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Impact of a LPV/r monotherapy on self-reported side effects and global health perception among antiretroviral-naive patients: 48-week analysis of the MONARK trial

B Spire[1], F Marcellin[1], I Cohen Codar[2], B Knysz[3], C Lascoux[4], MA Valantin[5], M Norton[6], P Ngo Van[2], JF Delfraissy[7]

1) Inserm U379/ORS PACA, France, 2) Abbott France, Rungis, France, 3) Klinika Chorob Zakaznych, Wroclaw, Poland, 4) Hosp St-Louis, Paris, France, 5) Hosp Pitie-Salpetriere, Paris, France, 6) Abbott Park, Chicago, USA, 7) Hosp Le Kremlin-Bicêtre, France.

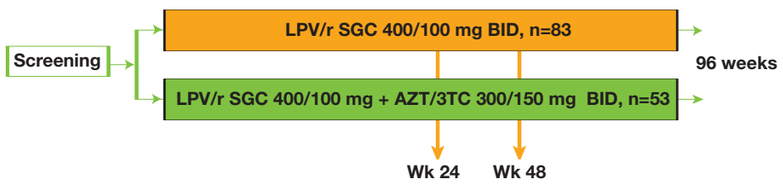
Background

Current guidelines for the management of HIV-infected patients recommend now the use of combination therapies. However, such combination therapies may not be optimal for long term management of the HIV disease for several reasons. Toxicities, cost and complexity of such regimens warrant the search for other options.

Lopinavir/ritonavir (LPV/r) is a potent antiretroviral drug. Preliminary data from randomized trials recently presented suggest antiviral activity of LPV/r used as a single-drug agent.

MONARK Study Design and Baseline Characteristics

MONARK (MONotherapy AntiRetroviral Kaletra) is a prospective, international, randomized, comparative trial designed to compare the antiviral activity of LPV/r single-drug regimen *vs*. a standard triple drug regimen, LPV/r in combination with AZT/3TC.



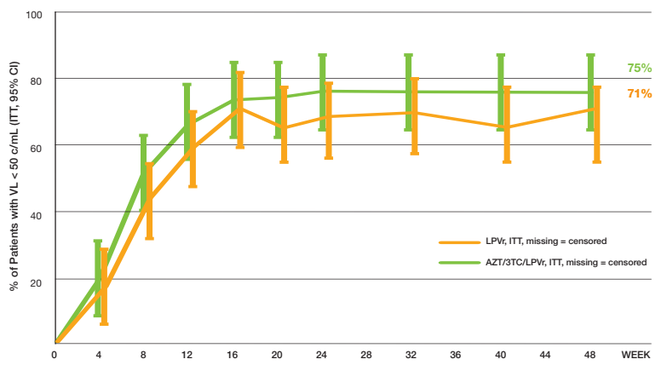
Entry criteria

• Antiretroviral naïve • HIV-1 RNA <100,000 c/mL • CD4 > 100 cells/mm^3

Baseline characteristics: Mean (range)

• HIV-1 RNA (log_{10} c/mL): **4.39 (1.70-5.87; mono)** *vs* **4.34 (2.85-5.36; Triple)**
• CD4 (cell/µL): **257 (86-1247; mono)** *vs* **234 (106-521; Triple)**

Week 48 Virologic Results



Primary efficacy endpoint was the proportion of patients with HIV-RNA < 400 copies/mL at Wk 24 (1) AND with HIV-RNA < 50 copies/mL at Wk 48 (2).

ITT, missing = censored

	LPV/r	LPV/r+AZT/3TC	*P-value*
(1) and (2)	53/81	40/53	***0.25***
	(65%)	(75%)	

OT, available VL

	LPV/r	LPV/r+AZT/3TC	*P-value*
(1) and (2)	53/66	40/41	***0.02***
	(80%)	(98%)	

Secondary endpoints included VL kinetics, changes in CD4 count and mt DNA, metabolic toxicity and fat redistribution, serious adverse events and psychosocial outcomes.

Similar immunologic response was noted in the 2 arms : median change from baseline to Week 48 was + 151 CD4 T cells/mm^3 for LPV/r and + 159 CD4 T cells/mm^3 for LPV + AZT/3TC arm.

This presentation reports the results of psychosocial outcomes (quality of life and self-reported symptoms).

Objective

PROs (Patient Reported Outcomes) are recognized as one of the major predictive factor of patient's adherence to therapy.

In this study, PROs are evaluated through self-reported QOL and symptoms in order to assess the impact of LPV/r monotherapy on PROs versus a standard triple-drug regimen.

Methods

Questionnaires

The two questionnaires which were used are the Augmented Symptom Distress Module and the WHOQOL-HIV Bref.

Augmented Symptom Distress Module

- This module collected subject's perception about the occurence of 22 symptoms commonly seen under HAART.
- Subjects were also asked about the discomfort associated with each symptom using a 4-point Likert scale (no discomfort at all, a little discomfort, quite discomfort, a lot discomfort).

WHOQOL-HIV Bref

- This instrument administered to trial participants explores 6 QOL domains: physical QOL, psychological QOL, level of independence, social relationships, environment and spirituality/religion and also allows an assessment of overall QOL and general health.
- Its 31 items concern the subjects' perceptions about the last 2 weeks, and 5 of these items are specific to PLWHA.

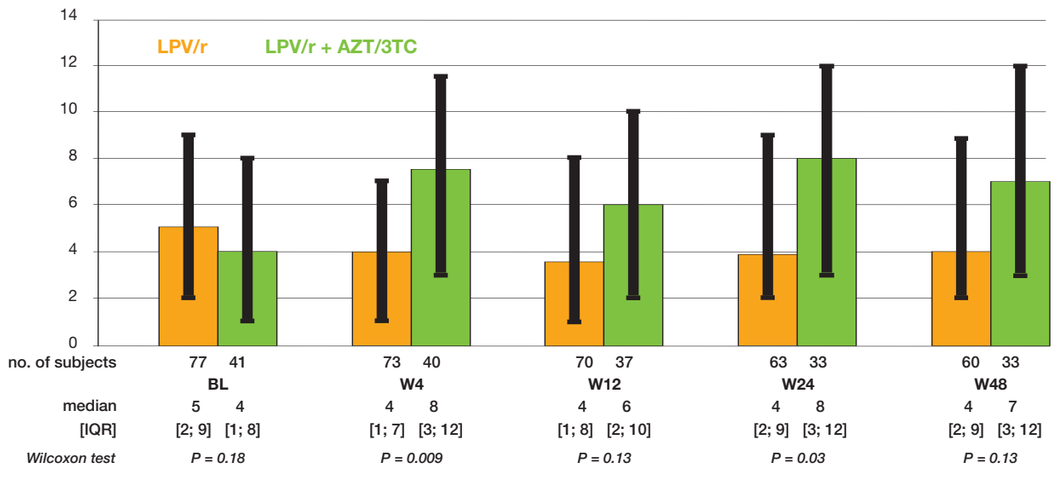
Statistical analysis

- Interest in subjects' personal experience with treatments justifies the use of on treatment analysis.
- Analysis excludes data posterior to subjects' changes of drug regimen
  - W48 data for 1 subject randomized on LPV/r.
- Data at discontinuation are reallocated to the closest protocol visit
  - For 4 subjects randomized to LPV/r who discontinued study at W4, W8, W12 and W20, respectively.
- Outcomes analysis
  - 6 QOL domain scores - Measure of overall QOL and general health
  - Total number of self-reported symptoms
  - Number of self-reported symptoms causing discomfort

Results

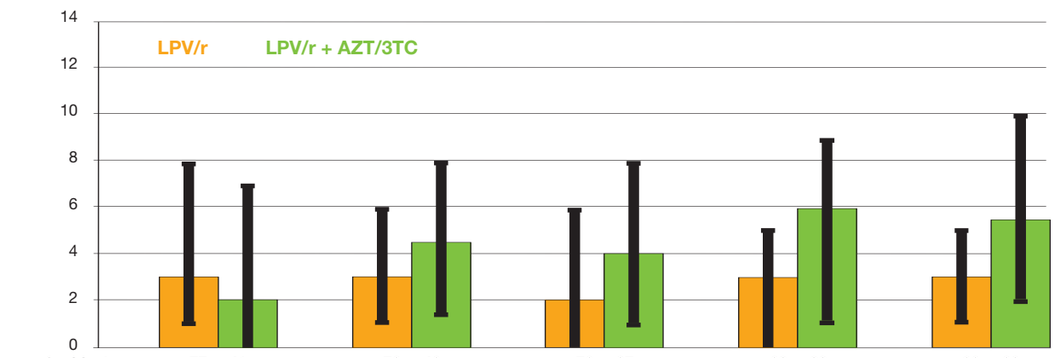
Response rate to self-reported questionnaires did not show significant difference between the 2 arms. The range was between 65 to 88%.

Total Number of Self-reported Symptoms



	BL	W4	W12	W24	W48
no. of subjects	77 41	73 40	70 37	63 33	60 33
median	5 4	4 8	4 6	4 8	4 7
[IQR]	[2; 9] [1; 8]	[1; 7] [3; 12]	[1; 8] [2; 10]	[2; 9] [3; 12]	[2; 9] [3; 12]
Wilcoxon test	*P = 0.18*	*P = 0.009*	*P = 0.13*	*P = 0.03*	*P = 0.13*

Number of Symptoms Causing Discomfort



	BL	W4	W12	W24	W48
no. of subjects	77 41	73 40	70 37	63 33	60 33
median	3 2	3 5	2 4	3 6	3 6
[IQR]	[1; 8] [0; 7]	[1; 6] [2; 8]	[0; 6] [1; 8]	[0; 5] [1; 9]	[1; 5] [2; 10]
Wilcoxon test	*P = 0.24*	*P = 0.03*	*P = 0.15*	*P = 0.03*	*P = 0.01*

Modeling over the Treatment Period

In order to summarize this information, we used a Poisson model to compare the no. of self-reported symptoms between treatment groups over the whole treatment period. This model used data collected during W4 to W48 and included treatment group as a factor. Time spent on study was used as an offset, and the model was adjusted on the no. of symptoms reported at BL.

Model outcome	Incidence Rate Ratio [95% CI] for LPV/r +AZT/3TC *vs* LPV/r	*P-value*
Total # of symptoms	1.3 [1.1; 1.6]	***p=0.001***
# of symptoms causing discomfort	1.4 [1.2; 1.7]	***p=0.0004***

Type of Reported Symptoms

Symptom	OR [95% CI]*	*P-value*
fatigue or loss of energy	1.5 [0.9; 2.7]	*p=0.12*
fevers, chills or sweats	1.3 [0.7; 2.4]	*p=0.41*
feeling dizzy or lightheaded	**2.6 [1.3; 5.0]**	***p=0.004***
pain, numbness or tingling in the hands or feet	1.5 [0.8; 2.8]	*p=0.22*
trouble remembering	1.3 [0.7; 2.5]	*p=0.35*
nausea or vomiting	**4.1 [2.3; 7.1]**	***p < 0.0001***
diarrhea or loose bowel movements	1.1 [0.6; 1.9]	*p=0.74*
felt sad, down or depressed	1.2 [0.7; 2.2]	*p=0.47*
felt nervous or anxious	**2.1 [1.2; 3.7]**	***p=0.007***
difficulty falling or staying asleep	1.4 [0.8; 2.6]	*p=0.26*
skin problems	1.5 [0.9; 2.7]	*p=0.12*
cough or trouble catching your breath	1.2 [0.7; 2.2]	*p=0.48*
headache	1.7 [0.9; 3.0]	*p=0.09*
loss of appetite or a change in the taste of food	**3.0 [1.6; 5.6]**	***p=0.0004***
bloating, pain or gas in your stomach	**2.5 [1.4; 4.5]**	***p=0.003***
muscle aches or joint pain	1.2 [0.7; 2.2]	*p=0.50*
problems with having sex	1.6 [0.8; 3.0]	*p=0.16*
changes in the way your body looks	1.6 [0.9; 3.1]	*p=0.12*
problems with weight loss or wasting	1.2 [0.6; 2.6]	*p=0.58*
hair loss or changes in the way your hair looks	1.5 [0.7; 3.3]	*p=0.31*
dull flank or loin or back pain	1.2 [0.7; 2.3]	*p=0.47*
painful urination	1.1 [0.4; 2.7]	*p=0.86*

* Odds ratio LPV/r +AZT/3TC vs LPV/r for the occurrence of the considered symptom logistic model with GEE

Post-hoc Analysis on Patients with Virological Response

Patients with VL< 400 copies/mL at W24 and VL< 50 copies/mL at W48 (n=93)

Model outcome	RR [95% CI] for LPV/r +AZT/3TC *vs* LPV/r	*P-value*
Total # of symptoms	1.3 [1.1; 1.5]	***p=0.004***
# of symptoms causing discomfort	1.4 [1.1; 1.6]	***p=0.002***

Quality of Life (QoL)

- No significant differences between treatment groups for:
  - perceived overall QOL at W24 and W48
  - perceived general health at W24 and W48
  - QOL domain scores at BL
  - changes in QOL scores between { BL and W24 / BL and W48
- Perceived general health improves significantly only in LPV/r arm

Evolution of subjects' perception between BL and W48

	LPV/r	LPV/r + AZT/3TC
always positive	14/61 (23%)	10/33 (30%)
always negative	17/61 (28%)	10/33 (30%)
from negative to positive	**26/61 (43%)**	**10/33 (30%)**
from positive to negative	**4/61 (6%)**	**3/33 (9%)**
Mc Nemar p-value	*p<0.0001*	*p=0.09*

Conclusion

Subjects receiving LPV/r monotherapy reported fewer symptoms over the treatment period than subjects receiving LPV/r+AZT/3TC.

Significant improvement of perceived general health was only observed on LPV/r monotherapy.

Such data confirm the interest of assessing the number of symptoms reported by the clinical trials participants as a treatment-sensitive proxy of their QOL.

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Patients

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Germany: Dr. Hans Jäger, Dr. Dirk Schurmann, Dr. Mark Oette, Dr.Keikawus Arastéh
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Poland: Pr. Andrzej Gladyzs, Pr. Andrzej Horban
Spain: Dr Pere Domingo, Dr Bonaventura Clotet, Dr Josep Ma Llibre, Dr Francisco Vidal

Sponsor

Abbott Laboratories France

Principal Investigator & Scientific Coordination

Pr. Jean-François DELFRAISSY
Le Kremlin Bicêtre Hospital - Paris, France

Statistical analysis of psychosocial endpoints

Dr Bruno Spire, Fabienne Marcellin
INSERM Research Unit 379
Southeastern Health Regional Observatory
Marseille, France.