

# Phase I/II Randomized Study: Therapeutic Dendritic Cell Vaccine Plus Pegylated $\text{INF-}\alpha$

Lorna Leal<sup>1</sup>, Elvira Couto<sup>1</sup>, Yolanda Romero<sup>1</sup>, Laia Miralles<sup>2</sup>, Tania González<sup>2</sup>, M. José Maleno<sup>2</sup>, Blanca Paño<sup>3</sup>, Judit Pich<sup>1</sup>, Núria Climent<sup>2</sup>, Sonsoles Sánchez-Palmino<sup>2</sup>, Carlos Nicolau<sup>3</sup>, José M. Gatell<sup>4</sup>, Felipe García<sup>1</sup>, **Montserrat Plana**<sup>2</sup>, for the DCV-3/RISVAC04 Study Group

<sup>1</sup>Infectious Diseases Department, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) - HIVACAT, University of Barcelona, Barcelona, Spain; <sup>2</sup>Retrovirology and Immunopathology Laboratory, AIDS Research Group, IDIBAPS - HIVACAT, Hospital Clinic de Barcelona, Barcelona, Spain; <sup>3</sup>Radiology Department, Hospital Clinic, Barcelona, Spain; <sup>4</sup>ViV Healthcare, Barcelona, Spain.

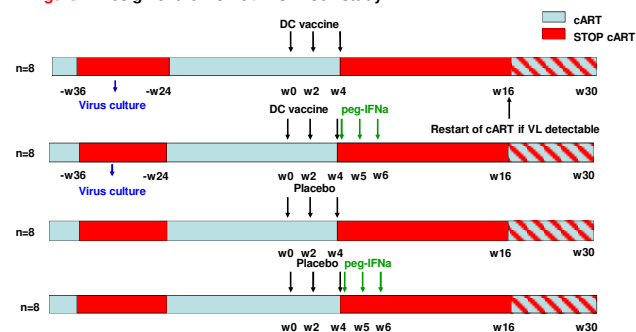
## Introduction and Objectives

A double-blind placebo-controlled randomized therapeutic vaccine trial with myeloid derived-dendritic cells (MD-DC) loaded with heat-inactivated autologous HIV-1 (HIAH) plus pegylated Interferon-alpha (pIFN) in HIV-1 chronic infected patients on antiretroviral treatment (ART) to achieve functional cure was performed. Clinical trial.gov EudraCT 2015-0011795-22.

## Material and Methods

36 patients on successful ART with  $\text{CD4}^+ \geq 450$  cells/ $\text{mm}^3$  were randomized 1:1:1:1 and 29 received at w0, 2 and 4 an ultrasound-guided inguinal intranodal dose of: 1) vaccine (V)  $10^7$  MD-DC pulsed with  $10^{10}$  HIAH (n=8); 2) V plus 3 doses of pIFN (VpIFN) at w4, 5 and 6 (n=6); 3) placebo (P) (n=7); and 4) P plus 3 doses of pIFN (PpIFN) at w4, 5 and 6 (n=8). ART was interrupted (ATI) at week 4 (Figure 1). The primary end-points were safety and proportion of patients with undetectable VL 12w after ATI (w16). Secondary end-points were  $\Delta$ VL set-point (set-point ATI-preART), and  $\Delta$ HIV-1 specific T cell responses (IFN- $\gamma$  ELISPOT) (w16-w0).

**Figure 1: Design of the DCV-3 / RISVAC04 study**



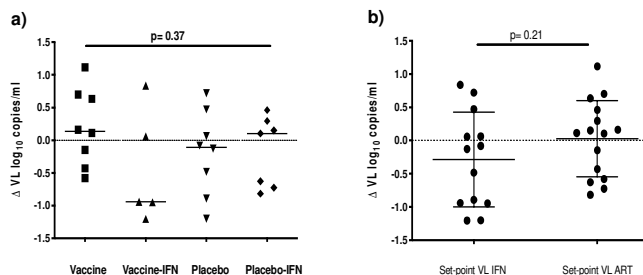
**Table 1: Baseline characteristics of the study participants and CD4 counts evolution**

Variables	All participants n=29 (100%)	Vaccine n= 8	Placebo n=7	Vaccine + IFNpeg n=6	Placebo + IFNpeg n=8
Median age (IQR)	46 (41-50.5)	49 (43-55.5)	47 (42-49)	43 (38.5-48.25)	44.5 (40-50.25)
Male	29 (100%)	8	7	6	8
Men who have sex with men (MSM)	27 (93%)	8	5	6	8
CD4 count (cells/ $\text{mm}^3$ ) at screening (median/IQR)	752 (705-1018)	751 (687-1206)	726 (642-1228)	933 (671-1203)	806 (708-864)
CD4 count (cells/ $\text{mm}^3$ ) after last vaccine - before ATI* (median/IQR)	739 (630-991)	790 (546-1542)	739 (614-1196)	770 (591-929)	721 (656-899)
CD4 count (cells/ $\text{mm}^3$ ) before restart ART* (median/IQR)	697 (488-768)	599 (488-744)	767 (489-816)	505 (459-644)	733 (561-828)

\*ATI: Analytical Treatment Interruption; \*ART: Antiretroviral Treatment

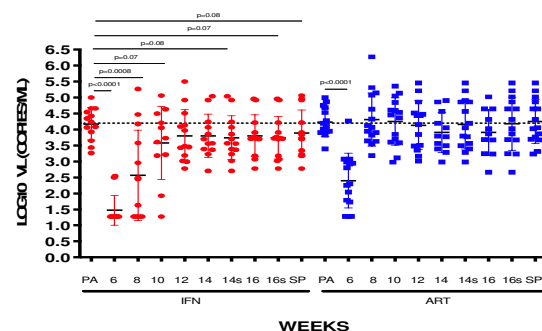
## Results

- All participants were male. The procedure was safe and well tolerated (Table 1). There were no adverse events definitively related to the study products.
- All patients had detectable VL at w16.  $\Delta$ VL set-point [ $\log_{10}$  mean (SE) copies/ml] was: 1) V 0.20 (0.21) 2) VpIFN -0.44 (0.38) 3) P -0.19 (0.23) 4) PpIFN -0.17 (0.20) (p=0.37) (Figure 2).
- A decrease  $>1\log_{10}$  in VL set-point was seen in 0, 3, 1 and 0 patients in V, VpIFN, P and PpIFN, respectively (p=0.05 and p=0.06 for the differences between VpIFN vs V, and VpIFN vs PpIFN, respectively) (Figure 3).
- At baseline, HIV-1 specific T-cell responses were lower in vaccines vs placebo groups [mean (SE) 900 (200) vs 2259 (535) SFC/ $10^6$  PBMC, p=0.028] (Figure 4).
- No significant differences in  $\Delta$ HIV-1 specific T-cell responses were observed between vaccine and placebo groups (p=0.09).
- No effect on T cell responses was observed with pIFN administration (Figure 4).
- A trend to significative negative correlation between  $\Delta$ VL and  $\Delta$ HIV-specific T-cell responses (w16-w0) was observed in vaccine and not in placebo groups (r=-0.56, p=0.09; r=0.28, p=0.43; vaccine and placebo groups, respectively) (Figure 5).

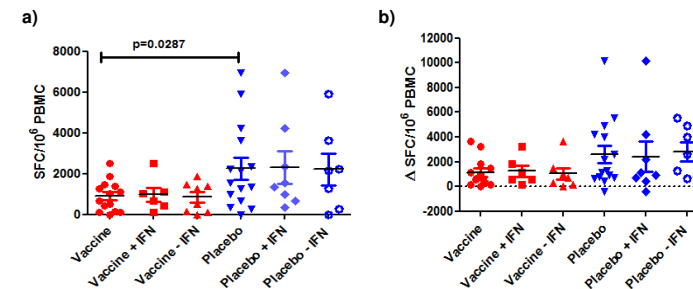


**Figure 2:  $\Delta$ VL set-point [ $\log_{10}$  mean (SE) copies/ml] for different groups of study:**

- a)  $\Delta$ VL set-point for patients receiving vaccine, vaccine + IFN, placebo and placebo + IFN; b)  $\Delta$ VL set-point for patient receiving IFN or not, independently of being vaccinated or not.

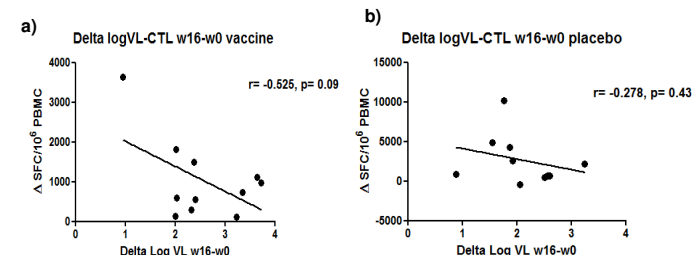


**Figure 3: VL [ $\log_{10}$  mean (SE) copies/ml] of patients receiving or not IFN:** VLs at pre-ART, weeks 6, 8, 10, 12, 14, 16 of follow up and set-point are represented for patients who received IFN or not, independently of being previously vaccinated.



**Figure 4: Total HIV-1-specific T cell responses measured by IFN- $\gamma$  ELISPOT:**

a) Individual responses and mean  $\pm$  SEM of SFC/ $10^6$  PBMC for the different arms of the study, at w0 (baseline); b) Changes of HIV-1-specific T cell responses at w16 for the different arms of the study ( $\Delta$  SFC/ $10^6$  PBMC (w16-w0)). No significant differences were observed between responses between vaccine and placebo groups (p=0.09). No effect on HIV-1-specific T cell responses was observed with administration of IFN.



**Figure 5: Correlations between changes in VL and HIV-1-specific T cell responses at w16:** Graphs represent the trend of inverse correlation between  $\Delta$ VL and  $\Delta$ HIV-1-specific T cell responses (w16-w0) in vaccine group (r=-0.525, p=0.09) (graph a) whereas no correlation was observed in placebo group (r=-0.275, p=0.09) (graph b).

## Conclusions

The combination of a MD-DC therapeutic vaccine and pegIFN $\alpha$  was safe. A very modest decrease in VL was observed in vaccine recipients and was correlated with an increase of HIV-1 specific T-cell responses.

## Acknowledgements

This study was partially supported by grants from FIS /ISCIII P12/01247, P115/00641, P115/00480, P118/00699, RIS (Red Temática Cooperativa de Grupos de Investigación en Sida) RD16/0025/0014 and HIVACAT.