

Title: Safety and Immunogenicity of MVA.HIVA by 3 Different Routes

Eftyhia Vardas¹, Giuseppe Pantaleo², Pierre-Alexandre Bart², Andrew Robinson³, Colleen Pieterse³, Richard Thomas⁴, James McIntyre¹, Glenda Gray¹, Mampedi Bogoshi¹, Simnikiwe Mayaphi¹, Patricia Fast⁵, Claudia Schmidt⁶, Jill Gilmour³, Tony Tarragona⁶, Carol Smith⁷, Len Dally⁷

¹Perinatal HIV Research Unit, HIV AIDS Vaccine Division, PO Box 114, Diepkloof, Johannesburg, South Africa, ²Division of Immunology and Allergy, VIC BT06 – CHUV, CH-1011 Lausanne, Switzerland, ³Medical Research Council, HIV Vaccine Research Unit, PO Box 70380, Overport, South Africa, 4067, ⁴Simbec Research Limited, Merthyr Tydfil Ind. Park, Cardiff Road, Merthyr Tydfil, South Wales, UK, CF48 4DR, ⁵International AIDS Vaccine Initiative (IAVI), 110 William Street, 27th Floor, New York, NY 10038-3901 USA, ⁶IAVI Core Laboratory, 369 Fulham Road, London, England, ⁷The EMMES Corporation, 401 N. Washington Street, Suite 700 Rockville, Maryland 20850, USA

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Introduction

Two candidate HIV vaccines¹ designed for Africa and developed by the Medical Research Council, Oxford in collaboration with University of Nairobi and IAVI, have been tested previously for safety and immunogenicity; the MVA.HIVA vaccine was always given at 5x10⁷ pfu intradermally, often after priming with a DNA vaccine bearing the same sequences.

Study IAVI #011 tested MVA.HIVA as a single vaccine given at two dosage levels and by 3 routes. It was planned as a companion study to IAVI #010 (Poster 324P), which² involved three dosage levels and 3 routes all given after priming with the corresponding DNA plasmid, pThr.HIVA. Volunteers were followed for 18 months with clinical and laboratory examinations and both T-cell and antibody assays were performed. The data are presented here by group; investigators, sponsor and volunteers will be individually unblinded after the study ends this month.

Methods

A total of 81 healthy HIV-seronegative volunteers were enrolled at 4 clinical trial sites (PHRU, Chris Hani Baragwanath Hospital, Johannesburg and MRC Durban, South Africa; CHUV, Lausanne; SIMBEC, Wales). Written informed consent was obtained from all participants. Safety assessments were made by interim medical history, clinical exam, and routine safety parameters. Local and systemic reactogenicity events were prospectively collected for a period of 14 days post-vaccination, other adverse events including serious adverse events were collected throughout the study. HIV specific T-cell responses were evaluated by ex-vivo IFN- γ ELISPOTS on frozen PBMC's in the IAVI Core Laboratory, Imperial College, London.

Results: Data are presented by group

Serious Adverse Events (SAEs): There were no Serious Adverse Events that were judged to be possibly, probably or definitely related to study vaccine.

Local reactions after MVA.HIVA by Dosage Group (all routes combined) Fig 1: Most volunteers had no (27%) or mild (73%) local reactions to the vaccination. Erythema and induration were the most frequently observed local reactions. Moderate or severe local reactogenicity was observed only in the Mid Dosage (MD) group: 7/42 (17%); there was none in the low dose (n=24) or placebo (n=14) group (Fisher's exact test; p = 0.0322). One volunteer in MD SC experienced severe pain and severe tenderness (defined as significant discomfort and/or taking NSAID), one in MD IM experienced severe induration (defined as diameter > 3cm) and one in MD IM experienced severe pain. **Local reactions after MVA.HIVA by Route (all dosage groups combined)**

Fig 2: Over all MVA dosage groups, moderate or severe local reactogenicity occurred in 1/24 (4%), 2/24 (8%) and 4/18 (22%) of volunteers following vaccination by SC, IM, and ID routes, respectively, showing no significant difference. (Fisher's exact test; p = 0.2132).

Systemic reactions after MVA.HIVA by Dosage Group (all routes combined) Fig 3: Volunteers in the MD group experienced moderate systemic reactogenicity, 3/24 (7%), at a frequency not significantly higher than LD: 0/24 (0%), or Placebo 0/15 (0%). (Fisher's exact test; p = 0.2934). There were no severe systemic reactogenicity events.

Results: Data are presented by group

Fig1: Maximum Local Reaction per Volunteer within 14 Days after MVA or Placebo Vaccination by Dosage Group (all routes combined)

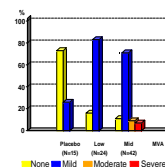


Fig2: Maximum Local Reaction per Volunteer within 14 Days after MVA Vaccination by Route (low and mid dosage groups combined)

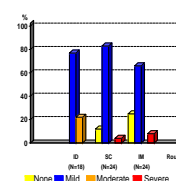


Fig 3: Maximum Systemic Reaction per Volunteer within 14 Days after MVA or Placebo Vaccination by Dosage Group (all routes combined)

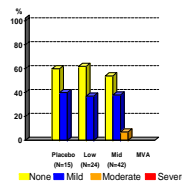
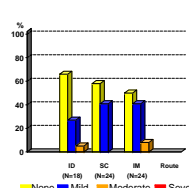


Fig 4: Maximum Systemic Reaction per Volunteer within 14 Days after MVA Vaccination by Route (low and mid dosage groups combined)



Systemic reactions by Route (all dosage groups combined) Fig 4:

Combining MVA.HIVA dosage groups, moderate systemic reactogenicity occurred in 0/24 (0%), 1/18 (6%) and 2/24 (8%) of volunteers following vaccination by SC, ID and IM routes, respectively, showing no significant difference (Fisher's exact test; p = 0.4839).

Following placebo, there were no moderate or severe local or systemic reactogenicity events.

Unsolicited Adverse Events (AE's): There was no difference between Placebo, LD and MD groups in the number of unsolicited adverse events that were possibly, probably, or definitely related to vaccine, and of moderate or greater severity. Placebo: 1/9 (11.1%), Low: 2/39 (5.1%), High: 3/18 (16.7%); Fisher's exact tests: p = 0.3150.

All statistical comparisons were made using Fisher's exact test (2-tailed). Statistical significance was indicated by p-values < 0.05.

Results (continued)

Most laboratory abnormalities were mild and judged not to be related to study vaccine.

Cardiac events were not prospectively collected, but there were no events suggestive of peri- or myocarditis were reported.

Immune responses (measured by IFN- γ ELISPOTS): Immune responses above the assay cut-off were seen in three volunteers. One volunteer from the LD group (IM) showed a response two months after the first vaccination; two volunteers from the MD group (SC and ID respectively) showed responses one month after the second vaccination. Each volunteer responded to 2 of 5 peptide pools covering the HIVA antigen. These responses were transient and not seen at other timepoints.

Conclusions

This recombinant MVA was safe when given at two doses, by three different routes. The higher of these doses, 5x10⁷ pfu, induced moderate and occasional severe local reactions, which resolved spontaneously, primarily pain and tenderness, erythema or induration. There was little systemic reactogenicity, no serious adverse events related to the vaccine, and no evidence of cardiac toxicity.

Cell-mediated immune responses detected by IFN- γ ELISPOTS were low. The timing used to measure responses in this study was not optimal². Recent work has shown that a DNA priming can augment the response to this MVA vaccine, but responses are modest, primarily limited to CD4 T cells³.

This work provides assurance that further studies with recombinant MVA-based HIV vaccines is likely to be safe.

References

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Volunteer Disposition

Group	Number	MVA Dosage/Route	
		Month 0	Month 2
		5x10 ⁷ pfu MVA (Low dosage, LD) or Placebo	
A	12/3	SC (12/3)*	SC (12/3)*
B	12/3	IM (12/3)*	IM (11/3)*
		5x10 ⁷ pfu MVA (Mid dosage, MD) or Placebo	
C	18/3	ID (18/3)*	ID (2/1)*
D	12/3	SC (12/3)*	SC (0/)*
E	12/3	IM (12/3)*	IM (0/0)*
Total Number	66/15		

*Enrollment into study started in November 2003 and was halted on 31 March 2004 during an investigation of preclinical data generated while the clinical study was ongoing. Subsequently it was found that these data presented no risk. In the interim, a decision was made to limit further clinical development of the vaccine for prophylactic use. No further vaccinations were given. Numbers in red indicate actual vaccinations given.