Poster #234

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Efficacy of Lopinavir/ritonavir in Multiple PI-Experienced Patients According to Mutational Patterns: Data from the French ATU Program

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BACKGROUND

Lopinavir/ritonavir (LPV/r, Kaletra™) is a novel HIV protease inhibitor (PI) that has shown significant antiviral activity and tolerability in clinical trials to date.

The co-formulation of LPV with a low dose of ritonavir, acting solely as a pharmacokinetic enhancer, results in substantially increased LPV drug exposure, minimizing the potential impact of variability in absorption and adherence.

The mean LPV C_{trough}/EC_{50} ratio (inhibitory quotient or IQ) for wild-type virus is >75 when LPV/r is dosed at 400/100 mg BID, contributing to the durability of virologic response and potentially providing a pharmacologic barrier to the emergence of viral resistance. However, virologic response to LPV/r may be compromised by mutations arising from prior PI therapy.

In a multiple PI-experienced study (M98-957), virologic response to therapy was associated with the number of baseline mutations and baseline LPV phenotype.

METHODS

From March 2000 to April 17, 2001, patients with no other treatment option available were treated with LPV/r through an ATU (Autorisation Temporaire d"Utilisation) granted by the French Drug Agency. At the time of the ATU completion, as of April 17, 2001, the overall enrollment in the LPV/r cohort was 3,819 patients.

A large collaboration with the French Virology Departments was conducted on a voluntary basis and was initiated to more extensively analyze a subpopulation of 179 patients with complete set of data:

- At baseline: Demographic data, prior and current ARV medications, genotype (including mutation polymorphisms in protease), HIV-RNA and CD4, both performed within 3 months prior to LPV/r initiation.
- Virological follow-up through 6 months

Statistical analysis was performed using Fisher's exact test and univariate logistic regression supported by stepwise logistic regression.

RESULTS

Baseline Characteristics

- Male: 85.4%
- Mean age: 42 years (range 26 – 71)
- Median plasma HIV RNA: 5.01 $\log_{10}$ copies/mL (range 3.07 – 6.34)
- Median CD4 count: 102 cells/mm³ (range 0 – 995)

Previous Antiretroviral Treatments

Prior ARV therapy is summarized in Figure 1. The majority of patients were previously treated with at least 3 PIs (74%), at least 4 NRTIs (90%), and at least 1 NNRTI (83%). Treatment experience with individual ARVs is summarized in Figure 2.

Figure 1. Number of Previous Antiretroviral Treatments

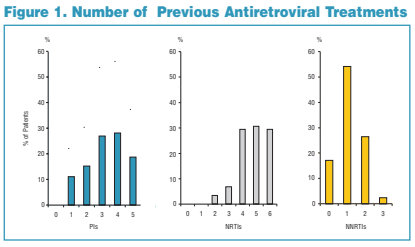
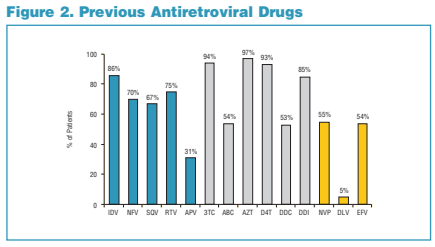


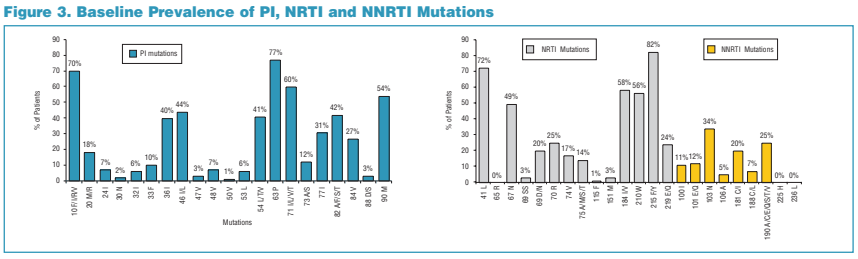
Figure 2. Previous Antiretroviral Drugs



Baseline Genotype

- The prevalence of baseline mutations in protease and reverse transcriptase is provided in Figure 3.
- The most common PI mutations occurred at positions 63, 10, 71 and 90.
- Most of the patients had thymidine NRTI resistance mutations (41, 67, 210, 215) and the lamivudine resistance mutation (184). For NNRTIs, a large proportion of patients had at least one mutation that confers cross-resistance to all NNRTIs currently available for therapeutic use (101, 103, 190).

Figure 3. Baseline Prevalence of PI, NRTI and NNRTI Mutations



LPV Mutation Score

- As presented in Figure 4, the number of PI-associated mutations within this population ranged from 0 to 11, with a median of 6 mutations. The median number of NRTI and NNRTI mutations was 5 and 1, respectively.
- The LPV mutation score includes the number out of 11 protease mutations previously described to be associated with reduced susceptibility to lopinavir (amino acids 10, 20, 24, 46, 53, 54, 63, 71, 82, 84 and 90).
- Within this population, the baseline LPV mutation score ranged from 0 to 9, with a median of 5 mutations. The majority of patients (113/179, 63%) had a baseline LPV mutation score of 4-7 (Figure 5).

Figure 4. Baseline Prevalence of PI, NRTI and NNRTI Mutations

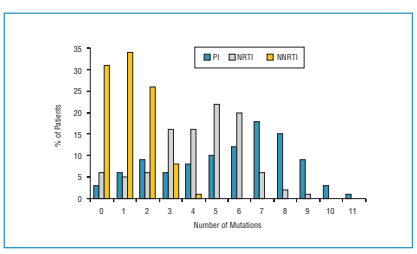
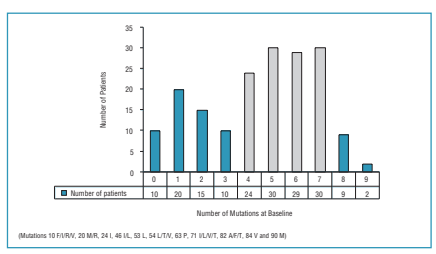


Figure 5. Baseline LPV Mutation Score

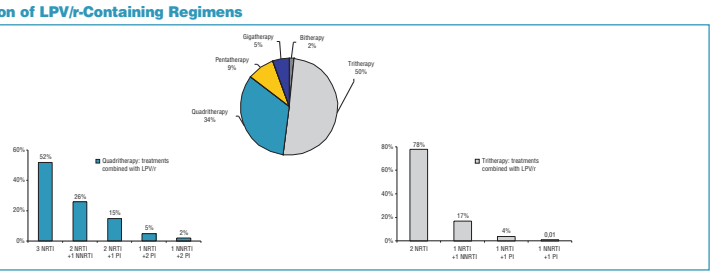


(Mutations 10 F/I/R/V, 20 M/R, 24 I, 46 I/L, 53 L, 54 L/T/V, 63 P, 71 I/L/V/T, 82 A/F/T, 84 V and 90 M)

Concomitant Antiretroviral Therapy

Concomitant ARVs in the LPV/r-containing regimens for the study population are provided in Figure 6. A large majority of patients received two or three additional drugs, which consisted in most cases of two NRTIs and 3 NRTIs, respectively. Fourteen percent of patients received more than three concomitant ARVs. Concomitant use of another PI with LPV/r was less frequent.

Figure 6. Description of LPV/r-Containing Regimens



Using genotypic resistance testing criteria suggested by the French authorities (AC11, October 2001), the drug susceptibility of ARVs used in the baseline regimen were classified as resistant, suspected resistant and susceptible. These criteria are summarized in Table 1.

Table 1. AC11 Interpretation of Genotype

Interpretation of Genotype: Protease Inhibitors		
PIs	**Resistance**	**Suspected Resistance**
IDV	M46I/L V82A/F/S/T I84V L90M + ≥2 mutations including: K20M/R, L24I, V32I, M36I, I54V, A71V/T, G73S/A, V771	L90M
SQV	G48V I84V L90M	V82A/F/S/T + ≥2 mutations including: I54V/L, A71V/T, G73S, V77I
NFV	D30N I84V N88S/D L90M	V82A/F/S/T + ≥2 mutations including: M36I, M46I/L, A71V/T, V771
RTV	V82A/F/S/T I84V	L90M + ≥2 mutations including: K20M/R, V32I, L33F, M36I, M46I/L, I54L/V, A71V/T, V771
APV (1)	I50V ≥4 mutations including: L10I, V32I, M46I/L, I47V, I54L/M/V, G73S, V82A/F/I/T/S, I84V, L90M	
LPV/r (1)	≥8 mutations including: L10F/I/R/V, K20M/R, L24I, M46I/L, I50V, F53L, I54L/T/V, L63P, A71/L/V/T, V82A/F/T, I84V, L90M	6 or 7 mutations including: L10F/I/R/V, K20M/R, L24I, M46I/L, I50V, F53L, I54L/T/V, L63P, A71I/L/V/T, V82A/F/T, I84V, L90M

(1) Recent data.

Table 1. AC11 Interpretation of Genotype (cont.)

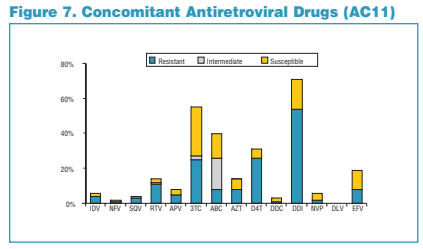
Interpretation of Genotype: NRTIS		
NRTIs	**Resistance**	**Suspected Resistance**
AZT	T215Y/F ≥3 mutations including: M41L, D67N, K70R, L210W, K219Q/E Q151M Insertion at codon 69	
3TC	M184V/I Insertion at codon 69	Q151M
ddI (1)	L74V ≥3 TAMs dont T215Y/F Q151M Insertion at codon 69	K65R
ddC (2)	T69D/N/S Q151M Insertion at codon 69	K65R
d4T	V75M/S/A/T T215Y/F ≥3 mutations including: M41L, D67N, K70R, L210W, K219Q/E Q151M Insertion at codon 69	
ABC (1)	≥6 mutations including: M41L, K65R, D67N, K70R, L74V, Y115F, M184V/I, L210W, T215Y/F, 219Q/E Q151M Insertion at codon 69	4 or 5 mutations including: M41L, K65R, D67N, K70R, L74V, Y115F, M184V/I, L210W, T215Y/F, 219Q/E
TDF (1)	Insertion at codon 69	K65R ≥4 TAMs including T215Y/F

(1) Recent data.
(2) Data missing on ddC resistance if presence of mutations to the other NRTIs. TAMs=M41L, D67N, K70R, L210W, T215Y/F, K219Q/E. TDF: tenofovir.

Interpretation of Genotype: NNRTIs	
NNRTIs	**Resistance**
EFV	L100I K101E K103N Y181C/I Y188C/L G190A/C/E/Q/S/T/V P225H
NVP	L100I K101E K103N V106A Y181C/I Y188C/H/L G190A/C/E/Q/S/T/V
DLV	L100I K101E K103N V106A Y181C Y188C/L G190E P236L

A large majority of patients did not receive multiple susceptible drugs as part of their antiretroviral therapy as demonstrated in Figure 7 and Figure 8 by a high level of resistance to concomitant drugs given in combination with LPV/r.

Figure 7. Concomitant Antiretroviral Drugs (AC11)



Immuno-Virological Response

Virologic and immunologic response was monitored through 8 months of LPV/r therapy (Figure 9). Virologic response was defined as a minimum viral load of <400 copies/mL and/or a decrease from baseline of at least 1.0 $\log_{10}$ copies/mL.

Figure 8. Number of Susceptible ARVs Used in Combination with LPV/r (AC11)

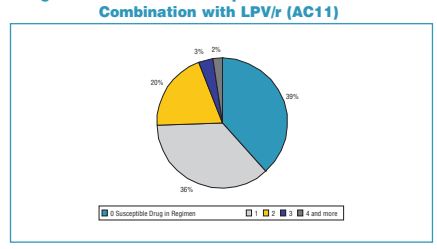
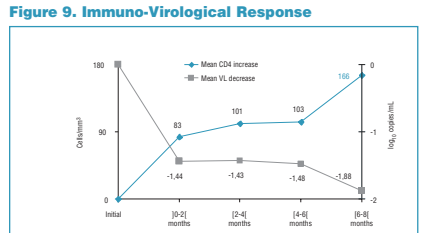


Figure 9. Immuno-Virological Response

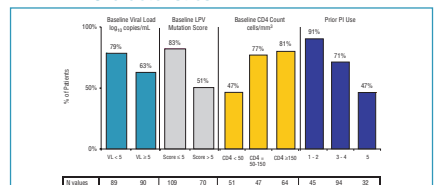


N CD4 values	126	101	89	47	29
Median	0	53	60	61	123
N VL values	179	154	134	59	27
Median	0	-1.66	-1.45	-1.52	-1.69

Analysis of Virologic Response with Respect to Baseline Characteristics

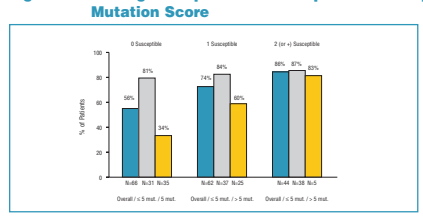
- Plasma viral load measurements were evaluated as a function of baseline plasma HIV RNA (<5 $\log_{10}$, >5 $\log_{10}$ copies/mL), baseline CD4 count (<50, 50-150, >150 cells/mm³), baseline LPV mutation score, and prior PI use (1-2, 3-4, 5) (Figure 10).
- In a univariate analysis, each of these parameters was statistically significantly associated with virologic response (p<0.011).
- If we consider LPV mutation score, response was observed in 91/109 (83%) of patients with LPV mutation score of 0-5, in contrast to 36/70 (51%) patients with a LPV mutation score of 6 or more (p<0.001).

Figure 10. Virologic Response Stratified by Baseline Characteristics



N values	89	90	109	70	51	47	64	45	94	32
P values	0.032		<0.001		<0.001			<0.001		

Figure 11. Virologic Response with Respect to Susceptibility to Concomitant ARVs and Baseline LPV Mutation Score



- In order to evaluate the potential impact of ARV drugs other than LPV/r on virologic response, concomitant drugs used in the baseline regimen were classified as susceptible or non-susceptible (i.e., intermediate or resistant). Virologic response was then evaluated on the basis of the number of susceptible drugs used in the baseline regimen. Results from this analysis are summarized in Figure 11.

Virologic Response Stratified by Baseline Genotype

- Longitudinal response with respect to the LPV mutation score was also examined in the subset of 102 patients with plasma HIV RNA data available within 90 days prior to initiation of LPV/r therapy and within Days 1-90 and Days 91-180 following initiation of LPV/r therapy (Figure 12).
- Response rates for patients with 0-5 mutations were higher than those of patients with ≥6 mutations through 6 months of therapy.
- The logistic regression model for virologic response in this study with respect to the baseline LPV mutation score is shown in Figure 13. Observed categorical rates are shown by the solid bars. Using a conservative measure (the lower 95% CI), the predicted response rate is >62% in patients with baseline LPV mutation score of 5 or fewer. The odds ratio per mutation was 0.72 (95% CI 0.61-0.85).

Figure 12. Longitudinal Response in Patients with Multiple Time Points

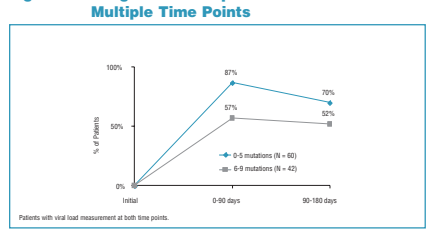
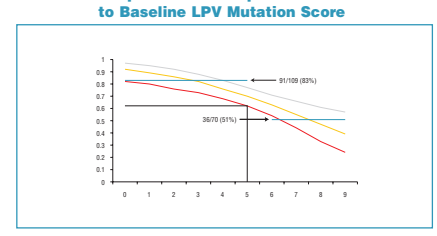


Figure 13. Logistic Regression Model of Virologic Response with Respect to Baseline LPV Mutation Score



- A stepwise logistic regression model of virologic response with respect to the following baseline parameters was performed (Table 2):
  - LPV mutation score
  - Baseline HIV RNA
  - Number of prior PIs
  - Number of prior NRTIs
  - Number of prior NNRTIs
  - Total number of prior ARVs
  - Number of concomitant PIs
  - Number of concomitant NRTIs
  - Number of concomitant NNRTIs
  - Total number of concomitant ARVs
  - Number of active PIs
  - Number of active NRTIs
  - Number of active NNRTIs
  - Total number of active ARVs
  - Baseline CD4

Table 2. Stepwise Logistic Regression Analysis

Baseline Parameter	Odds Ratio	p-value
LPV mutation score	0.726	0.0002
Baseline CD4	1.004	0.0093
Number of prior NNRTIs	0.541	0.016

CONCLUSIONS

Antiviral efficacy has been observed in this cohort of 179 LPV/r treated patients, in spite of extensive prior ARV-experience and a significant level of baseline genotypic resistance, as evidenced by a median of 6 PI mutations.

The high level of resistance to co-administered ARV agents suggests a significant contribution of LPV/r to the overall response observed.

The response rate was higher in patients who started therapy with lower baseline viral load, lower LPV mutation score, with higher CD4 cell count (>50 cells/mm³) and with less PI-experience.

The genotypic breakpoint of five or less was highly predictive of the extent of virologic response as seen in previous observations.[1]

LPV mutation score, baseline CD4, and number of prior NNRTIs were independently associated with response based on results from a multiple stepwise logistic regression analysis.

REFERENCES

1. Calvez, Cohen Codar, et al. Analysis of the Correlation Between Baseline Genotype Profile and Virologic Response to Lopinavir/r in 104 Multiple PI-Experienced Patients Treated Under the Lopinavir/r ATU. 5th International Workshop on HIV Drug Resistance and Treatment Strategies, Scottsdale, Arizona, June 2001 (Poster # 90).

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