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Pharmacokinetic/Pharmacodynamic Modeling of HIV Therapy

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INTRODUCTION

- Treating HIV infection is challenged by the rapid turnover and high reverse transcription errors of HIV viruses. In addition, highly active antiretroviral therapy (HAART), although potent, is associated with complex pharmacokinetics and drug interactions. Furthermore, long-term therapy is inavoidably associated with adherence problems. Thus, a significant proportion of patients eventually fail to control viral replication and develop resistant viruses during HAART.
- Interestingly, no PI resistance to lopinavir/ritonavir (LPV/r) has been noted to date in over 500 ARV-naïve adult subjects on LPV/r (Kaletra) + 2 NRTIs participating in Phase II and III adult and pediatric clinical trials, even in subjects who experienced viral load rebound (See Table 1 for example).
- Although wild type virus has previously been observed in some patients rebounding from HAART, the absence of protease inhibitor resistance in the above patient population is intriguing.
- Assuming similar fitness and infectivity, we have previously demonstrated that the probability of resistance development is the highest when drug concentrations fall between the IC_{50} of baseline virus and its first mutants.[1] A large resistance step size* can result in high selective pressure across a wide range of drug concentrations (Figure 1), hence increasing probability of resistance development.
- We have also demonstrated that under some adherence conditions, the commonly perceived benefit of having a drug with a long elimination half life ($t_{1/2}$) may increase the probability of resistance development, particularly when the resistance step size is large.[1]
- However, the effects of patient adherence on resistance development have not been systematically assessed for drugs with different PK and resistance characteristics.
- In this presentation, we demonstrate that the potential of resistance development for drugs with different PK properties and resistance step sizes* may not be the same for a given adherence rate, using a mathematical HIV treatment model via the Pharsight clinical trial simulator.
- Although it has been shown that drug-resistant mutants often have reduced fitness and/or infectivity, the effect of mutant fitness and infectivity on resistance development is not assessed in this presentation.

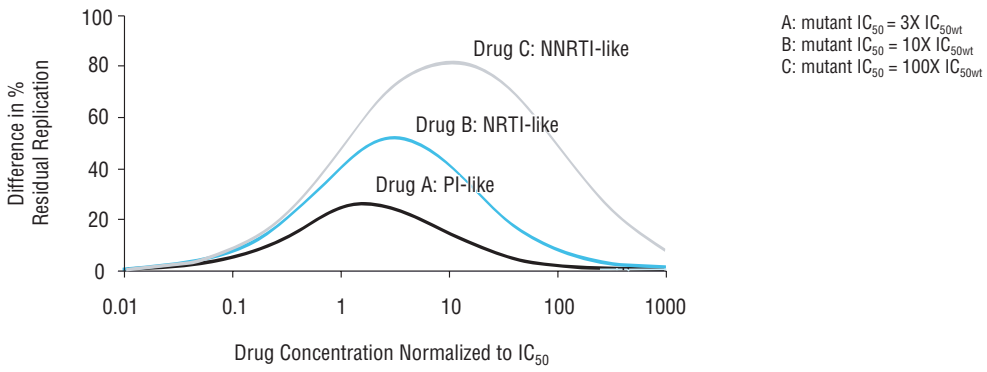
**Defined as the ratio in IC_{50} between wild type and first mutant or ratio in IC_{50} between one mutant and the next mutant). Resistance step size is generally small for protease inhibitors and large for non-nucleoside reverse transcriptase inhibitors.*

Table 1. Incidence of Resistance at Weeks 24-96 (Abbott Study 863)

	LPV/r (N=326)	NFV (N=327)
HIV RNA above 400 copies/ml	74	113
Genotype available	51	96
Resistance detected in protease	0/51 (0%)	44/96 (46%)[2]
3TC resistance	19/51 (37%)	78/96 (81%)

- Absence of any primary or active site PI resistance mutations in LPV/r arm was confirmed by phenotypic analysis.
- Consideration of NFV mutations includes D30N, L90M, and M46I/L.
- Overall adherence rates by pill count were similar between the two arms.
- Viral rebound rates were higher in low adherence population.

Figure 1. Large Resistance Step Size Produces High Selective Advantage over a Wide Concentration Range



Note: y-axis is selection advantage (or pressure) and is defined as the difference in % residual replication between mutant and wild type virus. % residual replication=100%•(1- [drug] / ([IC_{50}]+[drug]).

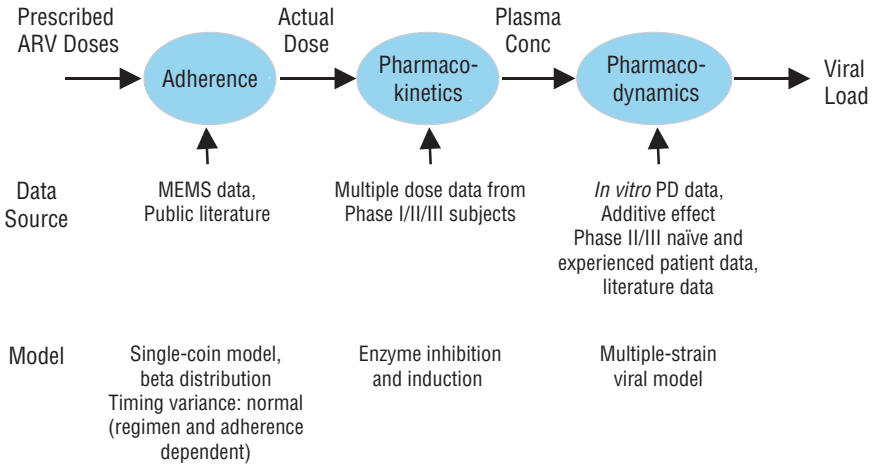
OBJECTIVE

To assess how various adherence rates affect the probability of resistance development for drugs with different PK and resistance properties using a mathematical HIV treatment model.

METHODS

I. The HIV Treatment Model

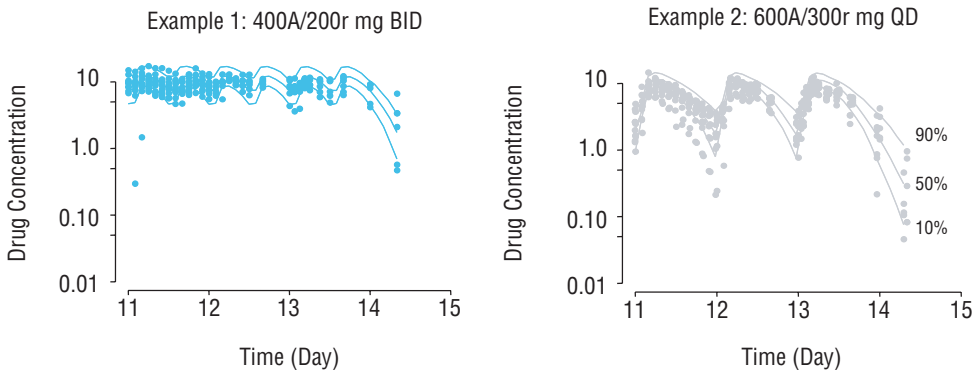
Figure 2. Basic HIV Treatment Model



- Adherence model accounts for between- and within-patient variability in dose taking.
- Pharmacokinetic model accounts for inhibitory and inductive interaction among HIV drugs.
- HIV infection model semi-empirically accounts for viral replication, infection, and death, and CD4 T cell turnover.
- Resistance model able to simultaneously monitor multiple viral strains. Each virus strain is characterized by resistance status with respect to NRTI, NNRTI, and PI. This model also allows specification of resistance step size, fitness, and mutation probability for each mutant.
- Other assumptions and parameterization
  - *wt* IC_{50} for PI and NNRTI are protein binding-adjusted values measured in the same experimental system; data from Abbott Laboratories.[3]
  - Antiviral activity of drugs: standard sigmoidal E_{max} model.
  - Assumed additive drug effect between two protease inhibitors.
  - NRTI effect was estimated as the additional effect over PI monotherapy based on Indinavir 028 data.

II. Performance of the HIV Treatment Model

Figure 3. The Model Describes Lopinavir/ritonavir PK Well



Note:
1. The plots show 10%, 50% and 90% simulated concentrations as well as individual observed data.
2. PK of other PIs can be reproduced based on literature data.

Table 2. Simulated vs. Observed Antiviral Response of LPV/r Clinical Trials Are Reasonable

	24-Week Response (%)			48-Week Response (%)		
Clinical Trials	**N**	**Observed**	**Simul***	**N**	**Observed**	**Simul***
LPV/r + 2 NRTIs[4] (Naïve)	95	95	96	92	93	94
LPV/r + 2 NRTIs + NVP[5] (PI-experienced)	64	84	86	56	86	82

** Simulated for 200 subjects; response is defined as plasma viral load <400 copies/mL.*

The model can be easily adapted to simulate treatments by other anti-HIV drugs.

III. Simulations to Assess Adherence Effects on the Probability of Resistance Development

Table 3. PK and Resistance Profiles of Three Model Drugs*

	LPV-like	NFV-like	EFV-like
Median IQ	80	3	450
Terminal $t_{1/2}$	1-2 Hr*	4 Hr	50 Hr
Resistance step size	2, 4, 8, 26X	2, 4, 8, 26X	20, 100, 200X

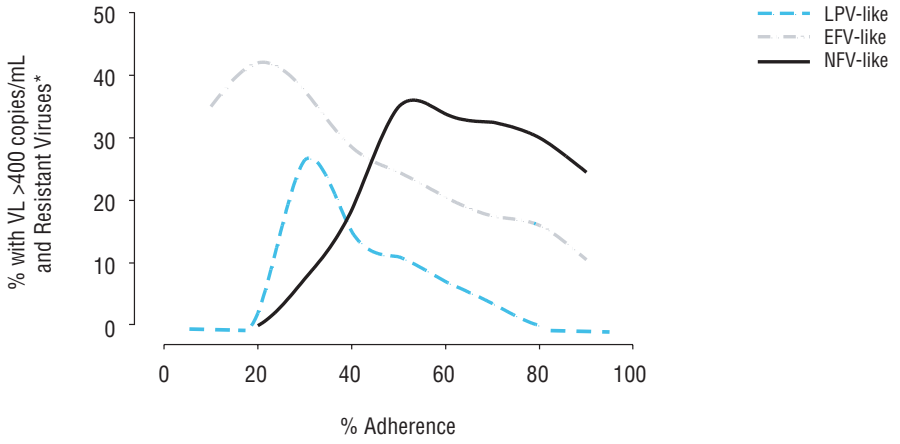
** In the absence of* in vivo *resistance data for LPV/r, we assumed that LPV-like and NFV-like drugs have small increments in resistance step sizes, but have PK characteristics similar to those of lopinavir/ritonavir and nelfinavir, respectively. This assumption simplifies the interpretation of the simulation results; however, it should be noted that the literature data and Abbott clinical trial data collectively suggest that the resistance step sizes for nelfinavir may be bigger than those assumed in the above table.*

** The EFV-like drugs have PK and resistance profiles similar to those of efavirenz.*

- LPV/r-like drugs
  - Achieve high mean IQ values relative to wild type viral susceptibility. Also have reasonably high IQ values relative to initial mutants because of small resistance step sizes.
  - The terminal $t_{1/2}$ for LPV-like drugs is modeled based on observed LPV/r PK (Figure 6); which is 9 to 10 hr during steady state, 1 to 2 hr during missed doses.
- EFV-like drugs
  - Achieve very high mean IQ values relative to wild type viral sensitivity; however, have significantly reduced IQ relative to mutants because of large resistance step sizes.
- NFV-like drugs
  - Achieve low mean IQ values relative to wild type virus as well as mutants, even though initial resistance step sizes are small.
- IQ (inhibitory quotient) is defined as the ratio of trough concentration/IC_{50}.
- Other simulation conditions:
  - Adherence: one-coin model
  - Fitness is assumed to be 0.7 for all mutants
  - Mutation rate = 10^{-5}
  - Treatment includes 2 NRTIs (IQ=1, $t_{1/2}$=15 hr)

RESULTS

Figure 4. Adherence Rates Have Distinctive Effects on the Probability of Resistance Development for the Three Model Drugs



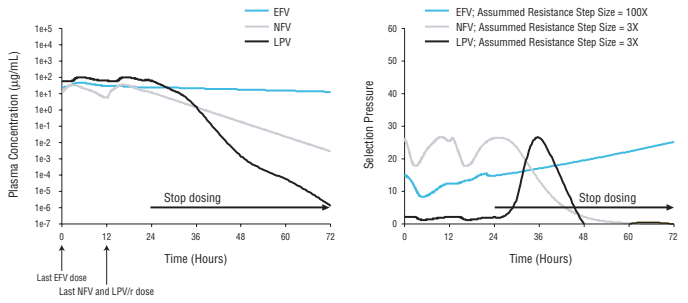
**Resistant viruses accounting for >20% of total viral load.*

- Under the specific simulation conditions and assumptions, our simulation results show that adherence rates have distinctively different effects for the three model drugs in treatment-naïve patients.
  - For populations with adherence rates >50%, the probability of resistance development appears to be the lowest for drugs with high IQ and small resistance step sizes, and is the highest for drugs with inadequate IQ values.
  - For populations with low adherence rates, the probability of resistance development is the highest for drugs with large resistance step sizes and long elimination half-life.
  - If drug concentration is very low relative to the IC_{50} of the wild type virus and initial mutants (i.e., during missing doses), then the probability of resistance development would also be greatly reduced.

DISCUSSION

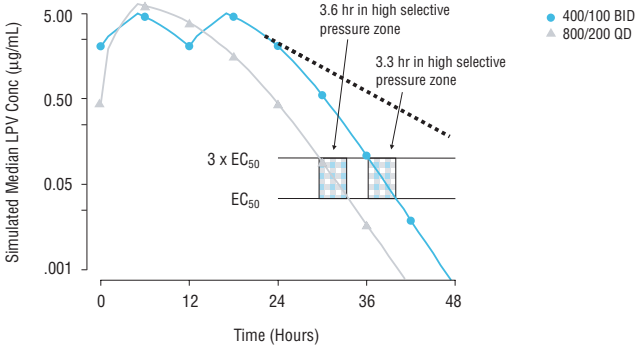
- This simulation demonstrates that drug PK, resistance step size and adherence rate are contributing factors to resistance development during drug therapy.
- The relationship between adherence rates and probability of drug resistance development are related to drug-specific PK properties and resistance step sizes.
- During good adherence, the probability of drug resistance development can be reasonably predicted based on drug-specific PK profiles and resistance step sizes. This is demonstrated by the consistency observed between the rank order in selection pressure (NFV>EFV>LPV) in Figure 5 in the 0-24 h region and the rank order in the probability of resistance development in the high adherence region in Figure 4 (NFV>EFV>LPV).
- Assuming good adherence, the probability of drug resistance development can be predicted based on drug PK and resistance step size. This is confirmed by comparing the high adherence region in Figure 4 and the 0-24 h 100% adherence region in Figure 5.
- The probability of resistance development is reduced if drug concentrations are high enough to also suppress initial mutants.
- Drugs having large resistance step sizes have increased probability to develop drug resistance because mutants have increased selective advantage over a wide concentration range (Figure 1).
- Thus, the commonly perceived benefit of having a drug with long elimination $t_{1/2}$ may increase the probability of resistance development during inconsistent adherence, particularly when the resistance step size is large (Figures 4 and 5).
- Also, during missed doses, the probability of developing drug resistance would be reduced if drug concentrations decline very rapidly through concentration windows favorable for resistance development (Figures 4, 5, and 6).
- The simulation results suggest that the lack of PI resistance development in PI-naïve population treated with LPV/r + 2 NRTIs may be due to the facts that the therapy provides an overall low selection pressure even during missing doses due to the following characteristics:
  - High LPV *in vivo* IQ values adequate to also suppress the growth of initial mutants (Table 3).
  - Small PI resistance steps (based on *in vitro* data), hence, narrow selective concentration windows with low selection pressures.
  - Rapid decline of LPV concentrations during missed doses, hence, short residence time inside selective concentration windows (Figures 5 and 6).

Figure 5. Plasma Concentration-Time and Selection Pressure-Time Profiles of EFV, NFV, and LPV During Steady State and After Missing Doses for Two Days



Note:
1. *Data are based on Abbott Laboratories data on file. EFV was dosed QD, NFV and LPV/r (400/100 mg) were dosed BID. Terminal plasma concentrations of NFV and LPV were observed data up to 48 h. EFV concentrations after 24 h were extrapolated assuming $t_{1/2}$ of 50 hr.*
2. *Selection pressure is defined under Figure 1.*

Figure 6. Due to Escalating Elimination Phase, the Estimated Duration of High Selective Pressure Zone for LPV Is Short



Assumption: The EC_{50} of the first mutant during LPV/r therapy is 3X higher than that of wild type virus.

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