

Intensification of HAART through the Addition of Enfuvirtide (ENF) in Naive HIV-infected Patients with Severe Immunosuppression Does Not Improve Immunological Response: Results of a Prospective Randomised Multicenter Trial (APOLLO – ANRS 130)

Véronique JOLY ¹, Catherine FAGARD ², Diane DESCAMPS ¹, Nathalie COLIN de VERDIERE ³, François RAFFI ⁴, Sophie TABUTEAU ², André CABIE ⁵, Michelle BENTATA ⁶, Patrick YENI ¹, Geneviève CHENE ² and the ANRS 130 APOLLO Trial Group

¹ Univ Hosp Bichat, Paris ; ² INSERM U897, Bordeaux ; ³ Univ Hosp St Louis, Paris, ⁴ Univ Hosp Hôtel Dieu, Nantes, ⁵ Pierre Zobda Quitman Hosp, Fort de France, ⁶ Univ Hosp Avicenne, Bobigny

BACKGROUND and OBJECTIVES

The proportion of patients with a CD4 cell count below 200/mm³ at time of HIV diagnosis remains high, reaching 30% in some cohorts.

Different studies have shown that there is an increased risk of clinical progression and death in patients with poor CD4 response after 6 months of HAART, including in patients with discordant CD4 and HIV RNA responses.

Increase immune reconstitution through intensification of initial antiretroviral therapy may reduce the risk of early clinical complications of HIV disease.

We studied whether intensification of HAART through addition of enfuvirtide (ENF) to a background HAART would improve the CD4 cell count response at Wk 24 in naive, severely immunosuppressed HIV-1 infected patients.

METHODS

Study design : multicentric, nation-wide, open-label randomised controlled trial.

Eligibility criteria : age ≥18, written informed consent, naive HIV-1 infected patients, either asymptomatic with CD4 <100mm³ or with past or present history of stage B or C HIV disease and CD4 <200mm³.

Treatment : patients were randomized into 2 groups :

-**Control group** : background regimen of tenofovir-emtricitabine and lopinavir/ritonavir (LPV/r) or efavirenz (EFV);

-**Enfuvirtide (ENF) group**: background regimen of tenofovir-emtricitabine and lopinavir/ritonavir (LPV/r) or efavirenz (EFV) plus ENF for the first 6 months of antiretroviral therapy.

Randomization was stratified on clinical stage and background antiretroviral regimen (LPV/r or EFV).

Primary outcome measure : proportion of patients with a CD4 count ≥ 200/mm³ at Wk 24.

Secondary outcome measures : change in plasma HIV-1 RNA levels and CD4 counts, proportion of patients with a CD4 count ≥200/mm³ at Wk 48, proportion of patients with HIV-1 RNA <50cps/ml at Wk24 and 48, clinical HIV related events, tolerance, proportion of patients who interrupted the therapeutic strategy allocated by randomization (ENF or not).

Analysis : Intent to treat (missing=failure); proportions compared using chi-square; medians compared using Mann-Whitney/Wilcoxon test.

PARTICIPATING CENTERS

Saint Jean hospital, Perpignan: H. Aumaitre, M. Medus, S. Neuville, M. Saada; **Avicenne hospital, Bobigny**: S. Abgrall, M. Bentata, O. Bouchaud, J. Cailhol, H. Cordel, R. Dhote, H. Gros, P. Honoré-Berlureau, T. Huynh, A. Krivitzky, R. Mansouri, M. Poupard, V. Prendki, D. Radia, F. Rouges, F. Touam, B. Warde; **Saint Louis hospital, Paris**: N. de Castro, N. Colin de Verdière, J. Delgado, S. Ferrer, S. Gallien, T. Kandel, M. Lafaurie, M. Lagrange, C. Lascoux-Combe, D. Le, J.M. Molina, J. Pavie, C. Pintado, D. Ponscarne, A. Rachline, W. Rozenbaum, D. Sereni, O. Taulera; **Saint Jacques hospital, Besançon**: J.M. Estavoyer, J.F. Faucher, A. Foltzer, B. Hoen, L. Hustache-Mathieu; **Pellegrin hospital, Bordeaux**: M. Dupon, H. Duron, C. Neau, J.M. Ragnaud, I. Raymond; **Necker hospital, Paris**: S. Boucuy, O. Loholary, J.P. Viard; **Bicêtre hospital, Le Kremlin Bicêtre**: C. Bechara, J.F. Deltraissay, J. Ghosn, C. Goujard, W. Kamoun, M. Môle, Y. Quertainmont; **Lariboisière hospital, Paris**: J.F. Bergmann, E. Boulanger, H. Castillo, M. Parruelo, A. Rami, P. Sellier; **Henri Duffaut hospital, Avignon**: G. Lapeau, G. Pichancourt; **Raymond Poincaré hospital, Garches**: L. Bernard, H. Berthé, J. Clarissou, M. Gory, J.C. Melchior, C. Perronne, S. Siegman, P. de Truchis; **Paul Brousse hospital, Villejuif**: O. Deradji, M. Malet, E. Teicher, D. Vittecoq; **Tenon hospital, Paris**: C. Chakvetadze, C. Fontaine, T. Lukiani, G. Pielloux, L. Sliama; **Bichat Claude-Bernard hospital, Paris**: D. Bonnet, S. Boucherit, N. El Alami Tabi, I. Fournier, A. Gervais, V. Joly, L. Jordaiche, J.J. Laurichesse, C. Loport, G. Pahlavan, B.C. Phung, P. Yeni; **Cochin hospital, Paris**: N. Bonnamy, A. Brunet, L. Guillevin, D. Salmon-Ceron, T. Tahi; **Henri Mondor hospital, Créteil**: C. Chesnel, S. Dominguez, P. Jouve, J. D. Lelièvre, Y. Levy, G. Melica, A. Sobel; **Pitié Salpêtrière hospital, Paris**: S. Ben Abdallah, M. Bonmarchand, F. Bricaire, S. Herson, M. Igertsira, C. Kallama, H. Kouadio, L. Schneider, A. Simon, M.A. Valantin; **Pierre Zobda Quitman hospital, Fort de France**: S. Abel, V. Beaujolais, A. Cabié, B. Liauthaud, S. Pierre François; **CHU Angers**: P. Abgueuen, J.M. Chennebault, J. Loison, E. Pichard, V. Rabier; **Saint André hospital, Bordeaux**: J. Delaune, I. Louis, P. Morlat, M.C. Pertusa; **Edouard Herriot hospital, Lyon**: F. Brunel-Delmas, P. Chiarello, F. Jeanblanc, J.J. Jourdain, J.M. Livrozet, D. Makhoul, J.L. Touraine; **Hôtel Dieu hospital, Lyon**: C. Augustin-Normand, F. Bailly, N. Benmakhlouf, C. Brochier, L. Cotte, V. Guerpel, K. Koffi, P. Lack, B. Lebouché, M. Maynard, P. Mialhes, S. Radenne, I. Schlienger, V. Thoirain, C. Trepo; **Sainte Marguerite hospital, Marseille**: M.P. Droguol, G. Fabre, O. Faucher, V. Frixon-Marín, J.A. Gastaut, E. Peyrouse, I. Poizat-Martin; **Gui de Chauliac hospital, Montpellier**: G. Le Facher, C. Merle de Boever, J. Reynes, C. Tramon; **Hôtel Dieu hospital, Nantes**: C. Allavena, E. Billaud, C. Biron, B. Bonnet, S. Bouchez, D. Boutolle, C. Brunet-François, H. Hùe, O. Mounoury, F. Raffi, V. Reliquet; **Les Oudairies CHD, La Roche sur Yon**: O. Aubry, J.L. Esnault, S. Leautez-Nainville, P. Perré, I. Snaud; **Archevêque hospital, Nice**: S. Bréaud, C. Ceppi, P. Dellamonica, F. De Salvador, J. Durant, S. Ferrando, J.G. Fuzibet, A. Leplatois, V. Mondain, I. Perbost, P. Pugliese, V. Rahelinirina, E. Rosenthal, F. Sanderson, M. Vassalo; **Pontchaillou hospital, Rennes**: C. Arvieux, J.M. Chapplain, C. Michelet, M. Ratajczak, M. Revest, F. Souala, P. Tattevin; **Civil hospital, Strasbourg**: C. Chéneau, P. Fischer, J.M. Lang, M. Partisani, D. Rey; **Bretonneau hospital, Strasbourg**: F. Bastides, J.M. Besnier, P. Le Bret, P. Choutet, J.F. Dailoux, P. Guadagnin, P. Nau, J. Rivalain, A. Soufflet; **Gustave Dron hospital, Tourcoing**: E. Aïssi, H. Melliez, S. Pavel, Y. Yazdanpanah; **De Brabois hospital, Nancy**: L. Boyer, C. Burty, L. Letranchant, T. May, S. Wassoumbou; **René Dubos hospital, Pontoise**: L. Blum, O. Danne; **Aubenas hospital, Aubenas**: M.A. Arthus, P. Dion;

RESULTS

From April 2006 to December 2008, 195 patients were randomized : 101 in ENF group and 94 in the control group. 194 patients were included in the analysis, since one patient randomized in the ENF group was excluded. (Figure 1).

At study entry, 140 patients (72%) had advanced HIV disease including 92 patients (47%) with an active AIDS event at time of randomisation (Table I).

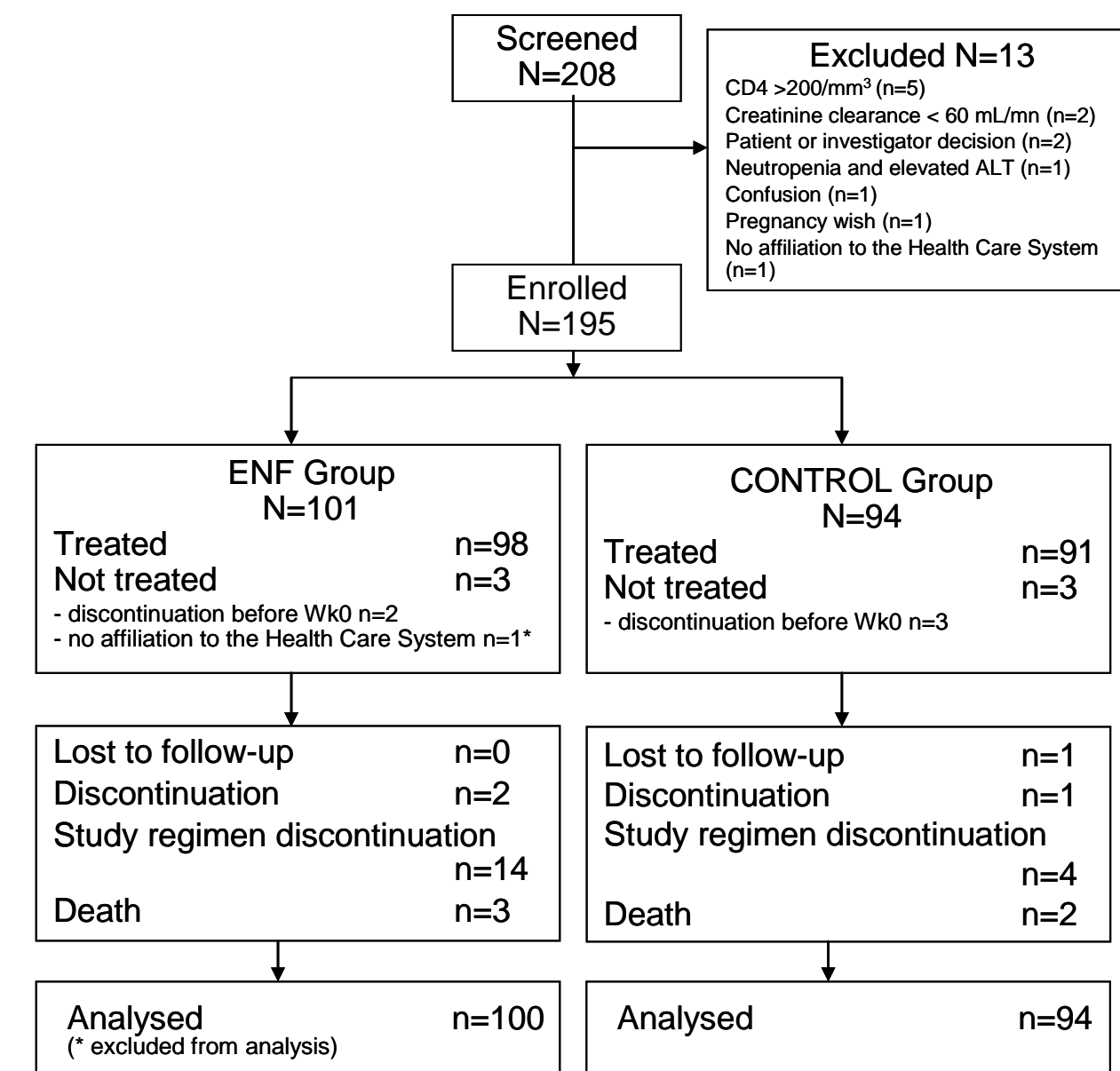


Figure 1 : Trial profile of ANRS 130 APOLLO trial

Among 14 patients who interrupted study regimen in ENFgroup, 10 patients stopped ENF for poor convenience or local discomfort.

Table 1 : Baseline characteristics in the ANRS 130 APOLLO trial

	ENF Group (n=100)	Control Group (n=94)	Total (n=194)
Age (yr) (median, IQR)	44 [39-49]	41 [35-49]	43 [37-45]
Female sex (%)	26	18	22
Stage C HIV disease (n, %)	73 (73)	67 (71)	140 (72)
Active AIDS event at Wk0 (n, %)	46 (46)	46 (49)	92 (47)
Baseline CD4 cell count/mm ³ (median, IQR)	34 [13-70]	27 [10-88]	30 [12-72]
Delay from 1st HIV diagnosis (months) (median, IQR)	1.4 [0.9-2.9]	1.4 [0.9-2.9]	1.4 [0.9-2.9]
HIV-1 RNA in log ₁₀ copies/ml (median, IQR)	5.4 [5.0-5.8]	5.4 [5.0-5.8]	5.4 [5.0-5.8]
Backbone treatment			
- Lopinavir (n, %)	79 (79)	77 (82)	156 (80)
- Efavirenz (n, %)	21 (21)	17 (18)	38 (20)

CD4 count : 34 patients (34%) in the ENF group and 36 patients (38%) in the control group reached the primary outcome of CD4 ≥ 200/mm³ at Wk 24 (p=0.53).

The median increase in CD4 cell count at Wk 24 was 113 [70-171] cells/mm³ in the ENF group versus 129 [78-197] cells/mm³ in the control group (P=0.29). The median value of CD4 cell count at week 24 was 145 [103-242] cells/mm³ in the ENF group versus 175 [116-268] cells/mm³ in the control group (P=0.19). CD4 trends from Wk 0 to Wk 48 according to randomisation group are presented on Figure 2.

HIV-1 RNA : 66 patients (73%) in the ENF group and 50 patients (58%) in the control group had a plasma HIV-1 RNA level below 50 cps/ml at Wk 24 (p =0.041). Trends in the proportion of patients with plasma HIV-1 RNA level below 50 cps/ml from Wk 0 to Wk 48 according to randomisation group are presented in Figure 3.

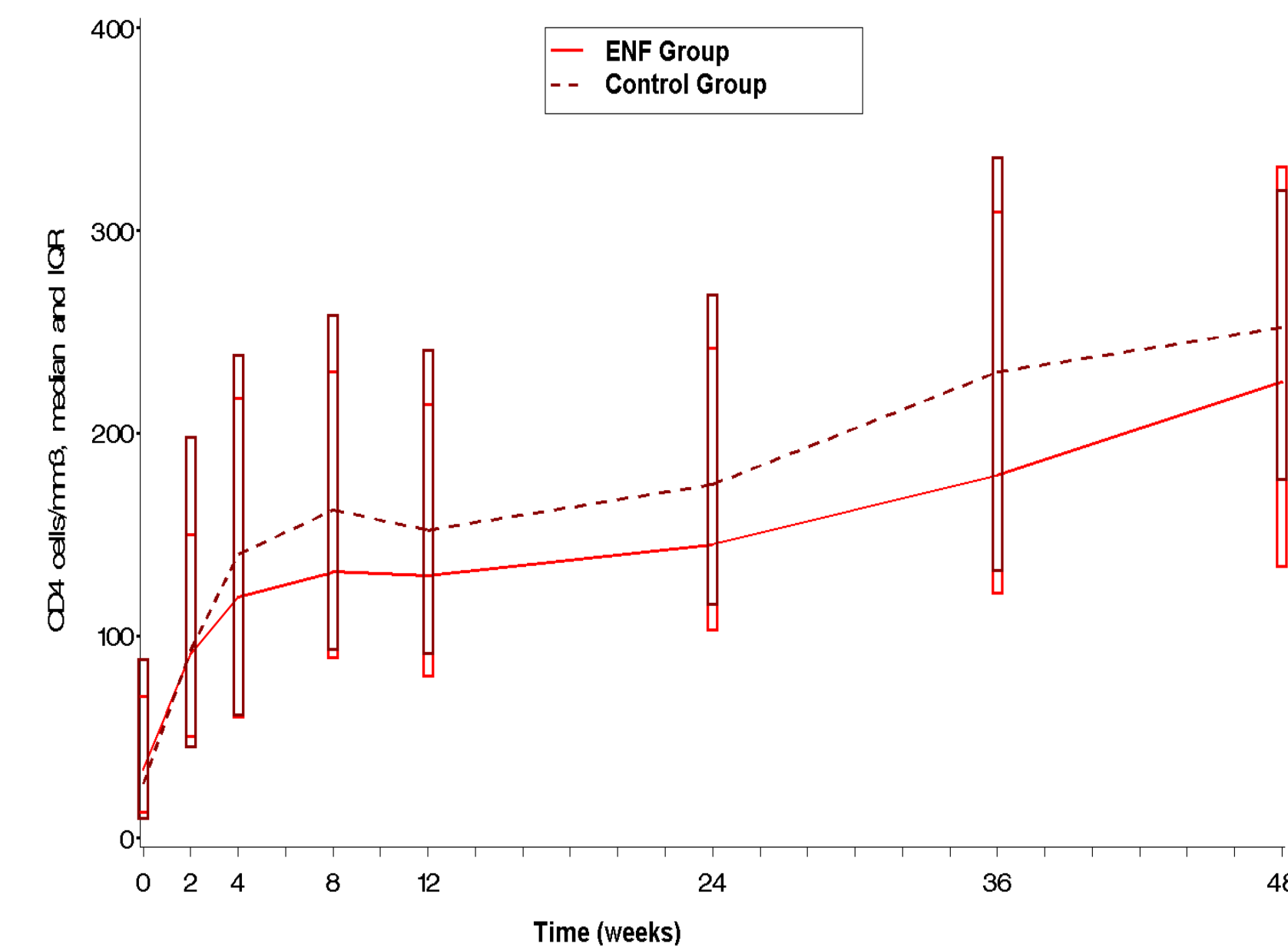


Figure 2 : Trends in CD4 count according to randomisation group, ANRS 130 APOLLO trial

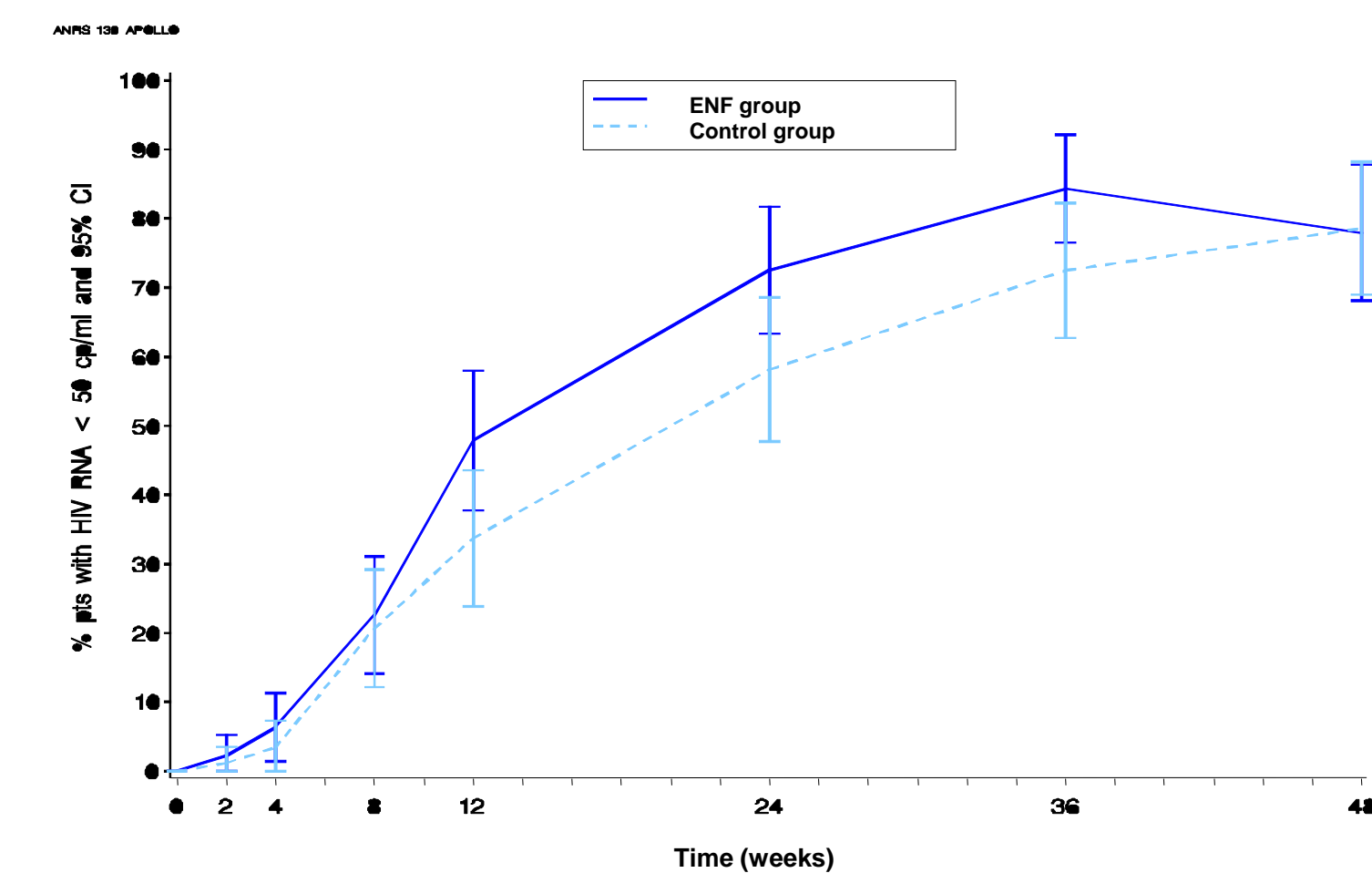


Figure 3 : Proportion of patients with HIV-1 RNA <50 cps/ml, ANRS 130 APOLLO trial

ACKNOWLEDGMENTS

We thank all the patients who participated in the study.

We thank Roche which provided enfuvirtide and Gilead which provided tenofovir-emtricitabine.

We thank members of the Data and Safety Monitoring Board (ML. Chaix, P. Flandre and P. Galanaud) and professionals of the INSERM U897/ANRS Clinical Trials Unit (A. Beuscart, and C. Wallet who monitored the study and C. Grondin who performed statistical analysis).



AIDS events and safety : 16 (16%) patients in ENF group and 13 (14%) in the control group presented AIDS-defining events (p=0.67). Grade 3 or 4 clinical adverse events occurred in 33 (33%) patients of the ENF group and in 39 (42%) patients of the control group (p=0.2).

Table 2 : Clinical adverse events in the ANRS 130 APOLLO trial

ADVERSE EVENT (AE)	ENF Group	Control Group	Total
At least one grade 3/4 AE, n patients (%)	33 (33%)	39 (42%)	72 (37%)
At least one stage C event, n patients (%)	16 (16%)	13 (14%)	29 (15%)
Stage C events, n events	22	18	40
Mycobacterial infection	6	4	10
Oesophageal candidiasis	3	5	8
CMV infection	4	1	5
Kaposi sarcoma	4	0	4
Cryptococcosis, cryptosporidiasis	3	0	3
HIV encephalitis	0	2	2
PML	0	2	2
Recurrent pneumonia	0	2	2
Lymphoma	1	0	1
Pneumocystis pneumonia	0	1	1
Salmonella	0	1	1
Cachexia	1	0	1

CONCLUSION

In this trial, conducted in naive, severely immunocompromised patients, the addition of ENF to standard HAART did not improve CD4 cell response at Wk 24, although enhancing the proportion of patients with HIV-1 RNA below 50 cps/ml.

Tolerance and clinical progression were similar in the two groups. Although patients had an advanced HIV disease, ENF was well accepted; 10% of patients interrupted ENF for bad tolerance or poor convenience.

The improved virological response in the ENF group suggested that the lack of enhanced CD4 response did not result from impaired adherence to antiretroviral therapy in this group.

Whether the addition of ENF to standard HAART could influence the emergence of resistant virus and HIV tropism is under investigation.

These results cannot be extrapolated to other class of antiretroviral drugs, such as integrase inhibitors or CCR5 inhibitors. Whether the addition of these compounds to HAART would be beneficial to improve the immune restoration warrants additional investigations.