Immunogenicity and VL Rebound after ATI in Chronic HIV Infected Patients Receiving MVA-B

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Goal

To evaluate a) the safety, b) immunogenicity of MVA-B administered by an IM injection on week 0, 4 and 16 in HIV-1 infected patients during concomitant successful antiretroviral therapy and c) the viral load control after an analytical interruption of cART

Introduction

Poxvirus-based vaccines have shown great potential as HIV vaccines. We present the safety and immunogenicity results of a phase I, double blinded, placebo-controlled therapeutical vaccine trial of an MVA vector expressing HIV-1 antigens from clade B (Bx08 gp120 and IIIB gag/pol/nef) in successfully cART-treated HIV-infected patients who underwent cART interruption.

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). Immunogenicity to the vaccine insert and the rest of the HIV proteome was assessed by IFNg ELISPOT using 15mers overlapping peptides covering the immunogen sequence (27 pools) as well as the viral sequence not targeted by MVA-B (17 pools). Optimal CTL epitopes were identified and their functional avidity was analyzed Responses to EBV were also assessed according to patient's HLA to rule out unspecific immune activation. A subgroup of 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) to assess a potential benefit in viral reactivatin with disulfiram to facilitate the elimination of latent viral reservoir. (García F et.al.) cART was discontinued 8 weeks after the last dose of MVA-B and viral rebound dynamics were assessed during the first 12 weeks of cART interruption.

Results

❖ **Safety:** Vaccinations were well tolerated with no grade 3 or 4 side effects reported and viral load (VL) was maintained below detectable levels in all patients while receiving cART and MVA-B challenges.

❖ **Immunogenicity:** minimal changes in breadth and total magnitude of HIV-specific responses were detected between vaccinees and placebos. A minor yet statistically significant increase in the responses targeting vaccine inserts of Gag and Env-gp120 was observed after 2 vaccinations and was maintained over time (median Gag responses of 290, 403 and 435 SFC/M PBMC at baseline, w6 and w24 respectively, p=0.02 and p=0.04) No changes in functional avidity was observed in Gag-specific responses as a result of vaccination. Responses to unrelated viruses (i.e. EBV) were not modified with MVA-B vaccinations.

❖**Viral rebound during analytical treatment interruption:** ATI was safe and well tolerated without major side effects. All patients rebounded after cART interruption. At week 12 after cART interruption, median reduction in VL (as compared to setpoint VL before any cART) was -0.24 vs -0.53 log copies/ml in MVA-B vs placebo, respectively (p=0.74). In the subgroup of patients that did not receive disulfiram, a delay in the rebound of VL in vaccinees was observed compare to placebos. The viral load delay in rebound was not well explained by measures of T-cell immunogenicity used so far.

Conclusion

MVA-B vaccination was a safe strategy to increase Gag and Env-gp120 specific T cell responses in HIV infected individuals with existing HIV-specific immunity but had only a marginal impact in VL rebound after cART interruption. A sieve analysis on the reemerging viruses is ongoing.

Figure 1. Clinical Trial Design

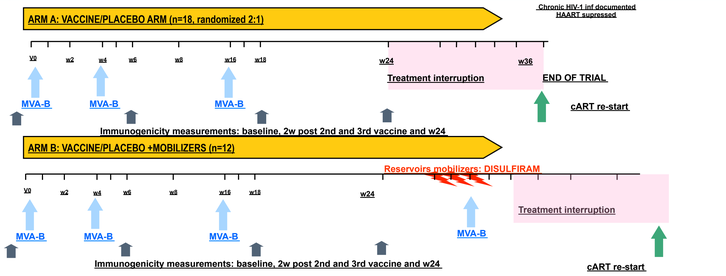


Table 1. Number of individuals suffering local or systemic side effects after any vaccination.

Local Reactogenicity	Grade I (# patients)	Grade II (#patients)
Pain	21	0
Redness	7	0
Itching	7	0
Induration	1	0
Systemic Reactogenicity	**Grade I (# patients)**	**Grade II (# patients)**
Headache	11	3
Malaise	14	2
Myalgia	11	0
Nausea/vomiting	4	0
Chills	11	1

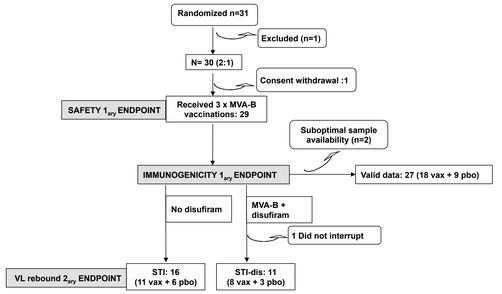


Figure 2. Minimal increase in Breadth and Magnitude of total HIV-specific responses during MVA-B vax

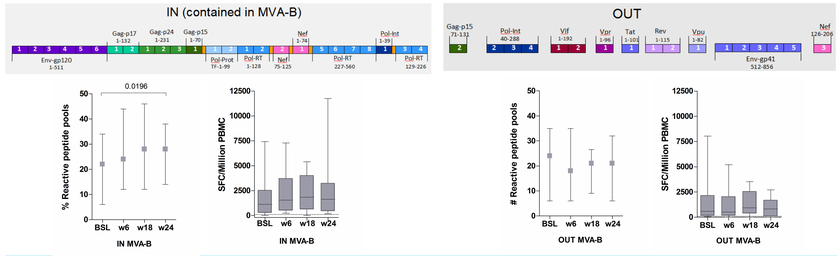


Figure 3. Increase in Gag and Env gp120 specific response in vaccinees vs placebo

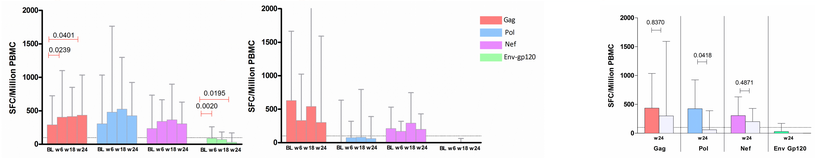
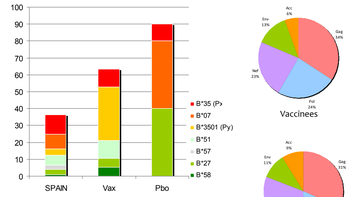
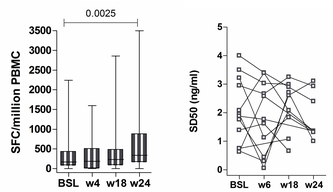


Figure 4. Increase in breadth of responses to defined CTL epitopes contained in the immunogen but without increases of functional avidity after vaccination.



Despite different frequency of protective HLA-alleles in vaccinees and placebo recipients, there was not a different dominance of Gag responses at baseline among groups



Increase in responses to Gag optimal epitopes, without change in the avidity of the responses

Figure 5. No unspecific immune activation in vaccinees (measured by EBV-specific responses in IFNg ELISPOT)

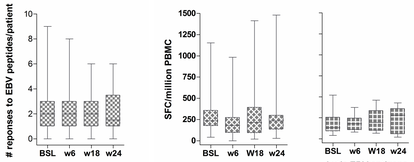
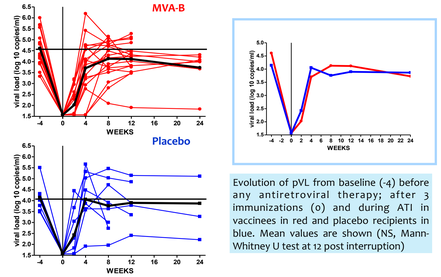
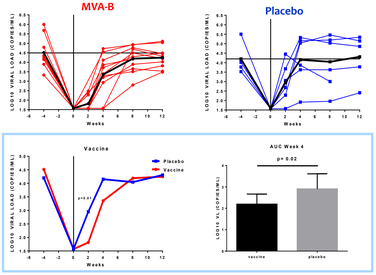


Figure 6. VL rebound after analytical treatment interruption

All group (19 vax + 9 pbo) | **Non-Disulfiram group (11 vax + 6 pbo)**



Evolution of pVL from baseline (-4) before any antiretroviral therapy; after 3 immunizations (0) and during ATI in vaccinees in red and placebo recipients in blue. Mean values are shown (NS, Mann-Whitney U test at 12 post interruption)



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