H-569

48-Week Final Results of Lopinavir/r (LPV/r)-Efavirenz (EFV) Combination (BIKS Study)

Contact information
Professor Francois Raffi
Infectiology Department
University Hospital - 44093 Nantes - France
Phone (33) 2 40 08 33 51 - Fax (33) 2 40 08 33 35
E-mail : francois.raffi@chu-nantes.fr

F. Raffi[1]*, C. Allavena[1], J.F. Delfraissy[2], A. Lafeuillade[3], M. Bentata[4], C. Katlama[5], P. Dellamonica[6], I. Poizot-Martin[7], C. Michelet[8], J.M. Besnier[9], V. Ferré[1] and the BIKS Study Team.

Infectious Diseases Dept. of [1]Nantes, [2]Bicêtre Paris, [3]Toulon, [4] Bobigny, [5]Pitié Salpétrière Paris, [6]Nice, [7]Marseille, [8]Rennes and [9]Tours, France.

BACKGROUND

❖**Recommended antiretroviral regimens include a nucleoside reverse transcriptase inhibitors (NRTI) component. Class-cross resistance and mitochondrial toxicity are recognized as problems with the class of NRTIs. With the availability of potent drugs from the other classes, evaluation of NRTI-sparing regimens is desirable.**

❖**Lopinavir/ritonavir (LPV/r) and efavirenz (EFV) are potent antiretrovirals (ARVs) and are the preferred agents among their respective classes.**

❖**Combination of these 2 agents requires dose adaptation, i.e. increase by one third of LPV/r dose, due to an induction of lopinavir metabolism by EFV (reduction of lopinavir AUC by 40%).**

STUDY DESIGN

Pilot, multicenter (16 centers), open label trial to evaluate the safety, immunological and virological activity of dual therapy with LPV/r (533/133 mg bid) and efavirenz (600 mg qd) in HIV-1 infected patients (**Bi**therapy of **K**aletra and **S**ustiva)

Entry criteria :
- HIV-1 infected adults
- CD4 cell count ≥ 100/mm^3
- Plasma HIV-1 RNA ≥5000 copies/mL

AND
- ARV naïve
- Or ARV experienced, but NNRTI naïve and ≤ 1 documented failure to PI-containing ARTwith less than 5 lopinavir-associated resistance mutations on screening protease genotypic testing (including L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, L90M)

Exclusion criteria :
- Recent HIV infection (< 6 months)
- Prior treatment with NNRTI, LPV/r
- Pregnancy
- Active drug abuse
- Significant biological abnormalities (Hemoglobin, Neutrophils, Platelets, ALAT, ASAT, creatinine)

❖Duration of the study : 48 weeks with a 24-month extension

❖Follow-up included at visit D0, W4, 8, 16, 24, 36, 48: Clinical examination, fasting lipids, standard laboratory tests, CD4 cell count, HIV-1 RNA (pVL)

❖Definition of
- Virological success : pVL< 400 copies/mL
- Virological failure :
  - 2 consecutive pVL>1,000 copies/mL x 2 if prior < 400
  - < 2 log reduction in pVL at W24,
  - 2 consecutive pVL> 400 copies/mL at W24 or beyond

❖Analyses
- Virological response : intent-to-treat, discontinuation and/or missing equals failure (ITT) and on-treatment (AT) analyses.
- Immunological response : AT analysis.
- Safety : all patients who received at least 1 dose of study drugs.

❖Primary Endpoint : percentage of patients with ARN VIH< 400 copies/mL at W24

RESULTS

Table 1 : Baseline Characteristics

	ARV-naive Patients (n=65)	ARV-experienced Patients (n=21)	All patients (n=86)
Male, (%)	55 (85)	15 (71)	70 (81)
Age, year			
Mean (± SD)	39.9 (± 9.9)	37.6 (± 8.6)	39.7 (± 9.6)
CD4 cell count, cells/mm^3			
Mean (± SD)	300 (± 172)	344 (± 325)	311 (± 218)
Median (range)	275 (71-992)	308 (82-1612)	276 (71-1612)
HIV-1 RNA, $\log_{10}$ copies/mL			
Mean (± SD)	4.95 (± 0.52)	4.53 (± 0.58)	4.84 (± 0.57)
Median (range)	4.98 (3.48-5.87)	4.60 (3.53-5.40)	4.87 (3.48-5.87)
≥ 5 $\log_{10}$ copies/mL, n(%)	31 (47.7)	6 (28.6)	37 (43.0)

Table 2 : ARV-Experienced Patients (n=21)

◆ Median ARV duration	5.2 years (0.1-17.3)
◆ Median prior ARVs	3 (2-6)
◆ PI naïve	n=12
◆ PI-experienced	n=9
• Genotype of protease gene	
- No mutation	n=3
- L63P	n=3
- L63P+A71T/A	n=1
- L10V+L63P+A71T	n=1
- V82I	n=1

Table 3 : Patient Disposition at Week 48

	ARV-naive patients	ARV-exp patients	All patients
• Patients enrolled	65	21	86
• Patients discontinuing by Week 48 n (%)	18 (28)	3 (14)	21 (24)
• Virological failure	1	0	1
• Drug-related clinical adverse event	6	1	7
- CNS symptoms*	3	0	3
- Cutaneous rash*	3	0	3
- Grade 4 dyslipidemia**	0	1	1
• Protocol violation	1		1
• Lost to follow-up	6		6
• Non adherence	1		1
• Pregnancy	1		1
• Patient's decision	1		1
• Other reasons	1[a]	2[b]	3

* EFV related ** LPV/r related *pruritus [a]tuberculosis in one case and psychiatric disorder in the other case

Table 4 : Virologic Results at Week 24 and Week 28 weeks

	HIV-1 RNA levels < 400 copies/mL				HIV-1 RNA levels < 50 copies/mL			
	N	n	%	95% CI	N	n	%	95% CI
AT analysis								
- **24 weeks**	72	67	**93**	85-97	72	59	**82**	72-89
- **48 weeks**	65	63	**97**	89-99	65	59	**91**	81-96
ITT analysis								
- **24 weeks**	86	67	**78**	68-85	86	59	**69**	58-77
- **48 weeks**	86	63	**73**	63-81	86	59	**69**	58-77

N : number of patients considered for analysis, n : number of patients with HIV-1 RNA levels below the stated threshold, AT: on treatment, ITT : intent to treat

Table 5 : Grade 3/4 Adverse Events

Event	Grade	Nb of patients	Nb of events	Possibly related to study drug(s)*
Body as a whole				
Asthenia	3	2	2	YES
Headache	3	2	2	YES
Myalgia	3	1	1	NA**
Dyspnea	3	1	1	NA
Cutaneous reaction				
Rash	3	3	4	YES
Urticaria	3	1	1	YES
Prurit	3	1	1	YES
CNS disorder				
Vertigo	3	1	1	YES
Sleep disorder	3	4	4	YES
Emotional liability	3	1	1	YES
Somnolence	3	1	1	YES
Depression	3	1	1	YES
Paranoid reaction	3	1	1	YES
Digestive system				
Abdominal pain	3	1	1	YES
Diarrhea	3	2	2	YES
Metabolic disorder				
Lipodystrophy	3	1	1	YES
Weight increase	3	1	1	YES
Gynecomastya	3	1	1	YES
Gout	3	1	1	NA
Hyperamylasemia	3	1	1	YES
SGOT elevation	4	1	1	YES
SGPT elevation	3	3	4	YES
	4	2	2	YES
Hypercholesterolemia	3	22	26	YES
	4	2	3	YES
Hypertriglyceridemia	3	9	11	YES
	4	2	3	YES
Miscellaneous				
Leukopenia	3	1	1	NA
Meningitis	3/4	1	1	NA
Pyelonephritis	3/4	1	1	NA
Abscess	3	1	1	NA
Sarcoma	3/4	1	1	NA
Bone fracture	3/4	1	1	NA

*as assessed by investigator, **"NA" not assessable

Figure 1

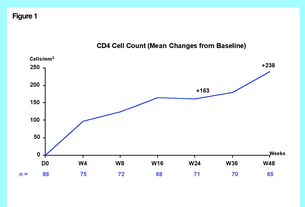


Figure 2

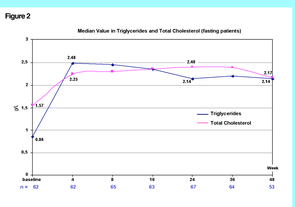


Figure 3

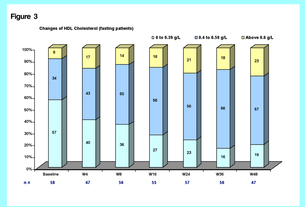
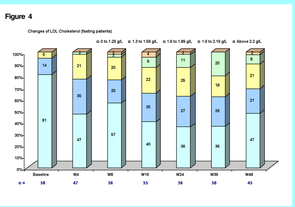


Figure 4



❖At W48, the mean change from baseline in CD4 cell count *(fig. 1)* and HIV-RNA was + 238 cells/mm^3 and –3.00 $\log_{10}$ cp/mL, respectively.

Analysis of pVL>400 copies/mL at Week 24 or Week 48

At Week 24
- Poor adherence n=1*
- Slow responder n=1
  (pVL<400 cp/mL at W28 and all subsequent controls;
  NB: baseline pVL>6 $\log_{10}$ cp/mL, pVL: 424 cp/mL at W24)
- Confirmed virologic failure n=1
  (genotype: at screening: wild type virus ; at Week 16: K103N)
- Blip n=2
  (pVL at W24 : 885 and 1,472 cp/mL, respectively ;
  both patients with pVL < 50 cp/mL at W16 and W28)

At Week 48
- Poor adherence n=2**

*genotype: wild type virus **genotype: wild type virus in 1 patient, K103N in the other one

% patients with pVL<400 cp/mL at Week 48 (ITT)

- Naïve patients vs pretreated patients (ITT, NC/D/M=F)
  71% 81% p=0.359
- Baseline pVL> 100,000 cp/mL vs Baseline pVL ≤ 100,000 cp/mL
  78% 69% p=0.351

❖Discontinuations : 21(24%) patients. Main reasons were :
- emerging adverse events (n=7)
- loss to follow-up (n=6),
- virological failure (at W24) (n=1).

❖Adverse event-related discontinuations occurred more frequently in the first 4 weeks (n=6) compared to Week 4-24 (n=1) and to Week 24-48 (n=0)

❖Of the 7 events requiring discontinuations, 6 were attributed to EFV.

❖Adherence (patients' self-report) < 80% : at least one episode during follow-up, n= 43 (50%)
- 5 did not complete the initial 24-week period for lost to follow-up or non adherence
- 2 discontinued the study between Week 24 and Week 48 for reasons unrelated to study drugs (pregnancy in one case and tuberculosis in the other case)

❖**Lipodystrophy assessment**

◆Reported during the study in 6 patients (5 were ARV-experienced at baseline)
- 3 had a prior history of lipodystrophy and experienced subjective self-reported worsening of body changes,
- 2 developed lipodystrophy after 4 and 16 weeks of therapy, respectively.
- 1 naïve patient developed mild cheek lipoatrophy after 36 weeks of treatment

◆No significant modification in waist/hip ratio of the total study population at Week 24 or Week 48 compared with baseline

DISCUSSION

❖Virological success was achieved in a high proportion of patients continuing the study *(table 4)* :
- At W24 : pVL < 400 cp/mL : 93% (AT) and 78% (ITT)
- At W48 : pVL < 50 cp/mL : 91% (AT) and 69% (ITT)

❖Virological failure was documented in 4 patients, of whom 3 were non adherent.

❖Among patients with detectable pVL at W24 or W48, genotypic testing showed :
- Absence of emergence of protease resistance mutations
- Emergence of K103N resistance mutation in 2 cases

❖ Most of discontinuations were not related to drug-related adverse events nor virological failure *(table 3)*.

❖ AE-related discontinuations occurred in 8% of the patients, mostly early.

❖ Most common treatment-related clinical grade 3 adverse events were CNS symptoms and cutaneous reactions, all related to EFV *(table 5)*.

❖ Incidence of Grade 3 gastro-intestinal intolerance was low (3.4 %).

❖After an initial increase at W4, fasting triglycerides and total cholesterol remained stable (mean change from baseline +1.25 and +0.58 g/L at W48, respectively) *(fig. 2)*.

CONCLUSION

❖**This pilot study has proven the concept of a NRTI-sparing regimen combining LPV/r and EFV.**

❖**At Week 48, LPV/r 533/133 mg bid + EFV 600 mg qd was associated with a high rate of virological success and sustained immunological response.**

❖**Comparative studies are needed to assess the role of NNRTI-PI/r dual combination in today's ARV strategy.**

❖**Selection of NNRTI-P/r regimenl should be optimized to achieve not only immuno-virological efficacy but also improved tolerability.**

BIKS Study Team :
Principal Investigator : Pr F. RAFFI ; **Coordination** : Dr C. ALLAVENA
Clermont-Ferrand : J. Beytout, Ch. Jacomet, C. Henquell ; **Marseille Ste-Marguerite** : J-A. Gastaut, I. Poizot-Martin, M.P. Drogoul, Y. Chettri, M.L. Loirec ; **Marseille Hôp. Nord** : J. Moreau, S. Mokhtari, Mme Charbit, Dr Bekkis ; **Muthouse** : G. Beck-Wirth, C. Michel, M. Bernomar, V. Ansieau-Picot, J.M. Delarbre ; **Nantes** : C. Rabreau, B. Bonnet, E. Billaud, C. Brunet, A. Huart, F. Bugnon , B. Milpied, V. Reliquet, H. Hue, E. André, E. Dailly, M-F. Kerguéris, V. Ferré, A. Lepelletier ; **Nice** : P. Dellamonica, M-A. Serini, V. Rahelinirina, M.C. Rigaud, J. Cottalorda ; **Paris-Pitié-Salpétrière** : C. Katlama, R. Tubiana, M-A. Valantin, A. Mohand, H. Schoen, Mme Lhogréau, M. Lassalle, S. Herson, M. Bonmarchand, C. Brançon ; **Paris-Bicêtre** : J.F. Delfraissy, C. Goujard, M.T. Rannou, C. Rousseau, C. Letiec, A. Karim ; **Paris-Bobigny** : M. Bentata, R. Mansouri, F. Rouges, F. Touam, P. Honoré, O. Launay, L. Belarbi, P. Klutze, R. Brianne, C. Allaoui ; **Paris-Saint-Louis** : J-M. Molina, M. Tourneur, Mme Mzreb, F. Ferchal ; **Rennes** :C. Michelet, P. Tattevin, C. Arvieux, F. Souala, J.M. Chaplain, C. Bouvier, B. Marie-Dit-Dinard, A. Ruffault ; **Toulon** : A. Lafeuillade, G. Hittinger, S. Chadapaud, V. Lambry, G. Philip, P. Jolly, A. Caharel, C. Poggi ; **Tours** : P.Choulet, J. M. Besnier, F. Bastides, V. Vauthier, P. Nau, I. Chartin, F. Barin ; **La Roche/Yon** : P. Perré, S. Leautez, C. Leroy, N. Roux, M.A. Desailly
Promotion : DRC, CHU Nantes
Grants : ARSIID, Abbott, Bristol-Myers Squibb,