

HCV Treatment, Screening and Monitoring: 2012-2015

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Professor

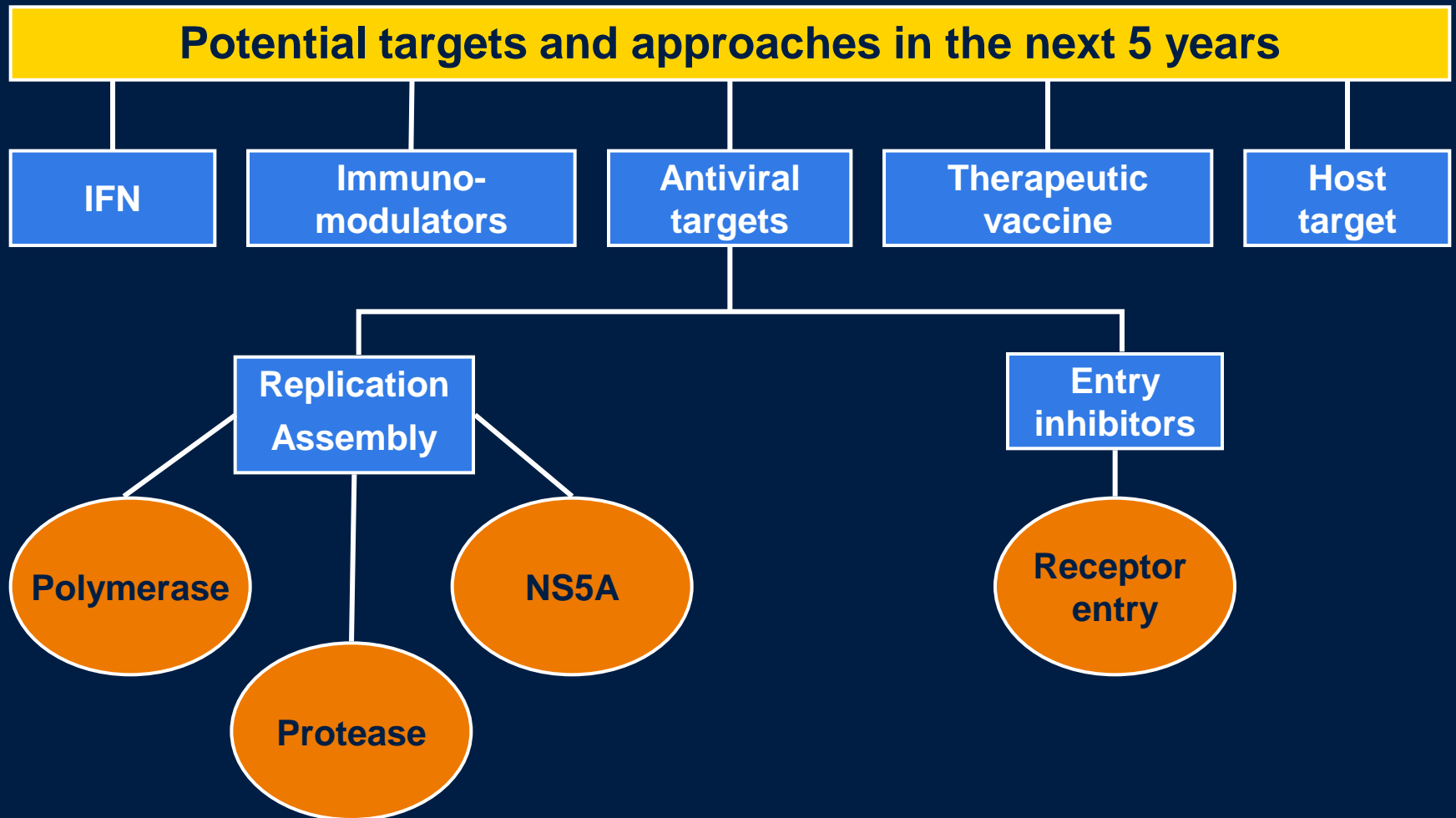
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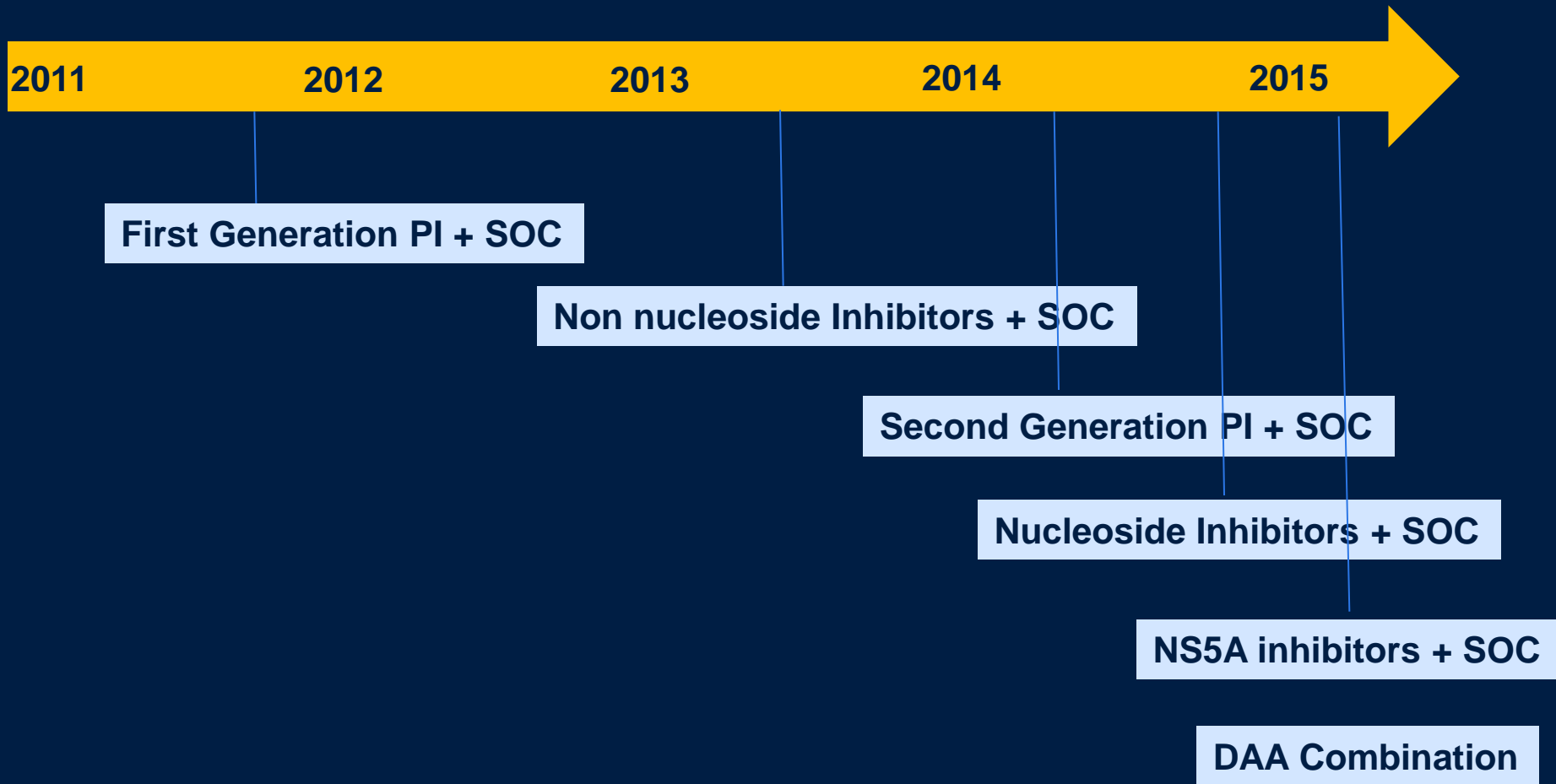
Outline

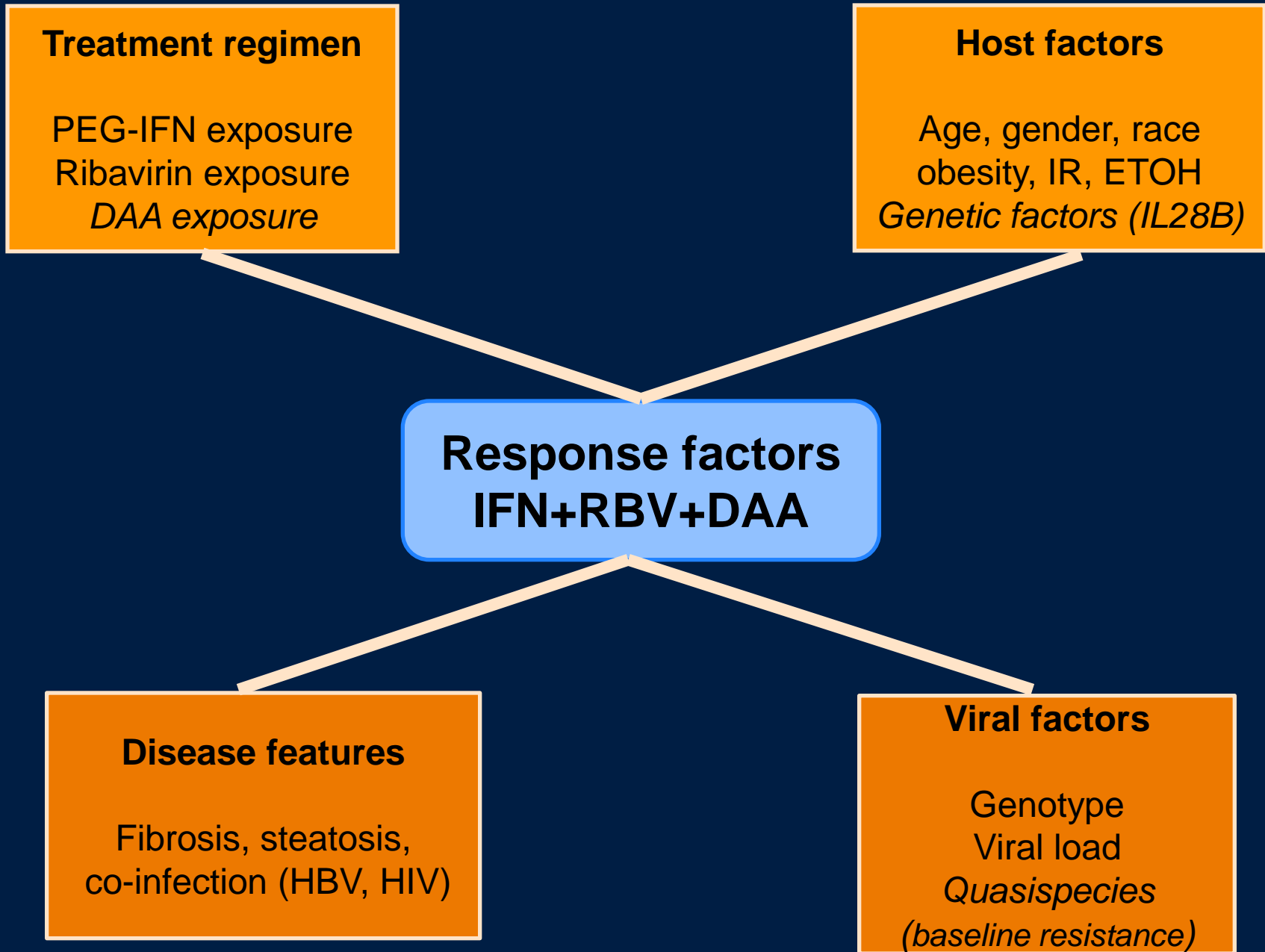
- **Therapeutic targets and timelines**
- **Host and viral factors that determine response**
- **Resistance impact and management strategies**
- **Response guided therapies**
- **Adverse events**
- **Treatment paradigms 2012-2015**

Potential Antiviral Targets and Approaches (2012-2015)



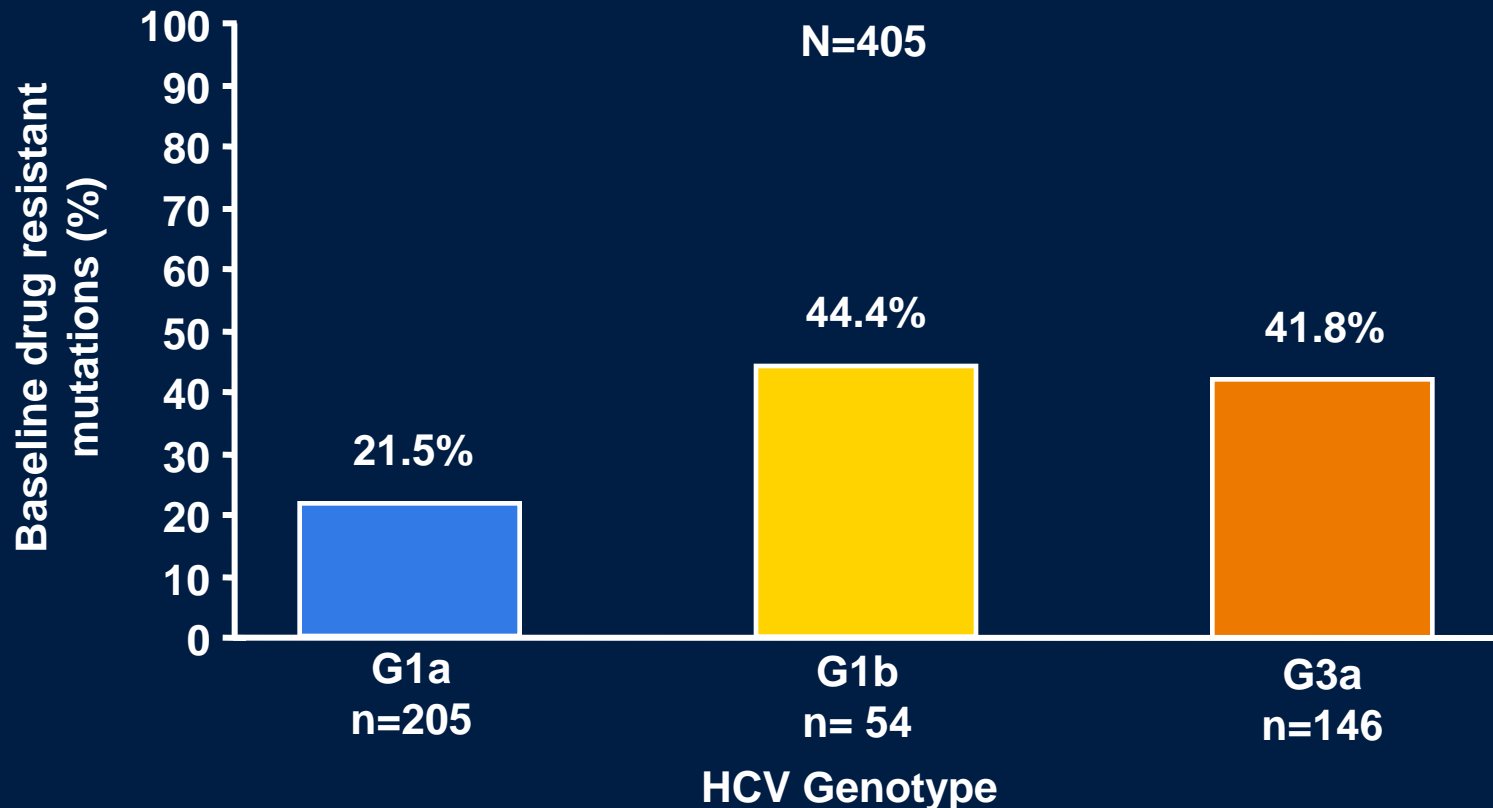
Timeline Assumptions For Direct Acting Antivirals (DAA)



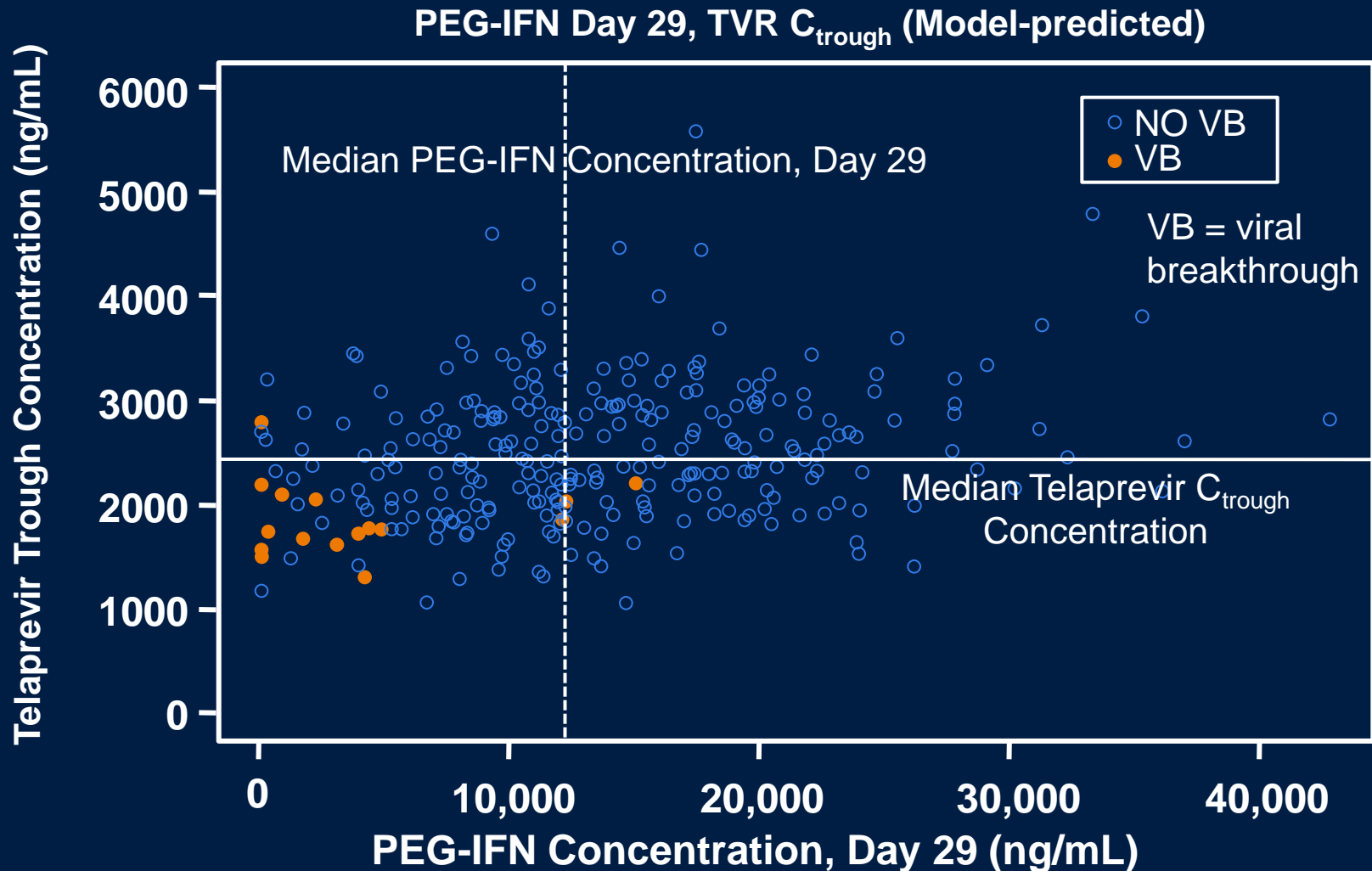


High Levels of Baseline Viral Mutations Exist in Treatment-naïve Patients

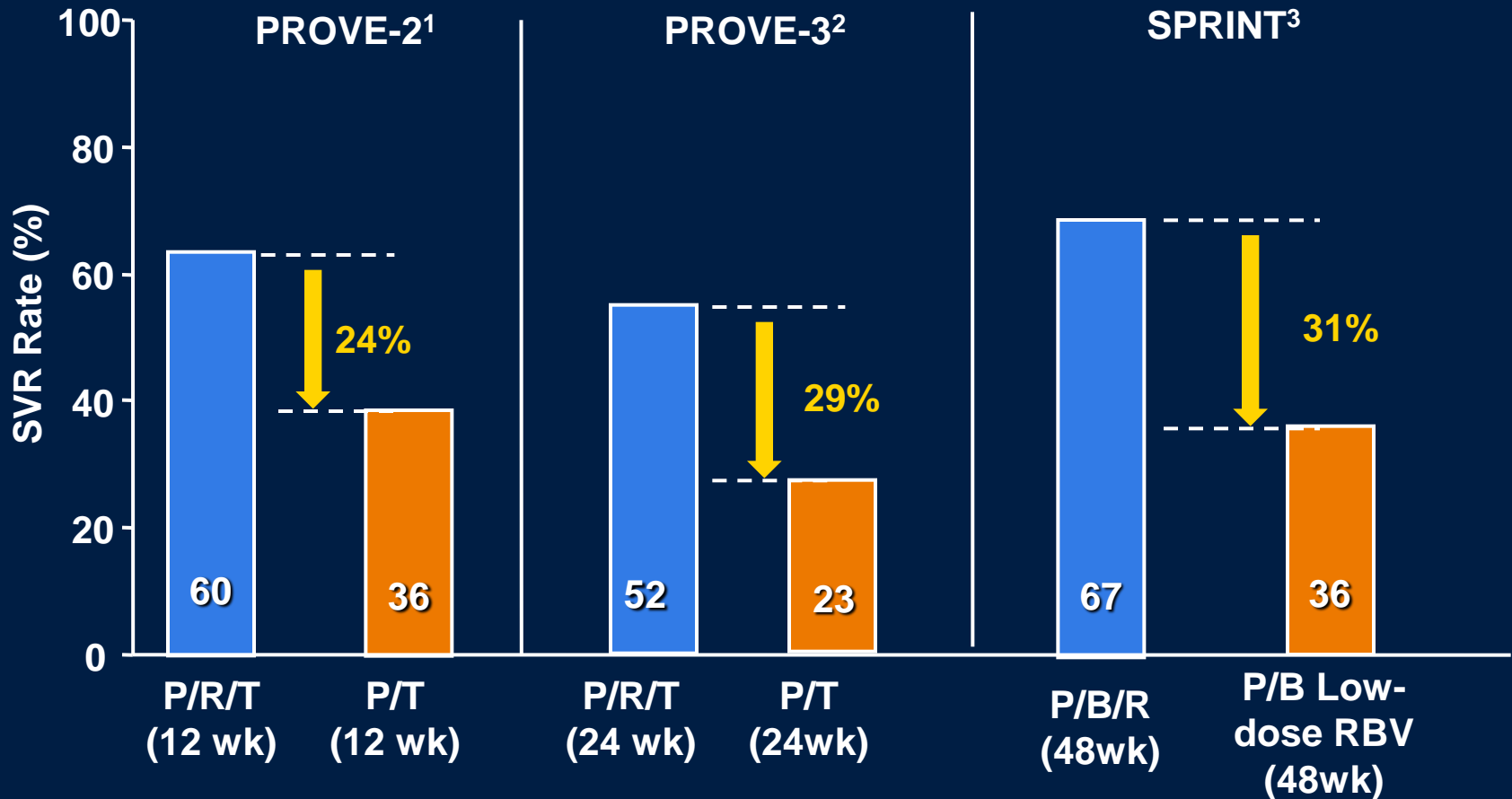
At baseline, drug resistance mutations in the NS3 protease or NS5B polymerase to a panel of 27 drugs in development were identified in a significant number of patients (5-9 % for Gen 1a)



Resistance Emergence Associated with Low IFN and Protease Troughs



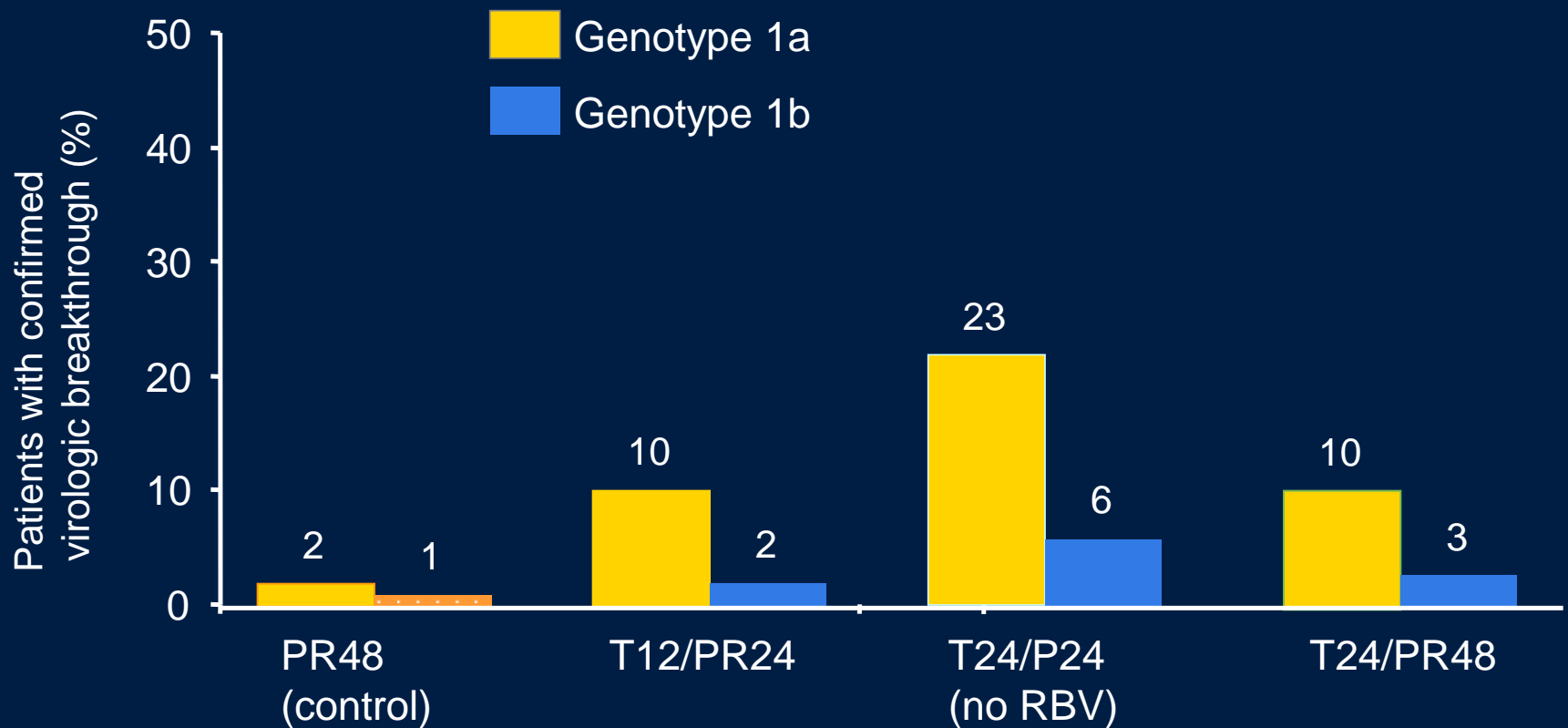
RBV is Critical for Protease Inhibitor Combination Therapy



P: PEG-IFN; R: Ribavirin; T: Telaprevir; B: Boceprevir

¹Hezode C, et al. *N Engl J Med.* 2009;360(18):1839-1850. ²Manns M, et al. (*Abstract 1044*). Presented at: European Association for the Study of the Liver. Copenhagen, Denmark; April 23-26, 2009. ³Kwo P, et al. (*Abstract 4*). Presented at: European Association for the Study of the Liver. Copenhagen, Denmark; April 23-26, 2009.

PROVE3: Virologic Breakthrough Impact of RBV and Viral Subtype



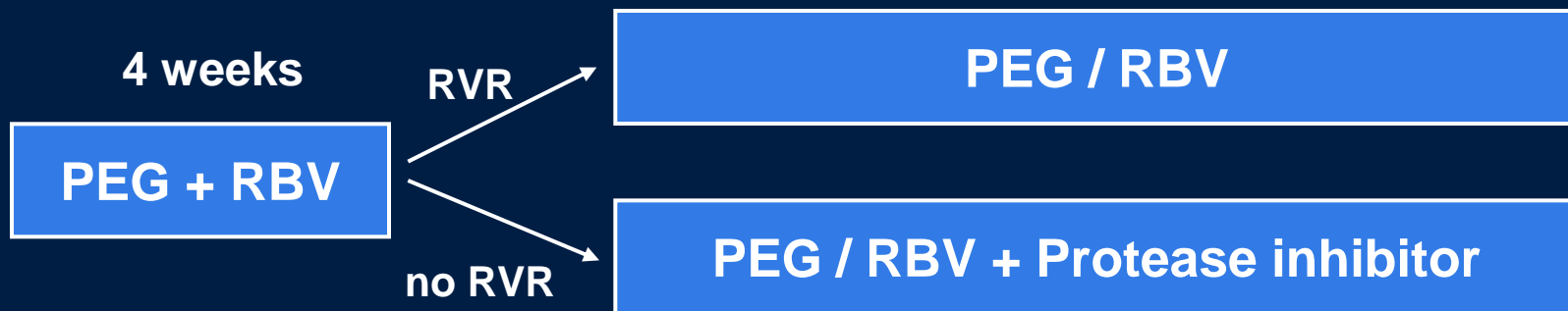
Resistance Will Impact Future Therapy

- **Pre-existing resistant variants to protease and nonnucleoside inhibitors are common**
 - Pretreatment evaluation (?)
 - On treatment monitoring
 - Viral load change
- **Barrier to resistance can be subtype dependent**
 - Subtyping will enter clinical practice
 - Adequate subtyping methodology
- **Strategies to limit resistance**
 - Optimize pK:
 - PEG (lead-in, choice and dose of IFN)
 - RBV (lead-in, use of growth factors)
 - DAA (dose, schedule, ritonavir boosting)
 - **Combination approaches**

Rationale for Lead-in Arm PEG-IFN or PEG-IFN + RBV

Cost-effective model (“Obama plan”):

- Identify IFN-sensitive patients who may not need DAA
 - Prevent additional adverse events, save costs, limit resistance risk



- Can we predict lead-in response by baseline factors
 - IL 28B CC genotype, viral load, fibrosis, etc....

Rationale for Lead-in Arm

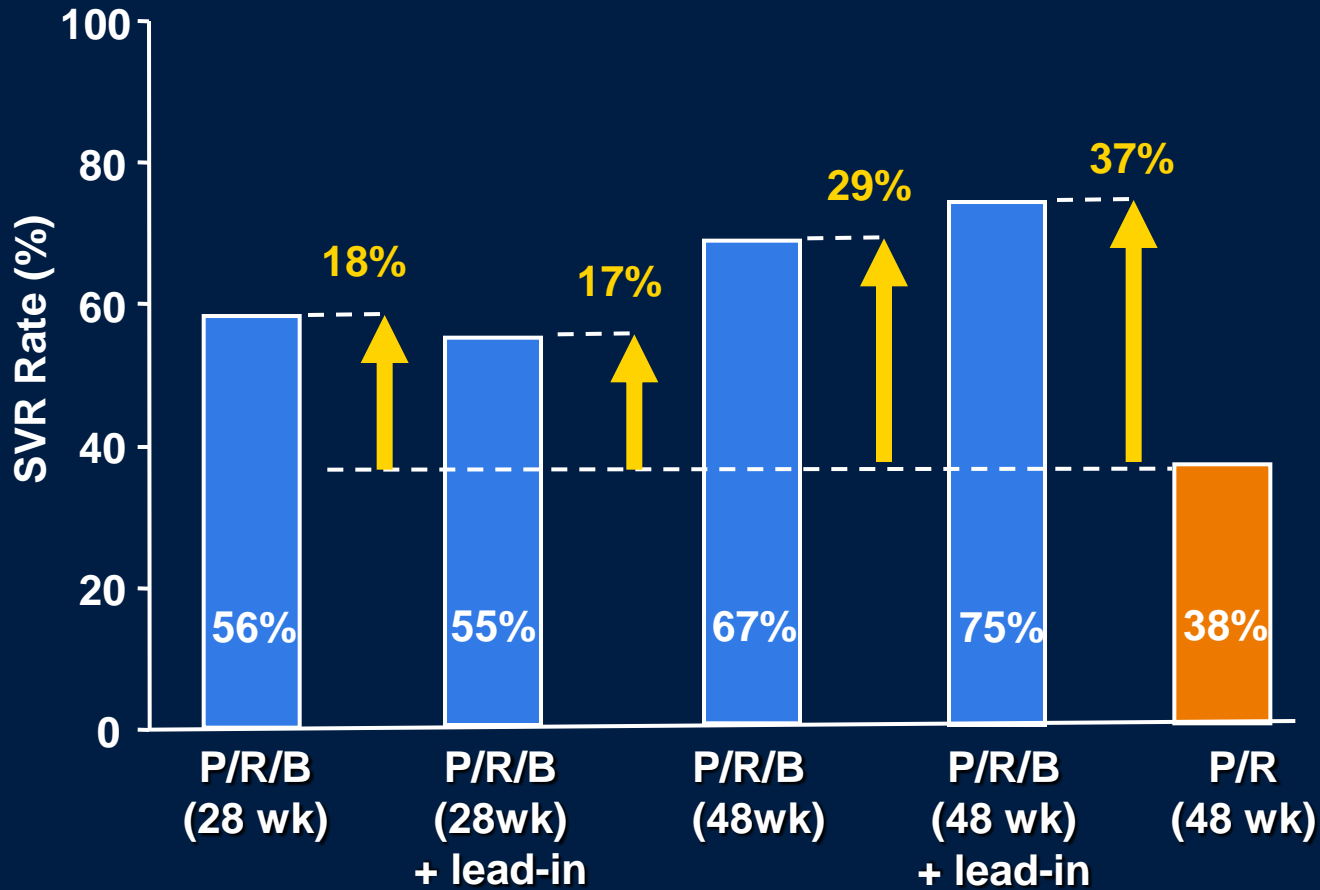
PEG-IFN or PEG-IFN + RBV

Optimization of DAA model:

- Decrease viral resistance development at time of protease introduction by:
 - Allowing a steady state of IFN and/or RBV to occur
 - Decreasing viral level



Impact of 4 Week Lead-in SPRINT-1

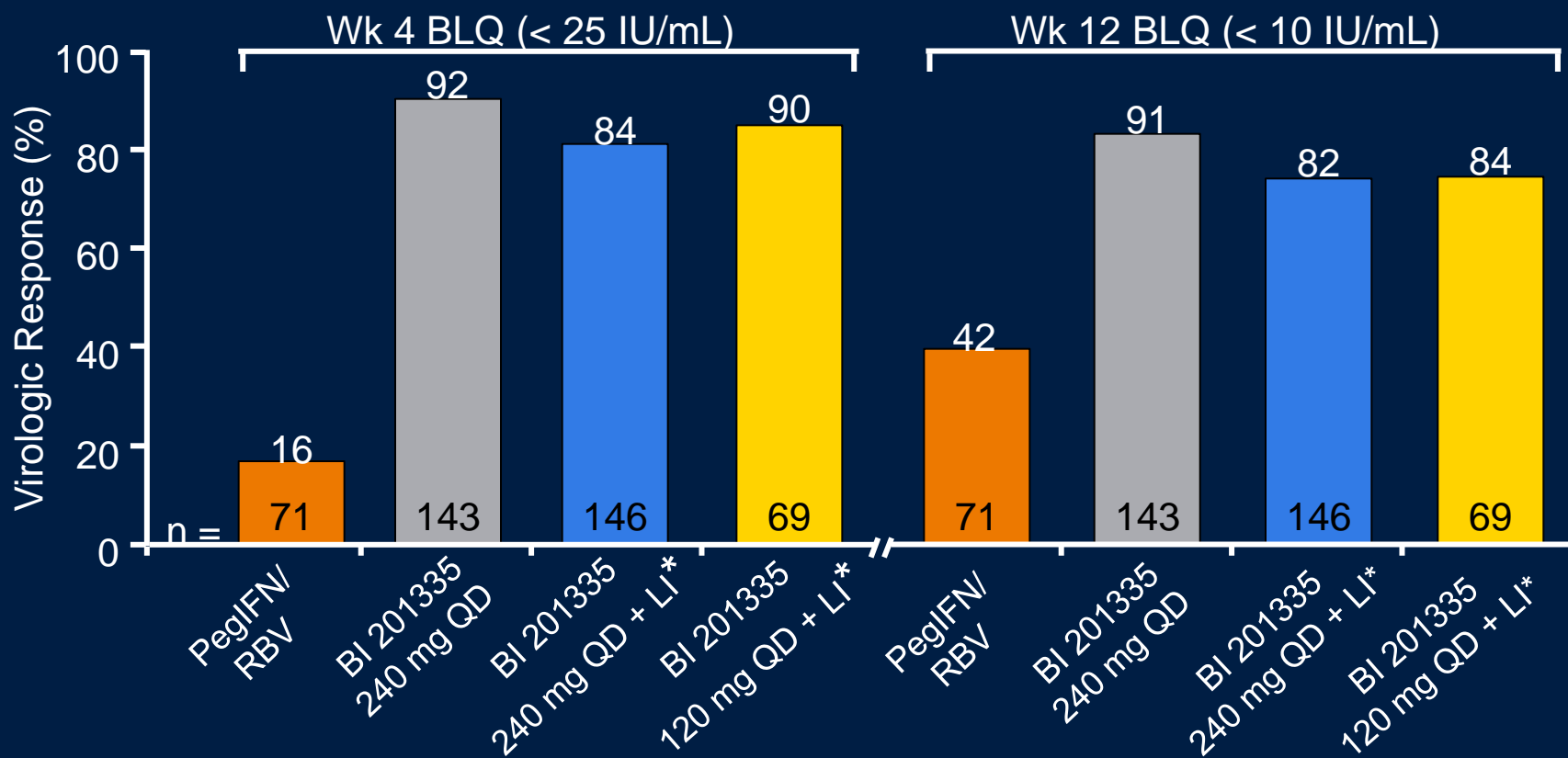


P: PEG-IFN; R: Ribavirin; B: Boceprevir

SILEN-C1

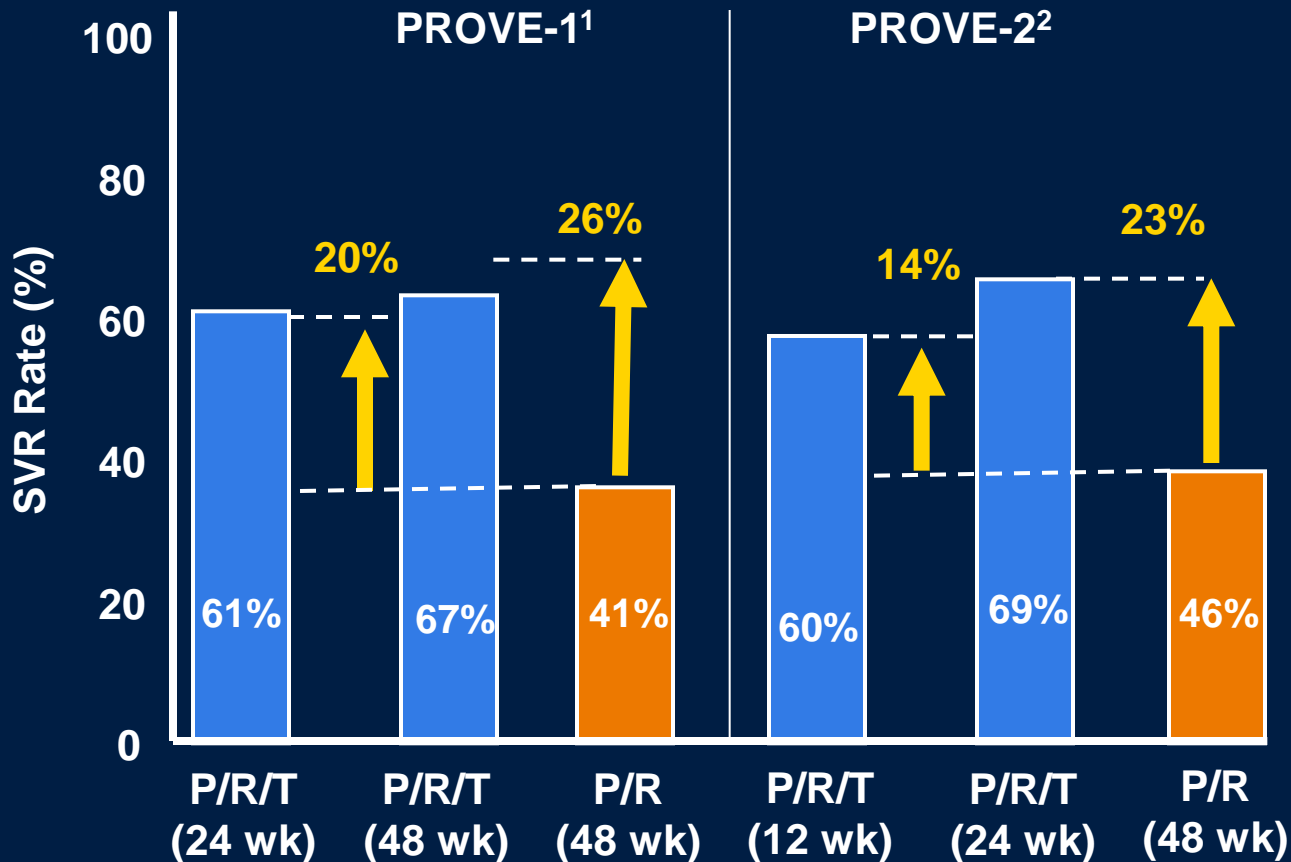
Protease Inhibitor BI 201335 + PEG-IFN/RBV

- No impact of 3-day PEG-IFN lead-in on early viral response
- Viral rebound similar in each BI 201335 group (2.8-3.5%)



Response Guided Therapy Remains Intact With Addition of DAA

Prove 1 and 2: Optimal Duration of Therapy in G1, Treatment-naïve Patients?

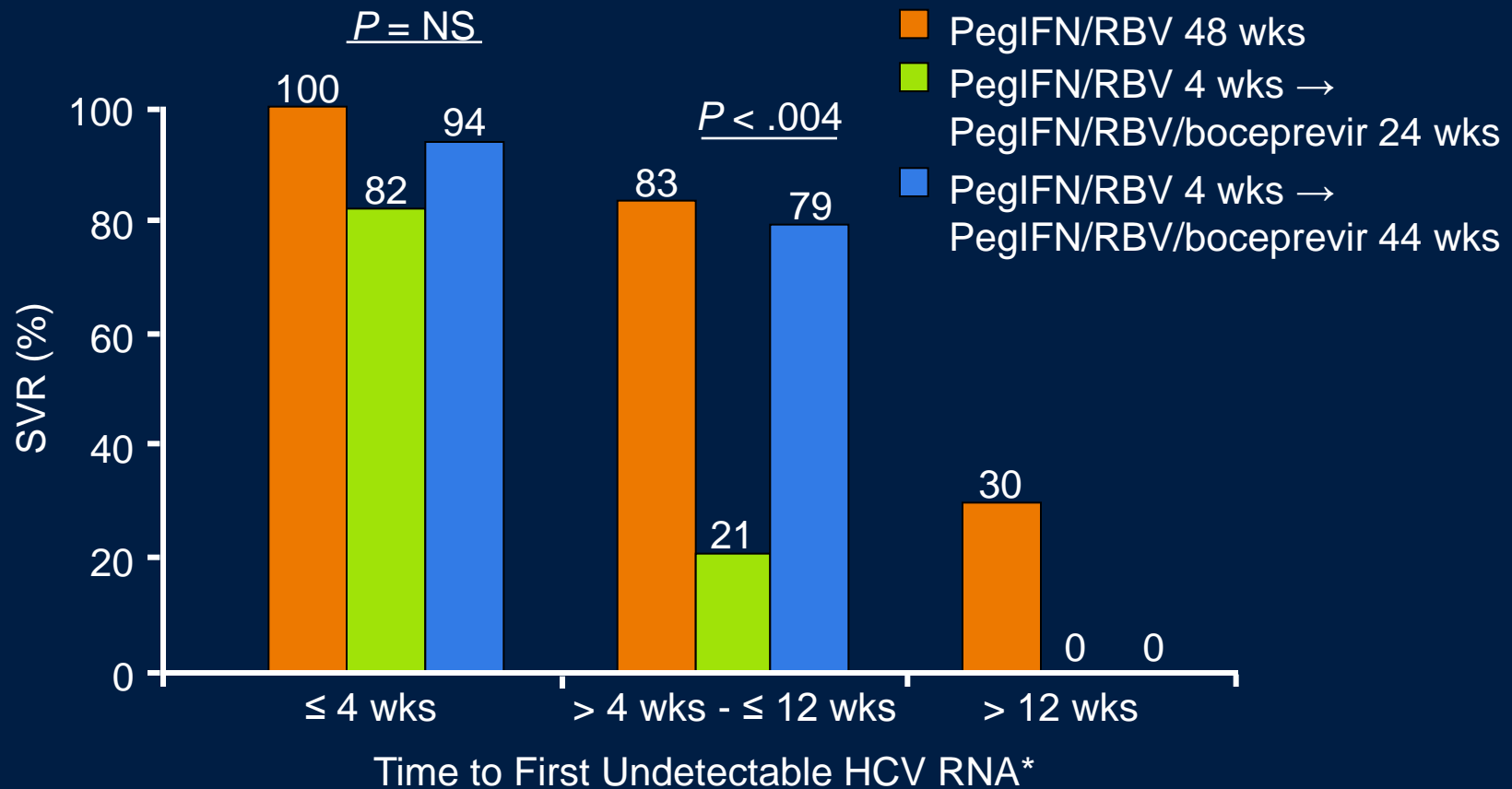


P: PEG-IFN; R: Ribavirin; T: Telaprevir

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

2. Hezode C, et al. *N Engl J Med*. 2009;360(18):1839-1850.

SPRINT-1: Response Guided Will Likely Maximize SVR



*Time after pegIFN/RBV initiation in control arm and time after boceprevir dosing in experimental arms.

Study C208: Response Guided Therapy and AE Management Plan Maximizes SVR

PEG-IFN/RBV cont for 48 weeks if HCV RNA detectable between wks 4-20

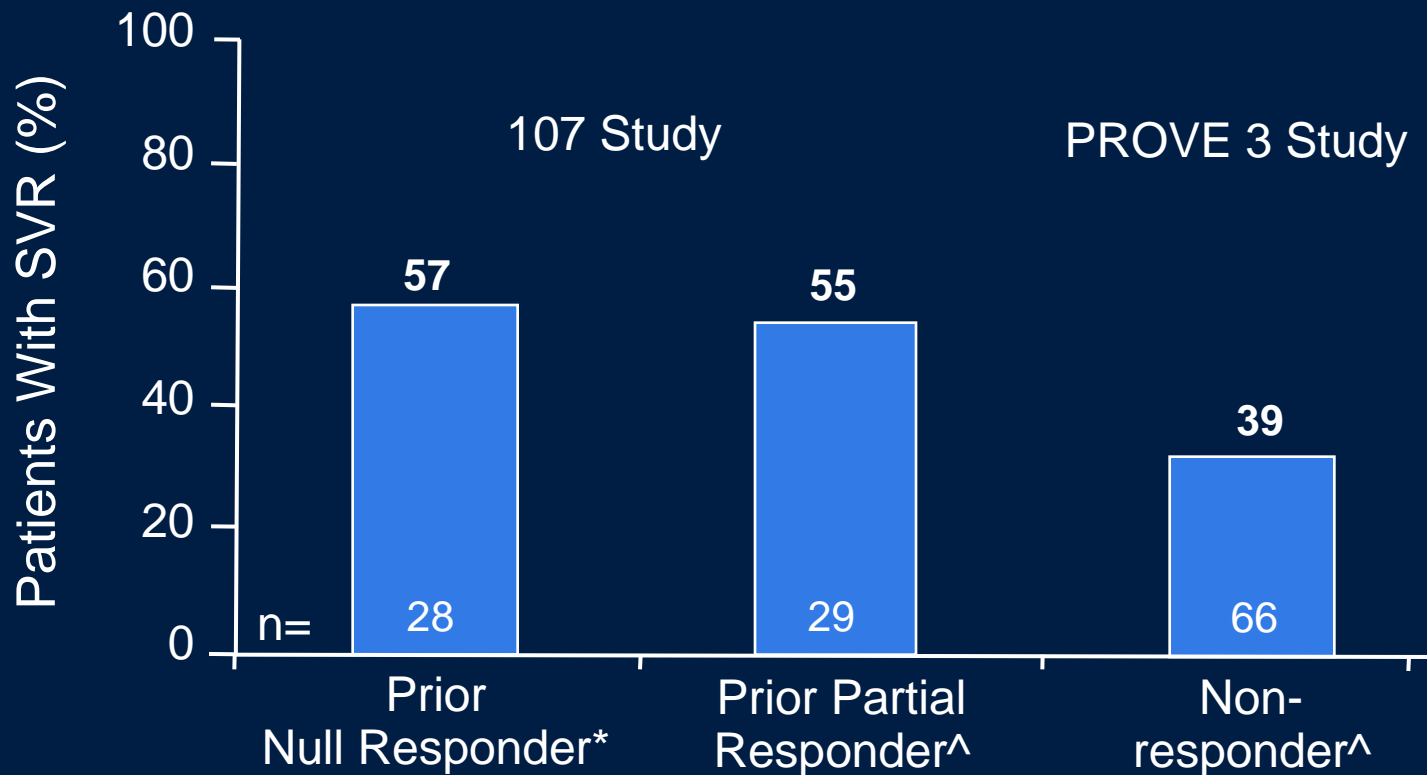
Outcome in ITT population	12-Wk TVR q8h + 24-Wk PegIFN alfa-2a/RBV (n = 40)	12-Wk TVR q8h + 24-Wk PegIFN alfa-2b/RBV (n = 42)	12-Wk TVR q12h + 24-Wk PegIFN alfa-2a/RBV (n = 40)	12-Wk TVR q12h + 24-Wk PegIFN alfa-2b/RBV (n = 39)
SVR, %	85	81	83	82
RVR, %	80	69	83	67
SVR in pts with RVR, % (n/N)	91 (29/32)	93 (27/29)	91 (30/33)	92 (24/26)

- Peg-IFN alpha 2a may offer higher RVR and greater % of patients who can shorten therapy
- RVR highly associated with SVR

Real Hope For IFN Nonresponder Population

SVR Rates With 12 Weeks Telaprevir + PEG-IFN/RBV in Treatment-Experienced Pts

G1 patients treated with TVR 750 mg q8h for 12 weeks + PEG-IFN +RBV for 24[^] or 48* weeks



SPRINT-1

Impact of INF-Responsiveness on SVR With PEG + RBV+ Boceprevir

HCV RNA Decline		
4 Week Lead-in	24 Week P/R/Boc	48 Week P/R/Boc
< 1 log	25%	55%
1-2 log	52%	70%
3-4 log	73%	81%
Undetectable	100%	100%

Graveyard for HCV Compounds is Filling Up Quickly!

AE management will become increasingly complex

ISIS 14803
(antisense)

UT-231B
(Imino sugar)

**Active
ribozyme**

VX-497
(IMPDH inhibitor)

New interferons
(R7025)

**CPG 10101
and ANA975**
(TLR agonist)

ACH-806/GS-9132
(NS4a)

BILN 2061
(protease)

JTK-003
(polymerase)

HCV-796
(polymerase)

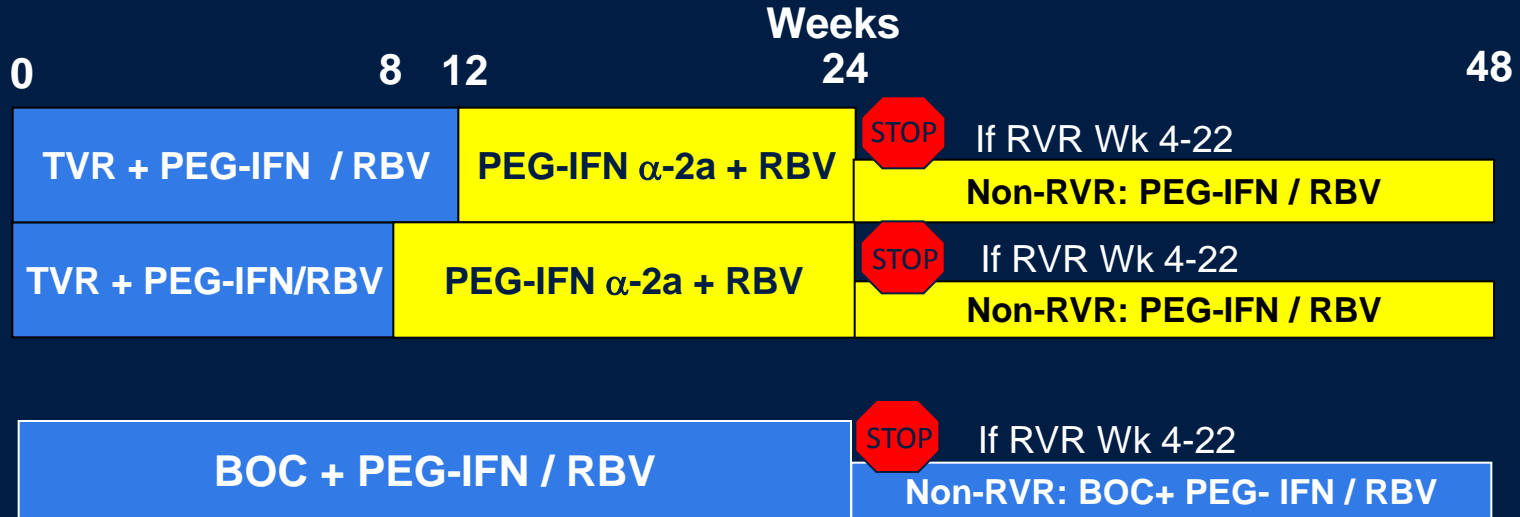
NM-283
(polymerase)

R803 and R1626
(polymerase)



Evolution of Therapy: 2012-2015

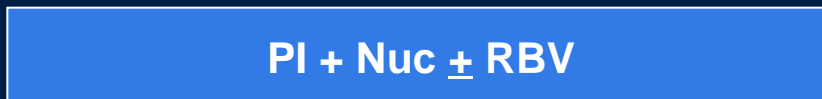
2012: Triple Therapy with Response Guided Duration is New SOC



2014: Quad vs new triple therapy options



2015: IFN- Free Regimens ?

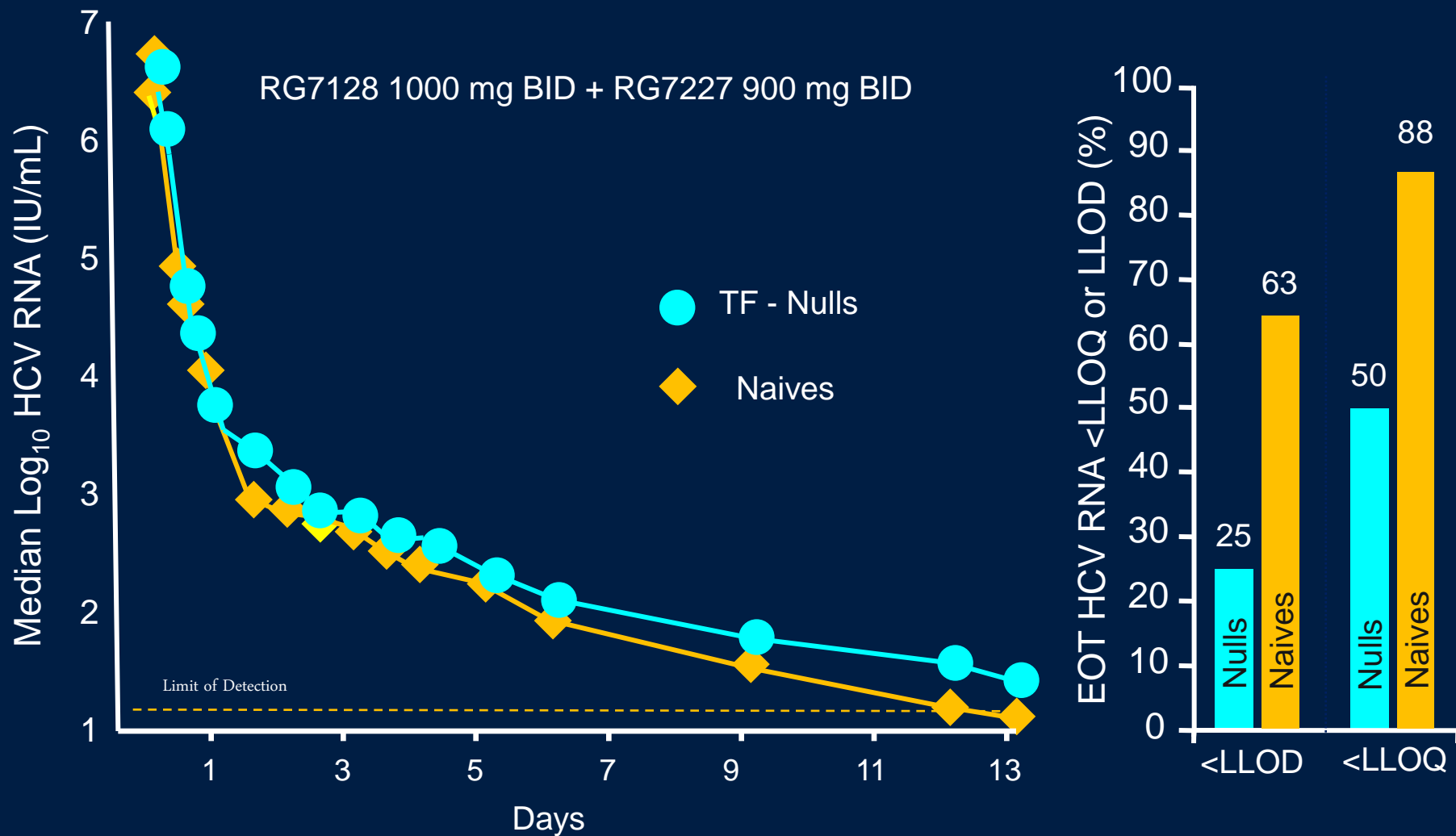


NS4 / NS5 inhibitors?

Nucleoside/tide Inhibitors: ? Game Changer

- **High *in vivo* potency**
 - 88% RVR with RG7128 in Genotype-1 Rx naïve patients
 - 90% RVR with RG7128 in Genotype 2, 3 non-responder patients
- **Broad genotype activity expected**
 - Demonstrated *in vitro* and *in vivo*
- **High barrier to resistance**
 - S282T variant identified *in vitro* has low fitness
 - No S282T variant at baseline in treatment naïve patients
 - No viral breakthrough observed in clinical trials to date
- **Potential to be used in combination regimens**
 - Low likelihood of drug-drug interactions
 - No dosing modifications for hepatic impairment
 - Resistance profile complementary to other drug classes

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



What Can Our Patients Expect in 2012-2015?

They can expect:

- Higher response rates
 - Naïve: SVR of 70%-80%
 - Nonresponder: 50-55%
- Truncation of therapy with RVR
 - 24 weeks for RVR
 - Exploration of 12 weeks for week 2 RVR
- Potential for combinations of novel agents

What Can Our Patients Expect in 2012-2015?

They can expect:

- Higher response rates
- Truncation of therapy with RVR
- Potential for combinations of novel agents

But...

- Novel drugs will still require IFN + RBV
- Resistance will be a new barrier
 - Subtyping and viral monitoring
- Adding a third drug = greater side effects
- Costs will be significant