

Exploring Theoretical Mechanisms for Lack of Resistance to Lopinavir/Ritonavir (LPV/r) in Antiretroviral (ARV)-Naïve Subjects

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BACKGROUND

- Kaletra is a coformulation of lopinavir (LPV) and ritonavir (r), where ritonavir acts as a PK enhancer for LPV by inhibiting the CYP3A-mediated metabolism of LPV.
- At the LPV/r clinical dose (400/100 mg BID), the mean LPV inhibitory quotient (IQ = trough conc/ IC_{50}) is >75-fold.
- In a Phase III clinical study in 326 ARV-naïve adult subjects on LPV/r plus d4T/3TC, no resistance to LPV/r has been noted to date, even in subjects whose viral replication was not completely suppressed (Table 1).

Table 1. Incidence of Resistance at Weeks 24-96 (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%)	41/96 (43%)
3TC resistance	19/51 (37%)	78/96 (81%)

* Absence of resistance to LPV confirmed by phenotypic analysis.

- Consistent with the lack of resistance development, the majority of the subjects who had viral rebounds were resuppressed in subsequent viral load measurements (Table 2).

Table 2. Resuppression After Genotypic Analysis (Through Week 96, Study 863)*

	LPV/r	NFV
Subjects with genotypic data	51	96
Subjects with HIV RNA values subsequent to genotype	26	43
Resuppression to <400 copies/mL after genotype	25 (96%)*	14 (33%)**
Resuppression with PI resistance	n/a	1/23
Resuppression with 3TC resistance but no PI resistance	9/10	3/10*

* p = 0.020
** p < 0.001

- Consistent with these results, in three Phase II studies of ARV-naïve patients dosed with LPV/r plus NRTIs for 48 to 144 weeks, no protease inhibitor resistance was observed.
- Although wild type virus has previously been observed in some patients rebounding from HAART, the virtual absence of resistance in the above patient population is intriguing.

OBJECTIVE

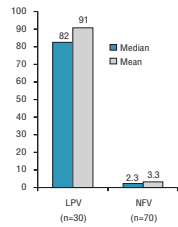
To explore the theoretical mechanisms for the virtual absence of PI resistance development in ARV-naïve patients treated with LPV/r plus NRTIs.

HYPOTHESIS

We hypothesize that the virtual absence of PI resistance development in naïve patients treated with LPV/r is due to the combination of the following characteristics of LPV/r:

- LPV has very high *in vivo* IQ (Figure 1).
- The incremental resistance step size (difference in IC_{50} between wild type and first mutant or difference in IC_{50} between one mutant and the next mutant) for protease inhibitors is generally small.
- LPV/r has an unique elimination profile, with an accelerated $t_{1/2}$ of 1-2 hr during missed doses, compared with a $t_{1/2}$ of 9-10 hours during routine BID dosing intervals. The late, rapidly declining phase is presumably due to declining ritonavir concentrations, and may prevent prolonged periods of sub-therapeutic concentrations.

Figure 1. Lopinavir and Nelfinavir IQ in Study 863*



- IQ data based on $C_{min,0-6h}$ of 30 LPV/r and 70 NFV randomly selected subjects and the protein binding adjusted IC_{50}

ASSUMPTIONS AND METHODS

- Since viral replication is rapid and reverse transcriptase has low fidelity, it is assumed that wild type (wt) and first mutants (mu) preexist at baseline in ARV-naïve subjects.
- The residual viral replication in the presence of drugs can be calculated using the following equation
% Residual Replication = $100\% - 100\% \cdot C_{min} / (C_{min} + IC_{50})$
- The selective advantage (selection pressure) of first mutants over wt viruses in the presence of drugs is defined as the difference in residual viral replication between the competing strains.
- The difference in % residual viral replication was simulated for three model drugs to which a single mutation produced the following change in susceptibility, compared to wt virus:

Model Drug	Resistance Step Size
A	3-fold
B	10-fold
C	100-fold
- Simulations using an HIV-treatment mathematical model* were performed to estimate the rate of resistance development as a function of resistance step size and inhibitory quotient/half-life (Simulation 1) and as a function of significantly different elimination half-lives (Simulation 2).
 - Simulation 1 (200 patients/scenario) — Effect of resistance step size and IQ/half-life
 - Adherence: mean 90%, beta distribution, one-coin model based on adherence data from Study 863*
 - Fitness of the mutant: 0.7 relative to wild type virus
 - Mutation rate = 10^{-5}
 - NRTI was included in the regimen (IQ=1, $t_{1/2}$ = 16 hr)
 - Simulation 2 (200 patients/scenario) — Effect of drug half-life
 - Adherence = 60%, one-coin model
 - Fitness of the mutant: 0.7 relative to wild type virus
 - Mutation rate = 10^{-5}
 - NRTI was not used in the simulation

RESULTS

Simulation of Selective Advantage

- The selective advantage of the first mutant over the wild type virus was simulated for three hypothetical drugs with 3-fold, 10-fold and 100-fold step sizes (Figure 2 and Table 3).
- The highest selective advantage was observed at drug concentrations between the two IC_{50} values.
- Maximum selective advantage for the model drugs were:

Drug A: ~27%
Drug B: ~50%
Drug C: ~82%
- For all three model drugs, very low drug levels (relative to the IC_{50} of wild type or baseline virus) produce very low selective advantage for mutants. However, for mutants with reduced fitness, low drug levels would favor the replication of the wild type virus.

Figure 2. High $IC_{50,mu}/IC_{50,wt}$ Ratio Produces High Selective Advantage over a Wide Concentration Range

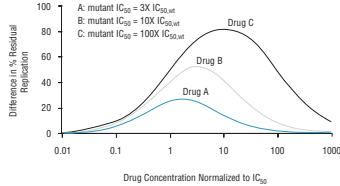


Table 3. Difference in % Residual Viral Replication Between Wild Type Virus and Mutant Is a Function of the $IC_{50,mu}/IC_{50,wt}$ Ratio and Drug Concentrations

Drug Concentration	Drug A $IC_{50,mu}=3X$	Drug B $IC_{50,mu}=10X$	Drug C $IC_{50,mu}=100X$
0.01X $IC_{50,wt}$	0.7%	0.7%	1.0%
$IC_{50,wt}$	25.0%	40.9%	49.0%
$IC_{50,mu}$	25.0%	40.9%	49.0%
$IC_{90,wt}$	15.0%	42.6%	81.7%
$IC_{90,mu}$	6.4%	8.9%	9.9%
75X of $IC_{50,wt}$	2.5%	10.4%	55.8%

HIV Treatment Simulation Results

- Treatment of 200 patients over 48 weeks of therapy was simulated.

Simulation 1: Effect of IQ/Half-life and Resistance Step Size on the Estimated Rate of Resistance (Table 4)

	Median IQ	Drug Half-life	Resistance Step Size
	82	Concentration-dependent	2X, 26X
	82	Concentration-dependent	2X, 4X, 8X, 26X
	2.5	4 hr	2X, 26X
	2.5	4 hr	2X, 4X, 8X, 26X

Table 4. Effect of IQ, Half-life and Resistance Step Size on Viral Response at Week 48

Median IQ	82	82	2.5	2.5
Half-life	Conc-dep.	Conc-dep.	4 hr	4 hr
Resistance step size	2, 4, 8, 26X	2. 26X	2, 4, 8, 26X	2, 26X
PI resistant*	3.5%	12.0%	31.0%	41.0%

Note:
* Plasma viral load >400 copies/mL and resistant viruses account for >20% of the total plasma viral load.
Concentration-dependent half-life: modeled based on LPV/r PK; 9 to 10 hr during steady state, 1 to 2 hr during missed doses.

- High IQ drug consistently produces better viral response.
- Smaller resistance step size reduces the probability of developing resistant virus.
- With high IQ, the model overestimates the actual resistance rate.

Simulation 2: Effect of Drug Half-life (Table 5)

- Simulation was performed for the following four scenarios for two drugs, one with a concentration-dependent $t_{1/2}$ (9-10 hr during steady state and < 2 hr after missing dose) and one with a 50 hr $t_{1/2}$:

Median IQ	Resistance Step Size
10	100X
100	100X
100	50X
2	10X

Table 5. Effect of $t_{1/2}$ on the Percentage of Patients with Resistant Virus at Week 48

Median IQ	10	100	100	2
Resistance step size	100X	100X	50X	10X
$t_{1/2}$: concentration-dependent	51.5%	30.5%	23.5%	47.0%
$t_{1/2}$: 50 hr	58.0%	37.0%	26.5%	34.5%

Note:
• Adherence (fraction of prescribed dose taken) was assumed to be 60%.
• Concentration-dependent half-life: modeled based on LPV/r PK; 9 to 10 hr during steady state, 1 to 2 hr during missed doses.

- Under the various simulation conditions for two drugs achieving the same IQ values with identical adherence, the drug with a longer elimination $t_{1/2}$ consistently produces larger % of mutants when resistance step size is large.
- The longer elimination $t_{1/2}$, however, appeared to be beneficial when the resistance step size is reduced.

DISCUSSION

- This modeling and simulation exercise demonstrates that the interaction between drug concentrations and resistance development is highly dynamic during HIV therapy.
- The probability of resistance development is the highest when drug concentrations fall between the IC_{50} of baseline virus and its first mutants. A large difference in IC_{50} values between the wt (or baseline) virus and its first mutant (i.e., large step size) will result in high selective pressure across a wide range of drug concentrations, hence increased probability of resistance development.
- Inadequate drug levels can also lead to resistance development even when the step size is small.
- Under some conditions, the commonly perceived benefit of having a drug with long elimination $t_{1/2}$ may increase the probability of resistance development, particularly when the resistance step size is large.
- The theoretical simulations suggest that since it is difficult to maintain 100% adherence during long-term therapy, the probability of developing drug resistant mutations would be reduced if a drug has the following PK properties, in addition to having small resistance step size:
 - High drug levels (multiples of the IC_{50} of the first mutant)
 - Reasonable $t_{1/2}$ to support variations in daily dosing time
 - Very rapid decline of drug levels during missing doses through concentrations that are highly selective
- Interestingly the PK profile of LPV/r at the recommended clinical dose has the three properties that are important for reduction in resistance development.

CONCLUSIONS

- The combined PK and PD characteristics of LPV (high *in vivo* IQ, small resistance step size, and the rapid decline of lopinavir concentrations during missed doses) are likely to contribute to the clinical observation of lack of resistant development in ARV-naïve patients treated with LPV/r.

REFERENCES

- Bernstein B, et al. Comparison of the emergence of resistance in a blinded phase III study with Kaletra™ (lopinavir/ritonavir) or nelfinavir plus d4T/3TC from week 24 through 96, 41st ICAAC, Chicago, IL, Dec. 16-19, 2001, Abstract I-1768.
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