

TheraVac-02: phase 1 study of HIV-1 vaccine MVA-B in HIV-1 infected patients

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Introduction

Therapeutic HIV-1 vaccines

Although combination antiretroviral therapy (cART) has declined HIV-related morbidity and mortality dramatically, cART is associated to toxicity and the development of resistance. Treatment interruptions are rapidly followed by virus relapses. 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.

TheraVac programme

The TheraVac programme, funded by the EU 5th Framework Programme, aims at the development of an HIV-1 therapeutic vaccine. The safety and immunogenicity of two promising highly attenuated vaccinia-based vaccines are evaluated in HIV-1 infected patients successfully treated with cART: NYVAC-B (TheraVac-01 study) and MVA-B (TheraVac-02). Both recombinant vaccines express the same four HIV-1 genes derived from clade B viruses: BX08 for *env*, and IIB for *gag-pol-nef*.

Study objectives

Primary objective is to evaluate the safety of MVA-B during 12 weeks after the first vaccination; secondary objectives include the evaluation of HIV-1 specific immune responses.

Methods

TheraVac-02 was a single center, open-label, one arm study. Ten HIV-1 (clade B) infected patients on concomitant successful cART, all recruited at Academic Medical Center, Amsterdam, the Netherlands, were vaccinated i.m. with $10^{7.5}$ pfu (1 mL) of MVA-B on day 0 and day 28, followed by frequent visits up to week 12 and visits every 3 months up to week 48. Immunisations took place between March and July 07. Specific vaccination related local and systemic reactions were recorded until week 12. Standard safety parameters, plasma HIV-1 RNA (pVL) and CD4⁺ and CD8⁺ T-cell counts were assessed at every visit. HIV-1 specific T-cell responses were evaluated by IFN- γ Elispot assays on cryo-preserved PBMC at baseline, week 2, 6, and 12. Here we present the results up to week 12.

Results (1)

Baseline characteristics

Male	10 (100%)	pVL < 40 copies/ml	10 (100%)
Age (years)	50 (29-70)	CD4-count (10 ⁶ cells/L)	520 (290-830)
Caucasian/ black	9/1	Nadir CD4 ⁺ T-cell count (10 ⁶ cells/L)	240 (190-330)
Homosex. transm. route	10 (100%)	Mean CD4-count in 6 months prior to start cART (10 ⁶ cells/L)	342 (200-560)
CDC class A	6 (60%)	HBsAg positive	0
CDC class B	4 (40%)	HCV Ag positive	0
Neg. history of smallpox	10 (100%)		
History of smallpox vacc.	8 (80%)		
Neg. history of HIV-vacc.	10 (100%)		

Safety

- Solicited vaccination-related AEs (local injection site or systemic reactions) were recorded in all patients, mostly of grade 1 (Fig. 1 and 2).
- Injection site pain was the most frequent local reaction reported in eight and six participants after vaccinations 1 and 2 respectively (Fig. 1).
- Seven AEs were NIH-DAIDS grade 2, of which three were considered possibly related (chills, malaise, and myalgia). All other AEs were grade 1.
- All patients had a pVL <40 copies/mL during the entire study period (except for "blips" of 63, 72, and 59 copies/mL in three patients at one time point).
- CD4⁺ T-cell counts remained stable over time (Fig. 4).

Results (2)

Solicited adverse events Injection site related

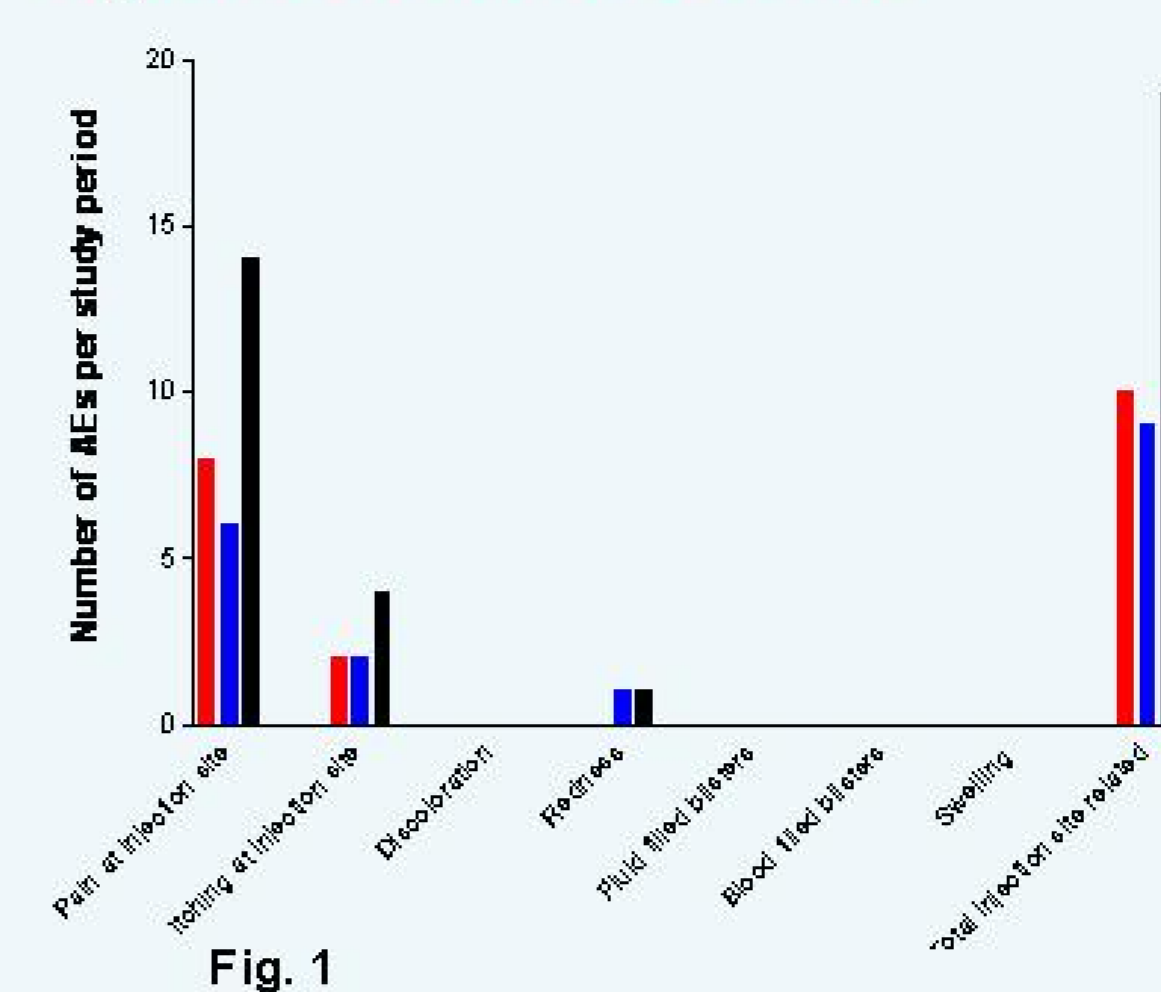


Fig. 1

Systemic

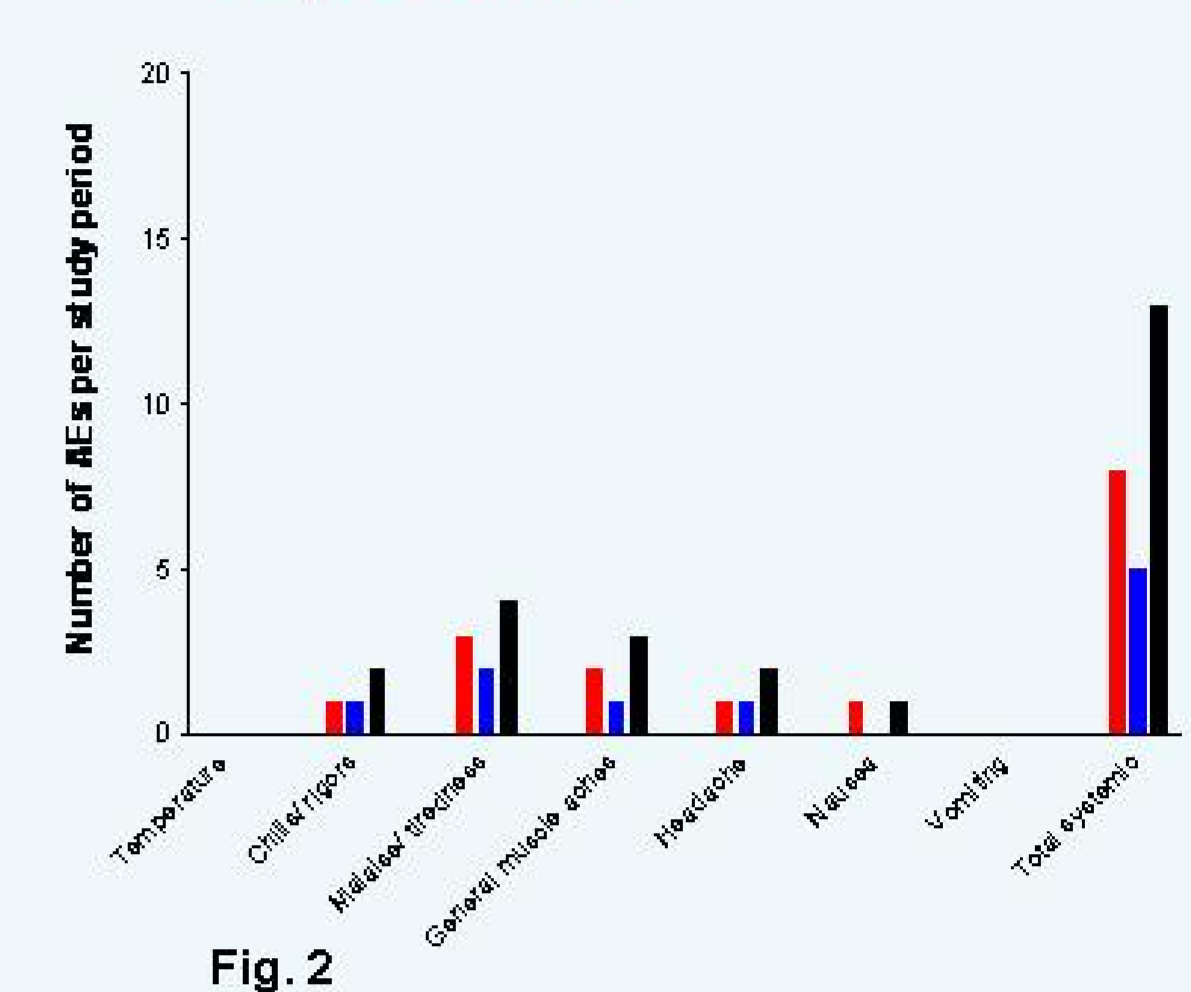


Fig. 2

All adverse events

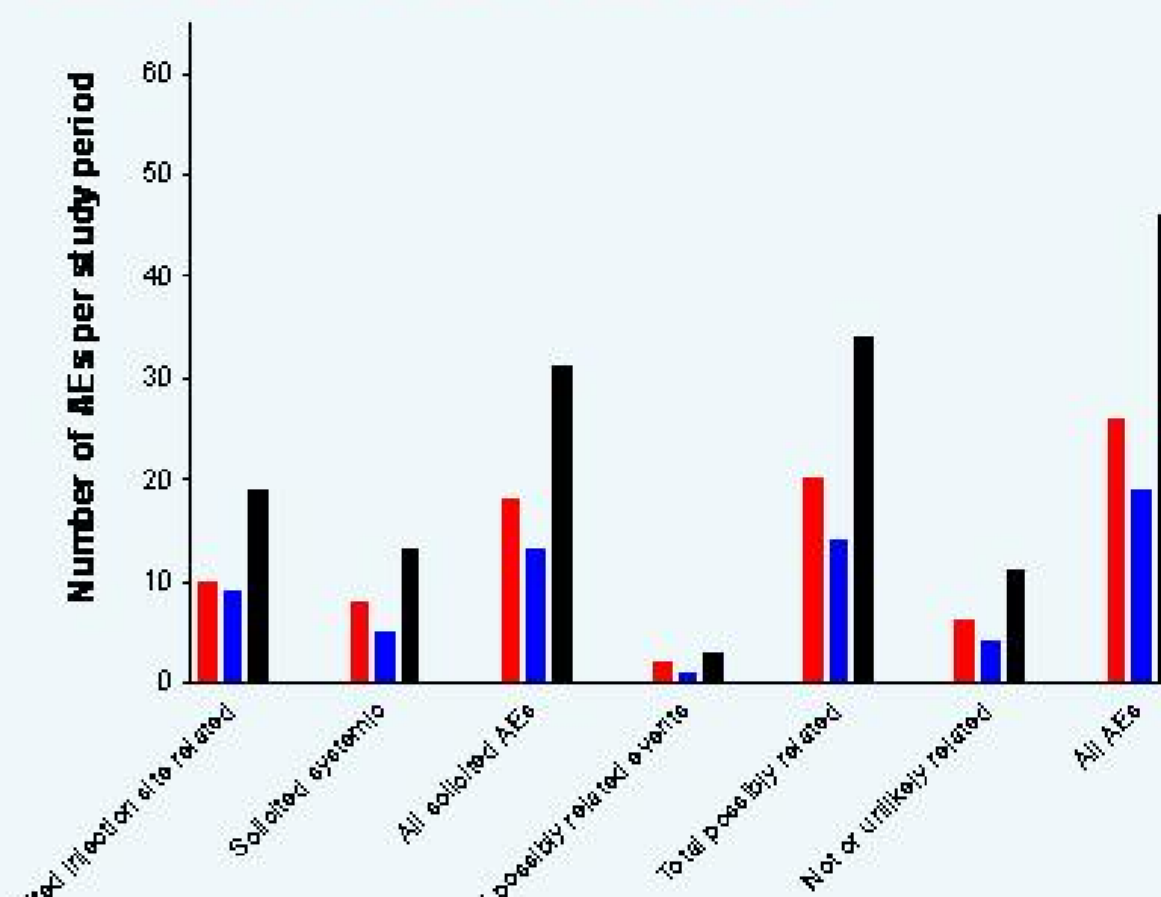


Fig. 3

CD4⁺ T-cell count

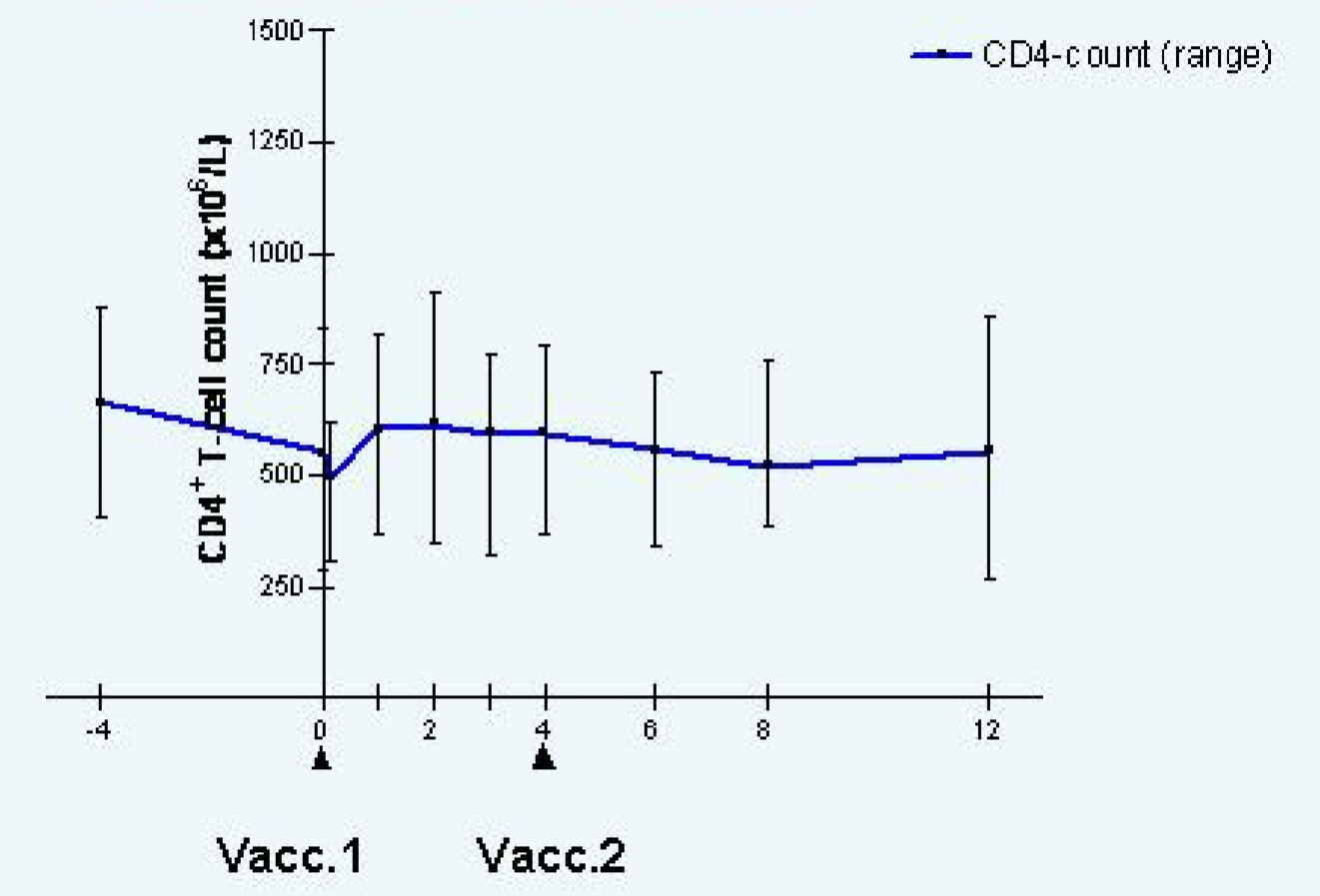


Fig. 4

Immunogenicity

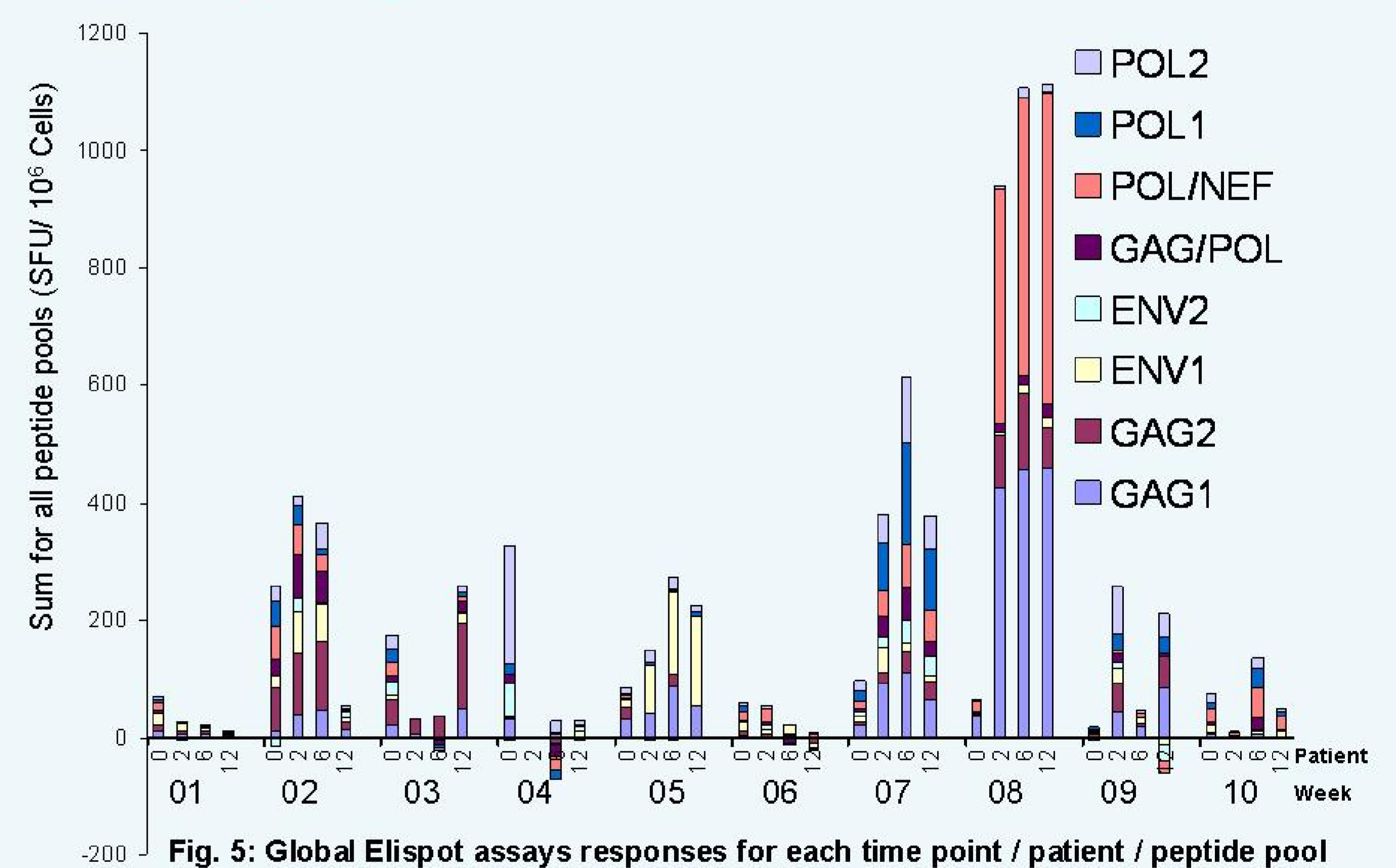


Fig. 5: Global Elispot assays responses for each time point / patient / peptide pool

- Six of the ten patients generated at least one new response (i.e. a negative response at baseline increasing > 55 SFU/10⁶ cells at at least one time point); four patients generated at least two responses.
- The two patients who had at least one positive response at baseline, did not significantly increase these responses after vaccination.
- The median fold increases of the sum of all responses were 0.97 (range 0.14-14.81) at week 2; 1.87 (0.17-6.35) at week 6; and 1.47 (0.07-17.60) at week 12. This means that MVA-B did not significantly induce HIV-1 specific T cell immunity, measured by Elispot in these ten patients.

Conclusion

MVA-B is safe and well tolerated in HIV-1 infected patients on concomitant successful cART. Six of the ten patients generated at least one new HIV-1 specific response.