Modeling & Simulation to Support HIV Drug Development Decisions

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Agenda

• Integrated HIV drug/disease modeling and simulation

• Examples
  – Maraviroc dose selection
  – Monotherapy dose selection by benchmarking
  – Strategic guidance for trial design

• Lessons learned; Q&A
To support clinical trial design decisions, we need to integrate several models.

- **Prescribed Doses** → **Adherence (Compliance)** → **Actual Doses** → **PK** → **Concentrations** → **PD, Viral Dynamics** → **Efficacy** → **Trial Outcome**

**Dimensions:**
Overall average; clustering (drug holidays); dose timing error; trends over time.

**Typical model:**
Compartmental, inter-subject & intra-subject variability, enzyme induction/inhibition, fitted with NONMEM.

**Typical model:**
Viral inhibition = conc. / (conc. + IC50); (1-inhibition) multiplies infectivity rate in predator-prey equations for virus & immune cells.

**Typical trial endpoints:**
% patients with viral load < 400 or 50 RNA copies/mL at 24 & 48 weeks; mean decrease in log10 viral load.

\[ \text{U} = \text{uninfected T-cells} \]
\[ \text{A} = \text{actively infected CD4 cells} \]
\[ \text{L} = \text{latently infected CD4 cells} \]
\[ \text{V} = \text{virus} \]
The 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.

* % of patients failing (viral load > 400 c/mL) for 2 or more resistance classes.
A high standard deviation of response in this add-on study makes it hard to distinguish among the study-drug arms.

The standard error with twice as many patients is $\frac{1}{\sqrt{2}} = 0.7$ as much—still not low enough to distinguish the three arms reliably.

Simulations can support decisions about doses, arm sizes, endpoints, inclusion/exclusion criteria, population, type of trial, etc.
A commercial model can be integrated with the drug-disease model to provide a more comprehensive decision basis.

Example: Develop QD as (a) 2 BID doses taken together, (b) a new formulation, or (c) neither?
- Worse PK for QD dosing → worse efficacy (drug-disease model)
- But better convenience → better adherence → better efficacy (drug-disease model)
- Moreover, possibilities of completely QD regimen → higher market share (commercial model)

Integrated modeling properly weighs these opposing effects.
Drug Model Explorer™ can be used to explore alternative trial designs...
and to make “apples-to-apples” comparisons with competitors.
• Integrated HIV drug/disease modeling and simulation

• Examples
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• Lessons learned; Q&A
Ex. 1. A Pfizer-Pharsight collaboration determined how monotherapy studies could efficiently support dose selection for the CCR5 antagonist maraviroc.*

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- Critical Issue
  - Monotherapy design to determine doses for Phase 2B/3 program.
    - Also to determine QD vs. BID dosing and food restrictions if needed
    - Go/no-go decisions implicit

- Approach & Technologies Utilized
  - Integrated PK-PD-trial model predicted response.
    - PK: based on healthy volunteer studies
    - PD: as described above
    - Trial endpoint: viral load drop after 10 days of monotherapy
    - Model was updated each time more data became available.
      - Before patient studies, key efficacy parameter IC50 had to be based on in-vitro data only
      - Update #1 after Stage 1 of 1st monotherapy study (2 dosed arms of 7-8 patients each)
      - Update #2 after Stage 2 of this study (2 more dosed arms)
      - Update #3 after 2nd monotherapy study (4 more arms, varying food & dose frequency)

- Results: Each model update was smaller with reduced prediction uncertainty.

- Impact: Monotherapy studies helped determine long-term doses. New confidence in the model might allow reducing a future Phase 2A to a single study, saving ½ year.

Maraviroc PK was complex but could be summarized simply for the integrated model.

- **Equivalent Constant Concentration (ECC)** is the constant plasma concentration that produces the same average viral inhibition over time as the full concentration time-profile.
  - Calculate by averaging inhibition = conc./(conc.+IC50) and then solving backwards for concentration.

- **Model:**
  \[
  \text{ECC} = (\text{base value}) \cdot (\text{total daily dose})^{d} \cdot (\text{QD multiplier})^{QD?} \cdot (\text{fed multiplier})^{Fed?} \cdot e^{e},
  \]
  where
  - QD? and Fed? are 0 or 1
  - base value, d, and the two multipliers are estimated
  - e expresses estimated inter-subject variability.

- The ECC model quickly showed that QD dosing did not substantially reduce relevant concentrations, relative to BID at the same daily total dose.

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Key parameters such as IC50 were estimated with monotherapy study data, with others fixed to literature estimates.

• NONMEM (NONlinear Mixed Effects Modeling) was used with all available monotherapy data.
  – **Before** Phase 2: in-vitro IC90 and receptor binding information used to select initial doses.
  – **After first 2** arms (25 mg QD & 100 mg BID): IC50 and selected literature-based viral dynamics parameters were updated, and Stage 2 was planned.
  – **After Stage 2** arms (50 & 300 mg BID), estimates changed much less, and the new high dose (300 mg BID) reduced viral load as predicted.
  – **After second study**, estimates changed very little, so parameters were reliable for this population and study type.

• Long-term Phase 2B/3 predictions and design were then based on a solid short-term model...
  – due to clear identification of dose-response (over **24-fold** range of doses).
  – Resistance development remained a key, unavoidable uncertainty
    • Response to long-term combination therapy was simulated under different scenarios.

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The measured mean viral load drop at the high dose was 1.6 log10, vs. 1.5 predicted after Stage 1—the model needed only minor adjustments.
Modeling and simulation proved useful before, during, and after monotherapy studies.

- **M&S improved monotherapy design**
  - Few patients per arm, sharing information across arms
  - Informative doses
  - Second monotherapy study predicted so well that “next time” it might be replaced by simulation

- **Added confidence to Phase 2B/3 dose selection.**

- **Tracked progress from highly uncertain predictions for Phase 2A to only moderately uncertain ones for Phase 2B/3.**

- **Model was a knowledge repository for:**
  - efficacy of maraviroc
  - efficacy of competitors
  - understanding of viral dynamics – useful for developing other antiretrovirals

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Ex. 2. How can dose selection for a first efficacy study of an antiretroviral benefit from experience with a similar compound?

• Critical Issue:
  – Doses for a first-in-patients monotherapy study
    • Key uncertainty was how to scale IC50 in-vitro to in-vivo (based on patient responses)

• Approach & Technologies Utilized
  – Use monotherapy data from a chemically similar “benchmark” antiretroviral previously developed.
  – Measure in-vitro IC50 & protein binding of both compounds in the same assays.
  – Find the benchmark’s scale factor and assume the same for the new compound.

• Results (Disguised)
  – 40-200 mg BID or 120-500 mg QD of the new compound are required 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 IC50 range implied a wide dose range, but allowed the most informative doses to be selected and improved upon pre-benchmarking uncertainty.
  – The in-vivo IC50 was much higher than in-vitro—valuable information for future drug development.
In general, predicted viral load drop increases with viral inhibition (or dose) and with time.

From simulations with an HIV viral dynamics model, without inter-subject variability or delay to steady-state PK (hence drug-independent). Typical levels of variability were found to have negligible effect on these means.
Benchmark-drug responses were similar at all but the low dose, but with enough exposure-response to estimate in-vivo IC50.

• 10-day viral load drops averaged 1.3 log10 for the low dose and 1.6 log10 for three higher doses.
  – These correspond to 60% and 80% average viral inhibition respectively.

• The benchmark drug in-vivo IC50 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 with the simple Emax model (C/(C+IC50)).
  – Response was projected with the viral dynamics model and compared to the data.
  – NONMEM adjusted the current in-vivo IC50 estimate to find the best fit to the data.

• Unfortunately, no clinical isolate IC50s were assayed in this study.
The PK for the benchmark drug was highly variable and poorly correlated with response, so plausible in-vivo IC50s could vary over a wide range.

![Graph showing viral load change vs. Cavg](image)

Predictions were smoother when plotted vs. Equivalent Constant Concentration, a better PK summary than Cavg.
NONMEM found the most likely in-vivo IC50 to be 100 ng/mL, with a range of 50-200 ng/mL.

NONMEM’s objective function was re-calculated with different fixed IC50s (with all other variables fixed), and a limit was applied to the objective function increase: 3.84 (chi-square value at 5% with 1 DOF).
The benchmark drug’s in-vivo IC50 range was translated to a range for both drugs’ in-vitro-to-in-vivo scale factor.

<table>
<thead>
<tr>
<th>Drug</th>
<th>In-vitro IC50 Source</th>
<th>In-vitro IC50 (ng/mL)</th>
<th>x Protein Binding Attenuation</th>
<th>x In-vitro-to-in-vivo Scale Factor</th>
<th>= In-vivo IC50 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benchmark</td>
<td>Clinical study</td>
<td>3.8</td>
<td>x 12</td>
<td>x 1.1 to 4.4</td>
<td>50 to 200 (from above)</td>
</tr>
<tr>
<td>New</td>
<td>Same</td>
<td>11</td>
<td>x 1.6</td>
<td>x 1.1 to 4.4</td>
<td>20 to 80</td>
</tr>
<tr>
<td>Benchmark</td>
<td>Lab strain</td>
<td>0.84</td>
<td>x 12</td>
<td>x 5 to 20</td>
<td>50 to 200</td>
</tr>
<tr>
<td>New</td>
<td>Same</td>
<td>3.1</td>
<td>x 1.6</td>
<td>x 5 to 20</td>
<td>25 to 100</td>
</tr>
</tbody>
</table>

Therefore the in-vivo IC50 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 or 120-500 mg QD.

![Graph showing Mean Viral Inhibition at Steady-State against Total Daily Dose (mg)].

Bars show 5%-95% range of interindividual PK variability for BID regimen. Additional variability arises from IC50s, viral dynamics, and measurement error.
These results could be translated to ten-day viral load drops using the ten-day inhibition-response curve.

These dose-response curves could also be summarized well by simple Emax models with a fixed Emax.
Considerations in the monotherapy dose selection included:

- **Low** doses, especially around the anticipated in-vivo IC50, are helpful to characterize dose-response, and to predict response if and when resistance develops.

- **Very high** doses are also desirable, as they may be required to provide protection after resistance develops.

- The uncertainty in the in-vitro-to-in-vivo scale factor is even greater than the calculated range, because the new drug may not have the same scale factor as the benchmark drug.
Ex. 3. Sensitivity analysis quickly resolved a dilemma facing an HIV drug team planning a 300-patient dose-finding study.

A new PK interaction study showed an unexpected reduction of one of the background-treatment drugs, only at the high dose of the new drug. The team first worried about the extra trial cost of compensating for this, then about the trial delay, but neither was key!

Expected Value: $300M + Extra trial cost (-$0.4M), 1/4y delay to market (-$8M)

Low dose succeeds?

Y

Expected Value: (p + (1-p)q) $300M - $8.4M

N

1-p

High dose succeeds?

Y

Expected Value:

Submit (with low dose): $300M

N

1-q

Stop (worst case): $0M

Y

Submit (with high dose): $300M

N

1-p

Stop: $0M

p $300M

Low dose succeeds?

N

1-p

Keep high-dose arm?

Y

Expected Value: $300M

N

1-p

Pick the alternative with the higher expected value...
The key was the high value given success, so only implausible combinations of success probabilities justify dropping the arm.

The analysis
- gave the team confidence in the decision to keep the high-dose arm
- weighed the pros and cons properly
- may have saved millions in expected value, if the team would have chosen to drop the arm.
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• Lessons learned; Q&A
Here are some lessons we’ve learned over eight years of supporting HIV drug development...

- **Resistant virus always develops sooner or later, so the best dose is the highest that doesn't cause uncompetitive side effects.**
  - Best-in-class drugs like Sustiva and Kaletra provide the highest viral inhibition.
  - The best dose might be higher than expected—use modeling to improve intuition.

- **The hurdles get higher with every approved drug.**
  - A slightly better follow-on drug isn't worth developing.
  - Drugs have been killed after a *successful* trial, because the competition got too stiff. Better market analysis might have led to killing the drug earlier.

- **Don't hang onto an underperforming drug too long.**
  - Preclinical studies leave a lot of uncertainty on both efficacy hurdles: (1) short-term response and (2) lack of long-term resistance development. If a drug passes the first hurdle, try the second as efficiently as possible.
  - Don't let misaligned incentives keep the "momentum strategy" going too long. Declare go/no-go decision points as needed.

- **In modeling, start and finish simple (let the middle get complicated).**
  - Get a feel for the model in a spreadsheet or DMX; focus effort with sensitivity analysis
  - Summarize the big model with analytical approximations and curves, such as long-term vs. short-term response curves.

- **Surprises from the model are either bugs or insights.**
  - Example: in 2001 we predicted Kaletra would work well in long-term monotherapy, unlike all other HIV drugs—but there wasn’t enough confidence in the predictions to test this in patients. Finally in 2003 a long-term monotherapy trial confirmed the prediction.
What questions do you have?

Submit Questions by clicking on the “Q&A” feature to the left of your screen.
Or contact me later at bpoland@pharsight.com.
Selected HIV references with Pharsight co-authors: