



**Abstract: P602**

## **Best practices in model-based HIV drug development**

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Over 20 HIV drugs are now approved by the FDA, and dozens more have reached at least early stage clinical development. In HIV, as in other therapeutic domains, the path to market for successful compounds is long, costly, and sometimes inefficient. Elias Zerhouni, MD, Director of NIH, has set Translational Research as a priority. Many NIH institutes have formed offices and programs to accelerate progress from discovery to market. FDA believes that "... A new product development toolkit-- containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques-- is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product." Pharsight has conducted over 20 HIV projects using model-based drug development techniques over the past seven years, in all development phases and covering critical issues in trial design, dose selection, trial sequencing, and development strategy. This experience covers most mechanisms of action including protease inhibitors, NNRTIs, NRTIs, and two novel mechanisms.

This presentation reviews best practices in the application of tools for providing quantified insight on HIV drug development decisions. Case examples will show how to integrate relevant sub-models, estimate key parameters from trial data, and simulate candidate trial designs. Key parameters critical in HIV include patient adherence or compliance to the prescribed regimen, compartmental pharmacokinetic parameters, viral inhibition (*in-vivo* IC50), virus and immune cell characteristics (depending on the patient population), and trial characteristics such as dropout rates. HIV disease models of varying complexity will be discussed, together with the presenter's views of the advantages and disadvantages of complex vs. simpler models. HIV models typically include at a minimum uninfected cells, actively infected cells, latently infected cells, and multiple viral strains. Differential equations describe the virus-cell interaction over time, including resistance development.

The goal of this presentation is to give the audience an improved ability to use model-based drug development techniques to accelerate HIV development decisions.

# Best Practices in Model-based HIV Drug Development

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## Abstract

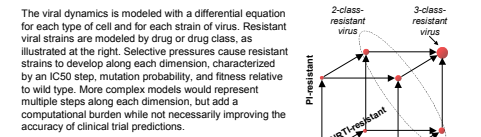
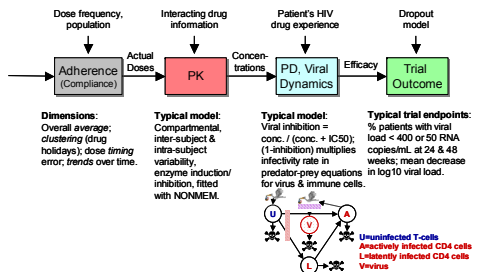
Over 20 HIV drugs are now approved by the FDA, and dozens more have reached at least early stage clinical development. In HIV, as in other therapeutic domains, the path to market for successful compounds is long, costly, and sometimes inefficient. Elias Zerhouni, MD, Director of NIH, has set Translational Research as a priority. Many NIH institutes have formed offices and programs to accelerate progress from discovery to market. The FDA believes that "... A new product development toolkit—containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques—is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product."

This presentation illustrates best practices in providing quantified insight on HIV drug development decisions, together with the authors' views of the advantages of simpler vs. more complex models. Pharsight has conducted over 20 HIV projects using model-based drug development techniques over the past eight years, in all development phases and covering critical issues in trial design, dose selection, trial sequencing, and development strategy. This experience covers most mechanisms of action including protease inhibitors, NNRTIs, NRTIs, and novel mechanisms. Case examples illustrate integrating relevant sub-models, estimating key parameters from trial data, and simulating candidate trial designs. Key parameters include patient adherence or compliance to the prescribed regimen, compartmental pharmacokinetic parameters, viral inhibition (based on in-vitro IC50), virus and immune cell characteristics (depending on the patient population), and trial characteristics such as dropout rates. The viral dynamics typically includes uninfected cells, actively infected cells, latently infected cells, and multiple viral strains. Differential equations describe the virus-cell interaction over time, including resistance development, and provide a rational basis for trial predictions.

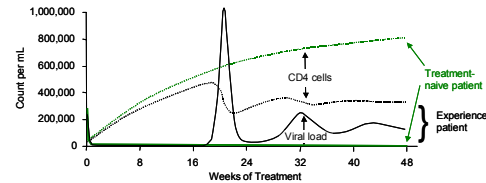
## Background, Methods

Model-based drug development is a key component of the FDA Critical Path Initiative, which offers "to improve drug development knowledge management and development decision making". This approach summarizes key data about the candidate and related drugs in the form of predictive, quantitative models. These models are then used to simulate the range of plausible outcomes for alternative future clinical programs. The results of these simulations provide the basis for key development decisions.

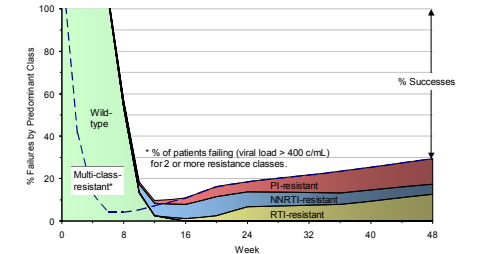
To support clinical trial design decisions, we often need to integrate two or more of the following models [2]:



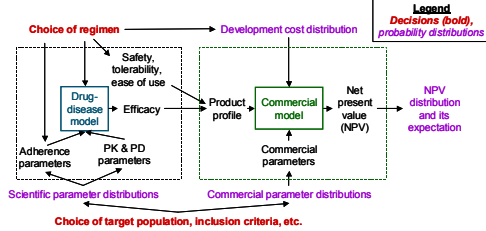
The integrated model shows how patients succeed or fail over time, depending on drug experience and individual factors:



Resistance modeling allows us to break down failures by predominant class of viral resistance:



To provide a more comprehensive decision basis, sometimes it is important to integrate a commercial model with the drug-disease model [4]:



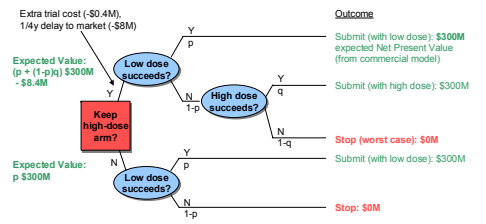
For example, integrated scientific-commercial modeling can properly weigh the pros and cons of developing a QD regimen or a new QD formulation for a BID drug:

- Worse PK with QD dosing (at the same daily level) weakens efficacy (drug-disease model)
- But better convenience improves adherence, which improves efficacy (drug-disease model)
- Moreover, possibilities of completely QD regimens improve higher market share (commercial model).

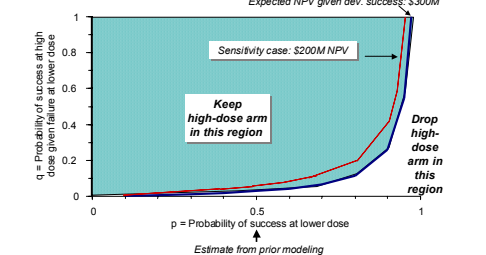
## Example 1: Trial Design

An HIV project team planning a 300-patient dose-finding study faced a dilemma. Several doses of a new drug were to be tested with a standard background regimen, but a new PK interaction study showed an unexpected reduction of the background drug at the highest dose of the new drug. The key development decision was whether or not to drop the high-dose arm. A blinded extra capsule of the background drug in the high-dose arm would compensate for the interaction, but would be expensive and might confound results by over-compensating. Skipping the high-dose arm would save time and money up-front and potentially avoid a delay to market, but at what risk of losing a drug?

We used a simple decision tree to weigh the alternatives and computed the expected value of each alternative by summing the probability-weighted expected values of each outcome:



Modeling showed that the key to the decision was the high value given success, so only implausible combinations of success probabilities would justify dropping the high-dose arm:



The analysis gave the team confidence in the decision to keep the high-dose arm, weighed the pros and cons properly, and may have saved millions in expected value, if the team would have chosen to drop the arm.

## Example 2: Dose-Finding

A Pfizer-Pharsight collaboration determined how two successive monotherapy studies could efficiently support dose selection for the Phase 2b/3 program of the CCR5 antagonist maraviroc [1]. An integrated PK-PD-trial model predicted viral load drop after 10 days of monotherapy and then extrapolated to long-term response. The model was updated each time more data became available: after Stage 1 of the first monotherapy study (2 dosed arms of 7-8 patients each), after Stage 2 of this study (2 more arms), and after the second monotherapy study (4 more arms, varying food & dose frequency). Each model update was smaller with reduced prediction uncertainty, adding confidence to long-term predictions.

**PK and Viral Inhibition Modeling:** Maraviroc PK was complex but could be summarized using the concept of Equivalent Constant Concentration (ECC). ECC is the constant plasma concentration that produces the same average viral inhibition over time as the full concentration time-profile. It is found by calculating the average inhibition with the full profile and then solving for ECC in the Emax equation: average inhibition = ECC / (ECC + IC50).

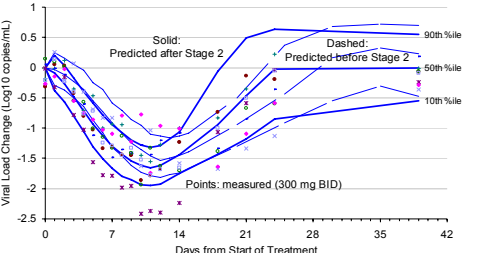
The best-fit model for ECC was of the form:

$$ECC = \text{constant} (\text{total daily dose})^d (\text{QD multiplier})^{2QD^2} (\text{fed multiplier})^{2Fed^2} e^c$$

where QD<sup>2</sup> and Fed<sup>2</sup> are 0 or 1; constant, d, and the two multipliers are estimated; and c expresses estimated inter-subject variability. This model quickly showed that QD dosing did not substantially reduce relevant concentrations, relative to BID at the same total daily dose.

**Viral dynamics estimations and simulations:** IC50 and key viral dynamics parameters were estimated with the monotherapy study data; other parameters were fixed to literature estimates. The estimation used NONMEM (NONlinear Mixed Effects Modeling) with combined PK and response data from the available monotherapy studies. Four sets of estimates were made over time:

- Before Phase 2: in-vitro IC90 and receptor binding information were used to select initial doses.
- After the first 2 arms (25 mg QD & 100 mg BID): IC50 and viral dynamics parameters were updated, and Stage 2 of the first monotherapy study was planned.
- After the Stage 2 arms (50 & 300 mg BID), estimates changed much less, and the new high dose (300 mg BID) reduced viral load as predicted. The measured mean viral load drop at the high dose was 1.6 log10, vs. 1.5 predicted after Stage 1, so the model needed only minor adjustments (see figure).
- After the second monotherapy study, estimates changed very little, so the model was deemed reliable for this population and study type.



Long-term Phase 2b/3 predictions and design were then based on a solid short-term model. However, resistance development remained a key, unavoidable uncertainty. Response to long-term combination therapy was simulated under different resistance scenarios.

**Conclusions:** Modeling and simulation proved useful before, during, and after the monotherapy studies. The study designs were able to use relatively few patients per arm, sharing information across arms. The most informative doses were assessed. The second monotherapy study was predicted so well that "next time," in a future Phase 2a, it might be replaced by simulation, saving about half a year of development time. Progress was tracked from highly uncertain predictions for Phase 2a to only moderately uncertain ones for Phase 2b/3. The model served as a knowledge repository for efficacy of both maraviroc and competitors, as well as for understanding of viral dynamics—useful for future antiretroviral development.

## Discussion

- During eight years of modeling to support HIV drug development, a number of themes have emerged. The modeling should:
- be focused and driven by the development decisions that the analysis is to support, e.g., the decision required commercial input but sensitivity analysis avoided a large modeling effort in Example 1
  - be data-driven, exploiting relevant data about the candidate and competing drugs, e.g., in planning first efficacy studies, try to benchmark response to relevant previously studied candidates, whether successful or unsuccessful
  - quickly determine if surprises are bugs or insights, e.g., surprisingly good long-term response was predicted for Kaletra monotherapy, which was attributed to model limitations in the face of the failure of all past long-term monotherapy, but was eventually confirmed in trials in 2003
  - start and finish simple even if the middle is complex, e.g., guide the model design with sensitivity analysis, and summarize the full model with analytical approximations (such as Equivalent Constant Concentration in Example 2) and long-term vs. short-term response curves.

## References

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