# Nouveaux traitements contre l'hépatite C

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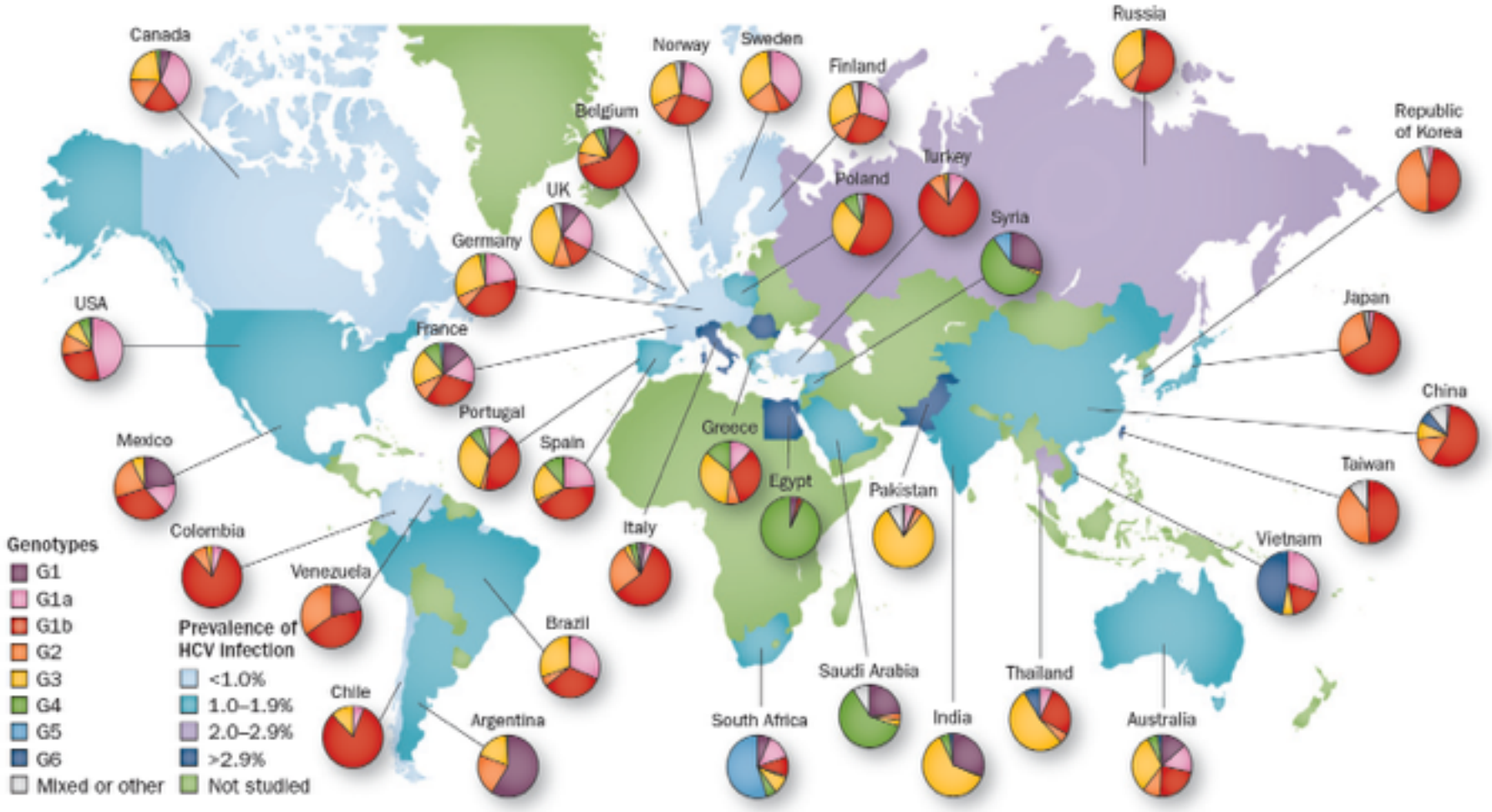
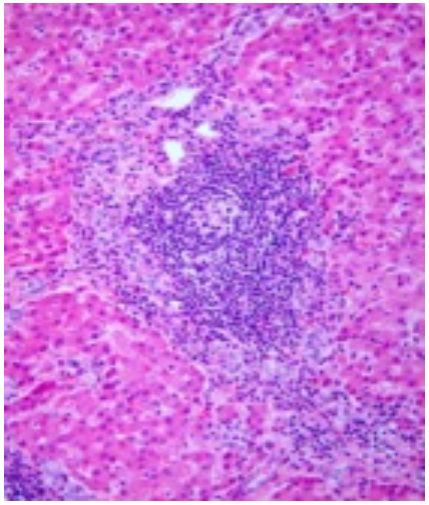
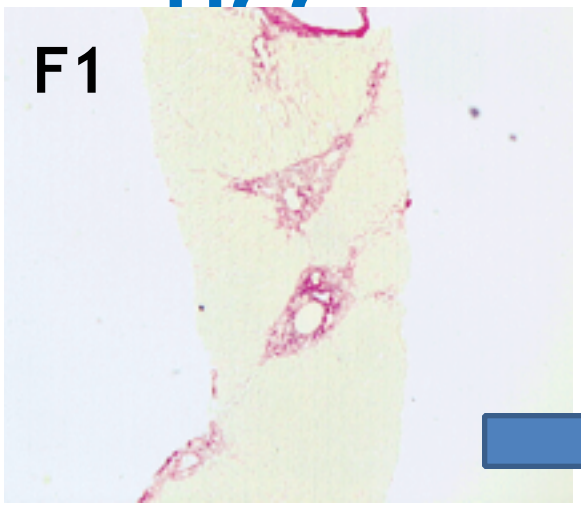
# HCV infects >185 million people worldwide

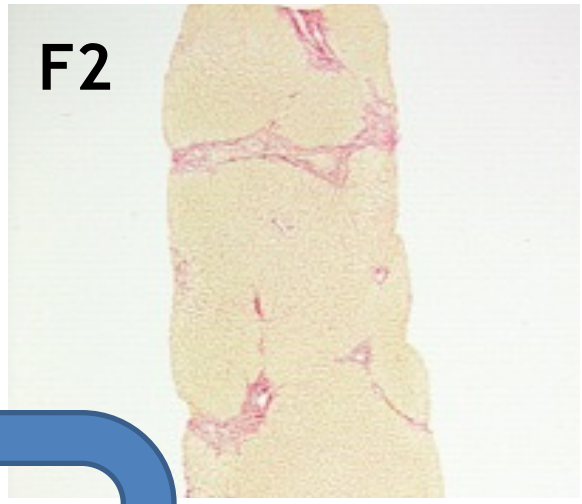


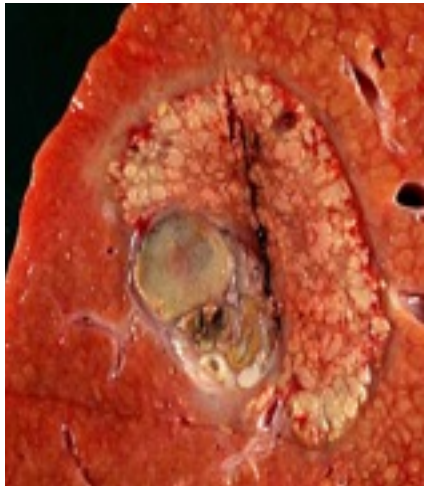

HAJARIZADEH *et al*. Nat Rev Gastroenterol Hepatol 2013;10:553-562
NEGRO and ALBERTI. Liver Int 2011;31 Suppl 2:1-3
HANAFIAH *et al*. Hepatology 2013;57:1333-1342

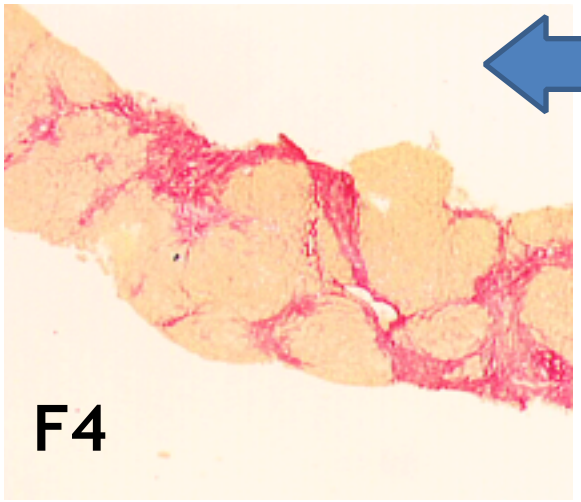
# Hepatitis C: a chronic inflammatory liver disease leading to cirrhosis and HCC

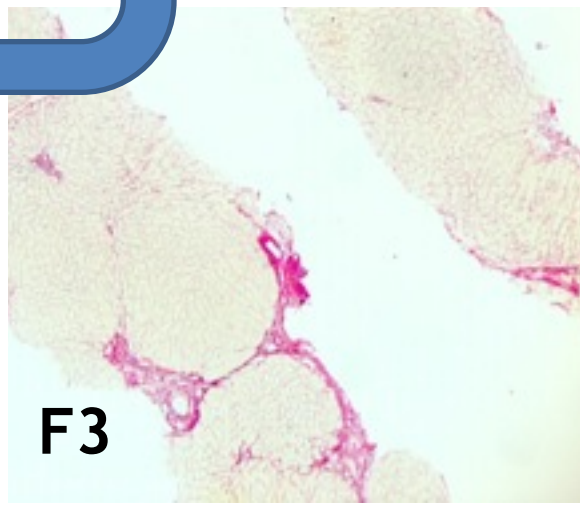




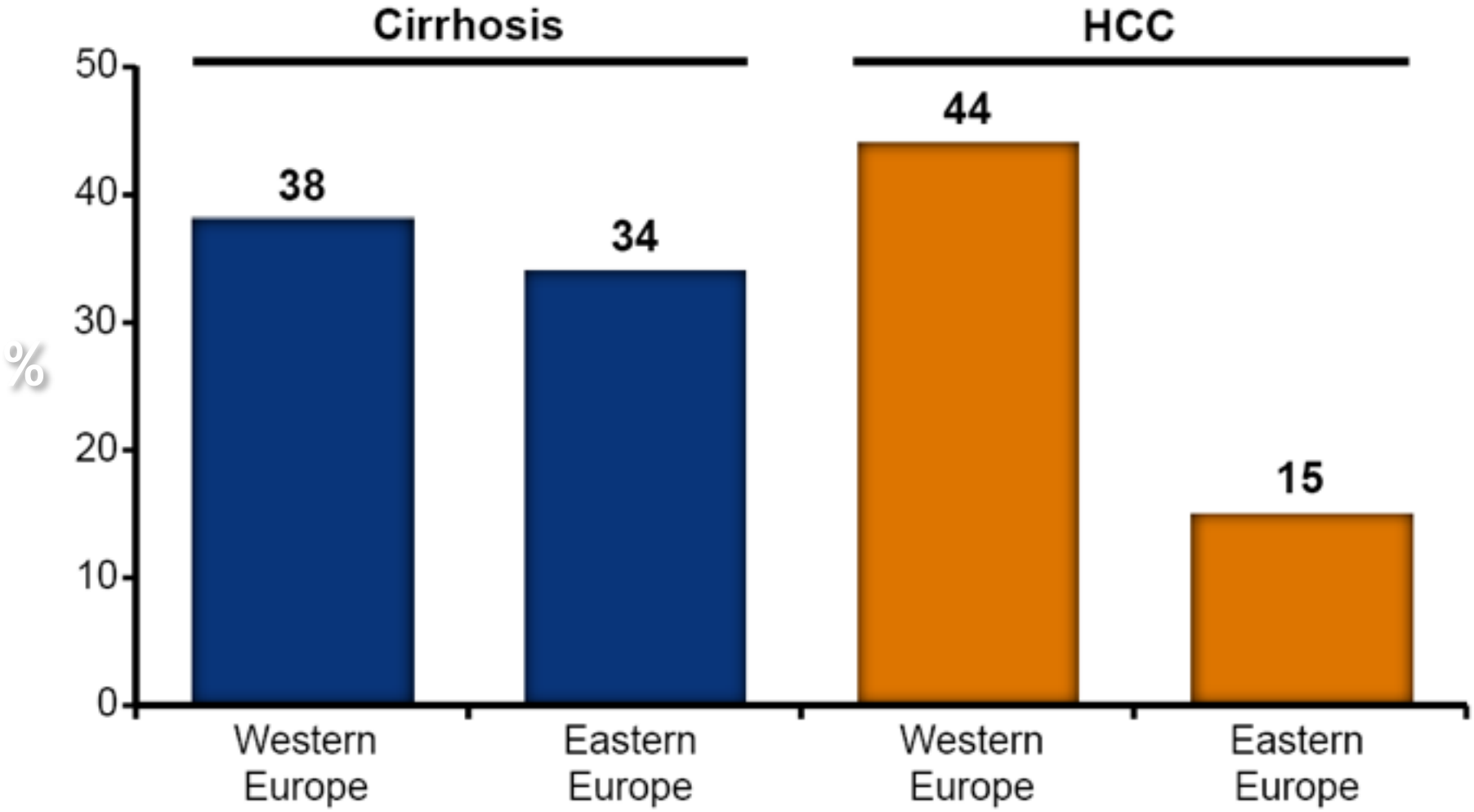





# Proportion of cirrhosis or HCC cases attributable to HCV (Europe)

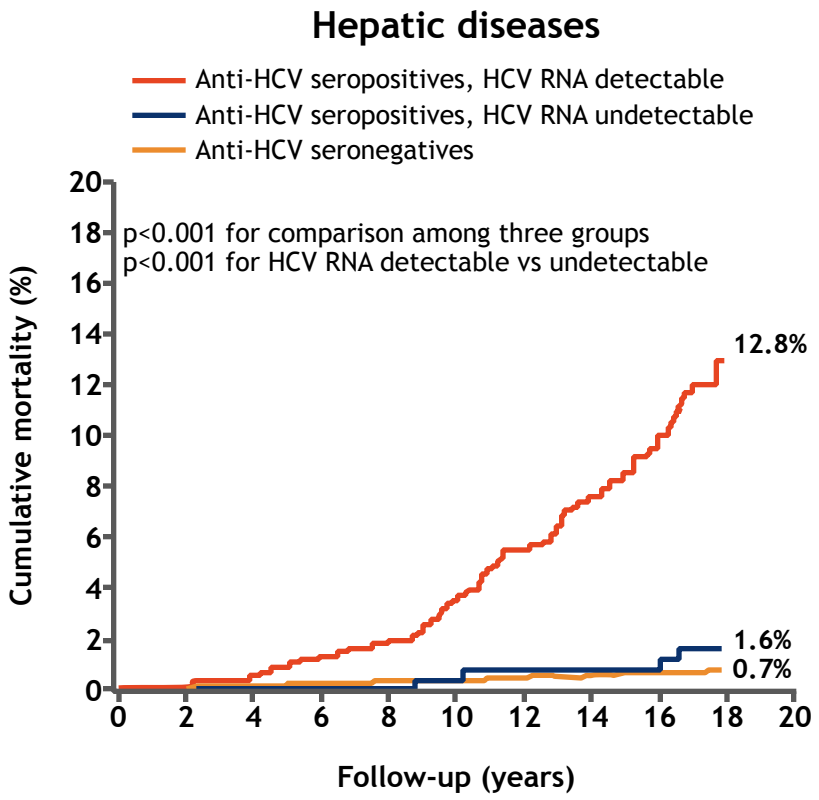


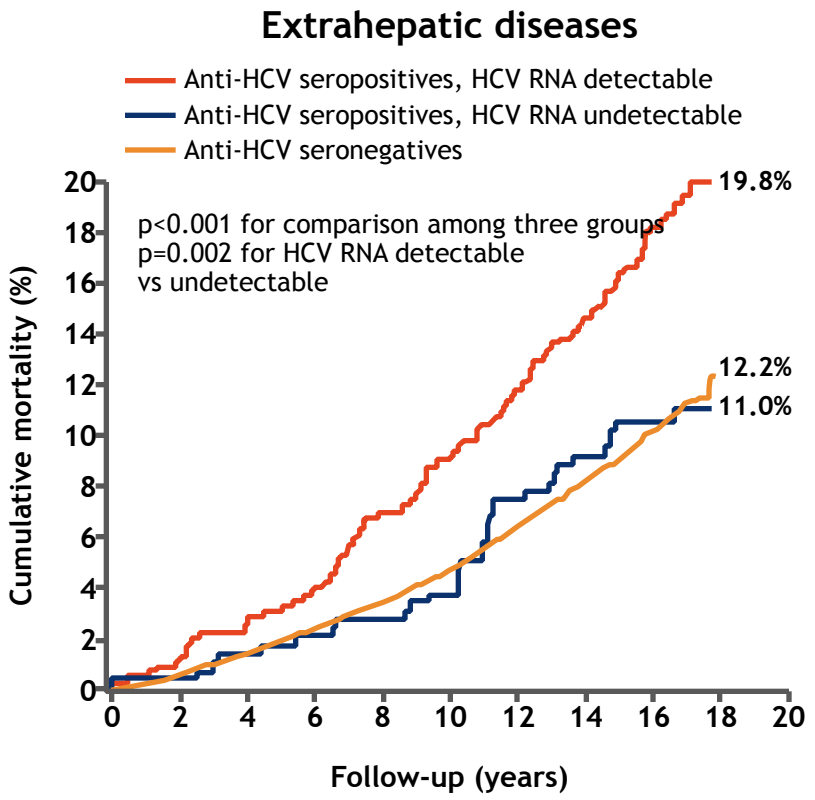

PERZ et al, *J Hepatol* 2006;45:529-38

# Chronic HCV increases mortality from hepatic and non-hepatic diseases

## The REVEAL HCV Cohort Study

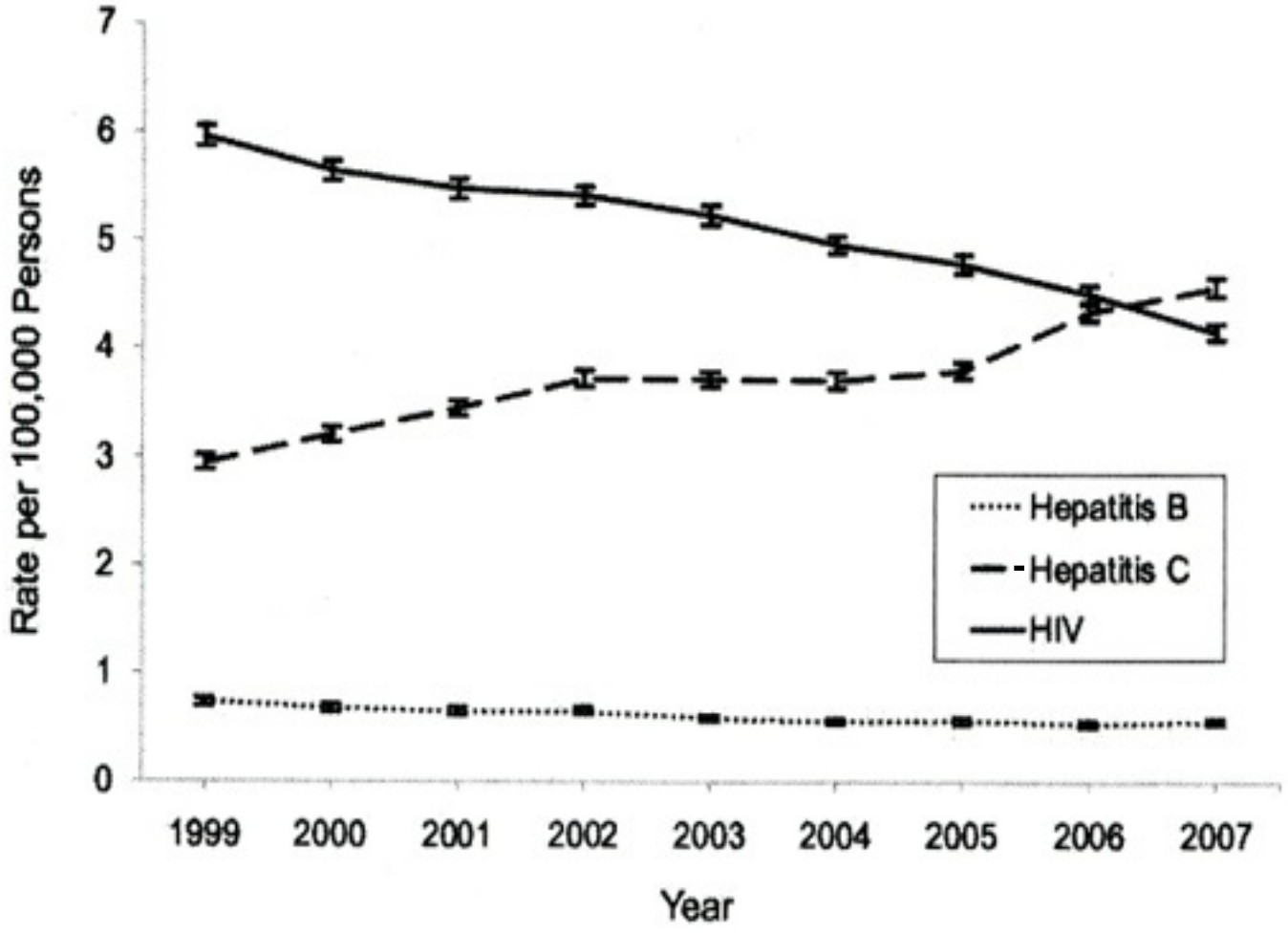
- 23 820 adults in Taiwan prospectively followed since 1991/2
- 1095 were anti-HCV positive; 69.4% had detectable HCV RNA




LEE et al, *J Infect Dis* 2012;206:469-477

# The growing burden of mortality associated with viral hepatitis in the US, 1999-2007 (CDC)



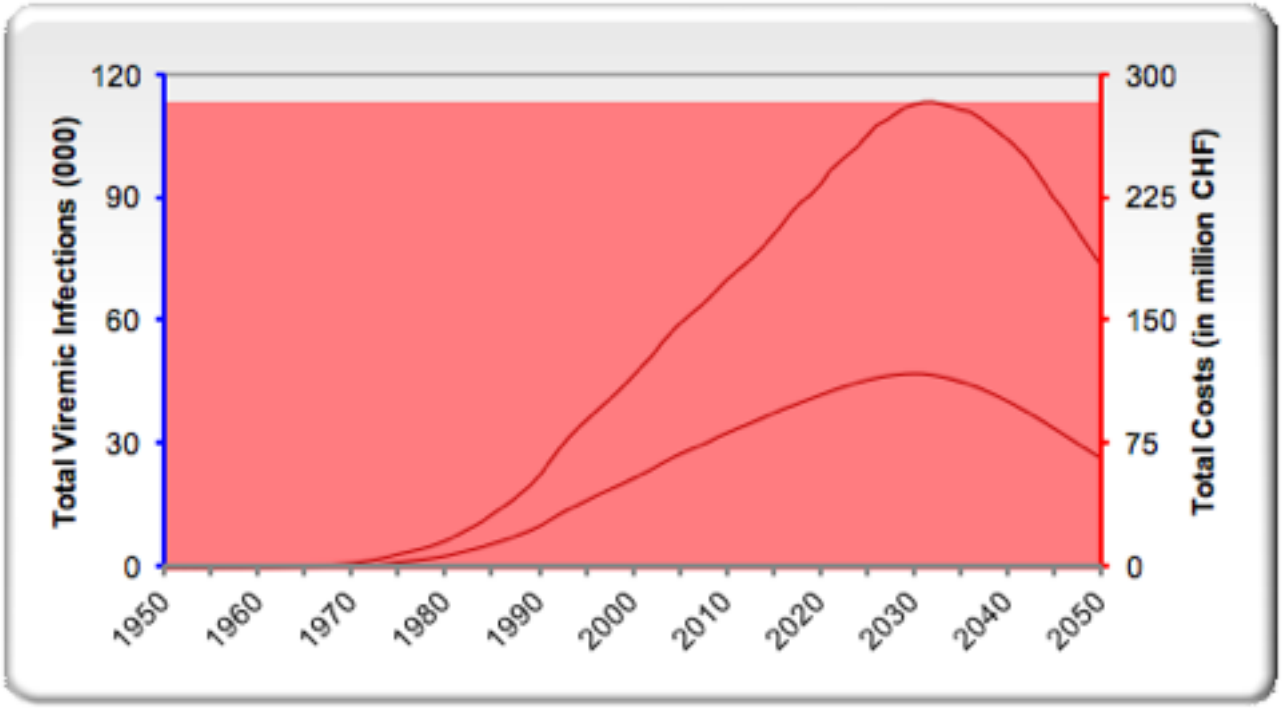

LY et al, *Ann Intern Med* 2012;156:271-8

# How many die of …. ?

| | Deaths in 2010 |
|---|---|
| *HCV* | *57,000* |
| *HBV* | *31,000* |
| *HIV* | *8,000* |

Global Burden Disease Study 2010 (COWIE *et al*, EASL 2014, oral presentation #86)

# In Switzerland, HCV prevalence peaked in 2003, but HCV-associated healthcare costs (excluding treatment costs) will peak in 2030




| | 2013 | 2030 |
|---|---|---|
| *Viremic cases* | *82,700 (37,200 - 93,400)* | *63,200 (25,900 - 71,800)* |
| *HCV-related costs (excluding treatment* | *89.6M (43.3M - 191.1M)* | *118.7M (43.9M - 282.9M)* |

BRUGGMANN *et al*, EASL 2014, poster 1285

# Treatment indications

- All treatment-naive and -experienced patients with compensated liver disease due to HCV should be considered for therapy
- Treatment should be prioritized for patients with advanced fibrosis (Metavir score F3 or F4)
- Treatment is justified in patients with Metavir score F2
- Indication for and timing of therapy should be individualized for patients with no or mild liver disease (Metavir scores F0 or F1)

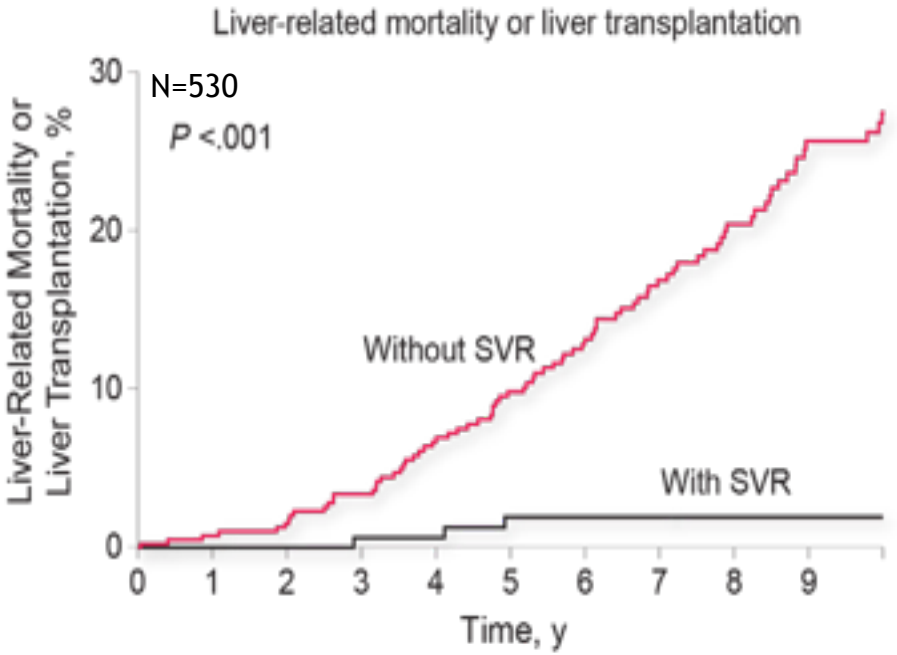
# Endpoint of treatment

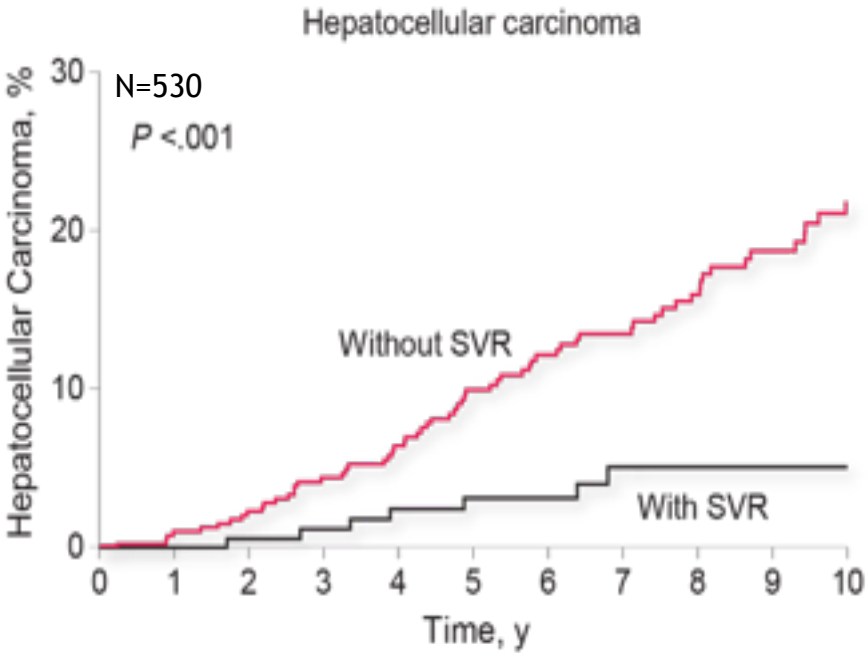
- The goal of treatment is to eradicate HCV infection to prevent cirrhosis, decompensated liver disease, HCC and death
- The endpoint is undetectable HCV RNA in serum 12 or 24 weeks after the end of treatment
- SVR corresponds to cure in 99% of patients, and is associated with improved clinical outcomes and survival

# Like any dogma, liver fibrosis is reversible


D'AMBROSIO et al, *Hepatology* 2012;56:532-43

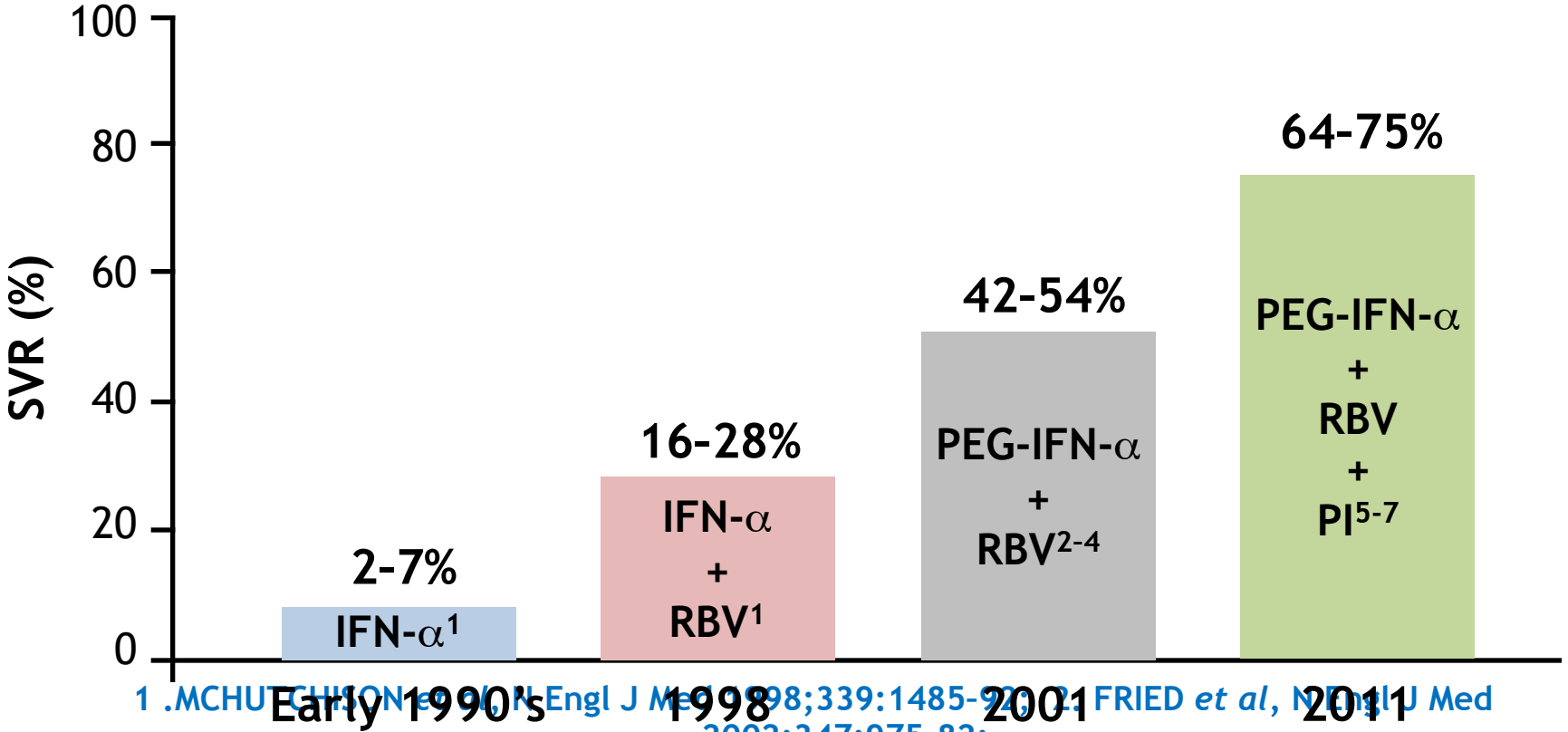
# SVR is associated with a reduction in liver-related mortality and risk of HCC



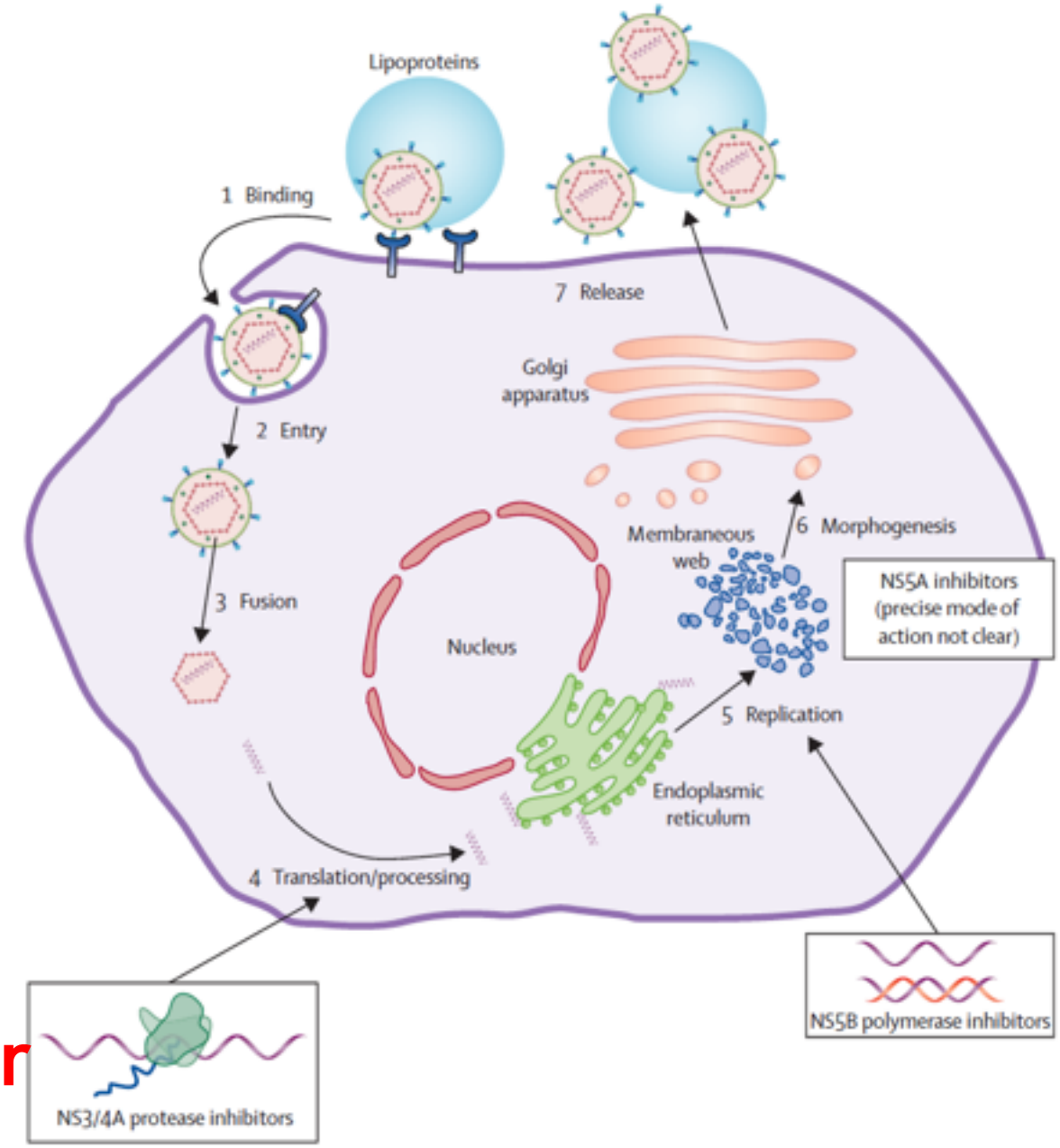




VAN DER MEER et al, *JAMA* 2012;308:2584-2593

# Sustained virologic response (SVR) after treatment of therapy-naïve HCV-1




1 .MCHUTCHISON et al, N Engl J Med 1998;339:1485-92; 2. FRIED *et al*, N Engl J Med 2002;347:975-82;
3. MANNS *et al*, Lancet 2001;358:958-65; 4. HADZIYANNIS et al, Ann Intern Med 2004;140:346-55;
5. JACOBSON *et al*, N Engl J Med 2011;364:2405-2416; 6 . SHERMAN *et al*, N Engl J Med 2011;364:1014-1024;
7. POORDAD *et al*, N Engl J Med 2011;364:1195-1206



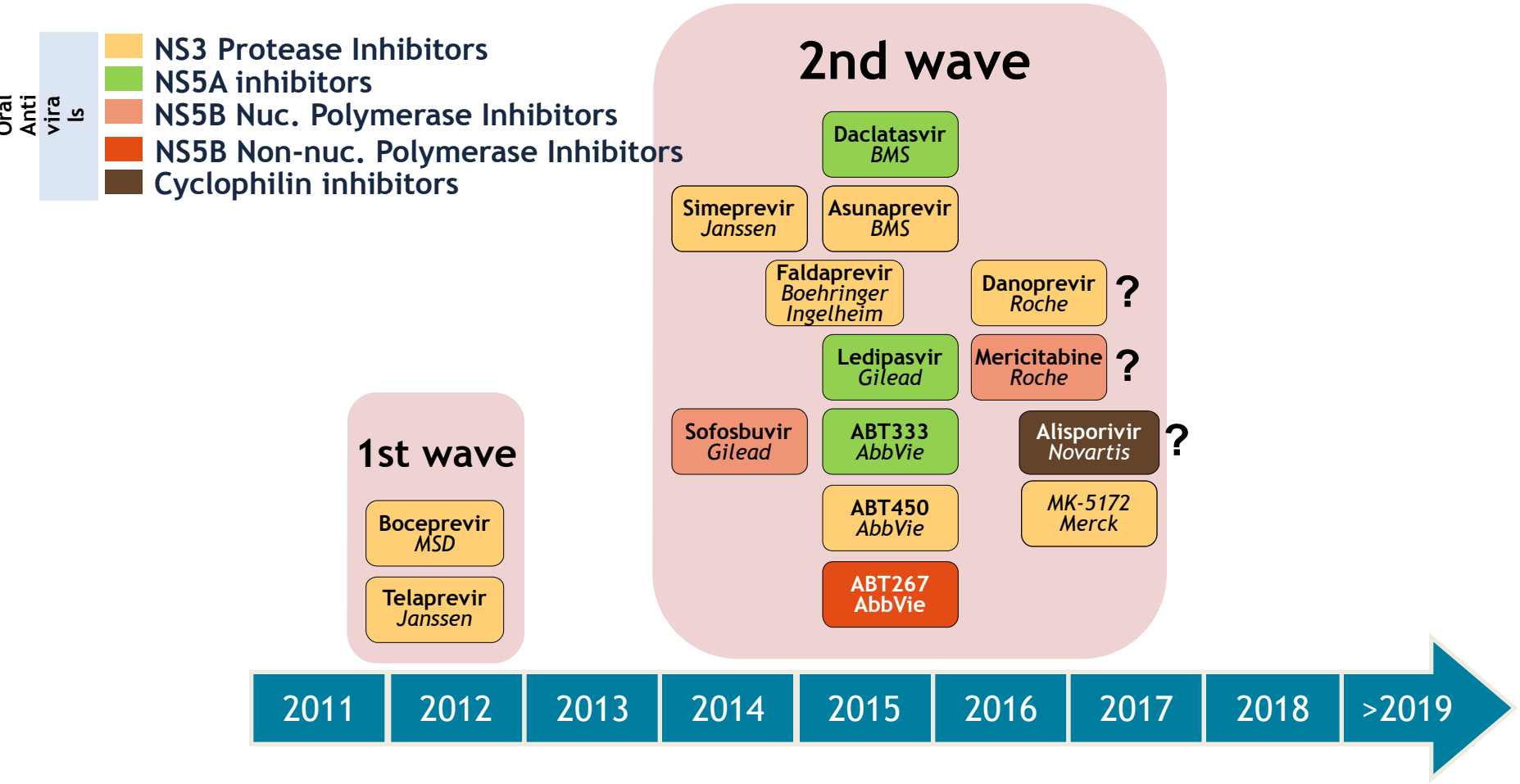

...previr

...asvir

...buvir

CORNBERG & MANNS, Lancet Infect Dis 2013;13:378-9

# Anti-HCV drug development pipeline



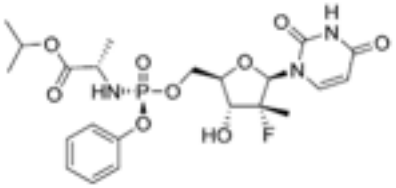

NOT EXHAUSTIVE

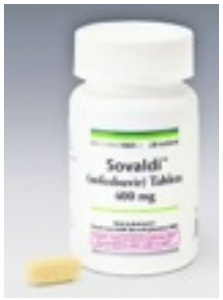
# IFN-free combination options*

| | NI | PI | NS5A | NNI | RBV | Genotype |
|---|---|---|---|---|---|---|
| ***Nucleotide analogue-based*** | | | | | | |
| *Gilead* | *Sofosbuvir* | *GS-9451* | *Ledipasvir* | | ± | *1-4* |
| *Roche* | *Mericitabin* | *Danoprevir/r* | | *Setrobuvir* | ± | *1, 4* |
| ***Nucleos(t)ide-free triple combo*** | | | | | | |
| *AbbVie* | | *ABT-450/r* | *ABT-267* | *ABT-333* | ± | *1* |
| *BMS* | | *Asunaprevir* | *Daclatasvir* | *BMS791325* | ± | *1, 4* |
| *Janssen/* | | *Simeprevir* | *GSK233680* | *TMC647055* | ± | *1* |
| ***Nucleos(t)ide-free second generation double combo*** | | | | | | |
| *Merck* | | *MK-5172* | *MK-8742* | | ± | *1, 2, 4-6* |
| *Achillion* | | *ACH-2684* | *ACH-3102* | | ± | *1* |
| ***Off-label options*** | | | | | | |
| *(na)* | *Sofosbuvir* | *Simeprevir* | | | - | *1* |
| *(na)* | *Sofosbuvir* | | *Daclatasvir* | | - | *1-3* |

*VX-135 and deleobuvir are not shown since currently on hold

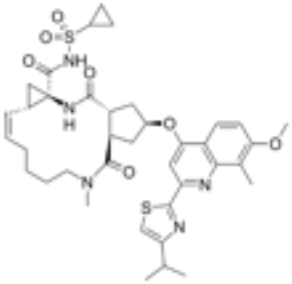
# Approvals expected in 2014

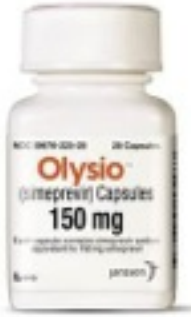





## Sofosbuvir (Sovaldi™)

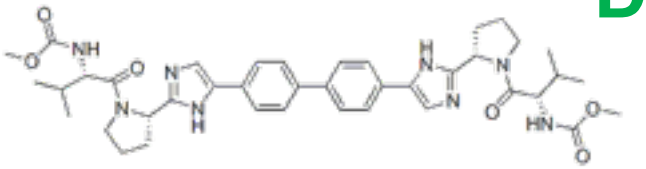
Nucleotide polymerase inhibitor
400 mg qd, all genotypes
High barrier to resistance






## Simeprevir (Olysio™)

NS3/NS4A serine protease inhibitor
150 mg qd, genotypes 1 and 4
Low barrier to resistance



## Daclatasvir (Daklinza™)

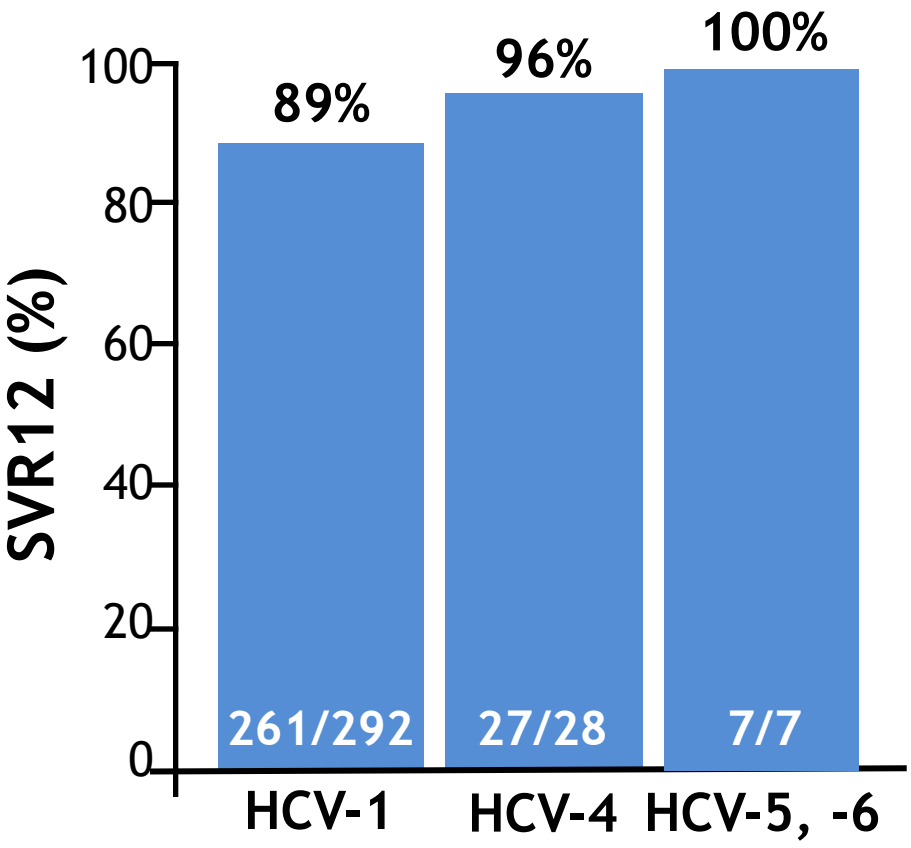
NS5A inhibitor
60 mg qd, all genotypes
Low barrier to resistance

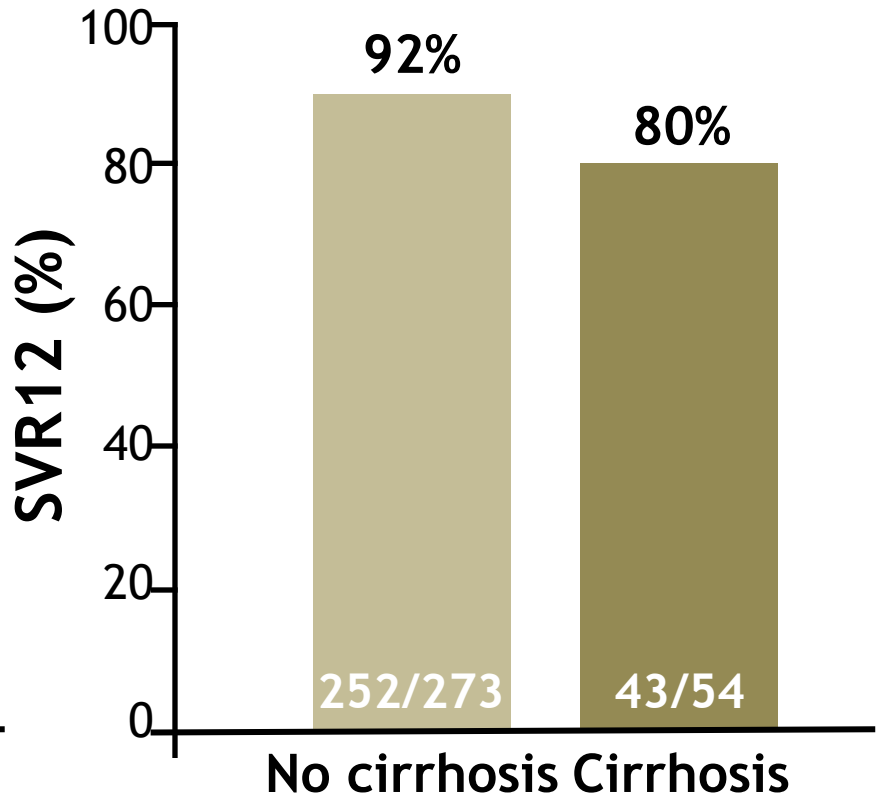
# The new options for 2014

| | |
|---|---|
| Pegylated IFNα + Ribavirin + Sofosbuvir | 12 weeks |
| Pegylated IFNα + Ribavirin + Simeprevir | 12 weeks + RGT 12/36 |
| Pegylated IFNα + Ribavirin + Daclatasvir | 12 weeks + RGT 12 |
| Sofosbuvir + Ribavirin | 12-24 weeks |
| Sofosbuvir + Simeprevir (± Ribavirin) | 12 weeks |
| Sofosbuvir + Daclatasvir (± Ribavirin) | 12-24 weeks |

# P + R + sofosbuvir (NEUTRINO study)

## (HCV genotypes 1, 4-6; treatment-naive)

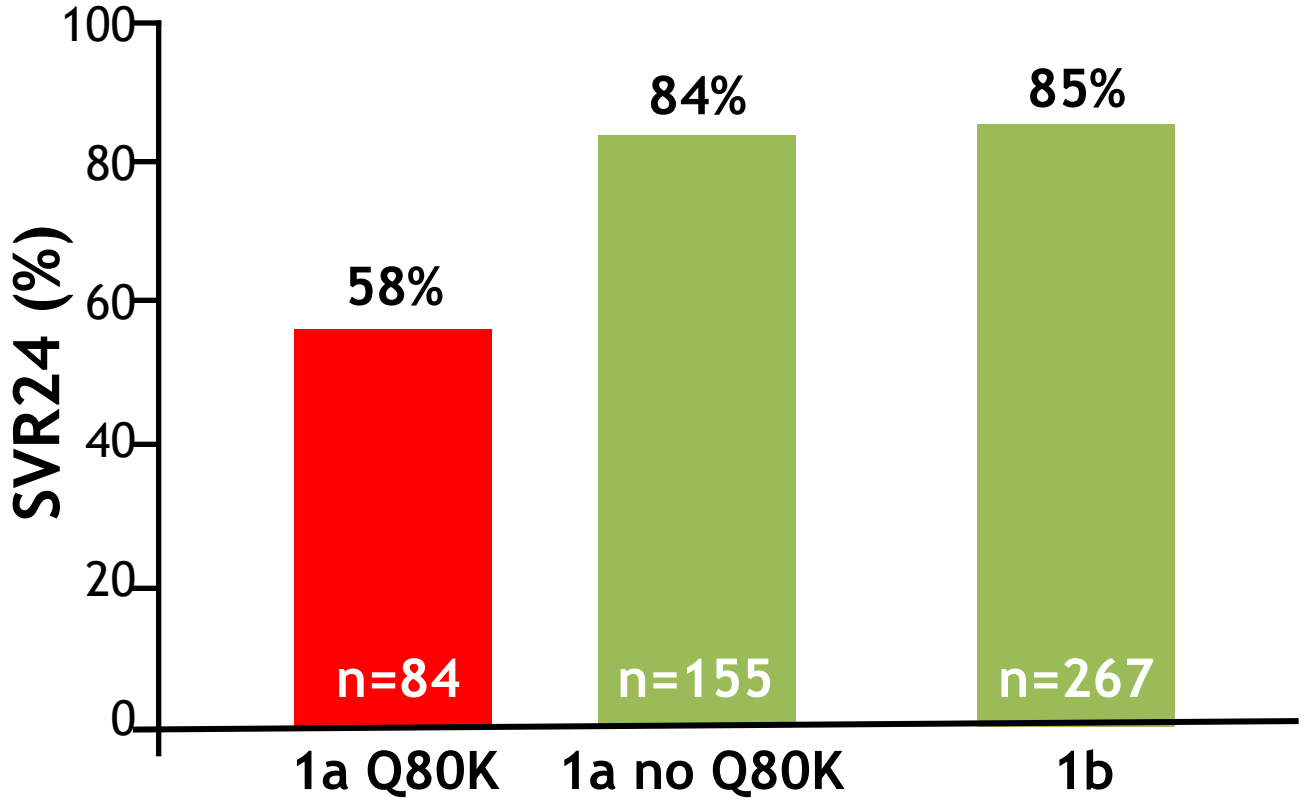



LAWITZ *et al*, N Eng J Med 2013

# P + R + simeprevir (QUEST-1/2 studies)

## HCV-1: role of subtype and Q80K substitution



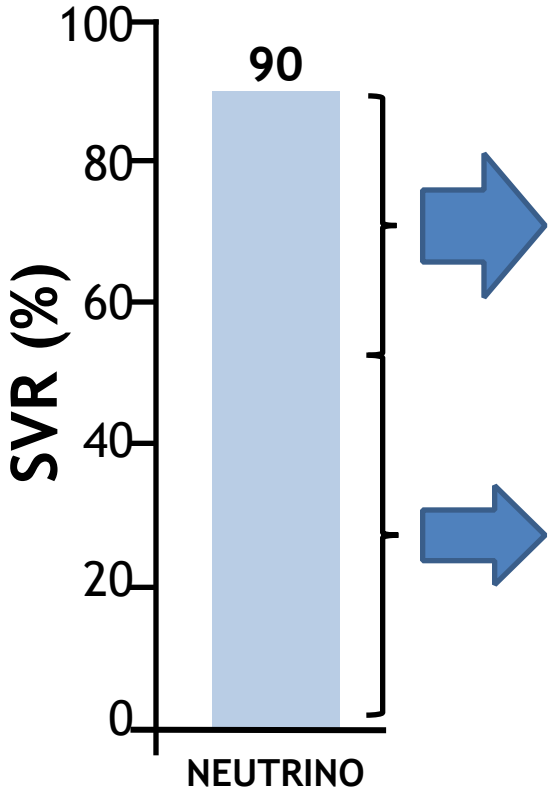

Prevalence of Q80K in the US: 1a, 32.5; 1b, 0.1%

JACOBSON *et al*, AASLD 2013; CHOE *et al*, AASLD 2013
FOSTER *et al*, EASL 2014; FDA AVDAC, October 24, 2013

# What about therapy-experienced HCV-1?

# Sofosbuvir in treatment-experienced HCV-1

- Phase II ELECTRON[1]: 1/10 (10%) reached SVR
- No data from the NEUTRINO[2] study, but....




**40% wouldn't.... meaning that SOF + P + R for 12 weeks allows reaching SVR in ~80% of prior failures to P + R**

**50% would have reached SVR with PR**

1. GANE *et al*, N Engl J Med 2013;368:34-44
2. LAWITZ *et al*, N Engl J Med 2013;368:1878-87

# Retreatment of HCV-1 PR relapsers with simeprevir + PR

## (PROMISE phase III study, SIM + P + R for 24-48 weeks)

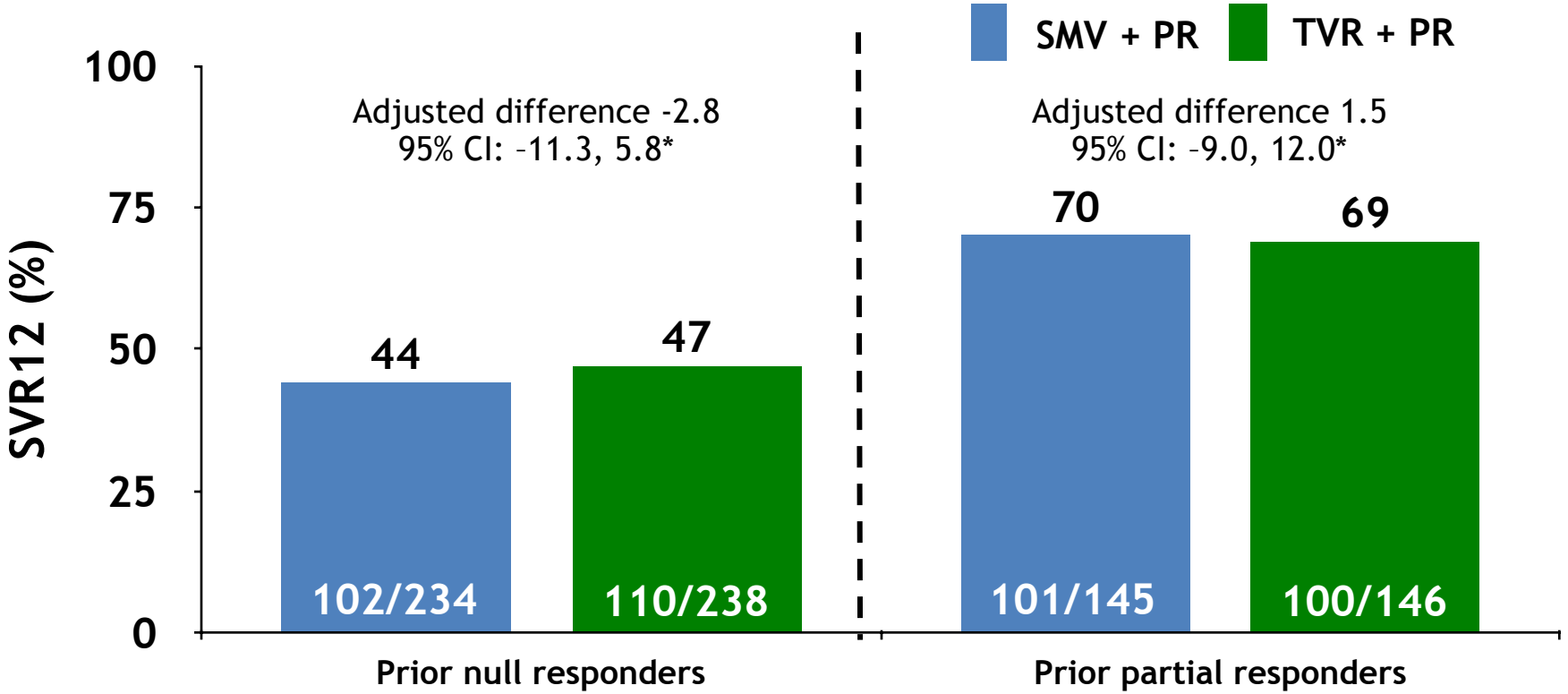
| | SVR12, n/N (%) | |
|---|---|---|
| | SMV/PR | PBO/PR |
| All patients | 206/260 (79.2*) | 49/133 (36.8) |
| All European patients | 161/184 (87.5*) | 40/90 (44.4) |
| Patients who met RGT criteria | 157/173 (90.8) | n/a |
| *IL28B* genotype CC | 38/41 (92.7) | 13/21 (61.9) |
| *IL28B* genotype CT | 106/121 (87.6) | 25/58 (43.1) |
| *IL28B* genotype TT | 17/22 (77.3) | 2/11 (18.2) |
| HCV GT 1a | 52/59 (88.1) | 8/22 (36.4) |
| HCV GT 1a with Q80K | 6/8 (75.0) | 4/7 (57.1) |
| HCV GT 1a without Q80K | 45/50 (90.0) | 4/15 (26.7) |
| HCV GT 1b | 109/125 (87.2) | 32/68 (47.1) |
| METAVIR score F0-F2 | 105/119 (88.2) | 34/70 (48.6) |
| METAVIR score F3 | 26/30 (86.7) | 2/9 (22.2) |
| METAVIR score F4 | 23/27 (85.2) | 3/10 (30.0) |

*p<0.001 vs PBO/PR

FORNS et al, EASL 2014 (abstract 13)

# HCV-1 prior therapy failures: simeprevir + PR

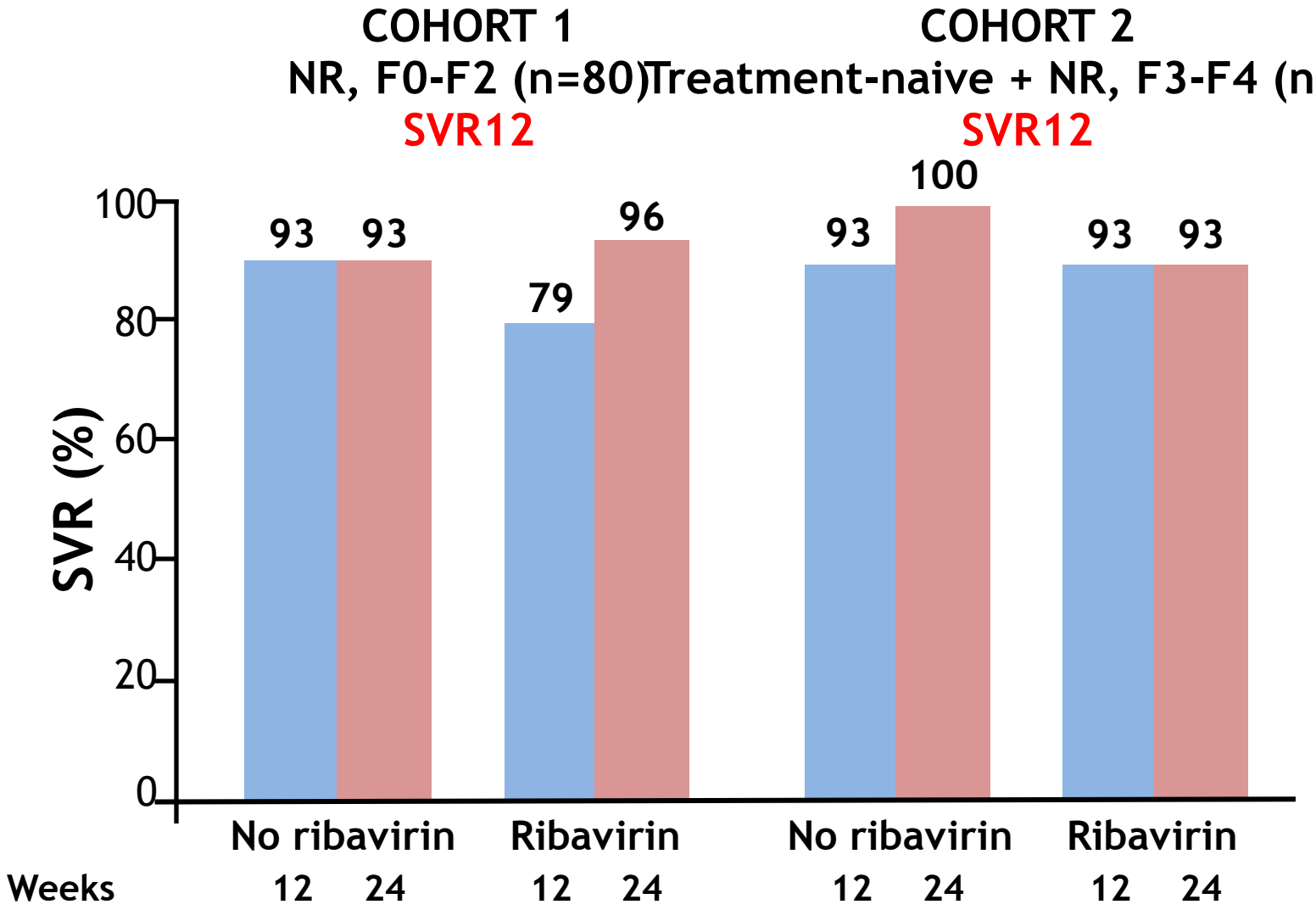
## (ATTAIN, non-inferiority phase III study)




REDDY *et al*, APASL 2014

# What about IFN-intolerant HCV-1?

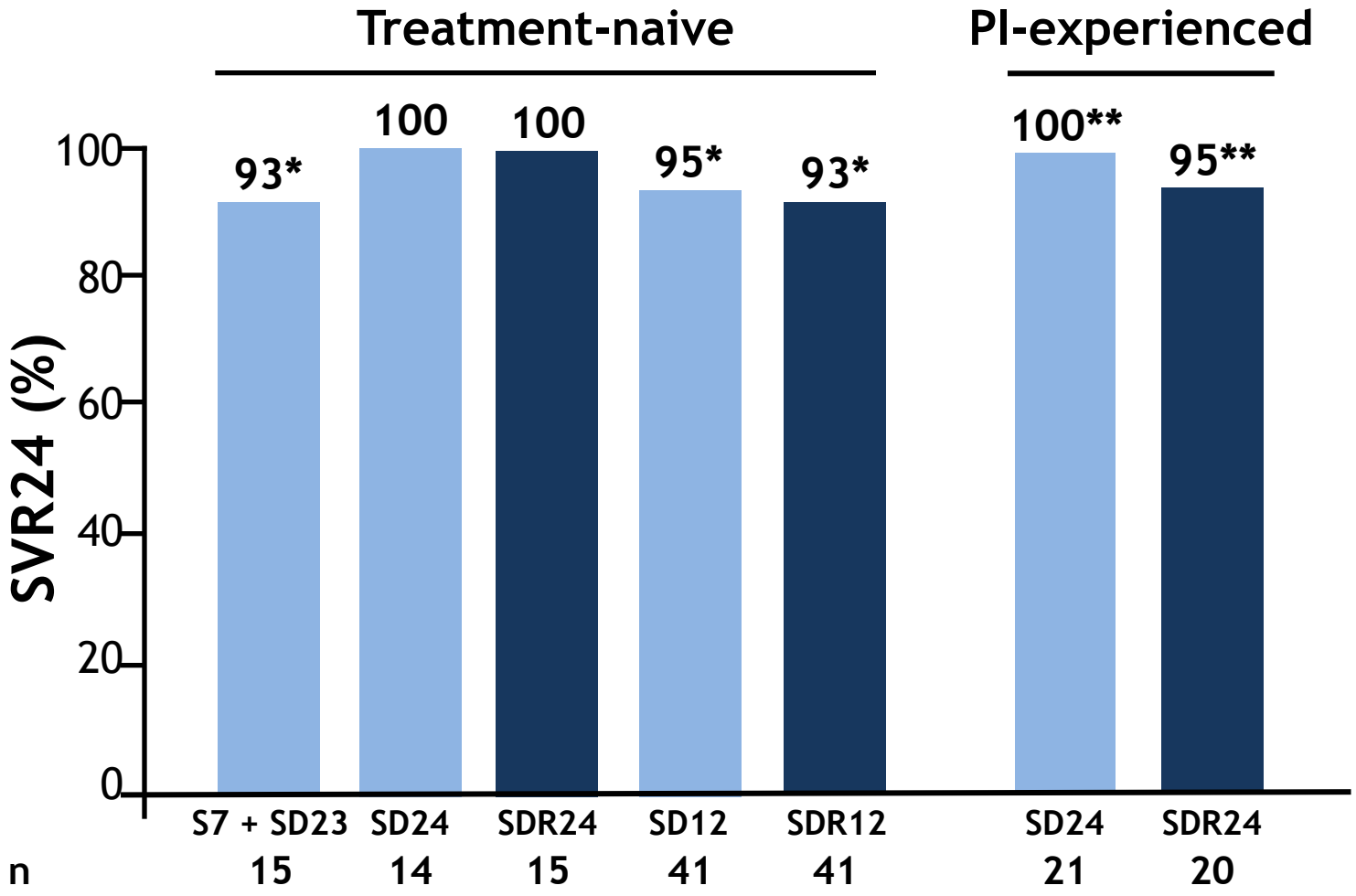
# SMV + SOF ± RBV in treatment-naive and prior null responders, HCV-1 (COSMOS phase II study)




SULKOWSKI *et al*, EASL 2014; LAWITZ *et al*, EASL 2014

# Sofosbuvir + Daclatasvir ± Ribavirin in HCV-1

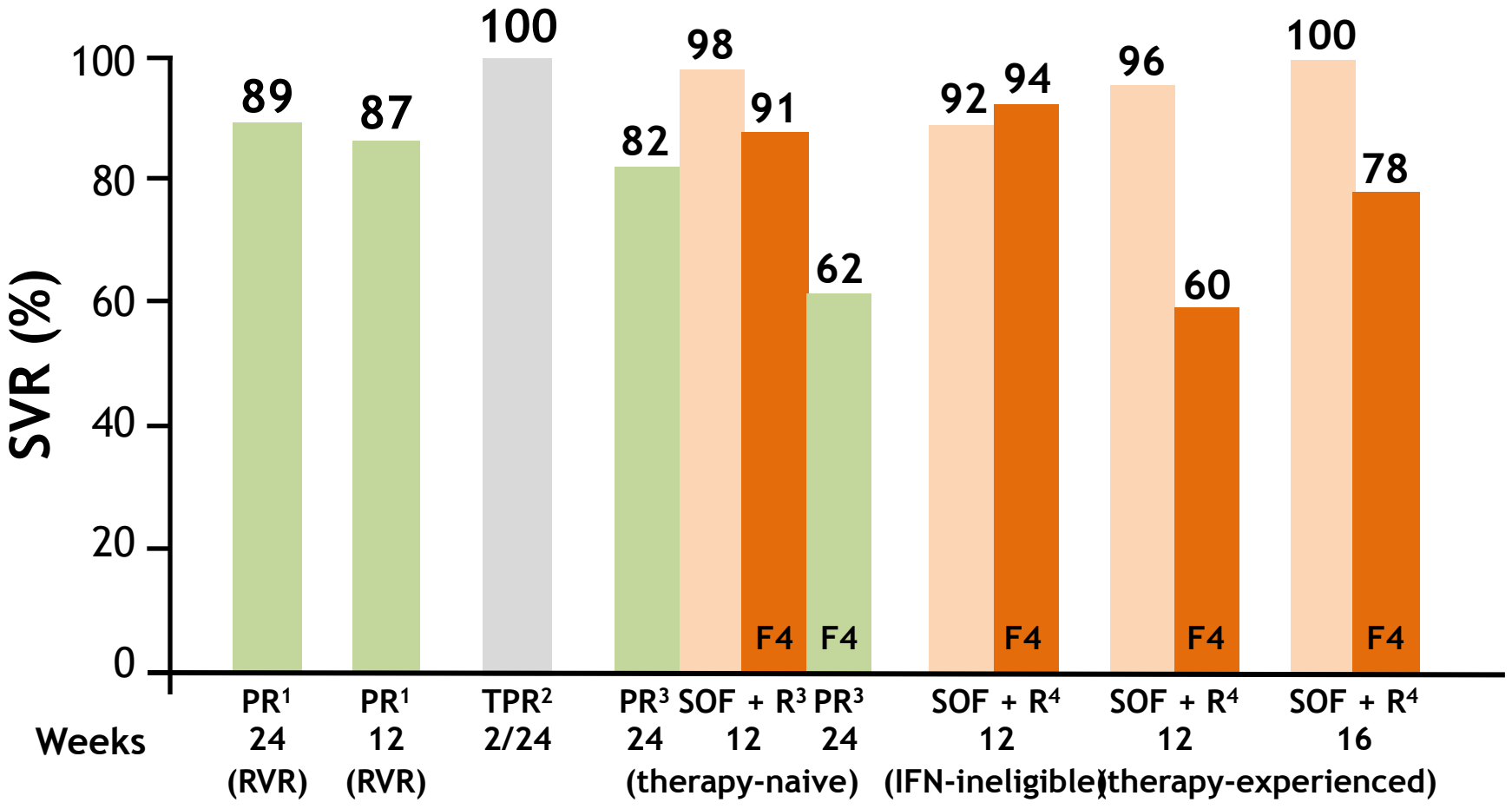
**(126 naive + 41 PI-experienced; 26 cirrhotics; AI444040 phase II study)**




*Considering 4 SVR36 and 1 reinfection, true SVR = 99% (125/126)
**SVR12 available only; considering 1 SVR24, true SVR = 100%

SULKOWSKI *et al*, N Engl J Med 2014 Jan 16 [ePub ahead of print]

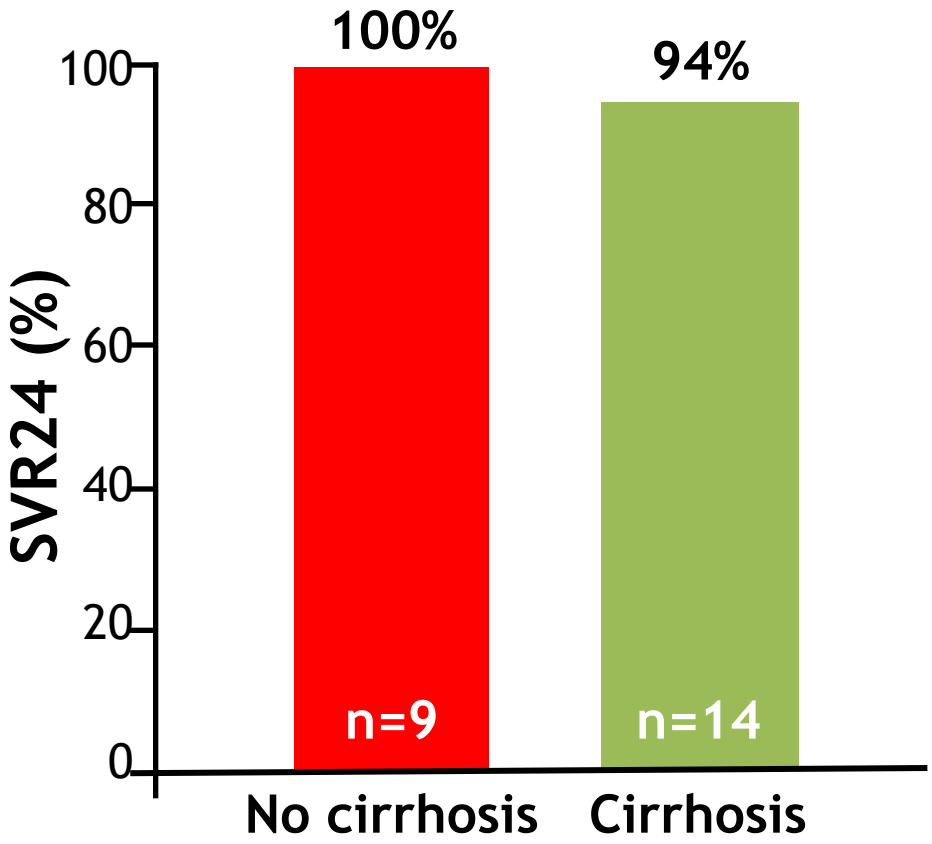
# 2014: the different options for HCV-2




1. MANGIA *et al*, N Engl J Med 2005;352:2609-17; 2. FOSTER *et al*, Gastroenterology 2011;141:881-9
3. LAWITZ *et al*, N Engl J Med 2013;368:1878-87; 4. JACOBSON *et al*, N Engl J Med 2013;368:1867-77

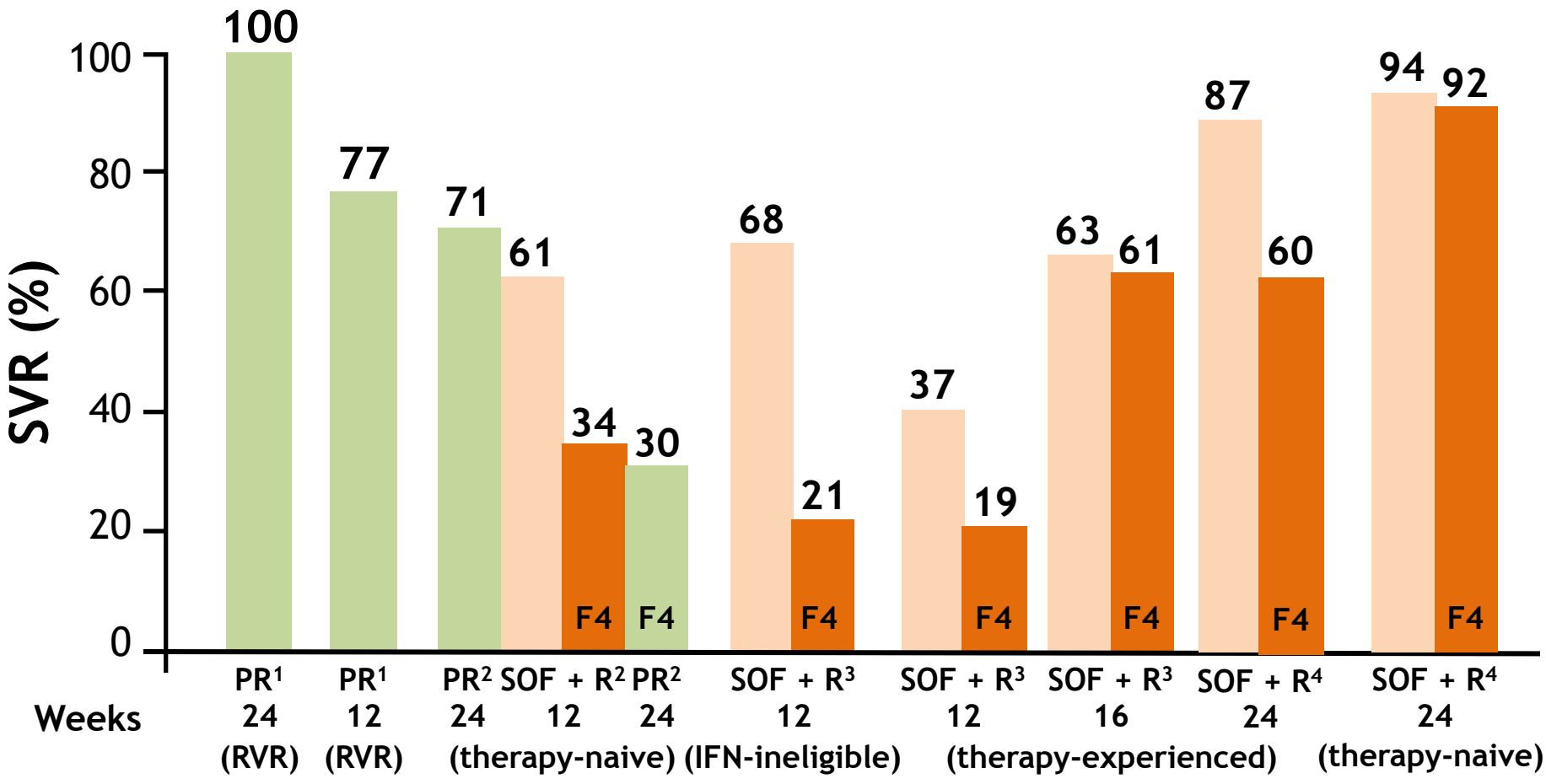
# P + R + sofosbuvir (LONESTAR-2 study)

## Phase 2, 12 weeks, HCV-2, treatment experienced




LAWITZ et al, AASLD 2013

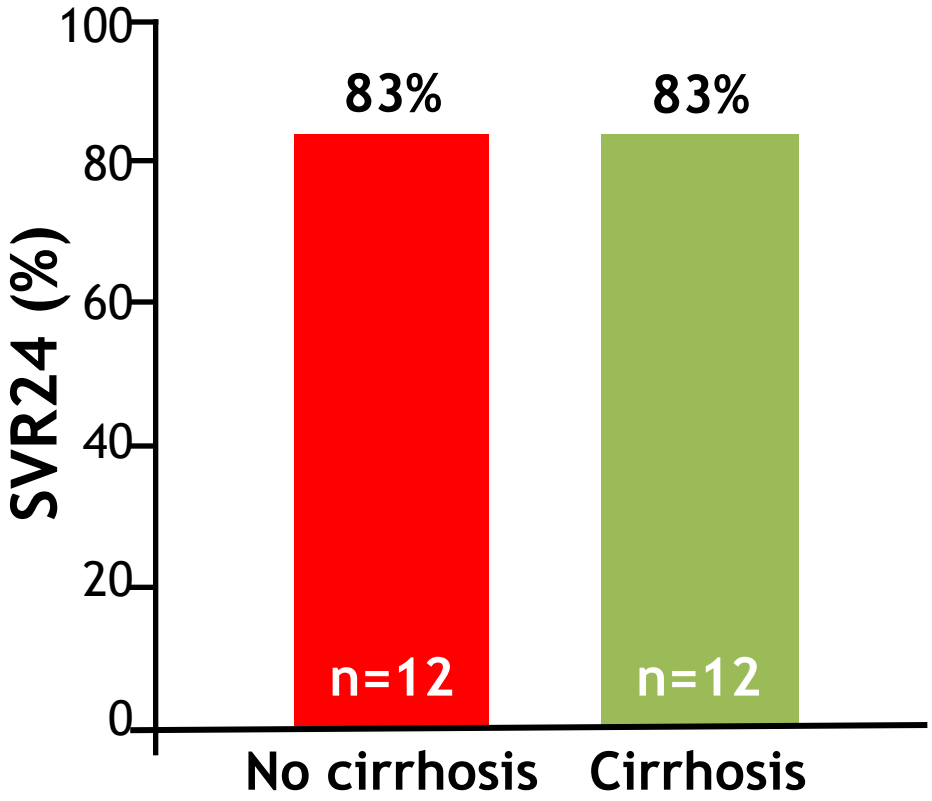
# 2014: the different options for HCV-3




1. MANGIA *et al*, N Engl J Med 2005;352:2609-17; 2. LAWITZ *et al*, N Engl J Med 2013;368:1878-87
3. JACOBSON *et al*, N Engl J Med 2013;368:1867-77; 4. ZEUZEM *et al*, N Engl J Med 2014

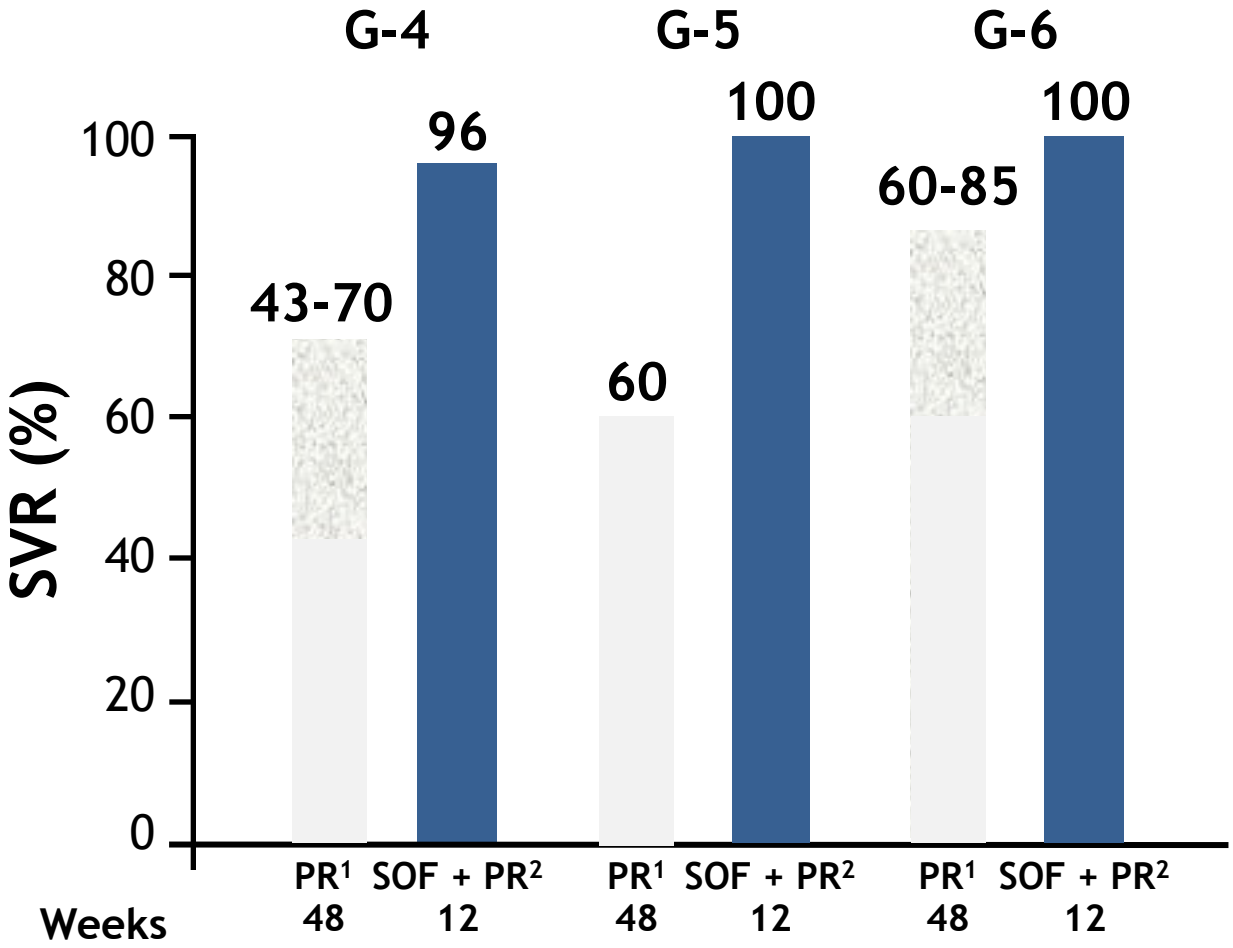
# P + R + sofosbuvir (LONESTAR-2 study)

## Phase 2, 12 weeks, HCV-3, treatment experienced




LAWITZ et al, AASLD 2013

# In 2014, all SOF-based options for treatment-naive HCV-4 to 6 will still contain PR

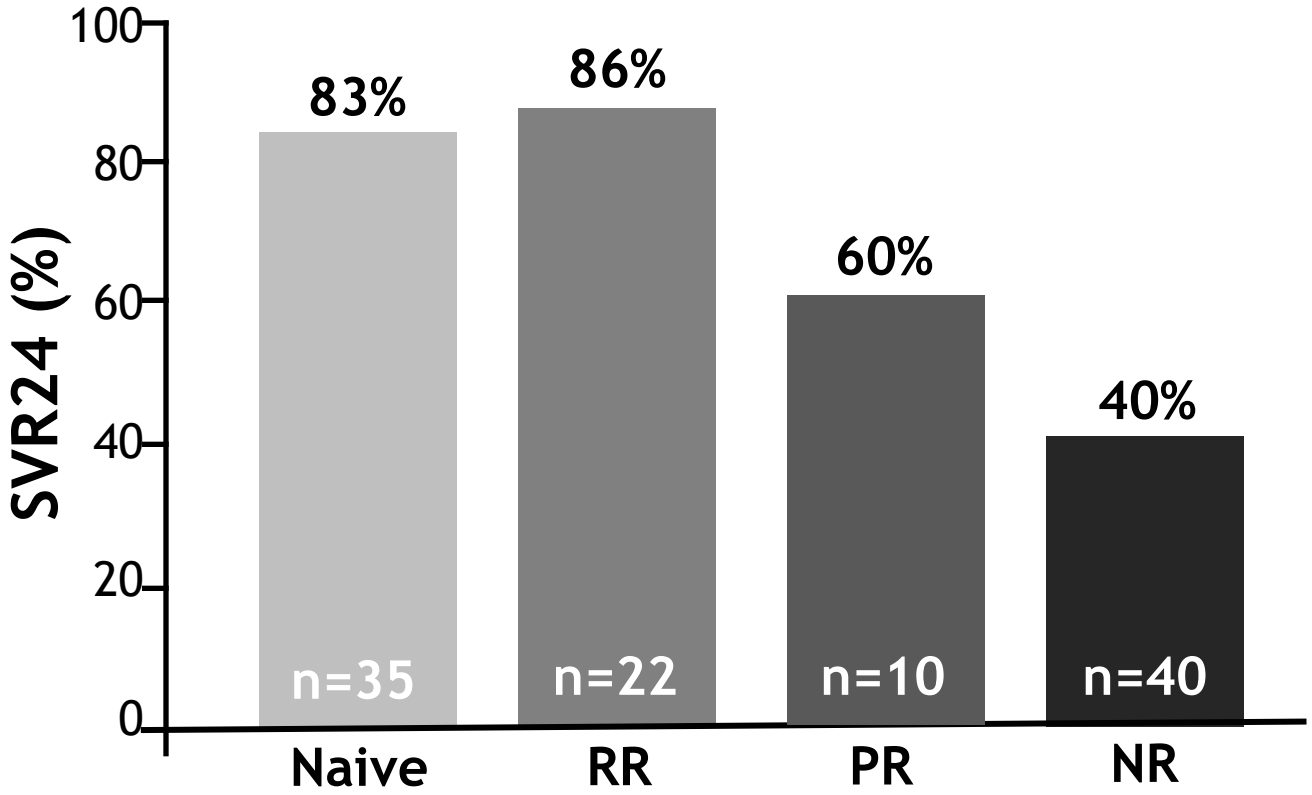




1. ANTAKI *et al*, Liver Int 2010;30:342-55
2. LAWITZ *et al*, N Engl J Med 2013;368:1878-87

# P + R + Simeprevir

## (treatment-naive or -experienced HCV-4: Phase III RESTORE trial)




MORENO *et al*, EASL 2014, late breaking poster 1319

# Patients with an indication for liver transplantation

- Patients with compensated cirrhosis and HCC should be treated with sofosbuvir + ribavirin until liver transplantation
- IFN-free combinations (sofosbuvir + simeprevir or sofosbuvir + daclatasvir) should be preferred
- Finite (12 weeks) therapy with sofosbuvir, pegylated IFN$\alpha$ and ribavirin is also acceptable (if tolerated)
- Patients with cirrhosis should undergo surveillance for HCC independently of SVR

# Impaired renal function

- These patients should receive an IFN-free (and possibly ribavirin-free) regimen
- No safety and efficacy data is available in this population, and the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown
- Sofosbuvir and simeprevir should not be administered to patients with eGFR <30 mL/min/1.73 $m^2$ or with end-stage renal disease until more data is available

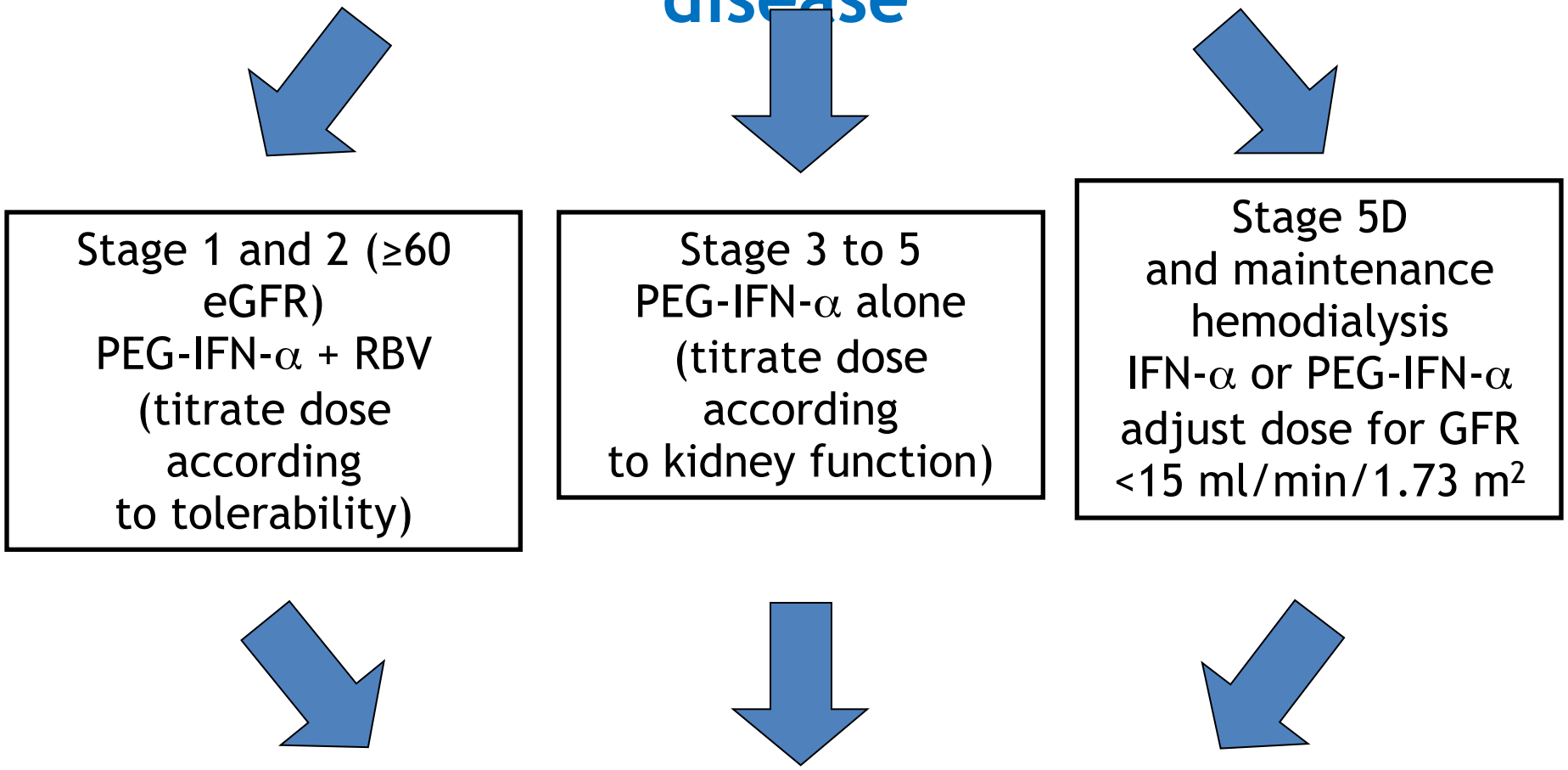
# Sofosbuvir in ESRD

- Renal clearance of major metabolite GS-331007
- Trial ongoing in ESRD, no interim data available
- Relative to patients with normal kidney function, exposure to SOF was 61%, 107% and 171% higher in mild, moderate and severe renal impairment
- SOF exposure is increased by 28% when given 1 h before HD, and by 60% when dosed 1 h after HD
- Hemodialysis can efficiently remove GS-331007 (53% extraction ratio)
- SOF not recommended when eGFR <30 ml/min

# Simeprevir in ESRD

- Exposure increased in ESRD even if most metabolism is hepatic
- Removal of SIM by HD is unlikely due to significant protein binding
- SIM contraindicated when eGFR <30 ml/min

# Determine stage of chronic kidney disease




If SVR, re-test for serum HCV RNA every 6 months and continue surveillance for HCC in cirrhotics

# Therapy of Hepatitis C in HD Patients

- All HD patients with compensated hepatitis C are candidates to IFN-$\alpha$ therapy
- Combination with ribavirin should be limited to clinical trials
- Patients with non-significant fibrosis (F0-F2) should also be placed on a kidney transplant waiting list
- Patients with advanced fibrosis should be treated and placed on kidney transplant waiting list <u>if SVR</u>
- Consider simultaneous liver/kidney transplant in patients with decompensated liver disease

# 2015

# Sofosbuvir/ledipasvir (single pill, once a day) ± RBV

## Results of phase III studies

| Study | Population | Treatment | Duration | SVR12 |
|---|---|---|---|---|
| ION-1 | HCV-1 treatment-naive (incl. 136/865 or 15.7% with cirrhosis) | SOF/LDV | 12 weeks | 99% |
| | | SOF/LDV + RBV | 12 weeks | 97% |
| | | SOF/LDV | 24 weeks | 98% |
| | | SOF/LDV + RBV | 24 weeks | 99% |
| ION-2 | HCV-1 treatment-experienced (including 88/440 or 20% with cirrhosis)* | SOF/LDV | 12 weeks | 94% |
| | | SOF/LDV + RBV | 12 weeks | 96% |
| | | SOF/LDV | 24 weeks | 99% |
| | | SOF/LDV + RBV | 24 weeks | 99% |
| ION-3 | HCV-1 treatment-naive (all non-cirrhotics) | SOF/LDV | 8 weeks | 94% |
| | | SOF/LDV + RBV | 8 weeks | 93% |
| | | SOF/LDV | 12 weeks | 95% |

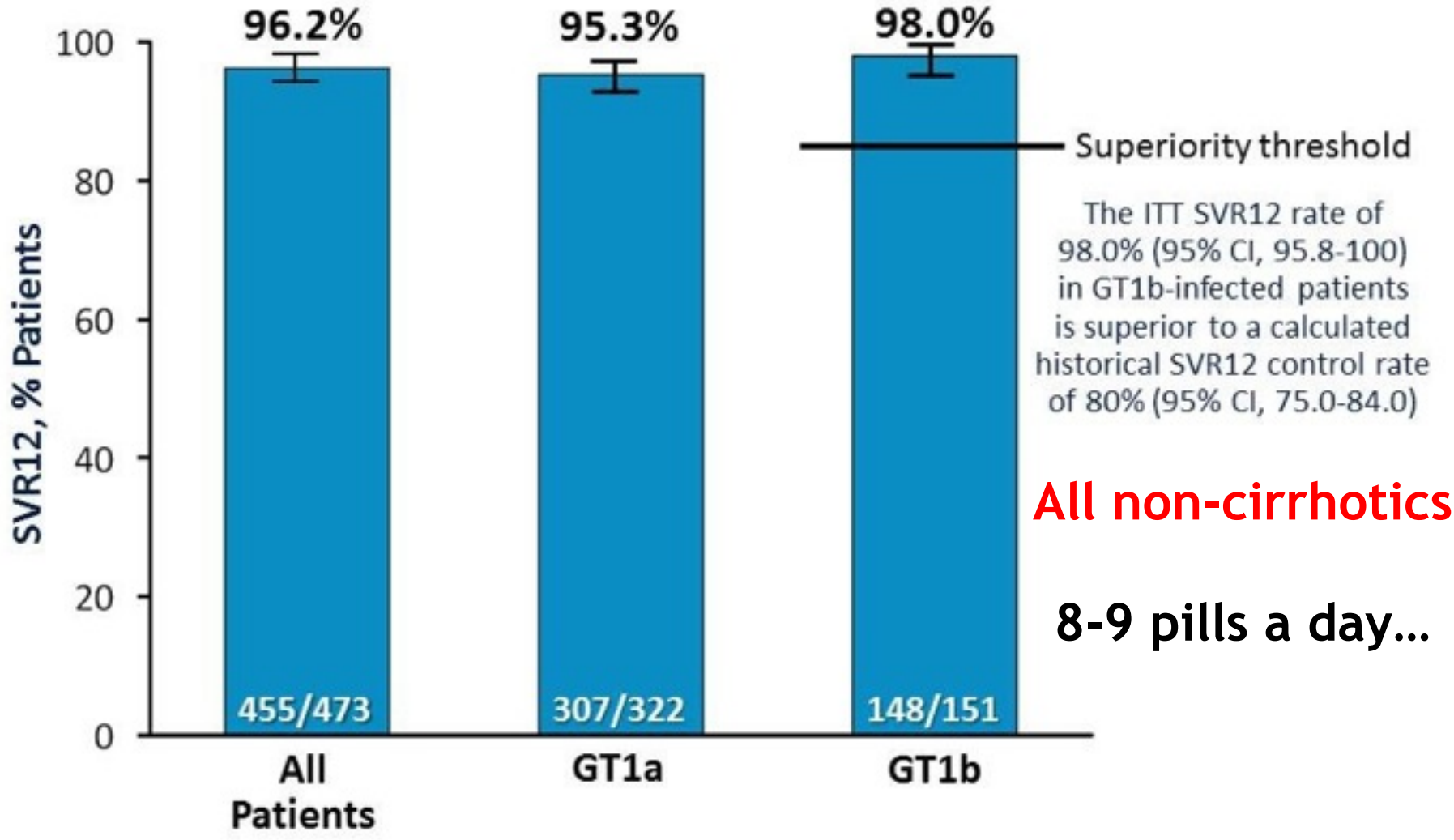
*Includes patients treated with PI-containing regimens

AFDAHL *et al*, N Engl J Med 2014; AFDAHL *et al*, N Engl J Med 2014

KOWDLEY *et al*, EASL 2014

# ABT-450/r/ombitasvir qd + dasabuvir bid + R bid, 12 weeks

**(SAPPHIRE-1 phase 3 study, HCV-1, n = 631 treatment-naive)**



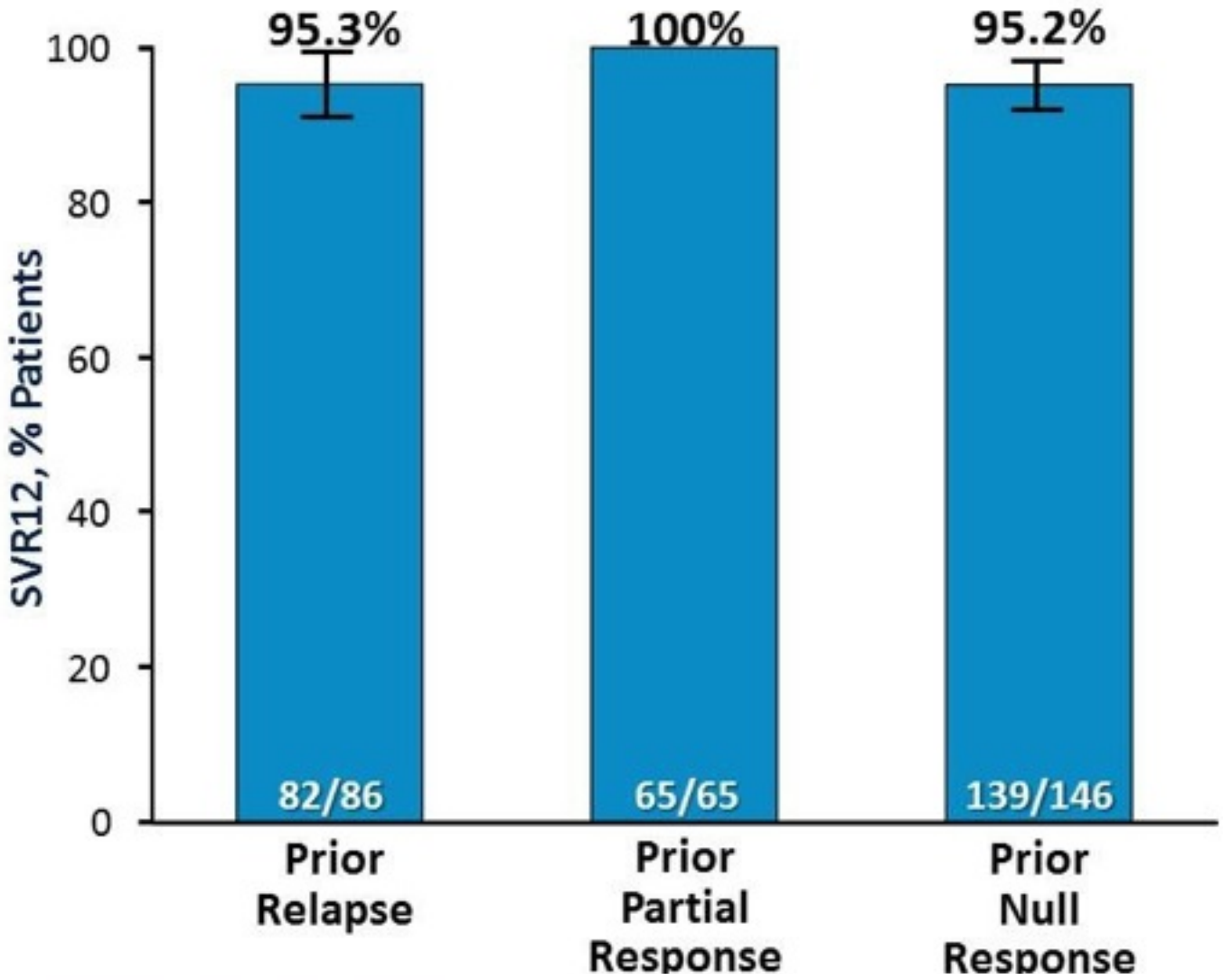

**All non-cirrhotics**

**8-9 pills a day…**

FELD et al, EASL 2014

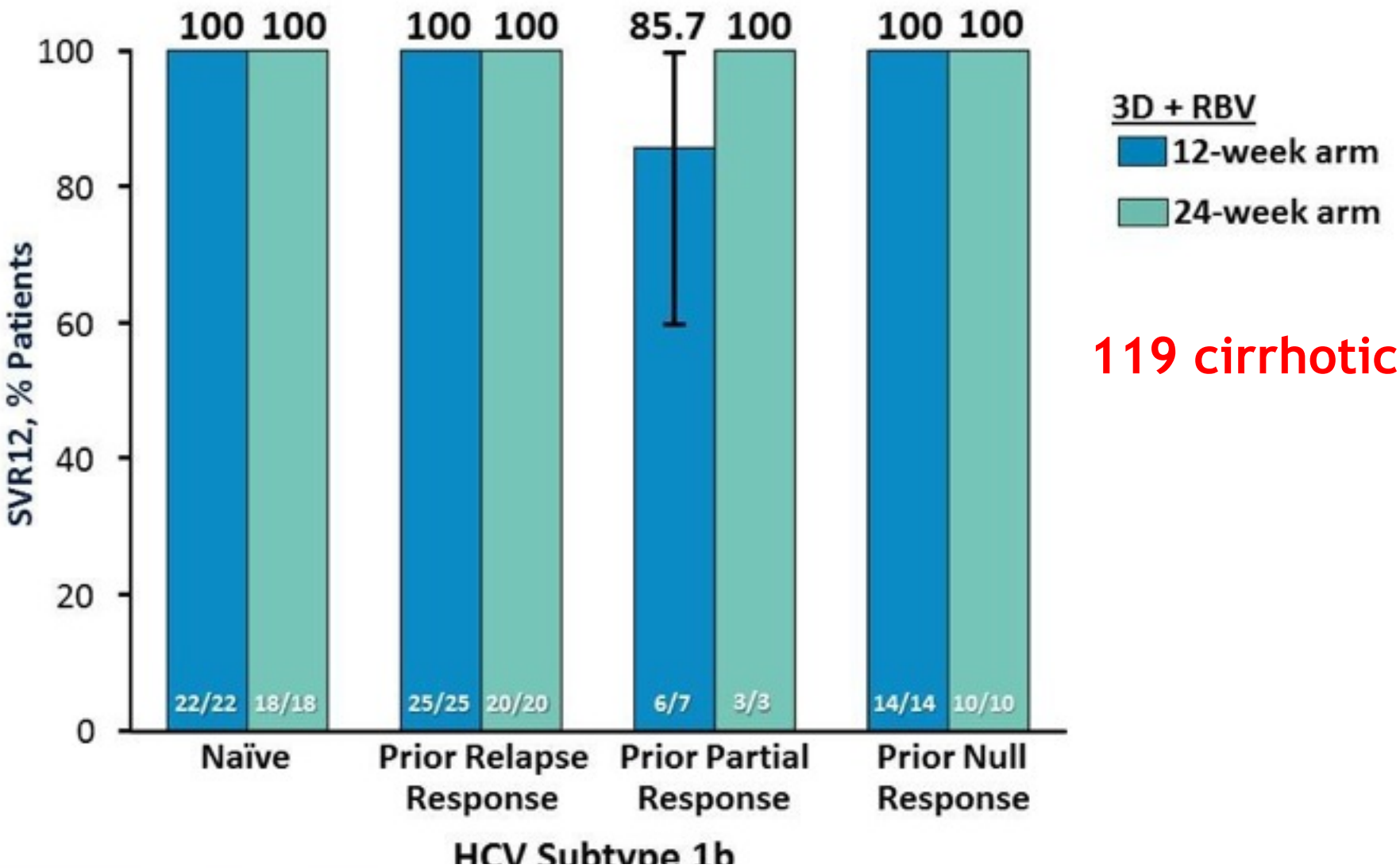
# ABT-450/r/ombitasvir qd + dasabuvir bid + R bid, 12 weeks

**(SAPPHIRE-2 phase 3 study, HCV-1, n = 394 treatment-experienced)**




ZEUZEM et al, EASL 2014

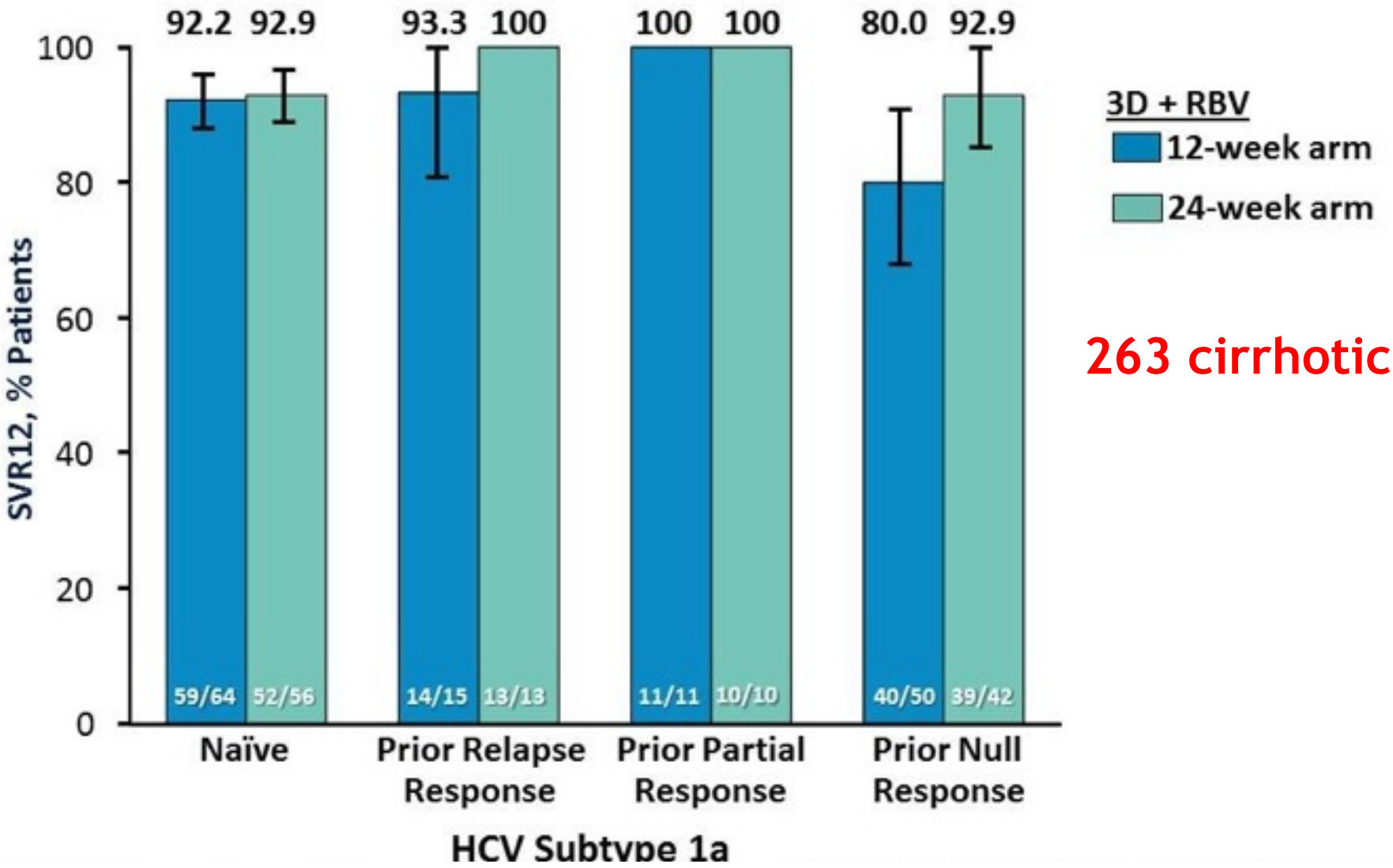
# TURQUOISE-II Results: ITT SVR12 Rates by Prior Treatment Response in HCV Subtype 1b




**119 cirrhotics**

POORDAD et al, EASL 2014

# TURQUOISE-II Results: ITT SVR12 Rates by Prior Treatment Response in HCV Subtype 1a




263 cirrhotics

POORDAD et al, EASL 2014

# IFN-free treatments: a summary

- Highly effective (>90% SVR)
- Virtually no side effects
- Simplified treatment schedules
  - Short duration, only a few pills
  - No more response-guided treatment
  - Baseline features have less influence on response (exceptions: cirrhosis, HCV-3)
- Negligible resistance

# HCV treatment: the next challenges

- Impact on long-term public health burden may require increased treatment uptake via increased diagnosis *via* ample screening strategies and proper linkage to care
- Treatment as prevention may become a reality (PWID, HIV+ MSM, heavy injectors)
- Treatment capacity will be constrained
- [cost per treatment] x [volume] will explode in the absence of agreements with the industry

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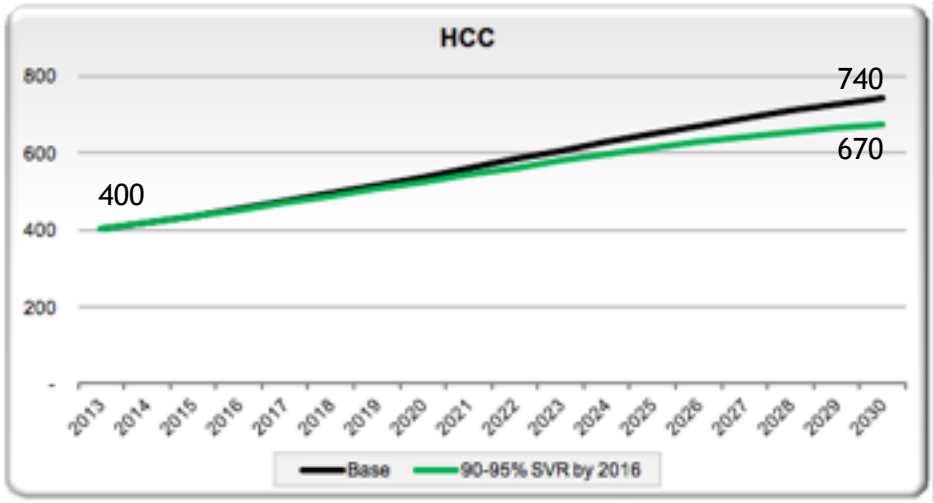
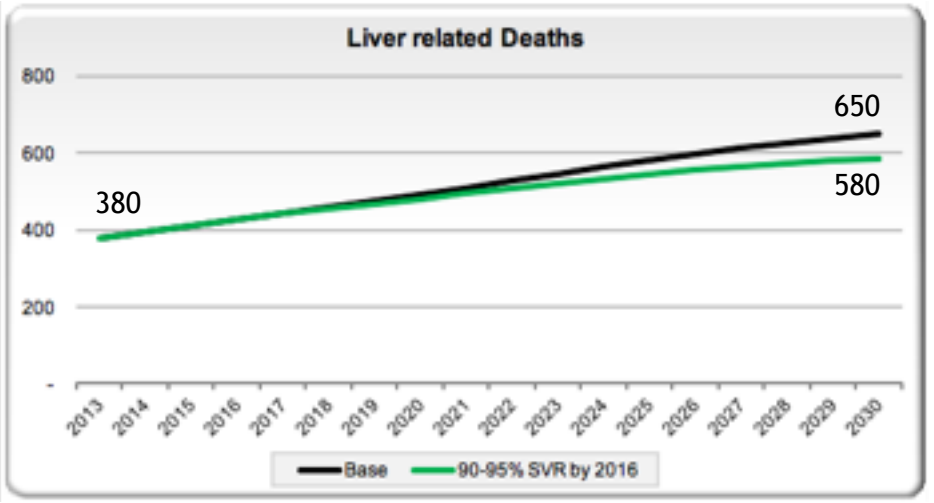
# Increasing SVR to 90-95% by 2016 will decrease HCV-related HCC cases and liver-related mortality by 10% in 2030

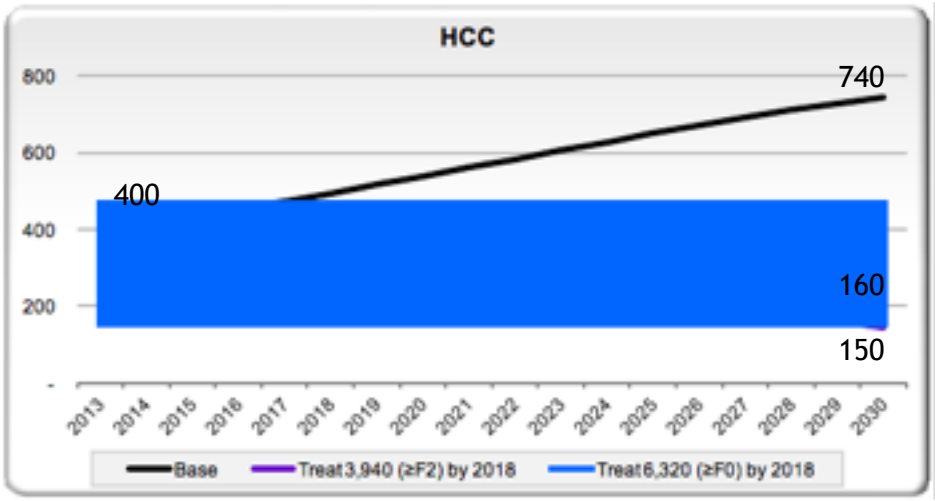


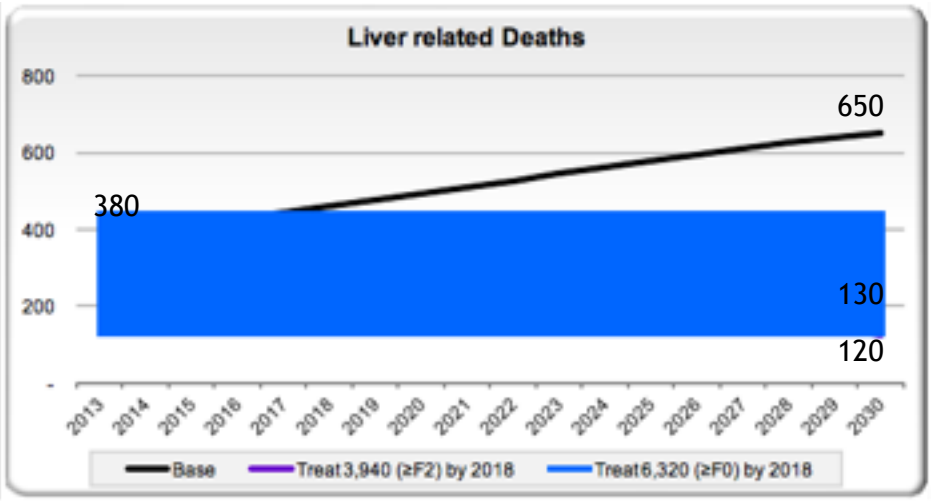




- Increasing SVR while maintaining an annual treatment uptake of 1,100 patients will decrease HCC and liver-related mortality by 10% by 2030
- Total viremic infections will decrease by 7% vs base case

BRUGGMANN *et al*, EASL 2014, poster 1285

# Only increasing SVR to 90-95% by 2016 *and* treating 3,940 patients by 2018 will decrease HCV liver-related mortality by 80%




- <u>The proposed scenario would require the diagnosis of 4,740 new viremic infections annually by 2020</u> (as compared with 1,050 in 2013)
- Expanding treatment access to ≥F0 patients would require treatment of 6,320 annually by 2018 to achieve the same reduction in HCC cases and liver-related mortality
- An estimated CHF 735 M and CHF 742 M in healthcare cost savings (excluding scenario and treatment costs) was projected for the scenario treating 3,940 ≥ F2 patients and 6,320 ≥ F0 patients, respectively

BRUGGMANN *et al*, EASL 2014, poster 1285

# Risk-based screening?

- Risk screening in all those >20 yrs could have identified 82% of all HCV infections, **but in fact has failed to do so**

TOMASZEWSKI *et al*, Am J Public Health 2012;102:e101-6

- Despite risk-based screening policies, 25-50% of patients are unaware of their infection

- General population screening?

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 61 / No. 4
August 17, 2012

# Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

# Baby boomer generation:
# "Rock'n'roll, drugs, sexual liberation, shaggy hair and.... HCV"*

- Persons born between 1945 and 1964 (baby boomers) account for 27% of the US population and 76% of all HCV infections
- Testing (and treating) baby boomers for HCV irrespective of risk factors would avert 47,189 more HCC, and 15,484 more liver transplant than risk-based screening

**MMWR Recomm Rep 2012 Aug 17;61(4):1-32**

*Jon Cohen, Science, 24 August 2012

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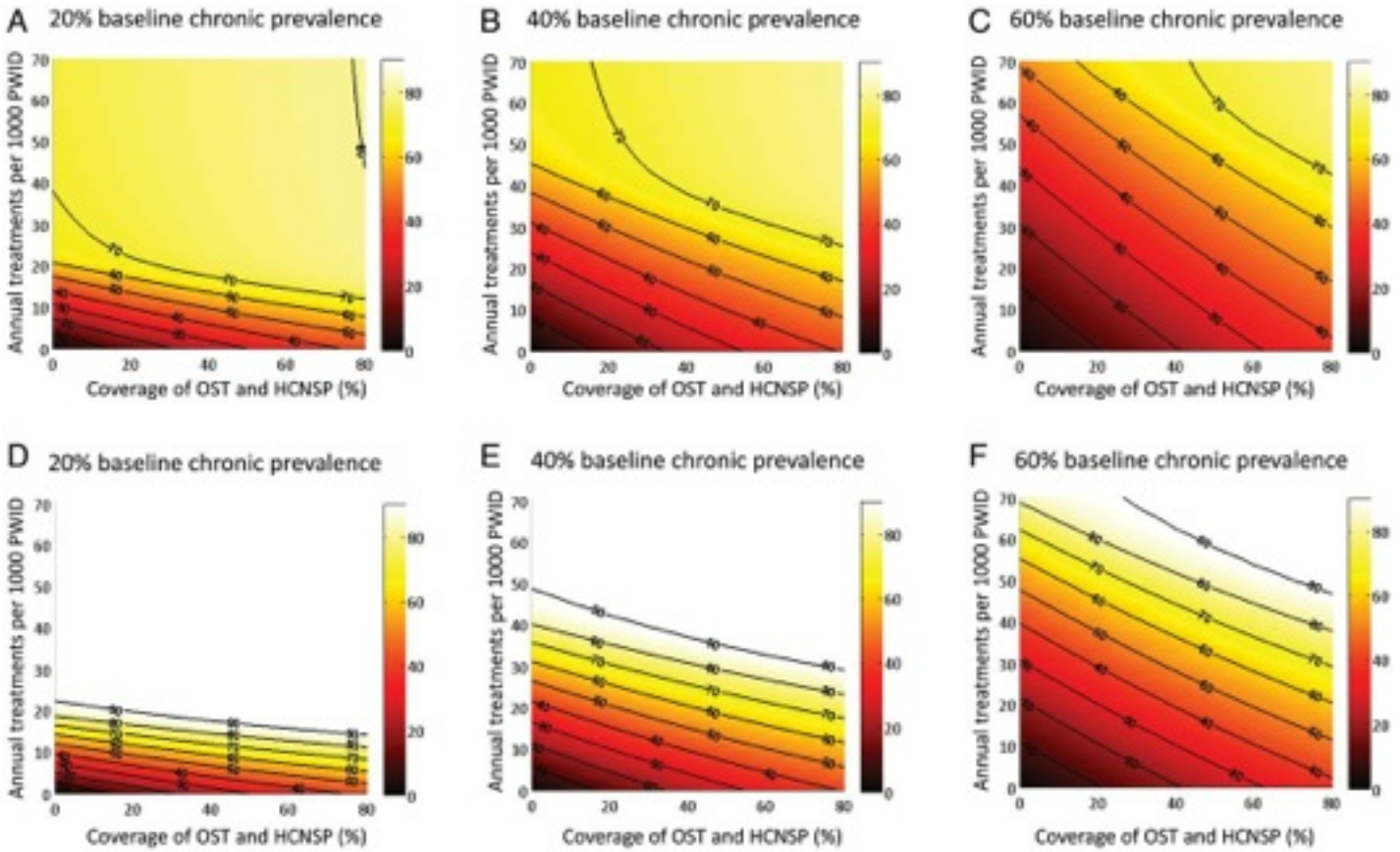
# Reducing the HCV prevalence among PWID

## Modeling the impact of antiviral therapy, opiate substitution (OST) and needle/syringe exchange programs (HCNSP) scale-up

**Treating with peg/riba**

**Treating with IFN-free DAA**




**Lines indicate the relative reduction in HCV prevalence at 10 years**

MARTIN *et al*, Clin Infect Dis 2013;57(suppl 22):S39-45

HEPATOLOGY
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EDITORIALS

# Treatment as Prevention: The Breaking of Taboos Is Required in the Fight Against Hepatitis C Among People Who Inject Drugs

- Treat irrespective of the risk of reinfection (people at risk of reinfection are the most likely to spread HCV)
- Decriminalize drug use
- Lower the cost of drugs (or face the consequences of patent flexibility policies)

BRUGGMANN P. Hepatology 2013;58:1523-5

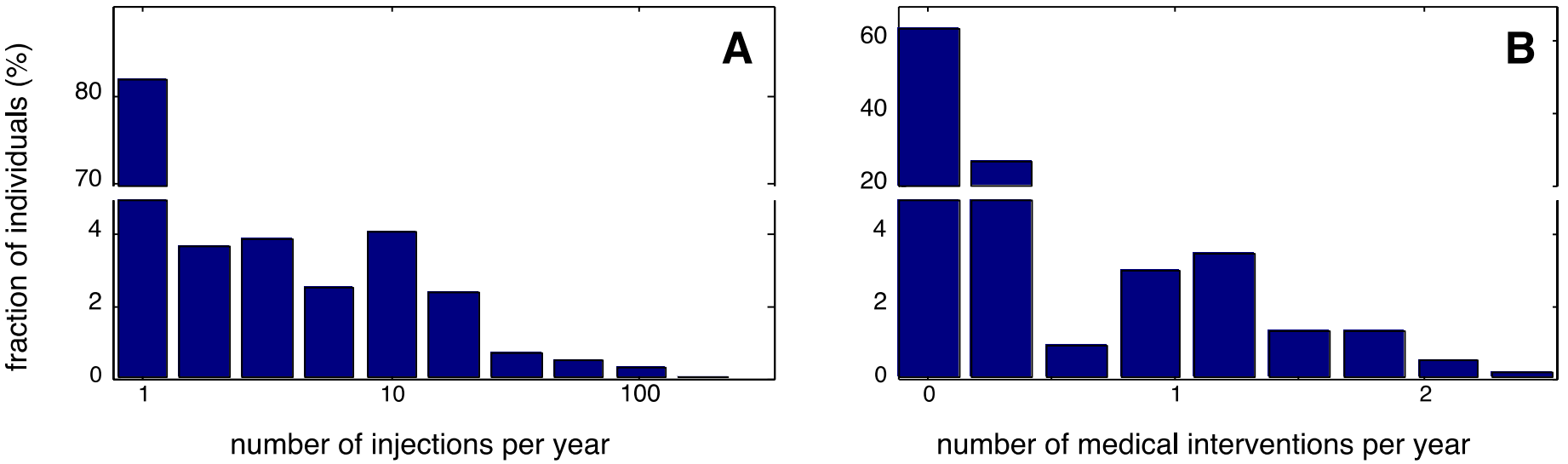
# Sexual transmission of HCV among HIV+ MSM

- Incidence of HCV among HIV-positive MSM has increased significantly after 1996[1]:
  - **0.23 per 100 py (1998)[2]**
  - **4.09 per 100 py (2011)[2]**
- Risk factors predisposing to HCV seroconversion:
  - History of inconsistent condom use[2]
  - Past syphilis[2]
  - Unprotected anal intercourse with multiple partners[3]
- Reinfection after eradication is possible[3]

[1]VAN DE LAAR *et al*, Gastroenterology 2009;136:1609-17
[2]WANDELER *et al*, Clin Infect Dis 2012;55:1408-16
[3]COTTE *et al*, Gastroenterol Clin Biol 2009;33:977-80

# HCV transmission via medical injections involve a core group of « heavy injectors »

**Zwyat Razin, 2002, n=4020**




The hypermedicalized 5% of the population receives >50% of all injections: they are the first ones to be infected and the first ones to transmit

**Should they be the first to be treated to prevent further spread?**

BREBAN *et al*, EASL 2013

# HCV treatment: the next challenges

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AASLD

EDITORIAL

# Expanding Access to Hepatitis C Virus Care: A Call to Deconstruct Individualized Therapy

- Complex, individualized care **is not the solution** for the control of the HCV epidemic
- Future regimens will be **simple**, allowing to expand the access to treatment by task shifting (as successfully adopted for HIV by the WHO)
- Recruit and train mid-level providers and primary care physicians as new treaters

ARONSOHN & JENSEN, Hepatology 2013 June 20 [ePub ahead of print]

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