Dynamics of Viral Load (VL) Rebound After cART Interruption in Chronic HIV Infected Patients Receiving MVA-B plus Disulfiram.

•Beatriz Mothe1, Sonsoles Sánchez2, Saray Corral3, Nuria Climent2, Alberto C. Guardo2, Lorna Leal2, Berta Torres2, José Luis Jiménez3, Judit Pich2, Joan Albert Arnaiz2, Agathe León2, María Angeles Muñoz-Fernández3 , Jose M Gatell2,
•Bonaventura Clotet1, Mariano Esteban4, Montserrat Plana2, Juan Carlos López Bernaldo de Quirós3, Christian Brander1, Felipe García2 for the RISVAC-03 Study.

1. Irsicaixa-HIVACAT, Hospital Germans Trias i Pujol, Badalona 2. Hospital Clinic-HIVACAT, IDIBAPS, University of Barcelona 3. Hospital Gregorio Marañón, Madrid 4.- Centro Nacional de Biotecnología, Madrid. Spain

Goal

We present the results of a substudy of a phase I, doubled blind placebo-controlled trial of an MVA-B therapeutic trial combined with disulfiram virus-reactivation treatmentt in successful cART-treated HIV-infected patients.

Introduction

In vitro data suggest that stimulation of HIV-1-specific T lymphocytes with a therapeutic vaccine could facilitate elimination of latent viral reservoir after virus reactivation with drugs (i.e disulfiram).

Material and Methods

Patients were randomly allocated to receive 3 intramuscular injections of MVA-B at 0, 4 and 16 weeks (n=20) or placebo (n=10). Twelve patients (8 MVA-B, 4 placebo vaccinated) received a 4th dose of MVA-B at week 36 followed by 2 months of disulfiram (250 mg qd). cART was discontinued in all 30 patients 8 weeks after the last dose of MVA-B and viral rebound dynamics were assessed during the first 12 weeks of cART interruption.

Results

- VL was maintained below detectable levels in all patients while receiving MVA-B or MVA-B/disulfiram on ART but rebounded in all patients after cART interruption.
- The dynamics of VL rebound were not significantly different between the disulfiram treated/untreated groups.
- Proportion of patients with VL rebound at weeks 2 and 4 after cART interruption was similar between groups (w2: 7/12 (58%) and 8/16 (50%), w4: 11/12 (92%) and 15/17 (88%), in MVA-B/disulfiram vs MVA-B, P = 0.66 and 0.74), respectively).
- At week 12 after cART interruption, mean (SE) change VL (as compared with set-point VL before any cART) was –0.72 (0.4) vs –0.35 (0.3) in MVA-B/ disulfiram vs MVA-B, respectively (P = 0.46).
- CD4 T cell counts declined similarly between groups after cART interruption.

Figure 1. Clinical trial design

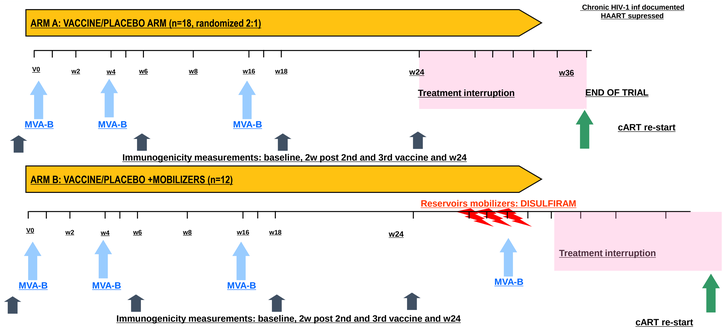


Table 1. Clinical characteristics of the patients and viral load and CD4

	Disulfiram untreated group		P	Disulfiram treated group		P	P*
	MVA-B	Placebo		MVA-B	Placebo		
N	12	6		8	4		
Age**	45 (41-51)	44(42-48)	0.85	40 (35-46)	42 (40-44)	0.78	0.46
Gender male (%)	11 (92)	4 (67)	0.25	8 (100)	3 (75)	0.33	0.63
Risk group hmx (%)	8 (67)	4 (67)	0.59	5 (63)	3 (75)	0.59	0.65
Baseline VL***	4.5 (0.3)	4.2 (0.3)	0.51	4.7 (0.2)	4.0 (0.2)	0.19	0.51
VL at week 0***	1.6 (0)	1.6 (0)		1.6 (0)	1.6 (0)		
VL at week2***	1.8 (0.1)	2.9 (0.4)	0.007	2.3 (0.2)	1.7 (0.1)	0.2	0.08
VL at week 4***	3.4 (0.3)	4.2 (0.5)	0.18	4.2 (0.5)	4.6 (0.4)	0.67	0.11
VL at week 8***	4.2 (0.2)	4.3 (0.5)	0.77	4.1 (0.3)	3.8 (0.4)	0.72	0.9
VL at week 12***	4.2 (0.1)	4.3 (0.5)	0.88	4.1 (0.3)	0.8 (0.4)	0.73	0.69
Baseline CD4**	364(334-484)	487 (429-817)	0.13	411 ((375-632)	274 (274-376)	0.21	0.19
CD4 at week 0**	722 (625-912)	873 (761-1183)	0.27	779 (620-871)	681 (512-1339)	0.93	0.85
CD4 at week 2**	707 (676-761)	790 (577-1116)	0.62	703 (595-1098)	992 (536-1083)	0.85	0.92
CD4 at week 4**	682 (551-764)	618 (491-879)	0.91	821 (556-1012)	835 (459-870)	0.71	0.81
CD4 at week 8**	616 (473-708)	607 (544-786)	0.69	609 (492-753)	682 (408-810)	0.97	0.98
CD4 at week 12**	558 (439-663)	607 (446-920)	0.29	676 (584-814)	609 (384-834)	0.52	0.32

* P for the difference between Disulfiram untreated and Disulfiram treated groups; ** Median (IQR); ***Mean (SE);
VL viral load: $\log_{10}$ copies/ml; CD4 T cell count: cells/mm^3

Figure 2. Viral load rebound after vaccination vs vaccination plus disulfiram. Absolute numbers and changes as compared with baseline viral load before any cART

P for the difference between Disulfiram untreated and Disulfiram treated groups; ** Median (IQR); ***Mean (SE);
VL viral load: $\log_{10}$ copies/ml; CD4 T cell count: cells/mm^3

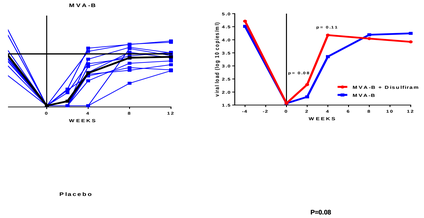


Figure 3. CD4 changes after vaccination vs vaccination plus disulfiram. Absolute numbers and changes as compared with baseline viral load before any cART

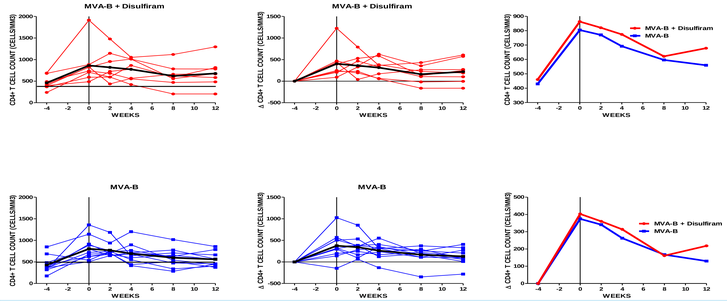
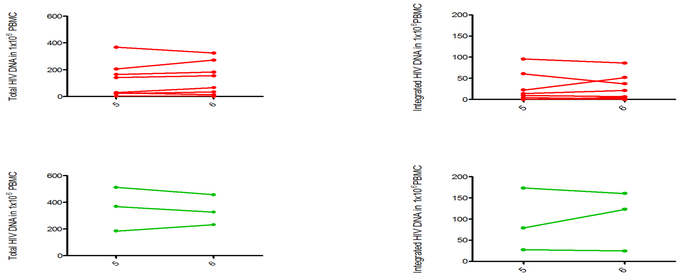


Figure 4. Frequencies of total (A: MVA-B and C: placebo) and integrated (B: MVA-B and D: placebo) DNA molecules in PBMCs cells before and after Disulfiram administration. Molecular forms of HIV were quantified by real-time PCR in longitudinal samples from vaccinated and no vaccinated individuals who initiated disulfiram . The time before (5) and after (6) Disulfiram initiation are indicated. No significant differences are observed.



Conclusion

A combination strategy of a therapeutic vaccine (MVA-B) plus disulfiram treatment neither prevented nor delayed viral load rebound after cART interruption as compared with MVA-B vaccination alone.

Acknowledgements

This study was partially supported by grants: SAF 2012-39075, EC10-153, FIS PI10/02984, TRA-094, FIS PS09/01297, RIS, HIVACAT. Special thanks to all volunteers participating in this study for their perseverance and dedication, without whom the phase I clinical trial would not have been made possible.

Poster Board Number: 346