abstract K-196
poster board 573

Simplification Therapy with Once-Daily Efavirenz, Emtricitabine and Didanosine in Patients Virologically Suppressed with a Protease Inhibitor-Based Regimen: Three-Year Follow-up of the Alizé-ANRS 099 Trial

JM Molina, V Journot, W Rozenbaum, P Yéni, C Rancinan, P Morlat, I Poizot-Martin, J Reynes, F Raffi, P Leclercq, P Palmer, P Dellamonica, Morand-Joubert, S Fournier, B Dupont, JF Delfraissy, P Dellamonica, JP Cassuto, G Chêne and the ALIZE-ANRS 099 Study Group

Hospitals of Paris, Bordeaux, Marseille, Montpellier, Nantes, Grenoble, Nice, and INSERM U593 Bordeaux, France

Jean-Michel Molina, M.D.
Saint-Louis Hospital, Department of Infectious Diseases
1, avenue Claude Vellefaux, 75010 Paris , France
tel: 011 33 1 42 49 90 66
fax: 011 33 1 42 44 90 67
e-mail: jean-michel.molina@sls.ap-hop-paris.fr

Introduction

We have demonstrated in the ANRS 099 ALIZE trial that simplification therapy with once-daily efavirenz (EFZ), didanosine (ddI), and emtricitabine (FTC) in HIV-1 infected adults with viral suppression receiving a protease inhibitor-based regimen was well tolerated and associated with sustained virologic suppression and immunological benefit during 48 weeks (Molina et al, JID, March 2005). Also, adherence to study medications was better with the once-daily regimen than with the PI-based regimen. Finally, there was a significant increase in HDL-cholesterol levels in the once-daily group compared with the PI group.

Because FTC was not available at the end of the trial, patients were offered to continue the study, which was extended for 3 years, and to receive the same once-daily combination

Objective

To assess the long-term safety and efficacy of a once-daily combination of FTC + ddI + EFV in patients randomized to the once-daily arm of the ALIZE trial and willing to continue therapy with the same combination after week 48 of the trial.

Study Treatment

Once-daily combination of FTC (200 mg per day) + ddI (< 60 kg: 250 mg per day / ≥ 60 kg: 400 mg per day) + EFV (600 mg per day) : 5 pills taken all together, at bedtime, at least two hours after dinner.
During study, the new formulation of EFV became available and patients received one 600 mg capsule of EFV, making the once-daily regimen only 3 pills/day.

Entry Criteria

Patients randomized to the once-daily regimen (FTC + ddI + EFV) of the ALIZE trial and willing to continue follow-up after week 48

At trial entry:	Patients receiving a PI-based HAART	Plasma HIV-RNA levels < 400 cp/mL in the 6 previous months
	Non nucleoside reverse transcriptase inhibitor naïve	CD4+ T-lymphocyte cell count ≥ 100/mm³
	No previous use of ddI monotherapy	
	3TC-based HAART if treated with NRTIs alone before PI-based regimen	

Study Design

Method	open-label multicentric cohort	
Accrual	178 patients in 58 French centers who reached week 48 of the ALIZE trial	
Follow-up	2 years after week 48, i.e. 3 years after trial randomization	
Endpoints	virological efficacy	virological failure : first occurrence of HIV-1 RNA ≥ 400 cp/mL
	immunological efficacy	median change of CD4+ T-lymphocyte cell count from baseline
	tolerance	grade 4 adverse events lipodystrophy and metabolic disorders
Analysis strategy	on available data only	
	for virological efficacy analysis	intent to treat analysis and on study treatment analysis
	for other analyses	on study treatment analysis

Results

Baseline Characteristics of Patients Randomized to the Once-Daily Group of the ALIZE Trial

N			178	
Gender	men	n (%)	152	(85)
Age	years	median (IQR)	41	(36 - 47)
HIV risk factors	homosexual	n (%)	86	(47)
	intravenous drug use		17	(10)
	heterosexual		60	(34)
	others or unknown		14	(8)
CDC Disease stage	AIDS	n (%)	50	(28)
Plasma HIV-1 RNA	ultra-sensitive assay	n < 400 cp/mL (%)	178	(100)
Lymphocyts CD4+ count	cells/mL	median (IQR)	509	(375 - 756)
Glucose	mg/dL	median (IQR)	88	(79 - 95)
Cholesterol	mg/dL	median (IQR)	216	(191 - 243)
HDL cholesterol	mg/dL	median (IQR)	45	(38 - 56)
LDL cholesterol	mg/dL	median (IQR)	3.7	(3.0 - 4.3)
Triglycerides	mg/dL	median (IQR)	137	(89 - 218)

IQR: interquartile range

Disposition of Patients - n

	M00	]M00-M12[	M12	]M12-M36[	M36
Continued					
on trial follow-up	178		175		147
on study treatment	178		152		125
Discontinued study treatment	-	23	0	27	
dead	0	0	0	0	
withdrew consent at baseline	3	-	-	-	
stopped study treatment		23		27	
for treatment adaptation	-	-	-	*5*	
for patient's choice	-	*3*	-	*5*	
for treatment failure	-	*5*	-	*2*	
for adverse effect	-	*15*	-	*8*	
for unknown reason	-	-	-	*7*	

Serious (grade 4) adverse events – patients with at least one event (n)

MedDRA System Organ Class	Description	]M00-M12]	]M12-M36]
Infections and infestations		7	3
Neoplasms benign, malignant and unspecified		1	1
Musculoskeletal and connective tissue disorders		2	2
Nervous System disorders	closed head injury + loss of consciousness	1	
Gastrointestinal disorders	pancreatitis, blood amylase increase	1	1
	others	2	2
Hepatobiliary disorders	hepatitic cytolysis	3	
Renal and urinary disorders	nephrolithiasis	1	
Respiratory, thoracic and mediastinal disorders		2	
Cardiac disorders	myocardial infarction		2
	pericardial effusion		1
Pregnancy, puerperium and perinatal conditions	abortion	1	1
Psychiatric disorders	depression, suicide attempt	2	2
	hallucination	1	
Investigations (biology)	CPK increase	3	2
	triglyceride increase	1	
	neutropenia	3	
Overall		**29**	**17**

Main Results

Among the 152 patients (85%) who continued the once-daily combination of FTC+ddI+EFV up to week 48, 147 (83%) were followed until year 3 and 125 (70%) remained on study treatment after 36 months.

During follow-up, the proportion of patients with virologic failure (plasma HIV RNA above 400 copies/mL) at month 36 reached only 6% in the on-treatment analysis and 23% in the intent-to-treat analysis.

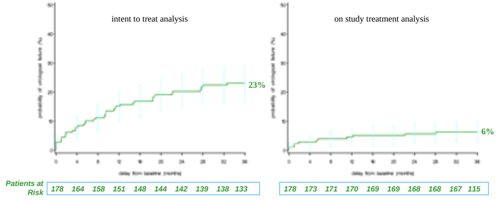
Median increase from baseline in CD4+ cell count was +44 cells/mm³ (vs 0: p<0.05) at month 36, in patients with a CD4+ cell count at study entry of 535 cells/mm³. Immune reconstitution was therefore slow.

The incidence of grade 4 adverse events stabilized after the first 48 weeks of follow-up, since 29 patients (16%) encountered a serious adverse event before week 48, and only 17 (10%) up to 36 months. No patient discontinued study treatment because of worsening of lipoatrophy.

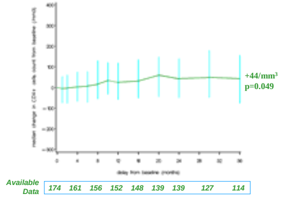
There was a slightly statistically significant increase in plasma glucose level (p<0.05), but the proportion of patients meeting the diabetes melitus definition (glucose > 126 mg/dL) remained very low, between 2 to 5% during follow-up. Interestingly, there was no increase in total cholesterol level or LDL cholesterol after 36 months with this combination. Yet, a significant increase in HDL cholesterol level already observed at week 48 was sustained up to month 36 (+11.6 mg/dL), and 42% of patients (20% at baseline) had a plasma HDL cholesterol level > 60 mg/dL at month 36, a level which is associated with protection against cardiovascular risk.

Of note, the incidence of lipodystrophy (both lipoatrophy and lipohypertrophy) remained unchanged after 36 months of therapy as compared to baseline. This is an interesting result with this new combination.

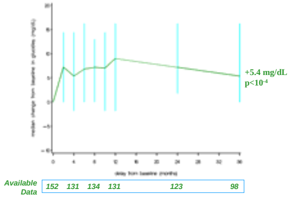
HIV-1 RNA – Kaplan-Meier Estimate of the Probability of Virological Failure (%)



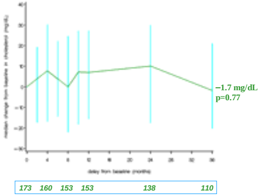
Lymphocytes CD4+ Cells Count - Median Change From Baseline (/mm³)



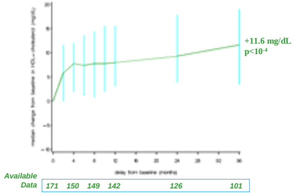
Glucose – Median Change From Baseline (mg/dL)



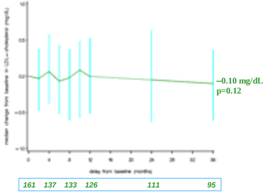
Cholesterol – Median Change From Baseline (mg/dL)



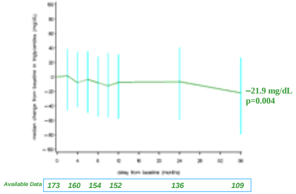
HDL Cholesterol – Median Change From Baseline (mg/dL)



LDL Cholesterol – Median Change From Baseline (mg/dL)



Triglycerides – Median Change From Baseline (mg/dL)



Lipodystrophies - n (%)

	lipoatrophy		lipohypertrophy		lipodystrophy	
	# / N	%	# / N	%	# / N	%
M00	76 / 174	44	53 / 174	30	91 / 174	52
M06	64 / 161	40	50 / 161	31	79 / 161	49
M12	67 / 150	45	45 / 150	30	78 / 150	52
M24	58 / 141	41	42 / 141	30	73 / 141	52
M36	48 / 120	40	31 / 119	26	59 / 120	49

n: at least one dystrophy; N: available data

Acknowledgments

This study was supported by a grant from ANRS – ALIZE study ANRS trial 099.
We thank Dr. F. Rousseau from Gilead who provided FTC up to the end of the trial.

Participating Centers

The following institutions and investigators participated in the Agence Nationale de Recherches sur le SIDA 099 Study :
Hopital Saint-Jacques, Belfort: Faller, Eglinger, Bettinger, Lamielle; **Hopital Robert Debre, Reims**: Deville, Remy, Beguinot, Rouger, Waldner-Combernoux, Brodard, Belkacem, Rosati; **Hopital Lagny-Marne-La-Vallee, Lagny**: Lagarde, David, Costa, Kinoo; **Hopital Avicenne, Bobigny**: Bentata, Honore-Berlureau, Alloui, Baazia, Brianne, Soreda; **Hopital Saint-Jacques, Besançon**: Laurent, Coquet, Drobacheff, Bettinger, Della-Negra, Essert, Mandy, Thalamy; **Hopital Jean Minjoz, Besançon**: Dupond, Vuitton, Coquet, Bettinger, Dessard-Choupay, Essert, Motkly; **Hopital Saint-Louis, Paris**: Clauvel, Oksenhendler, Gerard, Martinie, Mezreb, Sereni, Lascoux-Combe, Pintado, Prevoteau de Clary, Taulera, Molina, Balkan, Bani-Sadr, Colin de Verdiere, Fournier, Garrait, Hocqueloux, Kouchner, Loze, Ponscarme, Schnell, Tourneur, Palmer, Madelaine; **Centre Hospitalier d'Annecy, Annecy**: Bru, Gaillat, Bensalem, Charvier, Michon, Walter, Chanzy, Dervieux; **Hopital de Bicetre, Le Kremlin-Bicetre**: Delfraissy, Goujard, Nguyen Wartel, Quertainmont, Rannou, Rousseau, Segeral, Idri, Bocquentin; **Hopital Henri Duffaut, Avignon**: Lepeu, Assadourian, Martin, Tran-Quang; **Centre Hospitalier General, Aix-en-Provence**: Allegre, Blanc, Marquiant, Lagier, Langlade; **Hopital Chalucet, Toulon**: Lafeuillade, Chadapaud, Hittiger, Jolly, Lambry, Philip, Poggi, Juan; **Hopital Raymond Poincare, Garches**: Perronne, Bani-Sadr, Bernard, Berthe, De Truchis, Melchior, Saint-Louvent, Mathez, Paillet, Villard; **Hopital Necker, Paris**: Dupont, Lahoulou, Ngo, Broissand, Coriol, Vieville; **Hopital Tenon, Paris**: Rozenbaum, Baakili, Courtial-Destembert, Pialoux, Zatla, Chambost, Descamps, Guessant, Saufnai; **Hopital Antoine Beclere, Clamart**: Galanaud, Boue, Delavalle, Pignon, Cointe, Montes; **Hopital Bichat, Paris**: Regnier, Fournier, Gaudebout, Yeni, Hadjoudj, Benabdelmoumen, Meridda, Mandet, Vilde, Leport, Charlois, Gerbe, Pourteau, Railamazava, Chams-Harvey, Piquet; **Hopital Foch, Suresnes**: Bletry, Bouvier, Majerholc, Zucman, Honderlick, Hannachi; **Hopital Louis Mourier, Colombes**: Vinceneux, Bloch, Cordonnier, Lafon, Mortier, Simonpoli, Gaba, Pons-Kerjean, Taleb; **Hopital Henri-Mondor, Creteil**: Sobel, Brahimi, Godard, Houhou, Jung, Lascaux, Lesprit, Levy, Magnier, Poirier, Bouvier-Alias, Hamadas-Chang; **Hopital Pitie-Salpetriere, Paris**: Bricaire, Katlama, Gohsn, Schneider, Schoen, Amellal, Fievet, Guhel, Herson, Amirat, Bonmarchand, Brancon, Capitaine, Simon-Coutellier, Calvez, Malliti; **Hopital Saint-Antoine, Paris**: Girard, Meyohas, Berriot, Besse, Bollens, Fonquernie, Gaujour, Imbert, Picard, Charrois, Morand-Joubert, Daguenel-Nguyen; **Hopital Pierre Zobda-Quitman, Fort-de-France**: Sobesky, Abel, Beaujolais, Cabie, Dupin de Majoubert, Ducart, Lamaigniere; **Hopital de la Cavale Blanche, Brest**: Garre, Derrien, Legrand-Quillien, Lorillon; **Hopital Saint-Andre, Bordeaux**: Beylot, Lacoste, Bernard, Bonarek, Bonnet, Morlat, Garrigue, Pedeboscq; **Hopital Pellegrin, Bordeaux**: Ragnaud, Neau, Raymond, Garrigue, Dupin; **Hopital Edouard Herriot, Lyon**: Touraine, Berra, Brunel, Chiarello, Jeanblanc, Jourdain, Livrozet, Makhloufi, Tardy, Nageotte; **Hopital Hotel-Dieu , Lyon**: Trepo, Bailly, Benmakhlouf, Brochier, Cotte, Gueripel, Miailhes, Radenne, Rougier, Schlienger, Ritter, Trabaud, Bataillard; **Hopital Saint-Marguerite, Marseille**: Gastaut, Dinh, Drogoul, Fabre, Frixon-Marin, Poizot-Martin, Anglade, Tamalet, Bertault-Peres, Rigault; **Centre Hospitalier General, Meaux**: Allard, Pastor, Mabiala, Perrot; **Hopital Gui de Chauliac, Montpellier**: Janbon, Reynes, Baillat, Merle de Boever, Vidal, Montes, Floutard; **Hopital de l'Hotel-Dieu, Nantes**: Raffi, Allavena, Billaud, Bonnet, Brunet-François, Huart, Milpied, Reliquet, Sicot, Poirier, Lepelletier; **Hopital de l'Archet, Nice**: Dellamonica, Rahelinirina, Cassuto, Ceppi, Rozenthal, Benhamou, Achach, Rigault, Ruitort; **Hopital Bretonneau, Tours**: Choutet, Besnier, Didier, Nau, Barin, Rouleau; **Hopital Purpan, Toulouse**: Massip, Cuzin, Obadia, Izopet, Ane; **Centre Hospitalo-Universitaire de Caen, Caen**: Bazin, Dargere, Feret, Six, Verdon, Vabret, Chedru-Le Gros; **Hopital Hotel-Dieu, Clermont-Ferrand**: Beytout, Baud, Dydymski, Gourdon, Jacomet, Laurichesse, Henquell, Coudert; **Hopital du Bocage, Dijon**: Chavanet, Portier, Buisson, Duong, Grappin, Piroth, Bour, Alison; **Hopital Albert Michallon, Grenoble**: Brambilla, Leclercq, Gailland, Trapo, Morand, Schmuck, Boitard, Paris; **Hopital Gustrave Dron, Tourcoing**: Mouton, Cheret, Yasdanpanah, Bocket-Mouton, Dubar, Marrant; **Hopital de Brabois, Vandoeuvre-Les-Nancy**: Boyer, May, Finance, Georget, Perrin; **Centre Hospitalier de Compiegne, Compiegne**: Veyssier, Merrien, Darchis, Dagrenat, Liebbe; **Hopital Fleyriat, Bourg-En-Bresse**: Granier, Laurent, De Montclos, Rieu; **Centre Hospitalier Sud Reunion , Saint-Pierre-La-Reunion**: Arvin-Berod, Poubeau, Simac, Istria; **Hopital Beaujon, Clichy**: Fantin, Belmatoug, Landgraff, Lefort, Uludag, Zarrouk, Chams-Harvey, Bouton, Laribe; **Hopital Porte Madeleine, Orleans**: Arsac, Barthez, Hermeulin; **Hopital La Croix-Saint-Simon, Paris**: Raguin, Klein, Seguret; **Fondation Saint-Joseph, Paris**: Gilquin, Brecquevielle, Cros, Jaquin, Nguyen Van, Tersen; **Centre Hospitalier de Noyon , Noyon**: Grihon, Darchis, Teche; **Hopital Rene Dubos, Pontoise**: Blum, Danne, Blanchard, Chambraud.

Conclusion

The substitution of a PI-based regimen by a simple and convenient once-daily combination of emtricitabine, didanosine and efavirenz maintained a good suppression of plasma HIV-1 RNA levels and continued increases in lymphocytes CD4+ cell counts for 3 years without worsening of lipodystrophy or metabolic abnormalities.