# Applications of Discrete-Event Dynamic Simulation in HCV Treatment Dynamics

Bambang Adiwijaya (1,*), Joshua Henshaw (1), Maria Rosario (1), Holly Kimko (2), Varun Garg (1)
(1) Vertex Pharmaceuticals, Incorporated, Cambridge, MA, USA; (2) Johnson & Johnson, Raritan, NJ, USA
*e-mail: bambang_adiwijaya@vrtx.com

## Background:

The treatment objective in patients chronically infected with hepatitis C virus (HCV) is viral eradication, or a sustained viral response (SVR). For genotype 1 HCV, the most common genotype, current treatment is 48 weeks of peginterferon alfa and ribavirin (PR) and approximately 42% to 50% of patients achieve sustained viral response (SVR) with this treatment.(1), (2) Recently, telaprevir, an HCV NS3•4A protease inhibitor, has demonstrated antiviral activities to increase the SVR rates in regimens in combination with PR.(3), (4), (5), (6) Mathematical models of HCV dynamics in interferon and ribavirin treatment have been useful in predicting the percentage of patients achieving SVR.(7, 8) In treatment combinations with direct-acting antiviral(s) such as telaprevir, the HCV population must be considered as a mixed population, consisting predominantly of wild-type virus (WT) and a small population of variants with varying levels of sensitivity to telaprevir.(9), (10) Variants were estimated with lower fitness (lower replicative capacity) than WT; variants with higher level of resistance were estimated with lower fitness than variants with lower level of resistance.(11) The resistant variants exist at a low frequency prior to the start of treatment(12), (13) because they are less fit than WT.(11), (14) The resistant variants retain sensitivity to antiviral inhibition by PR treatment in vitro(15) and in patients.(16) Therefore, to quantify HCV RNA dynamic responses to telaprevir treatment, a multi-variant viral dynamic model must be considered.(11, 14)

## Objective:

To develop a multi-variant, HCV RNA dynamic model that predicts the virologic outcome of treatments with different combination regimens including telaprevir, peginterferon-alfa, and ribavirin (T/PR).

## Methods:

HCV RNA and drug exposure vs. time data from a total of 1162 patients who participated in clinical trials (Studies PROVE1, PROVE2, PROVE3, C208) evaluating regimens including peginterferon-alfa, ribavirin and telaprevir, were used to improve a model previously published.(11) A two-step approach of pharmacokinetic (PK) and pharmacodynamic (PD) modeling was implemented. The PK models of concentrations were implemented as follows: peginterferon-alfa as a one-compartment model, ribavirin as a three-compartment model(17), and telaprevir as a one-compartment model. The PD viral dynamic model accounted for viral populations as a mixture of quasispecies with varying fitness and sensitivity to telaprevir. Model-predicted telaprevir, peginterferon-alfa, and ribavirin pharmacokinetics were entered into the PD viral dynamic model. The PD parameters were estimated using HCV RNA data from PR and T/PR regimens in studies in treatment-naïve patients (PROVE1 and PROVE2). The predicted HCV RNA dynamics for treatment-naïve subjects were generated by simulations, with parameters re-sampled from the distributions of individual Bayesian estimates from the population approach. The predicted SVR rates were calculated by evaluating HCV RNA dynamics and entering the observed discontinuation rates into the model. The predicted SVR rates for different categories of prior PR treatment-failure subjects (nonresponder and relapser) were generated by simulating the HCV RNA dynamics in response to PR treatment, and by filtering the responses with the respective criteria of PR responsiveness. The modeling analyses were performed with and without the following eradication assumptions: (i) that eradication of each variant is a discrete event occurring at variable times during treatment, and (ii) when variants were eradicated (levels were below the eradication limit), variants changed state from replicating to non-replicating. The PK models were implemented using NONMEM v6, and the PD model was implemented using Jacobian® software (RES group, Inc.).

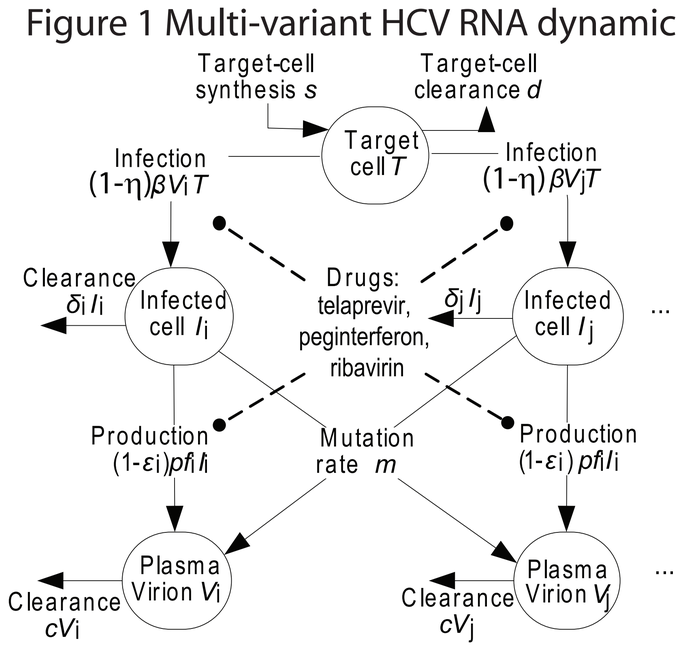
## Results:

The model was qualified by comparing the *a priori* predictions and the observed data from two subsequent studies (PROVE3 and C208). The model-predicted SVR rates were compared to observed SVR rates across different patient populations with various durations of treatment and two dose-schedule regimens. Sensitivity analysis was performed on the model with and without the assumption of eradication during treatment. The results suggested that the model with eradication assumption resulted in predicted outcomes that were more consistent with the observed outcomes in Phase 2 studies.

## Conclusions:

To match the observed clinical outcomes, a model of viral eradication in regimens containing telaprevir, peginterferon, and ribavirin needed the assumption that HCV variants were eradicated during treatment. The different on-treatment times when variants were eradicated in the model suggested that the optimal durations of telaprevir treatment and of PR treatment may be different.

## Figure 1 Multi-variant HCV RNA dynamic model



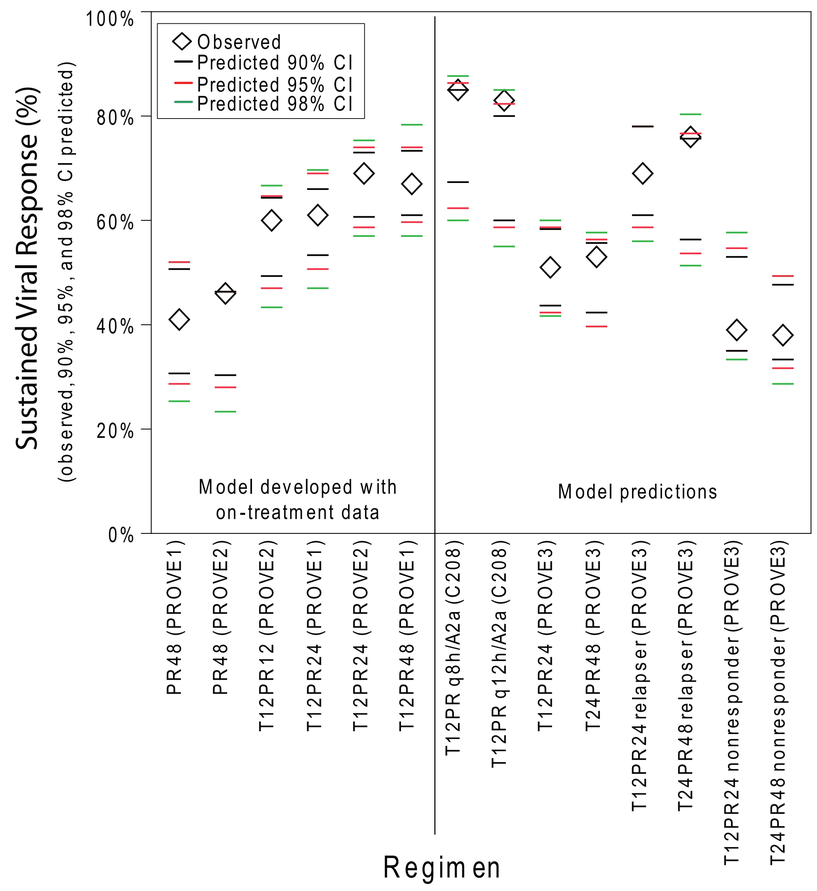

| | |
|---|---|
| *(dot above) a variable* | Time-derivative of a state variable |
| $T$ | Healthy target cells |
| $s$ | Target cell synthesis rate |
| $d$ | Target cell degradation rate |
| $\eta$ | Blockage of infection |
| $\beta$ | Infection rate |
| $V_i$ or $V_j$ | Plasma virion "*i*" or "*j*"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

$$\dot{T} = s - dT - (1-\eta)\beta T \sum_i V_i \qquad (1)$$

$$\dot{I}_i = \begin{cases} (1-\eta)\beta T V_i - \delta_i I_i & \text{if } V_i \geq \mathrm{SVR}_{def} \\ 0 & \text{otherwise} \end{cases} \quad \forall i \qquad (2)$$

$$\dot{V}_i = \begin{cases} \sum_j p m_{j,i}(1-\epsilon_j) f_j I_j - cV_i & \text{if } V_i \geq \mathrm{SVR}_{def} \\ 0 & \text{otherwise} \end{cases} \quad \forall i \qquad (3)$$

## Figure 2 Model verification: Comparison between observed and predicted SVR rates in Studies PROVE1, PROVE2, PROVE3, and C208

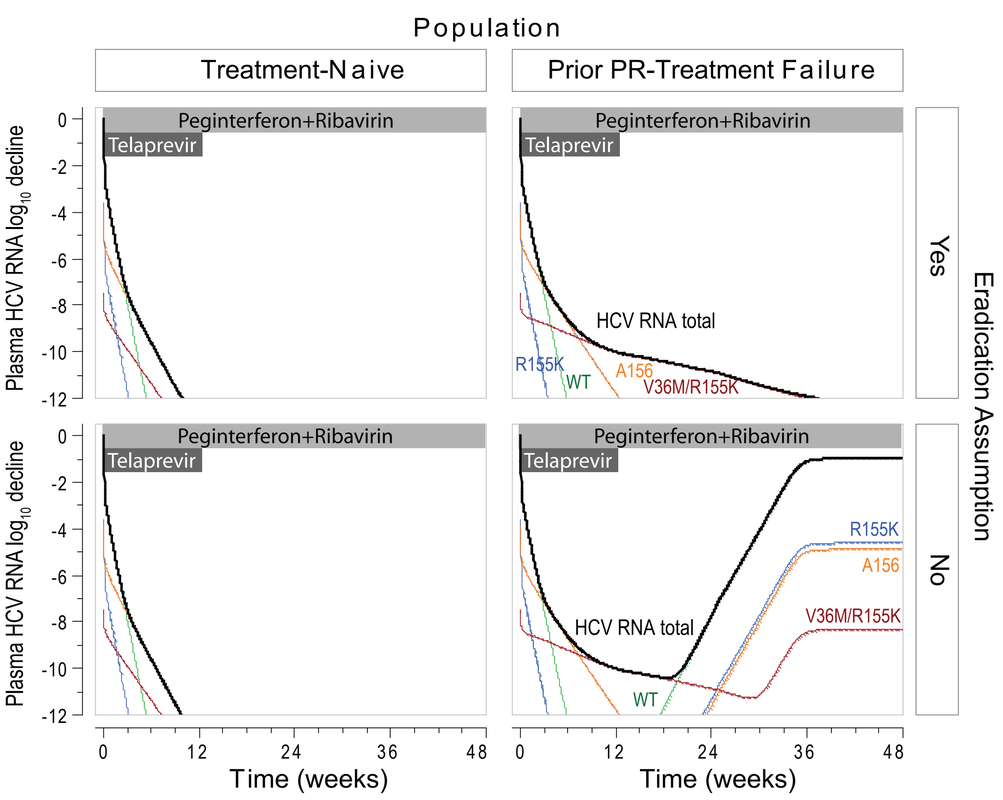



Assumptions: The predictions of Study PROVE3 by prior PR responses (overall, prior relapsers, prior nonresponders) were calculated from a subset of simulated treatment-naïve subjects who had a HCV RNA response of PR treatment that was in agreement with the following definitions: overall PR48-treatment failure, not reaching viral eradication by 48 weeks of PR treatment; prior relapsers, undetectable HCV RNA at the end of treatment but not reaching viral eradication by 48 weeks of PR treatment; prior nonresponders: never had undetectable HCV RNA during 48 weeks of PR treatment.

Notes: The T12PR12 arm (N=17) from PROVE1 and the prior viral breakthrough population from PROVE3 (N=7 in T12PR24 and N=8 in T24PR48) were not included because the sample sizes were too small to predict SVR. The control group (PR48) from PROVE3 was not added because by definition they were failures to PR (SVR rate = zero). Some bounds overlap and therefore are not visible in the figure.

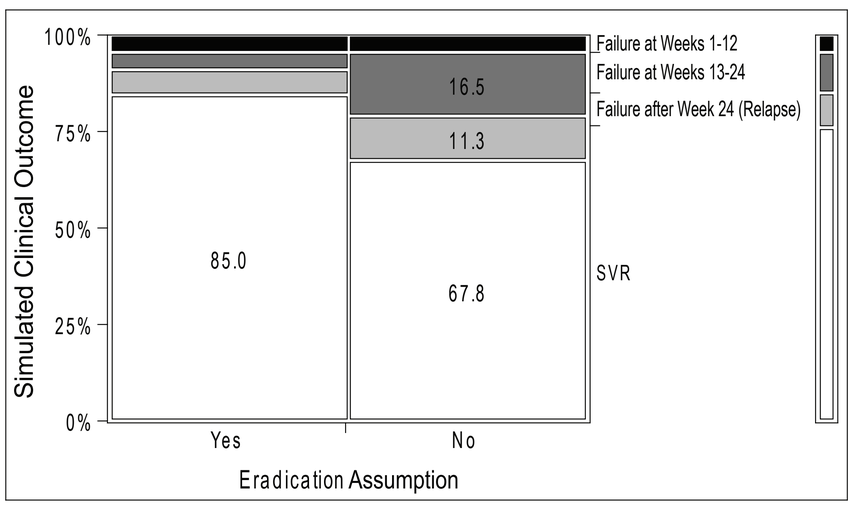
## Figure 3 Simulated viral dynamics of typical subjects on T12PR48 treatment by assumed eradication

Notes: The simulations were for a typical genotype 1a subjects treated with a combination regimen of 12 weeks of telaprevir and 48 weeks of peginterferon and ribavirin, with PR responsiveness of a typical simulated treatment-naïve and a PR-treatment failure subjects. The parameters for the typical PR treatment-failure subject were obtained from median in simulated subjects who failed to reach eradication with 48 weeks of PR treatment. The sensitivity to eradication assumption were performed as follows: "Yes", if variants cannot replicate when their levels are below eradication limit; "No", if variants can replicate when their levels are below eradication limit. The limit of eradication was chosen to be $10^{-5}$ IU/mL, or HCV RNA decline of -12 $\log_{10}$ in a typical patient with HCV RNA baseline level of $10^7$ IU/mL.




## Figure 4 Predicted clinical outcome among treatment-naïve subjects who completed T12PR24 treatment by assumed eradication

Notes: The simulations were for simulated treatment-naïve population, with genotype 1a:1b ratio of 1:1. The sensitivity to eradication assumption were performed as follows: "Yes", if variants could not replicate when their levels were below eradication limit; "No", if variants could replicate when their levels were below eradication limit. The simulated clinical outcomes were defined as follows: Failure at Week 1-12, HCV RNA returns back to detectable levels in the first 12 weeks (during telaprevir treatment); Failure at Week 13-24, HCV RNA levels return back to detectable level during Weeks 13-24 of therapy (during PR treatment, after completion of 12-week of telaprevir treatment); Relapse, HCV RNA undetectable at the end of treatment, but did not reach eradication; SVR, eradicated prior to treatment stoppage. The observed failure rate at Weeks 1-12 were 7%(3), 1% to 5%(4), and 3% to 10%(6); the observed failure rate at Weeks 13-24 were 0% to 1%(4), and 0% to 5%(6); the observed relapse rate in T12PR with PR durations of 24 to 48 weeks (with denominator of all subjects) were 1% to 4%(3), 10%(4), and 2% to 5%.(6) Compared to the simulated outcomes without eradication assumption, the simulated outcomes with eradication assumption matched the observed clinical outcomes better.




## Acknowledgements

Tara Kieffer, Karen Eisenhauer, Robert Kauffman, Frances Smith, Doug Bartels, James Sullivan, Ann Kwong, Shelley George, Scott McCallister, Karen Kumor (employees of Vertex Pharmaceuticals Incorporated)
Maria Beumont-Mauviel, Rudolph Van Heeswijk, Gaston Picchio (employees of Tibotec Inc)

Presented at the 19th meeting of the Population Approach Group in Europe, Berlin, Germany, 8-11 June, 2010

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