

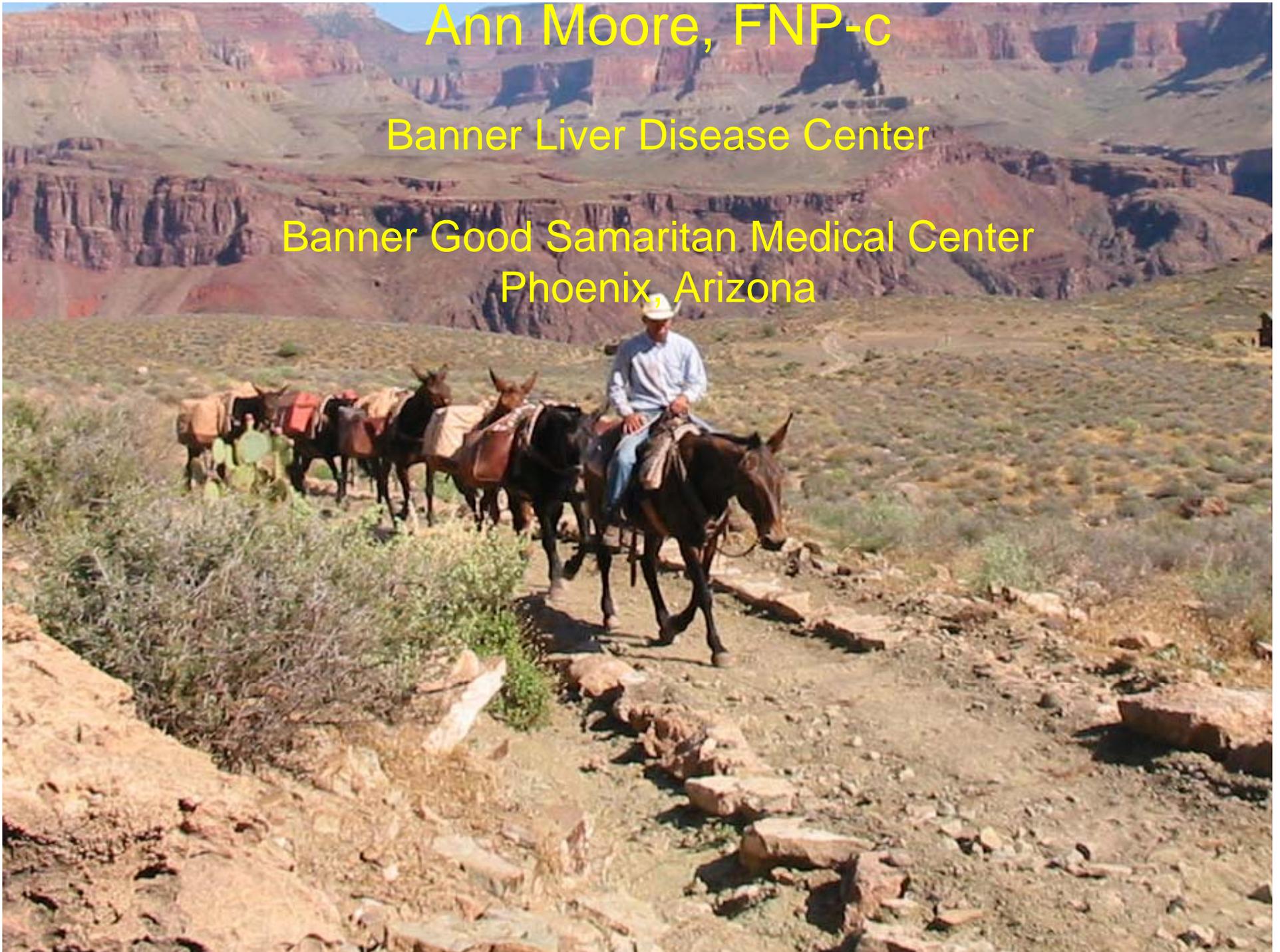
# HCV TREATMENT IN 2011:

INTEGRATING NEW THERAPIES INTO CURRENT TREATMENT ALGORITHMS

Ann Moore, FNP-c

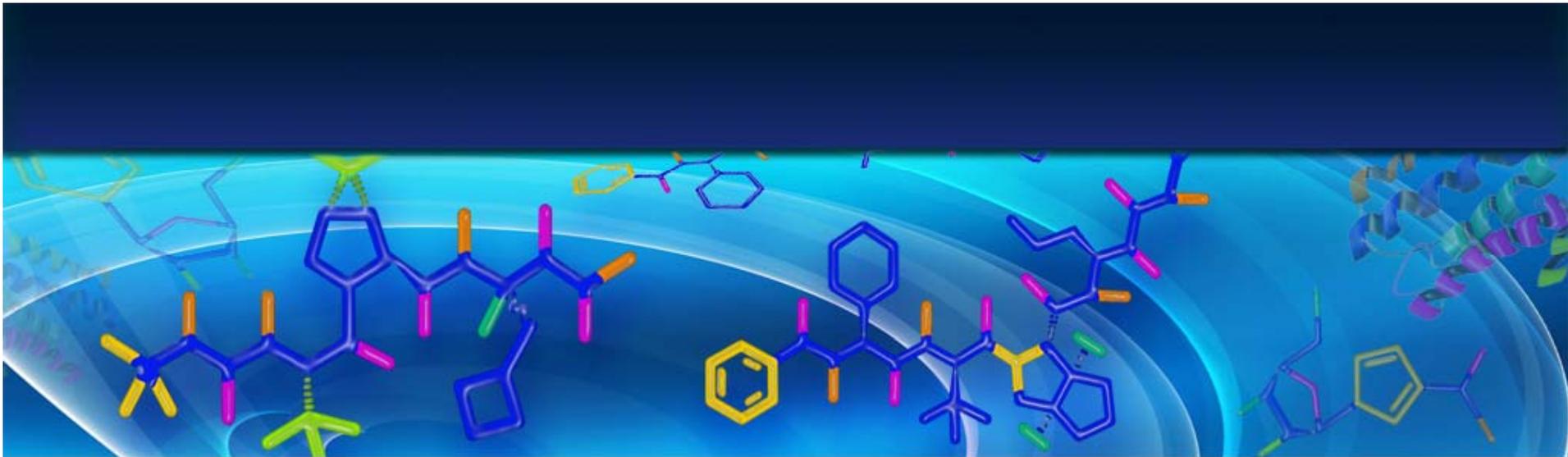
Banner Liver Disease Center

Banner Good Samaritan Medical Center  
Phoenix, Arizona



# Banner Good Samaritan Medical Center, Phoenix, Arizona





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## Disclosures:

Advisory Board or Speakers Bureau:  
Genentech, Gilead, Merck, Salix, Vertex, Bayer

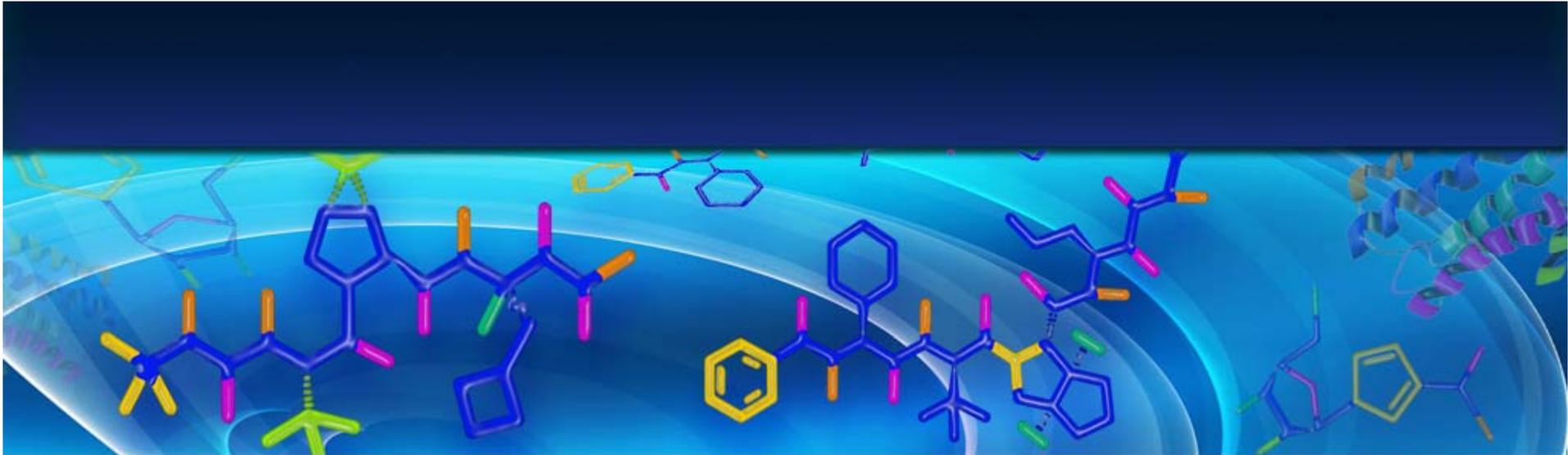
No off-label discussion

No conflicts of interest

# Banner Liver Disease Center Liver Transplantation Program

- Largest comprehensive liver program in the region
- 5 hepatologists, 3 surgeons, NP, PA
- Arizona's first liver transplant in 1983
- 500 liver transplants by mid-2011
- 5 regional satellite clinics
- Major focus on HCV, HBV, NAFLD, HCC, ALF





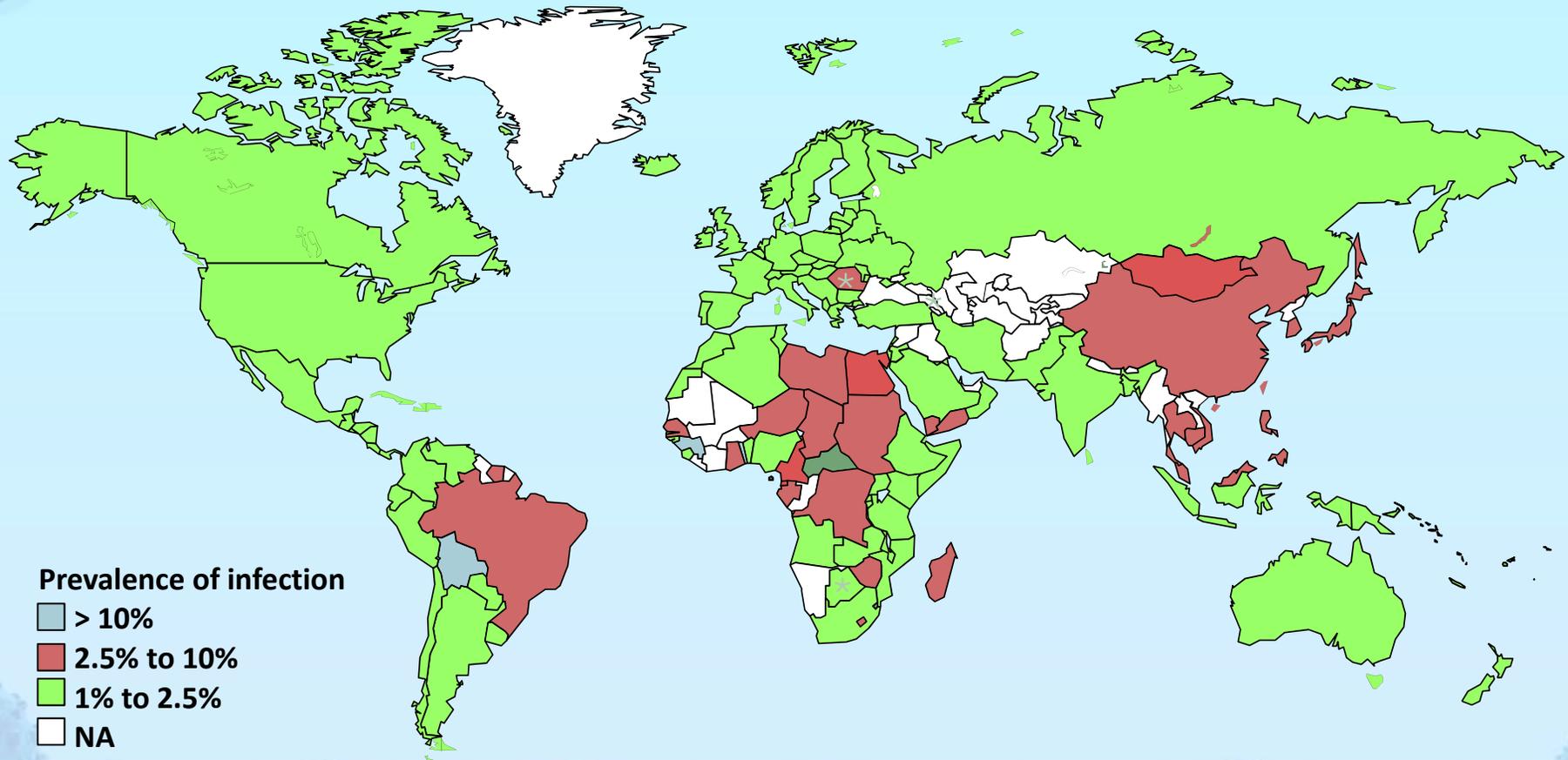
# **HCV TREATMENT IN 2011:**

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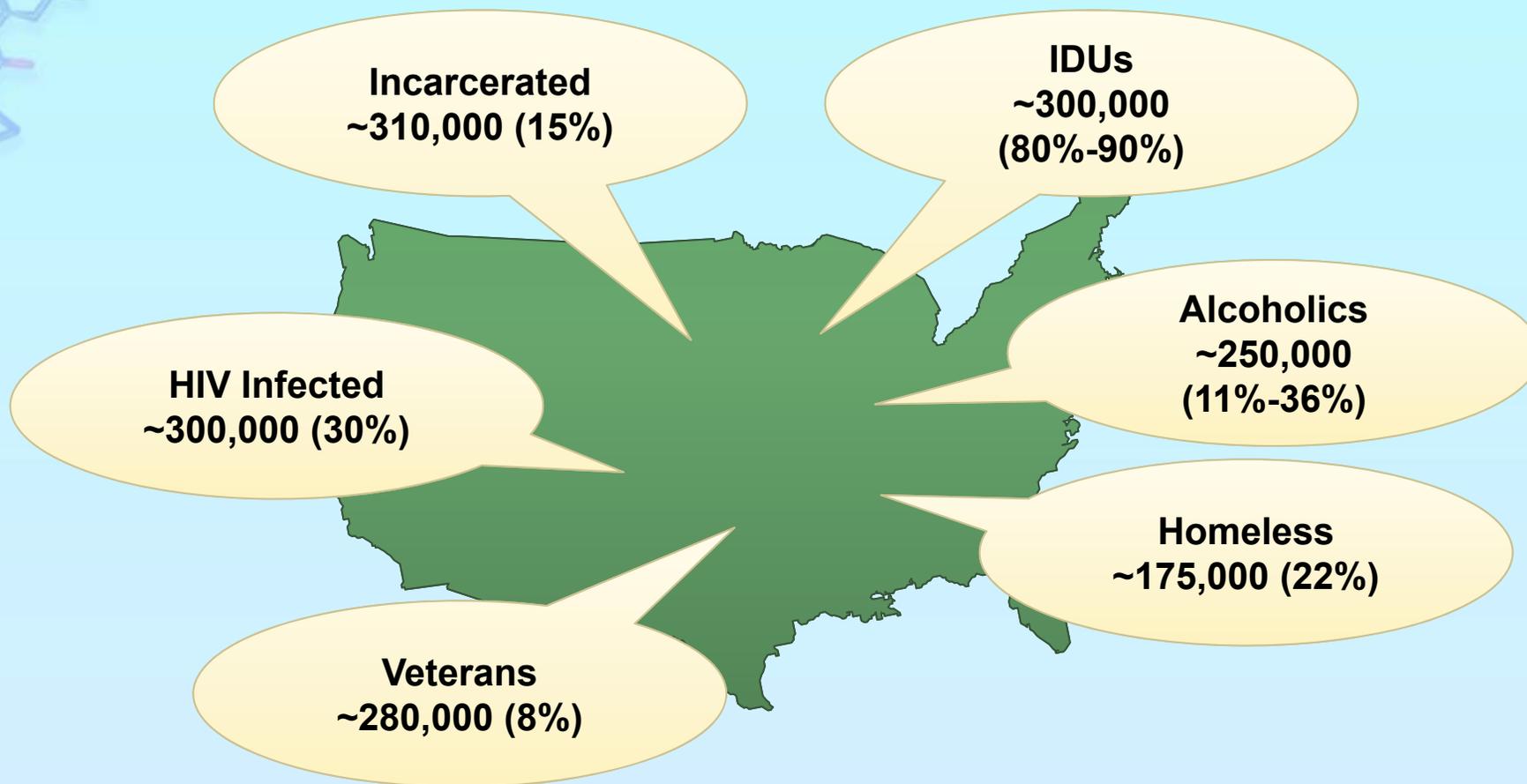
## **Burden of the HCV Epidemic**

# HCV Infection Worldwide

- 170 million persons with HCV
- 3-4 million newly infected each year

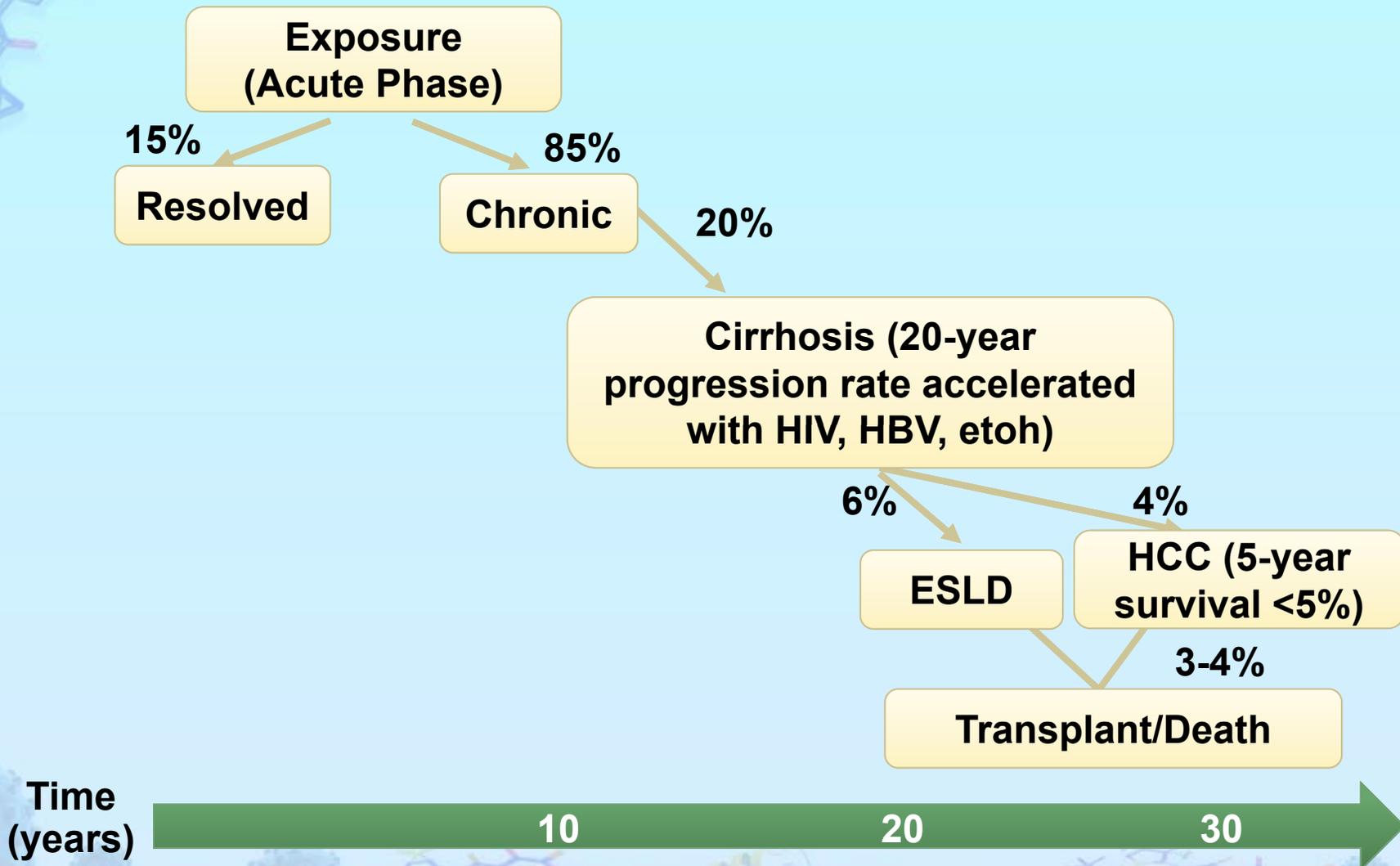


# HCV Prevalence in High-Risk US Populations

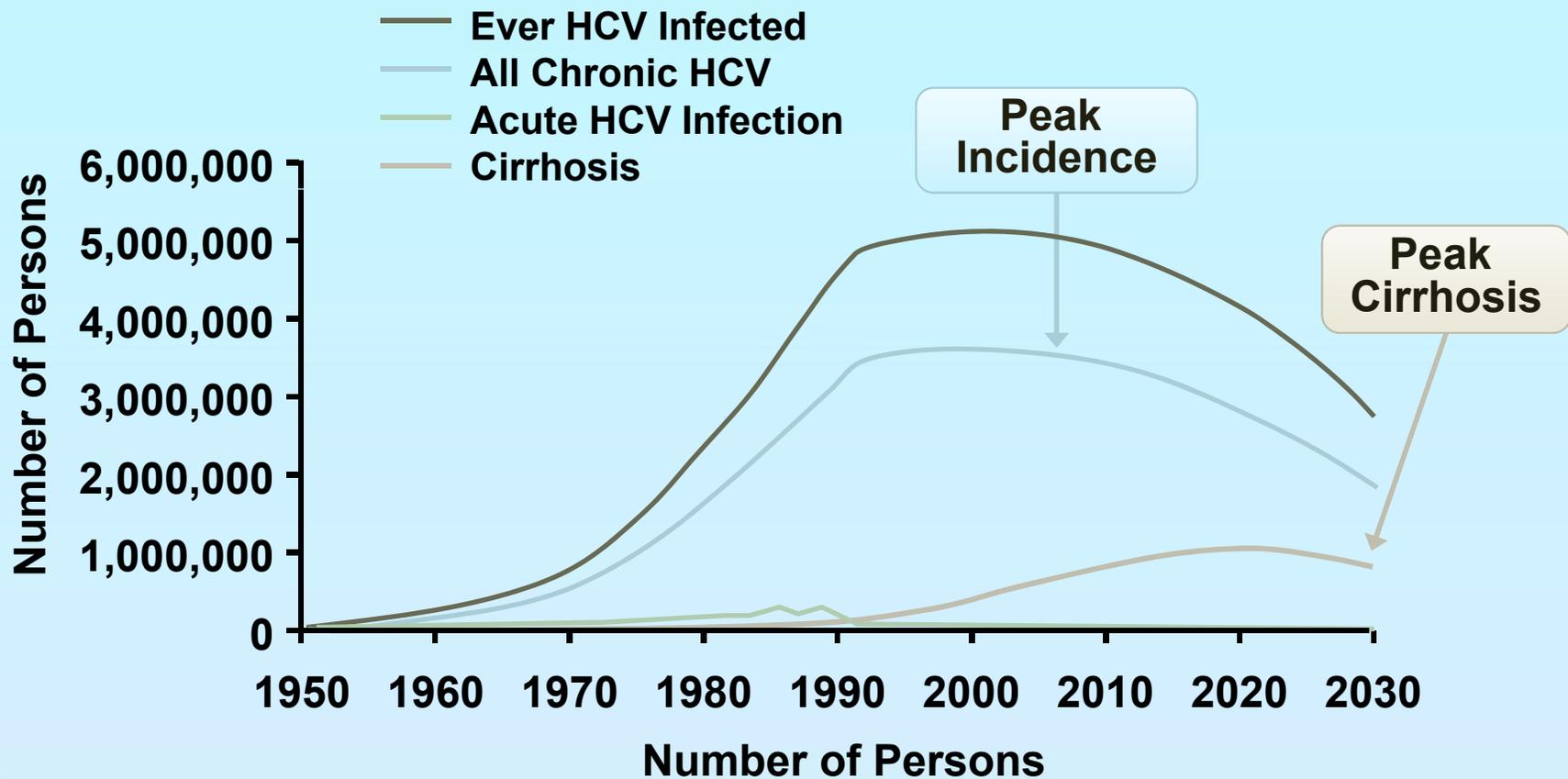


Weinbaum C, et al. MMWR Recomm Rep. 2003;52(RR-1):1-36. Edlin BR. Hepatology. 2002;36(5 suppl 1):210-219. National Survey on Drug Use & Health (NSDUH). NSDUH Report. 2003. Khalili MA, et al. Clin Inf Dis. 2000;31:154-161. LaBreque DR, et al. In: Hepatitis C Choices. 2002. Alter MJ, et al. N Engl J Med. 1999;341(8):556-562. Nyamathi AM, et al. J Gen Intern Med. 2002;17(2):134-143. Bräu N, et al. Am J Gastroenterol. 2002;97(8):2071-2078. Jonas MM. Hepatology. 2002;36(5 suppl 1):S173-S178.

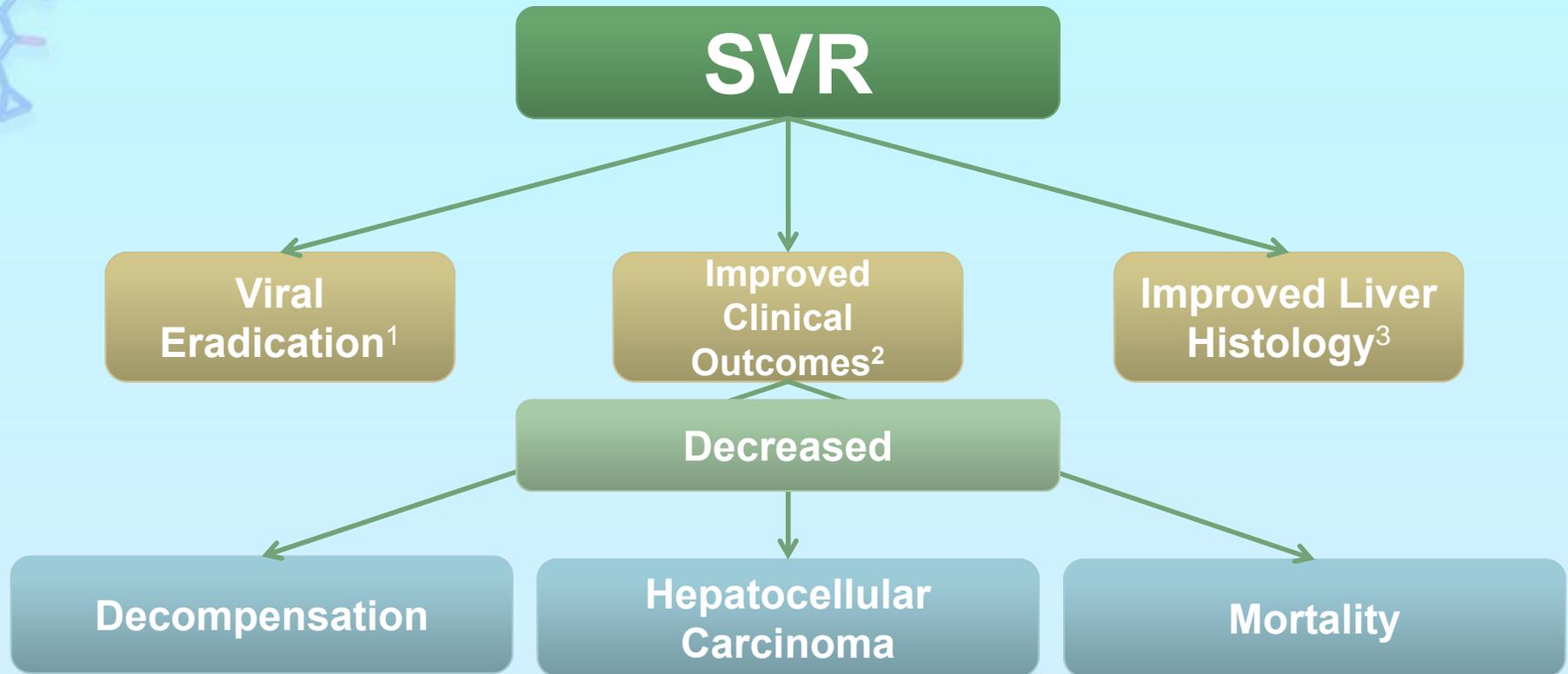
# HCV Infection: Natural Disease Progression



# The Changing Face of HCV in the US



# Sustained Virologic Response (SVR) Leads to Improved Outcome

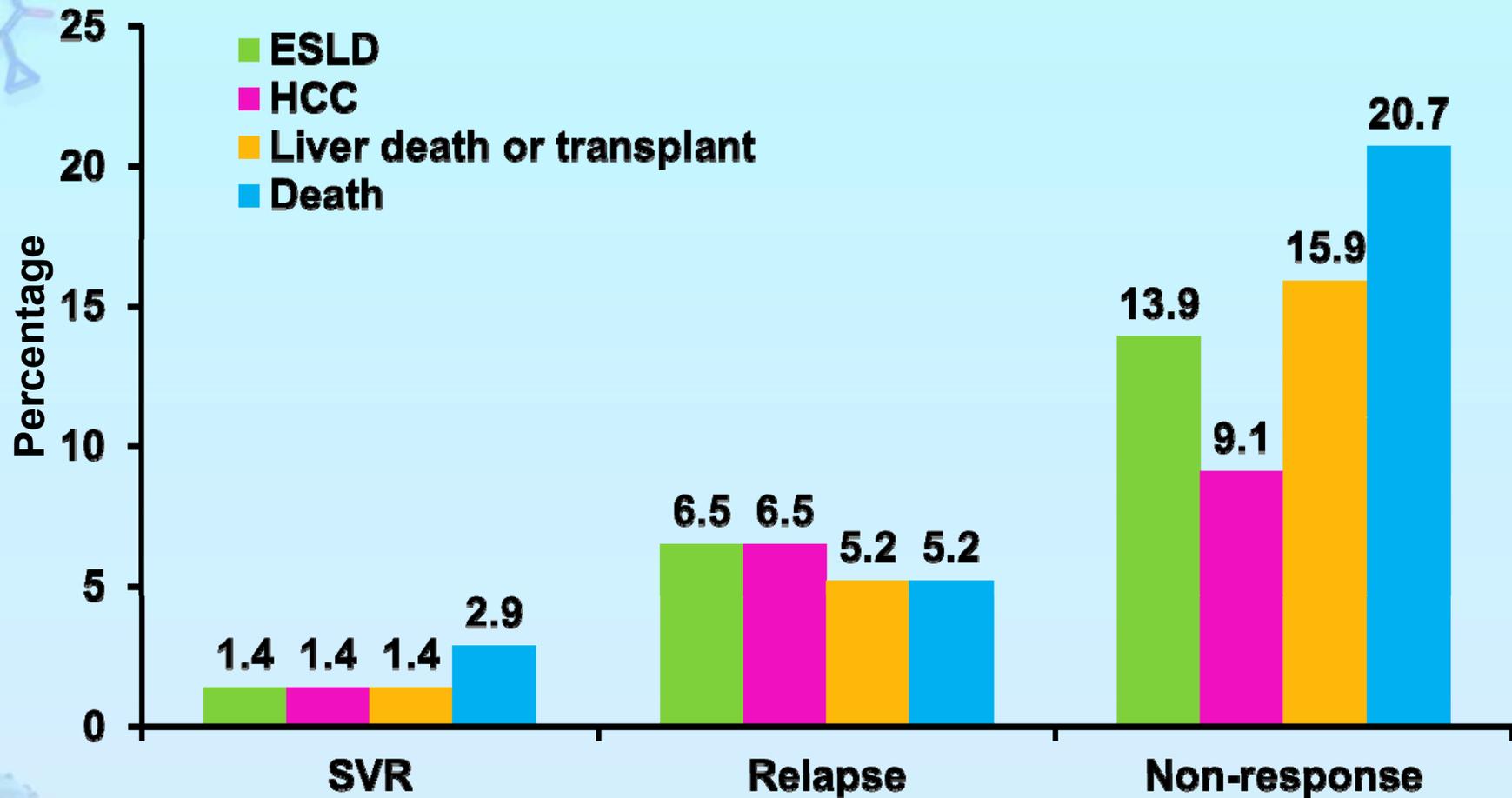


1. Maylin S, et al. Gastroenterology. 2008;135:821-829.

2. Poynard T, et al. Gastroenterology. 2002;122:1303-1313.

3. Veldt BJ, et al. Ann Intern Med. 2007;147:677-684.

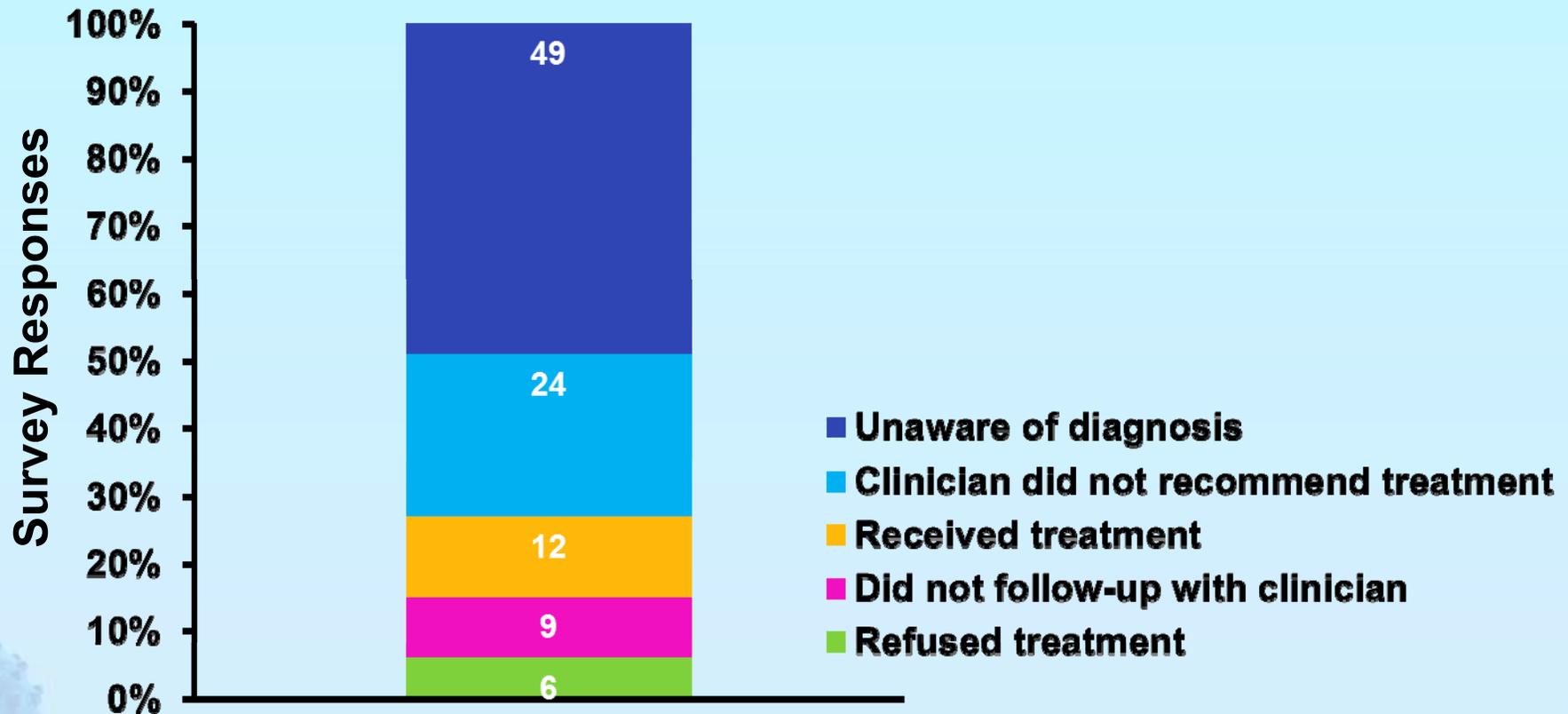
# SVR is Associated with Lower Incidence of ESLD, HCC or Death: Results from the HALT-C Trial



*Treatment of prior nonresponders with advanced fibrosis pegIFN alfa-2a + RBV*

# Reasons for Lack of HCV Treatment

Among Respondents (N=133) to the National Health and Nutrition Evaluation Survey (NHANES) Hepatitis C Follow-Up Questionnaire

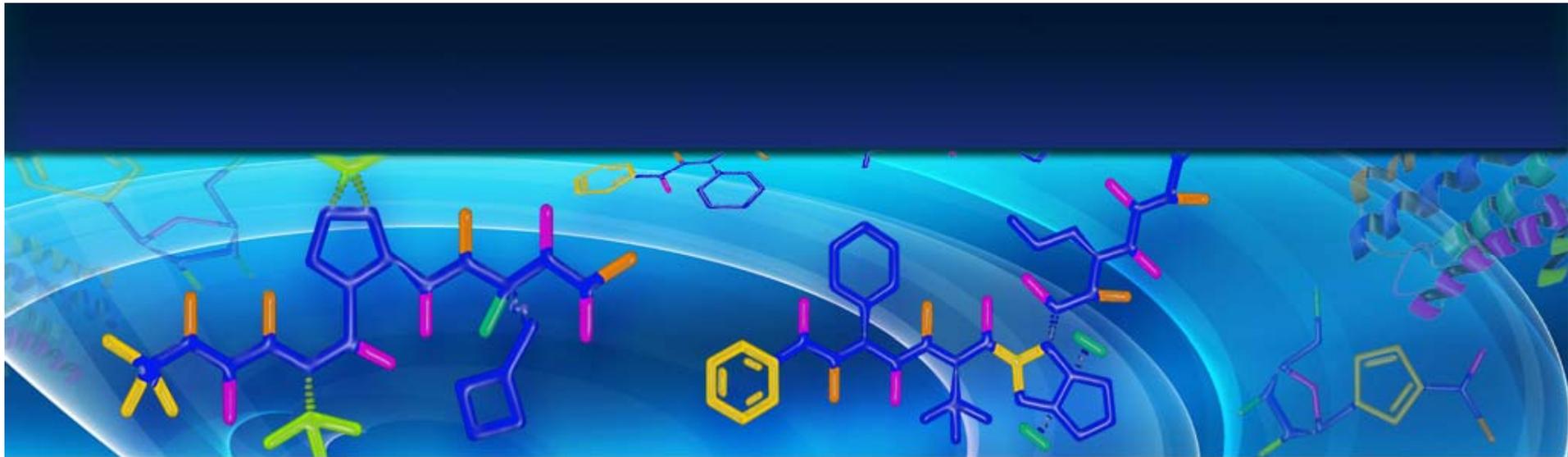


# Burden of HCV Disease

- Liver disease due to chronic HCV is a major cause of morbidity and mortality
  - Impact is expected to peak in ~ 2020
- Sustained virologic response (SVR) = cure
  - Decreased risk of liver complications
  - Decreased risk of death
- In 2010, Institute of Medicine report noted limited awareness and called for more action to address viral hepatitis in the US

# Institute of Medicine Report *Recommendations for Viral Hepatitis in the US*

Surveillance	Knowledge & Awareness	Viral Hepatitis Services
<p>CDC should:</p> <ul style="list-style-type: none"> <li>➤ Evaluate HCV public health surveillance system</li> <li>➤ Develop agreements with state health departments to support HCV surveillance</li> <li>➤ Support targeted surveillance</li> </ul>	<p>CDC should work with key stakeholders to:</p> <ul style="list-style-type: none"> <li>➤ Develop HCV educational programs for providers</li> <li>➤ Develop and evaluate innovative and effective outreach programs to               <ol style="list-style-type: none"> <li>1) target at-risk populations, and</li> <li>2) increase public awareness</li> </ol> </li> </ul>	<p>Federally funded health insurance programs should:</p> <ul style="list-style-type: none"> <li>➤ Incorporate guidelines for risk-factor screening as required component of preventive care</li> </ul>



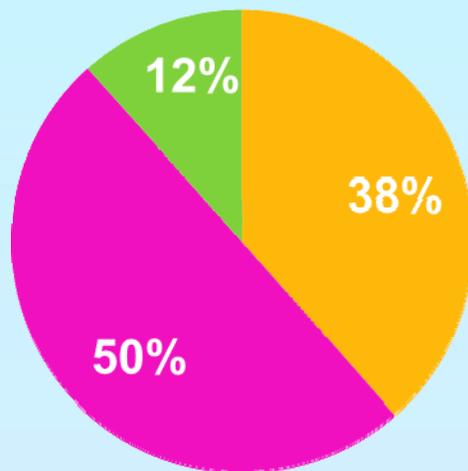
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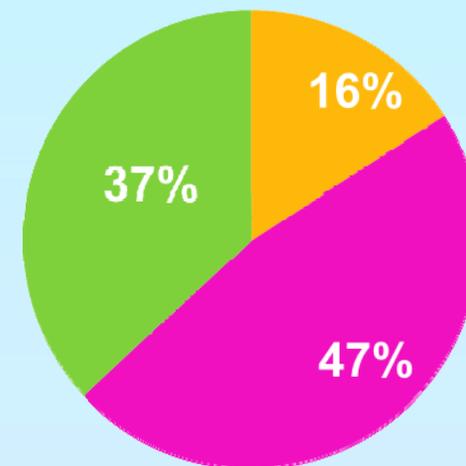
## **HCV Treatment Issues and Guidelines**

# Favorable II28B Genotype is more Common Among Caucasians than African-Americans

**Caucasian  
(n=871)**

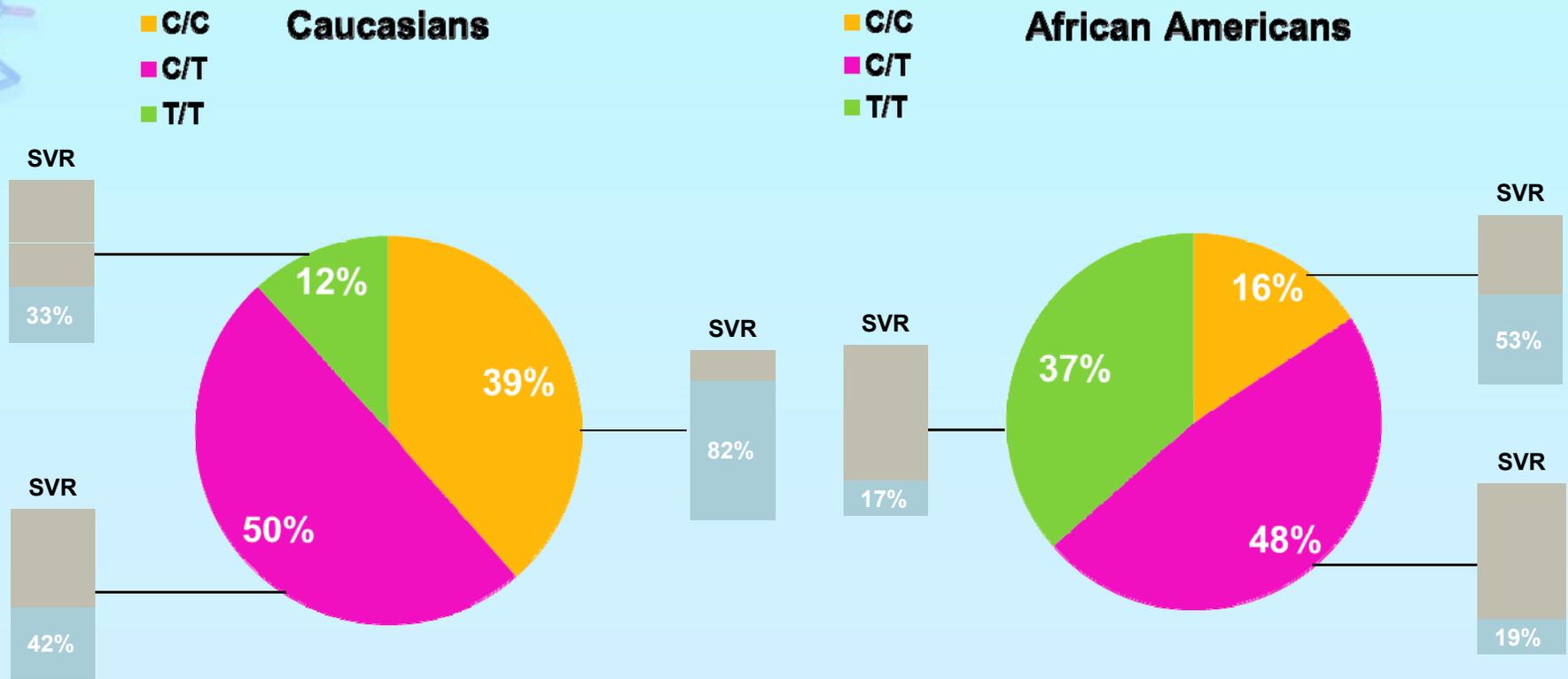


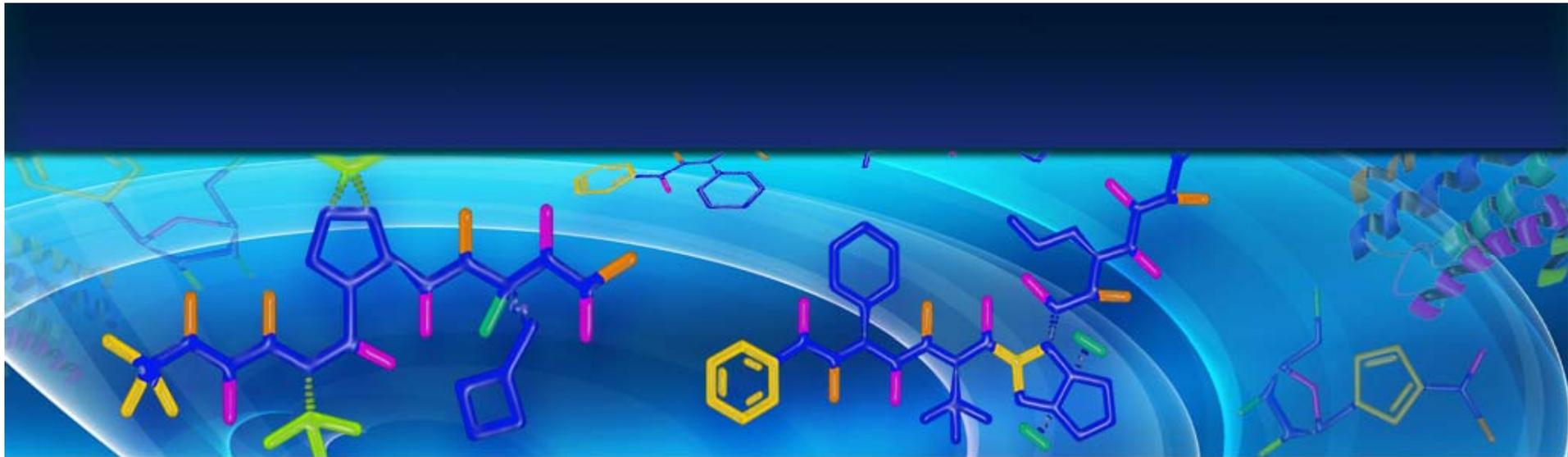
**African American  
(n=191)**



■ CC   ■ CT   ■ TT

# IL28B Less Common in African-Americans and Affects SVR



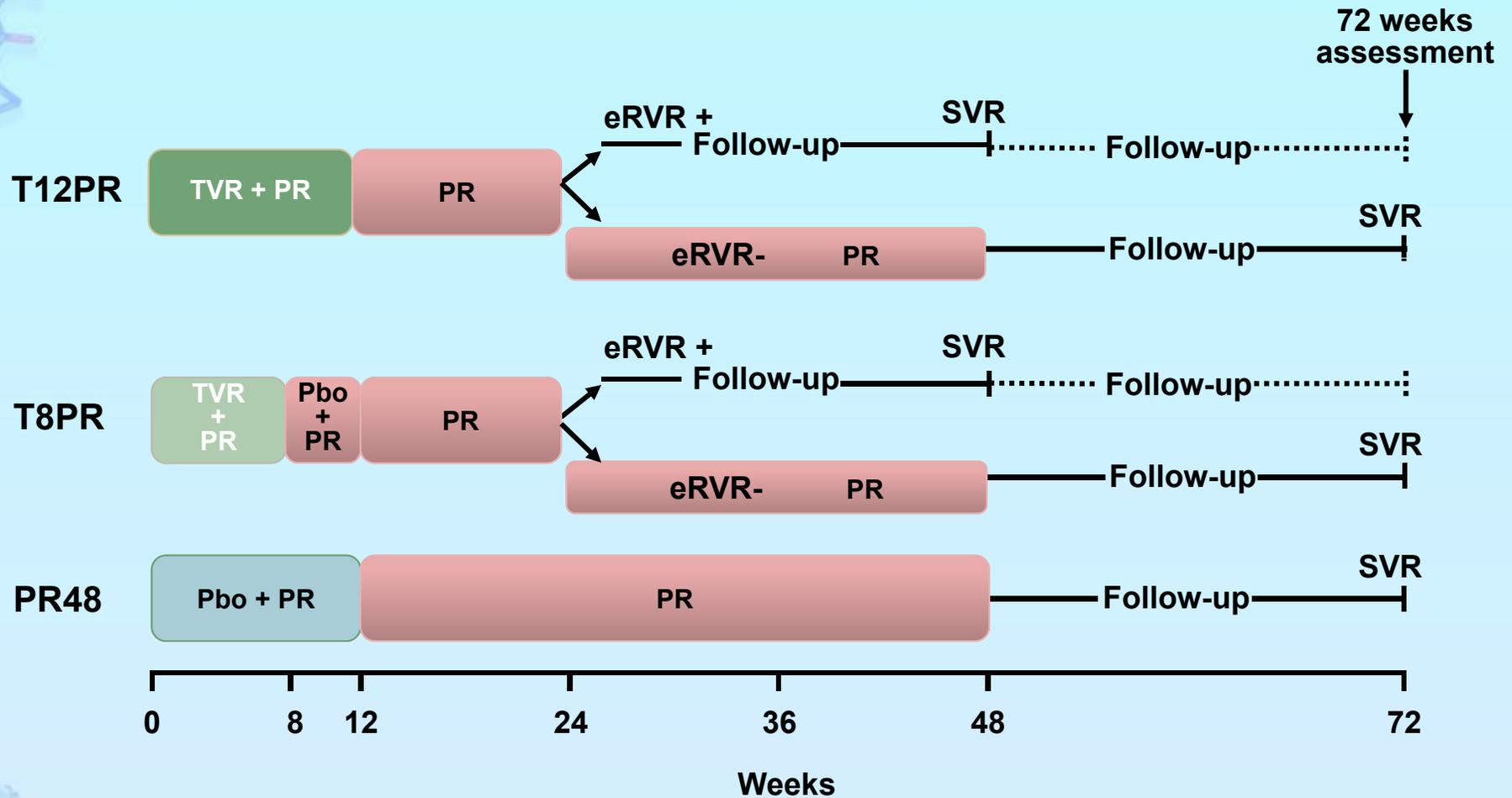


# **HCV TREATMENT IN 2011:**

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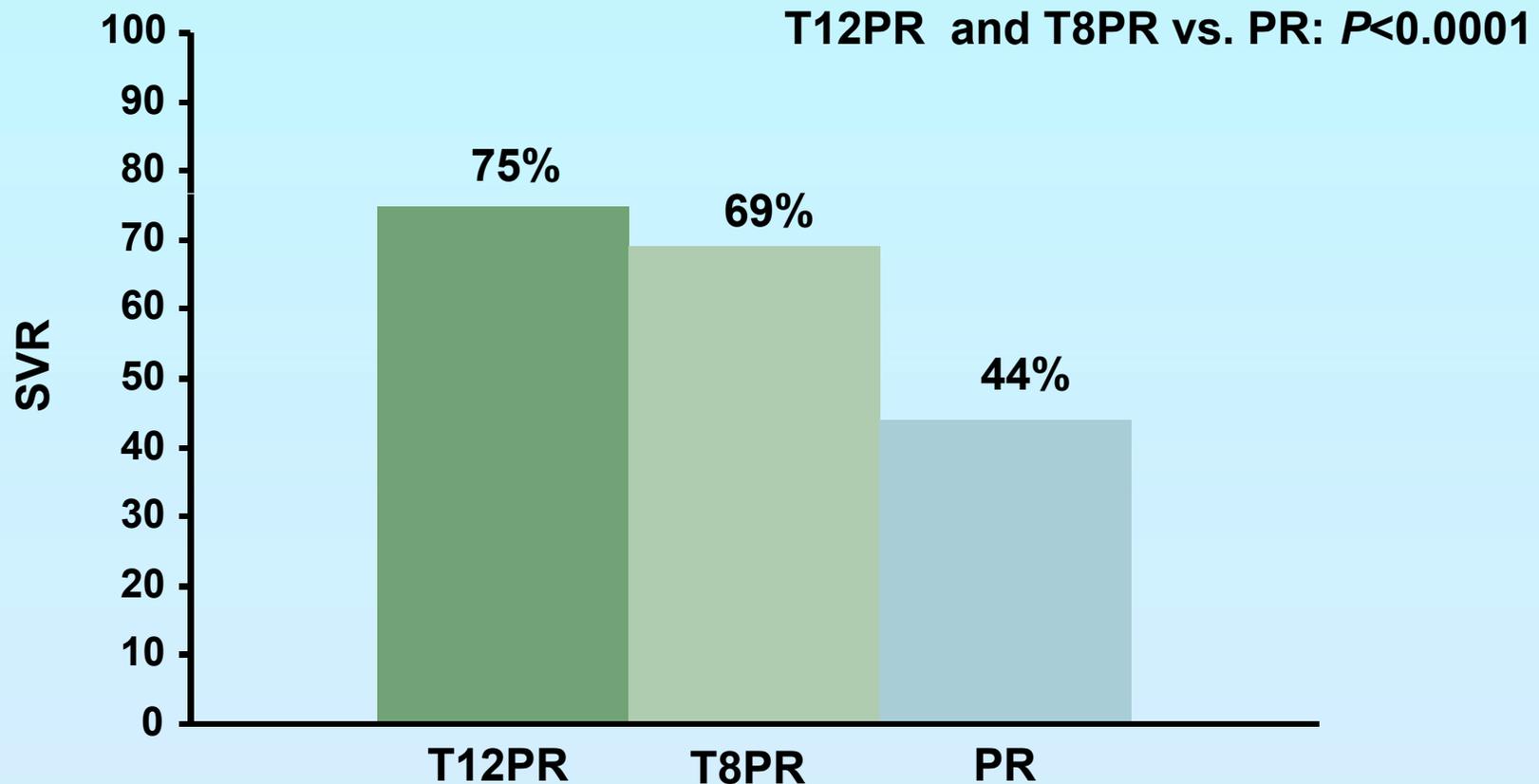
## **HCV Protease Inhibitor: Treatment-naïve Patients**

# ADVANCE: Telaprevir + PegIFN/RBV in Treatment-Naïve, Genotype 1 HCV Patients

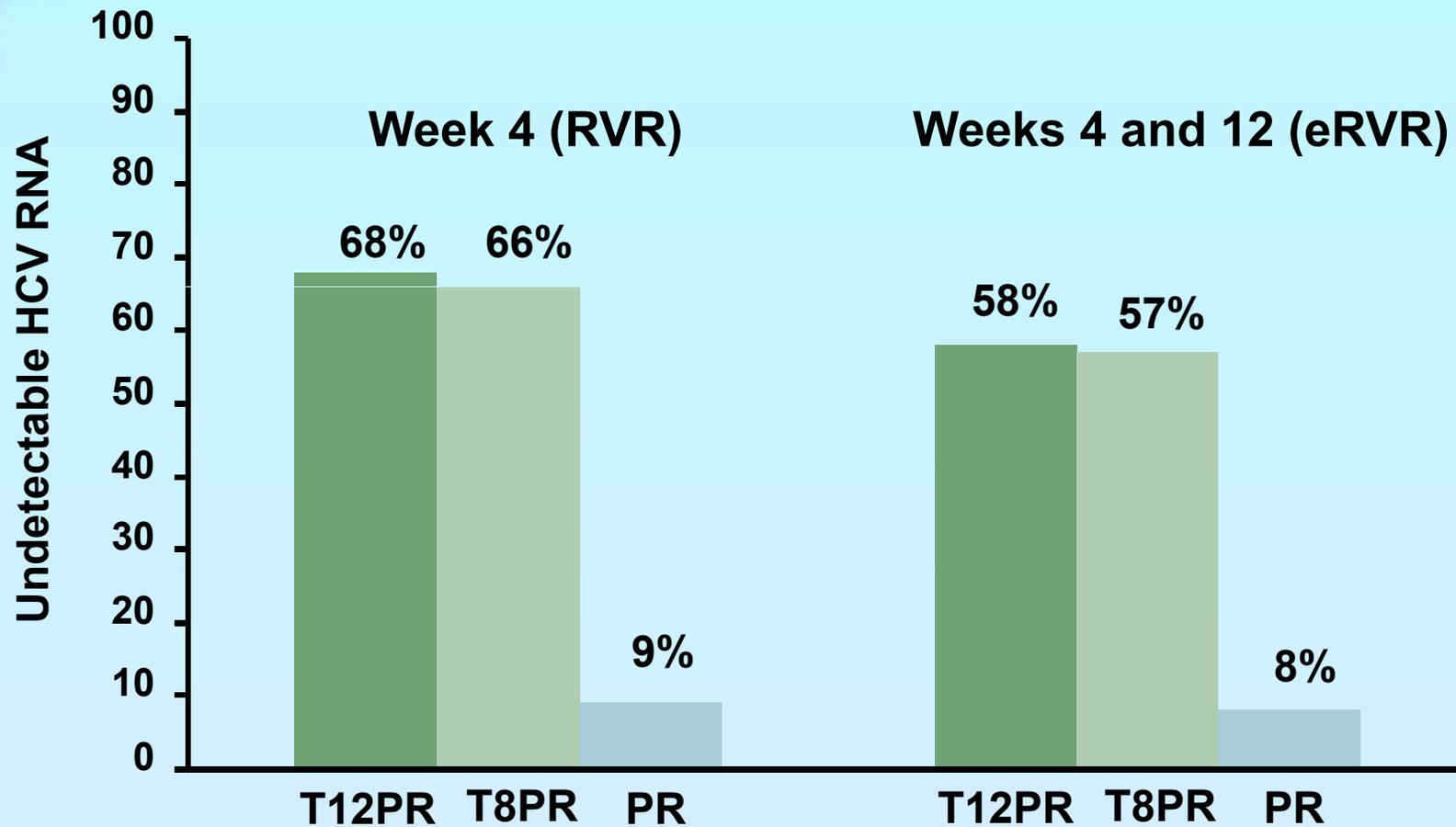


eRVR= undetectable HCV RNA by Taqman v2.0 at weeks 4 and 12

# ADVANCE: Achievement of SVR

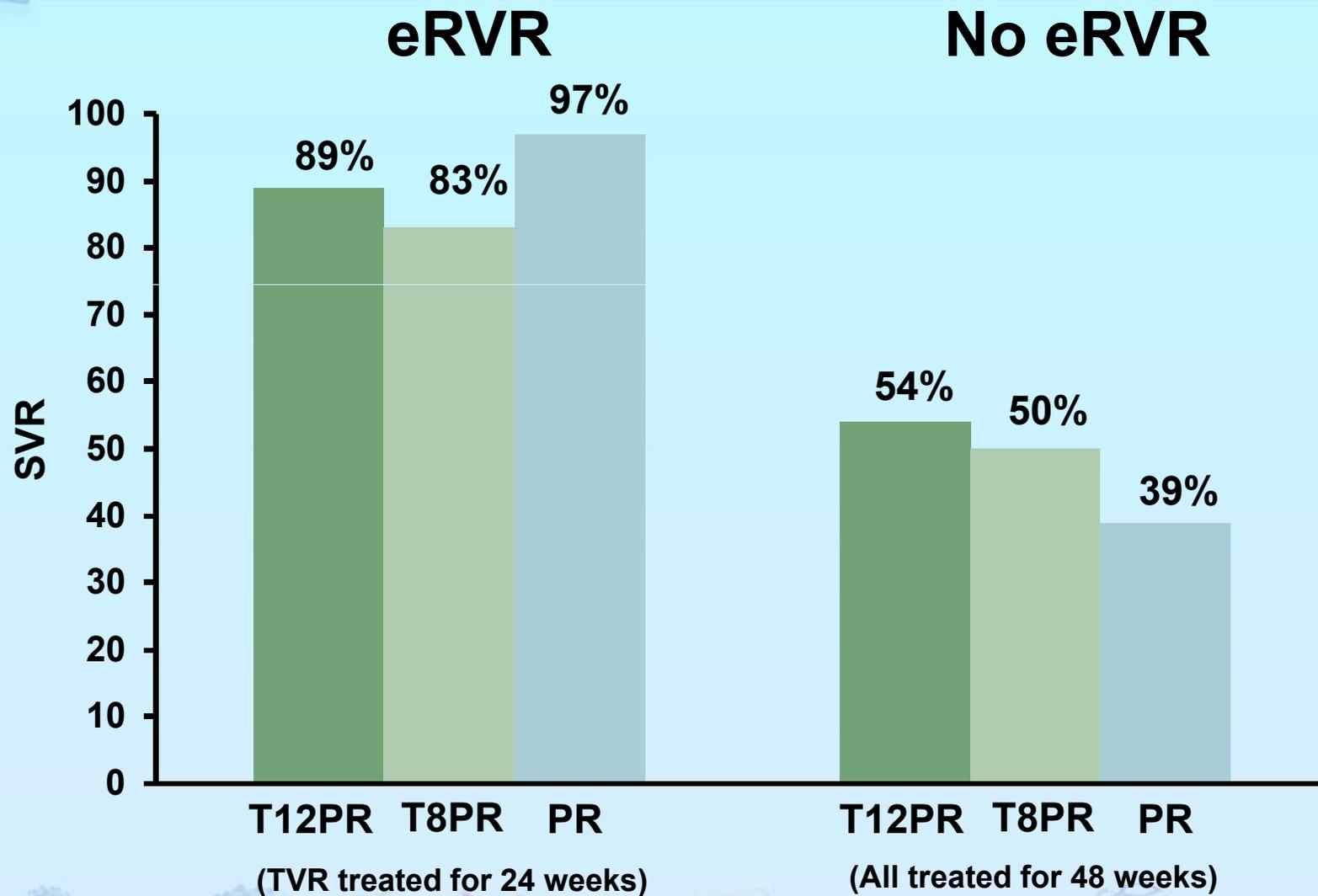


# ADVANCE: RVR and eRVR

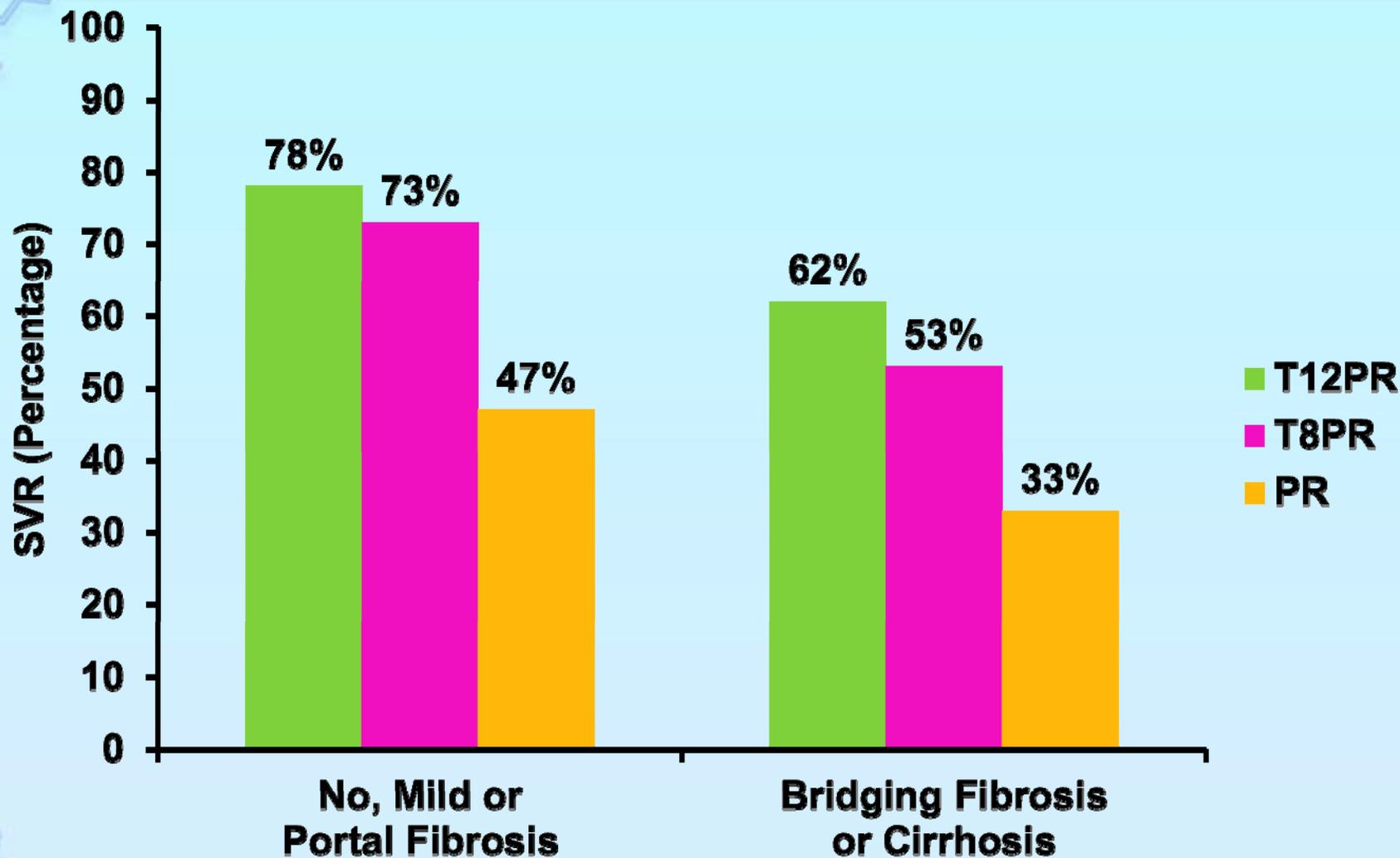


RVR = Undetectable HCV RNA at Week 4  
eRVR = Undetectable HCV RNA at Weeks 4 and 12

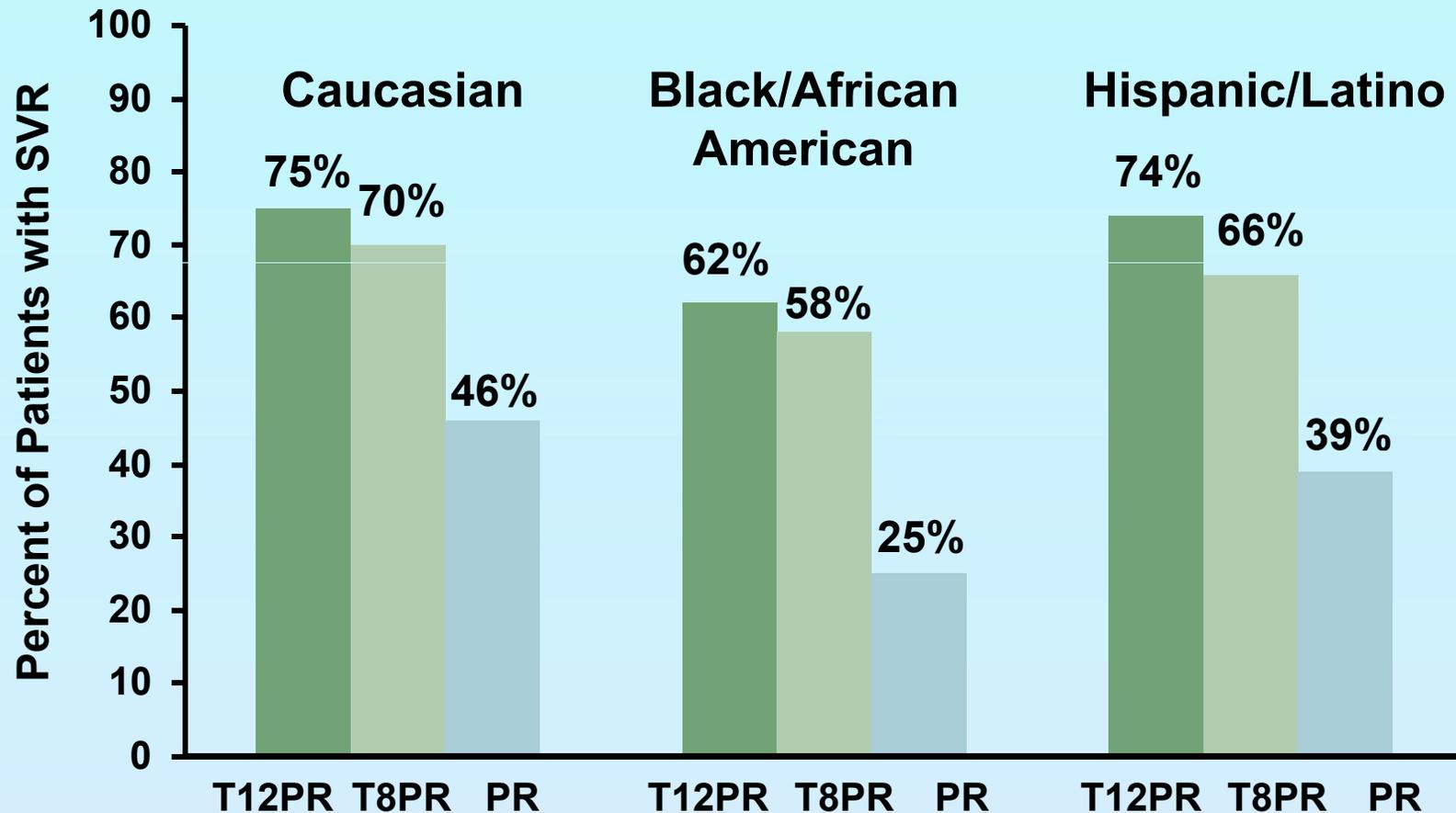
# ADVANCE: High SVR with eRVR



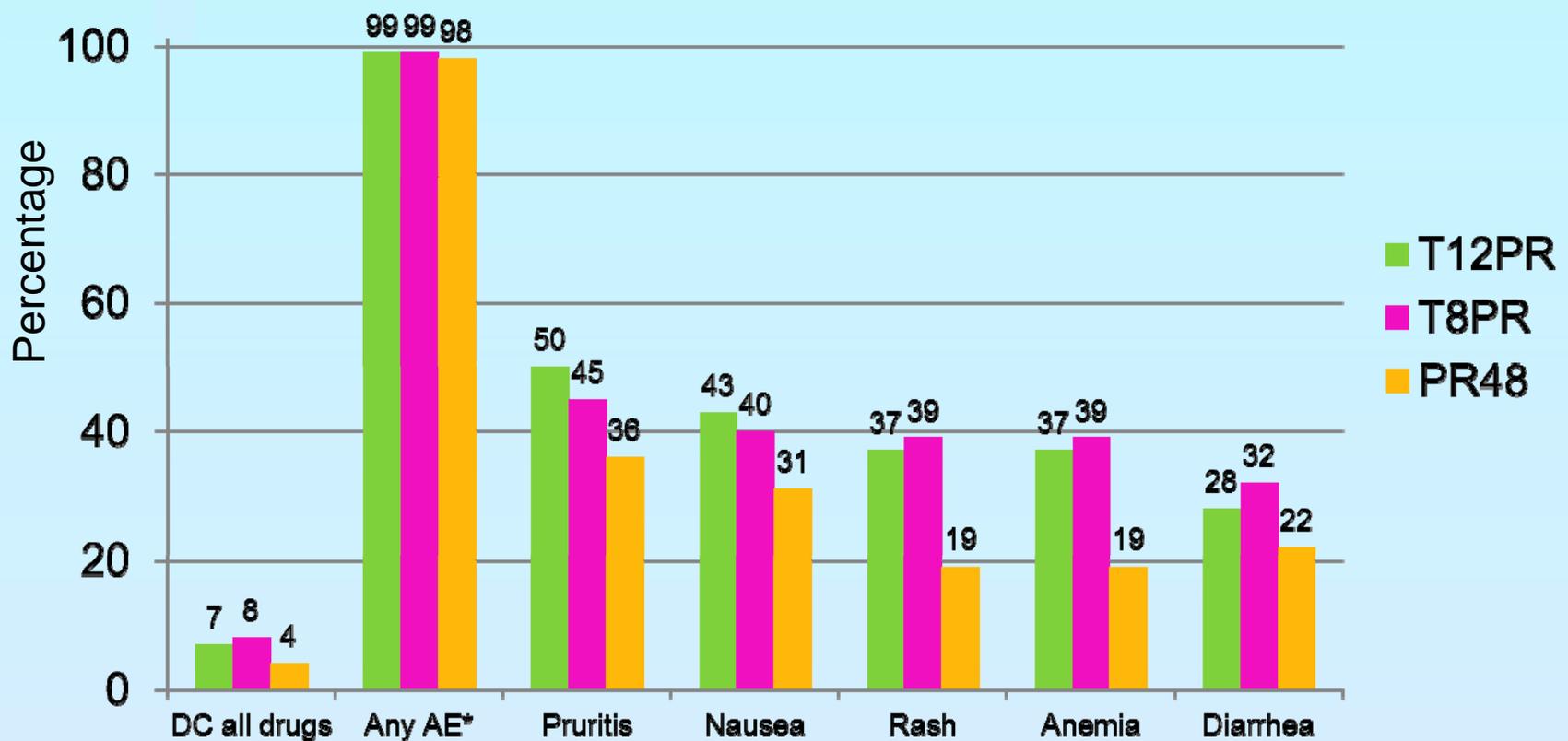
# ADVANCE: SVR Rates By Fibrosis/Cirrhosis



# ADVANCE: SVR By Race/Ethnicity

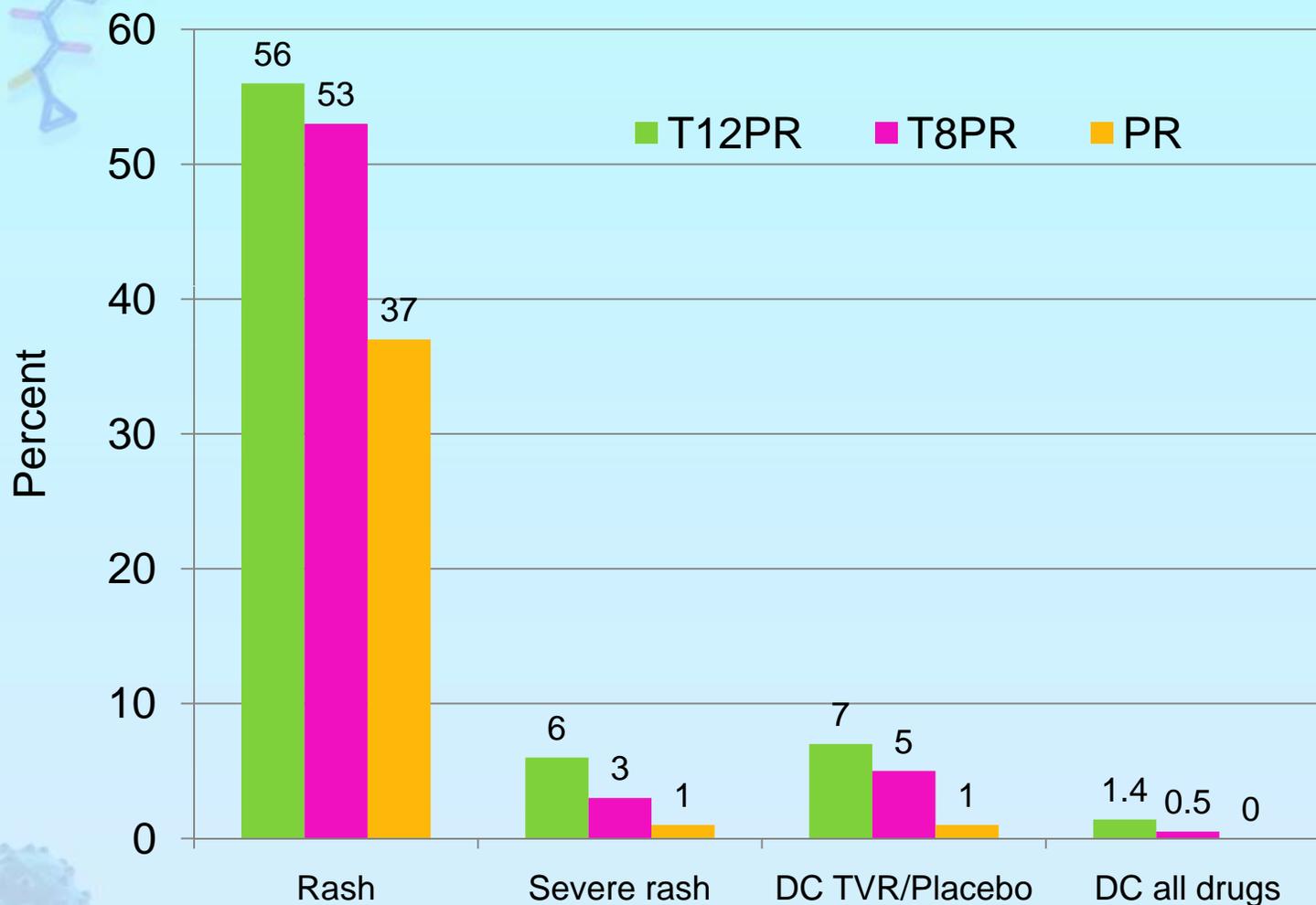


# ADVANCE: Adverse Events

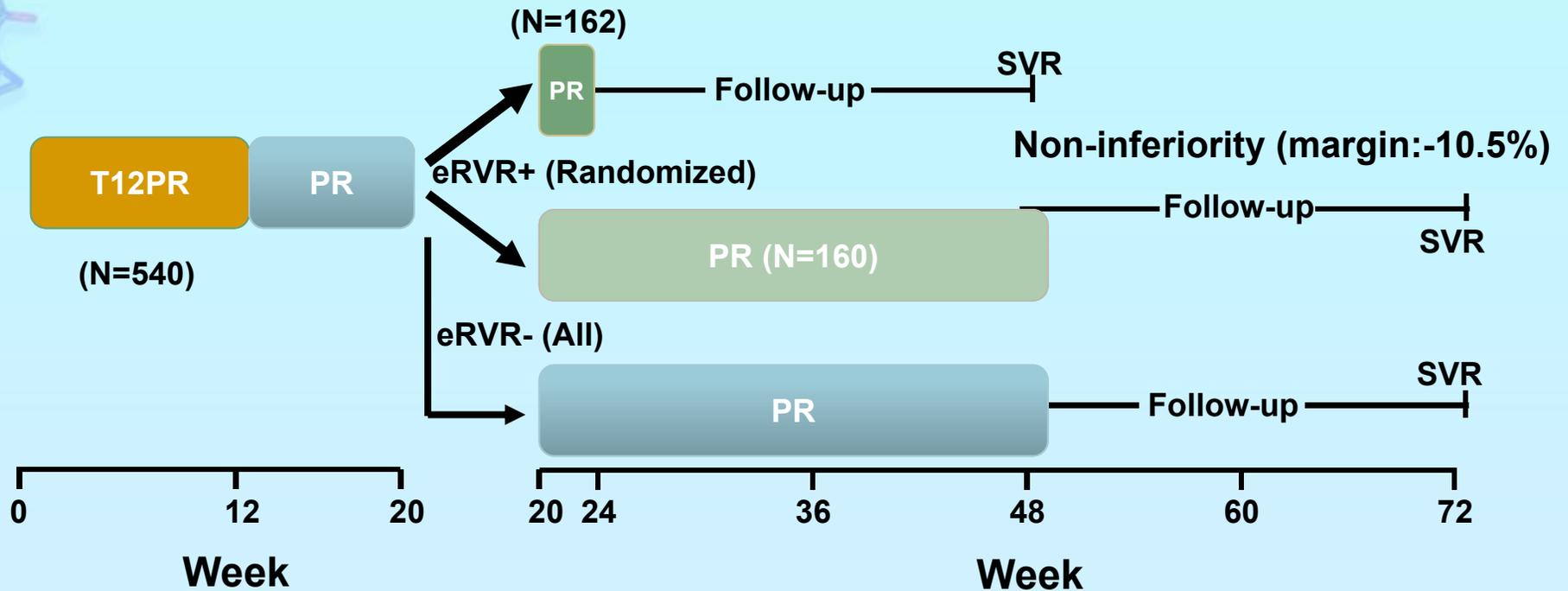


\*No difference regarding fatigues, headache, insomnia, influenza-like illness, pyrexia

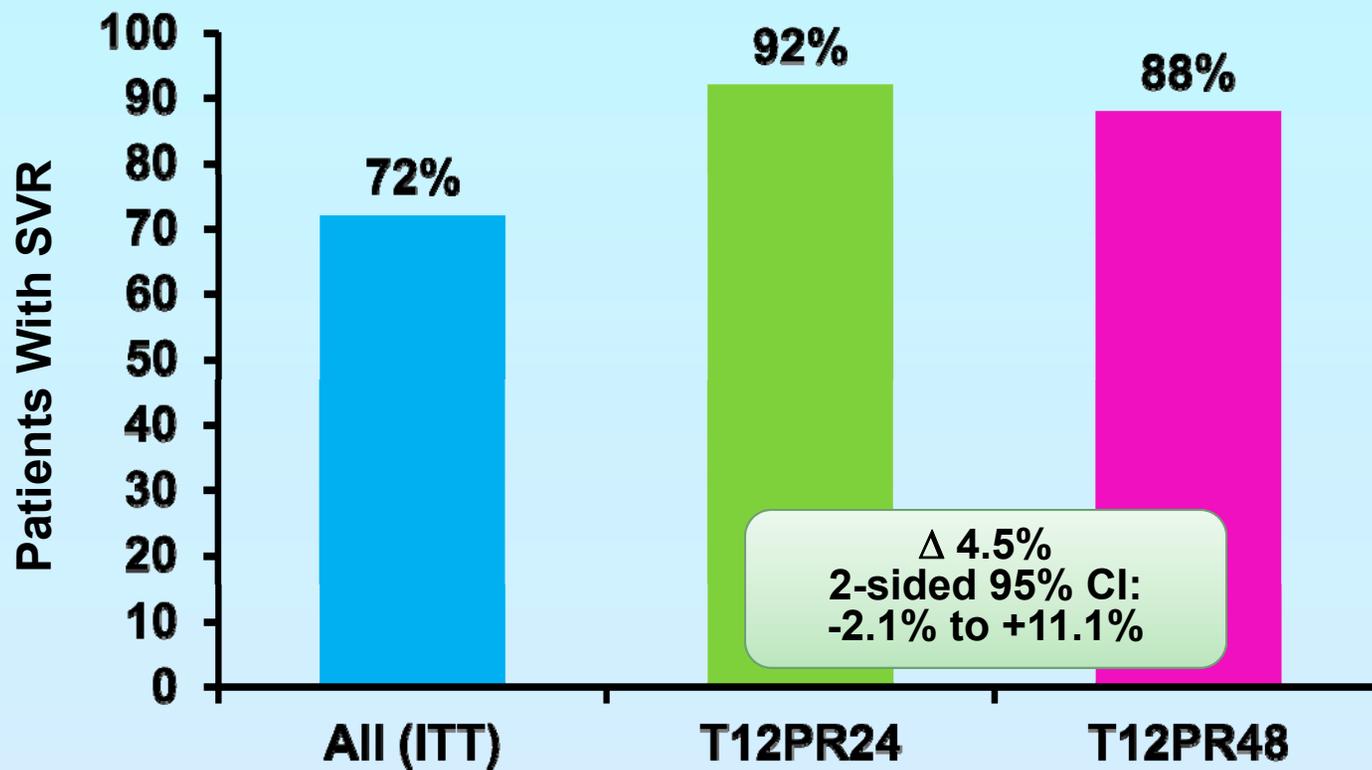
# ADVANCE: Rash During TVR/Placebo Phase



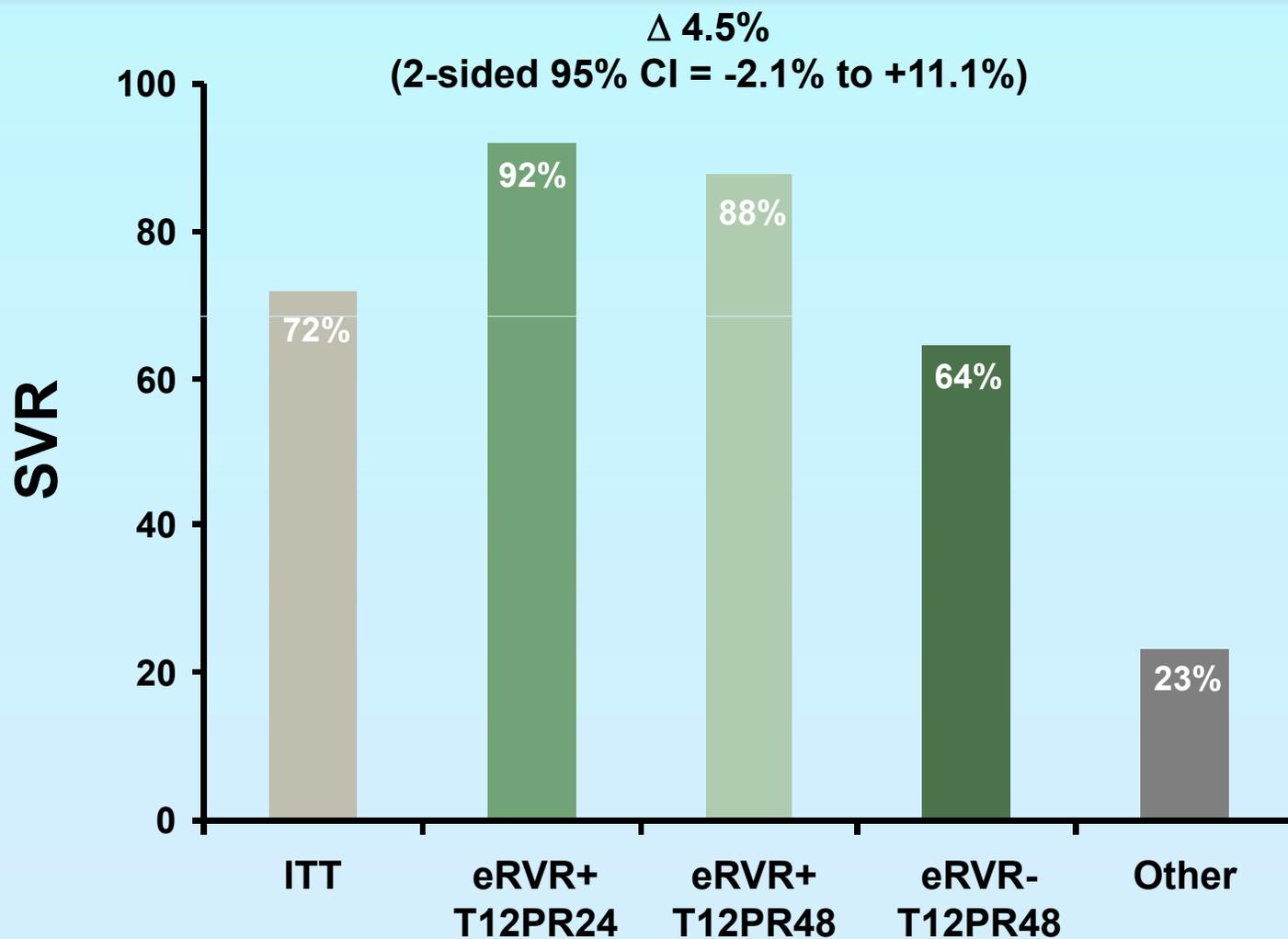
# ILLUMINATE: Telaprevir + PegIFN/RBV for 24 or 48 Weeks in Treatment-Naïve, Genotype 1 HCV Patients with eRVR



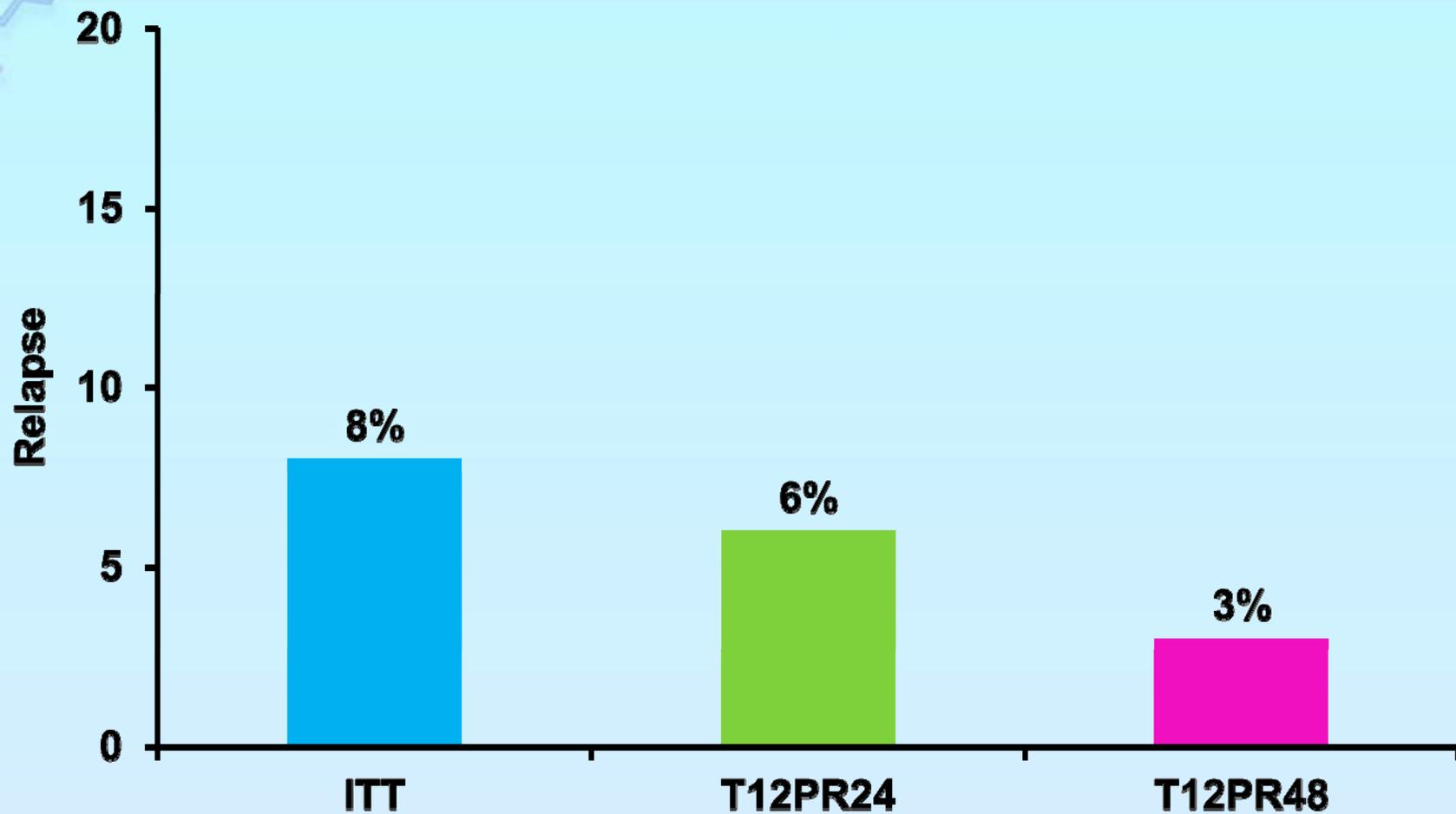
# ILLUMINATE: SVR Rates



# ILLUMINATE: SVR Rates in All Treatment Groups



# ILLUMINATE: Relapse Rates



# ILLUMINATE: Common AEs Leading to TVR Discontinuation

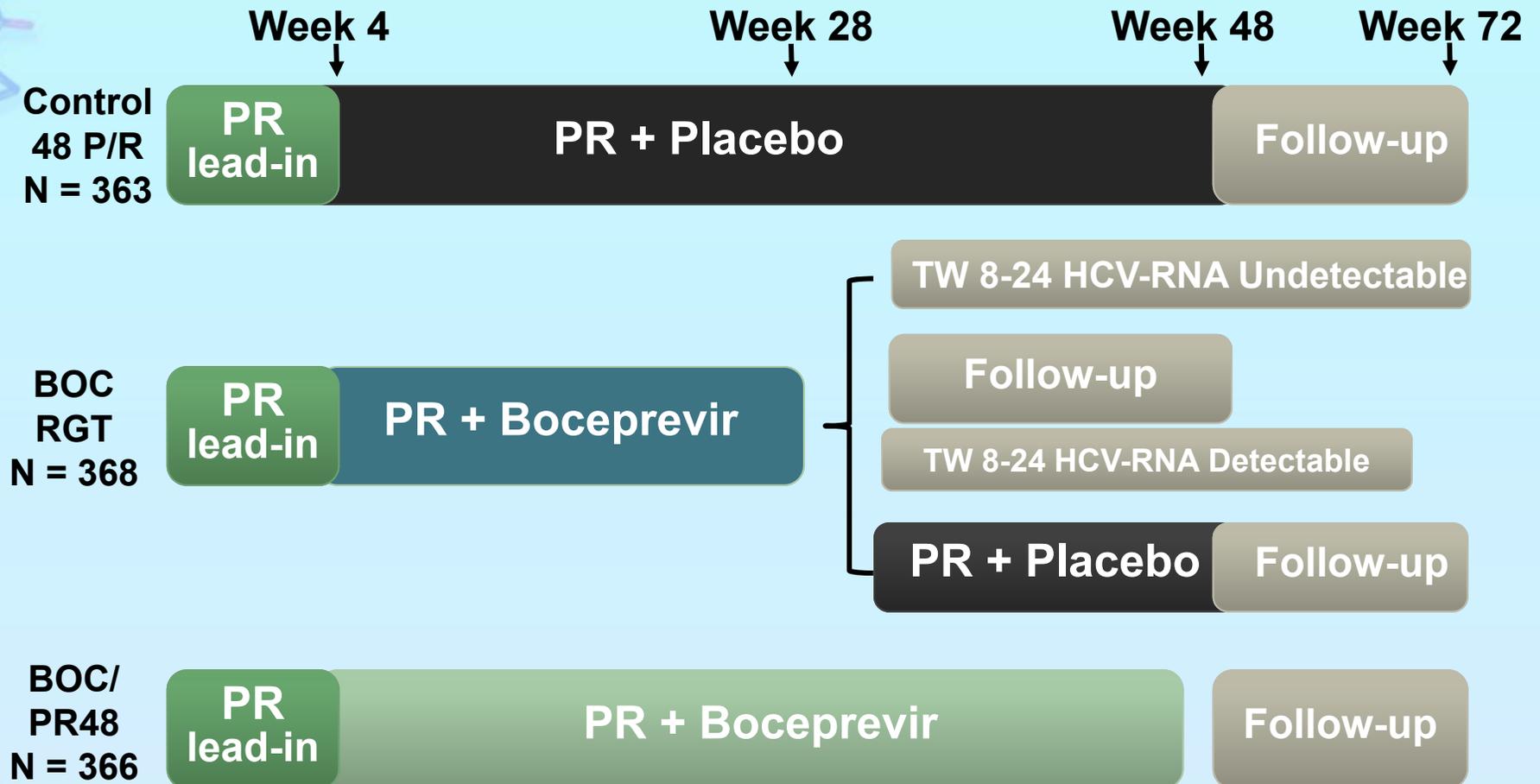
## Discontinuation of All Study Drugs During TVR Treatment

Any Adverse Event	7%
Rash	1%
Anemia	1%

## Discontinuation of TVR During TVR Treatment

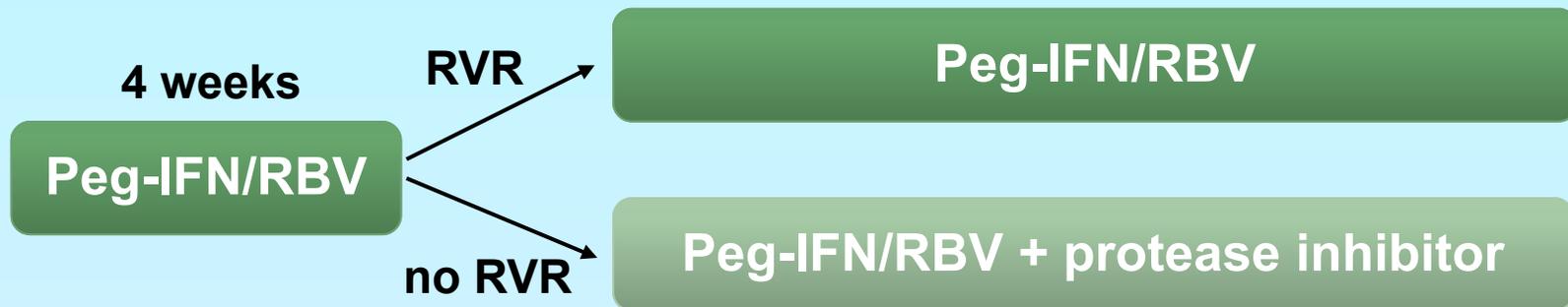
Any Adverse Event	21%
Rash	7%
Anemia	2%

# SPRINT-2: Study Design



# SPRINT-2: Potential Rationale for Lead-in Phase

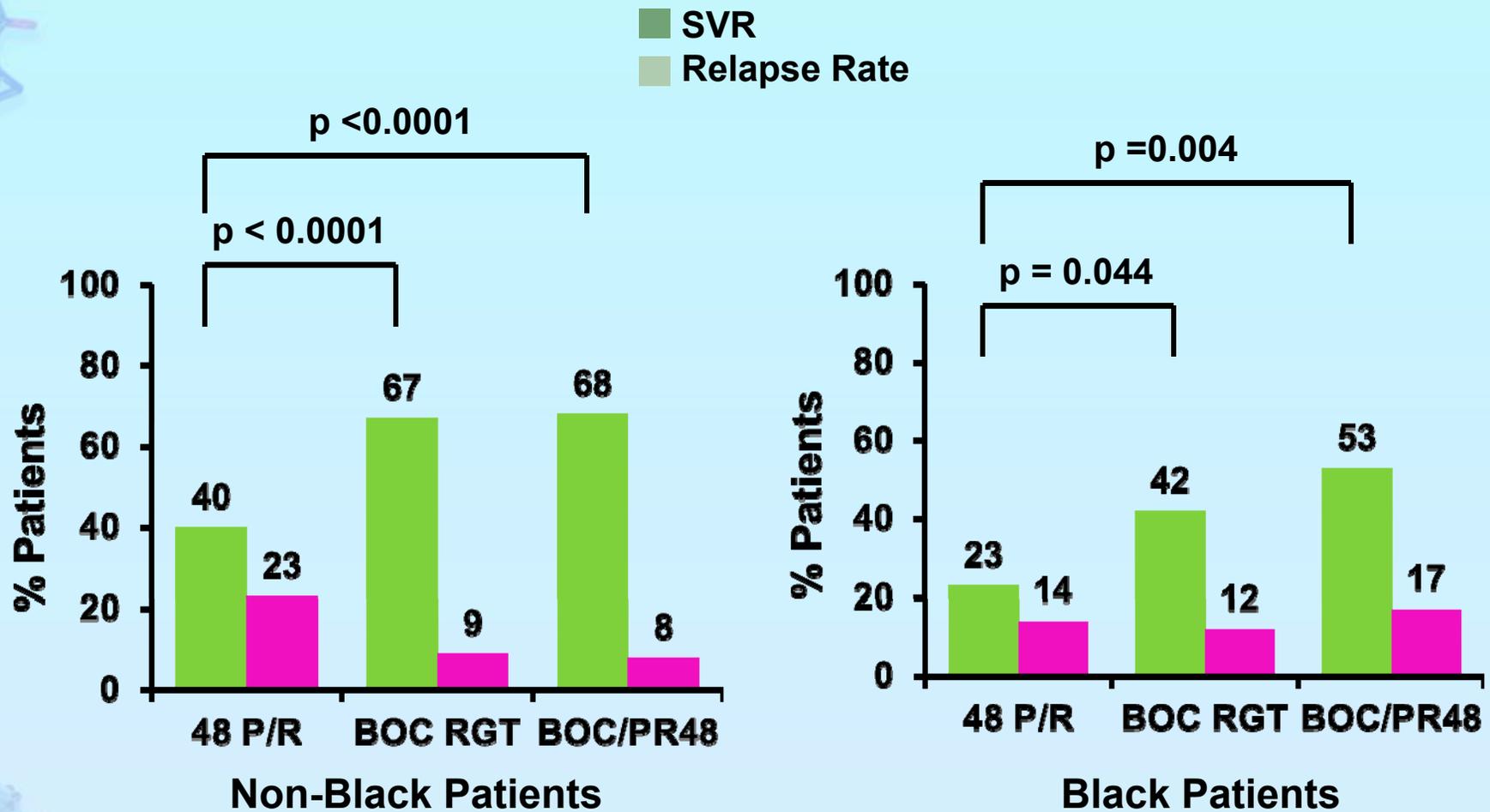
- Avoidance of use of cost and unnecessary drug use
  - **Identify interferon-sensitive patients who may not need DAA**



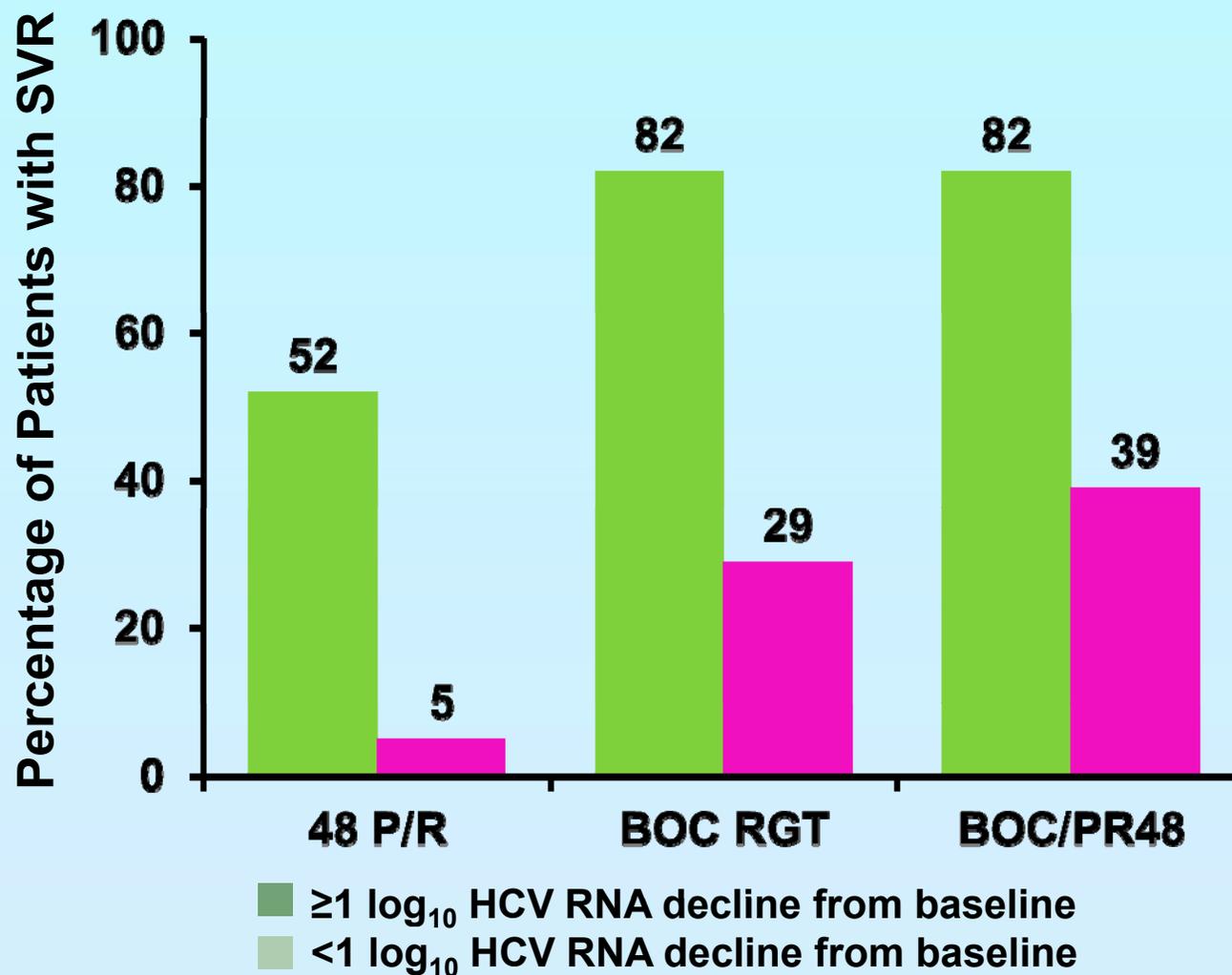
- Optimization of DAA
  - **Decrease viral resistance development at time of DAA introduction and enhance response-guided therapy strategy**
  - **Inform on-treatment decision-making based on likelihood of response**



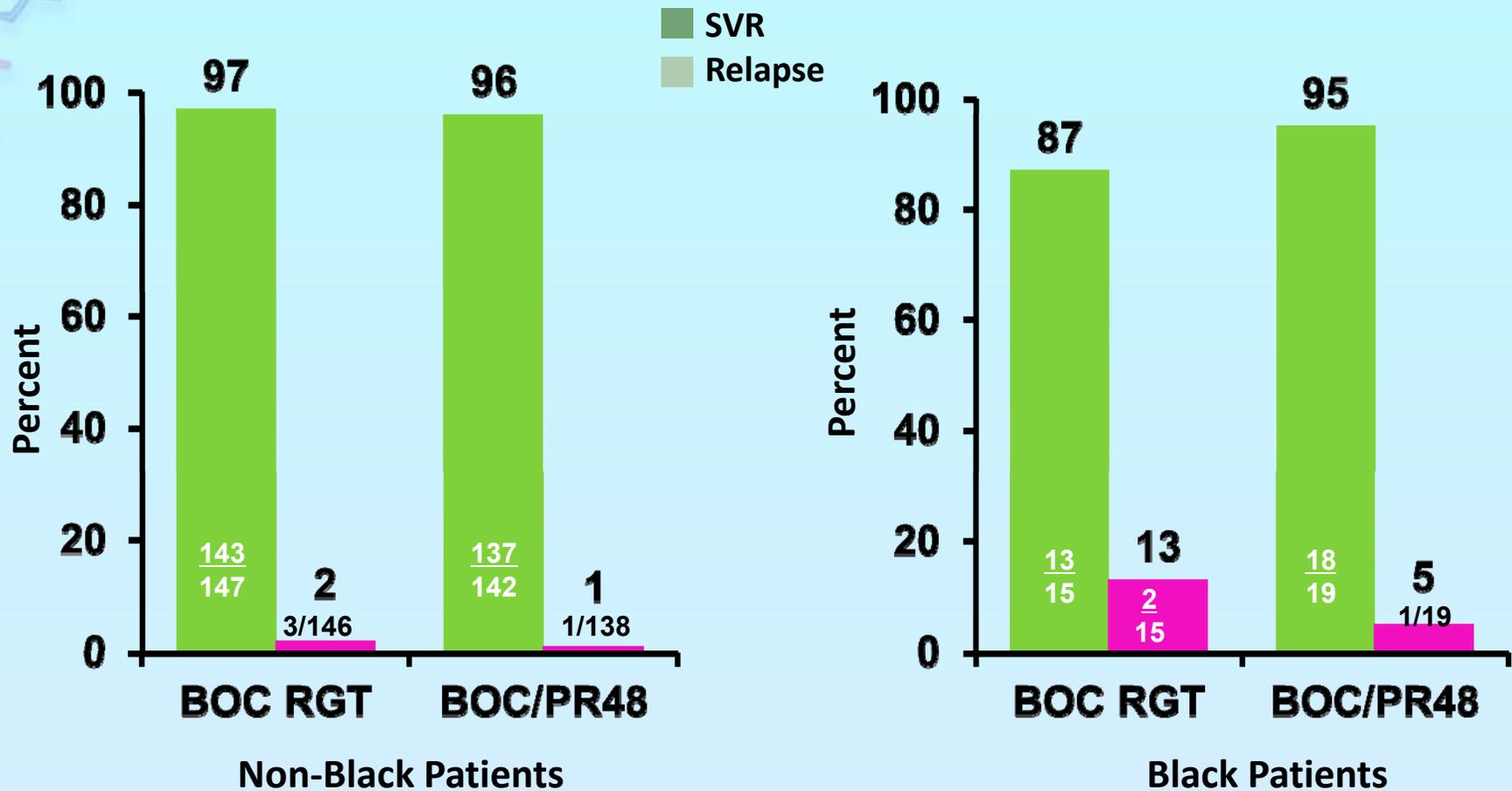
# SPRINT-2: SVR and Relapse Rates (ITT)



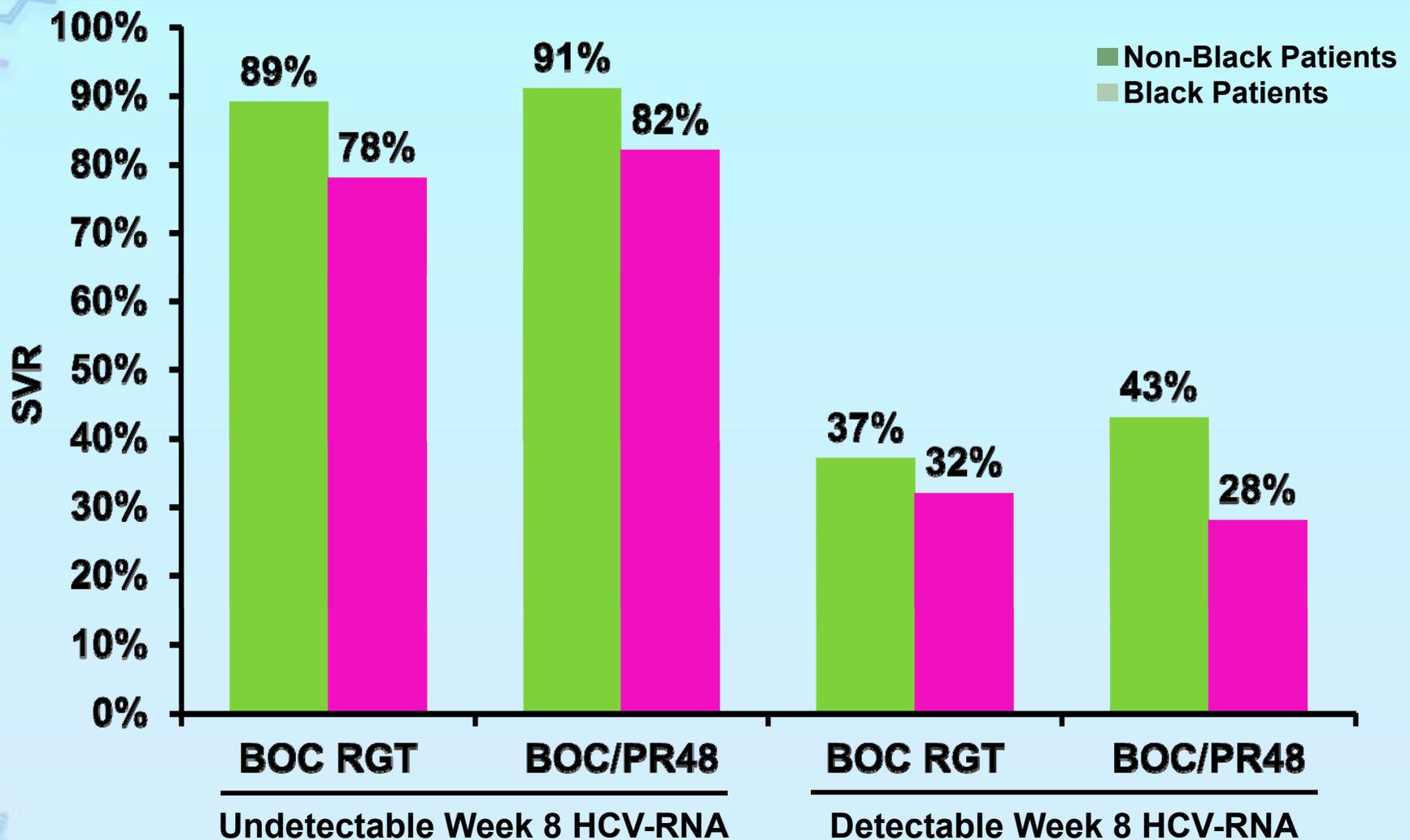
# SPRINT-2: SVR Based on Week 4 PR Lead-in in Non-Black Patients



# SPRINT-2: Virologic Response Rates for Undetectable HCV RNA Levels Weeks 8 to 24



# SPRINT-2: SVR Rates Based on Week 8 HCV RNA



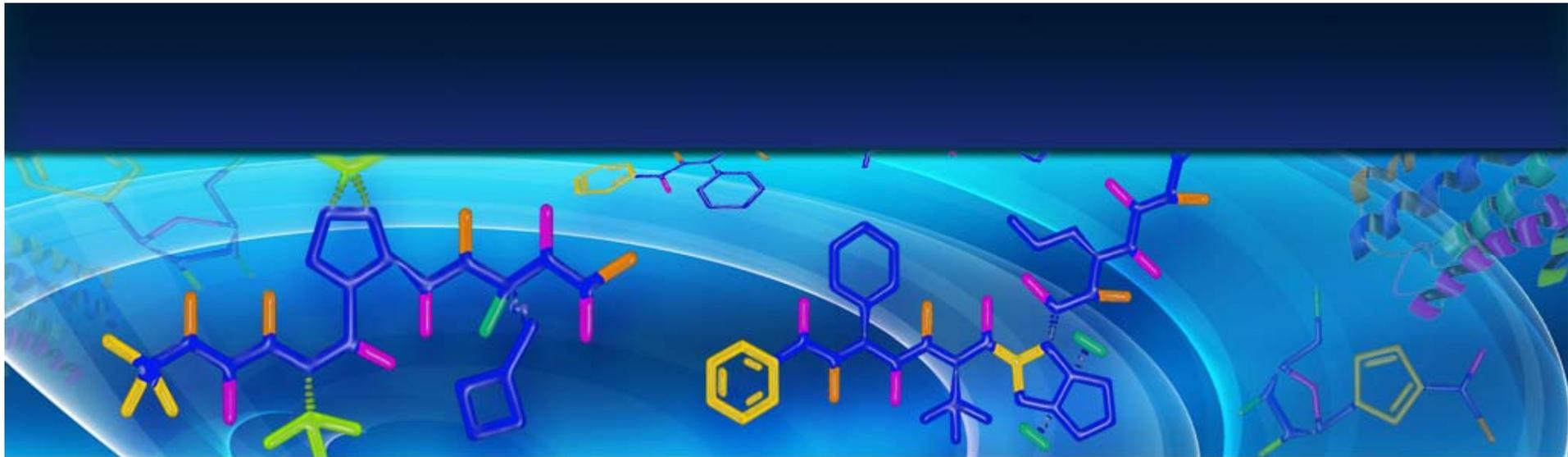
# SPRINT-2: Common Treatment-Related Adverse Events

Adverse Event	PR48	RGT	BOC/PR48
Anemia	29%	49%	49%
Dysgeusia	18%	37%	43%

**No difference between arms in: Fatigue, headache, nausea, chills, pyrexia, insomnia, alopecia, decreased appetite, pruritis, neutropenia, influenza-like illness, myalgia, rash, irritability, depression, diarrhea, dry skin, dyspnea, dizziness**

# Treatment Paradigm for HCV Genotype 1 Naïve Patients

- Telaprevir (12 weeks) + PegIFN/RBV
  - HCV RNA at week 4
  - Response Guided Therapy (RGT) based on HCV RNA at week 4 (Treatment for 24 or 48 weeks)
  - Common AEs: rash, anemia
- Boceprevir (24 weeks) + PegIFN/RBV
  - PegIFN/RBV lead-in for 4 weeks
  - HCV RNA at week 4 and 8
  - RGT based on HCV RNA at week 8 (Treatment for 28 or 48 weeks)
  - Common AE: anemia



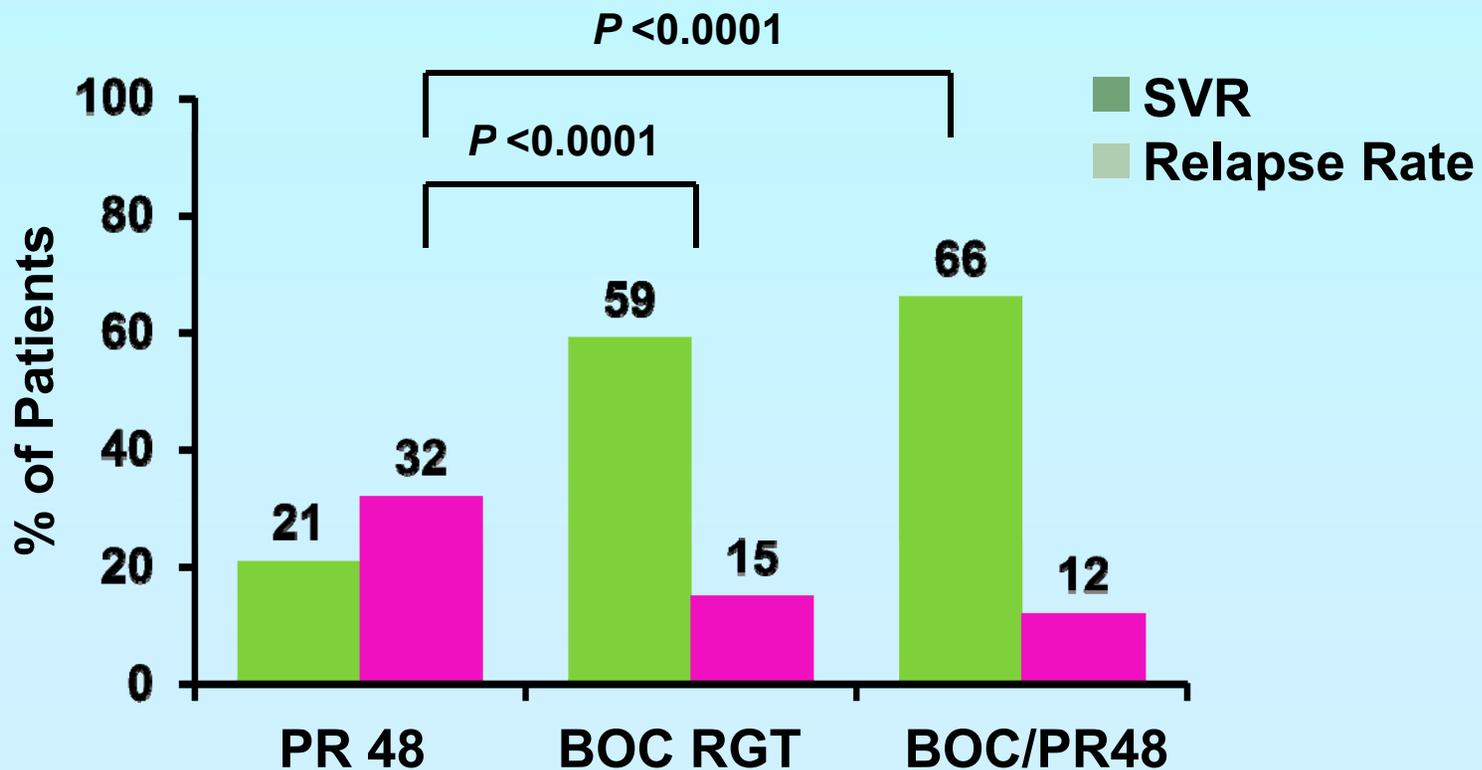
# **HCV TREATMENT IN 2011:**

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## **HCV Protease Inhibitor: Treatment-experienced Patients**



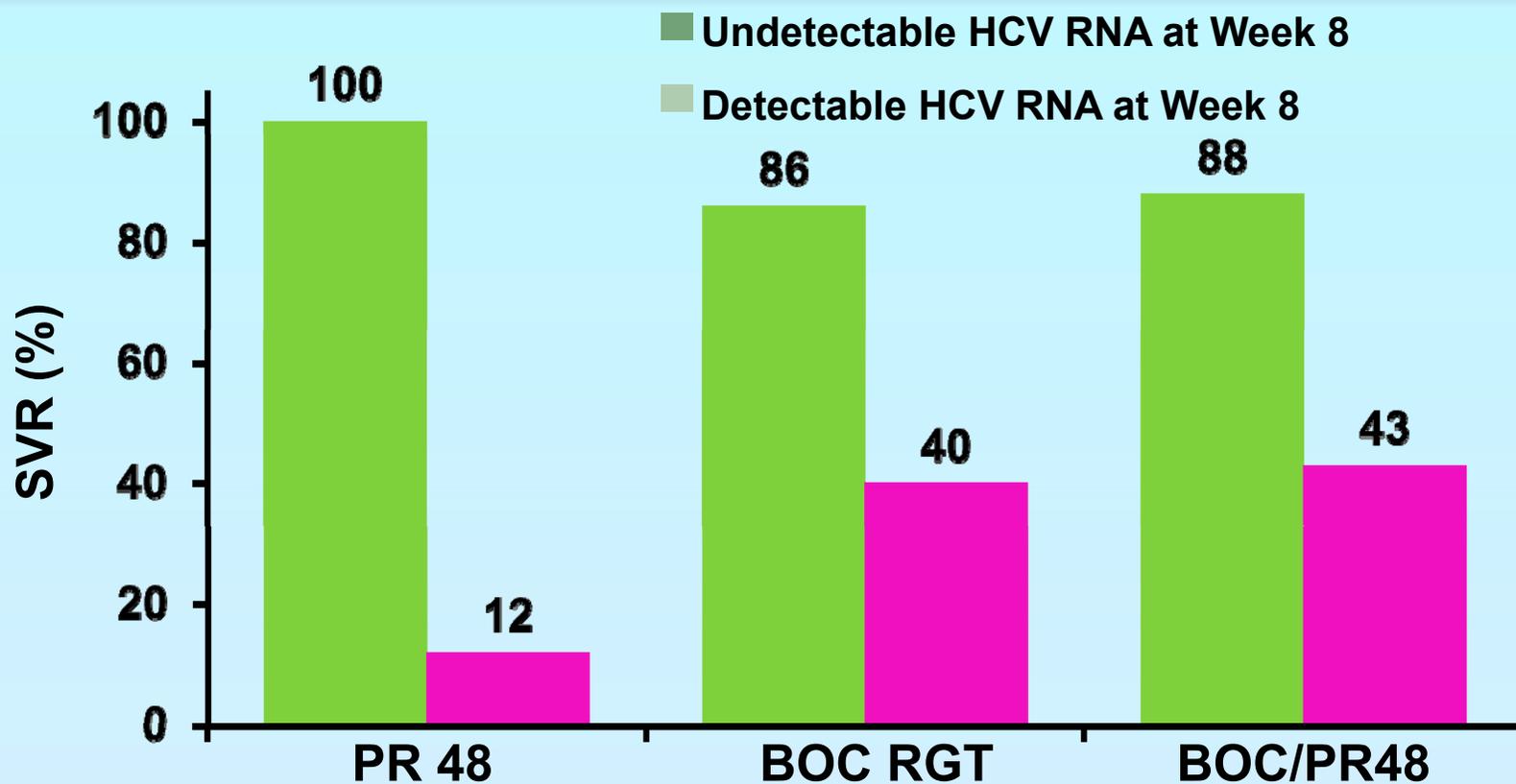
# RESPOND-2: SVR and Relapse Rates (ITT)



SVR rates in BOC RGT and BOC/PR48 arm not statistically different (OR, 1.4; 95% CI [0.9, 2.2])

12-week HCV RNA level used if 24-week post-treatment level was missing. A sensitivity analysis where missing data was considered as non-responder, SVR rates for Arms 1, 2 and 3 were 21% (17/80), 58% (94/162) and 66% (106/161), respectively.

# RESPOND-2: SVR by Week 8 HCV RNA Response (ITT)



- 46% of patients in the BOC RGT arm were eligible for shorter therapy
- ~6 times as many patients on BOC regimens (46%-52%) achieved undetectable HCV RNA at week 8 compared to control (9%)

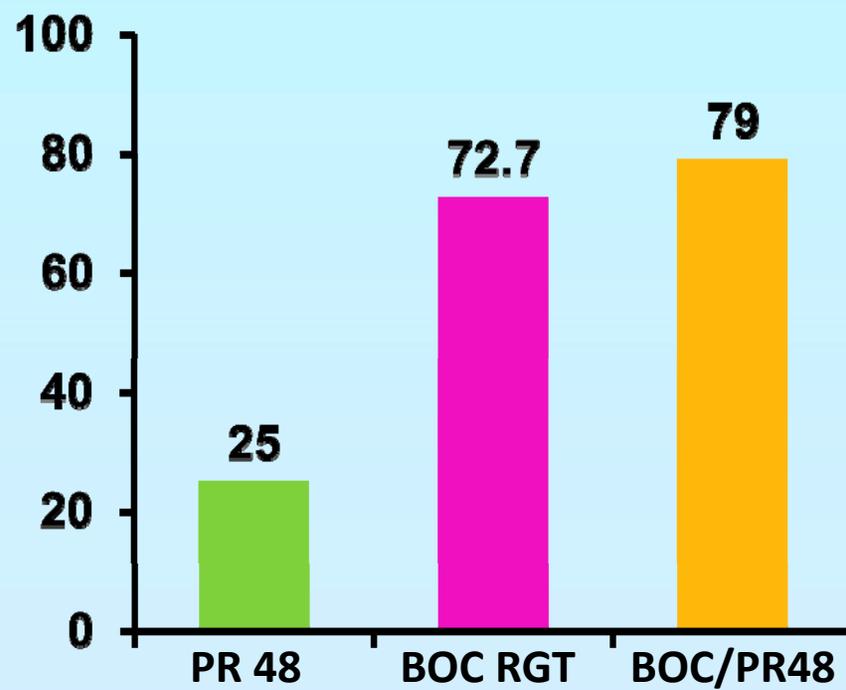
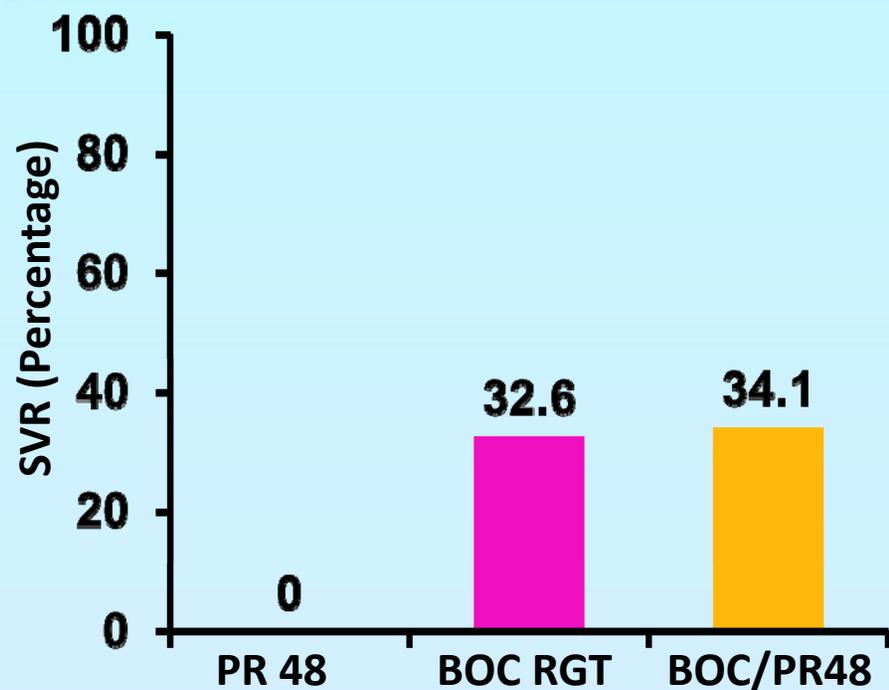
# SVR by Historical Response: Non-responders and Relapsers

	48 P/R	BOC RGT	BOC/PR48
<b>Non-responder, n/n</b>	2/29 (6.9%)	23/57 (40.4%)	30/58 (51.7%)
<b>Relapser, n/n</b>	15/51 (29.4%)	72/105 (68.6%)	77/103 (74.8%)

# RESPOND-2: SVR by Week 4 PR Lead-In Response

<1 log<sub>10</sub> Viral Load Decline

≥1 log<sub>10</sub> Viral Load Decline



# RESPOND-2: Adverse Events

Adverse Events (%)	PR48	RGT	BOC/PR48
Anemia	20	43	46
Dysgeusia	11	43	45

**No significant difference between arms in: Fatigue, headache, nausea, chills, influenza-like illness, myalgia, pyrexia, insomnia, dyspnea, pruritis, decreased appetite, alopecia, asthenia, cough, diarrhea, arthralgia, irritability, dry skin**

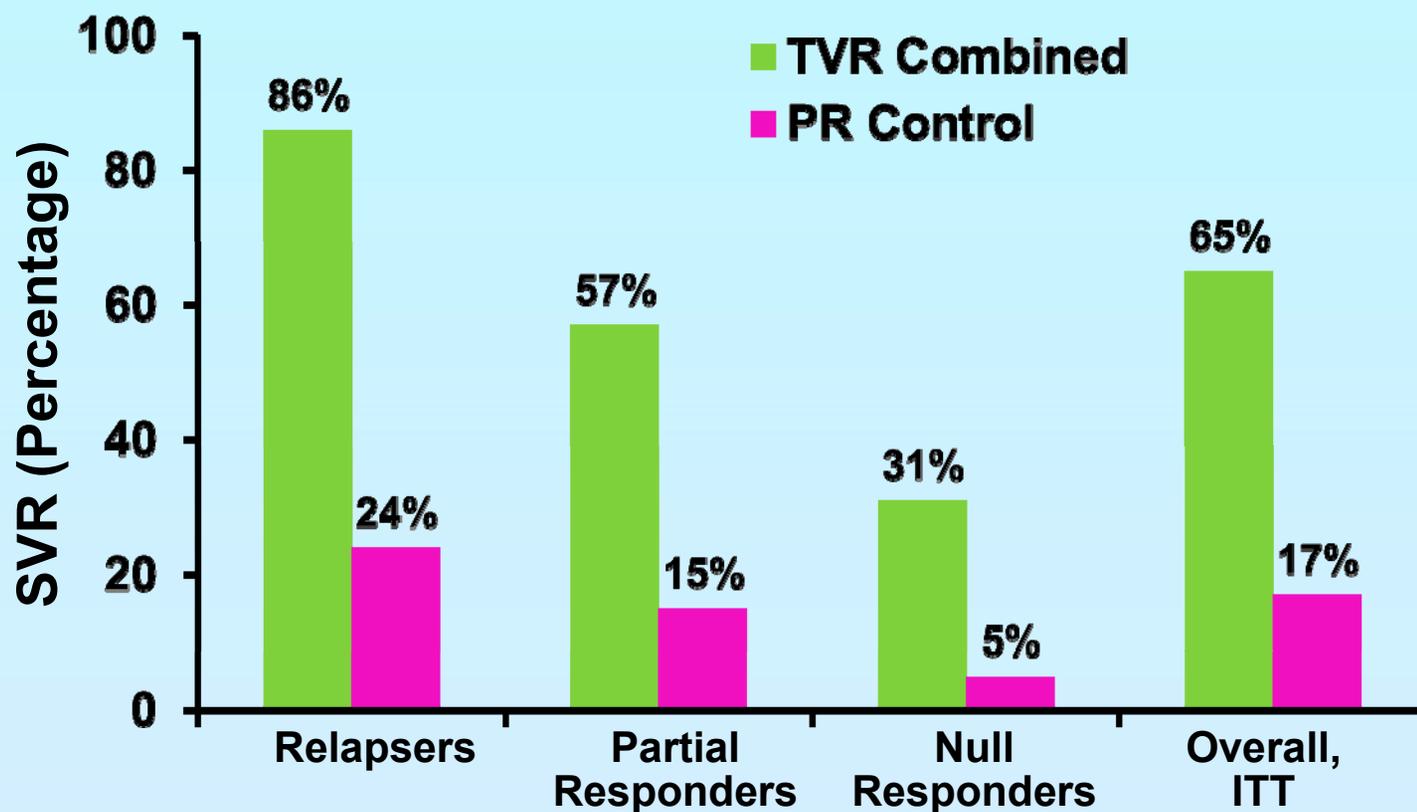
# REALIZE: Telaprevir in Genotype-1 Prior Nonresponders

	Weeks 0	4	12	16	48	72
<b>T12/PR48 (N=266)</b>	T + P + R		P + R			Follow-up
<b>T12(DS)/PR48 (N=264)</b>	P + R	T + P + R	P + R			Follow-up
<b>PR48 (N=132)</b>	P + R					Follow-up

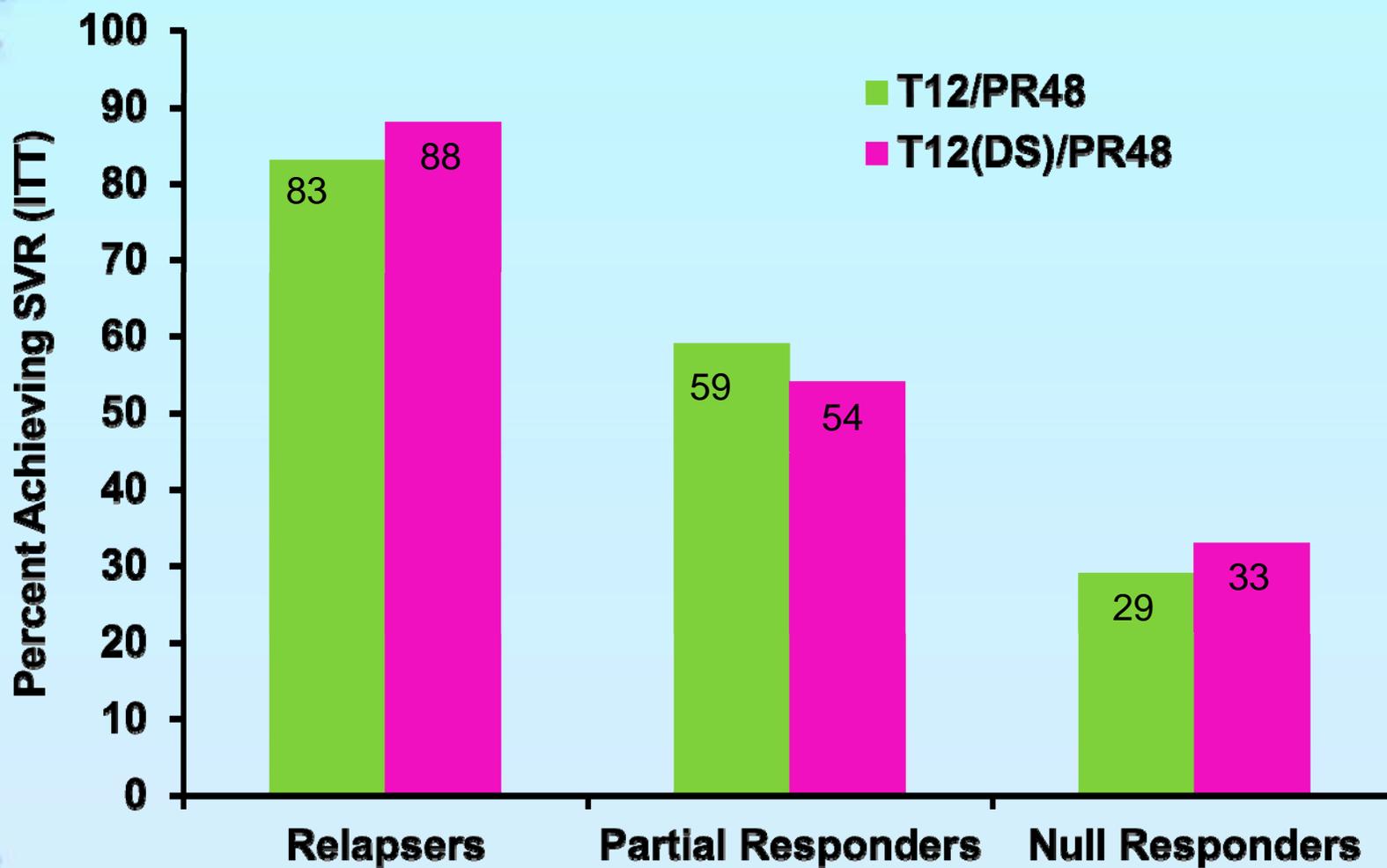
P = PegIFN  $\alpha$ -2a 180  $\mu$ g/week; R = Ribavirin 1000-1200 mg/d; T = Telaprevir 750 mg q8h.

Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00703118>. Accessed January 11, 2011.

# REALIZE: SVR by Prior Response



# REALIZE: Similar SVR in Simultaneous and Delayed Start TVR Arms



# REALIZE: Safety and Tolerability

- Most common AEs in order of frequency
  - Fatigue, pruritis, headache, rash, flu-like symptoms, nausea, and anemia
- Majority of AEs mild to moderate

## Discontinuation Rates of All Study Drugs Due to AEs

Adverse Event	Combined TVR Arms	Control
Any	4%	3%
Anemia	0.6%	0%
Rash	0.4%	0%

# Treatment-experienced

- Prior treatment response is an important factor
  - SVR rate: Relapser > partial non-responder > non-responder
- Lead-in with PegIFN/RBV indicates interferon responsiveness and likelihood of SVR
- Treatment regimens:
  - Telaprevir (12 weeks) + PegIFN + RBV for 48 weeks
  - Boceprevir (36 weeks) + PegIFN + RBV for 36 weeks (if HCV RNA undetectable at week 8) or 48 weeks

# Strategies to Minimize Risk of Viral Breakthrough

- Maximize adherence to all 3 drugs in the regimen
  - Thrice-daily dosing with protease inhibitors
- Multidisciplinary team, including pharmacists
- Aggressive management of side effects
- Careful assessment of viral response kinetics and application of “stopping rules” for protease inhibitors
  - Assess HCV RNA at treatment week 4 of protease inhibitor-based therapy
- HCV eradication = no resistance

# DRUG INTERACTIONS

- Contraindicated with drugs highly dependent on CYP3A4/5 for clearance
  - INCREASED TOXICITY of concomitant med
  - Potential for loss of Protease activity

MANY COMMON MEDS ARE IN THE  
Contraindicated, Not Recommended, or Use  
with Caution Categories.

# INDICATIONS

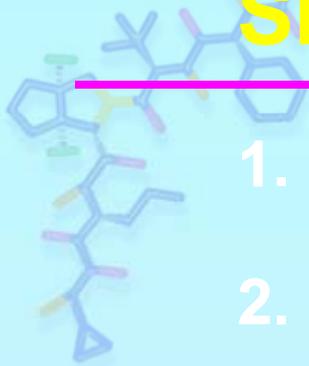
- Genotype 1 only (for now)
- Never as Monotherapy
- Prior Null responders will not have as robust of response
- Retreatment with other protease not recommended
- No HIV or transplant patients (for now)
- Compensated Liver Disease, treatment naïve or previously treated.

# DOSING

- Victrelis (boceprevir)
  - 800 mg (four 200 mg pills) 3 x daily (7-9 hours apart with light snack or meal)

## Incivek (telaprevir)

750 mg (two 375 mg tabs) 3x daily (7-9 hours apart with meal or snack containing 20 gms fat)



## Side Effects and AEs due to PEG/RBV

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1. PEGIFN: Flu-like symptoms
  2. PEGIFN: Mood alteration (depression, SI/SA)
  3. PEGIFN: Autoimmune reactions (thyroid, other)
  4. PEGIFN: Leucopenia and thrombocytopenia
  4. PEGIFN: Infection risk (especially in pts with cirrhosis)
  5. RBV: Hemolytic anemia
  6. RBV: Rash, mucosal irritation
  7. Black box warnings
- 



# Side Effects and AEs due to Protease Inhibitors

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1. TPV: Rash (management protocol/strategy)
  2. TPV: Anemia (transient, usually not requiring EPO)
  3. TPV: Anal pain
  4. BCP: Anemia (may require EPO)
  5. BCP: Dysgeusia
-

# SAFETY

- Same rules as applied to Interferon/RVN
- PAY ATTENTION TO DRUG -DRUG INTERACTIONS
- FUTILITY RULES
- WEEK 4, 12:  $> 1000$  IU (Incivek)
- Week 12:  $> 100$  IU (Victrelis)
- Week 24: Any detectable virus (Both)

# Hepatitis C: The Perfect Storm



# Hepatitis C: “The Perfect Storm”

- Affects over 4 million Americans
- Major cause of Hepatocellular Carcinoma, Cirrhosis, and Liver Failure
- Population with HCV aging, presenting with more advanced disease
- New treatments promising, but increasingly complex to use and difficult to tolerate
- Very high cost of treatment

# Hepatitis C: “The Perfect Storm”

- Large percentage of patients on public insurance
- Number of experienced “treaters” inadequate and expected to diminish
- Availability of new therapies expected to cause many more patients to seek treatment
- Lack of public awareness and disease advocacy

# Hepatitis C:

- Stakeholders need to consolidate efforts to raise awareness and develop advocacy
- Stakeholders: Patients, Physicians, Pharmaceutical Companies, Hospitals and Healthcare Organizations, Government
- Programs to train providers to properly treat HCV
- Optimize role of NP/PA and/or PCP
- HIV treatment model?

# Thank you!

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