

Using *in vitro* and literature data to predict effects of new antiretrovirals

Bill Poland, PhD

Lead Scientist, Pharsight Corporation

bpoland@pharsight.com

ASCPT, 4 April 2008

Agenda

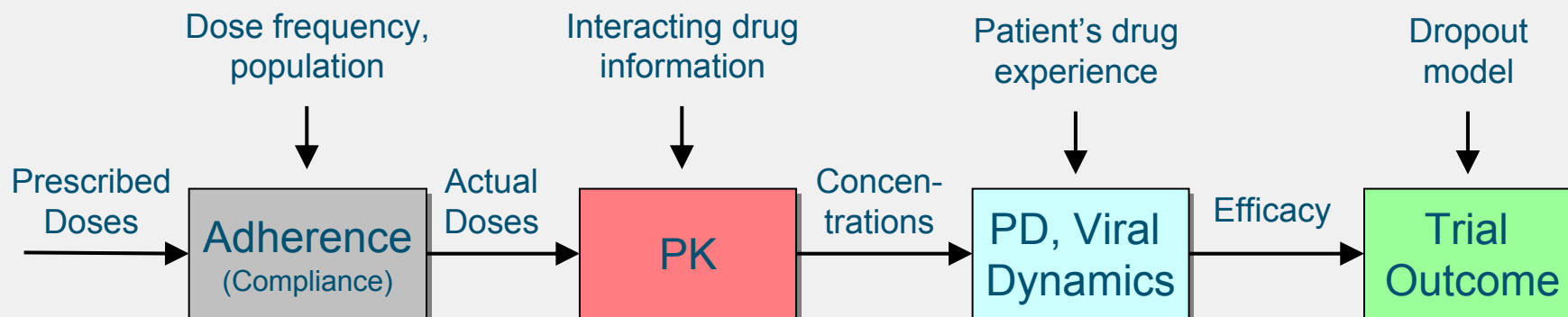
Integrated antiviral drug-disease-trial modeling

Approaches Using *In Vitro* and Literature Data

Examples:

- Planning a Phase 2A trial by comparing to a more advanced drug
- Understanding a Phase 2B failure

To support antiviral development planning, it is important to integrate relevant models.

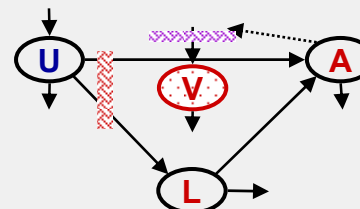


Typical model:
 Distribution for interpatient variability in overall *average* doses taken/doses prescribed;
 sometimes *clustering* (drug holiday) submodel; normal dose *timing* error

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

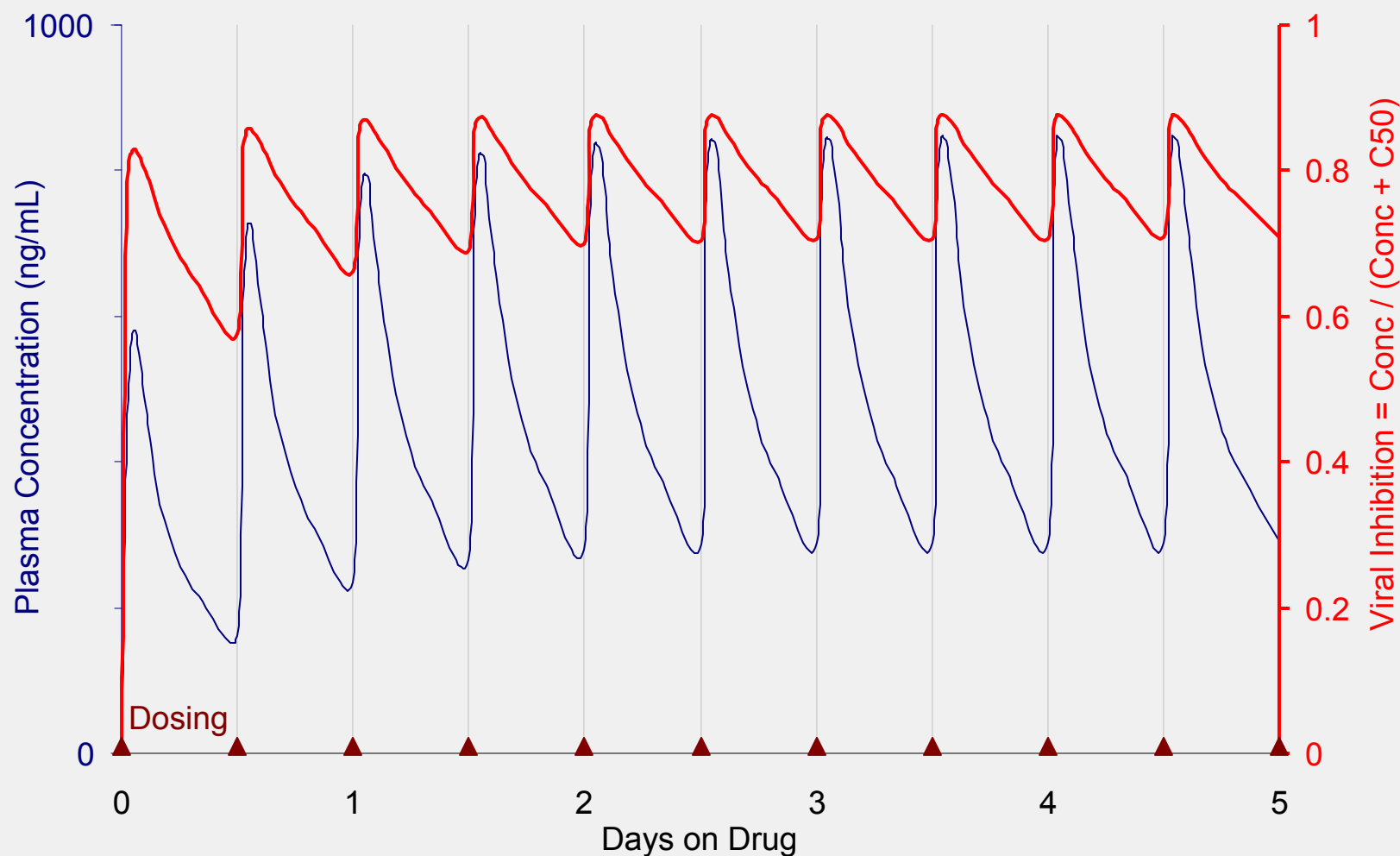
Typical model:
 Viral inhibition = $\text{conc.} / (\text{conc.} + C50)$;
 (1-inhibition) multiplies infectivity rate in predator-prey equations for target cells & virus, with multiple viral strains.

Typical trial endpoints:
 Fraction of patients with viral load < 50 copies/mL after 48 weeks treatment (“success rate”); mean decrease in \log_{10} viral load.



U=uninfected cells
A=actively infected cells
L=latently infected cells
V=virus

Viral inhibition is typically modeled as a simple function of concentration, giving it a more blunt sawtooth time-profile than concentration.

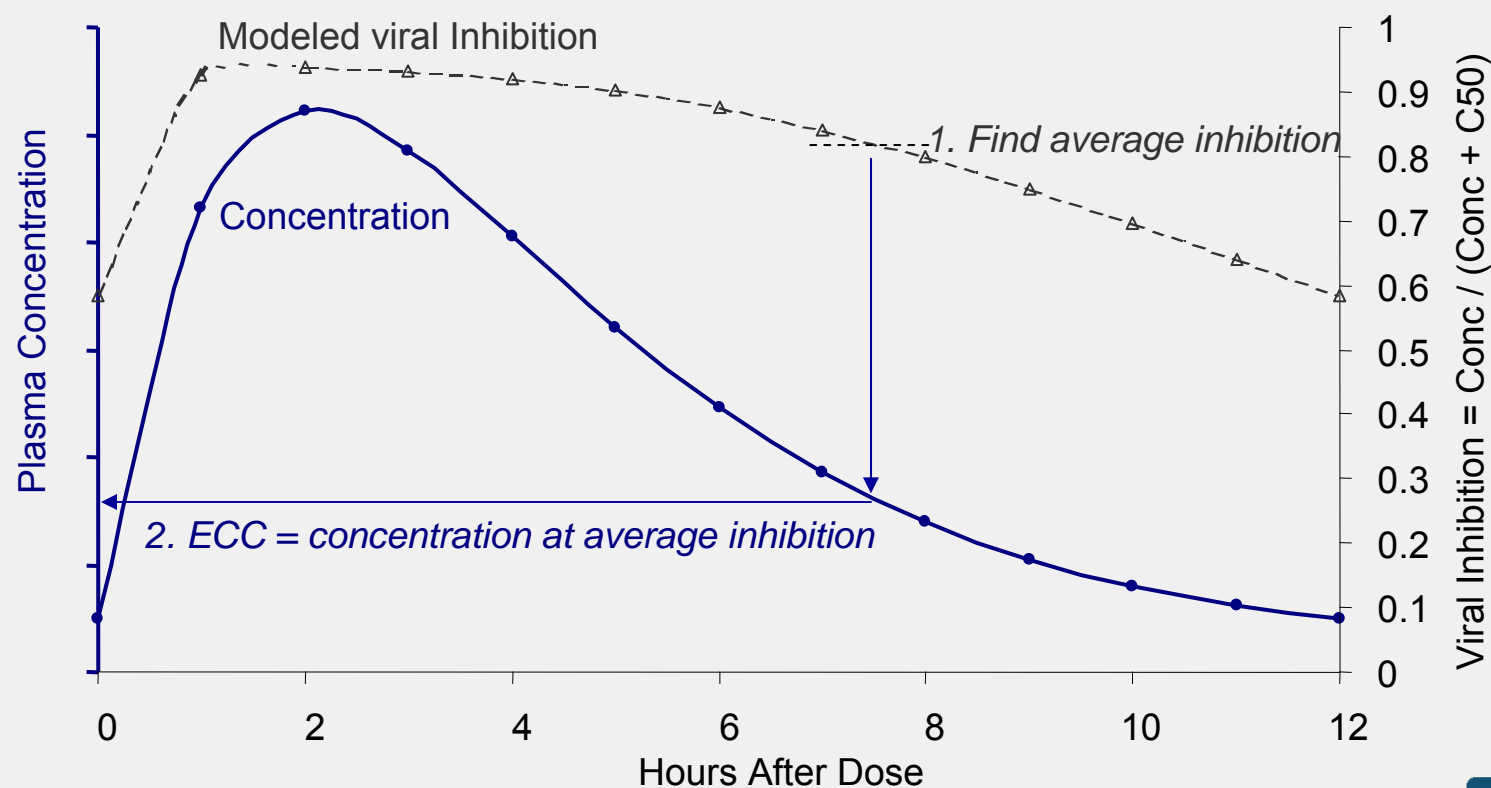


PK-PD modeling can be simplified with “equivalent constant concentration” (ECC).

ECC is the concentration that gives the same *average* effect (viral inhibition) over time (typically one inter-dose interval) as the true time-varying concentration.

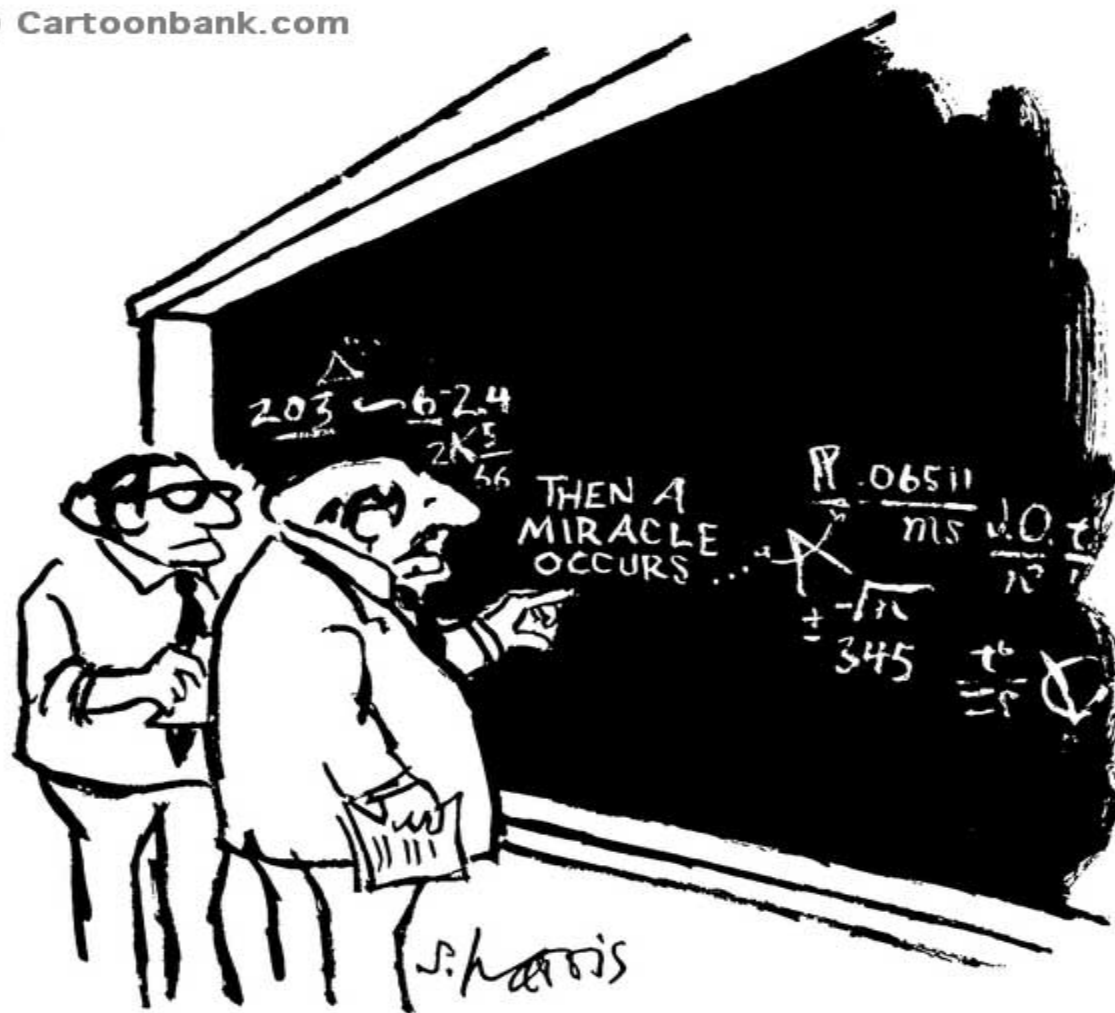
- It is most useful after concentrations reach steady-state, because then it is constant.

It can be used to quickly calculate equivalent doses for new formulations, once-a-day vs. twice-a-day dosing, etc., as well as to predict long-term response.



Are you up for some math?

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"I think you should be more explicit here in step two."

What's that "C50" in the viral inhibition and ECC calculation?

It's the concentration that gives half the maximum viral inhibition in a patient.

- Viral inhibition affects viral load, so it's an inhibitory concentration for drug effect.

C50 and viral inhibition are unobservable, so we estimate them with an integrated PK-PD-viral dynamics model and monotherapy study data.

- They depend on the model used!
- C50 can be quite different from *in vitro* IC50 (which we would correct for protein binding attenuation before comparing).

The simplest Emax inhibition model is

$$\text{Inh}(t) = C(t) / (C(t) + C50) = 1 - 1 / (1 + C(t)/C50)$$

Solving for C(t):

$$C(t) = C50 \text{ Inh}(t) / (1 - \text{Inh}(t))$$

Inhibition depends only on ratio of conc. to C50.

Conc. for any given inhibition

Therefore

$$\text{ECC} = C50 \text{ Inh}_{\text{avg}} / (1 - \text{Inh}_{\text{avg}})$$

Conc. for avg. inhibition

We could easily incorporate a Hill coefficient to get a more general Emax model.

Reproductive ratio calculated with ECC allows fast approximation of long-term success rate of an antiviral regimen.

Reproductive ratio R_0 = average number of secondary infected cells produced by the first infected cell (introduced in a wholly susceptible population).

- It varies across patients and time.

The virus is suppressed only if $R_0 < 1$.

R_0 ignoring latently infected cells (a simple generalization) is just

$$\lambda \beta' p / (d d_A c)$$

where β' is $\beta(1-\text{inhibition})$ if being treated. This pops out of the basic viral dynamics equations:

Uninfected cells U: $dU/dt = \lambda - \beta' U V - d U$

Infected cells A: $dA/dt = \beta' U V - d_A A$

Virus V: $dV/dt = p A - c V$

Birth rates

Infection rate

Death/clearance rates

R_0 varies by patient, so the long-term success rate is just the fraction of patients for which $R_0 < 1$ with treatment.

- Note more variability pushes more patients' $R_0 > 1$, i.e., it increases failures.

How can we best estimate all these parameters from available clinical trial data? Literature data helps.

Even in the simplest model we need the 6 parameters constituting R_0 , and each drug's C50 for viral inhibition (with interindividual variability).

At best our data includes concentrations and viral loads by patient and time.

- CD4 cell counts are hard to use because only *activated* CD4 cells enter viral dynamics.

Literature helps for some parameters, but ranges are wide. So we fix some parameters to mid-range literature values and estimate the rest using short-term monotherapy data.

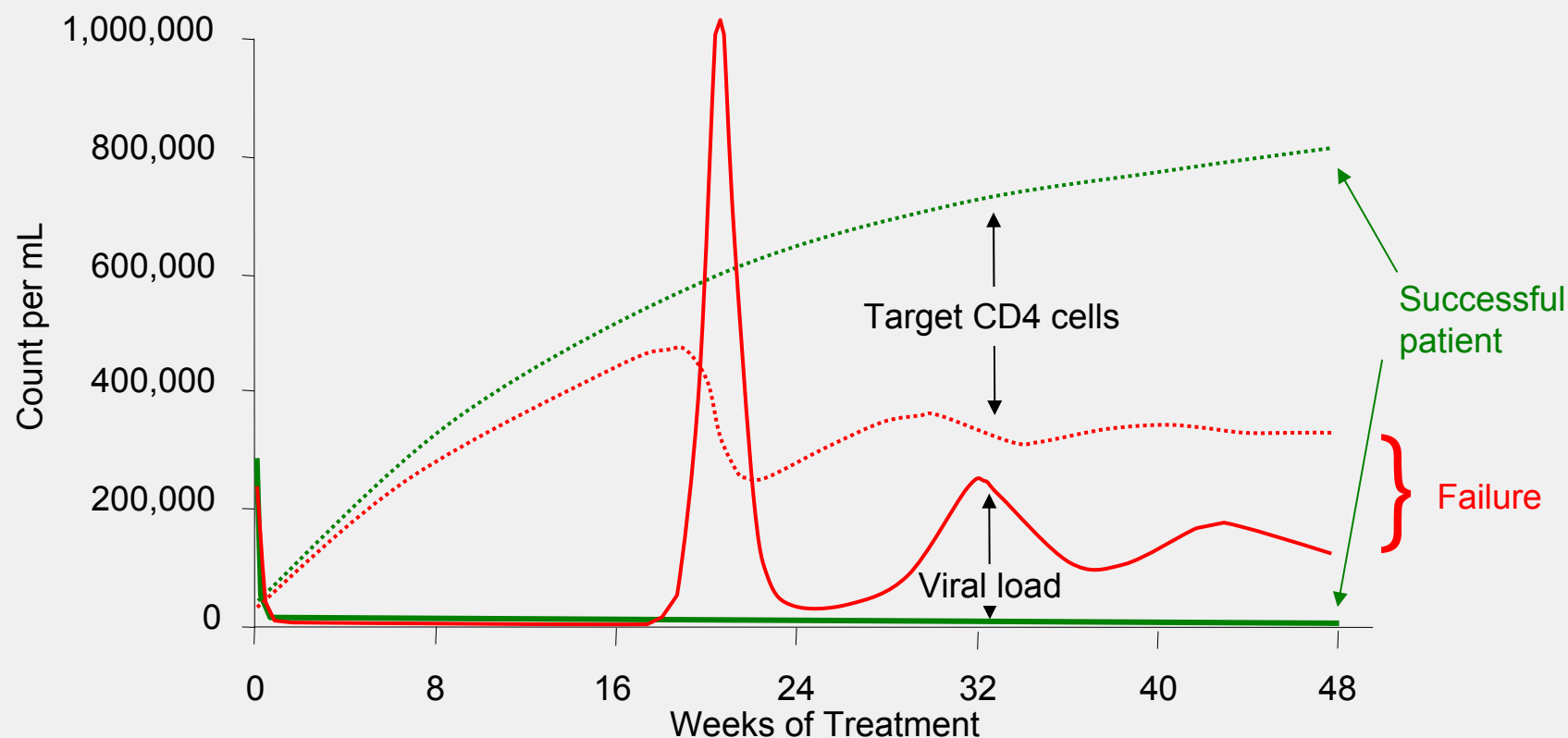
It turns out we can eliminate a parameter by rescaling by the steady-state constants (making the variables dimensionless):

- At steady-state

$U = \lambda / [d \max(1, R_0)]$	so	$U' = (d/\lambda) U = 1 / \max(1, R_0)$
$A = (\lambda/d_A) [1 - 1/\max(1, R_0)]$	so	$A' = (d_A/\lambda) A = 1 - 1/\max(1, R_0)$
$V = (d/\beta^i) [\max(1, R_0) - 1]$	so	$V' = (\beta^i/d) V = \max(1, R_0) - 1$

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.

The model shows how each patient succeeds or fails over time, depending on individual adherence/PK/PD factors.



Failures occur because of:

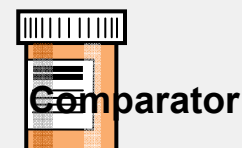
- High baseline **IC50s** to drugs in regimen (common in experienced patients)
- Low drug **concentrations**, perhaps due to high clearance or inadequate **adherence** in this patient
- High pre-treatment **reproductive ratio** (measure of virus/immune system balance)

By simulating hundreds of patients in specified populations, we predict success rates and can adjust trial design to increase them.

Some ways to use *in vitro* and literature data to predict efficacy of an early-phase antiretroviral:

1. With *in vitro* IC50 and protein binding data, as well as PK data, for both the new drug and a comparator drug that also has response results, we can benchmark against this drug (Example 1).
2. Without a comparator, we can still scale the protein-binding-adjusted *in vitro* IC50 to an *in vivo* C50 range using a range of plausible scale factors, and then apply PK and literature-based viral dynamics to predict dose-response.
3. With short-term response and PK data, we can estimate the *in vivo* C50 directly (Example 2), and (with enough data) refine the literature-based viral dynamics. Then we can extrapolate to any dose.

To predict short-term dose-response from:



- | | | |
|--|---|---|
| 1. <i>In vitro</i> data, PK, Dose-Response | → | <i>In vitro</i> data, PK
Benchmark |
| 2. – (literature-based viral dynamics) | | <i>In vitro</i> data, PK
Scale to <i>in vivo</i> |
| 3. – (literature-based viral dynamics) | | Short-term response, PK
Estimate C50, refine viral dyn. |

In all cases, we can extrapolate short-term dose-response to **long-term** accounting for combination drug contributions, resistance, adherence effects, etc.

We can also simulate plausible scenarios for *in vivo* C50 and other uncertainties, and search for a **trial design** that maximizes expected learning about the true C50 and dose-response (Example 1).

Example 1: Effective doses for a first efficacy study can be predicted by comparison to a further advanced drug.

Issue

- A company needed to select doses for a Phase 2A monotherapy study, based on Phase 1 PK and *in vitro* IC50 and protein binding assays. But how to scale *in vitro* IC50s to *in vivo*?

Approach

- Use monotherapy data by patient from a similar “benchmark” antiretroviral.
- Estimate its *in vivo* C50, using its PK and response data in a drug-disease model.
- Measure *in vitro* IC50 & protein binding of both drugs in the *same* assays.
- Find the benchmark’s scale factor; assume the same for the new drug.

Results

- Predicted daily & twice-daily doses to reach a target 80% viral inhibition.
- This inhibition level would produce a mean 1.6 log₁₀ drop in viral load in 10 days, comparable to successful antiretrovirals.

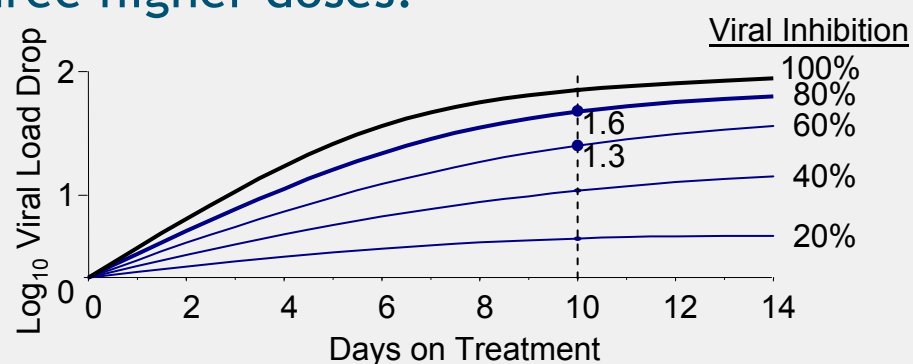
Impact

- A wide (four-fold) C50 range implied a similarly wide dose range, but allowed the most informative doses to be selected and improved upon pre-benchmarking uncertainty.
- The *in vivo* C50 was much higher than *in vitro*—valuable information for future drug development.

Benchmark-drug responses were similar at all but the low dose, but with enough exposure-response to estimate an *in vivo* C50.

10-day viral load drops averaged 1.3 \log_{10} HIV RNA copies/mL (20-fold reduction—not competitive) for the low dose and 1.6 \log_{10} (40-fold reduction—competitive) for three higher doses.

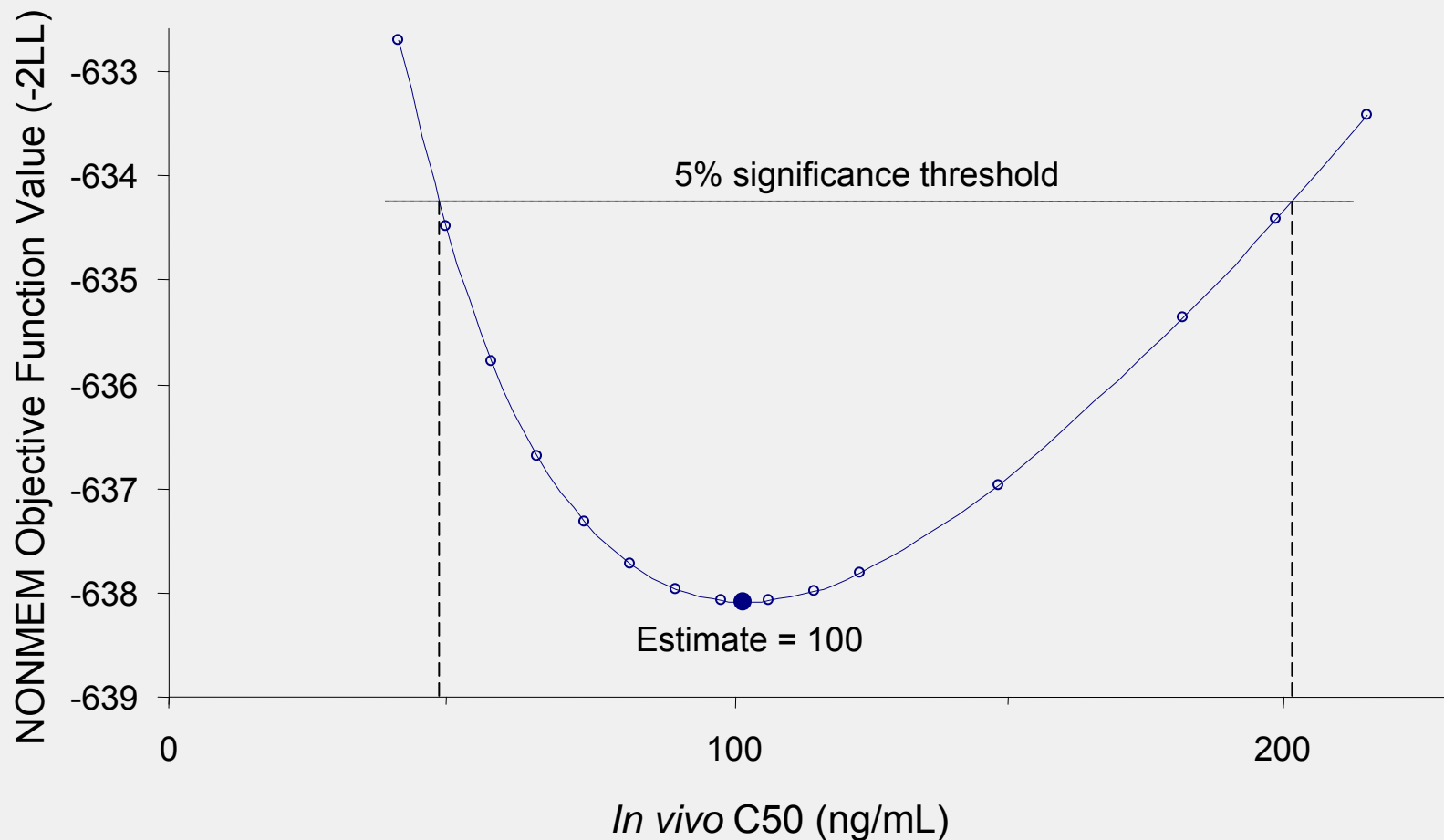
- These corresponded to 60% and 80% average viral inhibition respectively based on model simulations.



The benchmark drug *in vivo* C50 was estimated with NONMEM, run with all available PK and response data.

- PK modeling “filled in” concentrations between measurements for each patient.
- Viral inhibition was calculated as $C / (C + C50)$.
- Response was projected with the viral dynamics model and compared to the data.
- NONMEM adjusted the *in vivo* C50 estimate to find the best fit to the data.

NONMEM found the most likely *in vivo* C50 to be 100 ng/mL, with a range of 50-200 ng/mL.

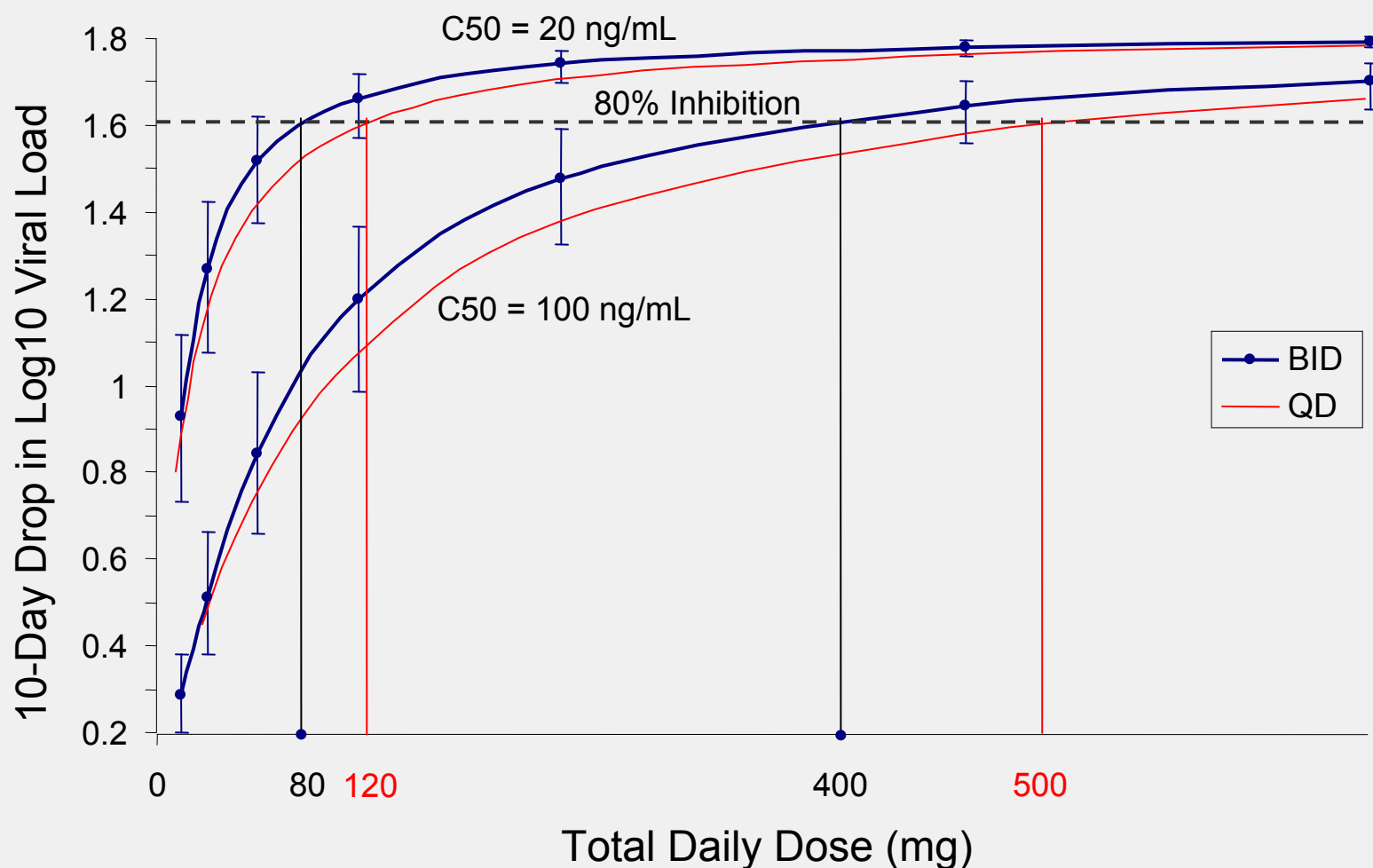


This range for the benchmark drug was translated to a range for the new drug.

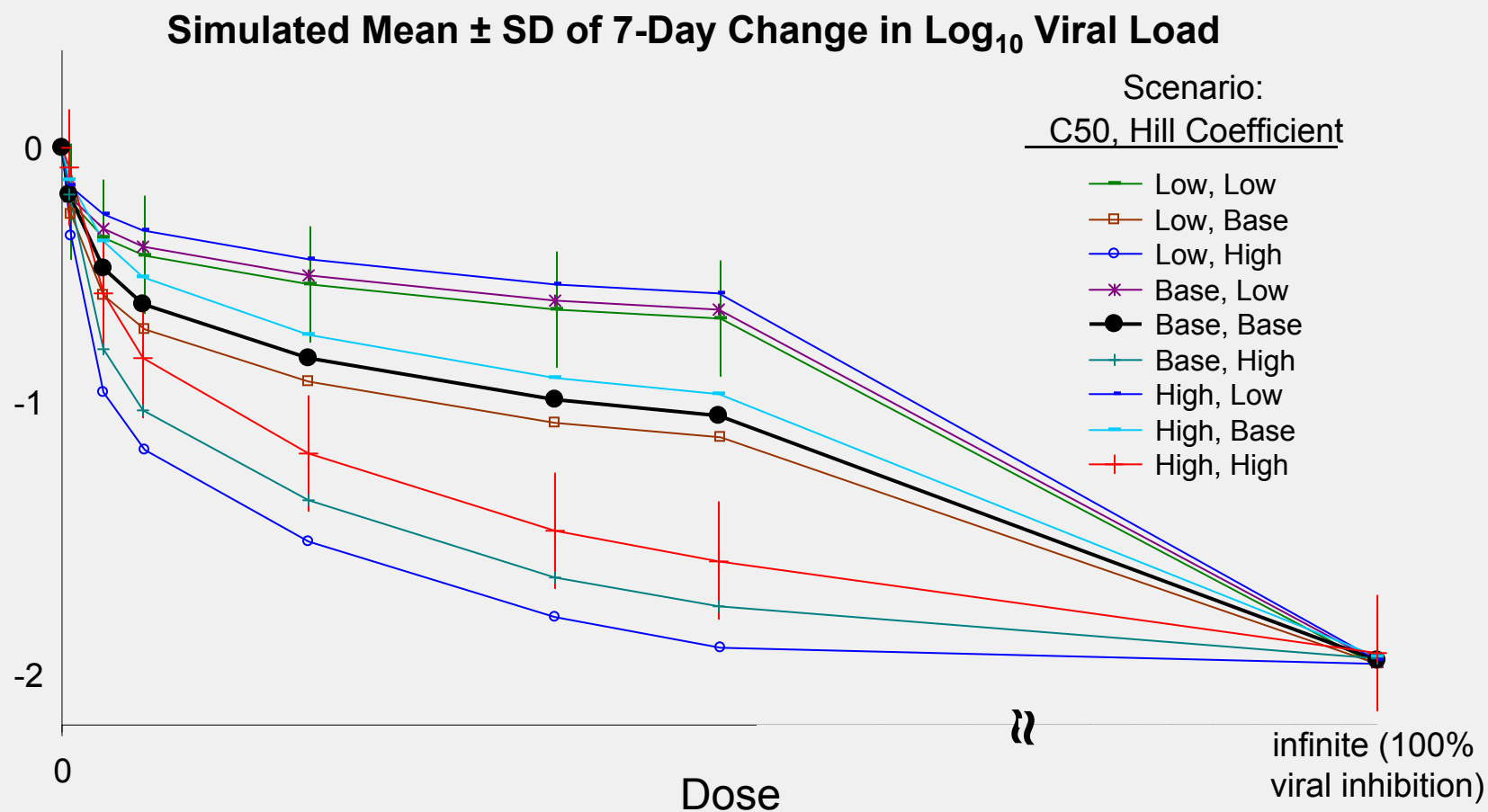
Drug	<i>In vitro</i> IC50 Source	<i>In vitro</i> IC50 (ng/mL)	x Protein Binding Attenuation	x <i>In-vitro-to-in-vivo</i> Scale Factor	= <i>In vivo</i> C50 (ng/mL)
Benchmark	Clinical Study	3.8	x 12	x <u>1.1 to 4.4</u> ²	= 50 to 200 ¹ (from above)
New		11	x 1.6	x <u>1.1 to 4.4</u> ³	= <u>20 to 80</u> ⁴
Benchmark	Lab Strain	0.84	x 12	x <u>5 to 20</u> ²	= 50 to 200 ¹
New		3.1	x 1.6	x <u>5 to 20</u> ³	= <u>25 to 100</u> ⁴

Therefore the *in vivo* C50 of the new drug was predicted to be ~20 to 100 ng/mL.

A combined PK/PD model predicted that to reach a target 80% inhibition would require 40-200 mg BID (80-400 mg/day), or 120-500 mg QD.



To optimize design of first efficacy studies, dose-response was simulated across a range of scenarios to determine the design that maximizes learning (minimizes ED95 SD).



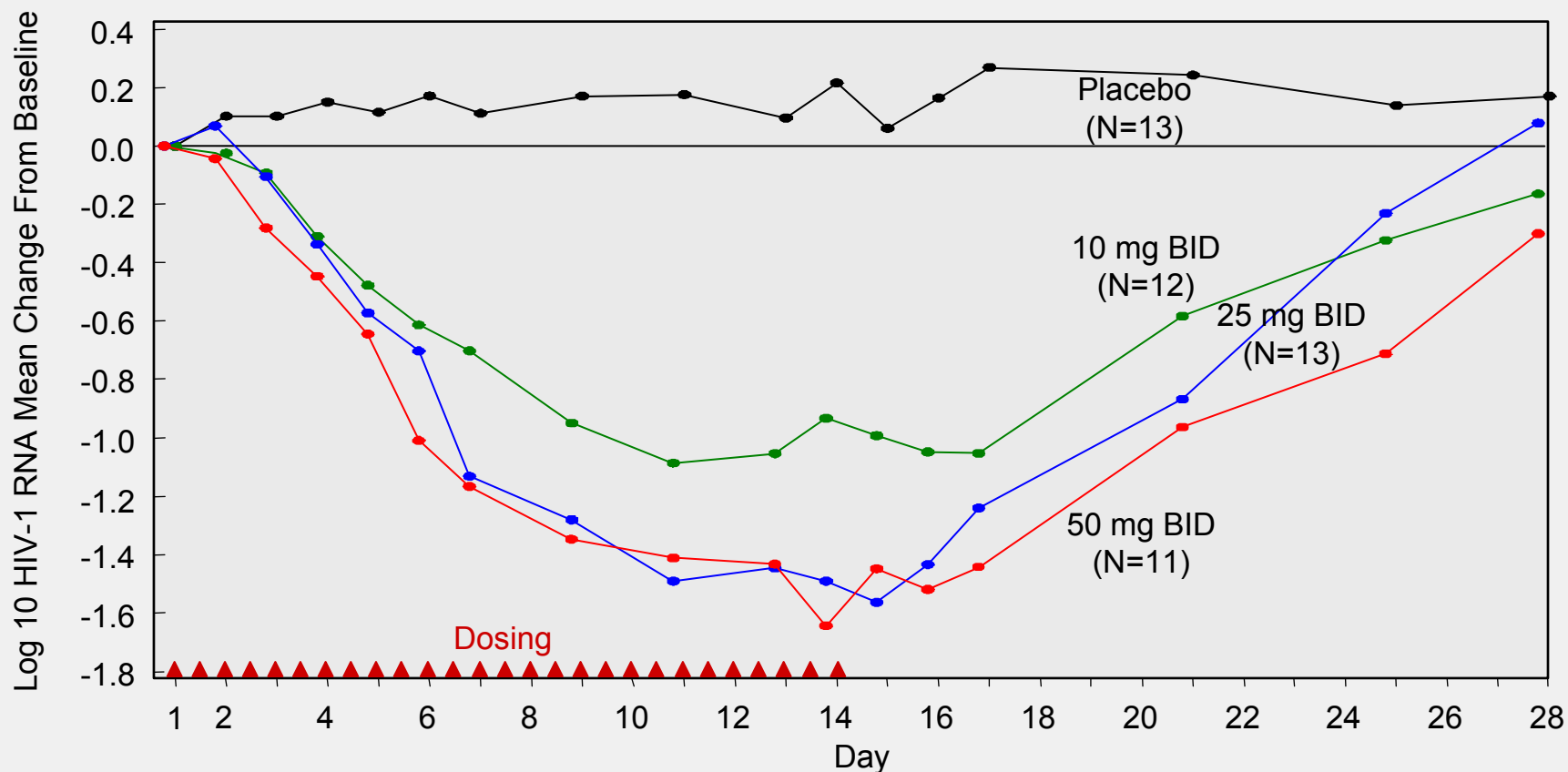
↑ ↑ ↑
Example set of doses tested in study design optimization

Example 2: A Phase 2B trial of a novel-mechanism HIV drug failed due to insufficient response. Could we have predicted a minimum competitive dose?

The study tested 25, 50, and 75 mg QD.

A previous monotherapy study had tested 10, 25, and 50 mg BID, with potentially misleading results...

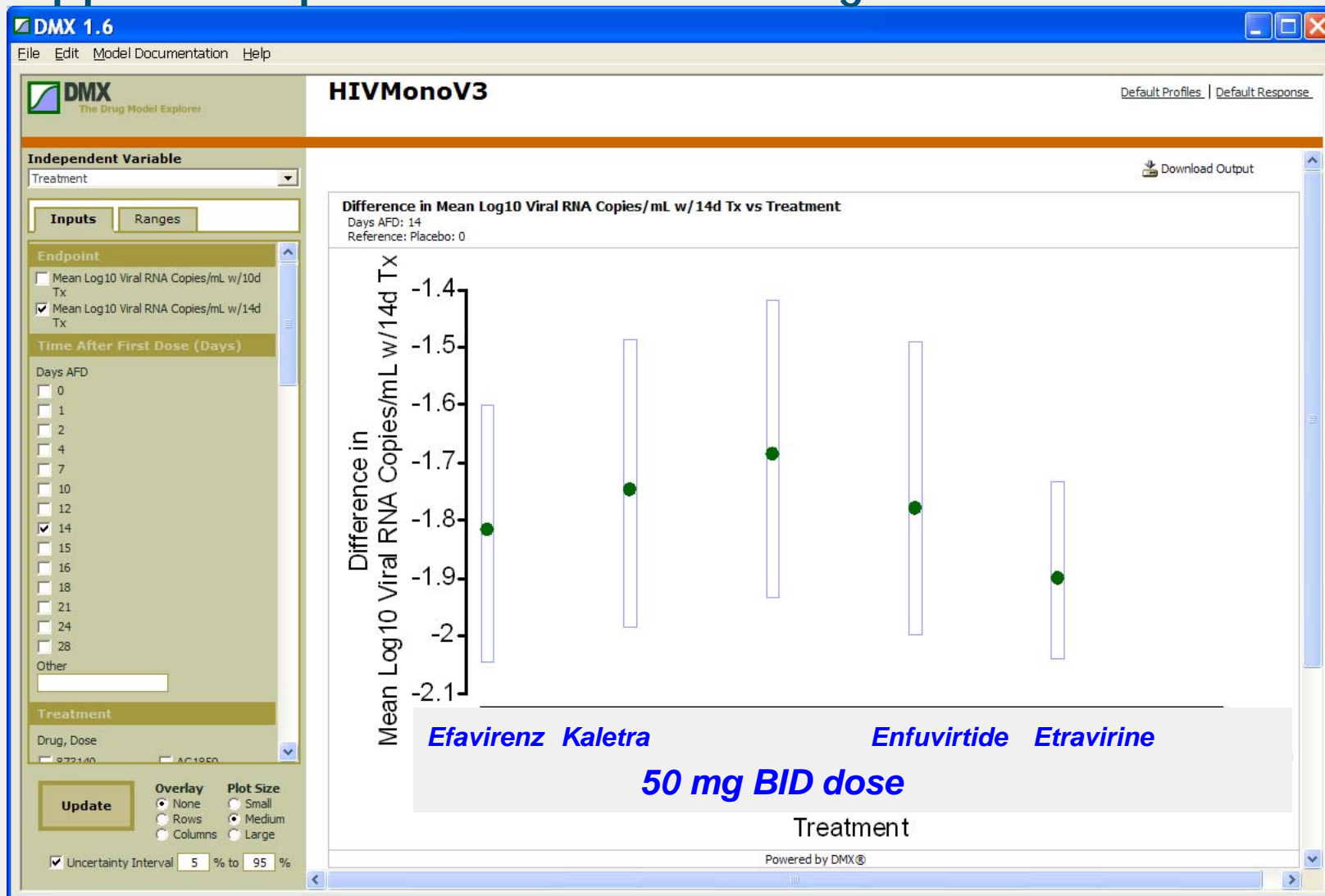
The monotherapy study showed similar dose-response at the two highest doses. Was this E_{max} or chance?



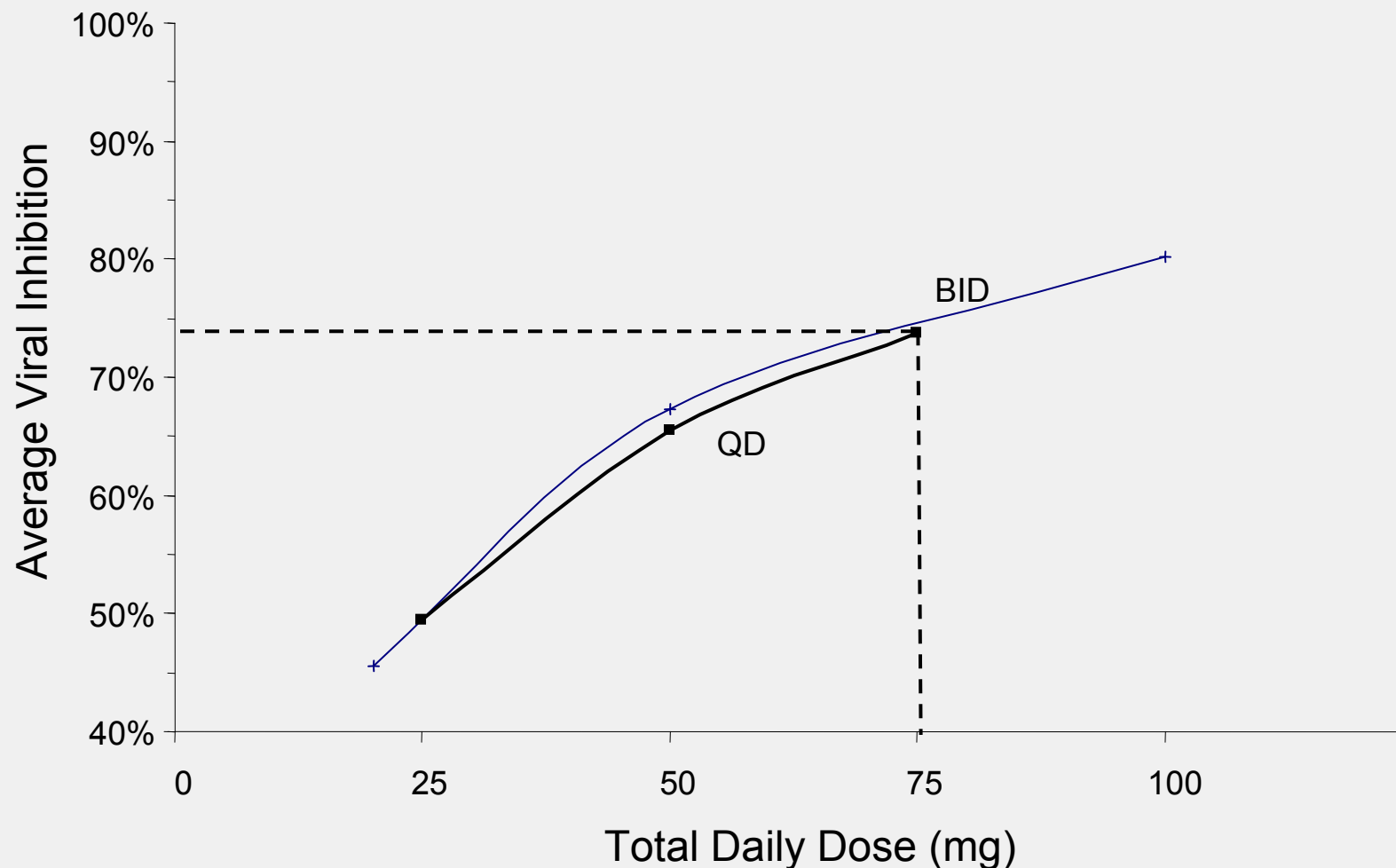
Source: Schuermann D et al. 2005, 3rd IAS Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Abstract TuOa0205, <http://www.thebody.com/conf/ias2005/pdfs/TuOa0205.ppt>.

Baseline viral load: 4.3, 4.4, & 4.8 \log_{10} for 10, 25, & 50 mg respectively.

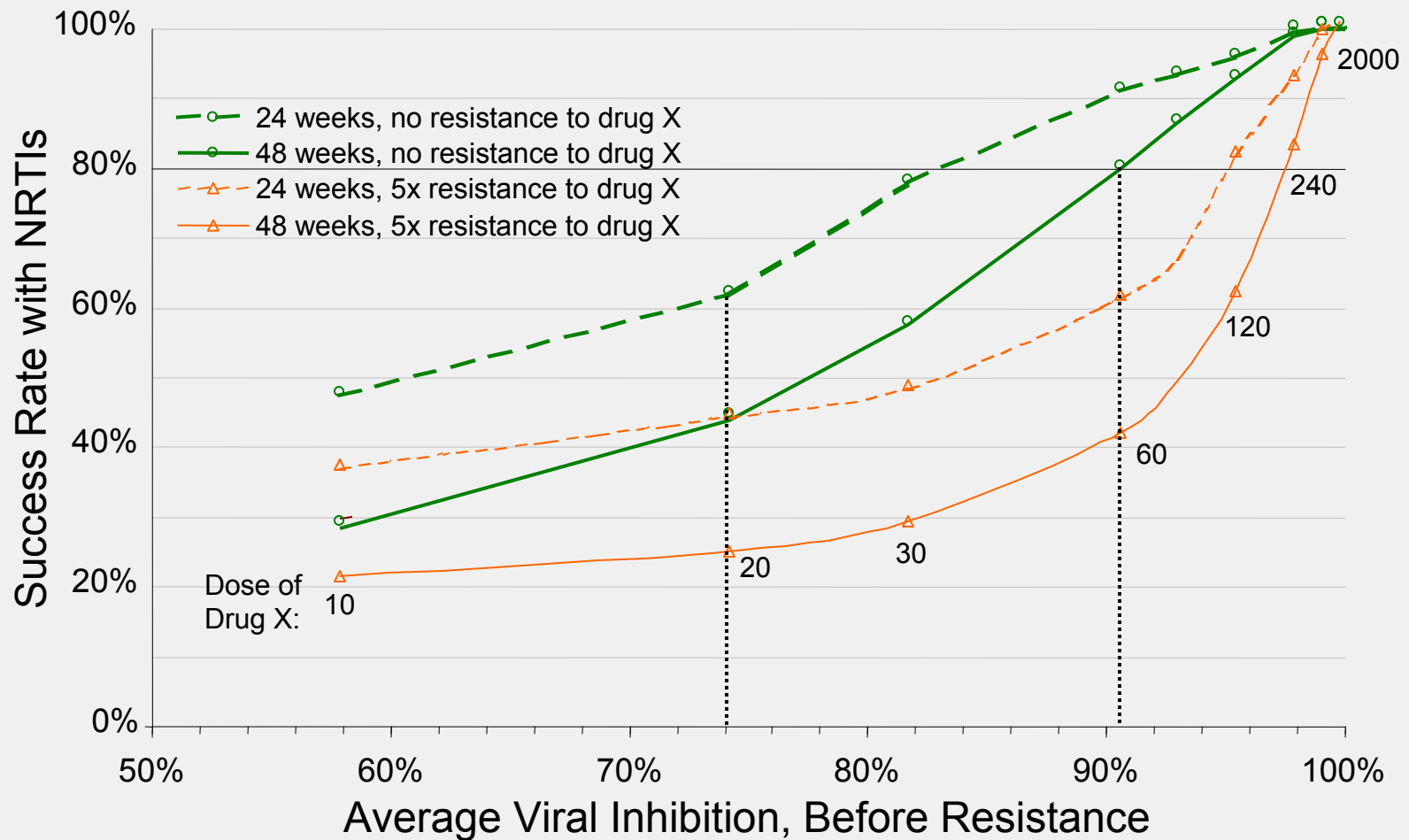
Higher responses should have been achievable at higher exposures, based on literature data converted to apples-to-apples comparisons with modeling and simulation.



An *in vivo* C50, estimated using the BID response data and a PK model based on literature data, implied that the high QD dose would achieve only 74% average viral inhibition.



But 90% viral inhibition would be needed to achieve an 80% 48-week success rate even without resistance, based on simulations of a similar drug with NRTIs.



The 74% inhibition of the high daily dose is predicted to give a success rate of at best **62%** by 24 weeks. **This probably explains the trial failure.**

In summary:

To support antiviral development planning, it is important to integrate some or all of adherence, PK, PD/viral dynamics, and trial outcome models.

PK-PD modeling can be simplified with equivalent constant concentration (the concentration that gives the same average effect over time as the true time-varying concentration), and reproductive ratio (to approximate steady-state response).

With side-by-side *in vitro* IC50 and protein binding data, as well as PK data, we can benchmark against a comparator drug that also has response data.

Without a comparator, we can still scale *in vitro* to *in vivo* with a range of plausible factors.

With short-term response and PK data, we can estimate the *in vivo* C50 directly and extrapolate to any dose.

Then we can search for a trial design that maximizes, on average, learning about the true *in vivo* C50 and dose-response.

Acknowledgments:

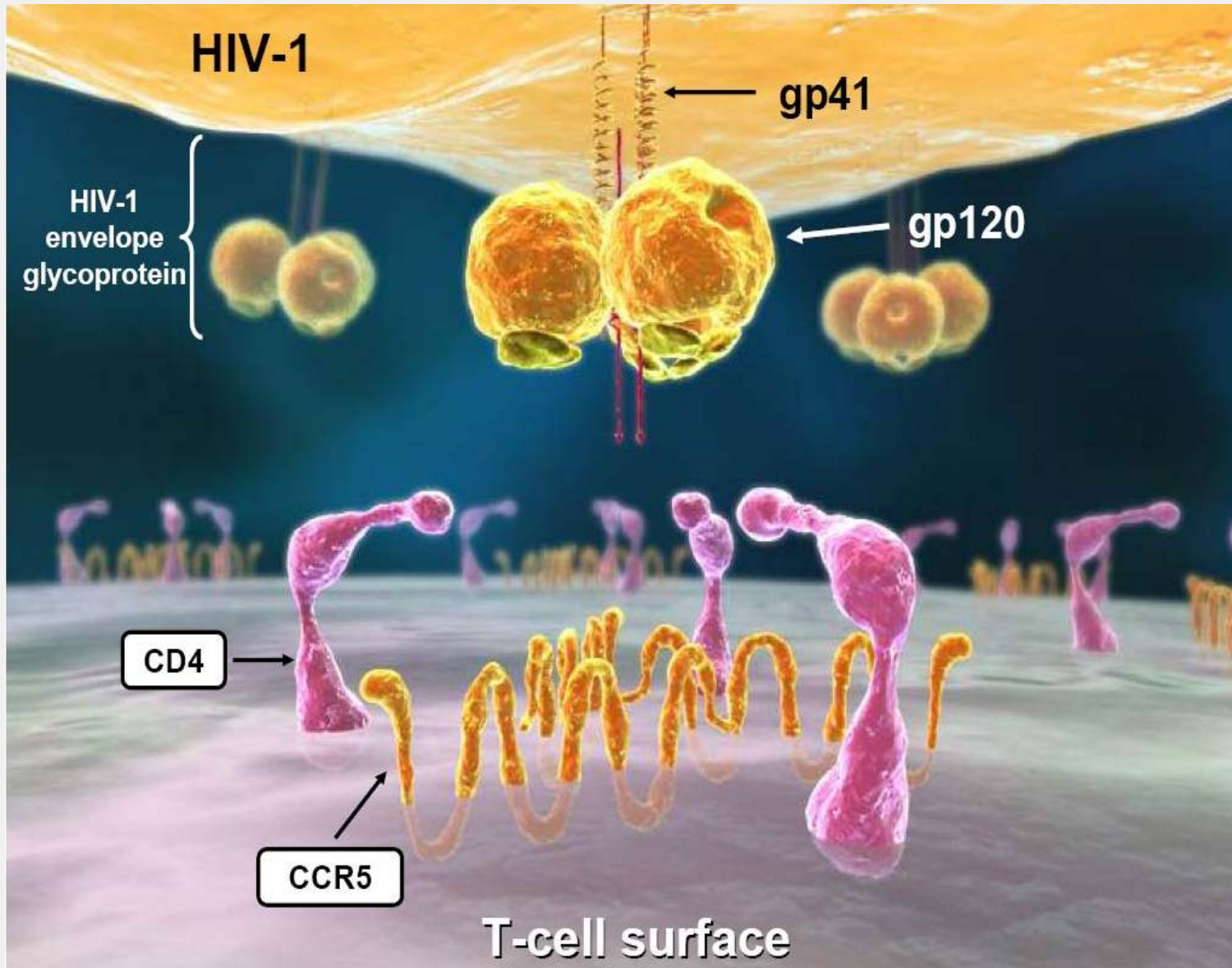
Lynn McFadyen, Maria Rosario (Pfizer)

Anther Keung (Schering-Plough)

Conflict of Interest Statement:

The author through his employer has provided consulting services to numerous pharmaceutical companies, which provided the basis for this material.

Time for Q&A!



From Perros, M., "From CCR5 to Maraviroc, The discovery of an new antiretroviral agent", www.ihlpres.com/pdf%20files/bridging_presentations/Perros.pdf