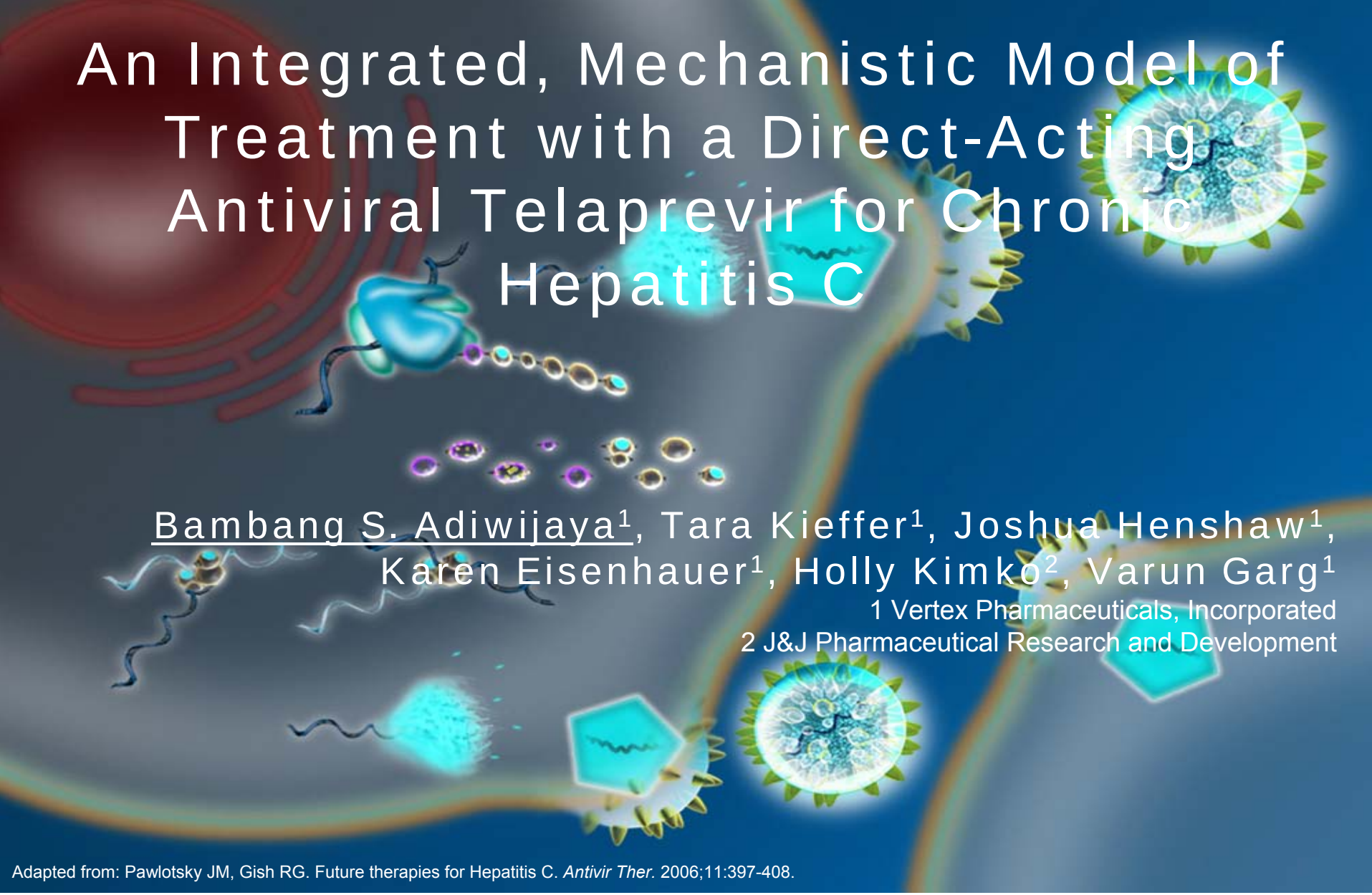
An Integrated, Mechanistic Model of Treatment with a Direct-Acting Antiviral Telaprevir for Chronic Hepatitis C

Bambang S. Adiwijaya[1], Tara Kieffer[1], Joshua Henshaw[1], Karen Eisenhauer[1], Holly Kimko[2], Varun Garg[1]

1 Vertex Pharmaceuticals, Incorporated

2 J&J Pharmaceutical Research and Development



Adapted from: Pawlotsky JM, Gish RG. Future therapies for Hepatitis C. *Antivir Ther.* 2006;11:397-408.

Population Approach Group in Europe; Athens, Greece 2011

Introduction

- Hepatitis C is a significant disease affecting ~170M people worldwide[1]
- Goal of HCV treatment is viral eradication (sustained virologic response; SVR)
- Telaprevir is an HCV protease inhibitor[2-4]
  - Telaprevir (T) in combination with peginterferon-alfa/ribavirin (PR) significantly increased SVR in genotype 1 patients compared to PR alone
  - Incidences of rash and anemia were more frequent with telaprevir than with placebo
- The goals of modeling analyses:
  - Predict SVR rates by T and PR durations

1 WHO website: http://www.who.int/vaccine_research/diseases/viral_cancers/en/index2.html

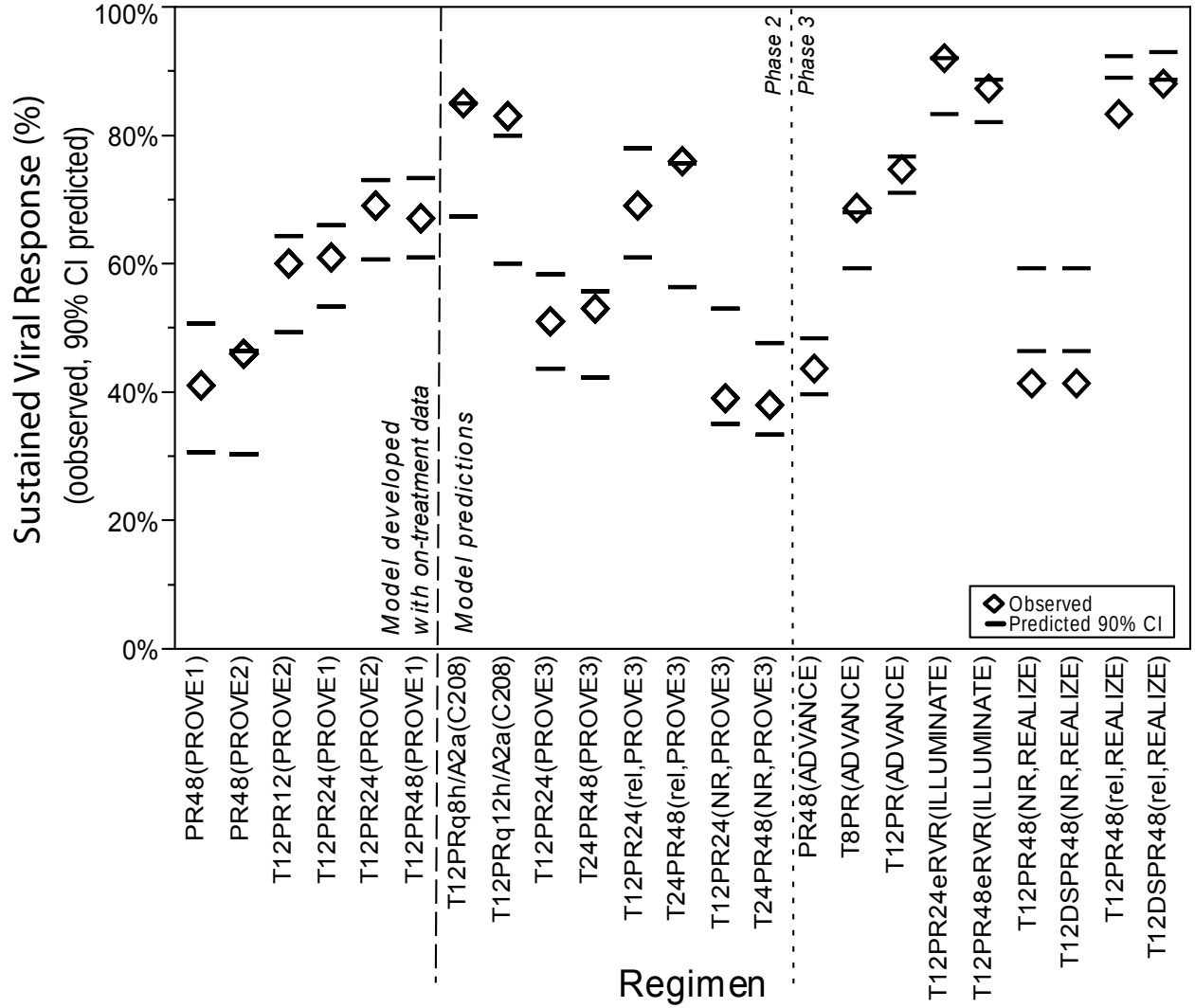
2 Jacobson I, et al., Hepatol. 2010; 52: 427A; 3 Sherman KE, et al., Hepatol. 2010; 52: 427A; 4 Foster GR, et al. Hepatol Int 2011; 5(1): 14

Data Sources for Model Development

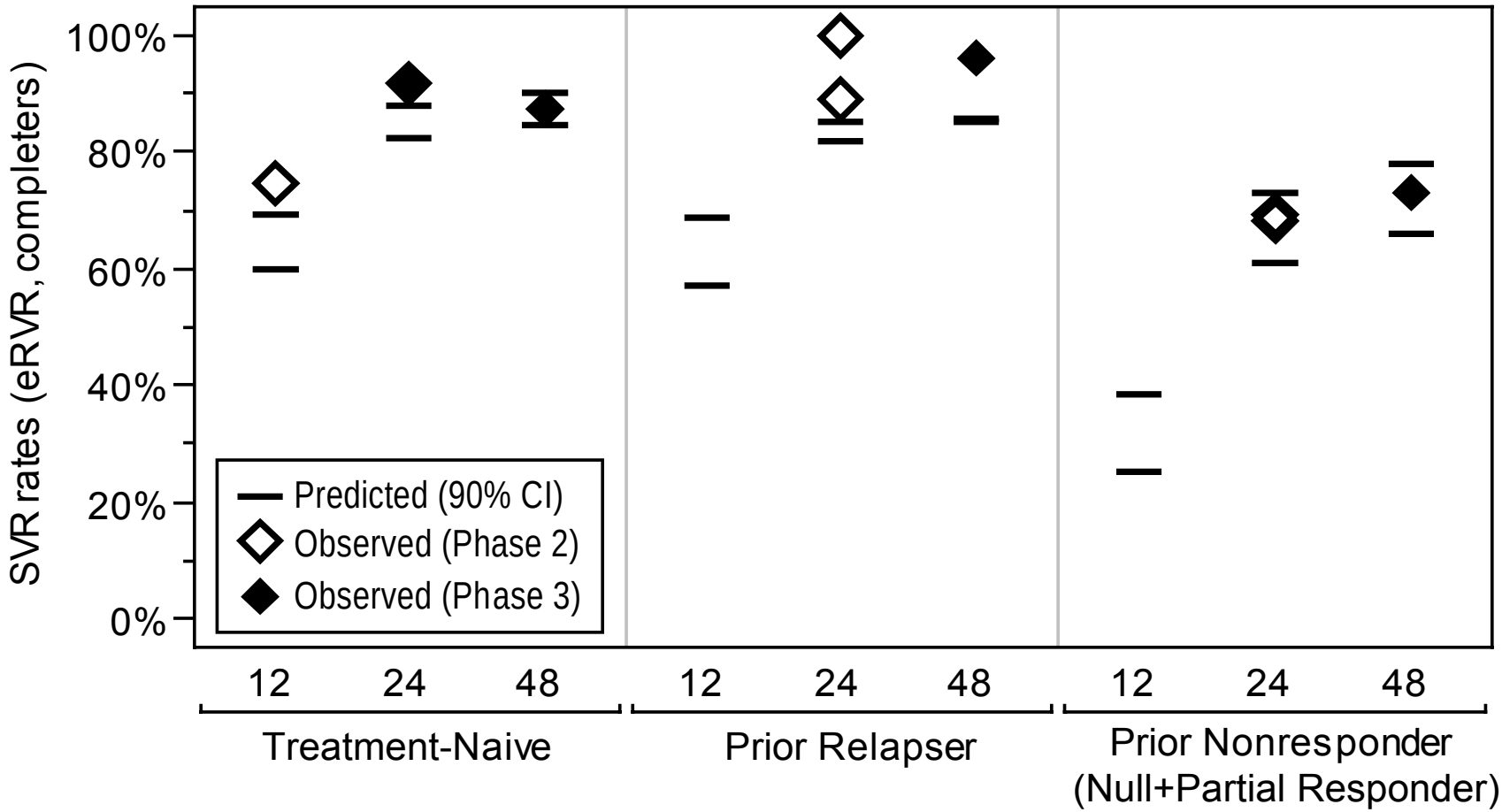
Study Name	Ph	Population	Regimens	N	Note
101	1	Treatment-naïve and prior PR-treatment experienced	Telaprevir monotherapy (14 days, different doses)	28	Estimation: on-treatment data; Prediction: SVR rates
PROVE1	2	Treatment-naïve	PR48 T12PR24 T12PR48	75 79 79	
PROVE2	2	Treatment-naïve	PR48 T12PR12 T12PR24	82 82 81	
C208	2	Treatment-naïve	T12PR (T: 750mg q8h) T12PR (T: 1125mg q12)	40 40	Prediction: SVR rates
PROVE3	2	Prior PR-treatment experienced	T12PR24 T24PR48	115 113	
ADVANCE	3	Treatment-naïve	PR48 T8PR T12PR	361 364 363	
ILLUMINATE	3	Treatment-naïve	T12PR24 T12PR48	162 160	
REALIZE	3	Prior PR-treatment experienced	PR48 T12PR48 T12LIPR48	132 266 264	

Abbreviations: P: peginterferon alfa-2a; R: ribavirin; T: telaprevir; T12LI: 4-week delayed start of telaprevir treatment; PR48: 48 weeks of PR; T12PR24: 12 weeks of TPR + 12 weeks of PR; T12PR12: 12 weeks of TPR; T12PR: 12 weeks of TPR + 12/36 weeks of PR; T8PR: 8 weeks of TPR + 20/40 weeks of PR

Comparison Between Observed and Predicted SVR Rates



SVR Rates by PR Duration (+12-week telaprevir)

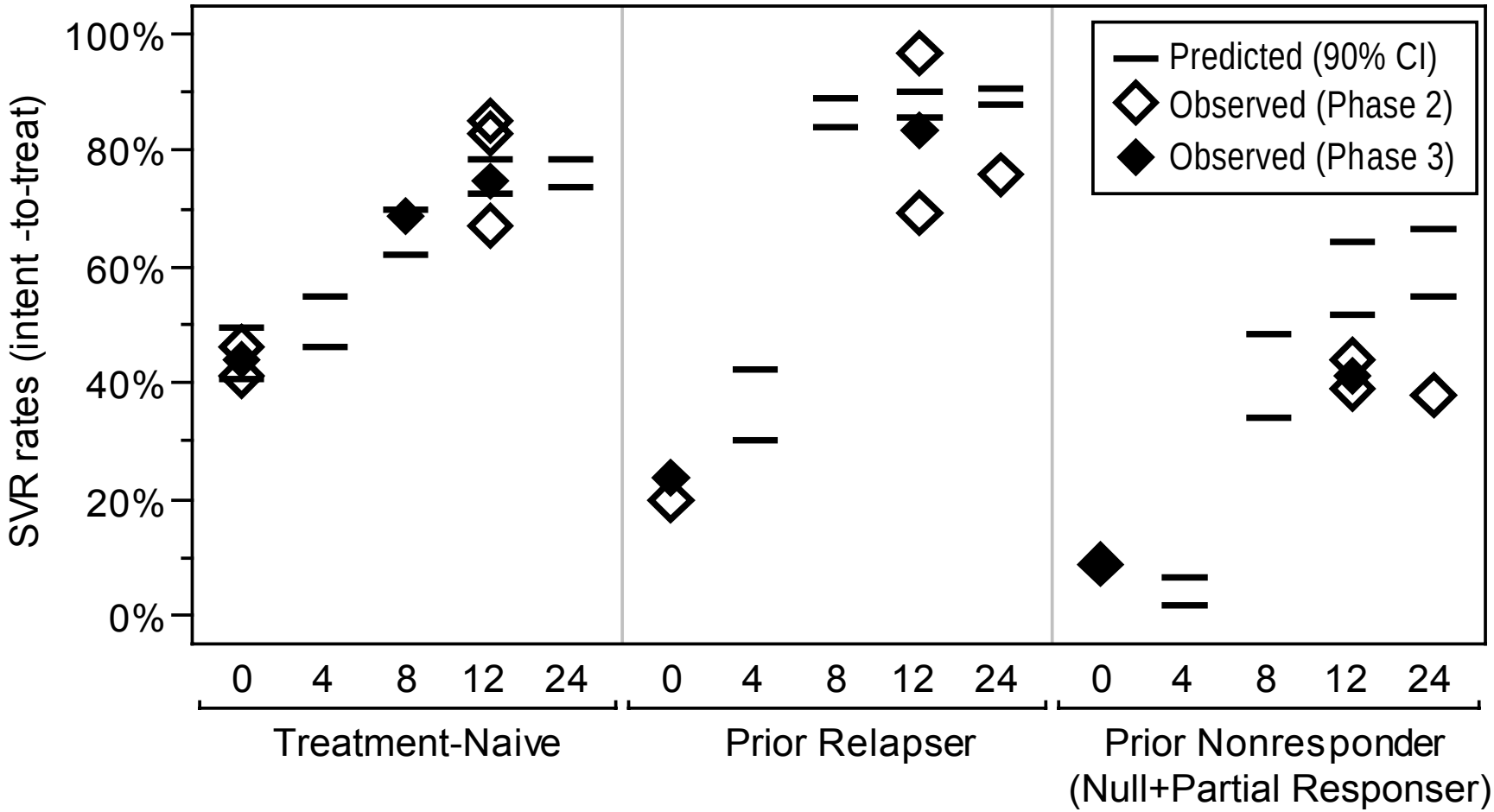


Peginterferon/Ribavirin duration (weeks) within Prior PR Response Population

eRVR= undetectable HCV RNA at weeks 4 and 12

Adiwijaya BS, et al., J. Hepatol. 2011; 54 (S1): S160

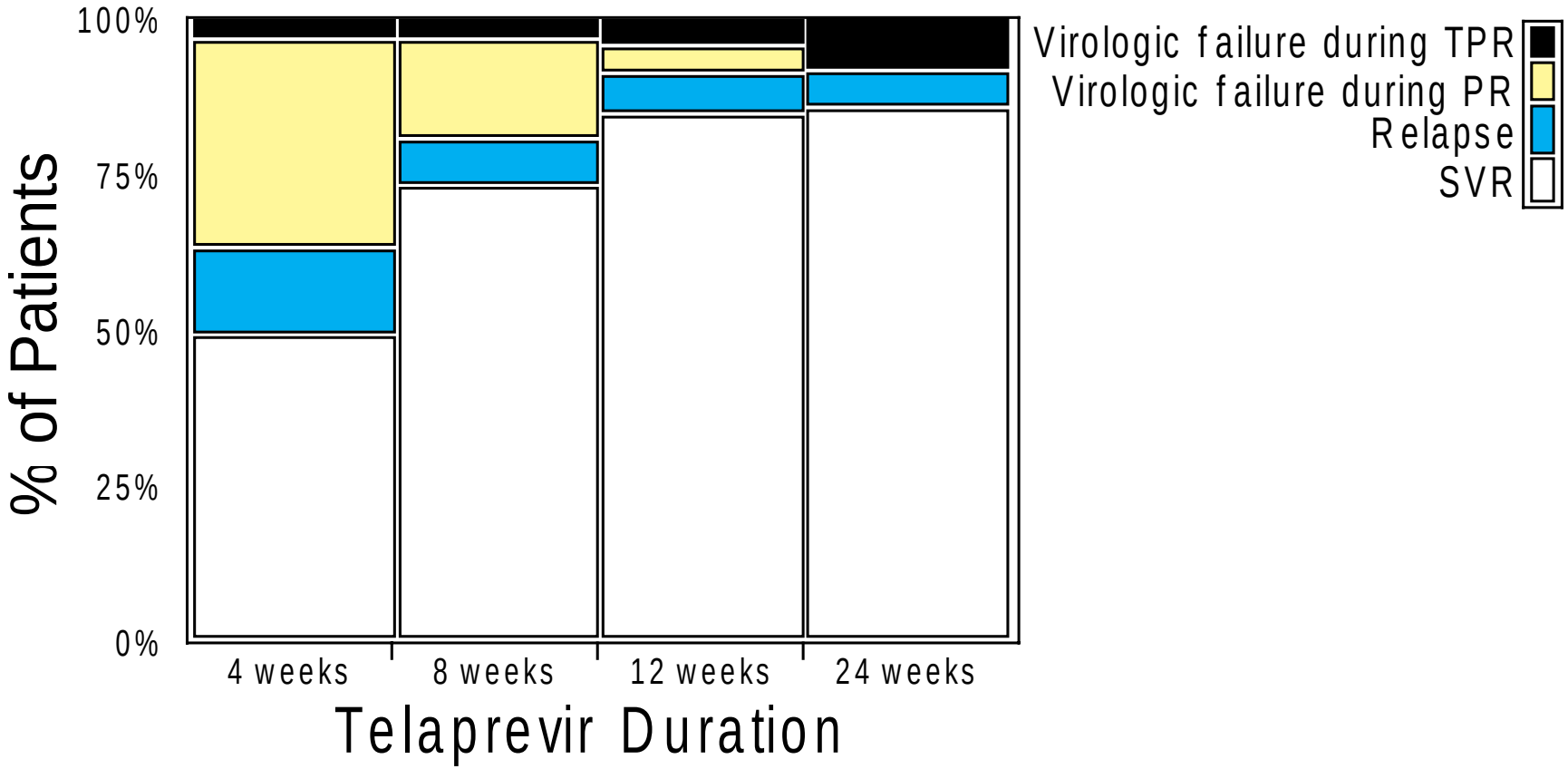
SVR Rates by Telaprevir Duration (+24- to 48-week PR)



Adiwijaya BS, et al., J. Hepatol. 2011; 54(S1): S160

Predicted Outcome by Telaprevir Duration

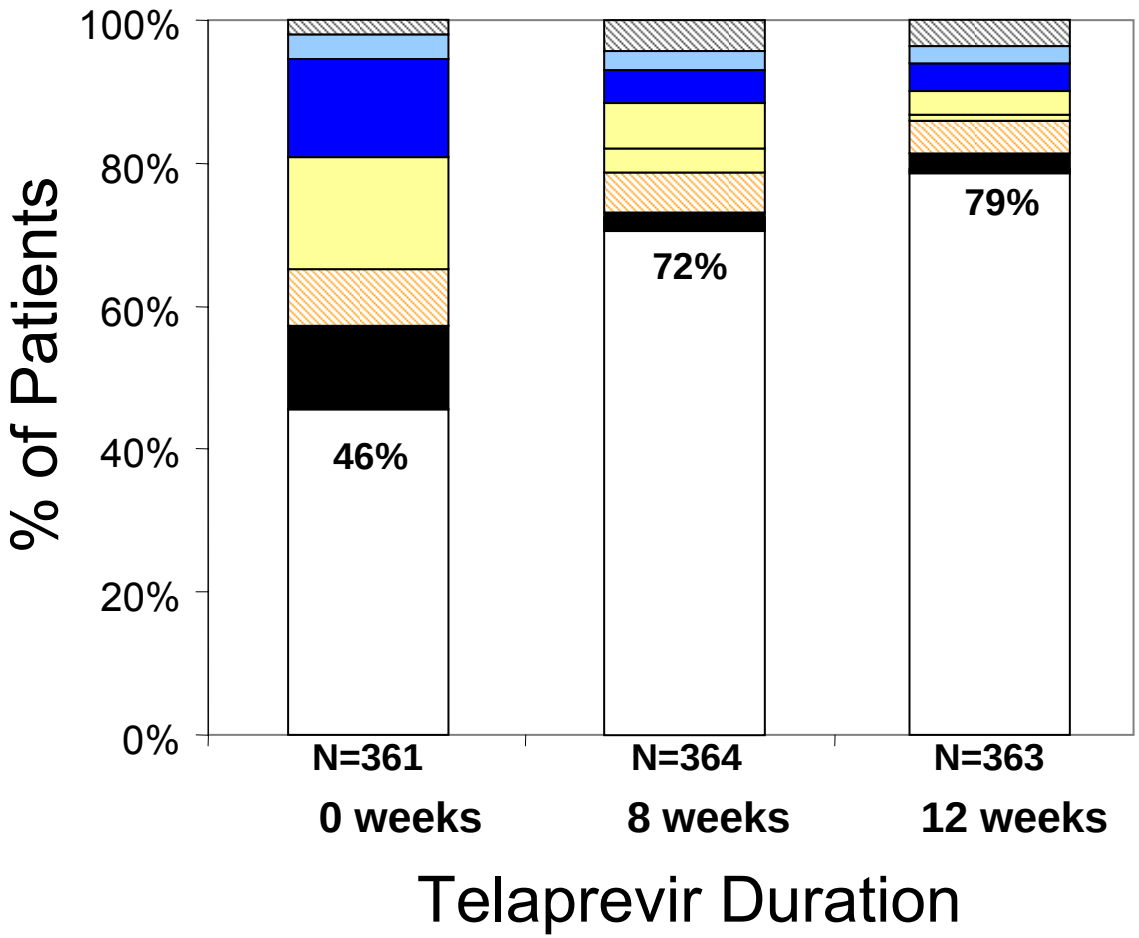
- In treatment-naïve completing 24-week PR treatment



Adiwijaya, BS, et al., J. Hepatol. 2011; 54 (S1): S160

Observed Outcome by Telaprevir Duration

- In treatment-naïve (ADVANCE Study)



SVR

On-treatment Virologic Failure

- TVR/Pbo stop (week 4 and 12)
- PR stop (week 24-40); Detectable at end of treatment (week 24 or 48)

Relapse

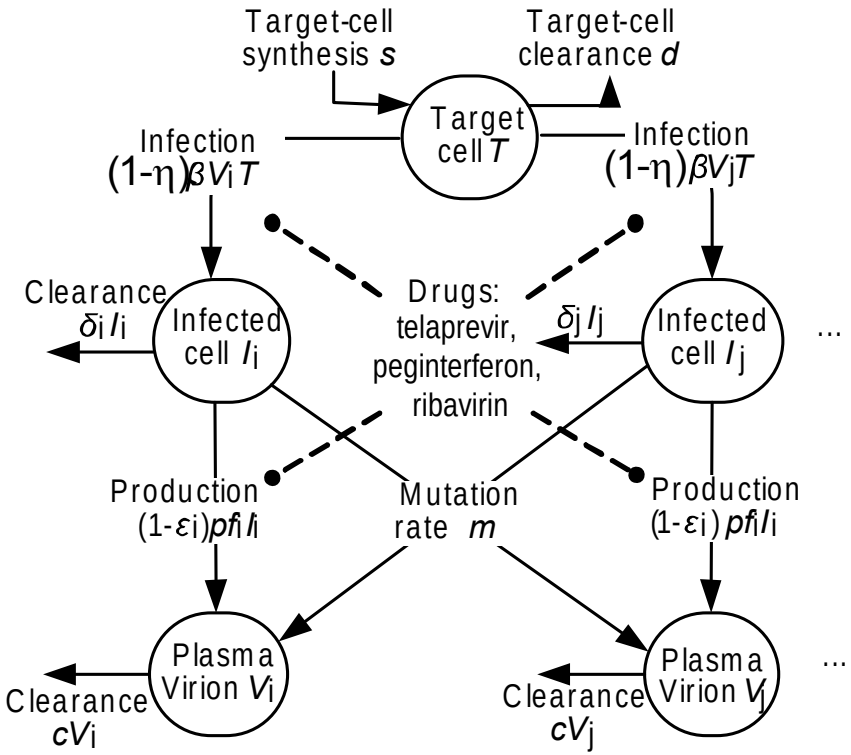
- Completers
- Non-completers

- Detectable at time of early discontinuation*
- Undetectable HCV RNA at EOT and discontinued study before SVR

* All but 2 of these patients discontinued before Week 12

Kieffer, et al., Hepatology 2010; 52 (S1): poster LB11

Methods: Schematic of Multi-Variant Viral Dynamic Model of TPR Regimen



(dot above) a variable	time-derivative of a state variable
T	Healthy target cells
s	Target cell synthesis rate
d	Target cell degradation rate
η	Blockage of infection
β	Infection rate
V_i *or* V_j	Plasma virion "*i*" or "*j*"
I_i	Variant-*i*-infected cells
δ_i	Variant-*i*-infected-cell clearance rate
p	Production rate of wild-type (WT)
$m_{j,i}$	Mutation rates from *Vj* to *Vi*
ε_i	Blockage of production
f_i	Variant-*i* fitness: production rate relative to WT
c	Plasma virion clearance rate
SVR_{def}	HCV RNA limit of eradication

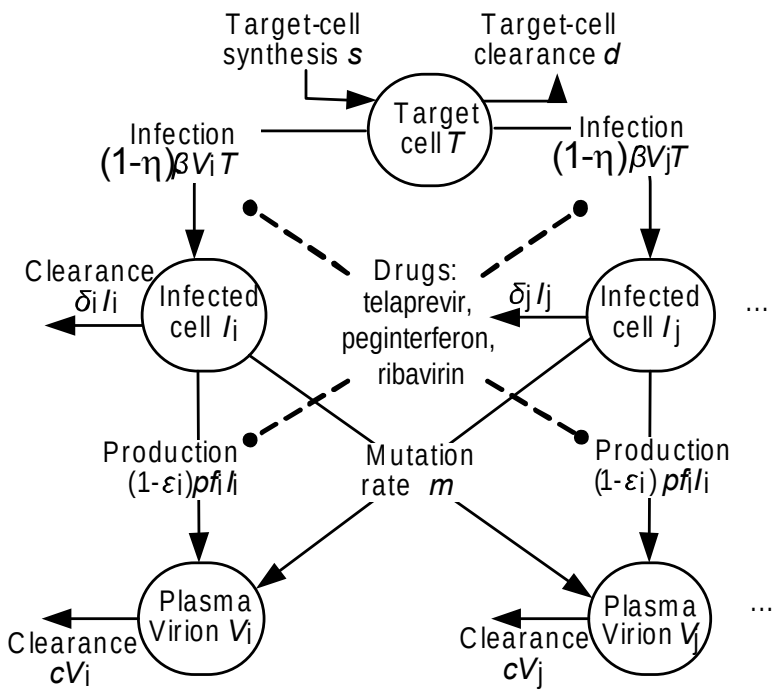
Methods: Schematic of Multi-Variant Viral Dynamic Model of TPR Regimen

Drug Potency (in vitro)

Resistance of viral variants (in vitro)

Pharmacokinetics of T, P, R

Dose and dose modifications of T, P, R



Covariates

HCV evolution during and after treatment

Clinical efficacy in short-term studies

Clinical efficacy in long-term studies

Mechanistic Insight 1: Resistance Often Results in Loss of Viral Fitness

WT (A156)

Active site

Ala156

Protease substrate

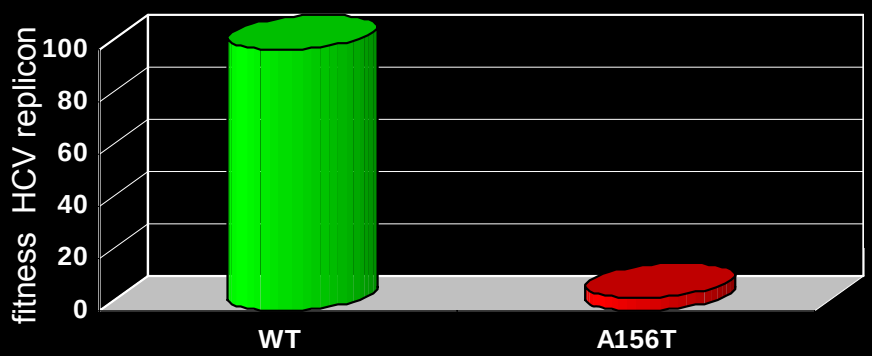
Resistant Variant (A156T)

Active site

Thr156

Protease substrate

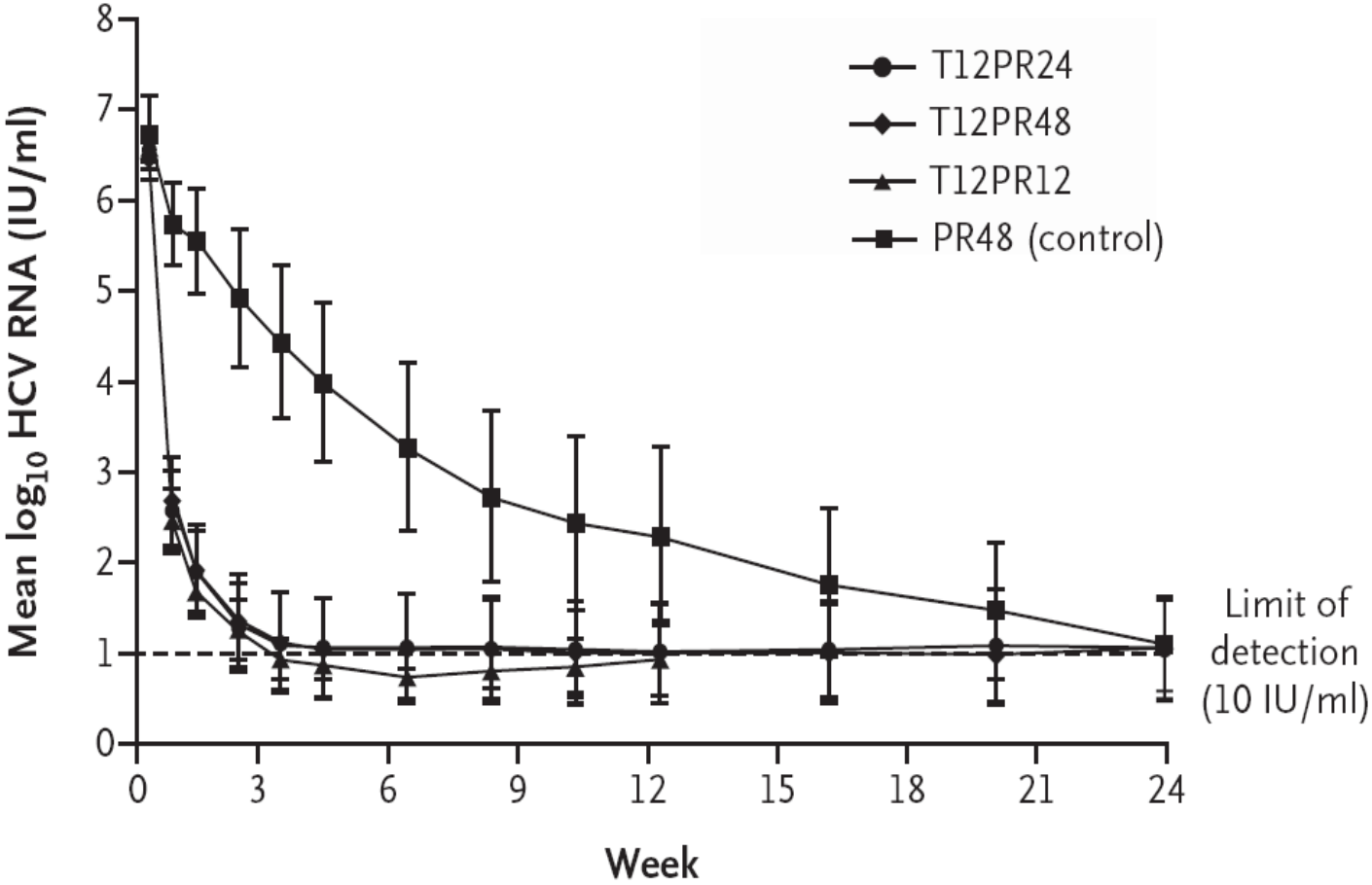
The A156T variant is less fit than WT



Steric hindrance prevents the substrate from efficiently binding to the mutant protease active site

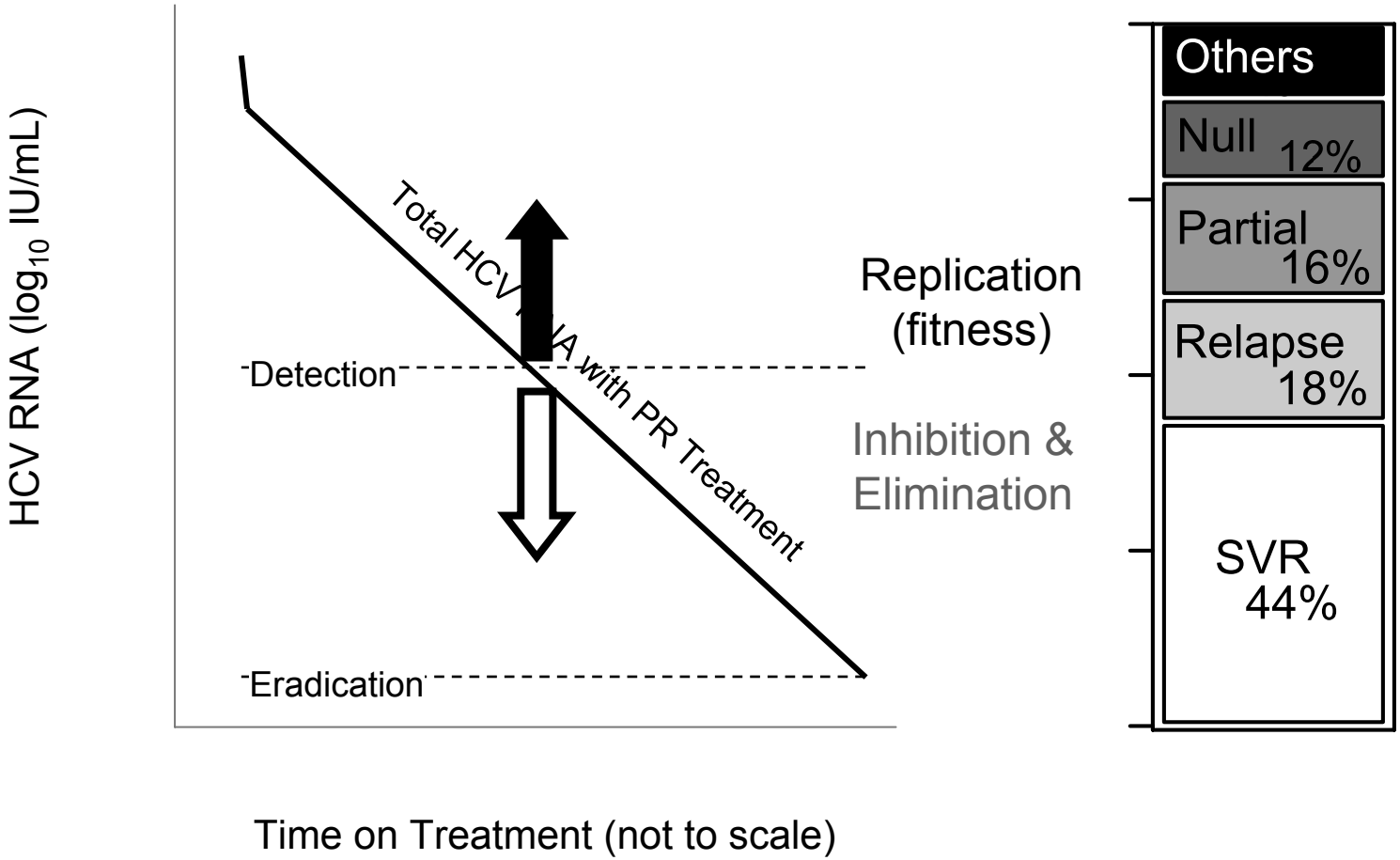
Lin C. J. Biol. Chem. 2005;280(44):36784-91

Response to PR and TPR Treatment

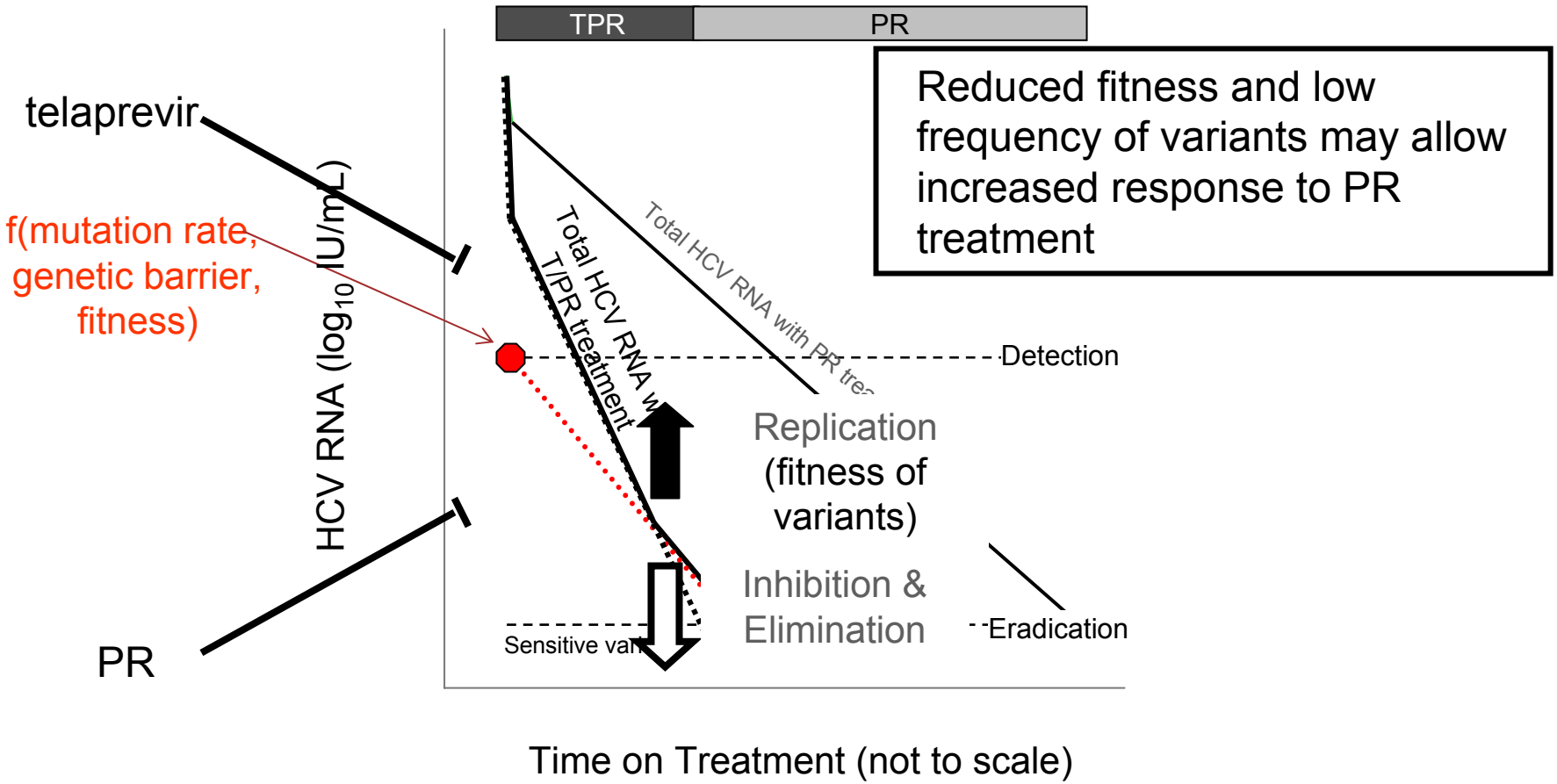


McHutchison, et al., NEJM 2009;360:1827

Response to PR Treatment is a Function of Replication, Inhibition, and Elimination

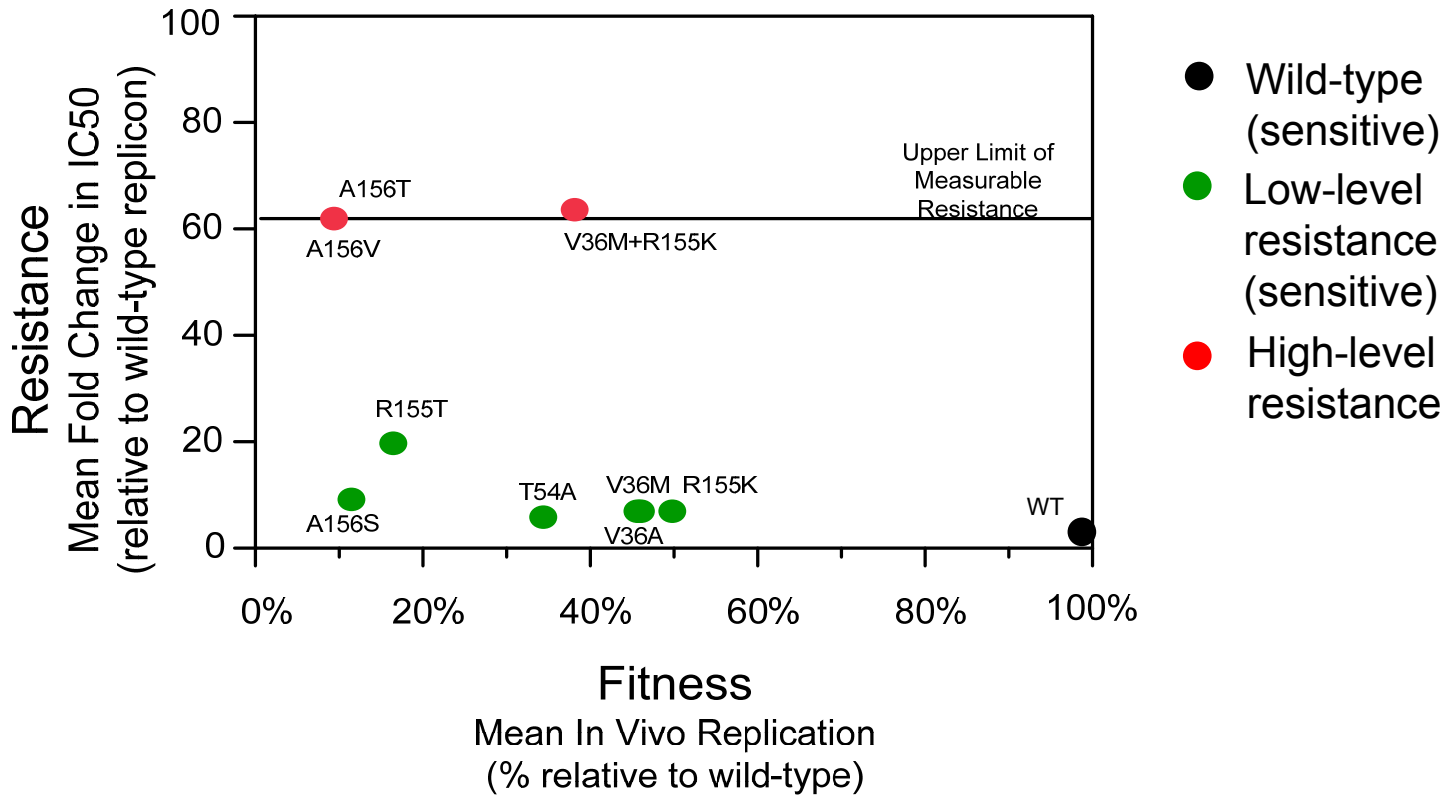


HCV Quasispecies Diversity Affects Viral Dynamics with Telaprevir-based Regimens



Resistance and In-Vivo Fitness of Variants

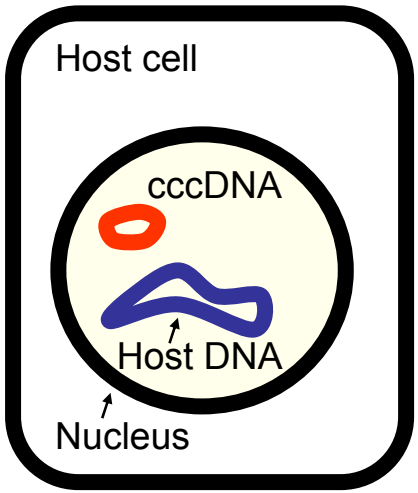
- HCV population as a mixture of variants[1,2] with varying resistance and fitness
- Variants (with mutation ≤2) pre-exist prior to treatment at lower frequency[3,4]
- Variants retain sensitivities to PR treatment in vitro[5] and in patients[6]



[1] Sarrazin et al., Gastroenterology 2007; [2] Kieffer, et al., Hepatology, 2007; [3] McPhee, et al, 1st international workshop HCV resistance 2006;
[4] Ralston, 2nd international workshop HCV resistance 2007; [5] Lin, et al., Antimicrob agents chemother 2004; [6] Forestier, et al., Hepatology, 2007

Mechanistic Insight 2: Eradication in HCV Treatment

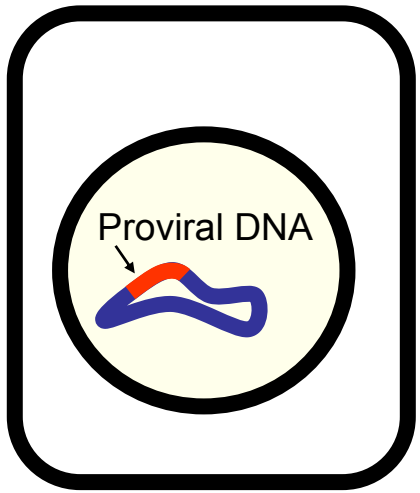
HBV



TREATMENT

Long-term reduction of viral replication to lowest possible level[1]

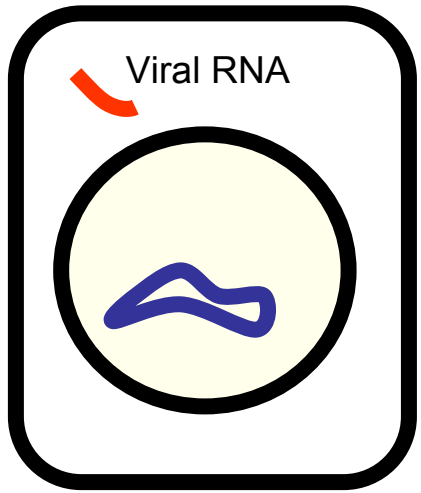
HIV



TREATMENT

Lifelong suppression of viral replication[2,3]

HCV



TREATMENT

Definitive viral clearance[1]

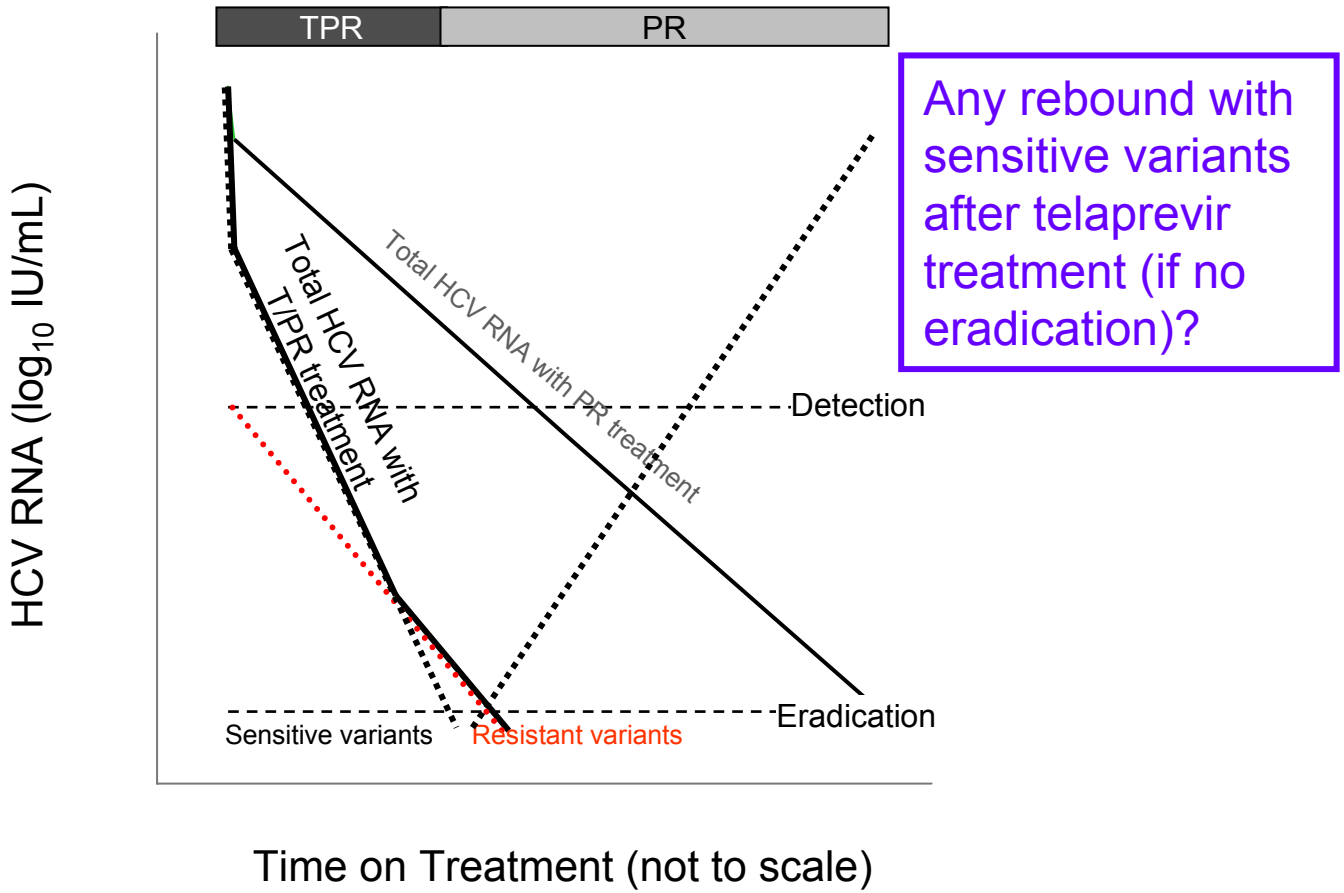
↓

SVR[1]

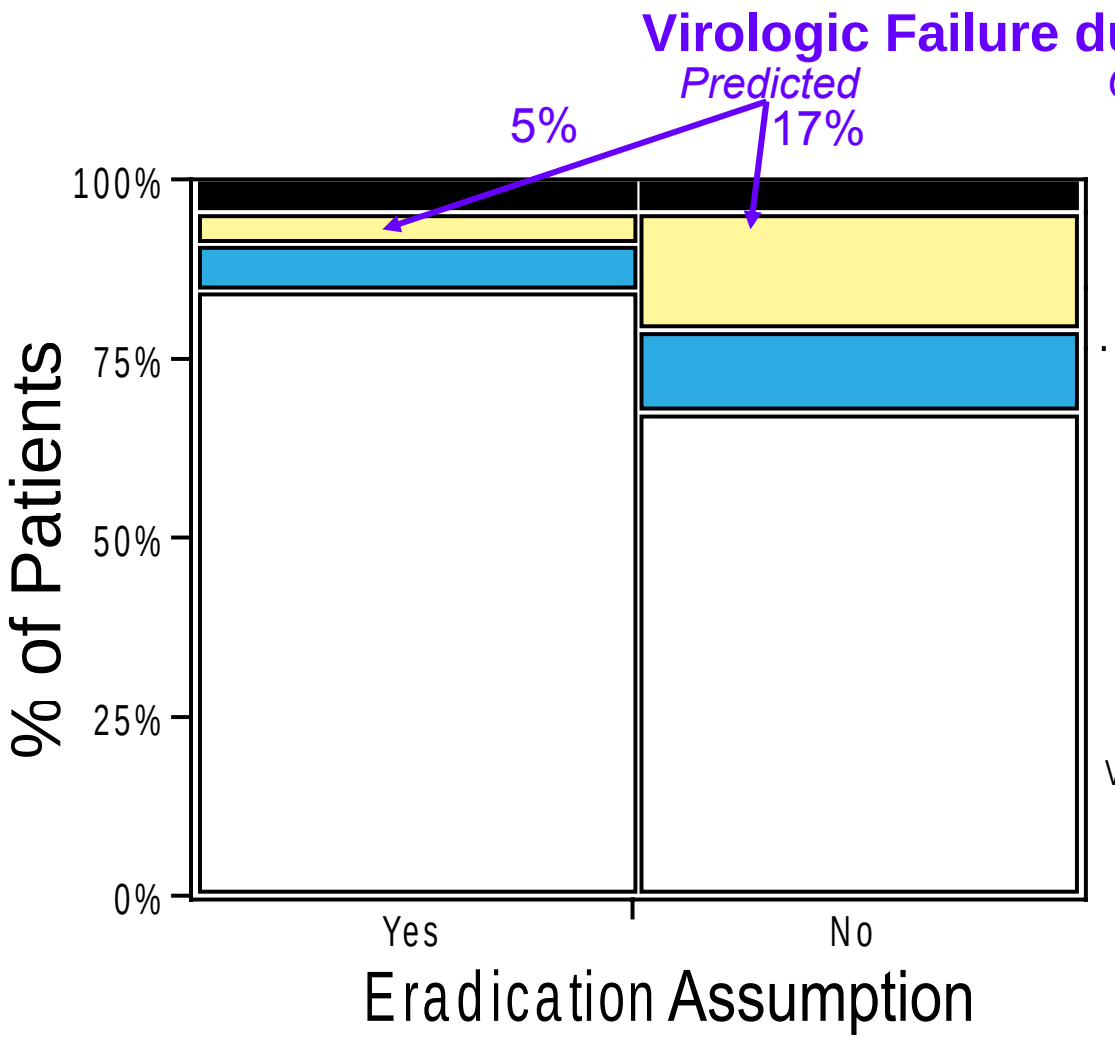
cccDNA = covalently closed circular DNA

1. Pawlotsky JM. *J Hepatol* 2006;44:S10-S13;
2. Siliciano JD, Siliciano RF. *J Antimicrob Chemother* 2004;54:6-9;
3. Lucas GM. *J Antimicrob Chemother* 2005;55:413-416

HCV RNA Dynamics With and Without Eradication



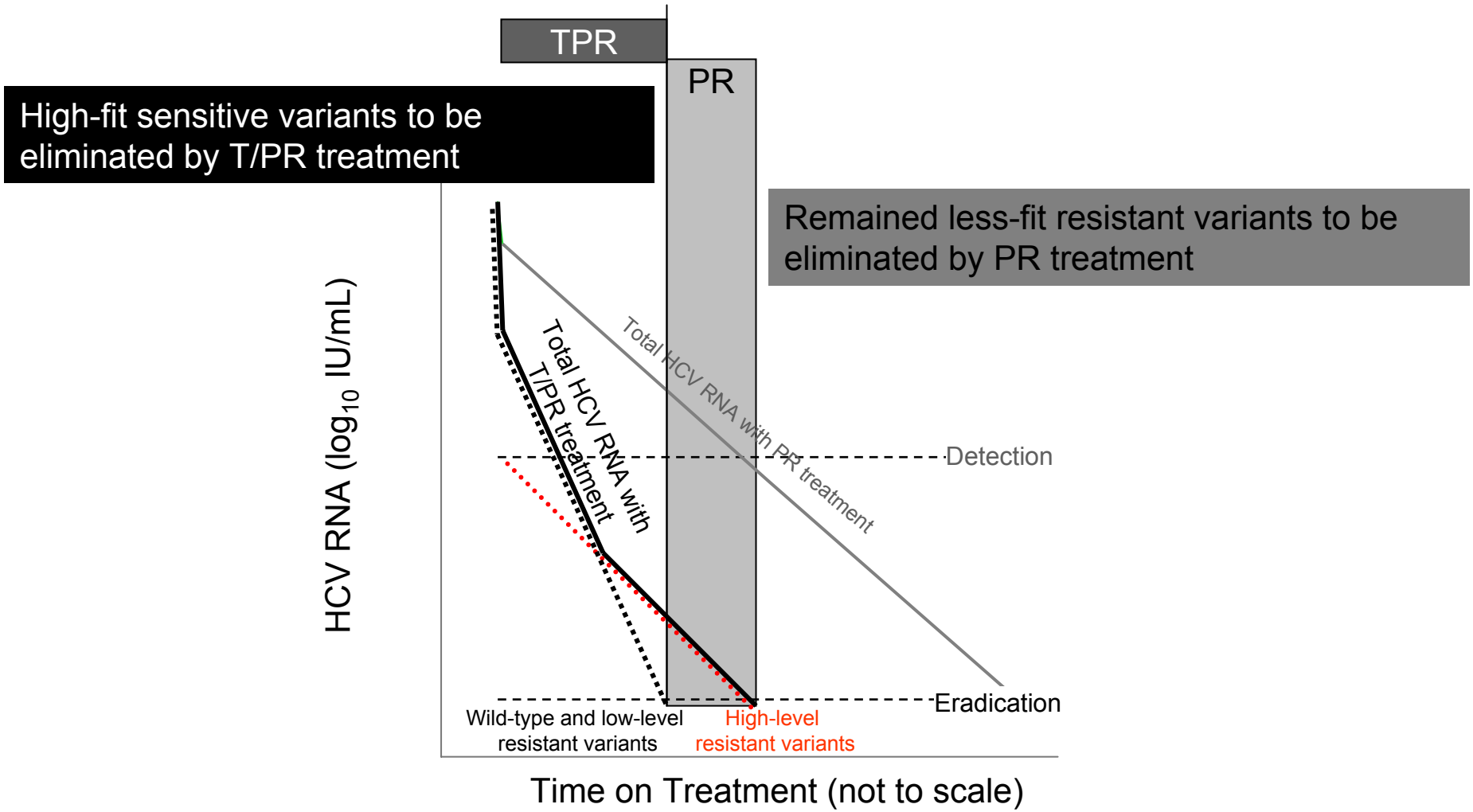
Sensitivity to Eradication Assumption: Clinical Outcomes for T12PR24 Regimen



P1[1]	P2[2]	C208[3]
7%	**1%, 5%**	**3%** to **10%**
n.a.	**0%**, **1%**	**0%** to **5%**
1%,4%	**10%**	**2%** to **5%**

(1) McHutchison, et al., NEJM 2009;360:1827
(2) Hézode, et al., NEJM 2009; 360:1839
(3) Forns, et al, J. Hepatology 2010;52 Suppl 1;S26
n.a. not available

Viral Eradication Guided the Optimal Durations of TPR Treatment



Conclusions

- A mechanistic viral dynamic model in response to telaprevir, peginterferon, and ribavirin treatment
  - Predicted SVR rates were similar to the observed SVR rates in most treatment-naïve and treatment-experienced patients
  - A useful framework to integrate in vitro, early-phase and late-phase clinical data
  - Applications to the design and analysis of optimal treatment regimen
- Model benefited from mechanistic insights
  - Roles of viral variant fitness and resistance
  - Variability in PR-treatment response
  - Viral eradication to guide the design of optimal durations

Acknowledgement

~3000 patients chronically infected with HCV who participated in telaprevir clinical trials

Investigators who participated in telaprevir clinical trials

Vertex Pharmaceuticals Incorporated:
Nathalie Adda
Doug Bartels
Leif Bengtsson
Shelley George
Robert Kauffman
Ann Kwong
Karen Kumor
Frances Smith
James Sullivan

University of Frankfurt:
Eva Herrmann
Stefan Zeuzem

Tibotec Inc:
Rudolph Van Heeswijk
Sandra De Meyer
Gaston Picchio

RES Group, Inc
Taeshin Park