PHASE I CLINICAL TRIAL OF A mRNA BASED THERAPEUTIC VACCINE AGAINST HIV-1 INFECTION

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BACKGROUND:

So far, the efficacy of therapeutic vaccines against HIV-1 infection has been modest. New inserts to redirect responses to vulnerable sites of HIV and vectors targeting dendritic cells (DC) pathways could be necessary to achieve the remission of HIV-1 infection. We performed the first-in-human clinical trial with naked mRNA (iHIVARNA) encoding HIV antigenic sequences (HTI sequence: comprising 16 joined fragments from Gag, Pol, Vif and Nef) rationally selected to redirect the responses to the most vulnerable viral targets combined with DC activation signals (TriMix:CD40L+CD70+caTLR4)

METHODS:

A single center, open-label, dose escalating phase I clinical trial was performed in 21 chronic HIV-1 infected patients who received 3 intranodal doses of mRNA at weeks 0, 2 and 4 as follow: TriMix 100μg (n=3), TriMix 300μg (n=3), TriMix 300μg+HTI 300μg (n=3), TriMix 300 μg+HTI 600μg (n=6), TriMix 300 μg+HTI 900μg (n=6) (Figures 1A and 1B). Dose escalation was performed only if less than 2 patients of the previous dose level would have a dose limitating toxicity (DLT). Primary endpoint was safety, and secondary-exploratory endpoints were immunogenicity (ELISPOT), changes in reservoir (HIV-DNA and caHIV-RNA), ultrasensitive plasma RNA (usVL) and transcriptome profiling (limma).

Figure 1A. Dose escalation flow chart. DSMB: Data and Safety Monitoring Board. DLT: dose limiting toxicity

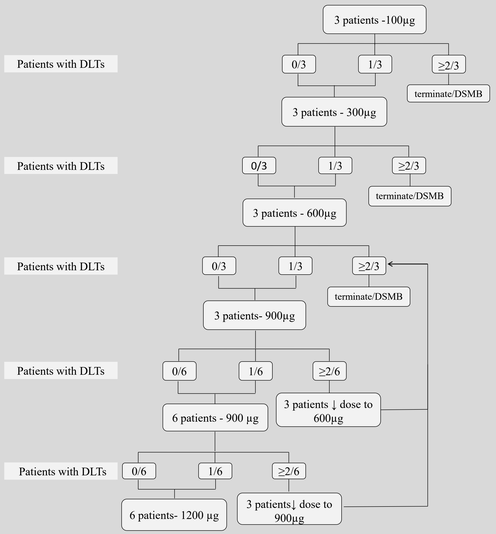
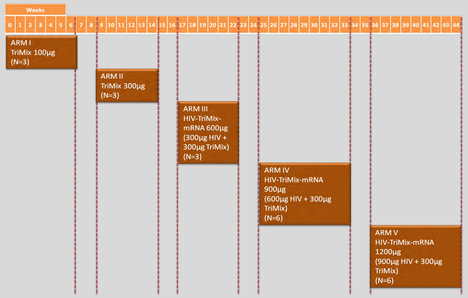


Figure 1B. Assignation of cohorts



RESULTS:

Overall, the vaccine was safe and well tolerated. No serious adverse events (AEs) were observed. There were 31 grade 1/2 and 1 grade 3 AEs, from which half of grade 1/2 and the grade 3 were definitely not related to the vaccination. Patients who received the highest dose showed a moderate increase in T cell responses spanning HTI sequence (IN) at week 8 whereas no changes were observed in responses against the rest of the HIV-1 proteome (OUT). In addition, the proportion of responders receiving any dose of iHIVARNA (n= 15) increased from 31% at w0 to 80% post-vaccination. This increase was not observed in patients receiving TriMix alone (n=6, from 50% to 67%). Vaccination did no impact on caHIV-DNA levels in any of the studied arms. However, caHIV-RNA expression and usVL were transiently increased in patients receiving the higher doses of TriMix+HTI at weeks 5 and 6. We did not observed differentially expressed genes in any of the groups-wise comparisons, although gene set analysis indicates some effect on pathways such as RNA metabolism and host response to viruses, but with very low significance levels.

Table 1. Clinical characteristics of participants

n=21	Group 1 (n=3)	Group 2 (n=3)	Group 3 (n=3)	Group 4 (n=6)	Group 5 (n=6)
Median age (range)	48 (48-51)	51 (48-51)	45 (37-46)	55 (53-57)	47 (43-55)
Male	2	2	2	4	6
MSM	2	2	2	4	6
Heterosexual (HTSX)	1	1	1	0	0
Intravenous drug user (IDU)	0	0	0	2¥	0
Hepatitis C virus (HCV) infection	0	0	0	2*	0
Median CD4 cell count at baseline (IQR)	762 (686-770)	726 (716-824)	821 (741-957)	829 (680-1124)	904 (868-1071)
Median CD4 cell count at week 6 (IQR)	672 (663-683)	938 (784-993)	643 (589-1040)	819 (640-928)	956 (805-1053)

¥former IDU, *both HCV infections were cured. MSM: Men who have sex with men. IQR: Interquartile range.

Table 2. Total adverse events classified by severity and relationship with the vaccination.

Variable	Value	Val	I	II	III	IV	V	All
Severity	Grade 1	N	3	4	1	9	2	19
		%	75	57	20	82	40	59
	Grade 2	N	1	3	3	2	3	12
		%	25	43	60	18	60	38
	Grade 3	N	0	0	1	0	0	1
		%	0	0	20	0	0	3
	All	N	4	7	5	11	5	32
Casual relationship	Obvious relationship	N	2	0	0	0	0	2
		%	50	0	0	0	0	6
	Probable relationship	N	0	0	0	0	0	0
		%	0	0	0	0	0	0
	Possible relationship	N	1	4	3	6	0	14
		%	75	57	60	55	0	44
	No related	N	1	3	2	5	5	16
		%	75	43	40	45	100	50
	Unknown	N	0	0	0	0	0	0
		%	0	0	0	0	0	0
	All	N	4	7	5	11	5	0000

Figure 4. Impact of the highest doses of iHIVARNA (Groups 4 and 5) in HIV-1 ultrasensitive plasma RNA.

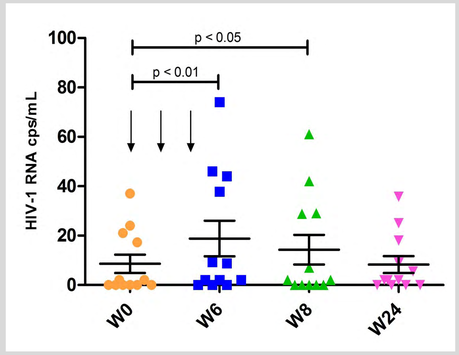


Figure 2. Changes in the magnitude of HIV-1 specific immune responses against IN and OUT pools as measured by ELISPOT at weeks 0, 2 and 4 that represent vaccine administration and w24 of follow-up

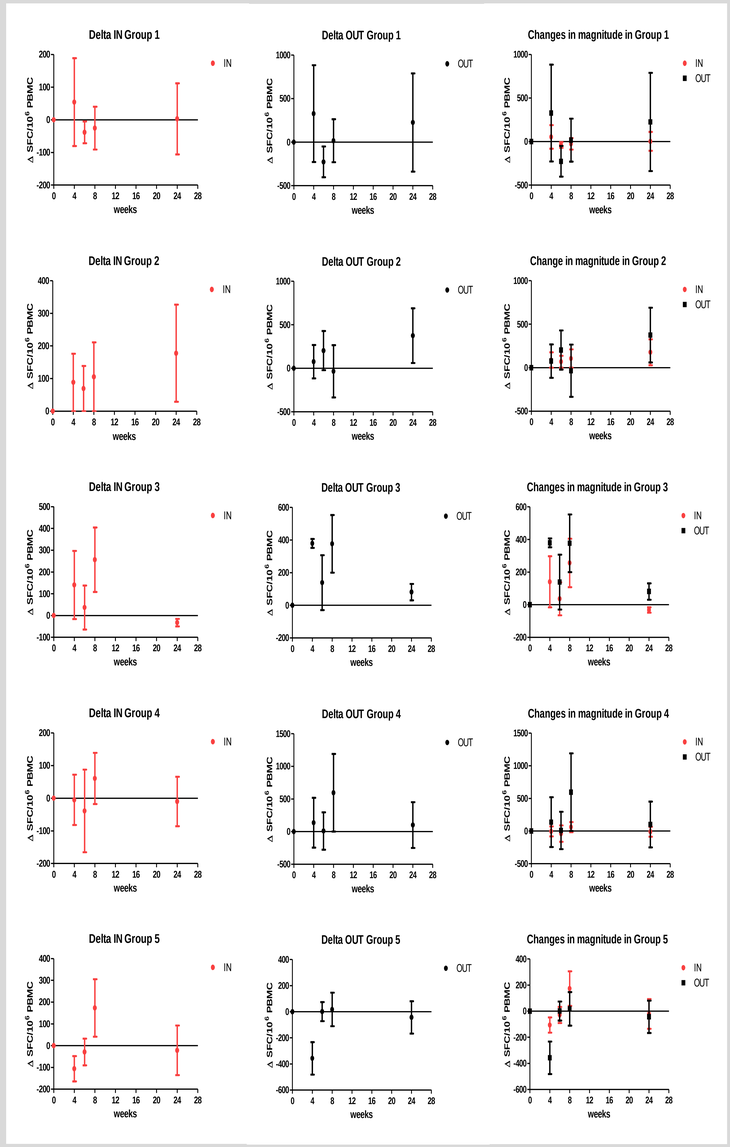


Figure 3. Impact of TriMix (Groups 1 and 2) or the different doses of iHIVARNA (Groups 3, 4 and 5) on HIV-1 cell-associated RNA.

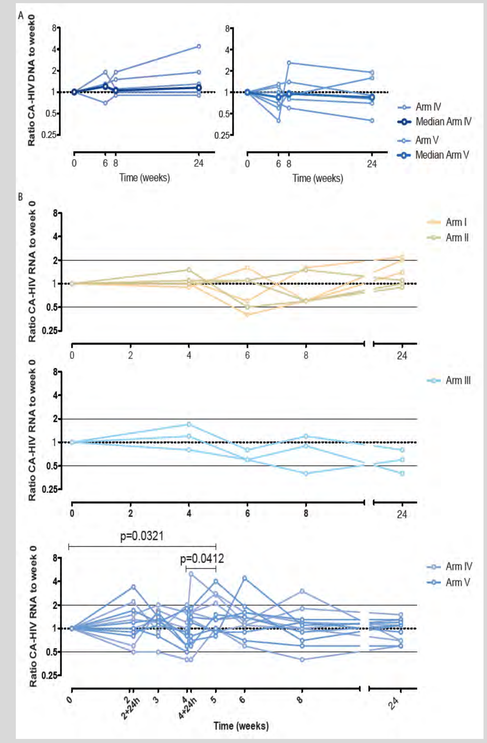
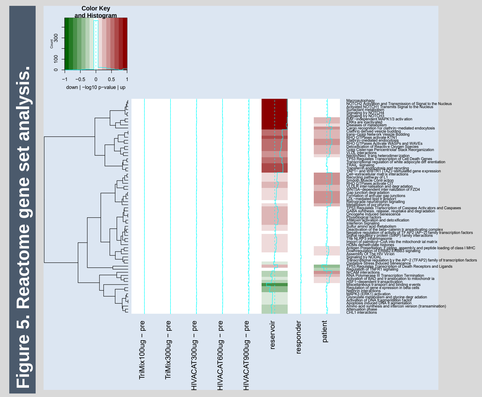


Figure 5. Reactome gene set analysis.



CONCLUSIONS:

This phase I exploratory dose-escalating trial showed that iHIVARNA was safe and well tolerated, was able to induce moderate HIV-specific immune responses and transiently increased caHIV-RNA expression. These data support further exploration of iHIVARNA in a phase II study.

"The research leading to these results has received funding from the European Comunity's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 602570 - the iHIVARNA project." © Copyright 2013-2017 iHIVARNA Consortium.

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