Where are we going with HIV vaccines?

Lynn Morris, Carolyn Williamson, Koleka Mlisana and Glenda Gray

The disappointing results from the HIV Vaccine Trials Network (HVTN) 502 phase IIB vaccine trial (also known as the STEP trial) has caused the scientific community to pause and wonder ‘What went wrong?’ and even worse ‘Is a vaccine against HIV possible?’ This trial demonstrated no potential benefit of the Merck Adenovirus 5 (Ad5) HIV vaccine, and in some participants with pre-existing immunity to Ad5, increased susceptibility to HIV infection.1 Some of the answers to the first question will come from a full analysis of this trial as well as the South African equivalent trial (HVTN 503/Phambili) that was halted last year. Attempting to answer the second question has brought about a re-think of current paradigms. This has resulted in a call for a back-to-basics approach, requiring a better understanding of both the virus and human immune responses to HIV.

History of vaccination

The history of vaccination is a good-news story—one from which we need to draw encouragement and inspiration in the wake of the failed Merck Ad5 vaccine. Smallpox was eradicated by vaccination with vaccinia, a virus related to smallpox; and polio should be eradicated in the near future. We have successful vaccines against measles, hepatitis A and B and many other viral infections—we know that vaccines work and in many cases we have a good idea of how they work. Part of the difficulty in making a vaccine against HIV is that we do not know the type of immune responses to stimulate in order to provide protection against either HIV infection or to control viremia. This is because unlike other viral infections, there is no spontaneous clearance of HIV from the body: once infection is established a person is infected for life. Thus, an HIV vaccine needs to do better than nature, which is no small task. Nevertheless, the immune response against HIV is extremely potent at keeping the virus in check for many years, although as a result of its remarkable ability to mutate, HIV evades and erodes these defences, eventually causing complete immune collapse. This exceptional variability, too, presents an enormous obstacle to vaccine developers, who are finding it difficult to design a vaccine which will protect against such enormous diversity.

How do vaccines work?

Most vaccines work by laying down a network of antigen-specific memory B and T cells that on exposure to the pathogen rapidly expand and control the infection. Neutralising antibodies, produced by B cells, are able to bind virus particles and probably restrict the initial burst of viremia; while cytotoxic T cells (CTL) kill virus-infected infected cells. Unfortunately, it has not yet been possible to stimulate broadly neutralising antibodies to HIV through vaccination, and indeed such antibodies are rarely ever made in HIV-infected humans. Many early vaccine efforts have focused on eliciting T-cell responses, as these responses have been associated with the initial control of HIV replication following infection, and some CTL responses have been shown to control virus replication. The Merck Ad5 vaccine was designed to stimulate CTLs, and while this did occur in a large proportion of the vaccinees, an early analysis of data has shown that these CTL responses failed to control the levels of virus in participants who became infected during the trial.2 This has caused much debate as to whether the failure of the Merck Ad5 vaccine was due to the vaccine per se or whether CTL are indeed a useful correlate of immune protection. Experimental evidence in monkeys has shown that CTL can control HIV replication in vivo and so the concept of inducing these immune responses remains solid.

What have we learned from HIV vaccine efficacy trials?

There is no doubt that the HIV vaccine field has suffered a number of major...
need to double them. But, we need to do it smartly and differently. There are many interesting approaches and novel ideas being discussed in basic research laboratories. We need to find a way to get these funded and fast-tracked in order to speed up the testing of potential efficacious vaccine products. This includes devising better ways to assess candidate vaccines and a robust go/no-go strategy. For example, there was considerable debate as to whether a large scale efficacy (Phase III) trial (called the PAVE 100 trial) of a DNA prime in combination with a different Ad5-vectored vaccine boost should go ahead. In the end a decision was made not to conduct this trial and in its place the HVTN 505, a smaller Phase II trial will start later this year in the U.S.A. among men who have sex with men. This is a small focused trial aimed to assess if the vaccine lowers viral load in the blood among individuals who subsequently become infected with HIV despite vaccination (as there was some hint of this in a subgroup analysis of the Merck Ad5 trial). It will be conducted on individuals who do not have pre-existing immunity to Ad5 and who are circumcised (uncircumcised men were at even higher risk in the STEP trial) to maximise safety. This vaccine is not expected to prevent HIV infection or be licensed, but it will help to inform us about the role of CTL and guide the next generation of vaccines. It is highly unlikely, given our current knowledge, that Ad5-vectored vaccines will be tested in South Africa, which has high rates of Ad5 antibodies and low rates of circumcision.

What role can South Africa play?

As the country with the most HIV infections in the world, South Africa has the greatest need for an HIV vaccine. The importance of starting a vaccine programme was recognised over 10 years ago and the South African AIDS Vaccine Initiative (SAAVI) is now an internationally respected contributor to the global effort. Two locally designed vaccines, a DNA vaccine and a Modified Vaccinia Ankara (MVA)-vectored vaccine containing genes from HIV strains circulating within South Africa are currently being tested in a Phase I safety trial in the U.S.A., with vaccinations due to start in South Africa later this year. Furthermore, South Africa has the infrastructure to run large-scale efficacy trials, as recently demonstrated by the Phambili trial. It is imperative that South Africa is not deterred by the recent setbacks and continues to build on the years of investment and hard work to make a major contribution towards this global health crisis.


