



Shot in the dark

STEP AIDS vaccine study discontinued

by James Wilton

On January 24th 2005, the HIV Trials Network (HVTN), the National Institutes of Health (NIH), and pharmaceutical corporation Merck & Company formed a unique partnership and announced they were advancing to a phase II proof-of-concept study using one of Merck's new HIV/AIDS vaccine candidates.

Initially, the V520 vaccine was described as one of the most encouraging to date, capable of protecting monkeys from HIV and inducing a strong immune response in early human trials. The study, known as STEP, set out to determine if the vaccine was capable of preventing HIV infection in humans, or decreasing viral loads among volunteers who became HIV infected during the period of the study.

The vaccine candidate chosen for the trial used a weakened adenovirus, known to be one of the viruses that cause the common cold, to which scientists attached HIV-like properties. The weakened adenovirus was unable to cause cold symptoms in vaccine recipients, but was capable of simulating an HIV infection in order to create an anti-HIV immune response. Unlike most vaccines that create antibodies, this vaccine was designed to create killer CD4 cells capable of recognizing and destroying HIV-infected cells.

The STEP study recruited 3,000 HIV-negative volunteers, between the ages of 18-45, who were considered to be high risk for HIV infection based on their sexual behaviour. The majority of study participants were men who have sex with men (MSM) and female sex workers located in North and South America, the Caribbean, and Australia. Half of the volunteers received the vaccine while the other half received a placebo in a randomized double-blind fashion.

Organizers of the study encountered a potential problem during the recruitment of phase of the trial. If, prior to receiving the vaccine, volunteers had been naturally exposed to the same common cold virus used in the study, then antibodies against the adenovirus would already be present in their blood. These antibodies could attach to the vaccine and disable it before the killer CD4 cells had the opportunity to respond. As a result, the trial investigators decided to study the effect of adenovirus antibodies on vaccine efficacy by ensuring that half of the volunteers recruited had low adenovirus antibody levels while the other half had high adenovirus antibody levels.

On September 21st 2007, preliminary data from the STEP study was analyzed and the decision was made to discontinue vaccinations immediately. Although the complex data is still

being analyzed, the results suggested that vaccinated individuals with high adenovirus antibodies were more likely to become infected with HIV than if they were given a placebo. Except for one heterosexual woman, all of the volunteers that became infected during the study were MSM and therefore the trial results can only be applied to this group. Of the 778 males in the high adenovirus immunity group, 22 out of 392 vaccine recipients became infected while only nine out of 386 in the placebo group became infected. Even among the individuals with no adenovirus antibodies, no protective effect was observed between the vaccine and placebo groups. The vaccine was also ineffective at reducing viral load in vaccine recipients that became infected during the course of the study.

At this time, it is unknown whether the increased susceptibility among study participants with high adenovirus antibodies was a direct result of the vaccine, differences in the study population, chance, or an unknown biological phenomenon. Follow-up analysis of the study populations revealed that vaccine recipients were more likely to engage in high risk behaviours, possibly explaining why a higher infection rate was observed in this group. Men with high adenovirus immunity were also more likely to be uncircumcised and therefore without the putative protective benefit of circumcision. Furthermore, the high level of adenovirus antibodies may be indicative of some other biological, social, or behavioural factor that places this group at a higher risk of contracting HIV. Organizers of the STEP trial will continue to monitor infection rates among volunteers in their search for answers to determine whether increased risk persists over time.

Regardless of the reason for increased susceptibility to HIV infection, the preliminary study results were determined to be unacceptable since over 90 percent of individuals in developing countries, where a vaccine is needed most, have high adenovirus immunity.

The future of adenovirus-based vaccines remains uncertain and the increased susceptibility to infection raises ethical issues that must be addressed before attempting another trial. Some scientists argue that the vaccine should never have proceeded to phase II trials because the pre-trial results were unconvincing.

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The pressure to produce an AIDS vaccine may be leading to vaccines entering clinical trials without adequate testing. Nonetheless, the study cannot be called a complete failure: the trial showed unprecedented engagement, commitment, and organization of all involved which allowed the study to quickly answer the questions it set out to answer.

For further information about the STEP study and other AIDS vaccines visit www.stepstudies.com/ and www.hvtv.org. ☺

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