

Protease Gene Mutations in a Trial Comparing First Line LPV/r Monotherapy to LPV/r + AZT/3TC (MONARK Trial)

C Delaugerre¹, P Flandre², ML Chaix¹, P Dellamonica³,
F Raffi⁴, H Jaeger⁵, D Schürmann⁶, P NgoVan⁷, M Norton⁸,
I Cohen Codar⁷, JF Delfraissy⁹, C Rouzioux¹

¹Virology Necker-APHP, Paris, France; ²Inserm U720 Pierre et Marie Curie University, Paris, France; ³Infectious Diseases, Nice, France; ⁴Infectious Diseases, Nantes, France; ⁵HIV Research and Clinical Care Centre, Munich, Germany; ⁶Infectious Disease, Berlin, Germany; ⁷Abbott France, Rungis, France; ⁸Abbott Laboratories, New Jersey USA; ⁹Internal Medecine, Bicêtre-APHP, France

Background

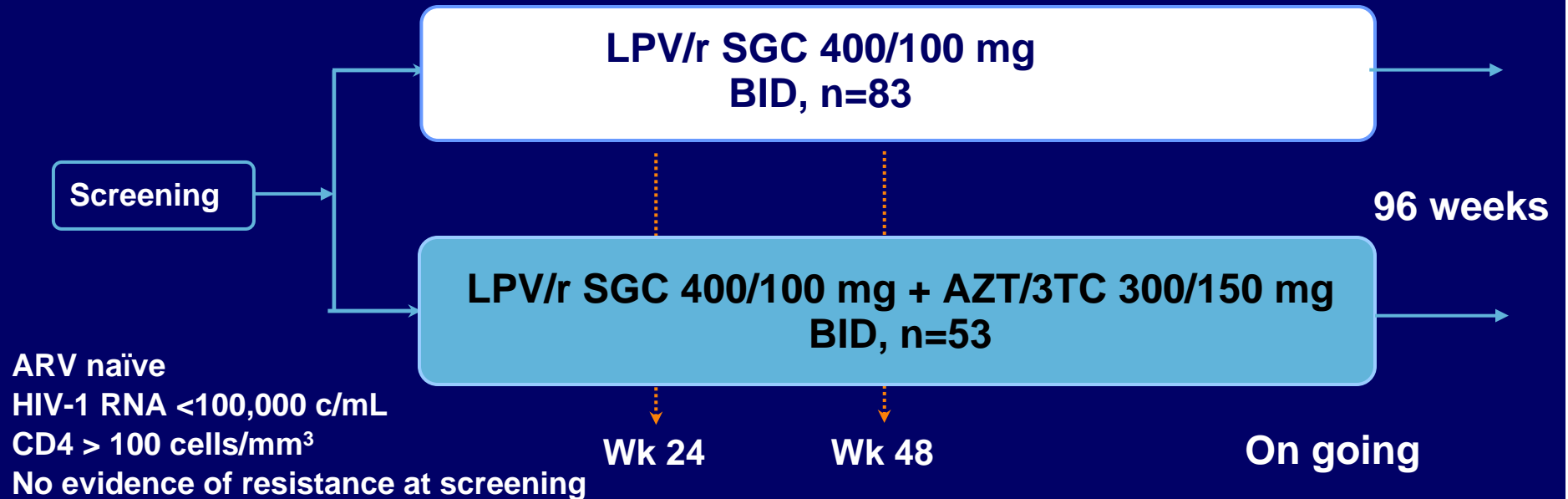
- In antiretroviral-naïve patients, combination therapy with LPV/r rarely selects for PI resistance
- During single-drug maintenance therapy with LPV/r in randomized trials, some cases of PI resistance have been described

	OK04 ¹	M03-613 ²	Kalmo ³
Subjects included in LPV/r monotherapy arm	100	92	30
Subjects qualifying for resistance testing	11	9	1
Isolates with PI mutations at failure	2^a	2^b	0

^a(1) L10F, M46I, V82A/V (LPV FC 2.7)
(2) I54V, V77I, V82A (LPV FC 0.7)

^b(1) L10F, M46L, V82A (LPV FC 4.3)
(2) M36I, A71V, G73S, L90M (LPV FC 2.24)

MONARK Study Design



Primary Endpoint : HIV-1 RNA <400c/mL at week 24 and <50c/ml at week 48

Sub-optimal response

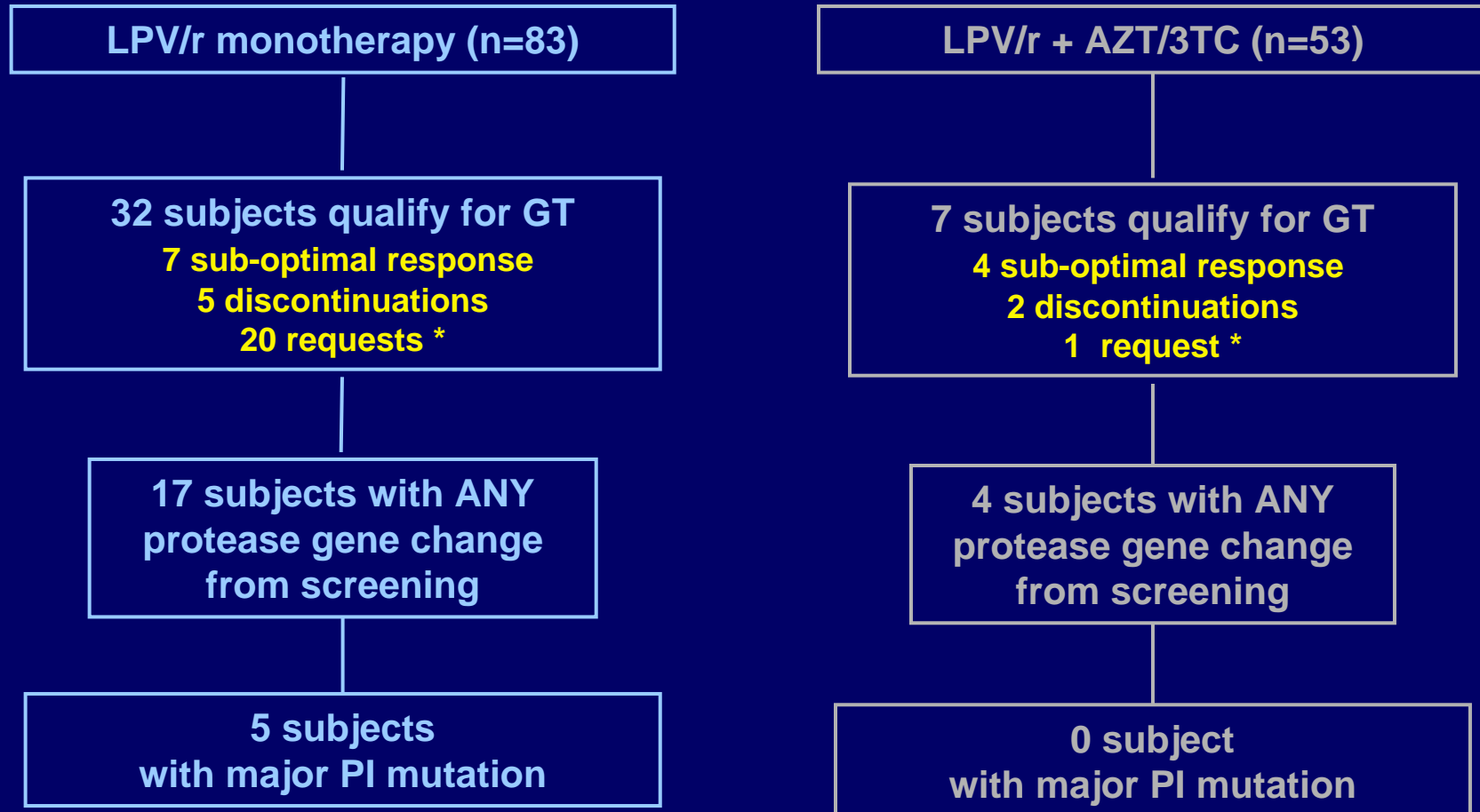
1. failure to achieve a decline in viral load of at least 1.0 log₁₀ copies/mL by week 4
2. failure to achieve a viral load below 400 copies/mL by week 24
3. any viral rebound ≥ 1 log, after HIV RNA < 400 copies/mL, confirmed by a second measurement at least 14 days later

Objective and Methods

- Our objective was to analyze protease resistance outcome in Monark study
- Genotypic resistance tests were performed by population based sequencing* in protease gene at :
 - screening
 - time of sub-optimal response
 - study discontinuation
 - if requested by investigator or suggested by study team for safety
- Phenotypes (Phenosense GT, Monogram Biosciences) were performed in all subjects who selected at least one major PI mutation

* Necker Virology Laboratory (ANRS technique)

Genotypic Resistance Testing (GT)

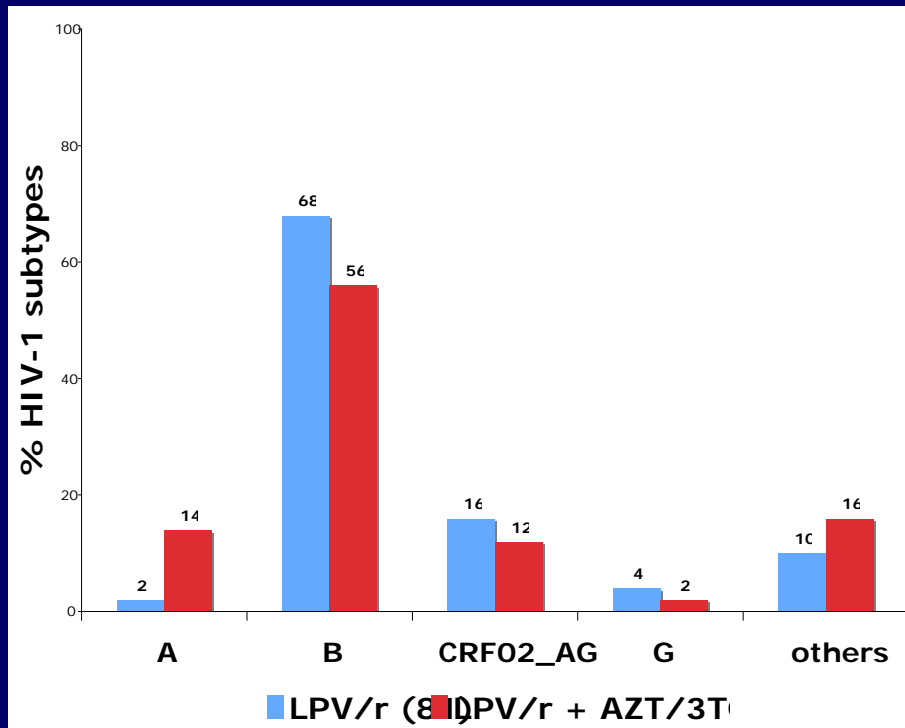


* 10 patients VL >500 c/ml after VL <50 c/ml
10 patients 2 VL >50c/ml

* 1 patient VL >500 c/ml after VL <50 c/ml

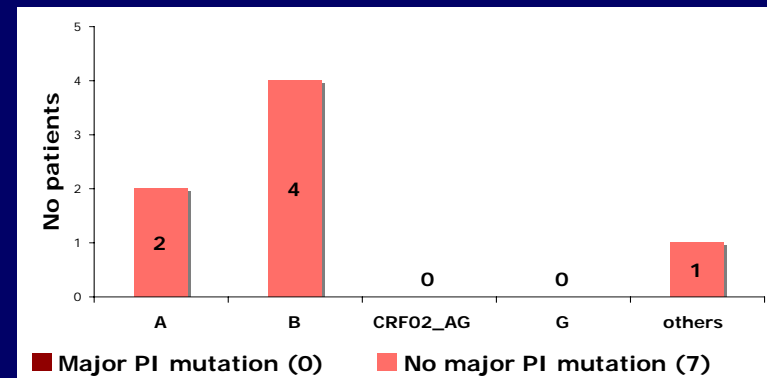
HIV-1 subtypes

Baseline HIV-1 subtypes



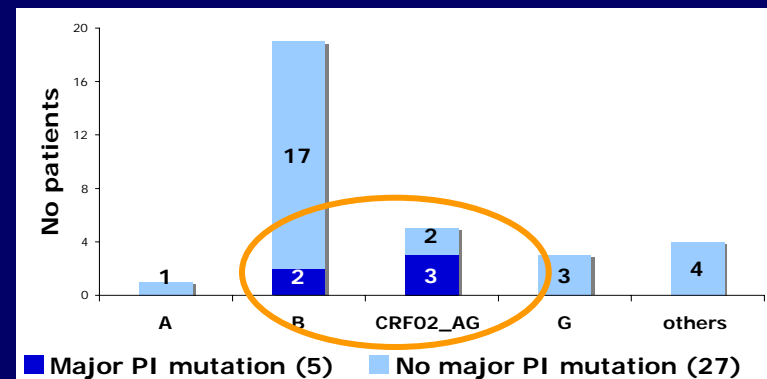
LPV/r + AZT/3TC

In 7 subjects qualify for GT



LPV/r Monotherapy

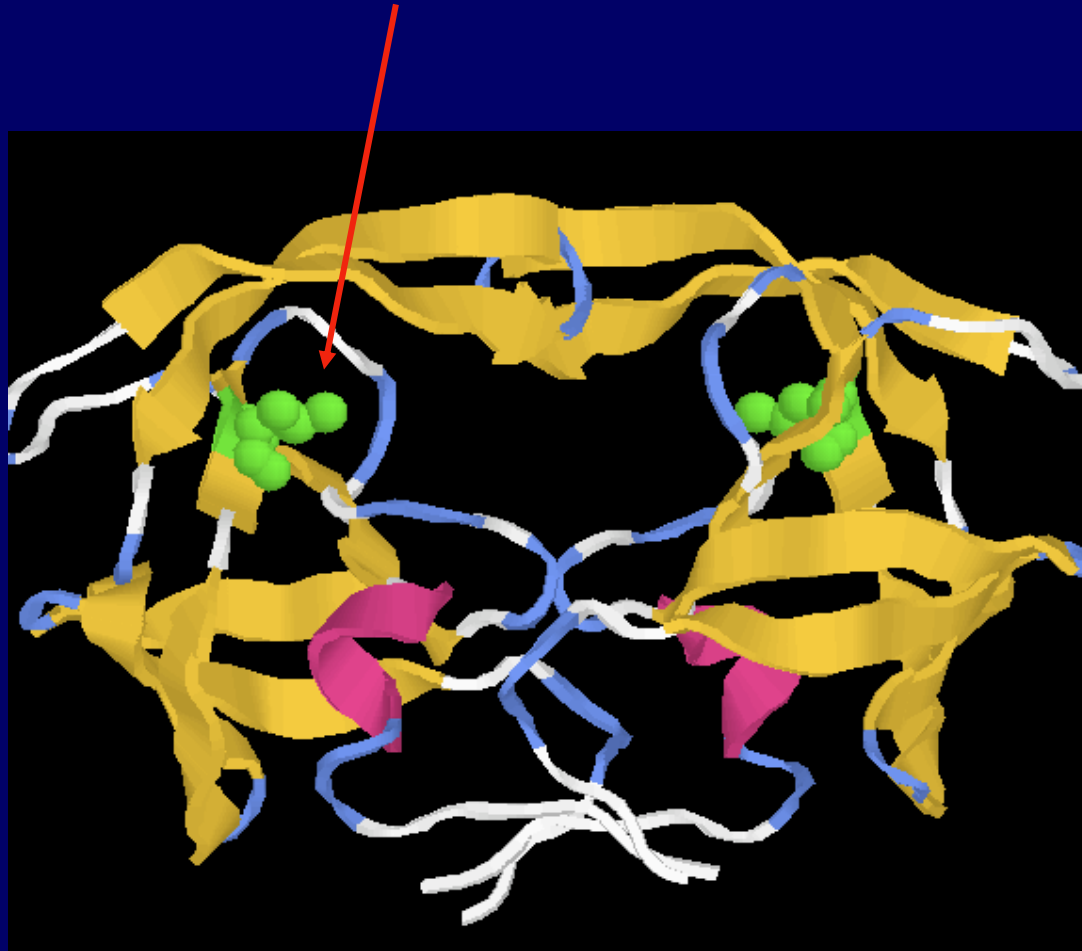
In 32 subjects qualify for GT



Resistance analysis in the 5 subjects in LPV/r arm with major PI mutations

IDE	Viral Subtype	Visit	Viral Load (log c/mL)	Protease genotype	LPV Fold Change
903	B	BL	4.8	L63P/S, V77I	1.16
		W40	2.9	M46I, L63P, V77I	1.40
310	CRF02_AG	BL	4.8	I13V, K20I, M36I, H69K	0.57
		W44	2.8	I13V, K20I, M36I, H69K, L76V	1.27
3103	CRF02_AG	BL	5.0	I13V, K20I, M36I, H69K	0.59
		W62	2.6	I13V, K20I, M36I, M46I, H69K, L76V	2.69
311	B	BL	4.4	L10L/I, L63P, A71A/T	1.49
		W76	3.1	L10F, V82A/V, L63P	1.13
3002	CRF02_AG	BL	4.6	I13V, K20I, M36I, H69K, L89M	0.87
		W90	2.5	I13V, K20I, M36I, H69K, L76V, L89M	NA

L76V mutation emerged in 3/5 patients



- All 3 patients were infected with HIV-1 CRF02_AG
- In 2 patients, L76V emerged alone
- This mutation is included in darunavir score (Power studies)

Risks factors: LPV/r arm

	N	Baseline*		VL [†] reduction at week 4	Last value within 4 weeks	
		VL [†]	CD4		VL* [†]	% Cmin LPV >75 ng/ml
No change from screening	15	4.7	249	-1.95	3.8	75% (n=3/4)
New mutation – no major IAS mutation	12	4.5	217	-2.13	4.3	75% (n=3/4)
Major IAS mutation	5	4.8	182	-2.11	3.1	100% (n=3/3)

* Median value

† log₁₀ copies/mL

No significant association was found between these variables (VL, CD4, Cmin LPV) and the occurrence of mutations in the AZT/3TC + LPV/R arm

Conclusions:

- Five out of the 83 (6%) subjects starting LPV/r monotherapy and none of the 53 subjects starting a LPV/r-based 3 drug regimen selected major PI resistance mutation
- The genetic barrier for the selection of PI resistance mutation appears to be lower with LPV/r monotherapy than with LPV/r-based 3-drug regimens
- The L76V mutation emerged in 3 subjects infected with HIV-1 CRF02_AG
- Full viral suppression was achieved in 3 subjects who selected a major PI mutation while on LPV/r monotherapy, after intensification with AZT/3TC

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Patients

36 Investigators (France, Germany, Italy, Poland, Spain)

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Francisco Vidal
Dr. Pascale Leclercq
Dr. Caroline Lascoux
Pr. Thierry May
Pr. Elisabeth Rouveix
Dr. Alain Devidas
Dr. Marie-Aude Khuong
Pr. Jean-Albert Gastaut
Pr. Yves Levy
Dr. Marc-Antoine Valantin

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Dr. Jäger
Dr. Schurmann
Dr. Oette
Dr. Arastéh

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Pr. Adriano Lazzarin
Pr. Mauro Moroni
Pr. Giovanni Di Perri
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Pr. Andrzej Gladys
Pr. Andrzej Horban

- **Spain**

Dr Pere Domingo
Dr Bonaventura Clotet
Dr Josep Ma Llibre
Dr Francisco Vidal

MONARK study team

Abbott France

DSMB