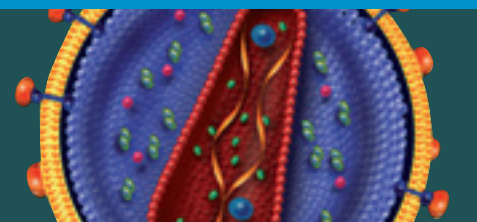


Genotypic analysis of the virological response to fosamprenavir/ritonavir in CONTEXT and TRIAD clinical trials

CROI 2007 LOS ANGELES
14TH CONFERENCE on Retrovirus and Opportunistic Infections



AG Marcelin¹, P Flandre¹, JM Molina², C Katlama¹, P Yeni³, F Raffi⁴, Z Antoun⁵, M Wirden¹, M Ait Khaled⁶ and V Calvez¹

¹ CHU Pitie-Salpetriere Paris, ² CHU Saint-Louis Paris, ³ CHU Bichat-Claude Bernard Paris, ⁴ CHU Nantes, ⁵ GSK France, ⁶ GSK UK

e-mail: vincent.calvez@psl.aphp.fr

Background

The aim of this study was to identify mutations associated with virological response to fosamprenavir/ritonavir (FPV/r) (700/100 mg bid) in Context and Triad clinical trials.

Patients and Methods

• **CONTEXT** (APV30003) was a Phase III, randomised, multicenter, open-label study comparing the efficacy and safety of two dosing regimens of fosamprenavir/ritonavir (700mg/100mg twice daily or 1400mg/200mg once daily) versus lopinavir/ritonavir (400mg/100mg twice daily) for 48 Weeks in protease inhibitor (PI) experienced HIV-infected adults experiencing virological failure.

Group 1: FPV 700mg BID + RTV 100mg BID + two RTIs (n = 107)

Group 2: FPV 1400mg QD + RTV 200mg QD + two RTIs (n = 105)

Group 3: LPV/RTV 400mg/100mg BID + two RTIs (n = 103)

Randomisation was stratified according to a subject's plasma HIV-1 RNA level at screening (1000-10,000 copies/mL; >10,000-100,000 copies/mL; >100,000 copies/mL).

• **TRIAD** (APV102002) is a Phase III, randomised, controlled, open-label, multi-centre three-arm study in heavily PI-experienced subjects (defined as ≥ 2 prior PI based regimen and a history of treatment with at least one ART from the three main available antiretroviral classes) comparing, in a 1:1:1 ratio, the following treatment groups:

Group A: 700mg FPV/100mg RTV BID [Standard Dose (STD)-FPV/RTV] + OBT (n = 21)

Group B: 1400mg FPV/100mg RTV BID [High Dose (HD)-FPV/RTV] + OBT (n = 21)

Group C: 1400mg FPV/533mg LPV/133mg RTV BID (FPV/LPV/RTV) + OBT (n = 21)

Virological methods:

- RT and protease resistance genotypic analysis were performed on plasma samples collected at baseline
- Reported mutations as listed at www.iasusa.org (update September 2006)

Statistical methods:

- Data from group 1 from CONTEXT and group A from TRIAD were pooled and analyzed.

- The virological response (VR) was defined as the decrease from baseline in HIV-RNA at week 12.

- Association between each protease mutation (codons 1 to 99) and VR was studied using the Kruskal-Wallis test. Mutations with prevalence >10% and p-value <0.10 were retained in this first step of the analysis.

- Jonckheere-Tepstra (JT) test was used to select the combination of mutations most strongly associated with VR, with a removing procedure technique.

Patients demographic and baseline Characteristics

	CONTEXT group 1 FPV/RTV BID N=107	TRIAD group A STD-FPV/RTV N=21
Gender		
Male, (%)	93 (87 %)	17 (81 %)
Age		
Median (years)	39	41
Range	(24,71)	(35,52)
CDC classification of HIV infection at baseline		
A: Asymptomatic or lymphadenopathy or acute HIV, n (%)	44 (41)	9 (43 %)
B: Symptomatic, but not AIDS, n (%)	29 (27)	5 (24 %)
C: AIDS, n (%)	34 (32)	7 (33 %)
Median plasma HIV-1 RNA (IQR)	4.13 (2.27, 5.95)	4.71 (4.44, 5.23)
Median CD4+cell count (IQR)	292 (12, 845)	279 (126, 508)
Hepatitis B test results		
Positive, n (%)	4 (4 %)	1 (5 %)
Hepatitis C test results		
Reactive, n (%)	16 (15)	4 (19 %)

Summary of Prior Antiretroviral Therapy

	CONTEXT group 1 FPV/RTV BID N=107	TRIAD group A STD-FPV/RTV N=21
No. of PIs taken		
No. (%) of Subjects		
≤ 2	94 (89 %)	5 (24 %)
3-4	12 (11 %)	5 (24 %)
≥ 5	-	11 (52 %)
Median duration of all prior PI exposure (Weeks)		
Median (range)	149 (8, 351)	346 (257, 381)
No. of NRTIs taken		
No. (%) of Subjects		
≤ 4	79 (74 %)	3 (14 %)
5-6	27 (26 %)	10 (48 %)
≥ 7	-	8 (38 %)
Median duration of all prior NRTI exposure (Weeks)		
Median (range)	257 (15, 702)	473 (432, 551)
No. of NNRTIs taken		
No. (%) of Subjects		
0	-	2 (9 %)
1	49 (46 %)	10 (48 %)
2	14 (13 %)	9 (43 %)
3	1 (< 1 %)	-
Median duration of all prior NNRTI exposure (Weeks)		
Median (range)	84 (4, 259)	90 (47, 132)

Most Common (>5%) RTI Initial Combinations Received by subjects in CONTEXT group 1 ITT(E) Population

Initial RTI Combinations	908/RTV BID N=107 n (%)
No. (%) of Subjects Taking Initial RTI Combinations	107 (100)
Lamivudine/tenofovir	22 (21)
Didanosine/tenofovir	15 (14)
Abacavir/tenofovir	11 (10)
Stavudine/tenofovir	14 (13)
Didanosine/stavudine	5 (5)
Stavudine/didanosine	5 (5)
Lamivudine/zidovudine	1 (< 1)

Concomitant N (t)RTI combinations and T20 in the Optimized Background in TRIAD group A

Most common ART used in optimized background	STD-FPV/RTV N=21
Any ART	19 (90%)
N(t)RTI s:	
Tenofovir + any other	11 (52%)
Lamivudine + any other	12 (57%)
Didanosine + any other	7 (33)
Abacavir + any other	6 (29%)
Other:	
T20	2 (10%)

Results

113 patients were included in the resistance analysis (CONTEXT, n = 97; TRIAD, n = 17) - 15 out of 128 patients were excluded because they had missing week 12 HIV-1 RNA value

Baseline Genotype:

Median number of PI IAS mutations (IQR)
- Major protease mutations 2 (0-2)
- Minor protease mutations 5 (3-7)

Virological response to FPV/r-containing regimen:

- Overall, the median VR was -1.86 [range; -3.59 to +1.08] log copies/ml.

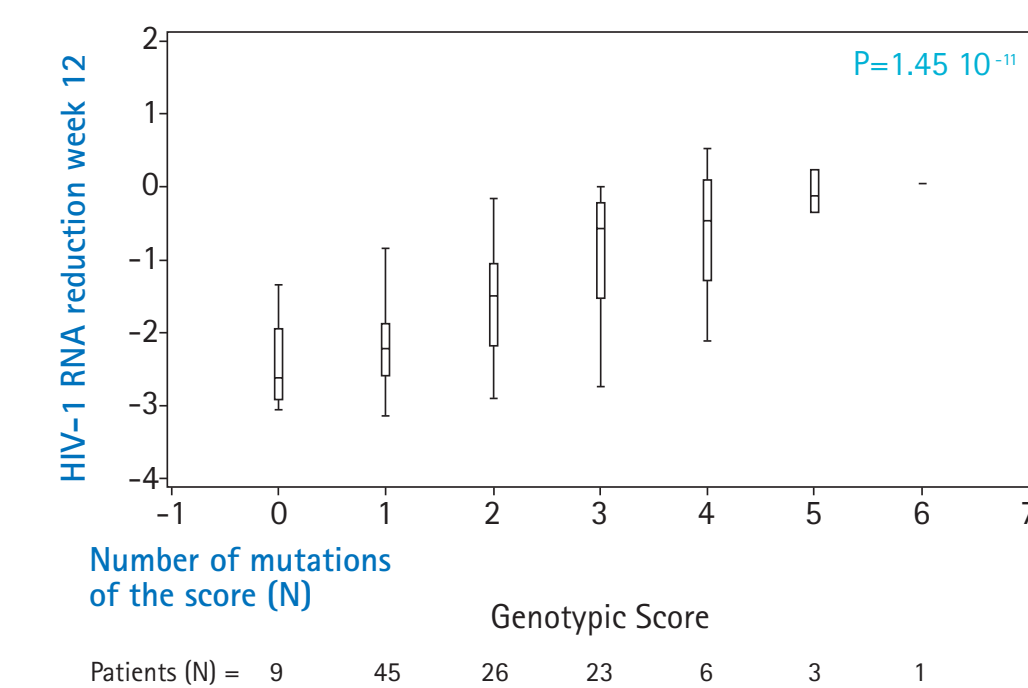
Mutations associated with week 12 virological response

All listed mutations are associated with a decreased VR				
Position	Amino acid	N	median HIV-1 RNA reduction at W12	p value
10	L (wild-type)	63	-2,1	0,0001
	F/I/N/Y	50	-1,21	
15	I (wild-type)	89	-1,94	0,0073
	I/V	24	-0,93	
33	L (wild-type)	100	-1,89	0,0068
	F/I	13	-0,36	
46	M (wild-type)	81	-2,09	0,0002
	I/L	32	-0,98	
54	I (wild-type)	89	-2,02	<0,0001
	A/L/V/M/S	24	-0,39	
60	D (wild-type)	99	-1,89	0,0038
	E/N	14	-0,34	
62	I (wild-type)	74	-1,94	0,0039
	V	39	-1,12	
63	L (wild-type)	11	-2,58	0,012
	A/S/T/P/Q/V	102	-1,7	
72	I (wild-type)	83	-1,89	0,065
	E/L/M/T/V	30	-1,38	
73	G (wild-type)	101	-1,89	0,008
	C/S/T	12	-0,71	
82	V (wild-type)	92	-1,95	0,002
	A/F/I/T	21	-0,75	
84	I (wild-type)	98	-1,91	0,0003
	C/K/V	15	-0,31	
89	L (wild-type)	102	-1,88	0,034
	I/M/V	11	-0,31	
90	L (wild-type)	70	-1,95	0,016
	M	43	-1,38	

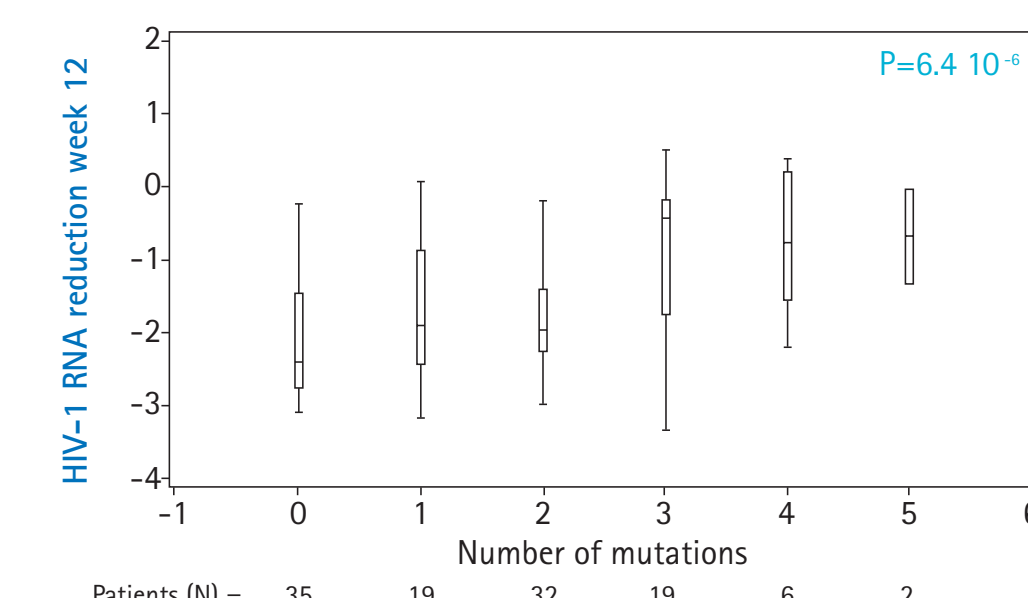
FPV/r genotypic score

The JT procedure did not retain mutations at codons 10, 33, 62, 72, 73, 82, 89 and 90 and led to select the following genotypic score: I15V + M46I/L + I54L/M/V + D60E + L63P/T + I84V, as providing the strongest association with VR.

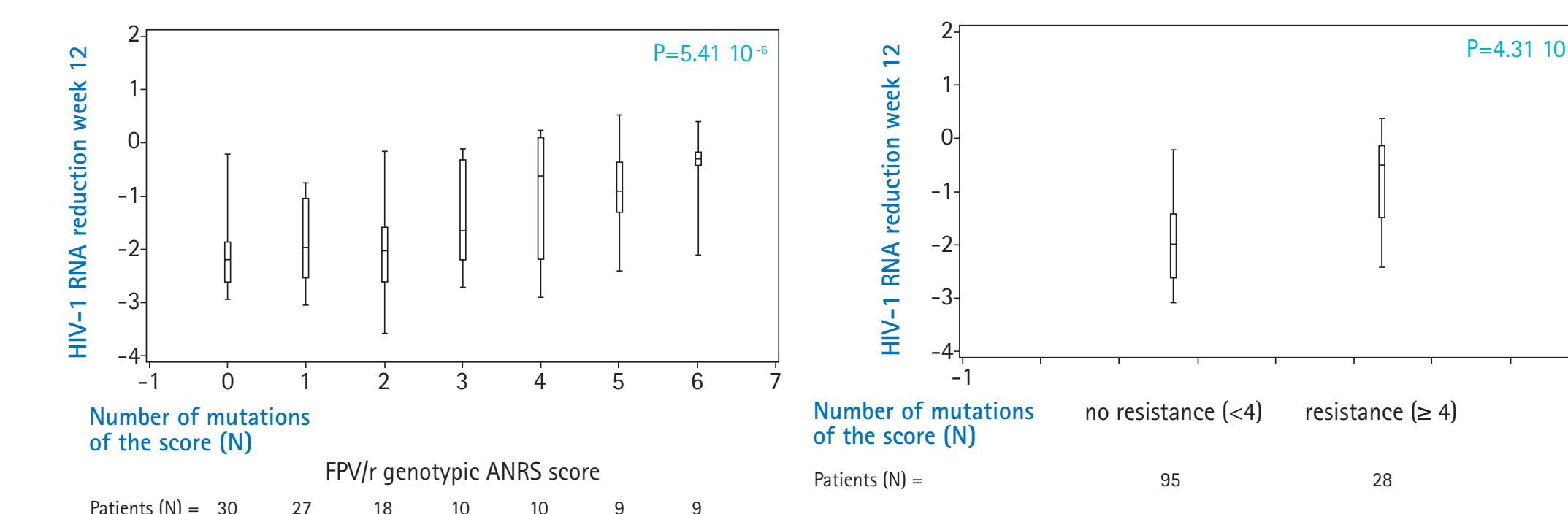
VR according to FPV/r genotypic score (I15V + M46I/L + I54L/M/V + D60E + L63P/T + I84V)



Impact of IAS PI mutations (major only) on the VR at week 12



Impact of FPV/r ANRS score* (L10F/I/V + L33F + M36I + I54A/L/M/S/T/V + I62V + V82A/C/F/G + I84V + L90M) on the VR at week 12. www.hivfrenchresistance.org *Masquelier B et al. XV Int HIV drug resist workshop 2006, Sitges, Spain, abstract 91.



This analysis was performed on 67 PI-experienced patients receiving FPV/r regime. The median (IQR) number of major protease IAS mutations was 2 (0-3) and minor protease IAS mutations was 1 (5-7).

Conclusion

We described the mutations associated to FPV/r virologic response at week 12 based on virologic data from a pooled analysis of FPV/r 700/100 mg BID arms of 2 different clinical trials conducted in PI-experienced patients. Among the genotypic score identified in this study: I15V + M46I/L + I54L/M/V + D60E + L63P/T + I84V

- Some of these mutations have been already identified as FPV/r resistance mutations in clinical trials using amprenavir and are already considered as FPV/r IAS mutations (M46I/L, I54L/M/V and I84V)
- Some of these mutations have been previously identified in the FPV/r ANRS score (I54L/M/V and I84V)
- The FPV/r ANRS score was highly predictive of the VR in this new dataset, providing an external cross validation of this score in an independent dataset.
- This study and the ANRS studies did not highlight the impact of either I50V or V32I + I47V that are known to be selected by amprenavir and FPV in patients failing first line regimen, that is in accordance to the fact that patients analyzed in both studies were not experienced before with amprenavir or FPV. That is the reason why in the ANRS algorithm the presence of I50V and/ or V32I + I47V is considered as resistance to FPV.

Although the statistical methodology used to determine FPV/r genotypic score and the median number of major and minor PI resistance mutations were similar in the present study and in the ANRS study, genotypic scores were not strictly identical, probably because of different patterns of mutations at baseline in the two different dataset. However, the presence of I54L/M/V and I84V in both scores probably reflect a high weight of these mutations.

In conclusion, the FPV/r ANRS resistance score recently proposed is a useful tool for the prediction of virological response to FPV/r in PI-experienced patients.

APV30003 INVESTIGATORS LIST: Australia (Mark Bloch, John Chuah, David Cooper, Robert Finlayson, Jennifer Hoy, Robert McFarlane, John Quin, Norm Roth, Cassy Workman), Belgium (Nathan Clumeck), Canada (Kevin A. Gough, Patrice Junod, Donald Kilby, John MacLeod, Anita Rachlis, Walter F. Schlech III, Fiona Small, Benoit Troitier, Christos Tsoukas), Chile (Carlos Beltran), France (Michelle Bentata, J. Francois Delfrayssis, Gilles Force, Herve Gallais, Jean Albert Gastaut, Bruno Hoen, Marie-Aude Khuong-Josses, Alain Lefeuvre, Jean Marie Lang, Jean-Michel Livrozet, Jean-Michel Molina, Willy Rozenbaum, Daniel Sereni, Pierre de Truchis, Daniel Vittecoq, Patrick Yeni), Germany (Keikawus Arasteh, Gerd Faetkenheuer, Stefan Fenske, Hans Jaeger, Stefan Maus, Andreas Plettenberg, Juergen Rockstroh, Reinhold Schimidt, Schlimo Staszewski) Italy (Adriano Lazzarin, Nicolo Piersantelli), Portugal (Antonio Diniz, Eugenio Teofilo) Puerto Rico (Jorge L. Santana Bagur, Gabriel A. Martinez) Spain (Maria Jesus Perez Elias, Bonaventura Clotet-Sala, Vicente Estrada, Pompeyo Viciana Fernandez, Jose Maria Gatell-Artigas, Enrique Ortega, Jose Maria Pena, Federico Pulido, Rafael Rubio, Agustin Munoz-Sanz), Switzerland (Enos Bernasconi, Miles Opravil, Amalio Telenti), UK (Philippa J. Easterbrook, Brian George Gazzard, Celia J. Skinner), US (Bisher Akil, Stephen L. Becker, Nicolaos C. Bellos, Daniel S. Berger, Andre Brutus, Paul Cimoeh, David. V. Condolesci, Gregg O. Cooley, Timothy P. Cooley, Edwin DeJesus, Thomas M. File, Jr., Gevais Frechette, Joseph C. Gathe, Jr., Jose A. Giron, Eliot Godofsky, Mitchell Goldman, Stephen L. Green, Patrick G. Haggerty, Barbara Hanna, Kevin King, G. Steven Kooshian, Pardeep Kumari, Anthony LaMarca, Danny J. Lancaster, Christopher Lucasti, Alberto Mestre, Robert A. Myers, Jr., Jeffrey P. Nadler, Ronald G. Nahass, Cheryl L. Newman, Robert Orenstein, David A. Parks, Gerald Pierone, Jr., Arnaldo R. Quinones, Bruce S. Rashaubam, Frank S. Rhame, Gary Richmond, Allan E. Rodriguez, James H. Sampson, Michael G. Sension, Gail Skowron, Kimberly Y. Smith, Corliss Steinhardt, Richard Stryker, Kimberly K. Summers, Karen T. Tashima, Nathan M. Thielman, Fahmida Visnegarwala, Barbara H. Wade, Charles M. Walworth, Lawrence J. Wheat, Michael Goldman, David P. Wright, Benjamin Young, Christine A. Zurawski)

APV102002 INVESTIGATORS LIST: Greece (Panagiotis Gargalianos-Kakolyris, George Chrysos, Marios Lazanas), Spain (Pere Domingo, Vicente Estrada, Federico Pulido, Rafael Rubio, Vicente Soriano, Jose Alberto Terrón, Miguel Giorgolas, Blai Coll, Vicente Abril, Joaquin Portillo), Canada (Sylvie Troitier, Donald Kilby, Graham Smith, Jean-Guy Baril, Ken Logue, Brian Conway, Christos Tsoukas, Fiona Smail), Germany (Andreas Plettenberg), France (Maria-Louisa Partisani, Jean-Michel Molina, Daniel Sereni, Alain Lefeuvre, Thierry May, Jean-François Bergman, Marie-Aude Khuong-Josses, Olivier Bouchaud, Gilles Pialoux, Dr Felicia David-Ouaknine), Belgium (Nathan Clumeck), Italy (Laura Sighinolfi, Francesco Mazzotta, Francesco Leoncini, Paolo Sacchi, Roberto Cauda, Anna Maria Cattelan, Giovanni Penco, Pietro Carmelino), Australia (Jonathan Anderson, David Cooper, Cassy Workman), UK (Martin Fisher, Margaret Johnson, Mia Huengsborg, Chloe Orkin, Philippa Easterbrook, Phillip Hay, Alan Winston, Hiten Thaker)