The quest for an AIDS vaccine: a scientific perspective

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In the 28 years since the human immunodeficiency virus has been identified as the cause of AIDS, we have learned at least as much about its molecular biology, life cycle and interactions with the human immune system as we have about almost any other virus. Yet, despite years of effort by hundreds of scientists around the world, we have been unable to develop a vaccine that protects people from infection by this most elusive of pathogens.

There are three major reasons HIV has proved such a formidable foe. First, it is by far the most variable virus scientists have ever encountered. How variable? Consider this: you will find more genetic variation in the HIV isolated from a single person who has been infected for a few years than you will find globally in the dominant strain of influenza during a flu season. Second, because no one is known to have cleared an HIV infection, we do not know what elements of the immune response must be engaged to block the virus – and thus cannot devise a vaccine to replicate such responses. Finally, the immune system has a very narrow window of opportunity in which to neutralize HIV before it establishes a life-long infection.

Despite these challenges, scientific research suggests that developing an effective AIDS vaccine is possible. For one thing, after becoming infected most people manage to keep HIV under control for a decade before showing signs and symptoms of disease, suggesting that the immune system is capable of suppressing the virus. For another, some people infected with HIV – referred to as elite controllers – suppress the virus to levels that are undetectable for an extended period of time. Studies in nonhuman primates show that administration of high doses of neutralizing antibodies against HIV can protect them from infection by a virus that is a combination of HIV and simian immunodeficiency virus (SIV), the monkey equivalent of HIV.

In collaboration with the International AIDS Vaccine Initiative (IAVI), Global Medicine pays special attention to the development of an HIV/AIDS vaccine. In this second of three episodes, IAVI explains the scientific challenges in the development of an AIDS vaccine.
Other animal studies too suggest HIV can be thwarted. Most notably, non-human primates vaccinated with a weakened (live attenuated) version of SIV are protected from disease when exposed to matching strains of SIV that have not been weakened. All this suggests that HIV is not invulnerable to the weapons of the immune system. If we can better understand which of those weapons work, how and in what combination, we should be able to design a vaccine that will teach the immune system all it needs to know to prevent HIV infection.

A historical perspective
AIDS researchers who first attempted to develop a vaccine against HIV, beginning in the late 1980s, sought to develop one that would work primarily by eliciting an antibody response – which is how most existing vaccines exert their effects. These scientists recreated a part of HIV – a virus envelope protein – and used it as an antigen in their vaccine candidate, hoping it would elicit neutralizing antibodies. Next, they assessed this vaccine candidate’s safety and ability to provoke an immune response in animal studies, and then tested it on volunteers in a series of closely monitored clinical trials. It became clear by the late 1990s that this approach would not work with HIV.

AIDS vaccine researchers then turned their attention to harnessing the other arm of the adaptive immune response: cell-mediated immunity (CMI). The CMI response dispatches T-cells to destroy those cells in the body that have already been infected by viruses. T-cells also release substances that inhibit HIV from replicating and spreading through the body. Today, there are around 30 AIDS vac-
cine candidates in the clinical pipeline, and nearly all are devised to elicit CMI responses. Yet the performance of CMI-based vaccines has so far been disappointing.

The failure of promising vaccine candidates reinforced a growing consensus that the development of an effective AIDS vaccine requires a renewed focus on the molecular details of HIV infection. Furthermore, many scientists, including those at the International AIDS Vaccine Initiative, have come to believe that an AIDS vaccine candidate will only be successful if it is devised to engage both CMI- and antibody-based immune responses.

Current priorities for AIDS vaccine research
As outlined in the figure, AIDS vaccine designers today have two key priorities. The first is to solve the neutralizing antibody problem. That is, to identify antibodies that can neutralize a broad range of HIV variants and design vaccine candidates capable of eliciting such antibodies in people. Because most vaccines work by harnessing the antibody response, solving this problem is vital to the AIDS vaccine effort.

Some important advances have already been made in this arena. Scientists have isolated four broadly neutralizing antibodies, determined their structures in atomic detail and figured out how each of them breaches HIV’s typically impregnable defences. This information is now being applied to design prototype HIV vaccines, though the effort is in its earliest stages today. At the same time, IAVI is working with research centres around the world to isolate more such antibodies from people infected with HIV, hoping to find new clues to AIDS vaccine design.

A second priority is to discover which T-cell responses are central to the control of HIV. Scientists are evaluating the immune responses of elite controllers to answer this question. They are also studying how live attenuated SIV vaccines are able to control SIV infection. Such studies in nonhuman primates have shown that if the virus strain in the vaccine is attenuated too much, it doesn’t have any effect. This suggests that vaccine candidates may be more effective if, like naturally occurring viruses of all kinds, they are designed to multiply after injection. Most AIDS vaccine candidates are constructed by inserting genes encoding HIV antigens into an unrelated and modified virus (a vector), often one that does not typically cause disease in humans. As an added measure of safety, such vectors are also rendered incapable of multiplying. This makes them very safe, but also relatively weak provocateurs of the immune response. To address this problem, IAVI and its partners have established a programme to design and systematically evaluate safe replicating vectors (those that retain their ability to multiply) and funnel the best of them into clinical trials.

The increasing knowledge about HIV and its vulnerability to the defences of the immune system is allowing scientists to work on the design of promising novel AIDS vaccine candidates that are likely to enter clinical trials in the coming decade. How those trials are conducted will be the focus of the third part of this series on the development of an AIDS vaccine.