HIV does have Achilles Heels or points of weakness. The development of an HIV vaccine is likely to require out of the box thinking. A global vaccination programme. The same could be done for HIV if a safe and effective vaccine is developed, which would enable researchers to use this knowledge to trick the immune system of uninfected people into making similar antibodies.

Two for the price of one

Developments in the field suggest it is unlikely that a single strategy will produce an effective immune response. Future vaccines are likely to combine more than one vaccine and may require regular booster shots, rather than a single dose.

Challenges?

Developing vaccines is never easy. It takes both money and time. But the development of an HIV vaccine poses many additional challenges. Chief among these is the inherent genetic diversity of the virus and the uncertainty of what it really takes to produce a protective immune response, not just an immune response. No perfect animal model exists that mimics all aspects of HIV-1 infection and disease progression in humans.

To date, vaccine trials have been performed using thousands of uninfected people, and watching to see how many are protected. Developments in the field of pre-exposure prophylaxis mean that, in the future, it will be unethical to deny high-risk groups these treatment options. Vaccine trials will thus need to include much greater numbers of individuals to ensure the studies are sufficiently powered to prove statistically significant benefits. Increased study size will make future trials even more costly to perform.

The world needs a vaccine

ARVs have transformed the HIV epidemic but for many, especially in Africa, the logistic costs and means that HIV remains a serious health risk. Caring for those infected and affected by HIV is a huge burden for individuals, communities and governments. The availability of a cost-effective, low-risk HIV vaccine will protect individuals and society.

Smallpox plagued mankind for centuries. It is estimated the smallpox virus claimed 350 million lives, but since 1978 this scourge has not taken the life of a single person. The smallpox virus was eradicated through an orchestrated global vaccination programme. The same could be done for HIV if a safe and effective vaccine is developed.

The development of an HIV vaccine is likely to require out of the box thinking. HIV does have Achilles Heels or points of weakness.
are being used to protect high risk individuals from contracting HIV, in a treatment regimen known as pre-exposure prophylaxis or alternatively post-exposure prophylaxis. It works but it is expensive, difficult to implement and the toxicity of the drugs results in significant adverse effects being reported among recipients, leading to poor compliance.

In an attempt to alleviate the adverse effects and improve drug delivery to the site of infection, several research teams, including South African CAPRISA group, have explored the option of providing ARVs topically i.e. by applying the drug directly to the genital mucosa. The CAPRISA study demonstrated this approach was able to afford protection, while minimizing the adverse effects.

ARVs have transformed the HIV/AIDS landscape, but the costs, both tangible and intangible, along with concerns over the emergence of drug resistant strains of HIV mean the development of an HIV vaccine remains an imperative.

Where do we stand?
Initially, the goal of vaccine development was to prevent transmission and to protect the individual from infection, thus stopping the unfolding epidemic. An understanding of the natural infection along with setbacks and frustrations over the last 30 years has seen scientists also consider developing a vaccine to slow the progression of the disease. Such a vaccine would enable the HIV positive to join the ranks of the elite controller (those infected with HIV but able to control the infection without antiretroviral therapy), while still providing protection to society as a whole, since the risk of transmission has been found to be proportional to the viral load within the infected individual. While the current emphasis on vaccine development lies in targeting antibody responses to prevent infection, both options are being pursued with the ideal vaccine being able to reduce transmission and reduce viral loads in those people who do become infected.

Progress to date
The fundamental principal behind any vaccine involves eliciting a protective immune response to the whole or a component of the organism, before infection occurs. It is critical that the immune response generated is protective. This has been the challenge in the current search for an HIV vaccine; the virus already produces a robust immune response in people infected, but the immunity is not protective.

A key area of focus has been to establish the “right” target. The experience from natural infections confirmed that the whole virus, albeit in an inactivated form, is unable to elicit such a protective effect. Attention shifted to the actual proteins themselves to try to expose the vulnerable parts, the vectors. Recombinant versions of these proteins have been formulated as “targets” and “vectors”. After that, the proteins inside the virus particle became the “target”; they combined a recombinant version of the gp120 protein with an adenovirus (HVTN 502).

The realisation that the antibody response against gp120 proteins was not sufficient to produce protection saw researchers switch track. Researchers formulated the “target” so that instead of producing an antibody response, the “target” would activate the cytotoxic T cells (CD8). This trial became known as the STEP trial and the target included several recombinant HIV proteins, including the surface proteins of the virus, gag, nef and pol, all packaged inside an adenovirus (HVTN 503).

Once more, the vaccine was able to produce a robust immunological response in recipients, but this was not protective. Disturbingly when the numbers were crunched, there was some suggestion that the vaccine may have increased the number of infections in uncircumcised men.

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Stepping in a different direction
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Back to basics with help from a pap virus
The trial which was the first to demonstrate a modest protective effect is the RV144 study, which was done in Thailand. This RV144 trial used the canary pox virus that contained three HIV genes namely the envelope, gag and protease (ALVAC-HIV). This was given in conjunction with another vaccine that just used the gp120 protein. Although neither of these vaccines had worked alone, using both together made a significant difference to the overall response. This trial reported that people who had received the vaccine showed a 31% reduction in new infections at the end of the trial. The benefit was particularly seen in the first year of the three-year study. In those people who received the vaccine but still became HIV positive, the vaccine did not help to reduce the viral loads.

Since the vaccine did not produce neutralising antibodies, the protection areas through some other mechanism, more than likely mediated by other kinds of antibodies. The trial will be repeated in South Africa. The success of the RV144 vaccine has served as a beacon of hope for the potential to develop a vaccine which can decrease transmission.

Future prospects?
Start at the front door
Eliciting an immune response it not enough. The average person infected with the HIV virus produces an immune response which controls the virus for many years. However, eventually the virus will escape the immune response and the person will develop AIDS. The immune response is not able to prevent the spread of HIV from the initial site of infection. To date, efforts have focused on either preventing infection or clearing the virus from the systemic circulation. But, the HIV battle is won or lost at the front door. Viral sequence analysis, known as single-genome amplification suggests it all begins with one virus.

It takes this virus several days to breach the boundary walls and slip into the lymphatic system. Once the virus reaches the systemic circulation, stopping it becomes incredibly difficult, maybe impossible. The state of play of the boundary, for example the genital mucosa, has a profound influence on whether a virus slips through. It is already clear that a thick layer of healthy epithelial tissue is more-or-less an impenetrable barrier. Animal studies suggest that exposure to vectors capable of providing lower, but persistent levels of antigen, are able to elicit a T cell memory response, which is able to provide protection following intra-rectal administration of highly pathogenic strains of SIV (SW is the monkey equivalent of HIV). Antibodies are also able to prevent infection in animal models.

Can some people make good antibodies?
But there are exceptions, namely the broad neutralisers. These are rare people who have cracked the code on how to produce broadly neutralising antibodies. Complex biology is helping them to create these unusually potent antibodies. One avenue currently being explored is the direct administration of these antibodies as a therapy. It is hoped that if the field of reverse vaccinology develops, researchers will be able to create an appropriate target, which will see those vaccinated with these antigens produce neutralising antibodies.