# TheraVac-01 : Safety and Immunogenicity of the HIV-1 Vaccine NYVAC-B in Chronic HIV-1 Infected Patients Successfully Treated with HAART in an Open-Label Phase I Study: week 12 results

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Pierre-Alexandre Bart[1], Joost Vermeulen[2], Alexandre Harari[1], Gonzalo Tapia[1], Erika Castro[1], Matthias Cavassini[1], Ferdinand Wit[2], Brigitte Autran[3], Joep Lange[2] and Giuseppe Pantaleo[1]

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

**Pierre-Alexandre BART, MD**
Vaccine and Immunotherapy Center
Division of Immunology and Allergy
BT 06 / CHUV
1011 Lausanne
Switzerland

pierre-alexandre.bart@chuv.ch
Tel +41 21 314 11 60
Fax +41 21 314 11 61


## 1. ABSTRACT


**Background:** HAART has led to a dramatic decline in HIV-related morbidity and mortality but has severe drawbacks. An effective therapeutic vaccine could evoke protective immune responses in HIV-1-infected patients under successful antiretroviral treatment, and thus enable HAART interruptions. The potential HIV-1 therapeutic vaccine NYVAC-B evaluated in this study is a recombinant attenuated vaccinia vaccine containing the HIV-1 clade B *env* gene and *gag-pol-nef* polygene. **Primary objective** is to evaluate the safety of NYVAC-B during 12 weeks after the first vaccination; **secondary objectives** include the evaluation of the HIV-1 specific immune responses.

**Methods:** 10 HIV-1 (clade B) infected patients successfully treated with 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 clinical 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, standard clinical and laboratory parameters, pVL and CD4/CD8 T-cell counts) are assessed at every visit. HIV-1 specific immune responses are assessed by IFNg ELISpot on cryopreserved PBMC 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.

**Results:** Safety and immunogenicity analyses until W12 are presented. After both vaccinations only grade 1 or 2 local injection-related adverse events (AE) were observed. There were **no serious AEs** 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 (median 2.54 fold increase at W6). Considering only >2-fold increased responses as significant, 90% of patients had at least 1 pre-existing response increased after immunization, 80% had ≥4 responses and 50% had ≥5 increased responses. Furthermore, 100% of patients generated ≥ 1 new response, and 56% generated ≥ 2 new responses. The responses elicited by NYVAC-B were directed against all 8 peptide pools (gag, pol, nef and env), but the highest were directed against gag.

**Conclusions: The recombinant HIV-1 vaccine NYVAC-B is safe and well tolerated. Furthermore it induces vigorous and broad HIV-specific T-cell responses in all vaccinated patients. The clinical efficacy has to be evaluated in a phase-2 study interrupting HAART after vaccination.**


## 2. INTRODUCTION

HAART has declined HIV-related morbidity and mortality dramatically, but HAART is associated to toxicity and resistance development. Furthermore, treatment interruptions are rapidly 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 **IIIB for *gag-pol-nef***.


## 3. OBJECTIVES and METHODS

| OBJECTIVES | ENDPOINTS | METHODS |
|---|---|---|
| **Primary Objective** | | |
| **SAFETY**<br>12 weeks evaluation | **Solicited Adverse Events:**<br>• General (fever, chills,headache, nausea, vomiting, malaise, myalgia)<br>• Local (pain, cutaneous reactions including induration)<br>**Other (unsolicited) Adverse Events**<br>**Safety laboratory parameters**<br>**CD4 cells count**<br>**Plasma HIV-1 RNA** | **Solicited** with specific questions the first 7 days after vaccination and reported during the first 12 weeks)<br>**Any Adverse Events reported during 48 weeks**<br>**Criteria evaluated at every visits during 48 weeks** |
| **Secondary Objectives** | | |
| **SAFETY**<br>48 weeks evaluation | **Same endpoints** as for primary safety | 48 weeks evaluation of the endpoints |
| **IMMUNOGENICITY**<br>48 weeks evaluation | **Cellular HIV-specific immune responses** after one and two vaccinations with NYVAC-B | **IFN-γ ELISpot** assays on cryo-preserved PBMC at weeks 0, 1, 2, 4 and at any following visit. |

## 4. STUDY DESIGN

This is a single center, open-label, one arm study. All patients were recruited at CHUV (Centre Hospitalier Universitaire Vaudois), Lausanne, Switzerland. Immunisations began in May 2006 and ended in August 06. Last follow-up visit will take 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** [x10⁶ cells/L] | 235 (190-410) |
| **Male / Female** | 10/0 | **Mean CD4-count in six months prior to start HAART** [x10⁶ 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/m² ] | 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).

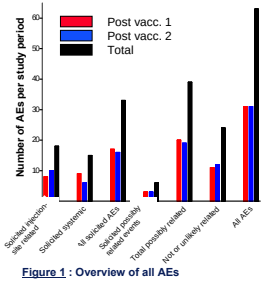


**Figure 1 : Overview of all AEs**

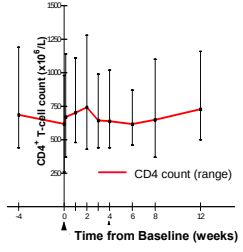


**Figure 2 : Mean CD4 counts over time**

## 7. IMMUNOGENICITY RESULTS

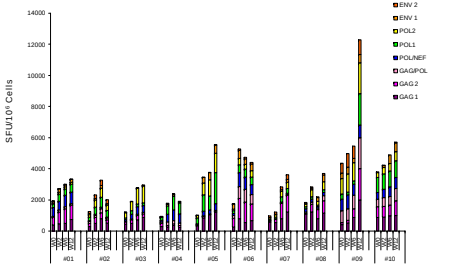


**Figure 3 : Global HIV-1 specific T-cell responses for each timepoint / patient / peptide pool as measured by IFN-γ ELISpot assays**

- A **new HIV-1-specific T-cell response** was generated in **9 out of 9 patients** (1patient already responded to all stimulations at Baseline), and 5 out of 9 patients have generated 2 new responses. **Nine out of 10 patients** had a least **1 response increasing by 2-fold**, and **8 out of 10** patients had a 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**.

**Table 4 : SFU fold increases compared to baseline (sum of all peptide pools)**

| | Week 2 | Week 6 | Week 12 |
|---|---|---|---|
| Median (range) | 1.55 (1.12 -3.43) | 2.54 (1.25-3.73) | 2.41 (0.98-3.69) |
| Mean (95% confidence interval) | 1.85 (1.21 -2.49) | 2.31 (1.69-2.94) | 2.32 (1.65-2.95) |

## 8. CONCLUSIONS

- Vaccination with **NYVAC-B** administered by IM injections 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 HIV-1-specific cellular immunity** as measured by ELISpot [see Figure 3].
- The combination of **good safety results** and **promising immunogenicity results** justify **further (phase 2) clinical studies with NYVAC-B.**


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