P0528

Efavirenz- versus two ritonavir-boosted protease inhibitor-based regimens in HIV-1-infected patients with advanced disease: 96-week results of a randomized trial (Advanz-3 Trial)

Christian Manzardo(1), Alberto C. Guardo(2), Elena Ferrer(3), Montserrat Loncà(1), Daniel Podzamczer (3), Pere Domingo (4), Adria Curran (5), Bonaventura Clotet (6), Anna Cruceta(1), Francisco Lozano(1), Iñaki Pérez (1), Montserrat Plana (2), J.M. Gatell (1), Jose M. Miro(1) and the Advanz-3 Study Group

1.Infectious Diseases Service, Hospital Clínic-IDIBAPS, Barcelona 2.Retrovirology and Viral Immunopathology Laboratory, AIDS Research Unit, IDIBAPS, Hospital Clínic, University of Barcelona, Barcelona, Spain 3. Hospital Bellvitge-IDIBELL, University of Barcelona, Barcelona 3.Hospital Bellvitge-IDIBELL, University of Barcelona, Barcelona 4.Hospital de Sant Pau, Universitat Autònoma de Barcelona, Barcelona 5 Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona
6 Hospital Germans Trias i Pujols, Irsicaixa, Universitat Autònoma de Barcelona, UVic, Badalona, Spain

Jose M. Miro
jmmiro@ub.edu

Christian Manzardo
cmanzard@clinic.ub.es

25th ECCMID Copenhagen, Denmark 25–28 April 2015

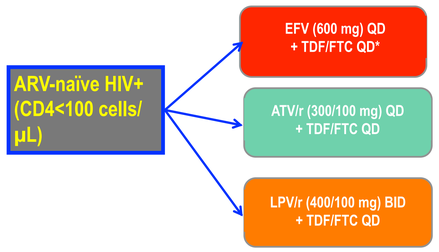
Abstract

Background: Few randomized clinical trials have investigated antiretroviral regimens in very advanced HIV-1-infected patients and few data are available on mid-term immune reconstitution in individuals with advanced disease. The objective was to study the immune reconstitution in very immunosuppressed antiretroviral-naïve, HIV-1-infected individuals by comparing an efavirenz-based regimen with 2 ritonavir-boosted protease inhibitor regimens.
Methods: Randomized, controlled, open-label multicenter clinical trial. Eighty-nine HIV-1–infected antiretroviral-naïve patients with <100 CD4 cells/mm3 were randomly assigned in a 1:1:1 ratio to efavirenz (n=29), atazanavir/ritonavir (n=30), or lopinavir/ritonavir (n=30) combined with tenofovir/emtricitabine. The primary outcome was median increase in CD4 cell count at week 48. Secondary endpoints included: virological suppression, qualitative immune recovery, safety, disease progression, and death through 96 weeks.
Results: In the on-treatment (OT) analysis, the median (interquartile range) increase in the CD4 count after 96 weeks was +284 (175-430) cells/mm3 in the efavirenz arm, +295 (221-444) cells/μL in the atazanavir/ritonavir arm, and +345 (227-437) cells/μL in the lopinavir/ritonavir (*P*=0.60). The percentage of patients achieving viral suppression by the intention-to-treat (ITT) and OT analyses were similar in all 3 treatment arms at 96 weeks (ITT: 75%, 60% and 58.6% -p=0.38- OT:100%, 100%, 90% -p=0.32- for the efavirenz, azanavir/ritonavir and lopinavir/ritonavir arm, respectively). Adverse events had a similar incidence in all 3 antiretroviral regimens. No patients died.
Conclusions: After 96 weeks of effective antiretroviral treatment, the immune reconstitution induced by an efavirenz-based regimen in advanced HIV-1-infected patients was similar to that induced by a ritonavir-boosted protease inhibitor–based regimen (ClinicalTrials.gov registration number: NCT00532168**).**

Background

Few randomized clinical trials have investigated antiretroviral regimens in very **advanced HIV-1-infected** patients and few data are available on mid-term **immune reconstitution** in individuals with advanced disease. The objective was to study the immune reconstitution in very immunosuppressed antiretroviral-naïve, HIV-1-infected individuals by comparing an efavirenz-based regimen with 2 ritonavir-boosted protease inhibitor regimens.

Study Design



Primary Outcome

- **Median increase in the number of CD4+ T-cells at 48 weeks in the 3 arms** (secondary analysis at week 96)

Secondary outcomes

- **Proportion of patients with a plasma HIV-1 viral load <50 copies/mL**
- **Incidence of side effects (including IRIS)**
- **Disease progression and death**
- **Changes in markers of immune activation and senescence, apoptosis, inflammation, bacterial translocation, and coagulation.**

Results

Figure 1. Study Flow diagram

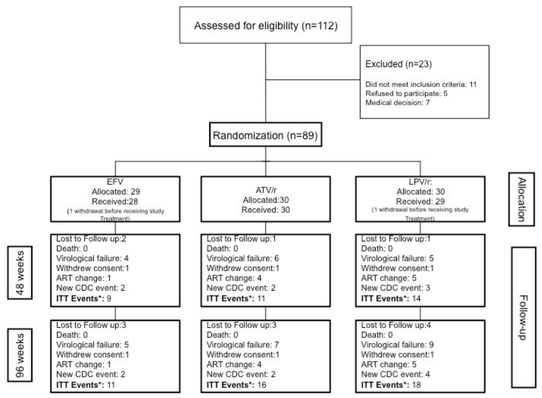


Table 1. Baseline characteristics

Characteristics	EFV (n=29)	ATV/r (n=30)	LPV/r (n=30)	All (n=89)
Age, y; median (range)	39 (25-68)	38.5 (22-55)	36.5 (26-69)	38 (22-69)
Male n (%)	21 (72.4)	27 (90)	25 (83.3)	73 (82)
Risk group, n (%)				
MSM	12 (41.4)	14 (46.7)	14 (46.7)	40 (44.9)
Heterosexual	13 (44.8)	13 (43.3)	11 (36.6)	37 (41.6)
IVDU	1 (3.5)	1 (3.3)	0 (0)	2 (2.3)
Other/Unknown	2 (7)	2 (7)	4 (13.3)	8 (9)
Origin, n (%)				
Spain/Western Europe	21 (72.4)	20 (66.7)	17 (56.7)	58 (65)
Latin America	5 (17.2)	8 (26.7)	11 (36.7)	24 (27)
Other	3 (10.3)	2 (7)	2 (6.7)	7 (7.8)
CDC category C at baseline, n (%)	12 (41)	17 (57)	13 (44)	42 (47)
PCP	8	12	8	28
Cerebral toxoplasmosis	-	2	2	4
Esophageal candidiasis	2	-	1	3
Extrapulmonary cryptococcosis	-	1	1	2
Extrapulmonary/disseminated TB	-	2	-	2
CMV disease	2	-	1	3
PML	-	1	-	1
Kaposi sarcoma	-	1	2	3
Isospora belli chronic diarrhea	1	-	-	1
CD4 cell count, median (IQR)	41 (25-66)	32 (21-59)	30 (18-53)	32 (20-59)
Plasma viral load (log10/mL), median (IQR)	5.12 (4.77-5.55)	5.48 (5.0-5.81)	5.15 (4.77-5.61)	5.27 (4.8-5.7)
HBsAg, n (%)	1 (3.6)	4 (13.3)	1 (3.5)	6 (6.9)
HCV+, n (%)	1 (3.6)	7 (23.3)	3 (10.3)	11 (12.6)
Glucose (mg/dL), median (IQR)	86 (78-100)	89 (83-98)	88(81-96)	88 (81-97)
Total plasma cholesterol (mg/dL), median (IQR)	163 (134-190)	163 (137-208)	158 (132-183)	163 (134-191)
HDL cholesterol (mg/dL), median (IQR)	38 (28-45)	40 (29-50)	36 (32-46)	36 (29-46)
Triglycerides (mg/dL), median (IQR)	142 (90-231)	148 (106-204)	163 (114-225)	153.5 (106-225)

Figure 2. (A) Median increase in CD4 + T-cell count according to the OT analysis; (B) Percentage of patients with CD4+ T-cell count >200/mm^3 according to the on-treatment analysis; Percentage of patients with a virological response (plasma HIV-1 RNA <50 copies/ mL) by the intention-to-treat (C) and on-treatment (D) analyses.

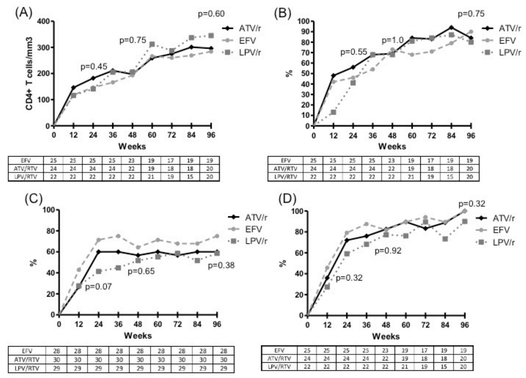


Figure 3. Inflammation, Immune Activation, Senescence and Bacterial Translocation selected markers

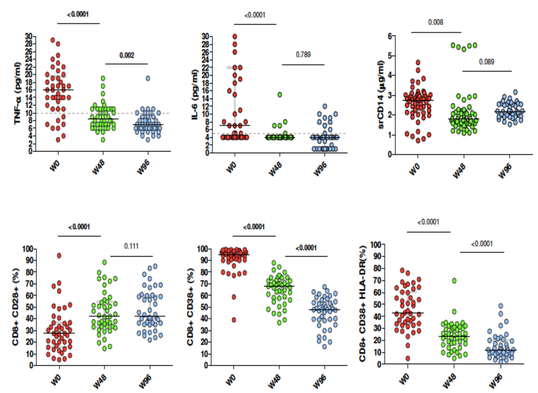


Table 2. Adverse events

	EFV (n=28)	ATV/r (n=30)	LPV/r (n=29)
Any adverse event*, n (%)	27 (96)	22 (73)	24 (83)
Related adverse event*, n (%)	16 (57)	11 (37)	16 (55)
Grade 3/4 adverse event*, n (%)	4 (14)	6 (20)	7 (24)
Severe adverse event*, n (%)	2 (7)	6 (20)	8 (28)
Adverse events leading to study drug discontinuation	1 (4)	3 (10)	5 (17)
Skin rash	1	-	-
Hyperbilirubinemia	-	2	-
GI events	-	1	2
TB	-	-	2
Toxic hepatitis	-	-	1
Grade 3/4 clinical adverse events*,[a]	3 (11)	4 (13)	3 (10)
Systemic	1	1	2
GI events	-	1	-
Respiratory	-	-	1
Urogenital	1	-	1
Skin	1	-	-
CNS	-	2	-
Grade 3/4 laboratory adverse events	1	4	3
Hyperbilirrubinemia	-	3	-
Elevated creatine kinase	-	-	1
Elevated transaminases	1	1	2
New C events, n (%)	2 (7)	2 (7)	4 (14)
Kaposi sarcoma	1	-	-
Pulmonary/Disseminated TB	-	1	2
Cervical cancer	1	-	1 §
PML	-	1	1
IRIS¶, n (%)	3 (11)	4 (13)	4 (14)
Kaposi sarcoma	1 (P)		
Pulmonary/Disseminated TB			2 (U,U)
PCP		1(P)	
Bacterial pneumonia			1 (P)
Toxoplasmosis	1 (P)		
VZV		1 (U)	
Molluscum contagiosum	1 (P)		
PML		2 (U,P)	1 (P)

Abbreviations: ATV/r, atazanavir/ritonavir; CNS, central nervous system; EFV, efavirenz; GI, gastro-intestinal; LPV/r, lopinavir/ritonavir; P, paradoxycal IRIS; PML, progressive multifocal leukoencephalopathy;
TB, tuberculosis; U, unmasking IRIS.
* Patients with at least one event.
[a] Excluding new CDC category C
§ Only this new CDC category C event occurred after week 48.
¶ All cases of IRIS occurred during first 48 weeks.

Conclusions

- Our study confirms previous data on the use of an NNRTI-based regimen in very advanced HIV-1–infected patients and give further data on laboratory and clinical evolution of advanced patients through 2 years of cART.
- This study confirms that efavirenz-based treatments can be used reliably in HIV-1–infected patients with very low CD4 T-cell counts and high plasma HIV-1 RNA levels, at least in those who are expected to have good adherence and do not present transmitted mutations.
- No significant differences in the decreased levels of markers of inflammation, coagulation, and bacterial translocation were observed between the treatment arms.
- Further controlled data are needed for other first-line regimens such as those comprising other boosted PIs such as darunavir or integrase inhibitors in patients with very advanced HIV-1 infection.

The trial was supported in part by the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Madrid (Spain), and Spanish Network for AIDS Research (RIS; ISCIII-RETIC RD06/006).