

# PK/PD modeling shows adherence can become critical with new HCV regimens

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27 June 2009



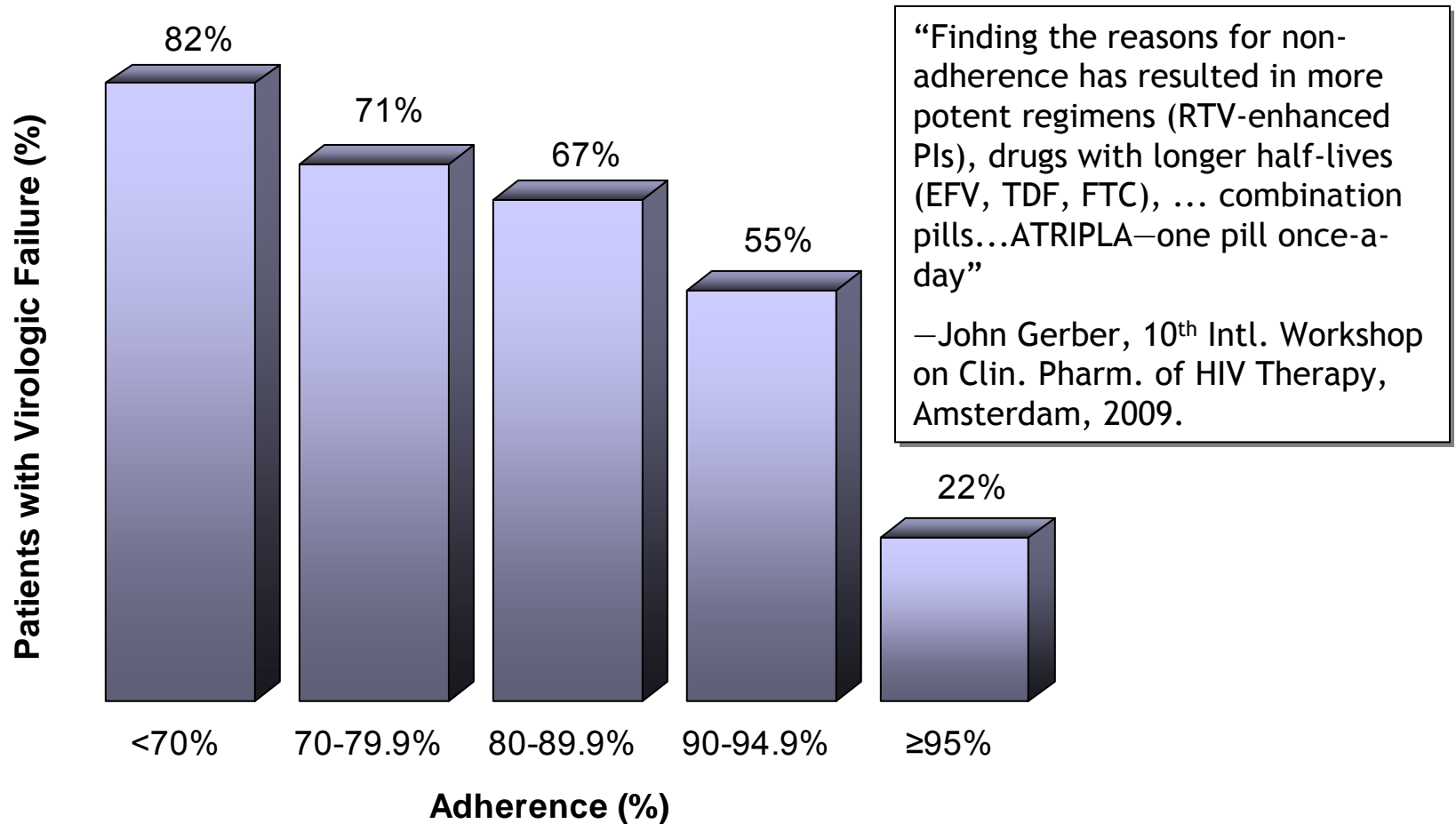
# Agenda

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- We can learn about adherence (compliance) from two decades of HIV treatment experience.
- We can simulate SVRs as a function of regimen and adherence, with integrated drug-disease models.
  - Mechanistic viral dynamics modeling is challenging but useful
  - An adherence sub-model can capture variability across and within patients as well as weakening of adherence over time.
- Short half-lives and high-resistance mutations make many investigational HCV drugs sensitive to adherence
  - especially without the forgiving standard of care backbone.
  - Classic viral dynamics models may underestimate this!



# In HIV therapy we learned adherence can be critical to successful viral suppression, especially with the older, less forgiving regimens.



Source: Paterson DL et al., Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection, *Ann Intern Med.* 2000;133:21-30 (99 protease inhibitor patients, various regimens and experience).



## Inadequate adherence leads to resistant mutations.

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- As drug concentrations become sub-therapeutic after missed doses, **resistant** virus—no longer suppressed—**outcompetes** wild-type virus—still suppressed.
  - One-step mutations are a stepping stone to multiple mutations of highly resistant virus.
- As drug concentrations continue to drop, **wild-type** virus is no longer suppressed and **outcompetes** the less fit resistant virus again.
- Thus there is a **window of** time with **selective pressure** favoring growth of resistant virus, every time a patient misses a dose or two.



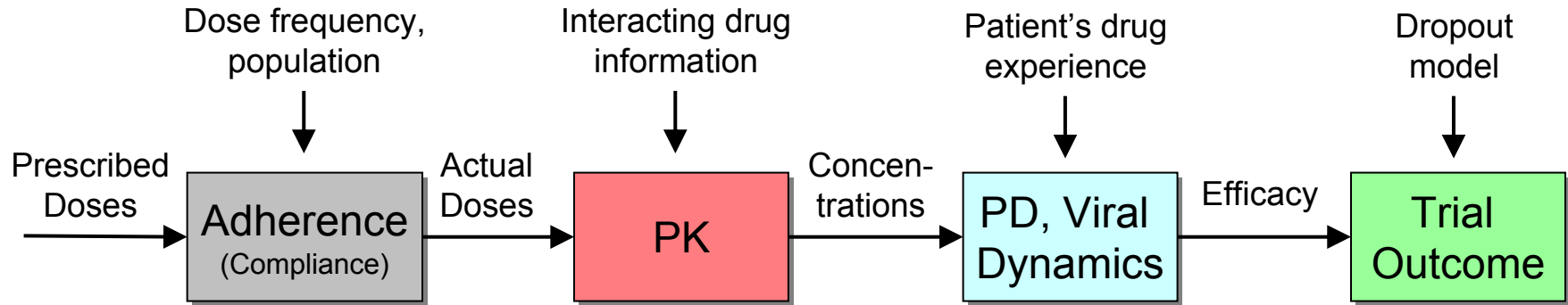
In HCV treatment, adherence has not been a big issue—so far.

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- PEG-IFN+RBV is a very forgiving regimen, because both drugs have long half-lives and do not induce resistance.
- **80-80-80 Rule:** take 80% of your prescribed interferon and 80% of your prescribed ribavirin for 80% of the time.
  - Ref.: McHutchinson et al. 2002, Adherence to Combination Therapy Enhances Sustained Response in Genotype-1-Infected Patients With Chronic Hepatitis C. *Gastroenterology* 123:1061-1069 ([www.spcorp.com.cn/upfile/McHutchisonGastroenterologyOctober2002.pdf](http://www.spcorp.com.cn/upfile/McHutchisonGastroenterologyOctober2002.pdf))
  - “controversial because it has not been studied in well designed prospective clinical trials ... questions of adherence will become even more important in the future with the development of anti-viral therapies such as HCV protease and helicase inhibitors...”  
([www.hcvadvocate.org/hepatitis/factsheets\\_pdf/Adherence.pdf](http://www.hcvadvocate.org/hepatitis/factsheets_pdf/Adherence.pdf))



# An integrated HCV drug-disease-trial model links relevant sub-models.

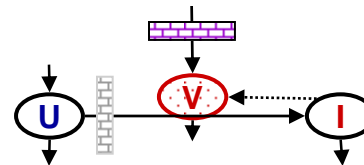


**Typical model:**  
 Distribution for interpatient variability in overall *average* doses taken/doses prescribed (0%-100%); sometimes *clustering* (drug holidays); dose *timing* error

**Typical model:**  
 Compartmental, inter-subject & intra-subject variability, sometimes enzyme induction/inhibition

**Typical model:**  
 Viral inhibition =  $\text{conc.} / (\text{conc.} + \text{IC}_{50})$ ; (1-inhibition) multiplies viral birth rate in predator-prey equations for target cells and virus, with multiple viral strains

**Typical trial endpoint:**  
 Proportion of patients with SVR

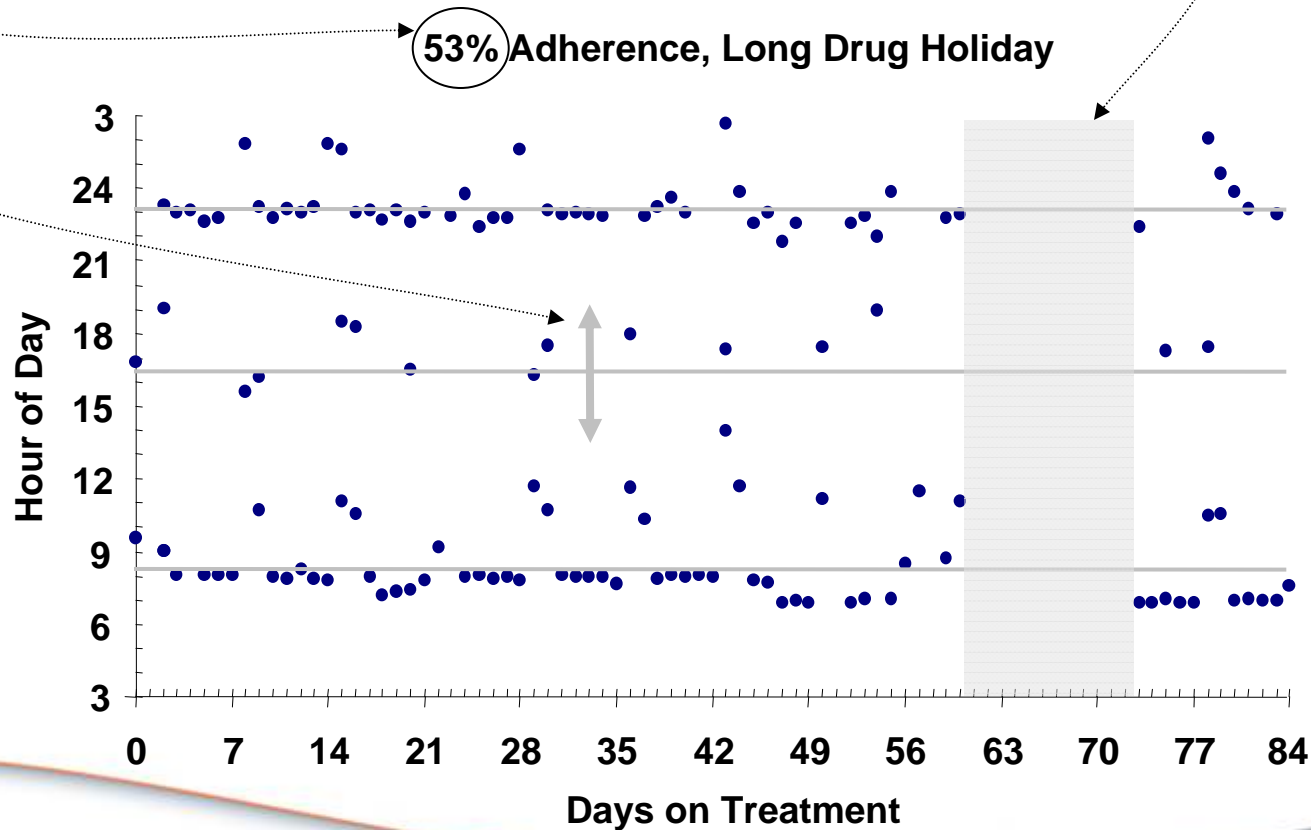


**U=uninfected cells**  
**I= infected cells**  
**V=virus**



# Several dimensions of adherence variability can be modeled.

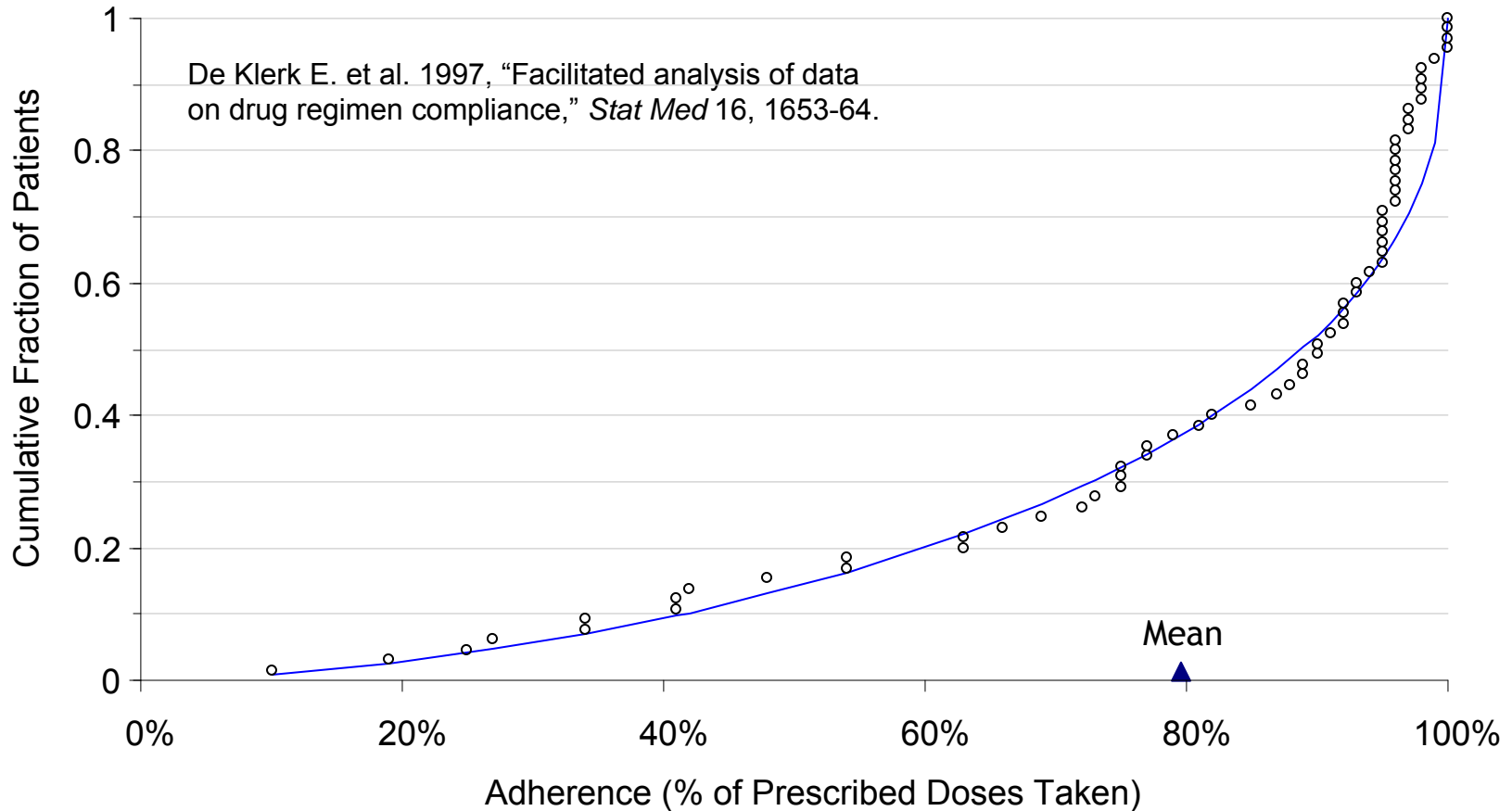
- Long-run proportion of prescribed doses actually taken
- Clustering of missed doses into “holidays”
- Dose timing error around prescribed dose times
- Adherence decrease over long periods (not shown)





# Variability across patients is high but can be approximated by a two-parameter distribution.

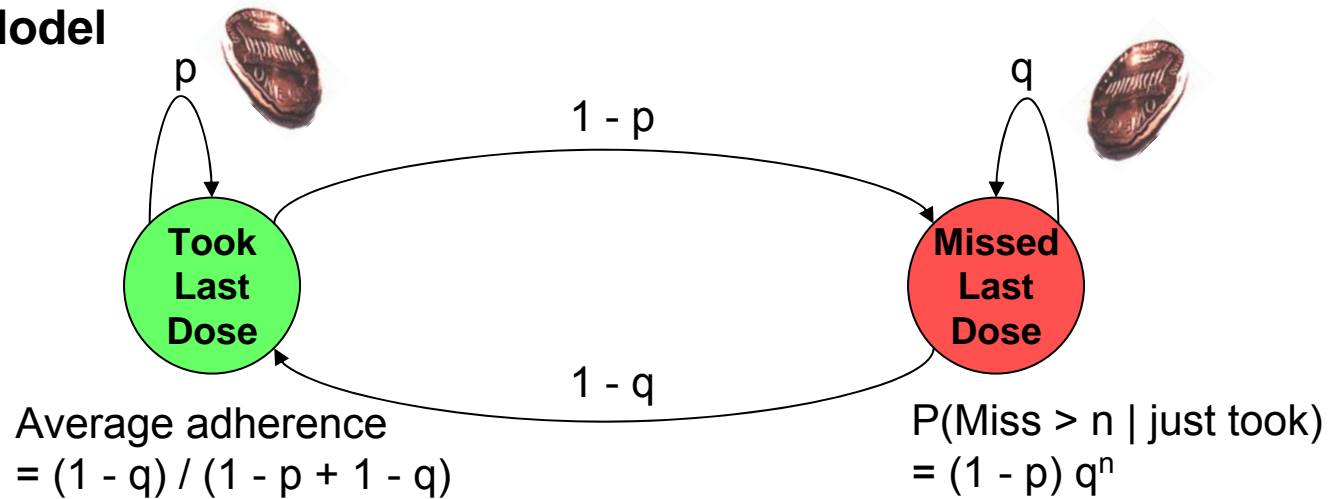
65 QD NSAID Patients' Average Adherences, with Fitted Beta Distribution



A Beta or log-odds-transformed normal distribution can be fitted to the mean and variance of the data.

 Individual dose-taking patterns can be modeled by a one-coin or two-coin Markov model and Normal timing error.

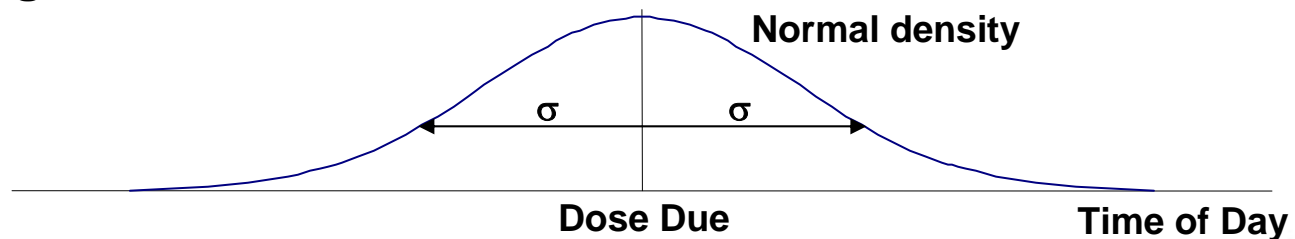
**Two-Coin Model**



**One-Coin Model**

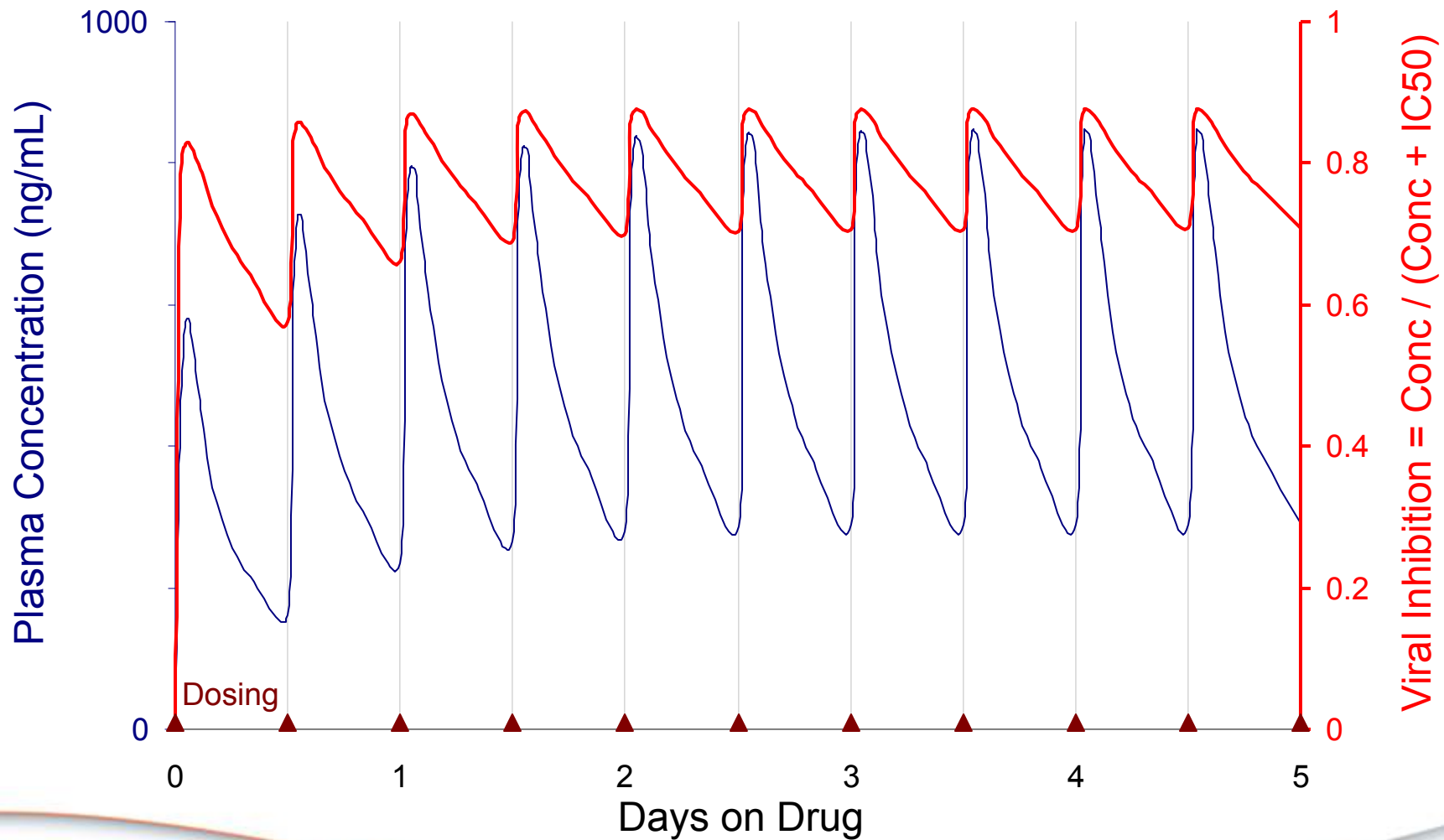
Special case of above with  $q = 1 - p$ , so  $P(\text{Take} \mid \text{just took}) = P(\text{Take} \mid \text{just missed})$ .  
 Then average adherence =  $p$ ,  $P(\text{Miss} > n \mid \text{just took}) = (1-p)^{n+1}$  (geometric distribution).

**Dose Timing**





PK models integrate a system of differential equations for drug absorption and clearance. Viral inhibition driven by concentrations in a simple Emax model has a more blunt sawtooth profile.



 Viral dynamics models describe hepatocyte infection and virus life cycle with differential equations. Resistant virus is easily incorporated.

## Hepatitis C Viral Dynamics in Vivo and the Antiviral Efficacy of Interferon- $\alpha$ Therapy

Avidan U. Neumann,\*† Nancy P. Lam,\*‡ Harel Dahari,  
David R. Gretch, Thelma E. Wiley, Thomas J. Layden,  
Alan S. Perelson

To better understand the dynamics of hepatitis C virus and the antiviral effect of interferon- $\alpha$ -2b (IFN), viral decline in 23 patients during therapy was analyzed with a mathematical model. The analysis indicates that the major initial

$$dT/dt = s - dT - (1 - \eta)\beta VT \quad (1)$$

$$dI/dt = (1 - \eta)\beta VT - \delta I \quad (2)$$

$$dV/dt = (1 - \epsilon)pI - cV \quad (3)$$

where  $T$  is the number of target cells,  $I$  is the number of productively infected cells, and  $V$  is the viral load. Target cells are produced at rate  $s$  ( $14$ ) and die with death rate constant  $d$ . Cells become infected with de novo infection rate constant  $\beta$  and, once infected, die with rate constant  $\delta$ . Hepatitis C virions are produced by infected cells at an average rate of  $p$  virions per cell per day and are cleared with clearance rate constant  $c$ . The possible effects of IFN in this model are to reduce either the production of virions from infected cells by a fraction  $(1 - \epsilon)$  or the de novo rate of infection by a fraction  $(1 - \eta)$ .

Neumann AU et al. *Science* 1998;282:103-107.

Neumann's seminal 1998 modeling paper showed IFN blocks virus production not cell infection ( $\eta=0$ ).

Dixit 2004 (*Nature* 432:922-924) incorporated ribavirin yielding uninfected virus with another differential equation.

Many refinements have been proposed, such as hepatocyte proliferation.

Challenge: obtaining reliable parameter values. For example, for the same short-term fit to viral load data we can get different long-term predictions by varying uninfected cell death rate.

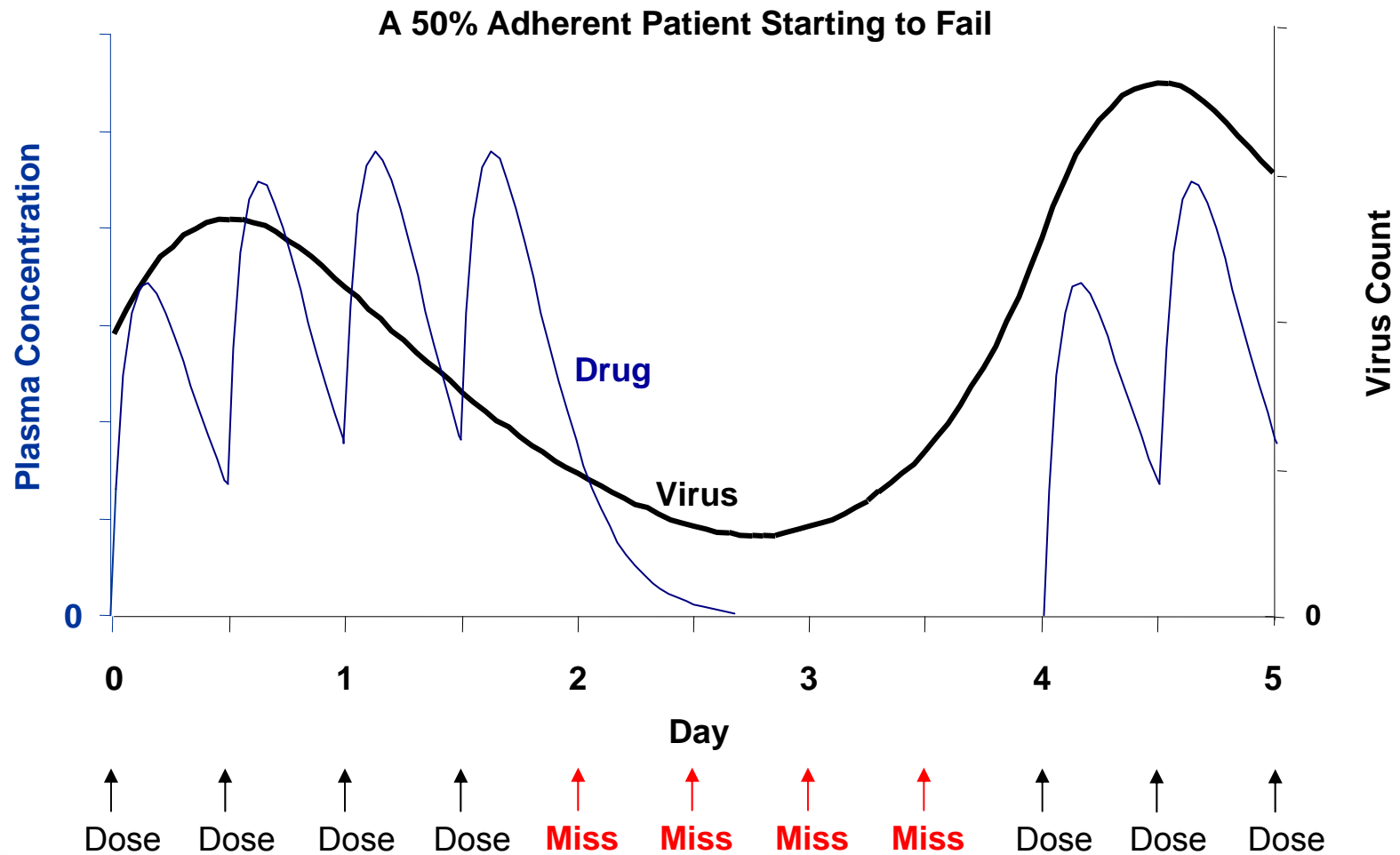


## Estimating the viral dynamics parameters is challenging. We fix some of them based on literature and use NONMEM or a similar program.

- We need at least 7 unobservable parameters: birth and death rates of uninfected cells and virus, infection rate constant and death rate for infected cells, and treatment potency (*in vivo* IC50)
  - plus interindividual variability (usually assumed lognormal) for these.
- These are not all identifiable from the usual data: short-term monotherapy viral loads by patient before, during, and (sometimes) after treatment.
  - We typically fix the viral turnover rates to mid-range literature values.
- Estimation tricks of the trade:
  - Assume all patients are at **steady state at baseline** before treatment. This constrains some parameters.
  - Eliminate an unobservable parameter by **scaling** the equations (so they are dimensionless).  
Ref.: Verotta D and Schaedeli F. Non-linear dynamics models characterizing long-term virological data from AIDS clinical trials. *Mathematical Biosciences* 176: 163-183, 2002.
  - Directly estimate **reproductive ratio**, a function of the parameters that determines whether the virus dies out (if  $< 1$ ) or has a steady state (if  $> 1$ ).
  - Summarize PK between doses with **Equivalent Constant Concentration**.  
Ref: Poland B. Equivalent Constant Concentration Summarizes Pharmacokinetics in HIV and HCV PK/PD Modeling. ACoP, Poster 36, Tucson, AZ, March 9-12, 2008. [http://tucson2008.go-acop.org/pdfs/36\\_Poland.pdf](http://tucson2008.go-acop.org/pdfs/36_Poland.pdf).
  - MAYBE estimate with **long-term** as well as short-term data, though this introduces lots of uncertainties: combination drug and resistance effects, dropouts, missing data, and of course adherence issues!

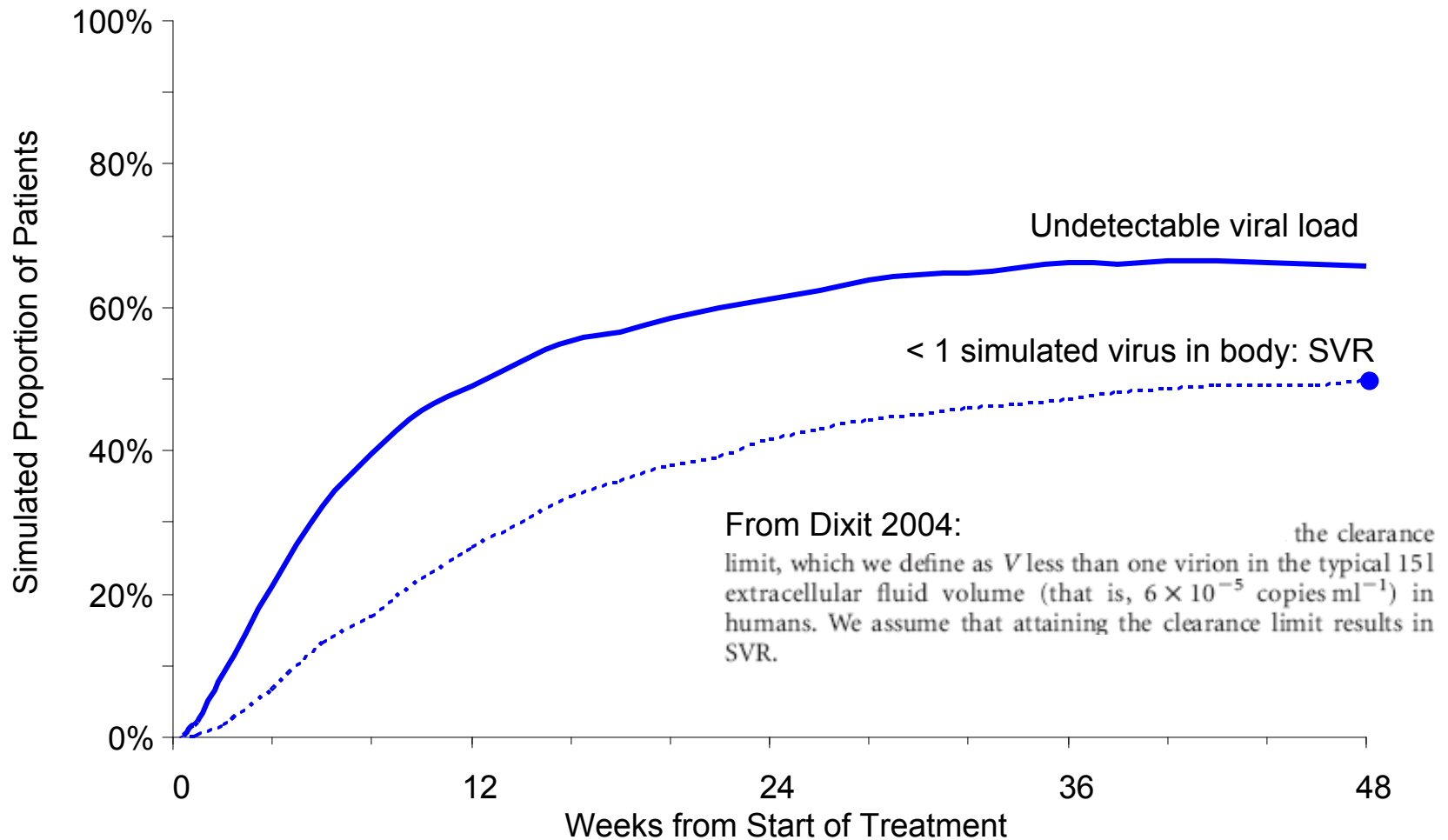


# The model predicts drug concentrations and viral load for any adherence pattern.





With a viral dynamics model we can simulate not only the proportion of patients with undetectable virus but the proportion with no more virus—which at end of treatment represents SVR rate.





## Models can test sensitivity of SVR to adherence in:

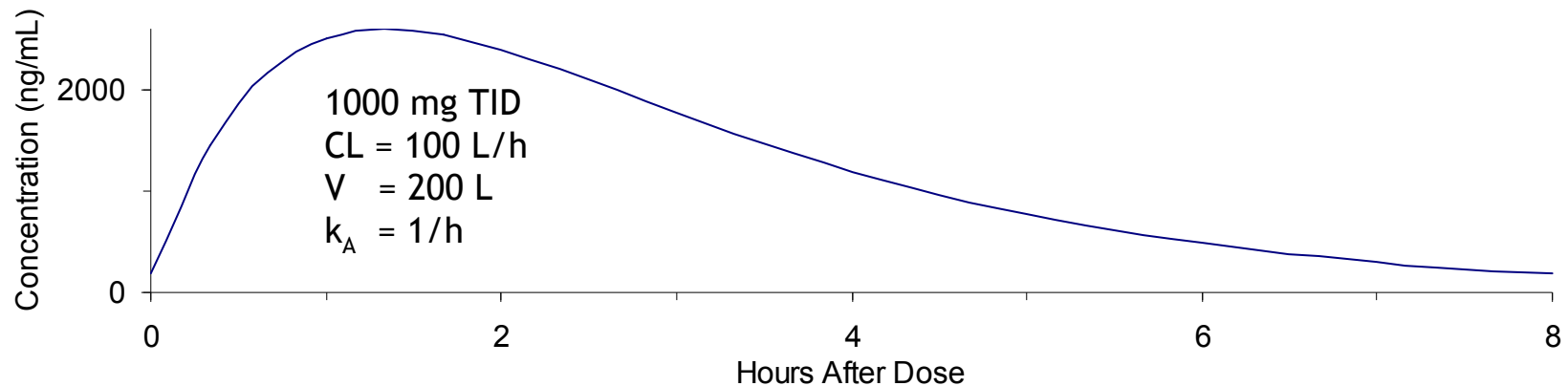
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- SoC treatment
- SoC + X treatment, where X needs to be dosed frequently and has highly resistant mutations
- X + Y dual treatment, where Y also needs to be dosed frequently and has highly resistant mutations.



## The illustrative simulations that follow make some assumptions:

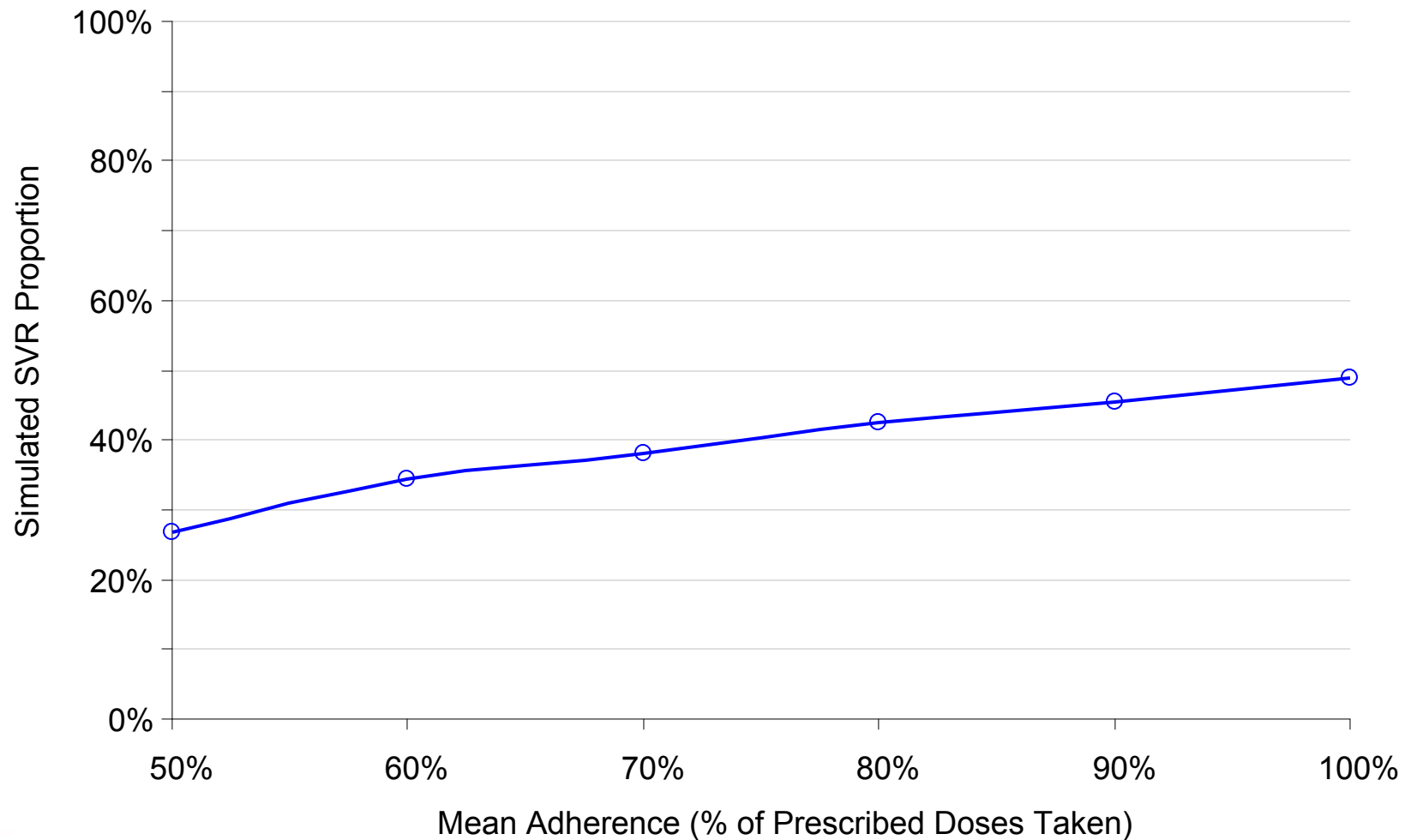
- For each adherence level, the same large patient population is simulated over a year
  - using Pharsight Trial Simulator 2.2.
- Drug X is given a fairly steep PK profile:



- IC<sub>50</sub> = 5 ng/mL but 100-fold resistance (IC<sub>50</sub>=500 ng/mL) is allowed to develop.
- Drug Y has the same PK and resistance profile as X; we'll ignore cross-resistance.
  - Four viral strains are modeled: wild-type, resistant to X only, resistant to Y only, and resistant to both.
- When a dose is missed, all drugs to be taken then are missed together.
- For each patient, overall adherence rate is a random draw from a distribution with the specified mean adherence. Individual misses are random, independent of previous misses
  - except for a sensitivity case with clustering of missed doses.

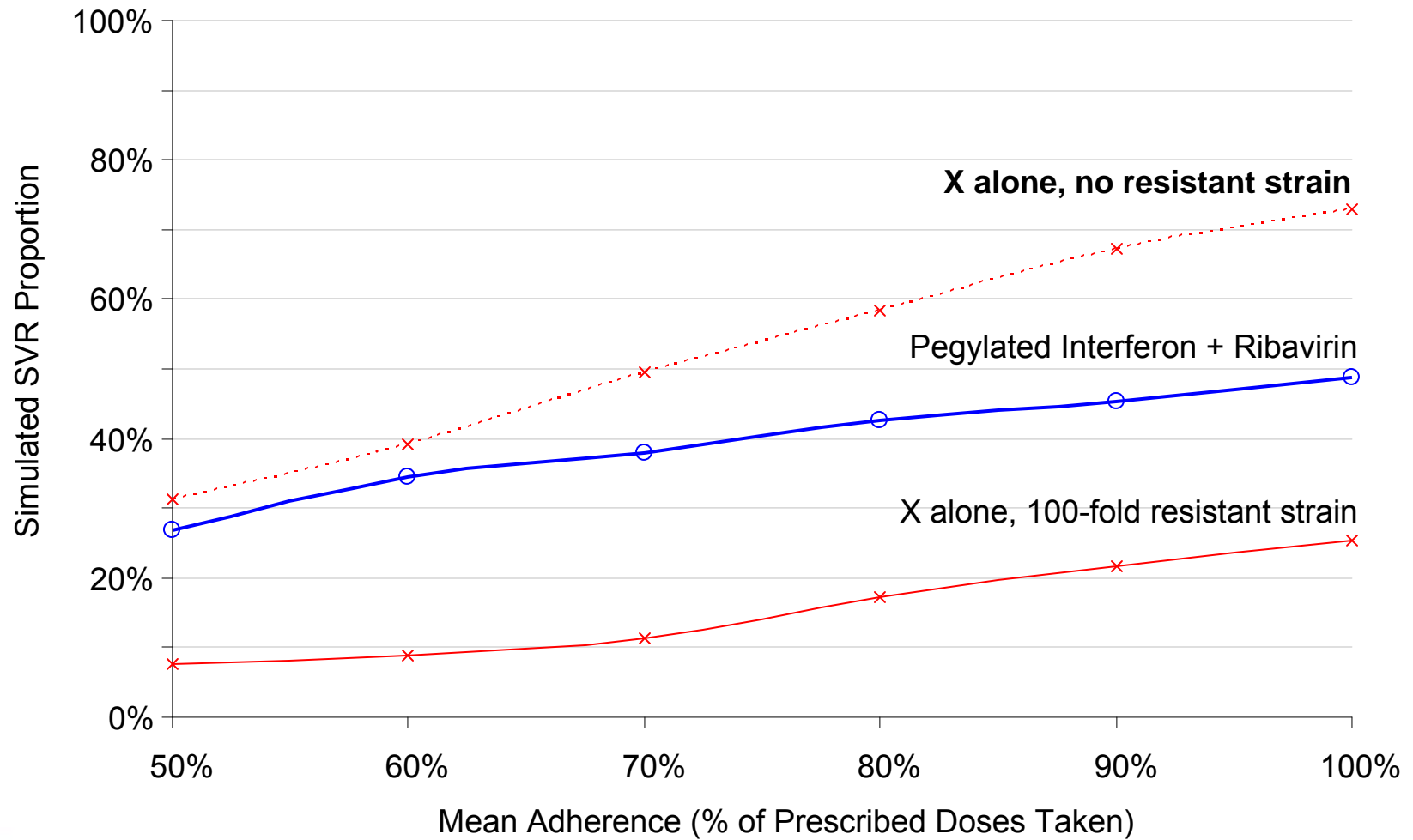


# This simulation of pegylated interferon + ribavirin in G1 patients shows modest sensitivity to adherence.



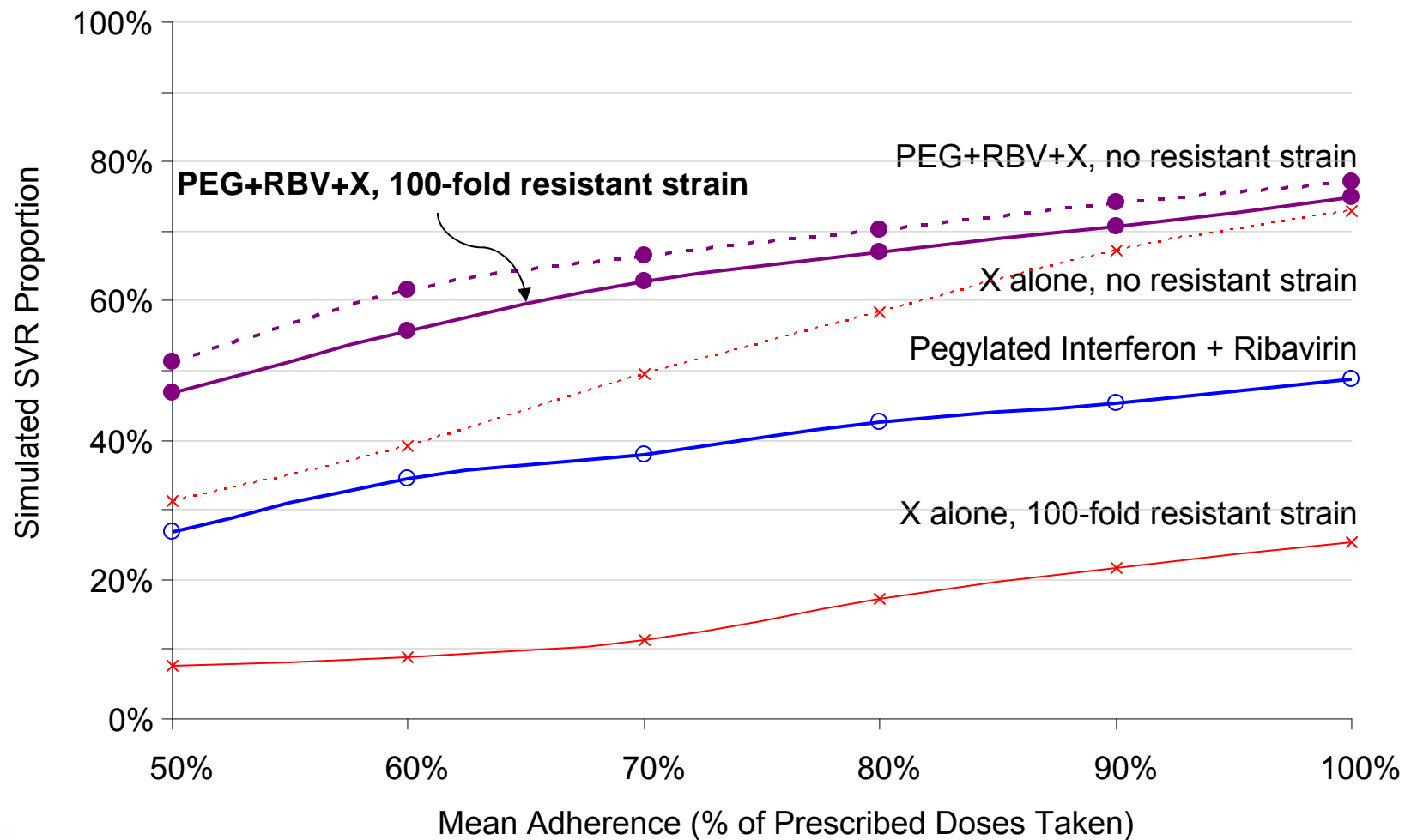


# Performance of drug X alone is more sensitive to adherence.



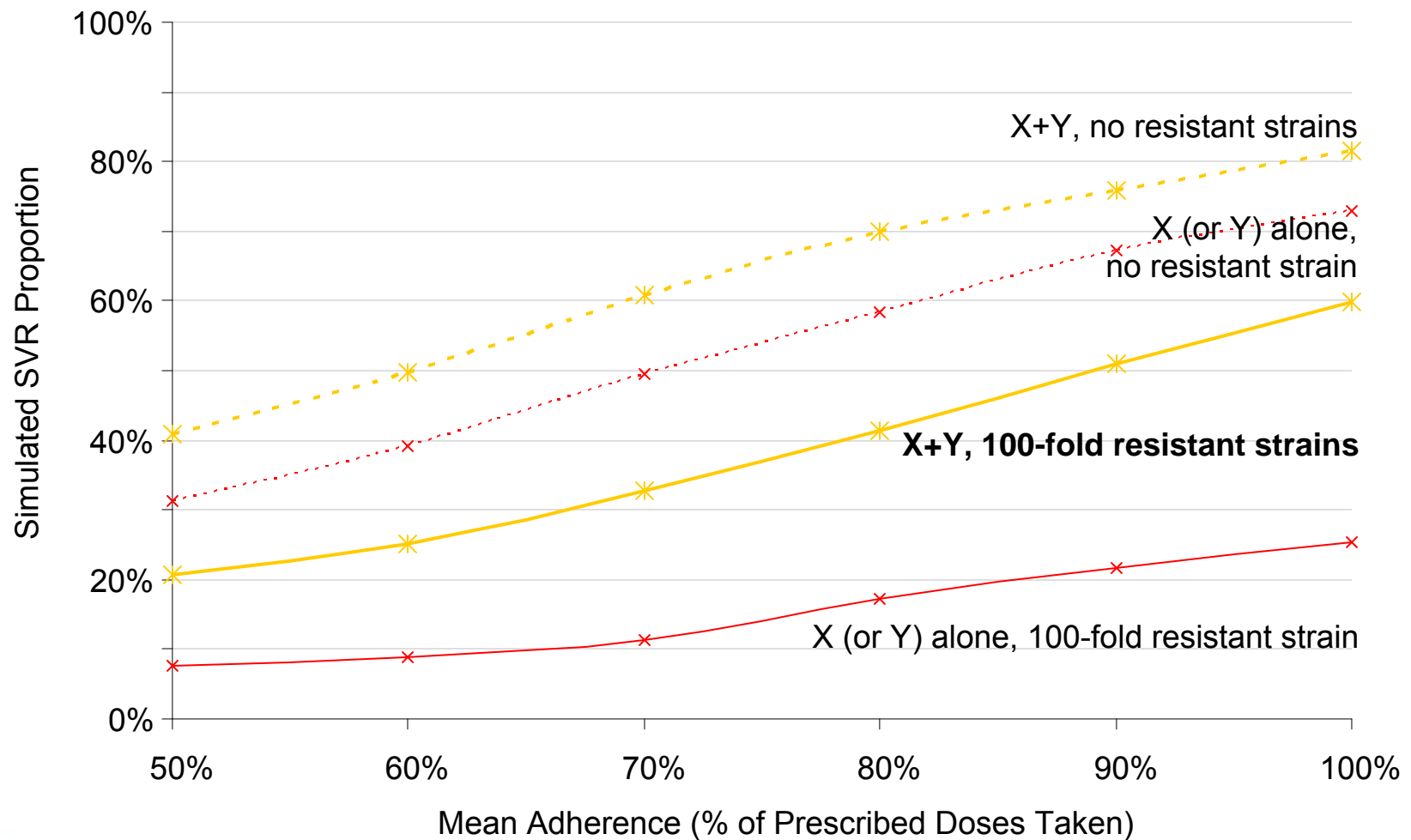


# Combining X with PEG+RBV reduces adherence sensitivity—and reduces the impact of a highly drug-X-resistant strain.



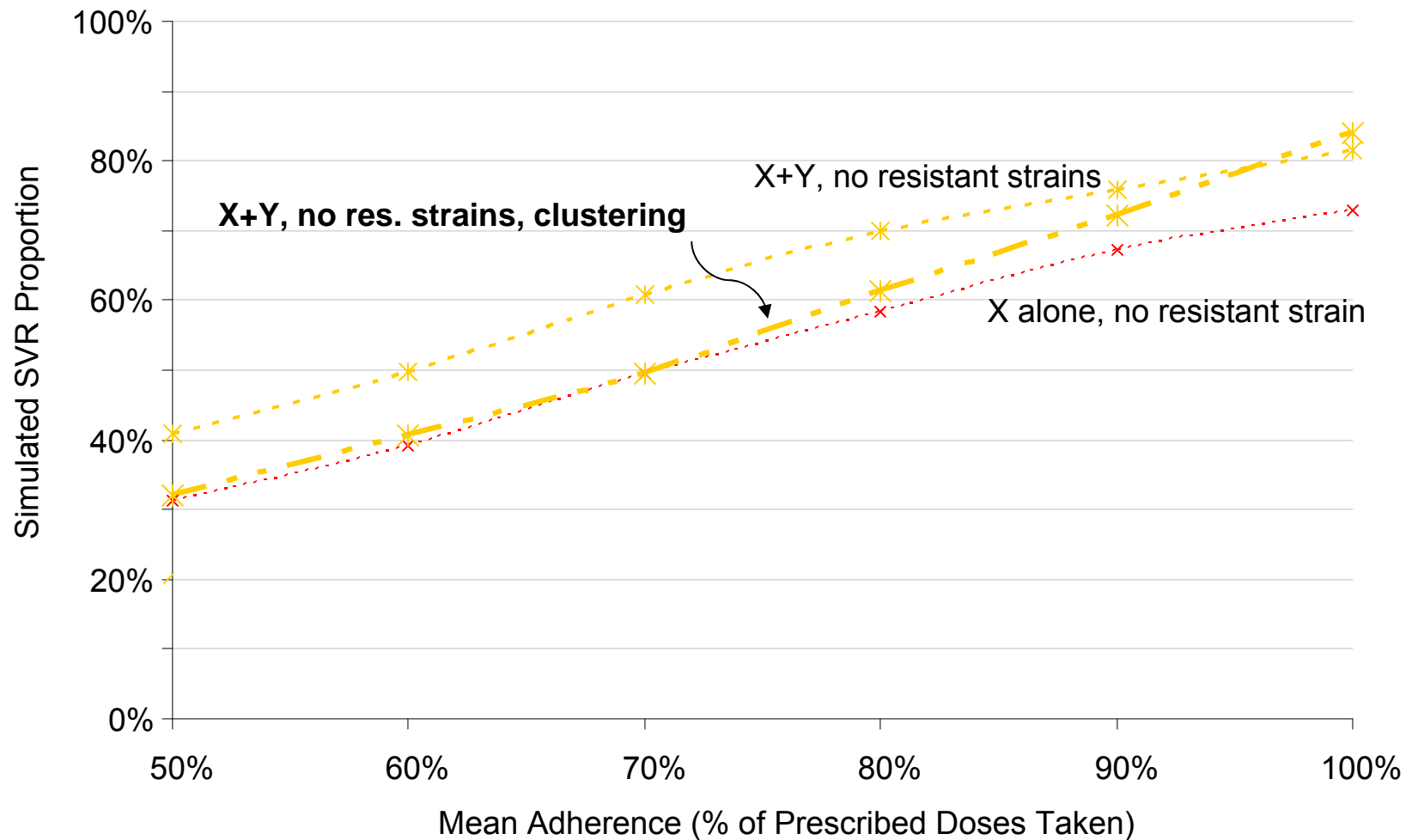


# Combining X with Y in dual therapy improves response but does not reduce sensitivity to adherence.





# Clustering of missed doses increases sensitivity further.



Clustering uses two-coin model with  $P(\text{take} \mid \text{missed last dose})$  set to  $\frac{1}{4}$  of  $P(\text{take} \mid \text{took last dose})$ .



In conclusion, short half-lives and high-resistance mutations can make investigational HCV drugs especially sensitive to adherence.

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- Adherence will become more important in regimens including such drugs and critical if they exclude PEG-IFN+RBV (or similar forgiving drugs).
  - As in HIV until the advent of forgiving drugs efavirenz etc. (which will also have analogues in HCV soon).
- Sensitivity to adherence is likely to be greater than the simulations illustrated, because:
  - the simulation model is not fully probabilistic, so it does not include non-pre-existing mutations arising during the window of **selective pressure** after missed doses
  - cross-resistance wasn't considered.
- Counsel patients; monitor adherence; try to simplify regimens to once or twice a day!



## Integrated modeling can address questions such as:

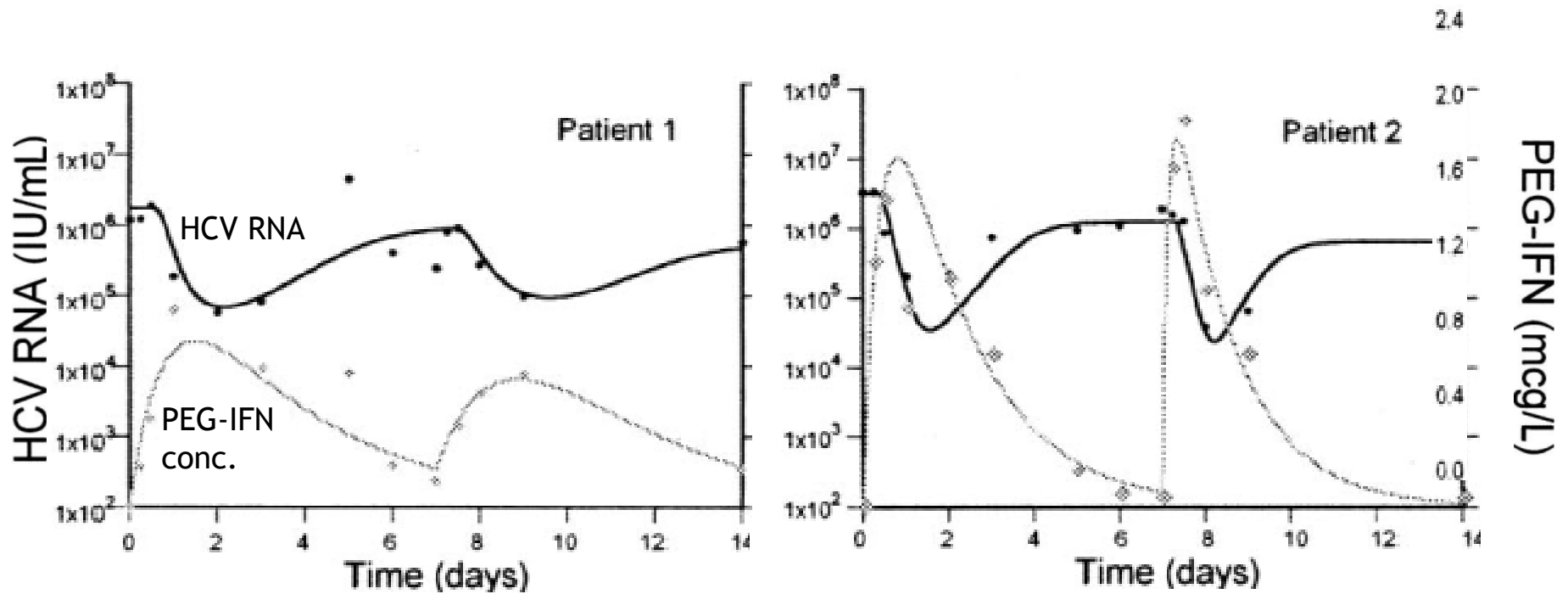
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- Will the adherence benefits of a BID or QD formulation outweigh the potential loss of therapeutic coverage?
- How do alternative regimens compare, e.g.,  
 $X + \text{SoC}$  vs.  $X + Y + \text{SoC}$  vs.  $X + Y$ ?
- How do alternative trial designs (doses, arm sizes, etc.) compare?
- Is a regimen likely to be competitive?



## Discussion Points (I)

Hypothesis: the weekly swings in viral load as PEG-IFN wears off would cause rapid resistance development for other drug classes.



Talal AH et al. 2006, *Hepatology* 43:943-953.



## Discussion Points (II): Adherence in Practice

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- Adherence tends to deteriorate over 48 weeks of treatment because of cumulative tolerability problems.
  - Especially ribavirin: self-reported results in Smith et al. 2007, *Annals of Pharmacotherapy* 41:1116-23 were 91% at 4 weeks, 85% at 12 weeks, 83% at 24 weeks, 76% at 36 weeks, 75% at 48 weeks
- Adherence correlates strongly across drugs in the regimen: doses are missed together.
- Measured adherence has been found to correlate strongly with SVR
  - both for standard of care drugs and third agents.



## Discussion Points (III): Reconciling HCV Treatment Models with Long-Term Data

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- Problem:
  - standard viral dynamics models seem to predict that undetectable rates increase and then perhaps plateau but not decrease ...
  - while Intent-To-Treat undetectable rates typically decrease (gently) over weeks 24-48.
- Resolution:
  - ITT undetectable rates are pulled down by non-virological dropouts (AEs, loss to followup) *and* missing data.
  - Removing these flattens undetectable rates over weeks 24-48.
  - Of course we need to model and subtract dropouts at the end to get realistic response rates.
- For modeling purposes Missing  $\neq$  Failure!  
Example rules for reducing bias in reported response rates over time:
  - Negative - Missing - Negative: treat as Negative.
  - Negative - Missing - Positive OR Positive - Missing - Negative: exclude missing patient from numerator & denominator.



## Discussion Points (IV): What Extensions to Standard Models Are Important?

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- This depends on the purpose.
  - Example: resistance development (except for drugs like IFN & RBV), dropouts, and adherence are usually important for predicting long-term trial outcomes, but may be unnecessary for short-term modeling.
- Problem: too many parameters, too little data already!
  - Recommendation: use the simplest model that explains the data reasonably well.
- Example extension: hepatocyte re proliferation
  - A modeler at another company wrote me: “I spoke to a couple of scientists from Perelson's group ... they got the same results with and without the proliferation terms” when resistance was also incorporated (though not when resistance was omitted).