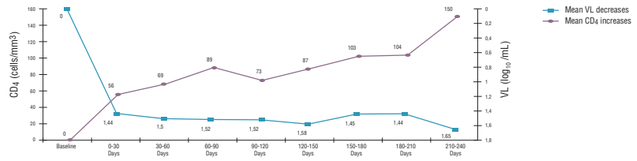
Immuno-Virological Response

Virologic response was defined as HIV RNA below 400 copies/mL and/or a decrease from baseline of at least 1.0 log_{10} copies/mL.

The longitudinal virologic and immunologic on-treatment responses are presented in Figure 10.

Figure 10. CD_4 Increase and Viral Load Decrease



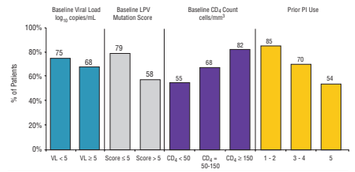
CD_4	N =	1052	392	525	427	286	165	134	82	55
VL	N =	1015	360	480	370	275	151	124	76	39

- After the first month of therapy, the mean HIV RNA decrease was –1.44 log_{10} copies/mL.
- The mean HIV RNA decrease was maintained at Months 3 and 6, with viral load decreases of –1.52 log_{10} copies/mL and –1.44 log_{10} copies/mL respectively.
- The mean CD_4 cell count increase from baseline to month 6 was 104 cells/mm³.

Study of the Virologic Response with Respect to Baseline Characteristics

Virologic response was evaluated with respect to baseline characteristics in a subgroup of patients (n=793) who had a genotype at baseline and at least one HIV RNA measurement after the start of LPV/r-containing regimen; plasma HIV RNA (<5 and ≥5 log_{10} copies/mL), LPV mutation score (≤5 and >5 mutations), CD_4 count (<50, 50-150, >150 cells/mm³), and prior PI use (1-2, 3-4, 5) (see Figure 11).

Figure 11. Study of the Virologic Response with Respect to Baseline Characteristics



N values	445	348	535	258	189	223	371	227	439	111
p values	0.037		< 0.001		< 0.001			< 0.001		

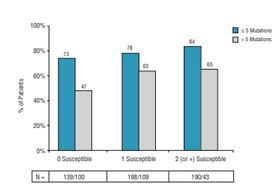
In a univariate analysis, each of these parameters was statistically significantly associated with virologic response.

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

In order to evaluate the virologic response to ARV drugs other than LPV/r; 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 ARV drugs used in the baseline regimen to which the virus was susceptible. Results from this analysis are summarized in Figure 12.

Figure 12. Virologic Response with Respect to the Susceptibility to Concomitant ARVs and Baseline LPV Mutation Score



N =	139/100	198/109	190/43

N = 779

Virologic response was higher in patients with LPV mutation score of 5 or less, compared to those with >5 mutations, and increased with use of other active drugs.

Safety Results

A total of 3819 patients were registered in the ATU through April 2001. During this time period, 356 cases describing 836 adverse events were reported on a voluntary basis.

The most frequently reported adverse events were diarrhea (2.67%), nausea (1.20%), rash (0.92%), hyperlipemia (0.89%), abdominal pain (0.86%), vomiting (0.79%), asthenia (0.68%) and fever (0.50%). Adverse events of special interest are presented in Table 4.

Table 4. Adverse Events of Special Interest

Adverse Events of Special Interest	Number of Patients (%)	Comments
Hyperlipemia	36 (0.94%)	8/36 (22%) premature discontinuation
Diabetes	6 (0.16%)	3 considered by the physician to be probably not, or not related to LPV/r, 2 considered by the physician to be possibly or probably related to LPV/r
Pancreatitis	7 (0.18%)	All of these patients had alternative risk factors reported including ddI use (4 patients) or alcohol use (1 patient)
Death	19 (0.50%)	None of the deaths were considered related to drug

CONCLUSIONS

Because of the retrospective and observational aspect of such analysis, data presented here may have some limitations. However, because of the high number of patients treated, the ATU process gives the unique possibility to learn more about antiretroviral drugs in real life conditions.

Virologic response is observed in this cohort in spite of extensive ARV experience and significant level of baseline genotypic resistance, as evidenced by a median of 5 PI mutations.

The significant contribution of LPV/r to the overall response is emphasized by the high level of resistance of concomitant drugs in the LPV/r-containing regimens and by the confirmation of a genotypic breakpoint of five or less mutations for LPV, highly predictive of the extent of virologic response, as described in previous observations.

Lower viral load, higher CD_4 cell count and less PI-experience at baseline were other predictive factors of a higher response rate.

The overall tolerance to LPV/r-containing regimens was good and adverse events were infrequent and rarely resulted in treatment discontinuation.

ACKNOWLEDGMENTS

Abbott Laboratories would like to acknowledge all physicians, virologists, and patients who participated in this program.

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Poster #1926

41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, December 2001

Pre-registrational Use of ABT-378/r in Heavily-Experienced Patients: The French ATU Program Experience

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BACKGROUND

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

Lopinavir, co-formulated with a low dose of ritonavir, takes advantage of the P450 cytochrome inhibitor properties of ritonavir. Lopinavir is exquisitely sensitive to the pharmacokinetic enhancement of ritonavir, resulting in substantially increased LPV drug exposure. The mean LPV ratio of C_{trough} (protein binding adjusted) to EC_{50} (Inhibitory Quotient or IQ) for wild-type virus is >75 at 400/100 mg BID dose. This high IQ potentially contributes to the durability of response by providing superior antiviral activity (Figure 1a, Table 1) and a pharmacologic barrier to the emergence of viral resistance.

However, virologic control may be compromised by mutations induced by previous PI therapies. Differences in efficacy may reflect the substantially different inhibitory quotients achieved with LPV/r antiretroviral (ARV) in naïve vs. PI-experienced patients (Figure 1b).

Figure 1a. Phase III ARV-Naïve Patients: HIV RNA < 400 copies/mL (Study 863, ITT: NC=F)

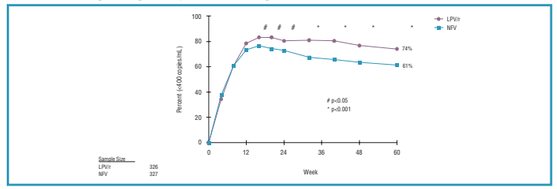
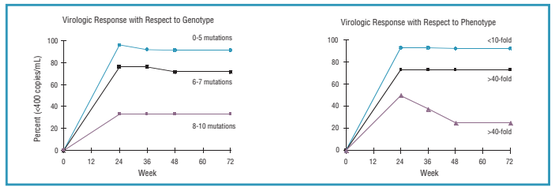


Figure 1b. Kaletra + EFV/NRTIs in Multiple PI-Experienced, NNRTI-Naïve Patients (Study 957)



Response to therapy in Study 957 was associated with the number of baseline mutations and baseline phenotype. Patients with less than five mutations or <10-fold phenotypic change in susceptibility had a better virologic response as compared to patients with more mutations (six or more) or greater phenotypic change in susceptibility (≥10-fold).

Table 1. Incidence of PI Resistance Through Week 60 (Study 863)

	LPV/r	Nelfinavir
HIV RNA >400 copies/mL	76	119
Genotype available	40	87
Resistance detected in protease	0	31

Absence of resistance to LPV/r was confirmed by phenotype

METHODS

Prior to marketing authorization, a program was developed to provide patients, who were failing currently available therapeutic options, access to potentially life-saving medications. A worldwide expanded access program (EAP) was initially conducted as a clinical trial; however, this EAP was rapidly switched in France through agreement with the Drug Agency to an “ATU” program (“Autorisation Temporaire d’Utilisation”, Provisional Authorization for Use) which was conducted from March 2000 to April 2001.

Selection criteria of the patient population at study initiation included CD_4 <200 cells/mm³ and HIV RNA >4 log_{10}. However, these were progressively removed to authorize the use of LPV/r in a broader PI-experienced population.

At baseline demographic data including HIV-RNA, CD_4 cell count, antiretroviral history and genotype were collected. Follow-up data was provided on a voluntary basis.

The overall enrollment in this cohort was 3819 patients. Analysis does not include 193 patients that were previously enrolled in EAP, as well as 179 nominative ATU participants. (Physicians had the possibility to request a “Nominative ATU” for patients who did not fulfill the selection criteria of the ATU, e.g., for children.)

RESULTS

Summary of Demographic and Disease Characteristics

A total of 3447 patients have been in the immuno-virological analysis. The mean baseline HIV RNA and CD_4 cell count for these patients were 4.66 log_{10} copies/mL and 202 cells/mm³, respectively.

Most patients in this cohort had advanced HIV infection; with 51.3% having experienced at least one CDC Class C (AIDS-defining) event.

Demographic and disease characteristics are presented in Table 2. Number (N) refers to number of subjects for whom specific data was available.

The number (N) of subjects with specific data available has been identified.

Table 2. Summary of Demographic and Disease Characteristics

Gender		**CD_4 Cell Count (cells/mm³)**	
Male	79.5%	<50	21.4%
Age (N = 1805)		[50 – 150]	24.5%
Mean	42 years	[150 – 300]	30.0%
Median	40 years	≥300	24.1%
CDC Classification (N = 3279)		Mean	202
Asymptomatic (Stage A)	16.8%	Median	165
Symptomatic (Stage B)	31.9%	Standard Deviation	178
AIDS – Indicator (Stage C)	51.3%	Minimum	0
HIV Diagnosis Date (N = 2753)		Maximum	1193
<1990	40.8%	**HIV RNA (log_{10} copies/mL)**	
1990 – 1995	41.4%	<5 log_{10} copies/mL	60.9%
≥1995	17.8%	≥5 log_{10} copies/mL	39.1%
		Mean	4.66
		Median	4.78
		Standard Deviation	0.92
		Minimum	0.70
		Maximum	7.05

N = 3447

Antiretroviral Experience

Information on pre-study antiretroviral therapy is available on 3412 ATU participants and is described in Figures 2 and 3.

Figure 2. Number of Previous Antiretroviral Drugs per Class

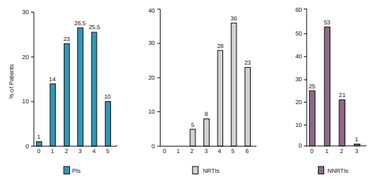
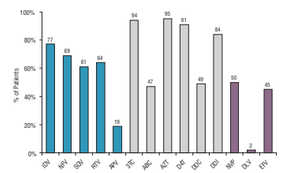


Figure 3. Previous Antiretroviral Drugs

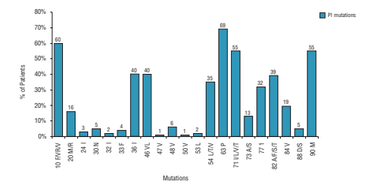


The majority of patients were previously treated with at least 3 PIs (62%), 5 NRTIs (59%), and 1 NNRTI (75%). Treatment experience with individual antiretrovirals is provided in Figure 3.

Baseline Genotype

HIV RNA sequences, obtained in this heavily-ARV experienced patient population according to the French guidelines (Rapport Delfraissy 2000), were provided for a subset of enrolled patients (Figures 4a and 4b).

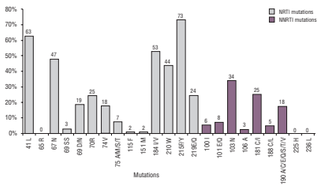
Figure 4a. Baseline Prevalence of PI Mutations



N = 1604

The prevalence of multiple baseline PI mutations associated with cross resistance to the PI class was high (Figure 4a). The most common PI mutations occurred at positions 63, 10, 71 and 90.

Figure 4b. Baseline Prevalence of NRTI and NNRTI Mutations

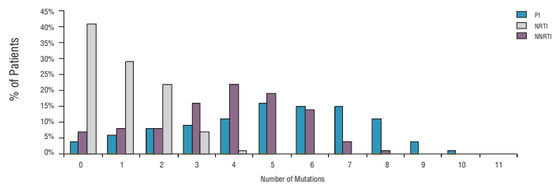


N = 1554

Most of the patients had thymidine NRTI (41, 67, 210, 215) and lamivudine (184) resistance mutations.

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, 181, 190).

Figure 5. Baseline Number of PI, NRTI and NNRTI Mutations



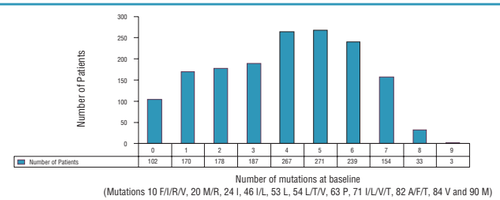
PI: N = 1604, NRTI and NNRTI: N = 1554

As presented in Figure 5, the number of PI-associated mutations within this population ranged from 0 to 11, with a median of 5 mutations. The median number of NRTI and NNRTI mutations was 4 and 1, respectively.

LPV Mutation Score

The LPV mutation score is the number of protease specific mutations identified 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).

Figure 6. Baseline LPV Mutation Score



N = 1604

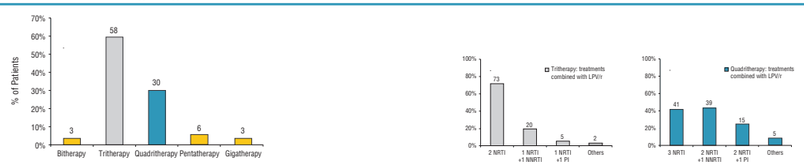
(Mutations 10 F/I/R/V, 20 M/R, 24 I, 46 I/L, 53 L, 54 L/T/V, 63 P, 71 I/L/V/T, 82 A/F/T, 84 V and 90 M)

- Within this population, the baseline LPV mutation score ranged from 0 to 9 (Figure 6), with a median of 4 mutations.
- Forty-eight percent of the patients (777/1604) had a baseline LPV mutation score of 4-6.

Concomitant Antiretroviral Therapy

Information concerning concomitant ARVs used in the LPV/r-containing regimens for the study population is provided in Figure 7.

Figure 7. Description of LPV/r-Containing Regimens



N = 1828

The majority of patients (58%) received two additional ARVs, which in most cases consisted of two NRTIs. A sizeable group of patients (30%) received three additional drugs, consisting mainly of either three NRTIs or two NRTIs plus one NNRTI. Nine percent (9%) of patients received more than three concomitant ARVs. Concomitant use of another PI was infrequent in this study population.

Using the algorithm of genotypic resistance defined by the French authorities (AC11, October 2001), the drug susceptibility of ARVs used in the baseline regimen was classified as resistant, suspected resistant and susceptible. These criteria are summarized in Table 3.

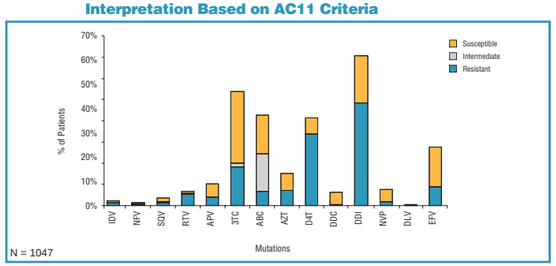
Table 3. AC11 Interpretation of Genotype

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
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
NRTIs	**Resistance**	**Suspected 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	

(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.

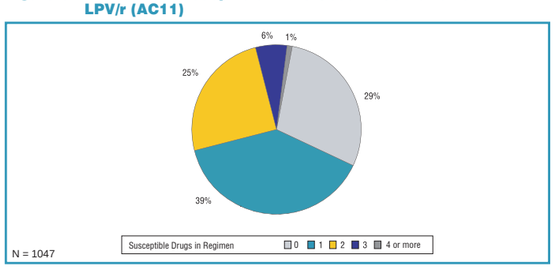
As presented in Figures 8 and 9, high levels of resistance to concomitant ARVs were observed, indicating that a large majority of patients did not receive multiple active drugs as part of their LPV/r-based regimen.

Figure 8. Concomitant Antiretroviral Drugs and Resistance Interpretation Based on AC11 Criteria



N = 1047

Figure 9. Number of Susceptible ARVs Used in Combination with LPV/r (AC11)



N = 1047