

## **DISCONTINUATION OF THE MERCK/HIV VACCINE TRIALS NETWORK PHASE II TEST OF CONCEPT TRIAL OF AN INVESTIGATIONAL CANDIDATE HIV VACCINE**

On 21 September 2007, an announcement was made by Merck & Co. and the HIV Vaccine Trials Network (HVTN) (which is funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health USA), that vaccinations had been discontinued in a trial of an Merck candidate AIDS vaccine. This decision was made based on recommendations from the trial's independent Data and Safety Monitoring Board (DSMB), which reviewed the interim results last week and came to a conclusion that the data obtained showed that the test vaccine was neither able to prevent HIV infection nor to reduce the intensity of viral replication in infected vaccinees. A second trial with the same product in Phambili, South Africa was also recommended to be discontinued.

The candidate AIDS vaccine (MRK-Ad5), produced by Merck is based on an attenuated Adenovirus 5 vector which has been engineered to incorporate parts of three HIV genes (gag, pol, nef). This vaccine candidate was designed to target cell-mediated immune responses which are believed to be of critical importance in controlling HIV infection at its earliest stages. The MRK-Ad5 candidate vaccine was extensively evaluated in multiple pre-clinical animal studies, as well as phase I human trials with very encouraging immunogenicity and safety results.

The trial (HVTN 502, Merck V520 Protocol 023) was designed as an international multi-centre, randomized, double-blind, placebo controlled phase II "test-of-concept" trial to enrol 3,000 HIV-negative volunteers from diverse geographical locations in the Americas, Australia and Africa, who would receive either three doses of vaccine or three doses of an inactive substance (placebo). The novel trial strategy, called phase II "test-of-concept" trial was chosen by the principal investigators in order to be able to quickly generate sufficient information on potential efficacy of this candidate vaccine. In order to ensure the safety of volunteers, the trial was designed in a "step-wise" basis, which had included an interim review of results by an independent DSMB after the enrolment of 1500 volunteers was completed. This protocol was reviewed by the WHO-UNAIDS HIV Vaccine Advisory Committee, which concluded that the proposed approach was scientifically sound.

The interim analysis conducted last week found that among 741 volunteers who received at least one dose of vaccine, 24 cases of HIV infections were observed,

as compared to 21 cases of HIV infection among 762 participants in a placebo group. The second end point of this trial evaluating the capacity of the vaccine candidate to reduce the virus load in vaccinees who nevertheless may become infected with HIV was not any different either between the vaccinated and placebo group.

This discontinuation of the trial, however, does not undermine the importance of this study for global HIV vaccine research and development efforts. In particular, this trial will generate extremely important scientific data following in-depth analysis, the results of which should provide answers to important scientific questions and allow for more rapid progress in the field of HIV vaccine development and trial design.

As of today, there have already been two phase III efficacy trials of an HIV vaccine completed with candidate vaccine produced by VaxGen in the USA and Thailand, both of which did not show any protection against HIV infection. A third large-scale phase III efficacy trial is under way in Thailand involving 16 000 volunteers; this trial which was also reviewed by an international DSMB was recommended to continue until completion in 2009.

Due to the numerous scientific challenges and unknowns, the World Health Organization's (WHO's) position with regard to the development of HIV vaccines has always been to promote parallel development and clinical trials of multiple vaccine strategies targeting all arms of the immune system, provided that they are based on solid scientific rationale and meet the highest international ethical standards.

Based on previous experience with immunization programmes, it is well recognized by WHO and its Member States that an effective vaccine for HIV/AIDS would be a highly valuable tool for controlling the AIDS pandemic. This is why WHO would like to applaud the individual scientists, research institutions from academia and the private sector, who are committed to ensuring continuous progress towards a safe, effective and affordable HIV vaccine. This enterprise is not easy, nor will it be fast and the world needs to be prepared for multiple "failures" and "negative results", which should be seen as part of a long-term battle against this devastating virus.

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WHO Initiative for Vaccine Research: [http://www.who.int/vaccine\\_research/en/](http://www.who.int/vaccine_research/en/)

Merck news release:

[http://www.merck.com/newsroom/press\\_releases/research\\_and\\_development/2007\\_0921.html](http://www.merck.com/newsroom/press_releases/research_and_development/2007_0921.html)

U.S. National Institute of Allergy and Infectious Diseases press release:

[http://www3.niaid.nih.gov/news/newsreleases/2007/step\\_statement.htm](http://www3.niaid.nih.gov/news/newsreleases/2007/step_statement.htm)

AIDS Vaccine Advocacy Coalition press release: [http://avac.org/pr\\_step\\_study.htm](http://avac.org/pr_step_study.htm)