Phase I/II Randomized Study: Therapeutic Dendritic Cell Vaccine Plus Pegylated INF-α

Abstract nº 2142

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

[1]Infectious Diseases Department, Hospital Clinic of Barcelona, Institut d´Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) - HIVACAT, University of Barcelona, Barcelona, Spain; [2]Retrovirology and Immunopathology Laboratory, AIDS Research Group, IDIBAPS - HIVACAT, Hospital Clínic de Barcelona, Barcelona, Spain; [3]Radiology Department, Hospital Clinic, Barcelona, Spain; [4]ViiV 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 2015-001795-22.

Material and Methods

• 36 patients on successful ART with CD4+ ≥450 cells/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 ΔVL set-point (set-point ATI-preART), and ΔHIV-1 specific T cell responses (IFN-γ´Elispot) (w16-w0).

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

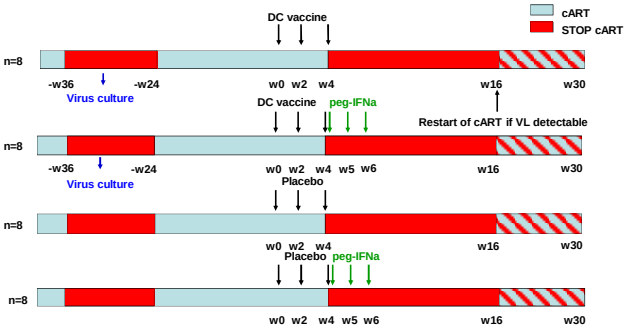

Table 1: Baseline characteristics of the study participants and CD4 counts evolution

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/mm^3) at screening (median/IQR)	752 (705-1018)	751 (687-1206)	726 (642-1228)	933 (671-1203)	806 (708-864)
CD4 count (cells/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/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. ΔVL 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 ΔHIV-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 ΔVL and ΔHIV-specific T-cell responses (w16-w0) was observed in vaccine and not in placebo groups (r=-0.56, p=0.09; r-028, p= 0.43; vaccine and placebo groups, respectively) **(Figure 5)**.

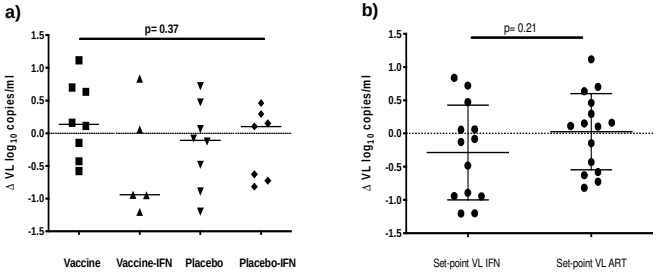

Figure 2: ΔVL set-point [$\log_{10}$ mean (SE) copies/ml) for different groups of study:
a)ΔVL set-point for patients receiving vaccine, vaccine + IFN, placebo and placebo + IFN;
b)ΔVL set-point for patient receiving IFN or not, independently of being vaccinated or not.

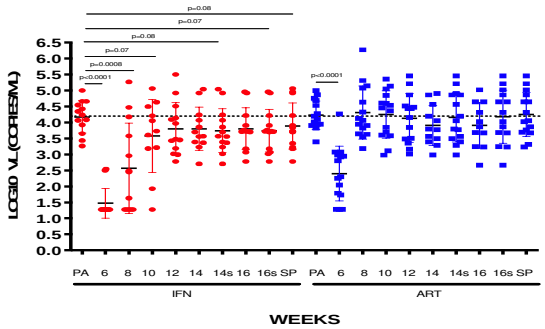

Figure 3: VL [$\log_{10}$ mean (SE) copies/ml) of patients receiving or not IFN:
VLs at pre-ART, weeks 6, 8, 10, 12, 14, 16 of follow up and set-point are represented for patients who received IFN or not, independently of being previously vaccinated.

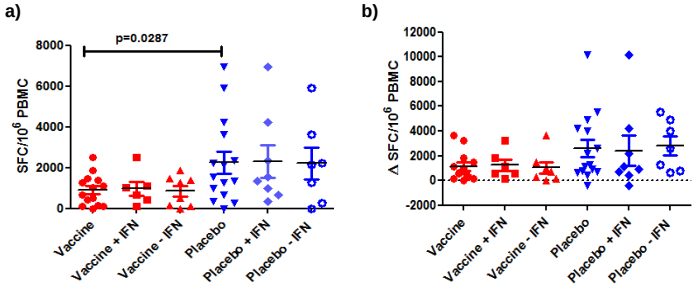

Figure 4: Total HIV-1-specific T cell responses measured by IFN-γ ELISPOT:
a) Individual responses and mean ± SEM of SFC/106 PBMC for the different arms of the study. at w0 (baseline); b) Changes of HIV-1-specific T cell responses at w16 for the different arms of the study (Δ SFC/106 PBMC (w16-w0)). 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.

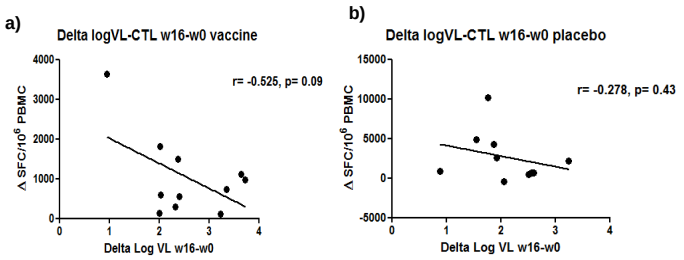

Figure 5: Correlations between changes in VL and HIV-1-specfic T cell responses at w16:
Graphs represent the trend of inverse correlation between ΔVL and ΔHIV-1-specific T cell responses (w16-w0) in vaccine group (r=-0.525, p= 0.09) (graph a) whereas no correlation was observed in placebo group (r=-0.275,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

Conclusions

The combination of a MD-DC therapeutic vaccine and pegIFNα 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 PI12/01247, PI15/00641, PI15/00480, PI18/00699, RIS (Red Temática Cooperativa de Grupos de Investigación en Sida) RD16/0025/0014 and HIVACAT.