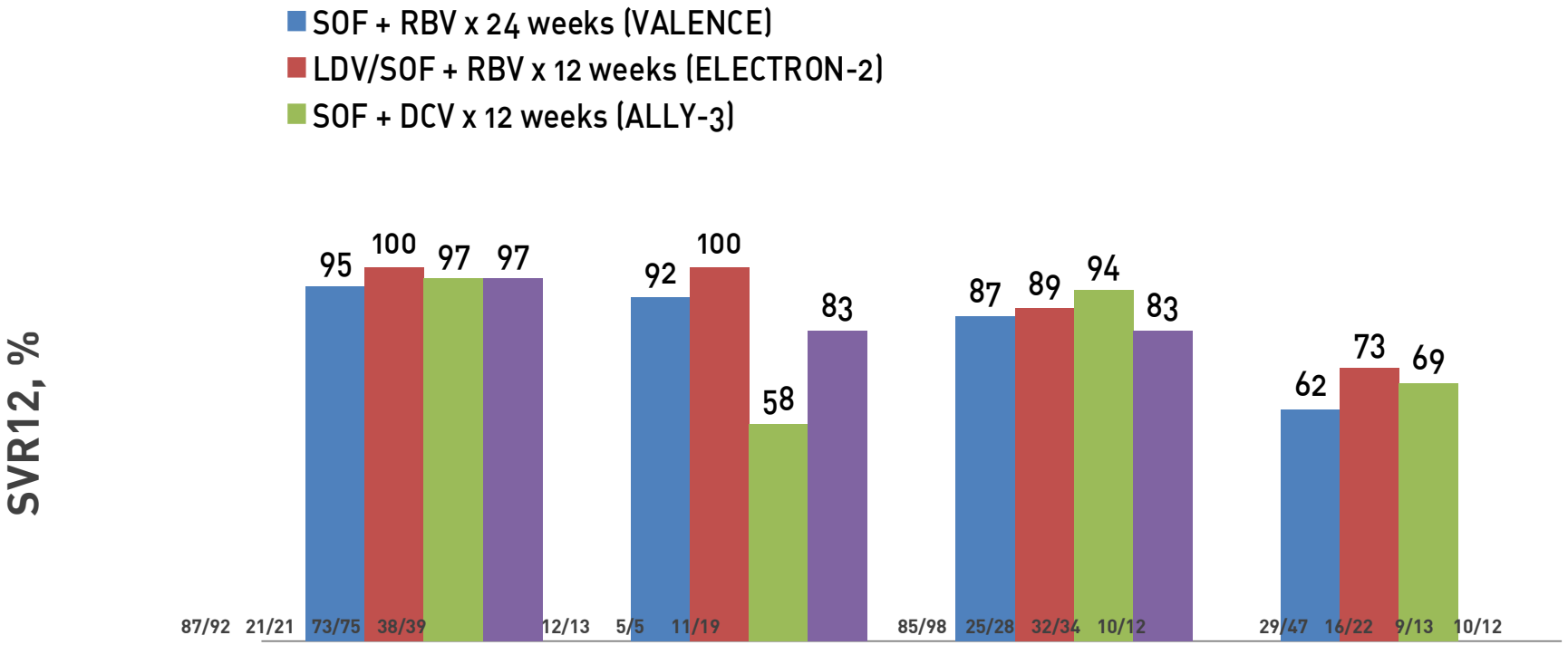
# SVR12 with PTV/RTV/OMV + DSV + RBV in Gt1 compensated cirrhosis




| Factor | *P* Value |
|---|---|
| *IL28B* TT genotype | .021 |
| Previous null response to pegIFN/RBV | .038 |
| GT1a HCV | .046 |

Fried MW, et al. AASLD 2014. Abstract 81.

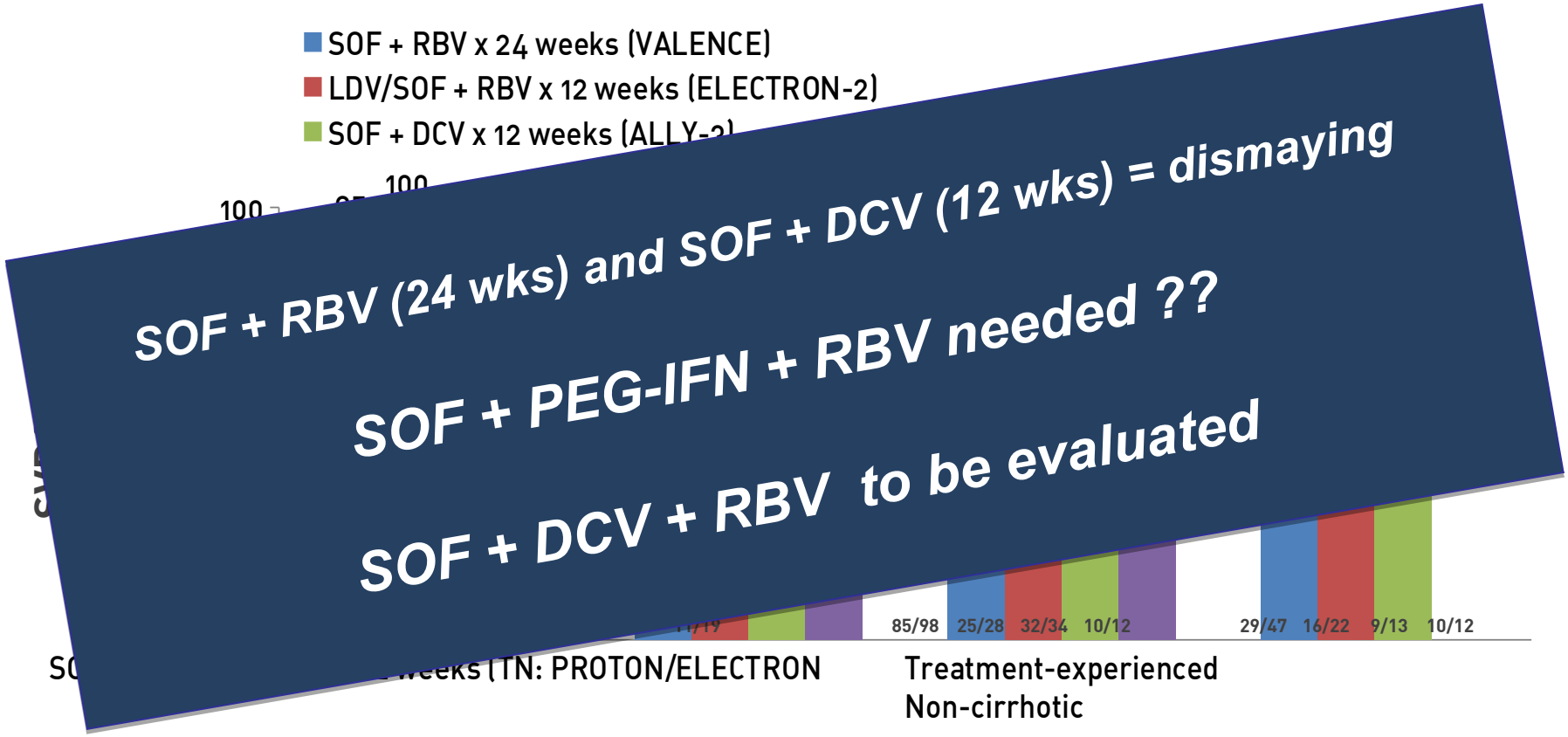
# HCV Gt 3: still a difficult genotype




**LDV/SOF + RBV for 12 weeks and SOF + DCV for 12 weeks are not EMA-recommended treatment regimens for GT 3**

Zeuzem S, et al. N Engl J Med 2014;370:1604-14; Gane E, et al. EASL 2014; Oral #6; Gane E et al. NEJM 2013;368:34–44; Lawitz E et al. Lancet Infect Dis 2013;13:401–408; Gane E et al. AASLD 2014, Poster #LB-11; Lawitz E et al. AASLD 2013, Oral #LB-4; Nelson M et al. AASLD 2014, Oral #LB-3.

# HCV GT 3: still a difficult genotype in cirrhotic patients




**SOF + RBV (24 wks) and SOF + DCV (12 wks) = dismaying**

**SOF + PEG-IFN + RBV needed ??**

**SOF + DCV + RBV to be evaluated**

**LDV/SOF + RBV for 12 weeks and SOF + DCV for 12 weeks are not EMA-recommended treatment regimens for GT 3**

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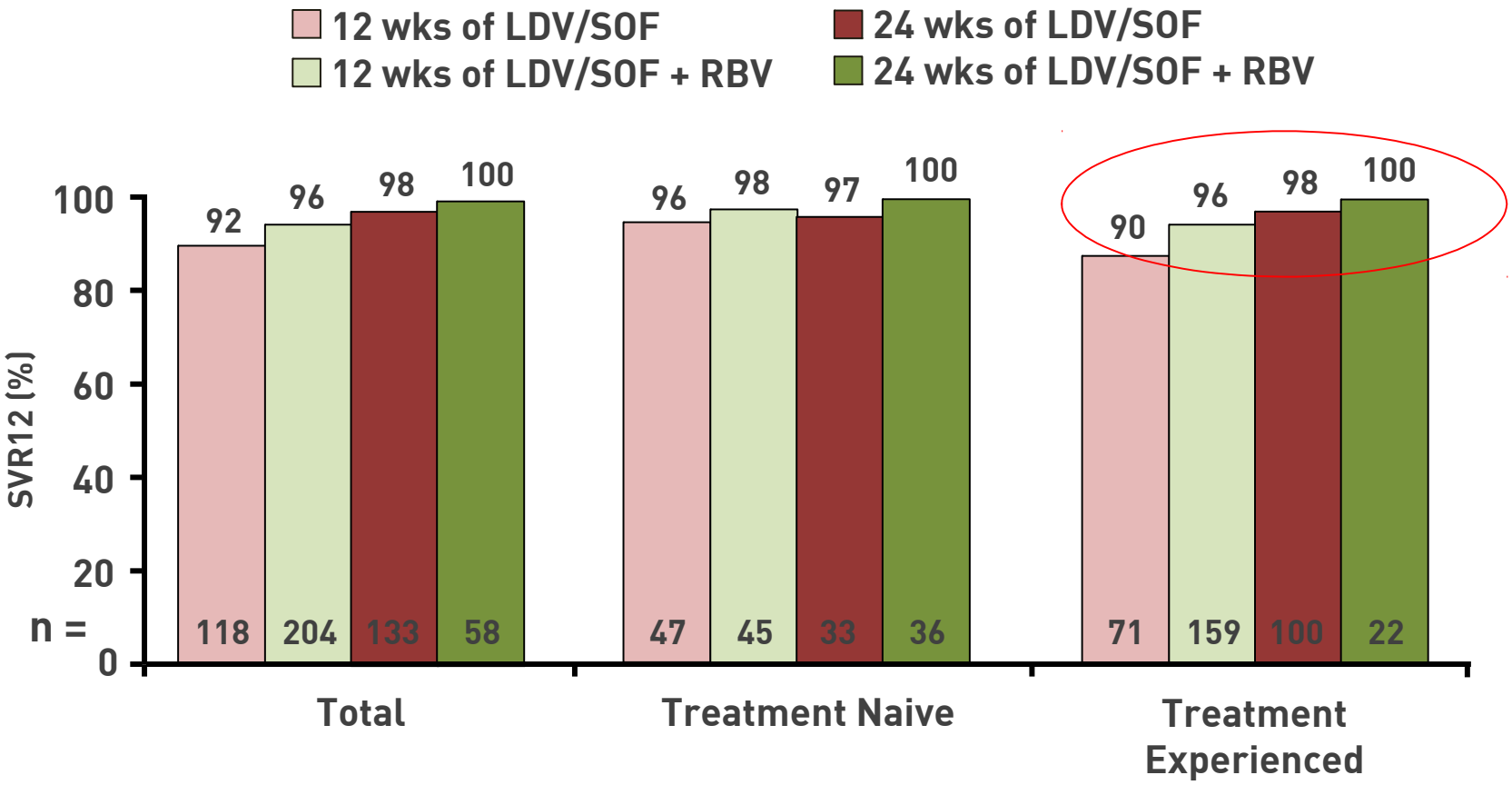
An Integrated Safety and Efficacy Analysis of >500 Patients With Compensated Cirrhosis Treated With Ledipasvir/Sofosbuvir With or Without Ribavirin

Marc Bourlière[1], Mark Sulkowski[2], Masao Omata[3], Stefan Zeuzem[4], Jordan Feld[5], Eric Lawitz[6], Patrick Marcellin[7], Robert Hyland[8], Xiao Ding[8], Jenny Yang[8], Steven Knox[8], Phillip Pang[8], Mani Subramanian[8], William Symonds[8], John McHutchison[8], Alessandra Mangia[9], Edward Gane[10], K. Rajender Reddy[11], Masashi Mizokami[12], Stanislas Pol[13], Nezam Afdhal[14]

# LDV/SOF efficacy in compensated Gt1 cirrhosis




Bourlière M, et al. AASLD 2014. Abstract 82.

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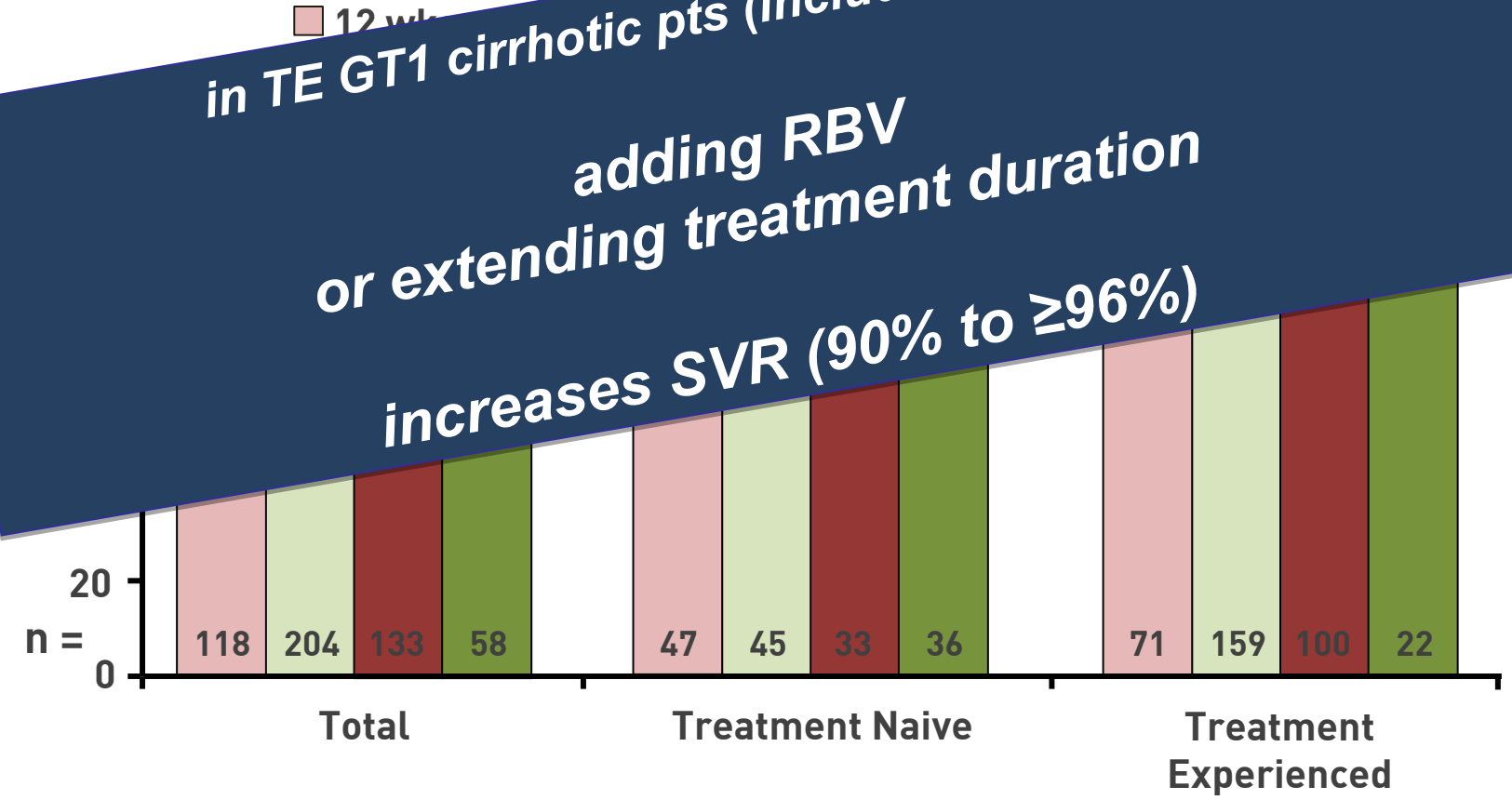
**in TE GT1 cirrhotic pts (including PI failures)**

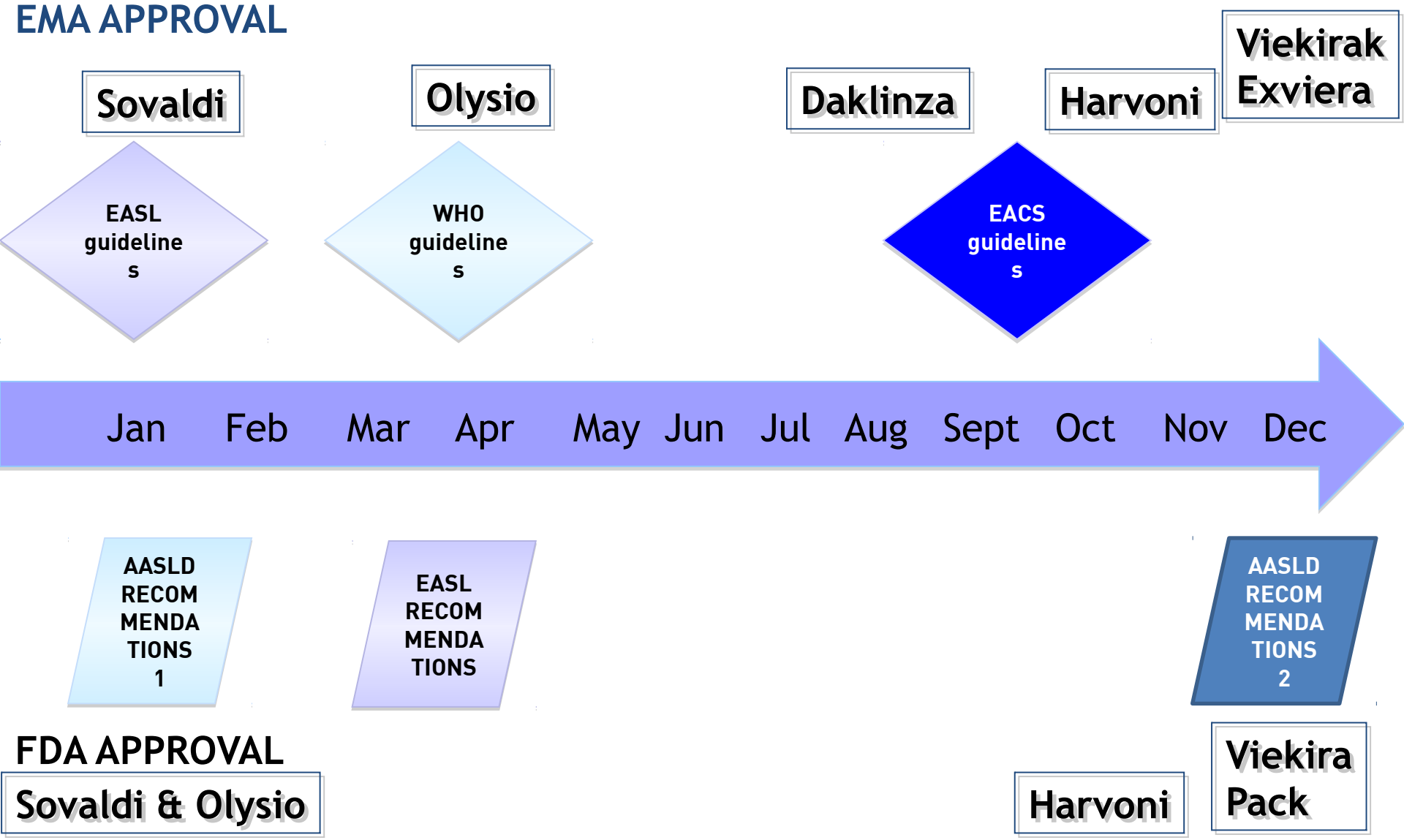
**adding RBV**
**or extending treatment duration**

**increases SVR (90% to ≥96%)**

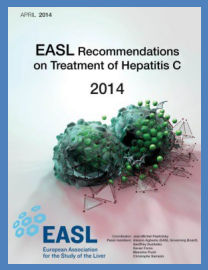



Bourlière M, et al. AASLD 2014. Abstract 82.

# 2014: HCV guidelines, recommendations & anti HCV drugs approval by International agencies



# EASL AND AASLD-IDSA RECOMMENDATIONS

| |  |  |
|---|---|---|
| Indications to treatment | **All treatment-naïve and -experienced** patients *with compensated disease due to HCV* **should be considered for therapy (A1)** | Treatment is **recommended for patients with chronic HCV infection** (IA) |

## IFN free DAA will expand the pool of treatable patients

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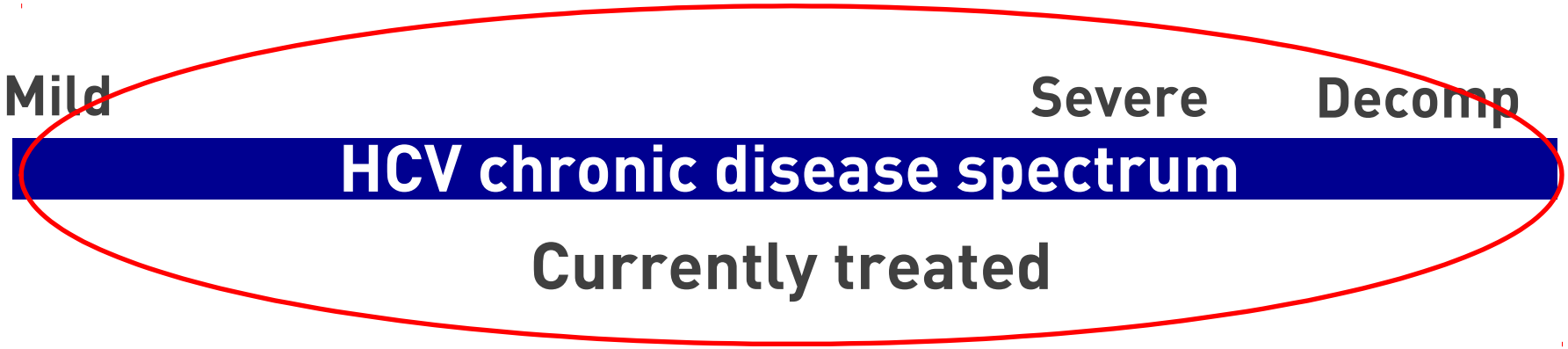
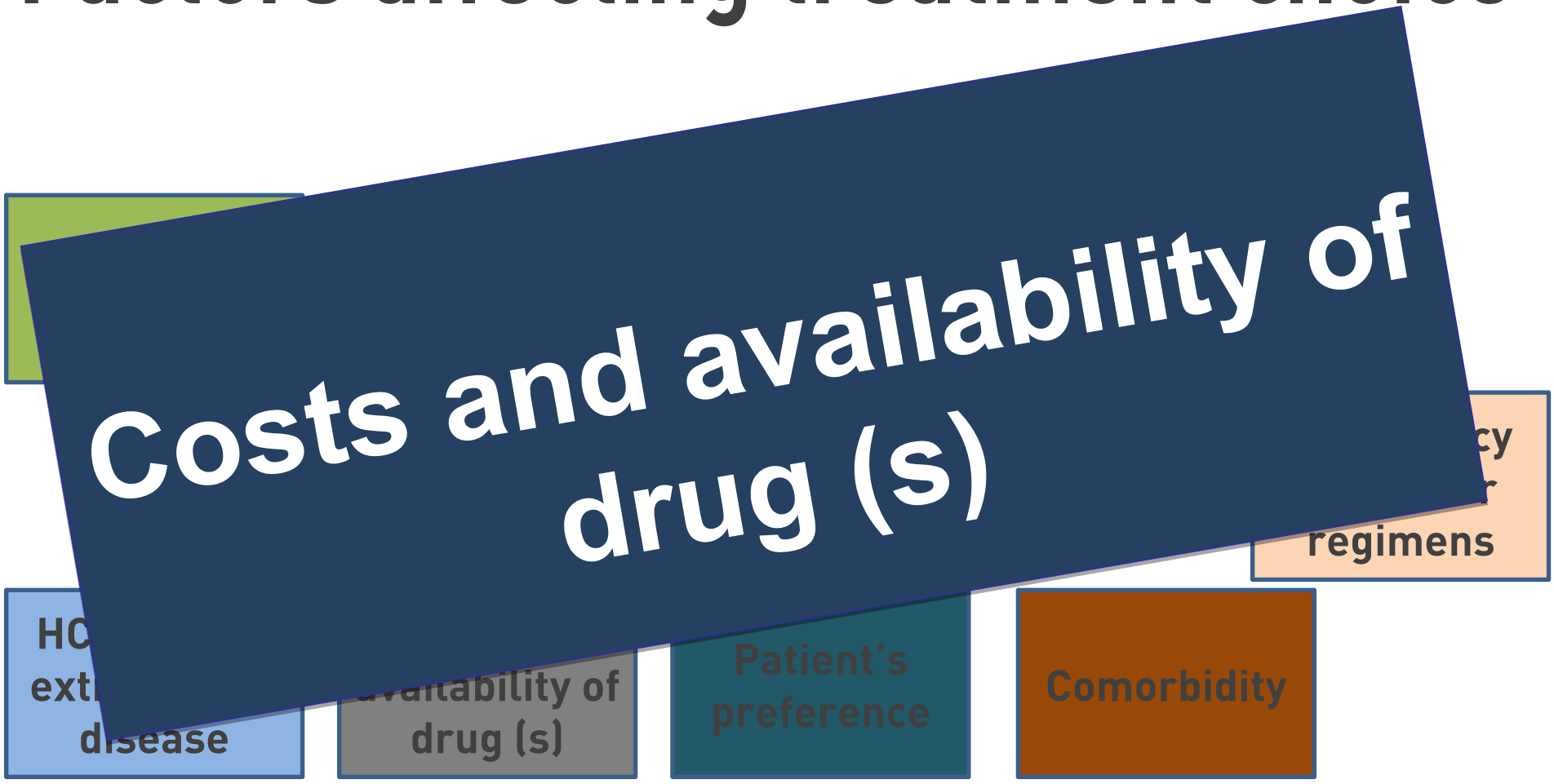



- By enrolling new patients at the extreme of the spectrum
- By enforcing need for mass screening for HCV

# Factors affecting treatment choice

- Disease stage/type
- Probability of SVR
- Urgency of HCV clearance
- Inability to tolerate P/R
- Expectancy for newer regimens
- HCV related extrahepatic disease
- Costs and availability of drug (s)
- Patient's preference
- Comorbidity

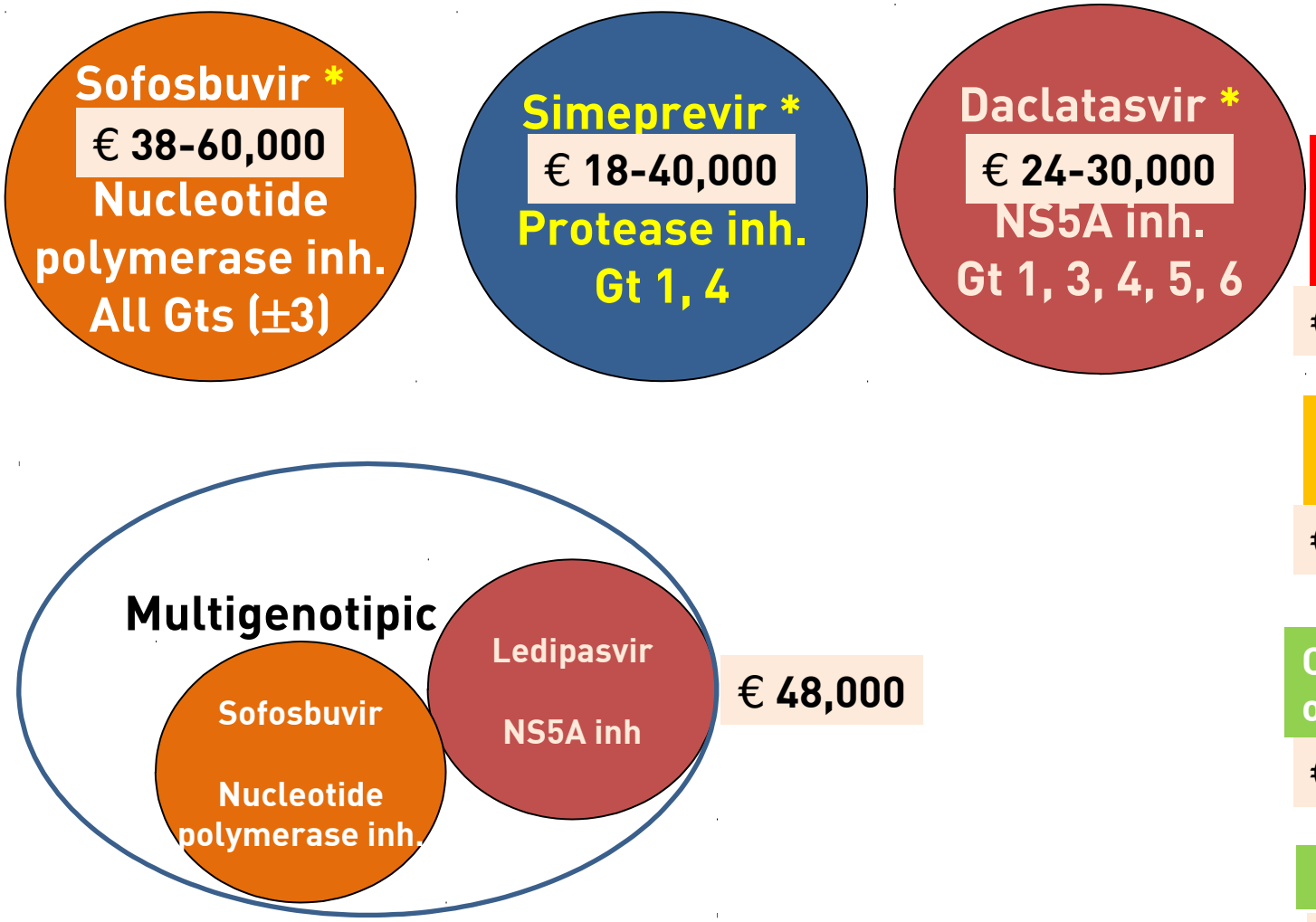
# Factors affecting treatment choice



# Factors affecting treatment choice


**Costs and availability of drug (s) will impact on HCV eradication**

# Current EU market prices for available DAAs (for 12 weeks of treatment)




Triple therapy with DAA, PEG IFN and ribavirin

€ 24-66,000

SOF (24 wk) and ribavirin, no IFN

€ 76-120,000

Off-label combination of two DAAs ± ribavirin

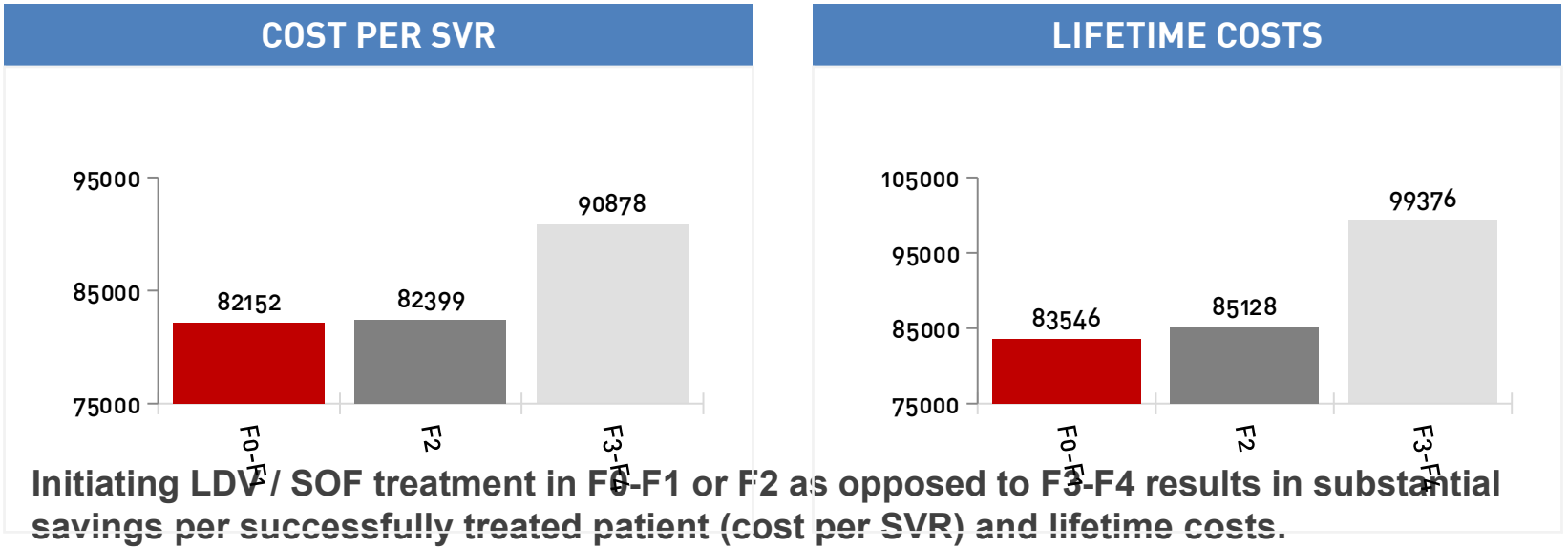
€ 42-100,000

FDC of two DAAs

€ 48,000

# Evaluation of Health Outcomes from LDV/SOF Treatment of Patients with Early vs. Advanced Liver Fibrosis

**Initiating LDV/SOF treatment at F0-F1 and F2 rather than F3-F4 reduces lifetime costs of treatment, and has a lower cost per SVR**




**Initiating LDV / SOF treatment in F0-F1 or F2 as opposed to F3-F4 results in substantial savings per successfully treated patient (cost per SVR) and lifetime costs.**

*Ahmed A, AASLD, 2014, #1751*

## EASL recommendations 2014

**In principle, all patients with chronic HCV infection are candidate to treatment,but in a situation of limited availability:**

- **F3-F4: Priority**
- **F2: Reasonable**
- **F0-F1: Debatable**

***Informed deferral of treatment for patients with mild disease***

**EASL Recommendations on Treatment of Hepatitis C, April 2014**

## AASLD/IDSA: Patients With F3/F4 Fibrosis Have Highest Priority for HCV Treatment

- When constrained resources prevent treatment of all HCV infection cases, highest priority should be given to patients with advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C
- Based on available resources, treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority

AASLD/IDSA HCV Management Guidance. October 2014.

## EASL recommendations 2014

In principle, all patients with
HCV infection

*…fied deferral of treatment*
*for patients with mild disease*

EASL Recommendations on Treatment of Hepatitis C, April 2014

## AASLD/IDSA: Pati… …ibrosis …ment

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Based on available resources, treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority

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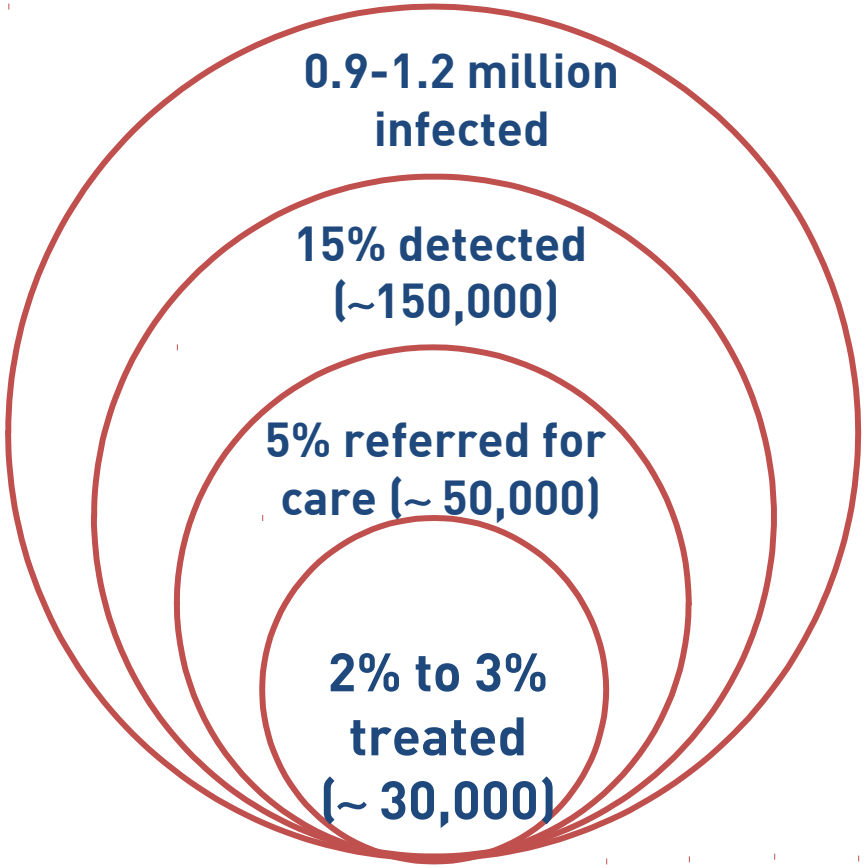
**Patients With F3/F4 Fibrosis**

**Have Highest Priority for HCV Treatment**

# Chronic HCV infection: an extrapolation of the Italian status

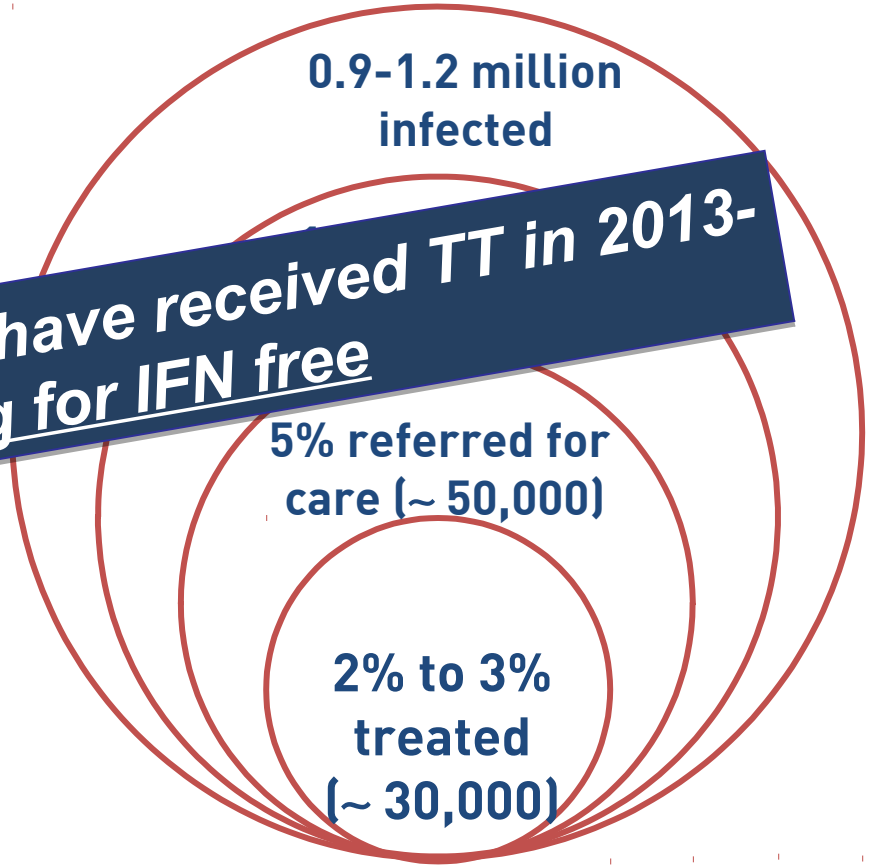



260.000 infected to be treated?

- **15.000 - 20.000*** urgent
- **60.000*** within 18 months

* Documento GdL Epatite C AIFA-MinSal-ISS-SIMIT-AISF-EPAC-CNT Aprile 2014

# Chronic HCV infection: an extrapolation of the Italian status




**Less than 4,000 Gt 1 patients have received TT in 2013-14: warehousing for IFN free**

**260.000 infected to be treated?**

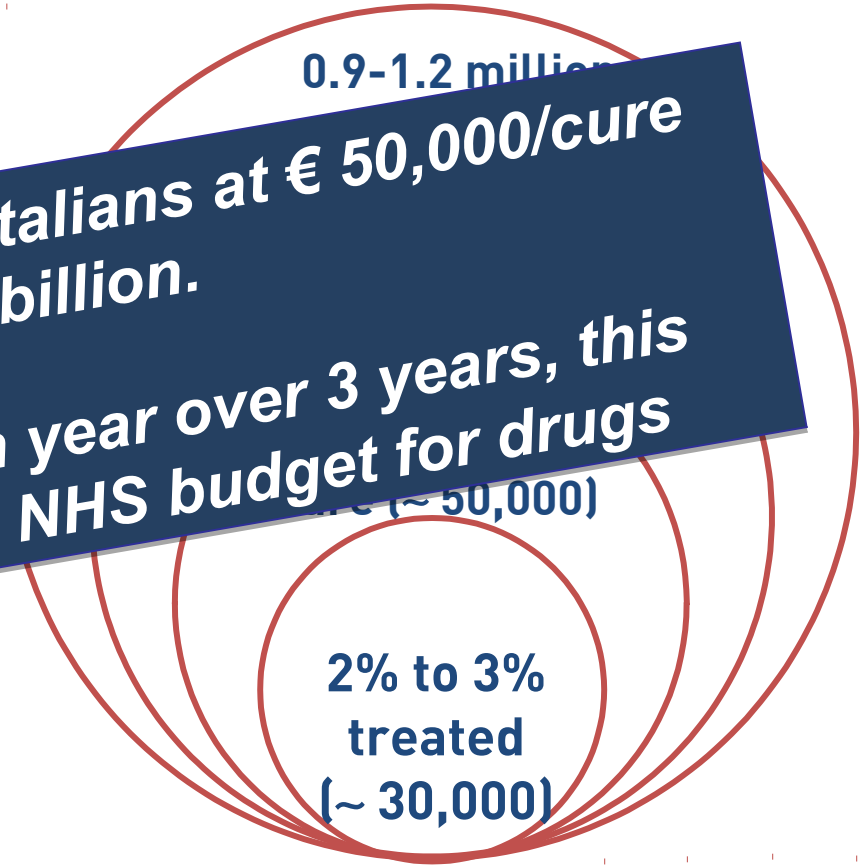
- **15.000 - 20.000* urgent**
- **60.000* within 18 months**

*** Documento GdL Epatite C AIFA-MinSal-ISS-SIMIT-AISF-EPAC-CNT Aprile 2014**

# Chronic HCV infection: an extrapolation of the Italian status

**The cost of treating 300,000 Italians at € 50,000/cure would be 15 billion.**

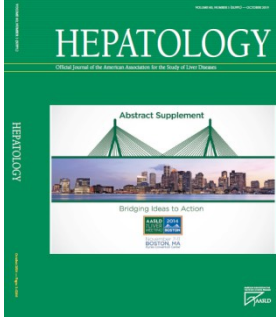
**Aiming to cure 50,000 each year over 3 years, this would absorb ≥ 1/5 of the NHS budget for drugs**




2 to be treated?

- 15.000 - 20.000* urgent
- 60.000* within 18 months

* Documento GdL Epatite C AIFA-MinSal-ISS-SIMIT-AISF-EPAC-CNT Aprile 2014




# Minimum target prices for production of Direct Acting Antivirals and associated diagnostics for developing countries

*Andrew M. Hill[2], Nikolien S. van de Ven[1], Bryony Simmons[1]*

Results: Predicted minimum costs for 12-week courses of HCV DAAs (patent expiry dates) were: US$50 for ribavirin 1200mg/day (generic), US$20 for daclatasvir 60mg/day (2027), US$102 for sofosbuvir 400mg/day (2029), US$90 for ledipasvir 90mg/day (2030), US$44 for MK-8742 (2028), and US$71 for MK-5172 (2030). Predicted minimum costs for 12 week courses of combination DAAs with the most consistent efficacy results were: US$122 per person for sofosbuvir+daclatasvir, US$152 for sofosbuvir+ribavirin (US$304 for 24 weeks), US$192 for sofosbuvir+ledipasvir and US$115 for MK-8742+MK-5172. Diagnostic testing costs were estimated at US$90 for genotyping (if treatment not pan-genotypic), US$34 for two HCV antigen tests (lower detection limit 2000 IU/mL) and US$22 for two full blood count, ALT and creatinine tests (before and during treatment).

Conclusions: Minimum costs of treatment and diagnostics to cure HCV were estimated at US$171-360 per-person, without genotyping or US$261-450 per-person with genotyping. These cost estimates assume that similar large-scale treatment programmes for HIV/AIDS can be established for HCV. Treatments with proven pan-genotypic activity will be required to avoid expensive pre-treatment genotyping. Further reductions in price could be achieved through shorter durations of treatment, if efficacy is shown in future trials.

# HCV THERAPEUTIC OPTIONS FROM AN ECONOMIC PERSPECTIVE

**Treat all identified cases with an optimal DAA (IFN-free) regimen**

- Maximal cures
- Minimal side effects
- High adherence
- Allows treatment by PCP

**Treat first with regimens that include IFN to capture easy cures and use DAA-only for Tx failures**

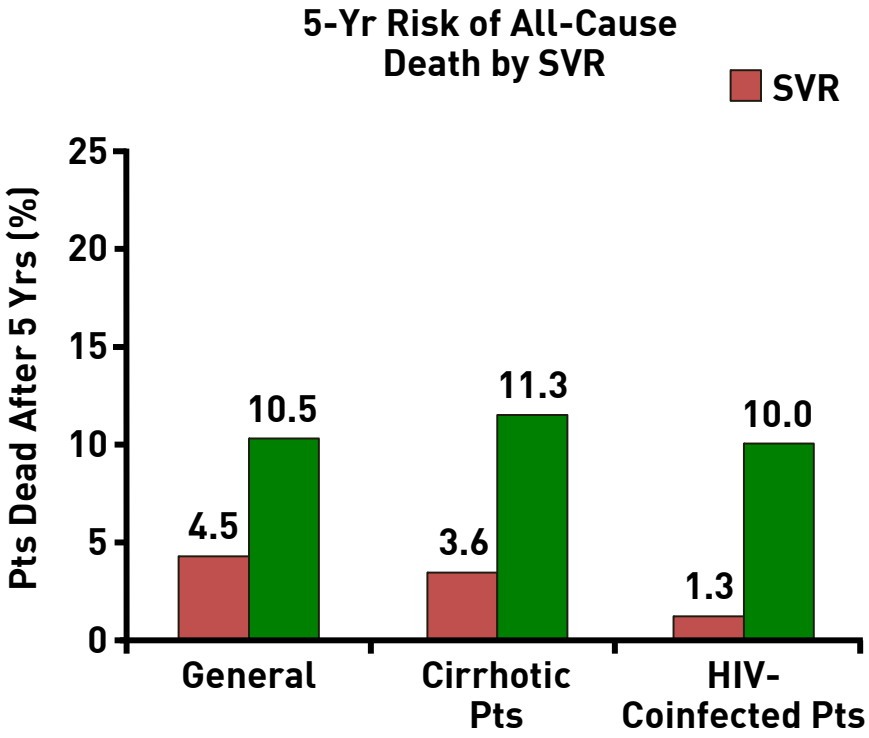
- Reduces cure rate
- Maximizes side effects
- Lowers adherence
- Requires specialist
- Requires 2nd Tx for some
- Only reduces cost by 20%
- Raises major ethical issue

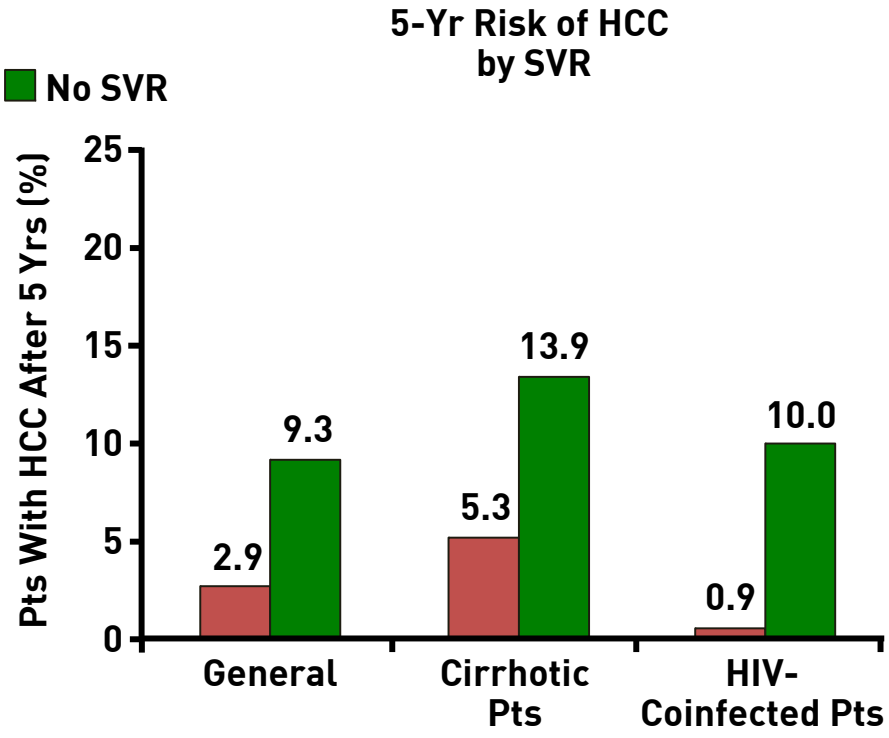
**Prioritize cases to spread costs; only treat those with stage $\geq$2 fibr.**

- Saves money but defers $\rightarrow$costs
- Reduces early cures/ 2nd trans
- Staging adds costs/Bx risk
- Risks missing fibrosis progress
- Severe cases harder to cure

# SVR associated with reduced 5-Yr risk of death and HCC in all populations

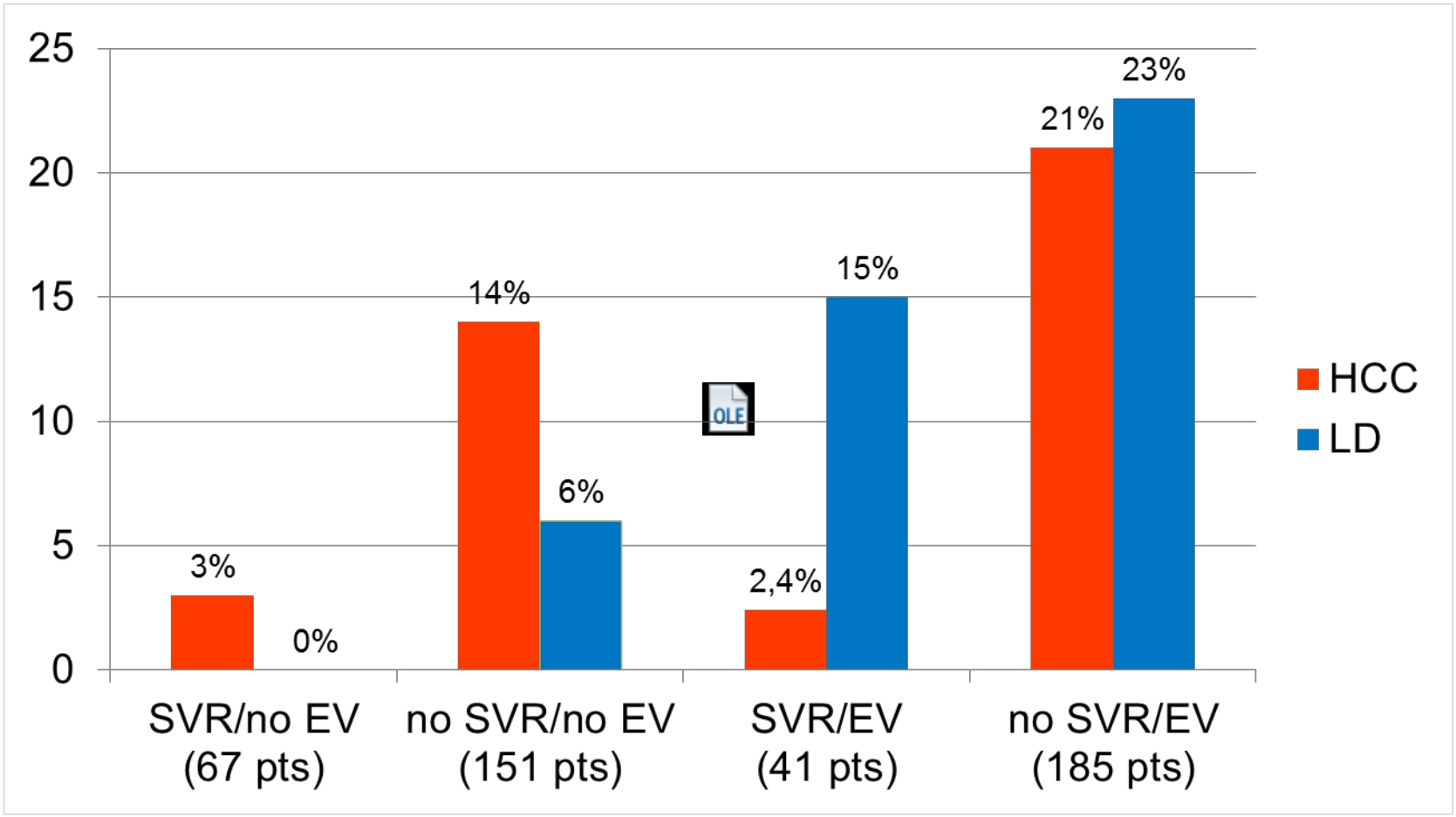
- SVR on IFN-based therapy was associated with substantial benefit vs no SVR
  - 62% to 84% reduction in all-cause mortality, 90% reduction in liver transplantation, 68% to 79% reduction in HCC



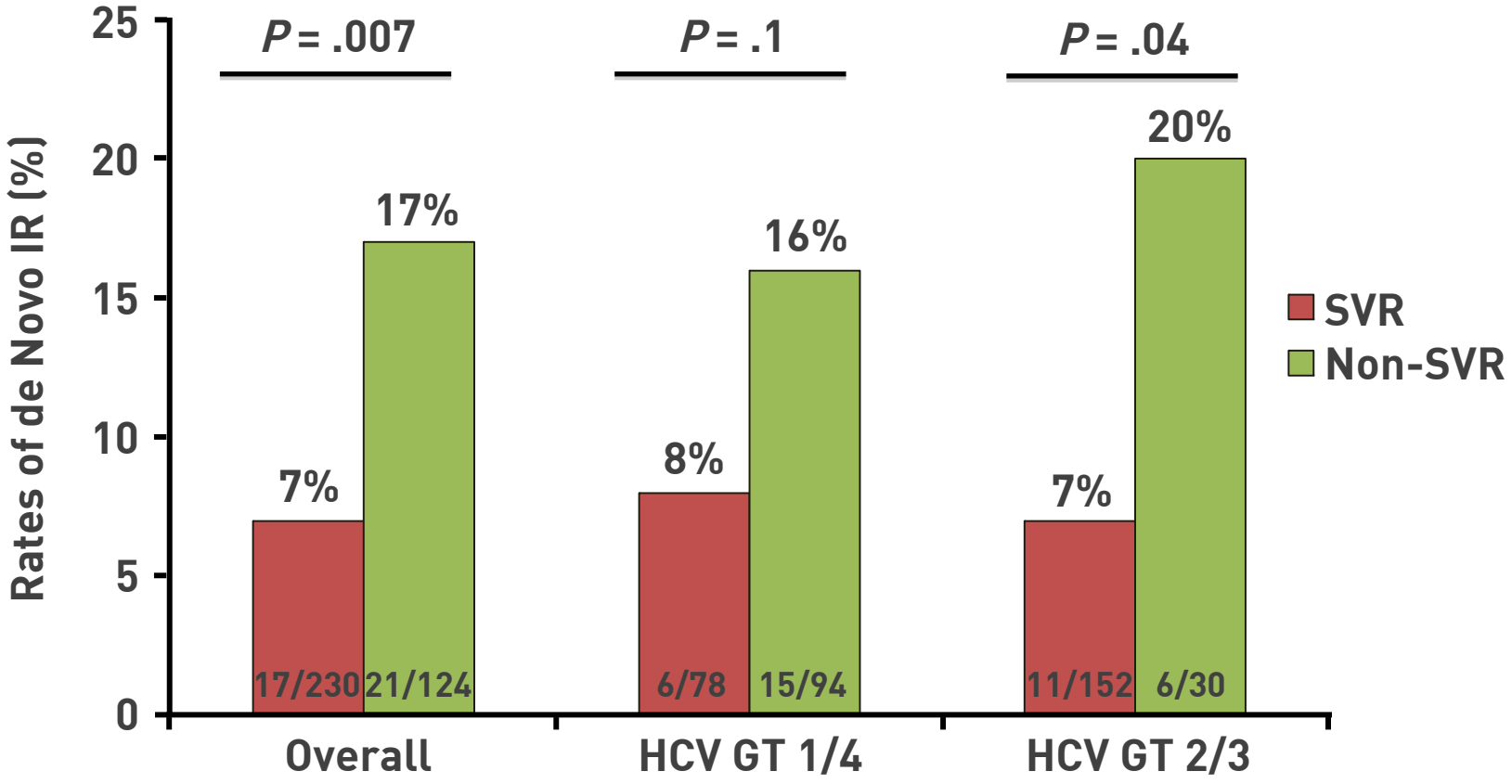

Hill AM, et al. AASLD 2014. Abstract 44.

# Deaths due to HCC or liver decompensation after P/R treatment in 440 patients with HCV cirrhosis




Di Marco V, submitted

# SVR Prevents Development of Insulin Resistance




Aghemo A, et al. Hepatology. 2012;58:1681-1687.

# HCV THERAPEUTIC OPTIONS
# FROM AN ECONOMIC PERSPECTIVE

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- High adh[illegible]

**what we can do**

**will probably not always be**

**what we should do !!**

- [illegible] specialist
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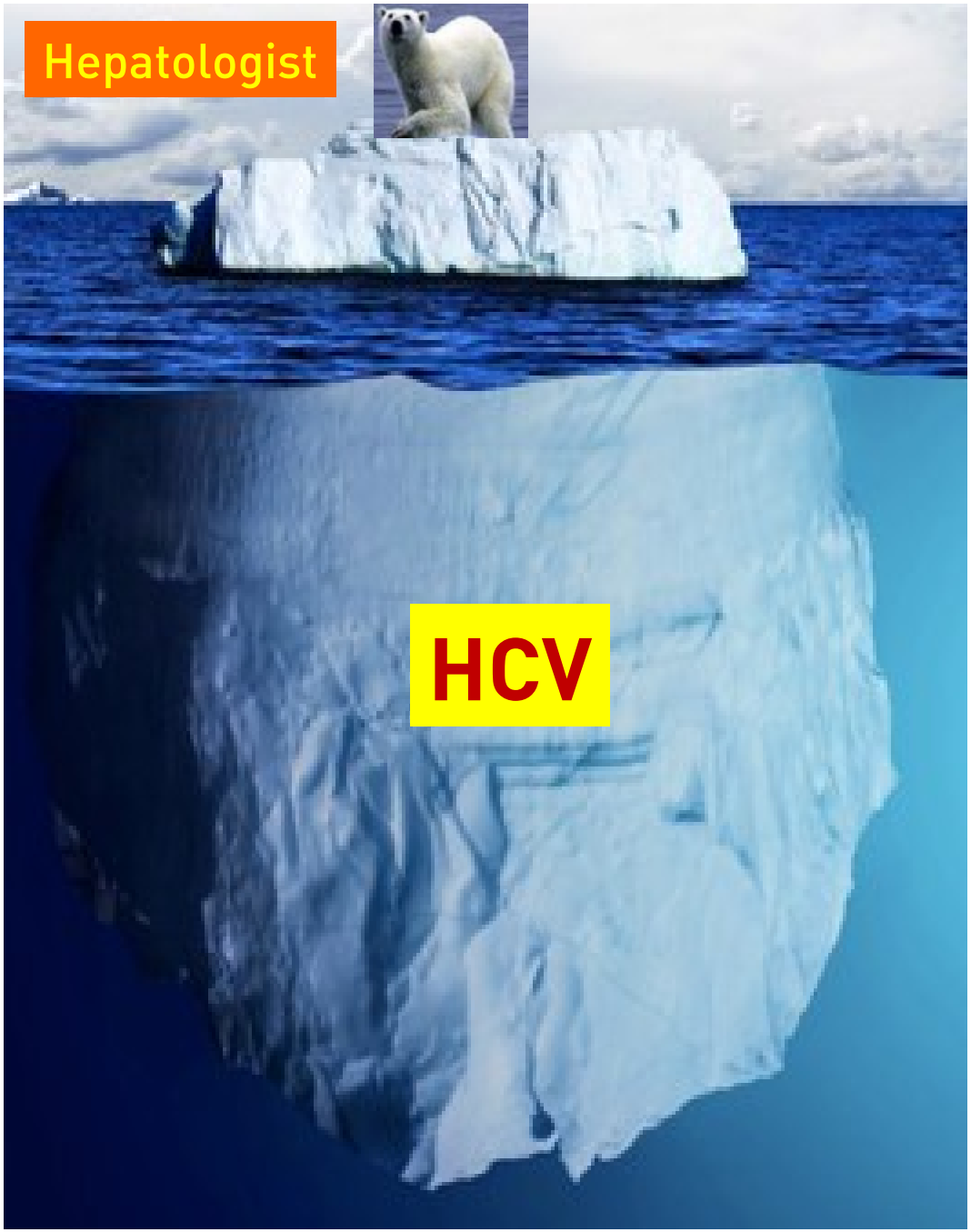
Hepatologist
HCV


Hepatologist
HCV