

TheraVac-01 : Evaluation of Safety and Immunogenicity of the HIV-1 Vaccine NYVAC-B in Chronic HIV-1 Infected Patients Successfully Treated with HAART

Pierre-Alexandre Bart¹, Alexandre Harari¹, Joost Vermeulen², Felicitas Bellutti Enders¹, Erika Castro¹, Matthias Cavassini¹, Ferdinand Wit², Brigitte Autran³, Joep Lange² and Giuseppe Pantaleo¹

¹Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; ²Academic Medical Center and IATEC, Amsterdam, the Netherlands; ³Faculté de Médecine Pierre et Marie Curie, Paris, France

Pierre-Alexandre BART, MD
Alexandre HARARI, PhD

Vaccine and Immunotherapy Center
Division of Immunology and Allergy
CHUV
1011 Lausanne
Switzerland

pierre-alexandre.bart@chuv.ch
alexandre.harari@chuv.ch

Tel +41 21 314 11 60
Fax +41 21 314 11 61

1. ABSTRACT

The HIV-1 therapeutic vaccine NYVAC-B evaluated in this study is a recombinant attenuated vaccinia vaccine containing HIV-1 clade B *env* gene and *gag-pol-nef* polygene. **Objectives** are: 1) to evaluate the safety of NYVAC-B during 12 weeks after the first vaccination; 2) to characterize HIV-1 specific immune responses.

Ten HIV-1 (clade B) infected patients on HAART with plasma HIV-RNA (pVL) <50 RNA copies/mL prior to inclusion were injected with 1 ml of NYVAC-B IM on week (W) 0 and 4, in the left and right deltoid muscle. Vaccination was followed by 2h of observation, and visits on day 1, W1, 2, 3, 4, 6, 8, 12, 24, 36 and 48. Safety parameters (vaccination-related local and systemic reactions, clinical and laboratory parameters, pVL and CD4/CD8 T-cell counts) were evaluated at every visit. HIV-1 specific immune responses were assessed on cryopreserved PBMC by IFN γ ELISpot at W0, 2, 4, 6, 8, 12, 24, 36 and 48 using 8 pools of HIV-1 peptides encompassing the *gag-pol-nef* and *env* regions, and by ICS with a panel of 193 HIV-derived optimal epitopes (W48).

After both vaccinations only grade 1 or 2 local injection-related adverse events (AE) were observed (no serious AE related to the vaccine). CD4 counts and pVL remained very stable over time. Global HIV-1 specific cellular responses (sum of all peptides pools) increased in all 10 patients (peak at W12). By ELISpot using 8 pools of HIV-1 peptides, increase of both CD4 and CD8 specific responses were detected after immunization, either due to expansion of pre-existing responses or generation of new responses. Moreover, ICS using 194 HIV-derived optimal epitopes showed that responses were polyfunctional, long lasting and mostly directed against gag.

The recombinant HIV-1 vaccine NYVAC-B is safe and well tolerated. Furthermore it induces polyfunctional CD4 and CD8 HIV-specific responses generally directed against gag.

2. INTRODUCTION

HAART has declined HIV-related morbidity and mortality dramatically, but is associated to toxicity and resistance development. Furthermore, treatment interruptions are frequently followed by virus relapses, reflecting the lack of restoration of a protective immunity against HIV under HAART. An effective therapeutic vaccine administered during therapeutic control of HIV-1 could restore a strong protective HIV-1 specific immune response, and thus enable treatment interruptions to limit long-term exposure to HAART.

The present study TheraVac-01 is part of the TheraVac program, funded by the EU 5th Framework Program. TheraVac aims to develop a HIV-1 therapeutic vaccine. In particular, the safety and immunogenicity of two promising highly attenuated vaccinia-based vaccines are evaluated in HIV-infected patients successfully treated with HAART : NYVAC-B (TheraVac-01 study) and MVA-B (TheraVac-02 study), both containing the HIV-1 *env-gag-pol-nef* polygene. HIV genes expressed in the recombinant vector are derived from clade B viruses: BX08 for *env*, and IIB for *gag-pol-nef*.

3. OBJECTIVES and METHODS

OBJECTIVES	ENDPOINTS	METHODS
Primary Objective		
SAFETY 12 weeks evaluation	Solicited Adverse Events: • General (fever, chills, headache, nausea, vomiting, malaise, myalgia) • Local (pain, cutaneous reactions including induration)	Solicited with specific questions the first 7 days after vaccination and reported during the first 12 weeks
	Other (unsolicited) Adverse Events	Any Adverse Events reported during 48 weeks
	Safety laboratory parameters CD4 cells count Plasma HIV-1 RNA	Criteria evaluated at every visits during 48 weeks
Secondary Objectives		
SAFETY 48 weeks evaluation	Same endpoints as for primary safety	48 weeks evaluation of the endpoints
IMMUNOGENICITY 48 weeks evaluation	Cellular immune responses after one and two vaccinations with NYVAC-B	IFN-γ ELISpot assays on cryo-preserved PBMC at W0, 1, 2, 4, 6, 8, 12, 24, 36 and 48. ICS at W48.

4. STUDY DESIGN

This is a single center, open-label, one arm study. All patients were recruited at the CHUV (Centre Hospitalier Universitaire Vaudois), Lausanne, Switzerland. Immunisations began in May 2006 and ended in August 06. Last follow-up visit took place in June 2007. All 10 patients were allocated to NYVAC-B (weeks 0 and 4).

Weeks	-4	0	1	2	3	4	6	8	12	24	36	48
Immunisations		X				X						
Safety	X	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X
CD4/CD8 counts	X	X	X	X	X	X	X	X	X	X	X	X
HIV-specific immunity		X		X			X		X	X	X	X
Vac.-specific immunity		X				X		X				
NYVAC-B disseminat.		X										

Table 1 : Schedule of immunisations, timepoints for Safety and Immunogenicity Evaluation

5. STUDY POPULATION

10 HIV-1 clade B infected patients (out of 15 screened with nucleotide sequencing of HIV *gag/pol* genes) were enrolled.

Number of subjects	10	Nadir CD4-count [x10 ⁶ cells/L]	235 (190-410)
Male / Female	10/0	Mean CD4-count in six months prior to start HAART [x10 ⁶ cells/L]	309 (210-410)
Age [years]	45 (30-60)	HIV-1 RNA [copies/ml]	< 40 (40-40)
Ethnic group : Caucasian	10	History of smallpox: Yes/No	0/10
Height [meter]	1.76 (1.72-1.83)	History of smallpox vaccination Yes/No	10/0
Weight [kg]	76 (67-94)	Signs of smallpox vaccination Yes/No	10/0
BMI [kg/m ²]	24.4 (20.4-30.7)	History of HIV vaccination Yes/No	0/10

Table 2 : Baseline characteristics

6. SAFETY RESULTS

No serious adverse events occurred. Solicited vaccination-related AEs (local injection site or systemic reactions) were recorded in all patients but one, but mostly of grade 1. Pain was the most frequent local reaction reported in 6 and 4 participants after vaccinations 1 and 2 respectively. 50% of patients reported malaise/fatigue after vaccination 1 and 10% after vaccination 2. Eight grade 2 events were reported after vaccinations, only 5 were considered related. The only grade 4 AE, CPK elevation, was not related to vaccine.

All patients had a pVL below 40 copies/ml on all timepoints (except one blip of 50 copies/ml on W4 in one patient). CD4 counts were very stable over time.

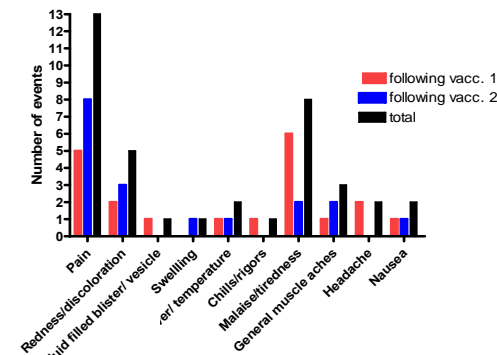


Figure 1 : Overview of all AEs

7. IMMUNOGENICITY RESULTS

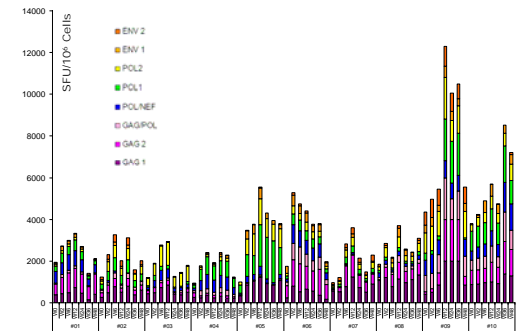


Figure 2 : Global HIV-1 specific T-cell responses for each timepoint / patient / peptide pool as measured by IFN- γ ELISpot assays

Using peptide pools, we observed that new HIV-1-specific T-cell responses were generated in 9 out of 9 patients (1 patient already responded to all stimulations at Baseline), and 5 out of 9 patients have generated 2 new responses.

Nine out of 10 patients (90%) had at least 1 response increasing by 2-fold, and 8 out of 10 patients (80%) had at least 4 responses increasing by 2-fold.

Responses elicited by NYVAC-B were directed against all HIV regions (*gag*, *pol*, *nef* and *env*), but the highest were directed against *gag*.

Furthermore, we have also mapped HIV-specific CD8 T-cell responses using a panel of 194 optimal HIV-derived CD8 epitopes. This enabled us to identify 38 pre-existing HIV-specific CD8 T-cell responses and to monitor the impact of immunization. Of interest, these responses not only significantly increased with regard to the magnitude ($P < 0.01$) but also became more polyfunctional ($P < 0.01$). Finally, this strategy also enabled us to demonstrate the generation of new HIV-1-specific CD8 T-cell responses following immunization.

8. CONCLUSIONS

- Vaccination with NYVAC-B administered by IM injection on day 0 and 28 in 10 HIV-1-infected patients during concomitant HAART is safe and well tolerated.
- Vaccination with NYVAC-B did significantly induce new HIV-1-specific cellular immunity as measured by ELISpot and expand the magnitude and functionality of pre-existing responses as shown by flowcytometry.
- The combination of good safety results and promising immunogenicity results justify further (phase 2) clinical studies with NYVAC-B.

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