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# Hepatitis C Choices in Care

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## Future of Western Management of Hepatitis C

Robert Gish, MD

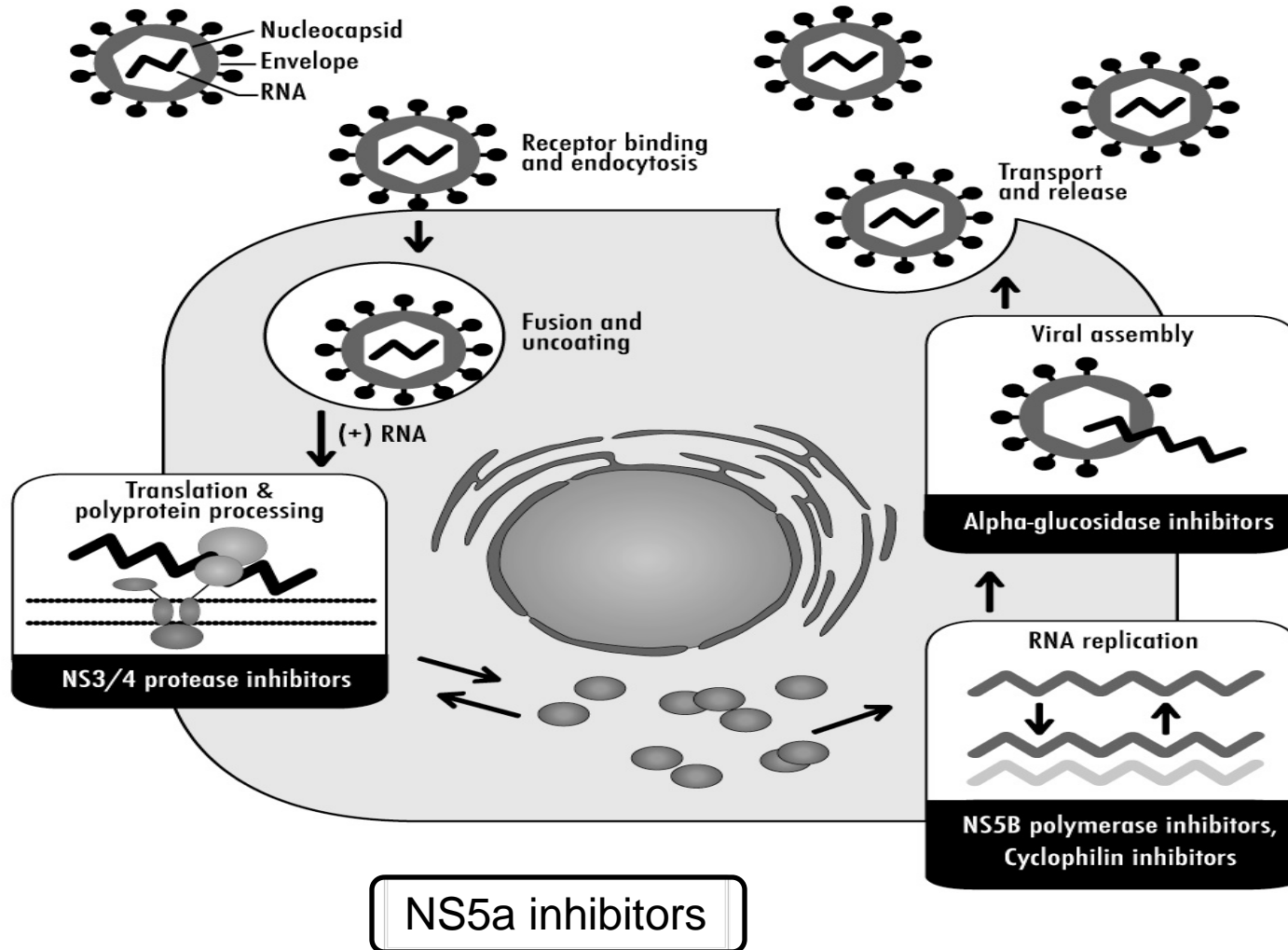


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# New Therapy Reality

- Pegylated interferon alpha will remain the platform for all hepatitis C therapy for the foreseeable future
- No FDA approved small molecule therapy, without interferon base, for at least 3 years and maybe longer

# HCV: “Drugable” Targets



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# New Therapies

Oral drugs (known as direct-acting antivirals, or DAAs) that specifically target certain steps in the hepatitis C virus life cycle are in late-stage development.

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# New Therapies

- HCV-specific protease inhibitors will be the first DAA class available.
  - Protease inhibitors block cleaving of viral proteins

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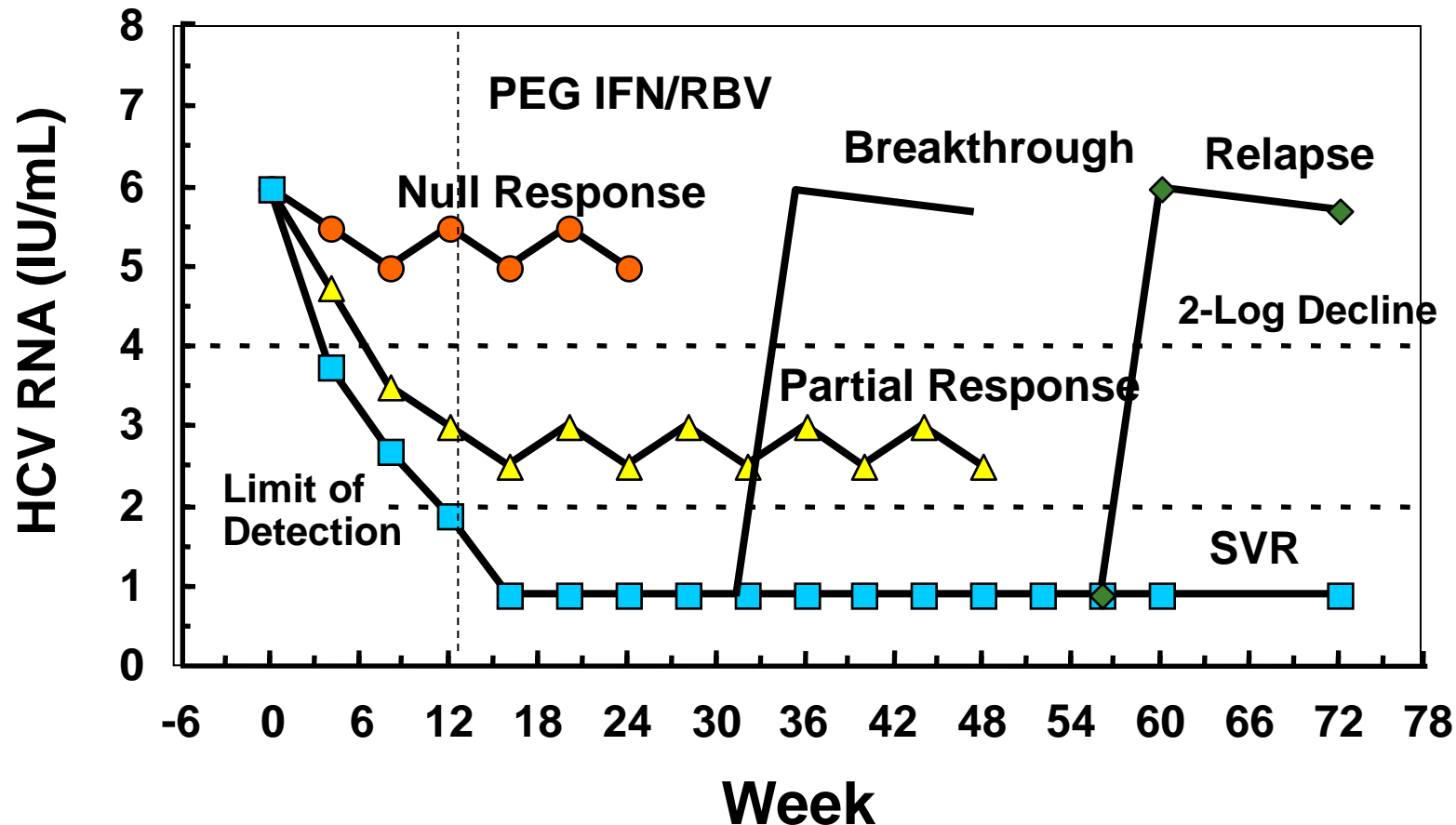
# New Therapies

- Nucleoside and nucleotide polymerase inhibitors
- Non-nucleoside polymerase inhibitors
- NS5a inhibitors
- Novel Interferons
- Other Immune Modulators
- Anti-fibrotics

For a complete list of drugs in the HCV pipeline visit:

<http://www.treatmentactiongroup.org/publication.aspx?id=3798>

# Definitions of Response to Anti-HCV Therapy



# Definitions of Response to Anti-HCV Therapy

- **Relapse**

HCV RNA becomes and remains undetectable during treatment but reappears after treatment is stopped.

- **Non-response**

HCV RNA drops by two logs but never becomes undetectable

- **Null response**

HCV RNA drops less than one log after four weeks and less than two logs after 12 weeks of treatment

- **Viral breakthrough**

HCV RNA reemerges after it becomes undetectable while on treatment

# Definitions of Response to Anti-HCV Therapy

- **Very rapid virological response (vRVR)**  
HCV RNA becomes undetectable after 14 days of treatment
- **Rapid virological response (RVR)**  
HCV RNA becomes undetectable after 4 weeks of treatment
- **Extended rapid virological response (eRVR)**  
HCV RNA becomes undetectable after 4 weeks of treatment and remains undetectable at week 12
- **Partial early virological response (pEVR)**  
HCV RNA drops by at least 2 logs at week 12

# Definitions of Response to Anti-HCV Therapy

- **Complete early virological response (cEVR)**  
HCV RNA remains undetectable after 12 weeks of treatment
  - **End-of-treatment response (EOT)**  
HCV RNA remains undetectable at the end of treatment
  - **Slow Virologic response (SR)**  
2 log drop at week 12 and HCV RNA negative at week 24
  - **Sustained virological response (SVR)**  
No HCV RNA detectable 6 months after completion of treatment
- **Cure**

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# Clinical Trial PHASE I

Looks at: safety & activity

- **Dose** (what is maximum tolerated dose)
- **Pharmacokinetics** (how much drug gets in, & how long it lasts)
- **Small & short-term** (monotherapy for 2 days to 2 weeks)

Phase Ia - Healthy volunteers

Phase Ib - People w/ HCV



# Clinical Trial PHASE II

Looks at: safety & efficacy (capacity to produce a certain effect, such as SVR)

- 12- 48 weeks of treatment, plus follow up
- Larger (>100 people)
- Randomized
- SVR is primary endpoint; RVR &/ or EVR are co-primary endpoints

Often used to choose dose and duration

Not a good idea to leap to conclusions about results, as these are too small--but can inform design of phase III

(example: 44% SVR rate in African Americans with SOC + an HCV protease inhibitor--based on 10% of study population--or 18/27 people)

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# Clinical Trial PHASE III

Looks at: safety & efficacy

- Effectiveness (a measure of the accuracy or success of a diagnostic or therapeutic technique when carried out in an average clinical environment)
  - Randomized
  - Surrogate (or clinical) endpoints
  - Large (can be 1000's of people)
  - Used to license medications

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# Clinical Trial PHASE IV

## **post-approval;**

- Diverse populations
- Long-term effectiveness & toxicities
- Treatment strategies

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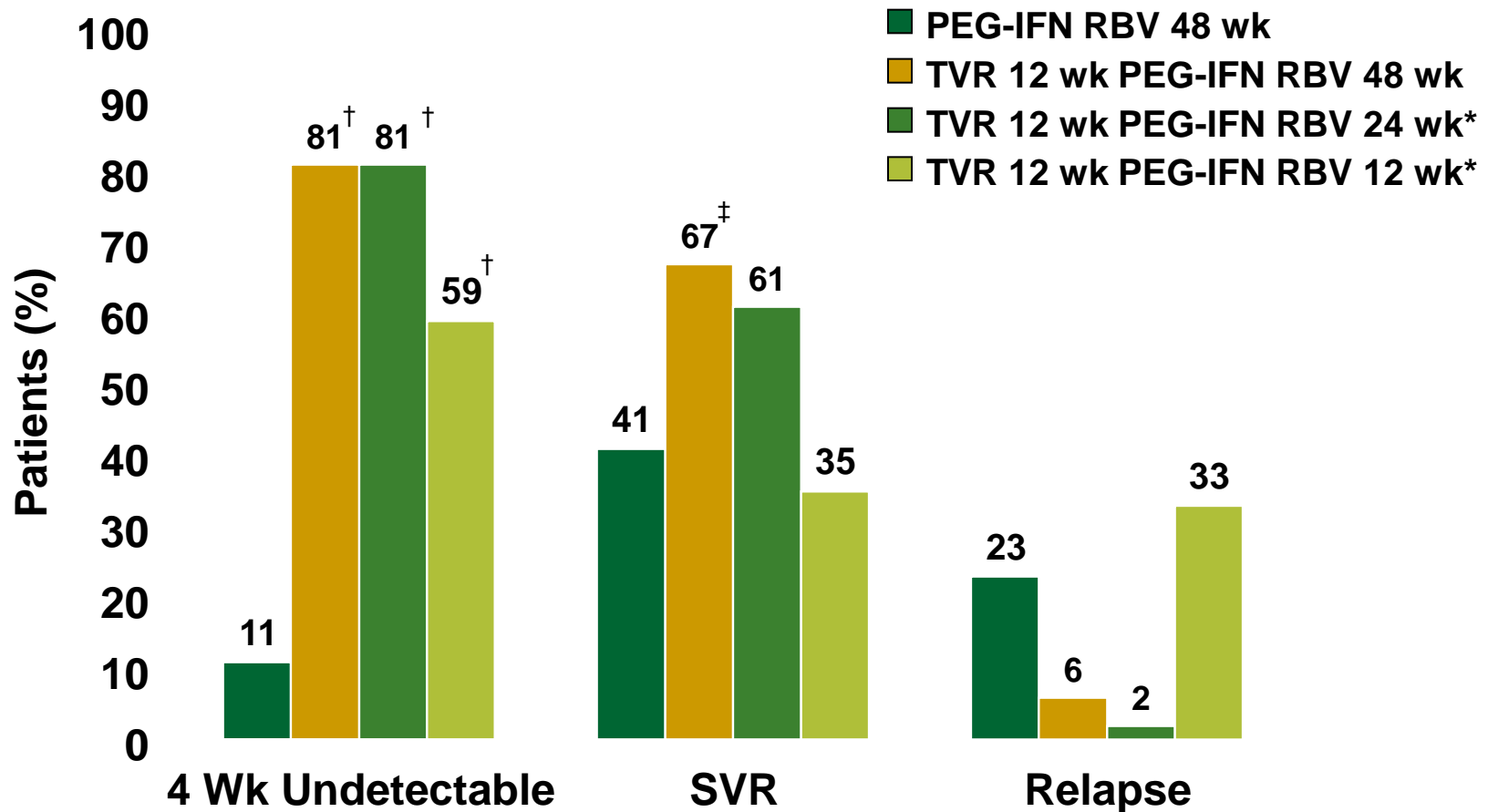
# Risks & Benefits of Trial Participation

**PHASE I**: high-risk (toxicity, risk of incorrect dose/resistance)

**PHASE II**: if you can take a risk, it might be a good idea

**PHASE III**: safer entry point; more is known about the drug & dose

# PROVE 1 Phase II: Response Rates (ITT)



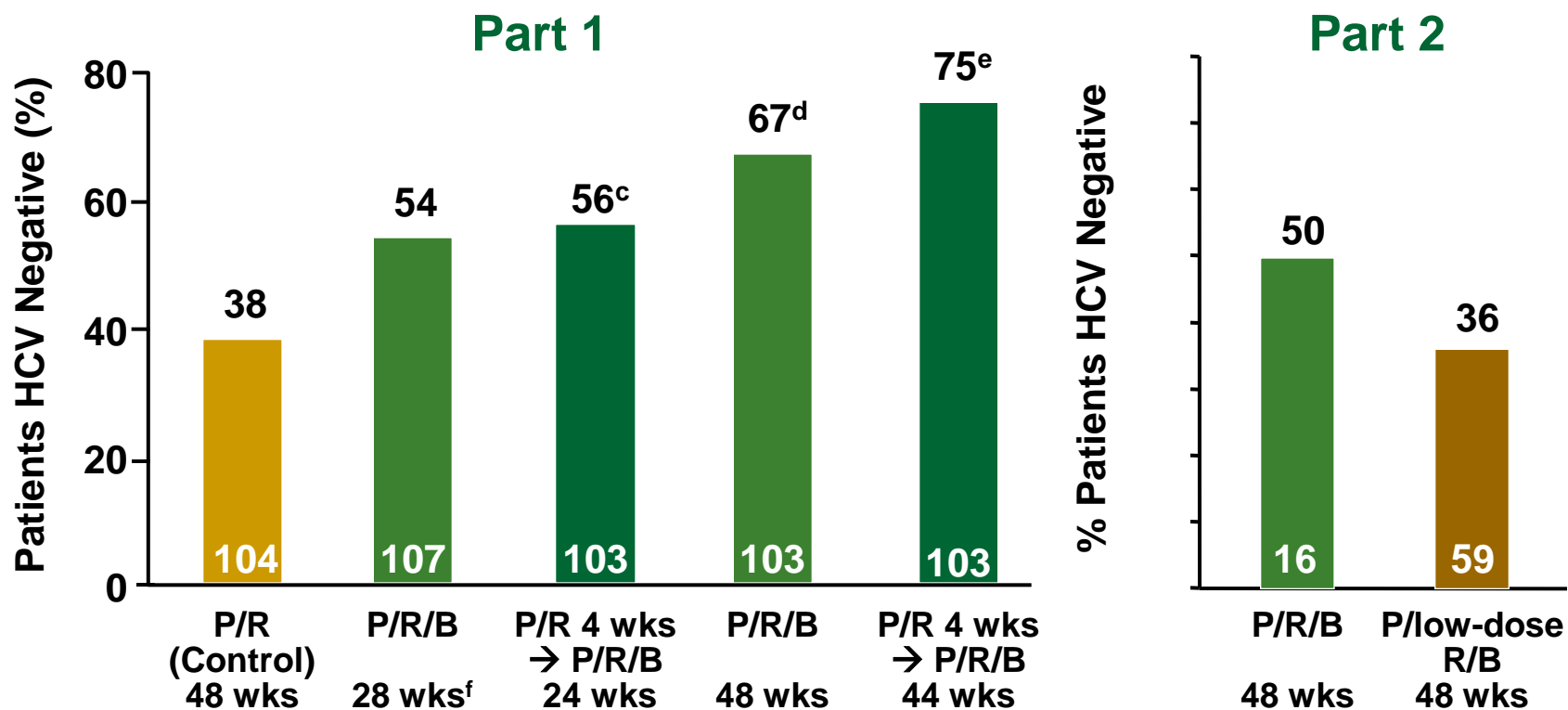
\*Patients stopping therapy at 12 and 24 weeks had achieved a RVR;

† $P=0.001$  vs control; ‡ $P=0.02$  vs control

McHutchison JG, et al. N Engl J Med. 2009;360(18):1827-1838.



# Boceprevir: Phase II Sustained Virologic Response<sup>a</sup>



P=PEG-IFN alfa-2b; R=RBV; B=boceprevir

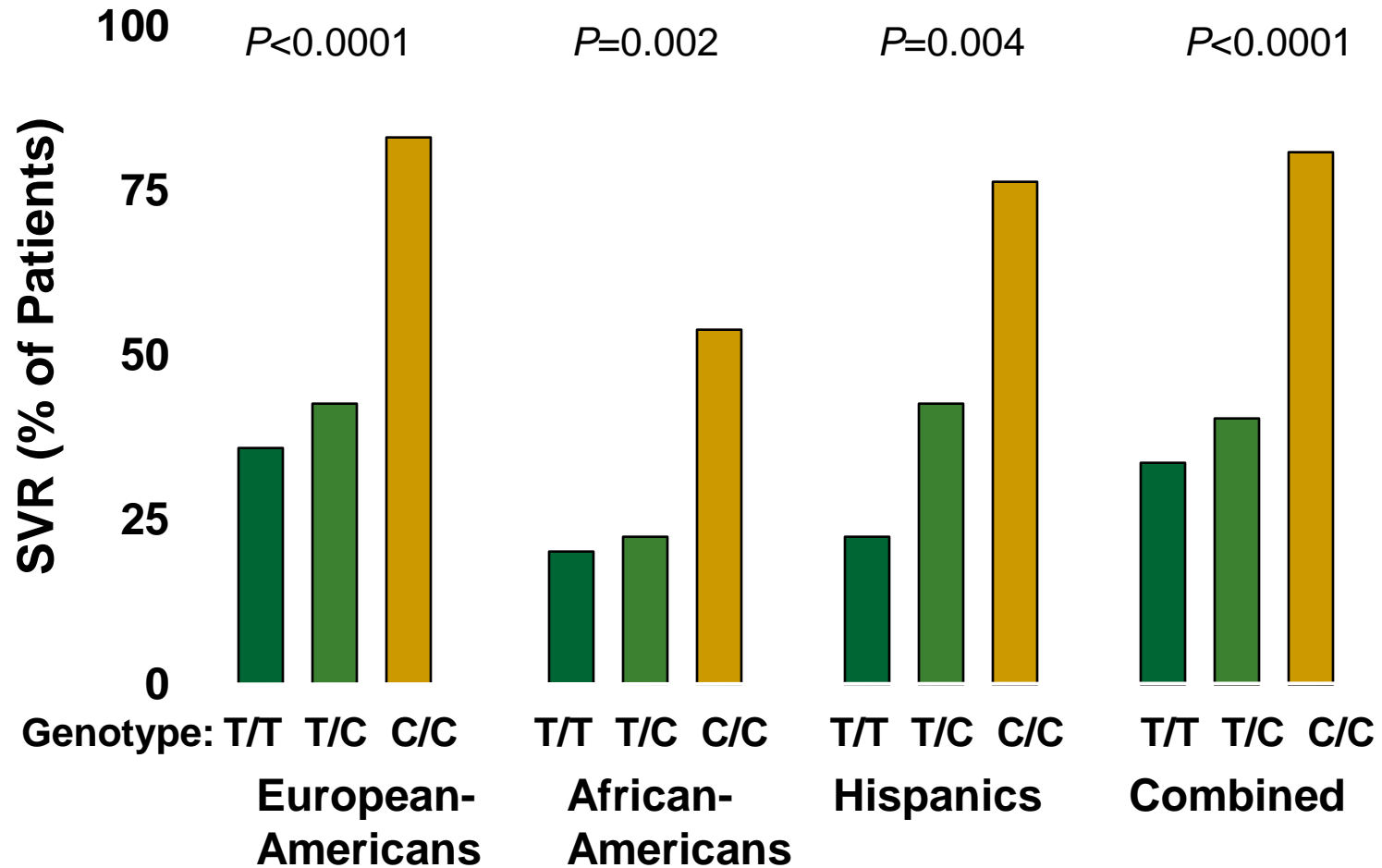
<sup>a</sup>Roche COBAS TaqMan LLD <15 IU/mL; <sup>b</sup>P=0.013; <sup>c</sup>P=0.005; <sup>d</sup>P<0.0001; <sup>e</sup>P<0.0001 compared to P/R Control;

<sup>f</sup>1 late relapser after follow-up week 24, not included n SVR

Kwo PY, et al. (AASLD Abstract 1582). *Hepatology*. 2009;50(S4):1035A.

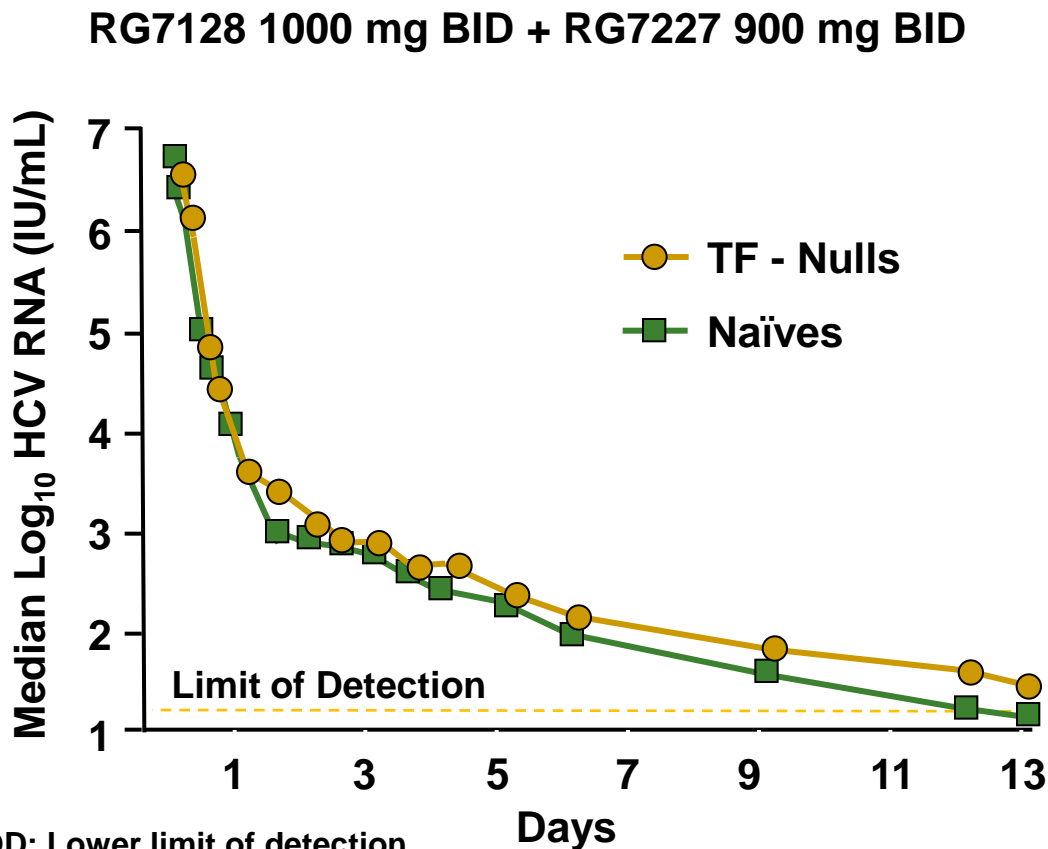


# SVR Influenced by *IL28B* Genotype

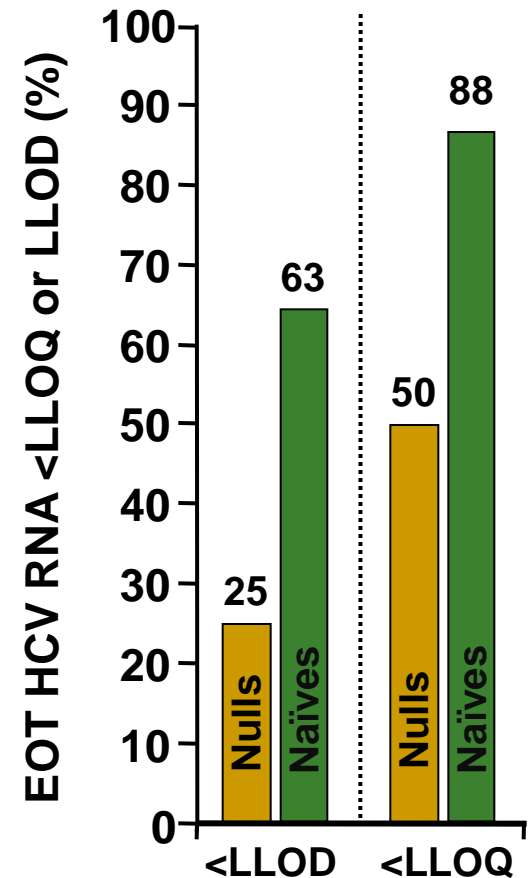


# INFORM-1: No Inteferon !

## Antiviral Activity in HCV G1 Interferon-Naïve and Null Responders with a BID Regimen of RG7128 + RG7227



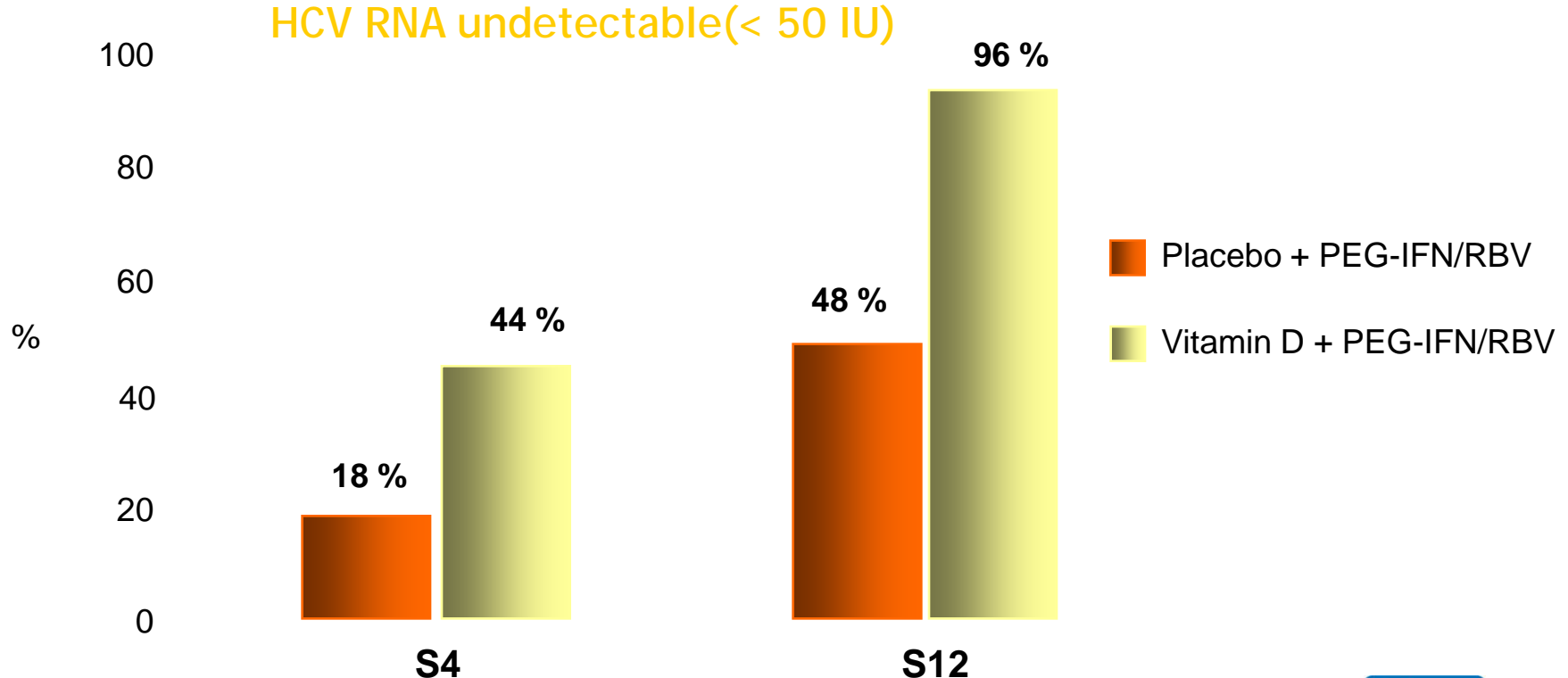
LLOD: Lower limit of detection  
LLOQ: Lower limit of quantification



# Vitamin D: Impact on virologic response

Randomized Study, 58 patients G1, treatment naïve

- PEG-IFN $\alpha$ -2b (1.5 mcg/kg) + RBV (1000-1200 mg) + Vit D (1000-4000 IU)  
(27 patients, median age 47, 50 % male, 55 % > F2)
- PEG-IFN $\alpha$ -2b (1.5 mcg/kg) + RBV (1000-1200 mg) + placebo  
(31 patients, median age 49, 60 % male, 18 % > F2)



# Graveyard for HCV Compounds is Filling Up Quickly!

**ISIS 14803**  
(Antisense)

**UT-231B**  
(Imino sugar)

**Heptazyme**  
(Ribozyme)

**Viramidine**  
(RBV analogue)

**Idenix compounds**  
2010



**BILN 2061**  
(Protease)

**JTK-003**  
(Polymerase)

**HCV-796**  
(Polymerase)

**NM-283**  
(Polymerase)

**R803**  
(Polymerase)

**CPG 10101**  
(TLR  
agonist)

**ACH-806/GS-  
9132**  
(NS4a)

**R7025**  
(Interferon-alpha )

**R1626**  
(polymerase)



# To Treat or not to Treat:

## A Constellation of Considerations

Genotype virus  
Genotype Patient (IL28)

Histologic stage  
20%+ life time risk  
Of cirrhosis

Duration of  
infection

Personal plans  
(marriage,  
pregnancy)

Age

Family and other  
support

Patient  
"mindset"

ALT

Occupation

Extrahepatic  
Features  
(Fatigue, EMC, PCT)

HIV coinfection

Contraindications  
& comorbidities  
Insulin Resistance

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# HCV Therapy – the bottom line

- No new agent before 2011
- All new therapies will be used in combination with PEG-IFN for the foreseeable future (2015)
- Ribavirin will still need to be used
- Combination therapy required with new DAA due to rapid development of resistance

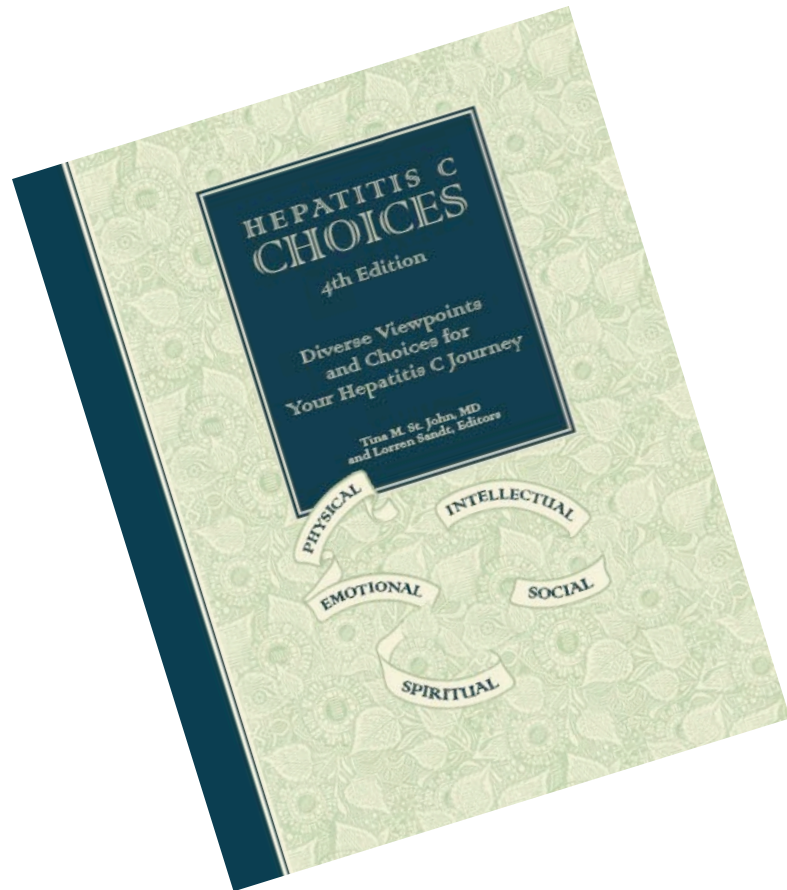
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# HCV Therapy – the bottom line

**Adherence is critical!**

**Successful HCV treatment must rapidly—and fully—suppress hepatitis C virus, & keep it *completely suppressed* throughout the course of treatment (12-72 weeks)**

# For more information



## 8: Western (Allopathic) Medicine Section 4: Future of Allopathic Hepatitis C Treatment

[http://www.hepcchallenge.org/choices/pdf/Chapter\\_08\\_04\\_OL.pdf](http://www.hepcchallenge.org/choices/pdf/Chapter_08_04_OL.pdf)

Visit us on line at [www.HepCChallenge.org](http://www.HepCChallenge.org)