Phambili trial – factsheet from the South African AIDS Vaccine Initiative

Background

The first large-scale phase IIb HIV vaccine trial in South Africa was stopped in October 2007 because results from a similar trial conducted in the USA showed that the test vaccine was not effective at preventing infection in volunteers.

In September 2007, the United States' National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, the pharmaceutical company Merck and the NIAID-funded HIV Vaccine Trials Network (HVTN) announced that immunisations in the HIV vaccine clinical trial known as the STEP study would be discontinued. The decision was based on recommendations made by an independent Data and Safety Monitoring Board (DSMB), which analysed early data and concluded that the vaccine did not prevent HIV infection nor reduce the amount of virus in those who became infected with HIV. The STEP study started in 2004 and was conducted in the USA, Australia, South America and the Caribbean. This study had enrolled mostly men who had sex with men and had enrolled 3000 volunteers.

Based on review of the STEP data, an independent South African DSMB concluded that there was no basis for anticipating more favourable results in the South African clinical trial known as the 'Phambili' study which was testing the same product in South Africa. Therefore, the trial was stopped in South Africa.

The Phambili trial in South Africa started in February 2007 and had enrolled 801 volunteers. The Phambili trial was conducted from five trial sites in South Africa under the auspices of the South African AIDS Vaccine Initiative (SAAVI) and the HVTN.

Approval

The Phambili trial was approved by the Medicines Control Council, the ethics committees of the University of the Witwatersrand, University of Cape Town, University of KwaZulu-Natal and the University of Limpopo. The institutional biosafety committees and the Genetically Modified Organisms committee in the Department of Agriculture reviewed and approved the trial in South Africa.

Monitoring

The Independent Data and Safety Monitoring Boards (DSMB), periodically review data from the trial, make recommendations, including for the stoppage or closure, based on safety and efficacy data, as it becomes available.

In the case of the Phambili trial the South African DSMB erred on the side of caution to stop and close the trial when the data from the STEP study of the same candidate vaccine indicated that it did not stop infection, it did not ameliorate disease progression, and that there was a small (but not statistically significant) possibility that those who received the vaccine might be more susceptible to infection.

The science

A test vaccine itself cannot cause HIV infection as they don't contain any live HIV. HIV vaccines are usually made up of synthetic fragments of HIV genetic material which themselves cannot cause HIV infection which are placed into a carrier – in this case the carrier is an adenovirus – one of the common cold viruses. In this case the vaccine was made from fragments of three HIV genes.

All the volunteers had to be HIV negative at the start of the study and were given ongoing risk-reduction counselling and access to other proven prevention methods to ensure as much as possible that they protected themselves from infection.

HIV vaccine trials are conducted according to the gold standard for clinical trials, namely as randomised, double-blinded (meaning neither the clinicians nor participants know if they have received the vaccine or the placebo), placebo-controlled studies, which are designed to minimise risk to clinical trial participants. These take place in a number of phases where safety of volunteers is always paramount. Any candidate vaccine or medicine, before it goes into the public health system, is tested in phase I, II and II studies. This is the only way to licence a successful vaccine. In this case an

intermediate efficacy trial was held using a relatively limited number of people before going into a large-scale phase III trial which would have involved much larger numbers of people.

The results of the trial and what they mean

Both studies were primarily looking at two outcomes – namely whether the vaccine presented infection with HIV in those who were negative and also whether the vaccine reduced the amount of virus in those who became infected during the study.

Results from the STEP study showed that the vaccine was not effective at either stopping or controlling infection. A total of 49 cases of HIV infection were seen among 914 male volunteers in the vaccine group compared to 33 cases among 922 male volunteers in the placebo group. This shows that the vaccine could not prevent infection. The virus levels were similar in both the placebo and vaccine groups. This means the vaccine could not control infection.

The data are not completely conclusive but there is a possibility that those who received the vaccine might have an increased susceptibility to acquiring HIV infection. The researchers don't know the reason for this but some of the factors which may be important include:

- pre-existing immunity to the cold virus (Adenovirus type 5) which is the carrier (people have different levels of immunity depending on previous exposure to the cold virus and this might be important in South Africa where there might be higher pre-existing immunity to adenoviruses). From the data, people with higher pre-existing immunity seemed to be more susceptible to HIV infection. Among 778 male volunteers who had high levels of pre-existing immunity to the carrier 21 cases of HIV infection were observed in those who had received the vaccine and 9 cases of HIV infection were observed in the volunteers who had received placebo;
- whether the men were circumcised or not (circumcision has been found in other studies to protect against infection);
- the type of HIV that people were infected with; and,
- population differences, demographic, geographic and biological reasons.

Further data analyses are ongoing to try and answer some of inconclusive questions. There are no data yet available from the Phambili study.

What will happen to the volunteers?

Based on this data from the STEP Study, volunteers in both the Phambili and STEP studies will be counselled about this possibility. All volunteers in the Phambili study are being told whether they received the vaccine or placebo and will receive further related tests and ongoing counselling.

Volunteers who became infected with HIV during the trials will receive appropriate medical treatment and care.

The Phambili sponsors and trial sites have taken the following steps:

- Counselling participants about the possibility of vaccine-related risk enhancement, along with a full explanation of the limited that are the basis for this counselling message.
- Unblinding the participants, i.e. clarifying to each participant as to whether he or she had received the candidate vaccine or the placebo (dummy vaccine).

The trial sites contacted people via SMS, by sending drivers to collect participants and by sending community liaison officers to participants. They also sent out letters explaining the data and implications for participants.

SAAVI has a dedicated community involvement programme called Masikhulisane. Masikhulisane educates and raises awareness about all aspects of HIV vaccine research and development and clinical research. This is done by contacting different sectors, e.g. the women, youth, trade union, traditional healer sectors, to facilitate workshops and awareness-raising and educational sessions. Masikhulisane's vision is a South African society working in a mutually beneficial and meaningful partnership with researchers within a vibrant human and legal rights environment. Masikhulisane believes in active and sustained community involvement in the HIV vaccine research and development process. For further information and workshops contact the Masikhulisane programme at (021) 938 0552.

Trial site communities are also encouraged to contact their Community Advisory Groups if they have further questions.

The future

It’s clear that the path to a successful HIV vaccine is going to be a long one. Results like these are disappointing but each trial teaches us a little more about what it might take to beat this virus. According to AVAC. we cannot say for certain that the vaccine itself increased the risk of acquiring HIV. We also cannot say that it did not. Under these circumstances, AVAC feels that the field should slow down and take as much time as it needs to explore the underlying causes of the observed trend before launching trials of similar candidates.

In the meantime, there are proven methods of protection including HIV/AIDS education and behaviour change, condom usage; medically supervised circumcision; needle-exchange programmes and the prevention of mother-to-child transmission. A successful vaccine will add to this arsenal of protective measures against HIV infection and AIDS.