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Studies of a prophylactic HIV-1 vaccine candidate based on modified vaccinia virus Ankara (MVA) with and without DNA priming: Effects of dosage and route on safety and immunogenicity ☆

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Abstract

Background: Two parallel studies evaluated safety and immunogenicity of a prophylactic HIV-1 vaccine in 192 HIV-seronegative, low-risk volunteers. Modified vaccinia virus Ankara (MVA) and plasmid DNA (pTHr) expressed HIV-1 clade A gag p24 and p17 fused to a string of 25 overlapping CD8+ T cell epitopes (HIVA).
Methods: These studies compared intramuscular, subcutaneous, and intradermal MVA at dosage levels ranging from 5×10^6–2.5×10^8 pfu. In Study IAVI-010, DNA vaccine was given as a prime at months 0 and 1, followed by MVA as a boost at months 5 and 8. In Study IAVI-011, MVA alone was given at months 0 and 2. Regular safety monitoring was performed. Immunogenicity was measured by the interferon (IFN)-γ ELISPOT assay on peripheral blood mononuclear cells (PBMC).
Results: No serious adverse events were attributed to either vaccine; most adverse events were mild or moderate, although MVA resulted in some severe local reactions. Five vaccine recipients had at least one positive IFN-γ ELISPOT response, but none were sustained.
Conclusion: This HIV-1 vaccine candidate was in general safe and well-tolerated. Local reactions were common, but tolerable. Detectable immune responses were infrequent.

Keywords: Prophylactic HIV-1 vaccine; safety; immunogenicity; prime-boost; MVA (modified vaccinia virus Ankara); DNA vaccine

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1. Introduction

The development of a safe and effective preventive HIV-1 vaccine remains a global priority. Plasmid DNA Vaccines alone have produced weak CD8+ responses in macaques, but have primed for much stronger responses when gene components have been inserted into viral vectors [1–3]. A number of viral vectors have been developed as recombinant DNA HIV vaccines, including canarypox [4–6], fowlpox [7], replication-deficient adenovirus-5 [1], Semliki Forest virus [8], and Venezuelan equine encephalitis virus [9], and the vector we have used in the study we report below, modified vaccinia virus Ankara (MVA). Over 55 phase I/II trials of HIV candidate vaccines, and one phase III trial have tested about 30 different candidate vaccines worldwide. At least another 27 trials are ongoing, comprising 27 phase I, four phase II and one phase I study. (http://www.iavireport.org/specials/OngoingTrialsofPreventiveHIVVaccines.pdf). To date the immune responses in these clinical trials have been small when compared with responses in macaques to the same vaccines and the phase III trial that has been completed has not demon strated protection from infection [10]. The aim now is to improve immune responses in man by, for instance, increasing the dose and number of immunizations or by testing different routes of immunization. Vaccine candidates based on (MVA), a virus-derived vector, have induced SIV-specific [11] and HIV-1 specific CD8+ T cell responses in rhesus macaques [2,3,12] and enabled protection against SIV disease in macaques [13–15]. These results supported development of several DNA- and MVA-vectored vaccine constructs [16]. Human studies have indicated a favorable safety profile for DNA and MVA vaccines against HIV-1 [16–18].

The selection of immunogens for HIV vaccines has been hampered by the lack of correlates of protection against HIV-1 infection and progression to AIDS. In chronically HIV-infected persons, there is evidence of a correlation between high levels of T helper responses specific for gag and decreased viraemia [19]. Likewise, there is a positive correlation between gag-specific CD4+ T-cell responses and concentrations of gag specific CD8+ T cell precursors, and an inverse correlation of these markers with plasma HIV-1 RNA levels [20]. Hence, an immunogen was designed to induce HIV-1 specific T-cell responses to gag and selected epitopes from other HIV-1 proteins [21]. Attempts to induce neutralizing antibodies were not part of this vaccine design. The immunogen was designed for areas where HIV-1 clade A predominates.

By 2000, pTHr.HIVA DNA and MVA.HIVA vaccine constructs were ready for clinical trials. Initial studies demonstrated acceptable safety at the dosage levels and routes tested [17](W. Jaoko, personal communication; F. Nakwagala, personal communication). Overlapping studies were planned to rapidly assess safety and immunogenicity of higher dosages of the MVA.HIVA vaccine administered by three different routes, either with or without pTHr.HIVA DNA priming. These were conducted as two separate trials, but are reported together because of their complementary design and objectives.

2. Materials and methods

2.1. Recruitment and study population

Male and female volunteers in Kenya, South Africa, Switzerland and the UK were recruited by presentations to members of community organizations, hospitals, colleges, and by advertisements to the general public. Volunteers were eligible if they were free of significant medical conditions by history, physical examination and routine laboratory parameters (hematology, clinical chemistry, urinalysis); 18–60 years old; HIV-1 vaccine-naïve; and not infected with HIV-1 or HIV-2. Lactating or pregnant females were excluded. Sexually active volunteers were required to use contraception until at least 4 months after their last vaccination. Serum HIV antibody tests, with pre- and post test counseling, were performed at regular intervals using a standard ELISA method.

Enrollment in IAVI-010 commenced in April 2003 and was completed by February 2004. Enrollment in IAVI-011 commenced November 2003, and was completed in March 2004.

2.2. Regulatory issues, data monitoring and trial management

The clinical trials were conducted according to ICH Good Clinical Practice (GCP) guidelines and with appropriate national regulatory approvals and ethical approvals. Written, informed consent was obtained from all volunteers.

The Data Coordinating Centre (DCC) at The EMMES Corporation (Rockville, MD, USA) provided randomization schemes. Study site staff, laboratory staff and volunteers were blinded to the allocation of placebo or vaccine but not to the route of MVA.HIVA or dosage level. Data were entered by an Internet-based Data Entry System (IDES) and assessed at the DCC for accuracy, completeness, consistency, and validity. A Trial Steering Committee supervised the studies and an independent Data Monitoring and Ethics Committee reviewed the safety data.

2.3. Investigational vaccines

The pTHr.HIVA DNA and recombinant MVA.HIVA vaccines were developed in partnership between the University of Nairobi, the Medical Research Council (MRC) Oxford, and the International AIDS Vaccine Initiative (IAVI) [21]. Both vectors express the same consensus sequence of HIV-1 clade A gag p24 and p17 fused to a string of 25 partially overlapping CD8+ T cell epitopes (HIVA) [21,22]. Cobra Bio-Manufacturing (Keele, UK) manufactured the pTHr.HIVA DNA vaccine and matching