

Integrated Adherence, Pharmacokinetic, and Pharmacodynamic Modeling to Design a Dose-Ranging Study of Capravirine with Kaletra in Treatment-Experienced Patients

P. Hawley¹, M. Amantea¹, B. Poland², J. Hammond¹, S. Raber¹, Y. Gao², A. Lertratanakul², and R. Wada².

¹Agouron Pharmaceuticals, Inc., a Pfizer Company, La Jolla, CA; ²Pharsight Corp., Mountain View, CA.
email: bpoland@pharsight.com

Background

- Capravirine (CPV, AG1549), a non-nucleoside reverse transcriptase inhibitor (NNRTI), exhibits potent in-vitro activity against NNRTI-resistant HIV isolates, including those with the K103N mutation.
- In March 2003 a randomized, double-blind study of CPV versus placebo started in patients who failed at least two anti-HIV regimens. It compares DAVG (average difference in log₁₀ viral load from baseline) at 24 and 48 weeks among groups receiving 0 (placebo), 200, 400, or 700 mg CPV BID, all with a background therapy of Kaletra, which is a protease inhibitor (PI) combining lopinavir (LPV) and ritonavir (RTV), and at least two nucleoside reverse transcriptase inhibitors (NRTIs).
- The pharmacokinetics (PK) of most HIV drugs has been well characterized, and the predator-prey relationship between HIV and CD4⁺ cells, with and without HIV drugs, has been modeled in varying detail (Nowak and May 2000). However, a realistic simulation of a clinical trial requires integration of PK and pharmacodynamics (PD), as well as models of patient adherence (complicance) to the regimen and trial events such as dropouts.
- The critical importance of adherence to HIV drug regimens is recognized, with failure rates increasing from 19% to 94% as adherence drops from >95% to <70% in one study (Paterson et al. 2000).
- An adherence and PK model can forecast the fraction of time Cmin exceeds an IC50 or IC90, but integration with PD is needed to measure the cumulative impact of falling under this level for different durations.
- Stand-alone PD/virus dynamics models assume static, average drug concentrations in predicting response; integration with PK provides realistic, continuously varying concentrations.

Objectives

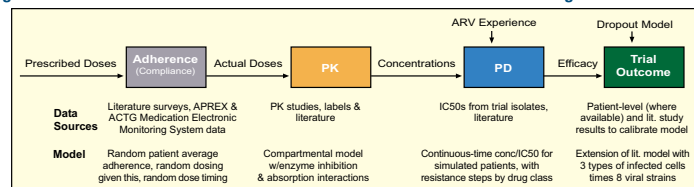
- To guide the design, including choice of arm sample sizes and doses, of the dose-ranging study of CPV with Kaletra.
- To build a platform for exploring alternative HIV regimens and simulating clinical trials with them.

Methods

Overview

Four linked models provided a tool for designing a new trial (Figure 1).

Figure 1. Linked Models Allow Realistic Simulations of Alternative Trial Designs.



Adherence Model

- Each simulated patient's overall adherence level is drawn from a two-parameter Beta distribution representing inter-patient variability (see Figure 2).
- At each prescribed dose time, each simulated patient takes all drugs with probability equal to this draw.
- If a dose is taken, the timing is drawn from a normal distribution around the prescribed dose time.
- Data: The Beta distribution's mean was set at 80%, based on literature surveys of BID regimens (Kastrissios and Blaschke 1997), and its standard deviation was based on a piecewise linear fit to results from many studies (Figure 3). The standard deviation of timing of BID dosing was set at 2 hours, based on Medication Electronic Monitoring System (MEMS) data from APREX 1998.

Figure 2. The High Inter-individual Variability in Adherence can be Summarized with a Simple Theoretical Distribution.

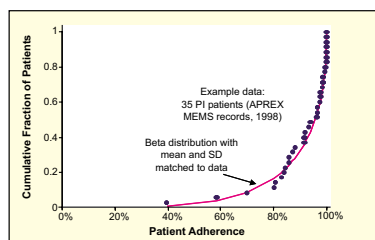
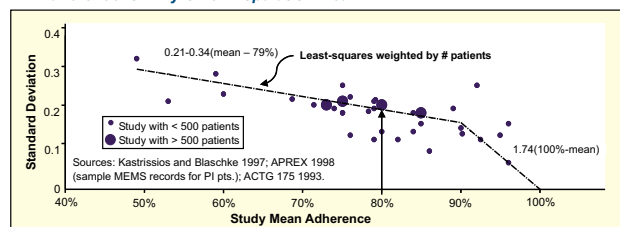


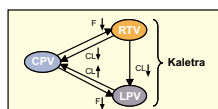
Figure 3. Standard Deviations from Past Studies Provide the Inter-individual Variability in Adherence for Any Given Population Mean.



PK Model

CPV reduces concentrations of LPV and RTV (Figure 4): at 700 mg BID CPV, a fourth 133/33 mg capsule of Kaletra is needed to approximate the AUC of the standard three capsules without CPV. But RTV, a CYP3A4 inhibitor, increases CPV concentrations dramatically as well as LPV concentrations. These interactions were modeled with linked one-compartment models with lagged first-order absorption and first or second order elimination. The parameters were estimated using subject-level data from Phase 1 PK studies.

Figure 4. CPV Interacts with Both Components of Kaletra, Postulated as Clearance (CL) and Bioavailability (F) Effects.



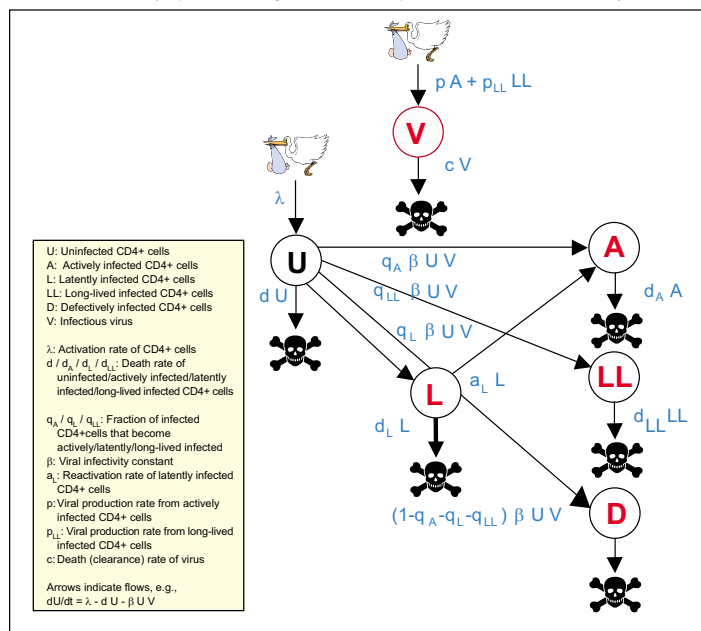
PD Model

- The basic disease model without drugs or resistant virus (Funk et al. 2001) is illustrated in Figure 5.
- Data sources: Funk et al. 2001, Perelson et al. 1997; β , λ , d , and q , estimated from CPV monotherapy study data.

Methods cont.

- NRTI, NNRTI, and PI drug concentrations are divided by their respective protein-binding-adjusted IC50s and used in simple Emax models for viral inhibition factor (0 to 1): $\text{concentration} / (\text{concentration} + \text{IC50})$.
- NRTIs were modeled with an intracellular half-life and an IC50 fitted to NRTI-only trial results.
- NNRTIs were combined with NRTIs by adding $\text{concentration}/\text{IC50}$ terms, giving a combined RTI-based inhibition that multiplies viral infectivity (β).
- PI-based inhibition multiplies viral productivity factors (p and p_{LL}).
- Resistance is modeled by replacing the virus and each type of infected cell with eight types, one for each of eight strains representing all combinations of NRTI resistance or not, NNRTI resistance or not, and PI resistance or not.
- Resistance to each of the three drug classes is characterized by a step size that multiplies wild-type IC50, by a percentage fitness relative to wild-type virus (100%), and by a probability of mutation to the class-resistant strain. Parameters were adjusted to fit long-term clinical trial results.
- Selective pressure in the presence of drugs at insufficient concentrations leads to resistant strains out-competing wild-type virus in the model.

Figure 5. HIV Dynamics are Modeled with Uninfected and Four Types of Infected CD4⁺ Cells, and Virus (Expanded to Eight Strains to Capture Resistance, Not Shown).



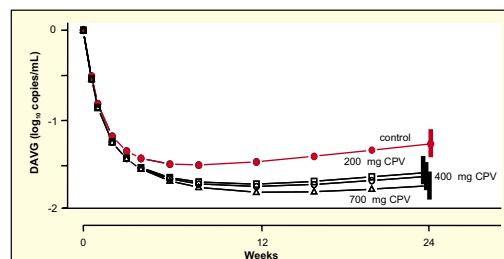
Trial Outcome Model

- Dropouts were modeled to occur more frequently in early weeks (declining hazard rate) and to increase slowly with dose.
- 50 replicates of the planned trial, each with 75 patients in each of the four arms, were simulated to approximate the distribution of possible trial results, for each of the base and sensitivity cases.

Results

- Base case simulations showed that 75 patients per arm should be enough to distinguish the CPV arms from control, but not nearly enough to distinguish among the CPV arms due to high standard deviations (Figure 6).
- Sensitivity analysis showed that uncertain inputs like average adherence and viral infectivity had strong absolute impacts but small impacts on the difference from control, assuming that inputs are consistent across arms.

Figure 6. Repeated Simulations of 75 Patients at 200, 400, and 700 mg Doses of CPV vs. Control Show that the ± 1 SE Bars Overlap, Making It Hard to Distinguish Among the CPV Arms.



Conclusions

- In highly experienced patients taking four or more anti-HIV drugs, response variability is very high, due largely to very long-tailed IC50 distributions. Increasing the number of patients helps to distinguish response among arms, but only slowly: the number of patients must quadruple to halve the standard deviation for each arm.
- Nevertheless, the three planned CPV arms are likely to provide a better understanding of dose-response than a simpler design with only two, given the likely non-monotonicity of dose-response.
- The model-based predictions will be compared to the forthcoming patient results.
- Despite the challenges of modeling highly experienced HIV patients with four-drug regimens for 48 weeks, trial simulation with integrated adherence, PK, and PD models can guide and improve design decisions for such trials.

References

- Funk G. et al. 2001. Quantification of in vivo replicative capacity of HIV-1 in different compartments of infected cells. *JAIDS* 26:397-404
- Kastrissios H. and Blaschke T.F. 1997. Medication compliance as a feature in drug development. *Annu Rev Pharmacol Toxicol* 37:451-475
- Nowak M.A. and May R.M. 2000. *Virus dynamics, mathematical principles of immunology and virology*. Oxford Univ. Press
- Paterson D. et al. 2000. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Int Med* 133:21-30
- Perelson A.S. et al. 1997. Decay characteristics of HIV-1 infected compartments during combination therapy. *Nature* 387:188-191