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Study of the Initial Response to Lopinavir/ritonavir in HIV Treatment-Experienced Patients: The ATU Pre-Registrational Cohort in France

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BACKGROUND

Lopinavir/ritonavir (LPV/r, Kaletra™, formerly known as ABT-378/r), is the most recently approved protease inhibitor (PI) for the treatment of HIV-1 infection in the United States and in Europe.

LPV is exquisitely sensitive to pharmacokinetic enhancement by ritonavir (RTV), its co-formulation with a low dose of ritonavir results in substantially increased LPV drug exposure. The mean LPV ratio of C_{trough} to protein binding adjusted EC_{50} (Inhibitory Quotient or IQ) for wild-type virus is >75 (at 400/100 mg BID dose), potentially providing superior antiviral efficacy and a potential pharmacologic barrier to the emergence of viral resistance.

Before marketing authorization was granted, a major objective of the development program was to give access to patients failing other available therapeutic options. This objective was reached worldwide through an expanded access program (EAP) carried out as a clinical trial. In France, the EAP was rapidly switched to an "ATU" program ("Autorisation Temporaire d'Utilisation", Provisional Authorization for Use) from March 2000 to April 2001. This was performed upon the request of the French Drug Agency and according to a law making drugs that are not yet registered, but which are potentially life-saving medications, available.

The overall enrollment into the ATU cohort was 3447 patients.

METHODS

The ATU Program was restricted in the beginning to advanced patients (CD4 <200 cells/mm^3, viral load >4 $\log_{10}$ copies/mL). It was progressively broadened to authorize the use of LPV/r in a larger PI-experienced population.

At baseline, demographic data, information on patient's history, HIV RNA and CD4 measurements, prior and current antiretroviral medications were collected by investigators. HIV RNA sequence was performed in a heavily ARV-experienced patient population according to the French guidelines (Rapport Delfraissy 2000) and clinicians were encouraged to provide the results, when available.

Subsequent follow-up data including HIV RNA and CD4 counts, as well as serious adverse events were provided on a voluntary basis.

Within the ATU overall population, 793 patients had a genotype at baseline and at least one HIV RNA measurement within 10 days after the start of LPV/r-containing regimen (Group A). These patients are the subject of this analysis. The association between the virologic response and mutations from the wild-type sequence, as well as the effect of specific mutations on virologic response, was assessed.

Within Group A, a subset of 92 patients, who were naive to NNRTIs, were treated in the ATU with a regimen containing LPV/r and a NNRTI as new drugs (Group B). The virologic response in this group will also be shown.

RESULTS

Demographic and Disease Characteristics (Overall Population, n=3447)

- 79% patients were male, with a mean age of 42 years.
- Most patients were late stage of HIV infection: 51.3% had a history of least one CDC Class C (AIDS-defining) event.
- A minority had progressive HIV disease; 152 new opportunistic infections occurred in 7.3% (251/3447) patients during the three-month period prior to LPV/r initiation.
- The median baseline HIV RNA was 4.78 $\log_{10}$ copies/mL (range 0.70 to 7.05).
- The mean baseline CD4 count was 202 cells/mm^3, (range 0 to 1193).

Demographic and Disease Characteristics

- Group A (n=793)
  - 83% patients were male.
  - The mean age was 41 years.
  - The median plasma HIV RNA was 4.88 $\log_{10}$ copies/mL (range 1.54-6.98).
  - The median CD4 cell count was 140 cells/mm^3 (range 0 to 995).
- Group B (n=92)
  - 83% patients were male.
  - The mean age was 42 years.
  - The median plasma HIV RNA was 4.74 $\log_{10}$ copies/mL (range 3.29-5.89).
  - The median CD4 cell count was 174 cells/mm^3 (range 1 to 747).

Antiretroviral Experience

- Prior ARV therapy is provided in Figure 2a (overall population). The profile history of prior ARV therapy was similar in Group A (data not shown). Figure 2b shows ARV therapy history for Group B.
- The majority of overall patients were previously treated with at least 3 PIs (62%), 5 NRTIs (59%), and 1 NNRTI (75%).
- Treatment experience with individual antiretrovirals is provided in Figure 3 (overall population). The profile history of treatment experience with individual antiretrovirals was similar in Group A (data not shown). Figure 3b shows treatment experience with individual antiretrovirals for Group B.

Figure 2a. Number of Previous Antiretroviral Drugs (Overall Population)

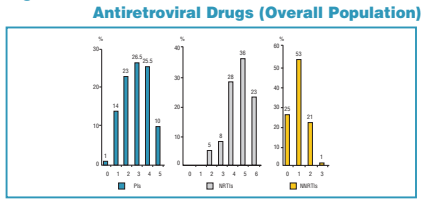


Figure 2b. Number of Previous Antiretroviral Drugs (Group B)

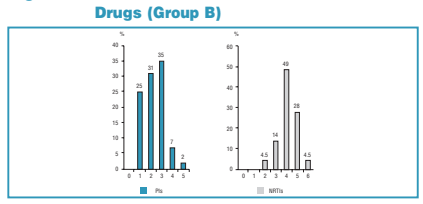


Figure 3a. Previous Antiretroviral Treatments (Overall Population)

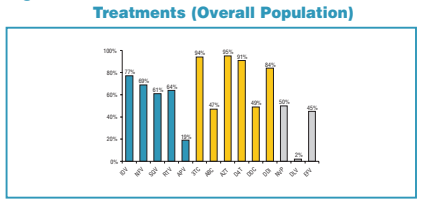
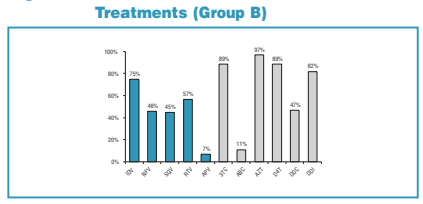


Figure 3b. Number of Previous Antiretroviral Treatments (Group B)



Baseline Genotype

- The prevalence of multiple baseline PI mutations associated with cross resistance to the PI class was high as shown in Figure 4a (Group A) and Figure 4b (Group B). The majority of isolates contained one or more primary mutations at positions 82, 84 and 90, as well as secondary mutations at positions 10, 46, 54 and 71.[1]
- Eleven mutations at amino acids 10, 20, 24, 46, 53, 54, 63, 71, 82, 84 and 90 have been associated with reduced LPV activity. The number of these mutations present is considered the mutation score. Within this population, the baseline LPV mutation score ranged from 0 to 9, with a median number of 4 mutations: Figure 5a (Group A) and Figure 5b (Group B).

Figure 4a. Baseline Prevalence of PI Mutations (Group A)

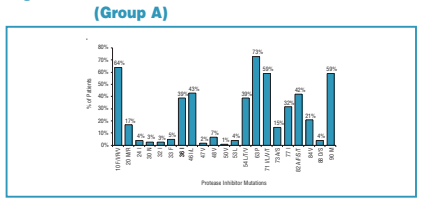


Figure 4b. Baseline Prevalence of PI Mutations (Group B)

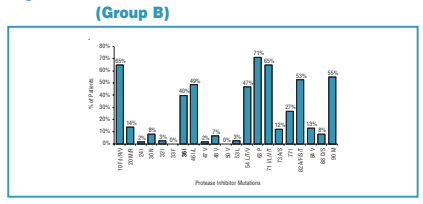


Figure 5a. Baseline LPV Mutation Score (Group A)

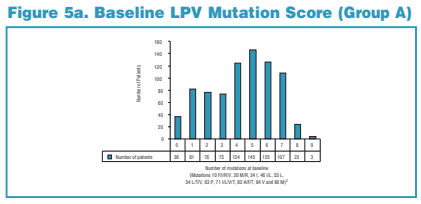
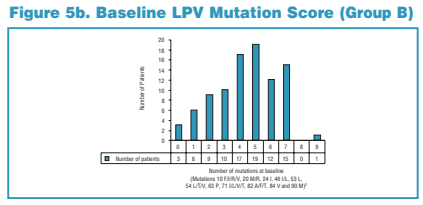


Figure 5b. Baseline LPV Mutation Score (Group B)



Concomitant Antiretroviral Therapy

- ARV drugs used concomitantly with LPV/r are shown in Figure 6a (overall population) and Figure 6b (Group B). The profile history of prior ARV therapy was similar in Group A (data not shown) as in the overall population.
- The majority of patients were treated with two drugs in addition to LPV/r, which were in most cases two NRTIs.
- A minority of patients received three additional drugs, consisting mainly of either three NRTIs, or two NRTIs and one NNRTI.
- Nine percent of patients (overall population) received more than three concomitant ARVs.
- Concomitant use of another PI was uncommon in this population.

Figure 6a. Description of LPV/r-Containing Regimens (Overall Population)

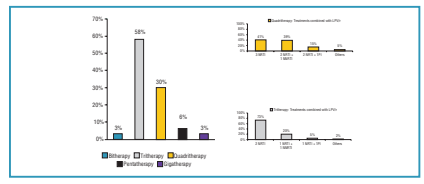
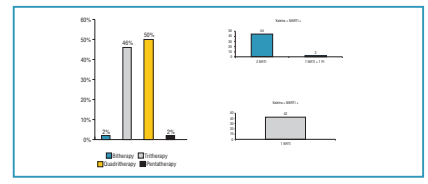


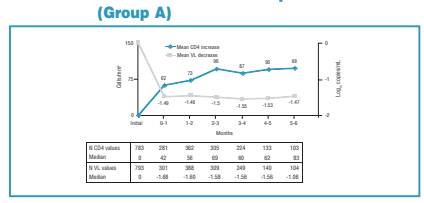
Figure 6b. Description of LPV/r-Containing Regimens (Group B)



Immunologic and Virologic Response

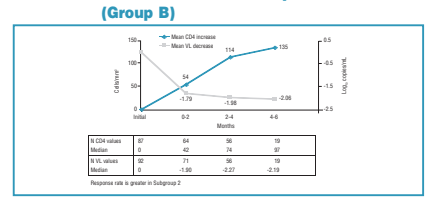
- Virologic response was defined as a minimum HIV RNA viral load <400 copies/mL and/or a decrease from baseline of at least 1.0 $\log_{10}$ copies/mL.
- The longitudinal virologic and immunologic responses are presented in Figure 7a (Group A) and Figure 7b (Group B).
- After the first month of therapy, the mean HIV RNA decrease reached –1.43 and –1.79 $\log_{10}$ copies/mL (Groups A and B, respectively). The decrease was –1.53 and –1.98 $\log_{10}$ copies/mL through month 3 and persisted through 6 months of therapy at –1.52 and –2.06 $\log_{10}$ copies/mL.
- Mean CD4 cell count increase from baseline was 97 and 135 cells/mm^3 (Groups A and B, respectively) through month 6.

Figure 7a. On Treatment Longitudinal Plasma HIV RNA and CD4 Response (Group A)



	Initial	0-1	1-2	2-3	3-4	4-5	5-6
N CD4 values	783	281	362	305	224	133	103
Median	0	42	56	69	80	82	83
N VL values	793	301	368	309	249	140	104
Median	0	-1.68	-1.60	-1.58	-1.56	-1.56	-1.06

Figure 7b. On Treatment Longitudinal Plasma HIV RNA and CD4 Response (Group B)



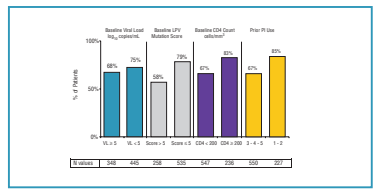
	Initial	0-2	2-4	4-6
N CD4 values	87	64	56	19
Median	0	42	74	97
N VL values	92	71	56	19
Median	0	-1.90	-2.27	-2.19

Response rate is greater in Subgroup 2

Study of the Virologic Response with Respect to Baseline Characteristics

- The study of the virologic response (at any time during the initial 6-month follow-up) with respect to the following baseline parameters was performed in Group A (Figure 8).
  - Baseline viral load (<5 and ≥5 $\log_{10}$ copies/mL).
  - Baseline CD4 count (<50, 50-150, >150 cells/mm^3).
  - LPV mutation score (≤5 and >5 mutations).
- Baseline CD4 count, LPV mutation score, and prior PI use are all significantly (p<0.01) associated with virologic response.

Figure 8. Study of the Virologic Response with Respect to Baseline Characteristics (Group A)



	VL ≥ 5	VL < 5	Score > 5	Score ≤ 5	CD4 < 200	CD4 ≥ 200	3 - 4 - 5	1 - 2
N values	348	445	258	535	547	236	550	227

Virologic Response According to Baseline PI Mutations (Group A)

- In Group A, the association between virologic response and the presence of individual PI mutations was analyzed using Fisher's exact test.
- In this univariate analysis, mutations at positions 10, 20, 36, 46, 54 and 82 were associated with lower response (Table 1).
- Baseline isolates containing the above mutations also contained a median of 5-7 other PI mutations.

Table 1. Virologic Response with Respect to Baseline Mutations

Amino Acid Position	Viro Resp with Mutation	Viro Resp without Mutation	P-value	Number of Subjects with a Mutation	Median (Range) of Other PI Mutations	Median (Range) of Other LPV Mutations
10	66%	83%	<0.001	506	6 (0-10)	4 (0-8)
20	59%	74%	<0.001	138	7 (1-10)	5 (0-8)
36	66%	76%	0.0046	313	5 (0-10)	5 (0-9)
46	67%	76%	0.0053	342	6 (0-10)	4 (0-8)
54	62%	78%	<0.001	310	6 (1-10)	5 (0-8)
82	62%	79%	<0.001	334	6 (0-10)	5 (0-8)

CONCLUSIONS

- Data from this cohort are observational in nature.
- The patients in this cohort were heavily ARV-experienced, with most having received all three ARV drug classes.
- Despite being heavily pre-treated with ARV drugs, many patients experienced an immunologic and virologic response.
- Baseline CD4 count, LPV mutation score, and prior PI use are all significantly (p<0.01) associated with virologic response.
- Mutation at positions 10, 20, 36, 46, 54 and 82 were associated with lower virologic response. These mutations were accompanied by a median of 5-7 other PI mutations.

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REFERENCE

1. Hirsch, MS, et al. Antiretroviral drug resistance testing in adults with HIV infection: Implications for clinical management. International AIDS Society – USA Panel. *JAMA* 1998;279:1984-91.
2. Kempf et al. *J. Virology*, 2001, 75, 7462-7469.