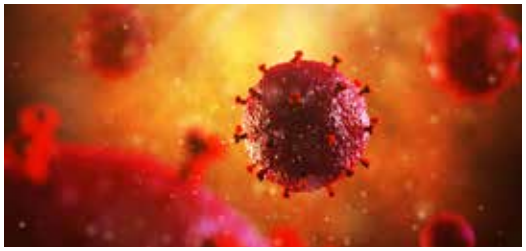


Why Are We Still Waiting for a Vaccine for HIV?

By Dr. John O'Brien, Gen Re, London

The current COVID pandemic, with its accompanying impact on daily life and activities, has made us all suddenly aware of the potentially devastating effects of a pandemic. It has potentially also distracted us from the other major pandemic of the 20th and 21st century.

According to the international AIDS vaccine initiative, 38 million people were living with HIV/AIDS in 2020. Approximately 1.5 million new HIV infections occur every year and the epidemic has claimed over 30 million lives. Even in sophisticated medical systems, a large percentage of infected people are not being treated with appropriate antiretroviral therapy. In the United States, only 66% of HIV cases diagnosed received appropriate treatment and only 57% are virally suppressed.[1]

The HIV virus, which appears to have originated in the Congo in the 1920s, first became well-known in the early 1980s when a number of men were diagnosed with opportunistic infections that would normally only occur in people with significantly impaired immune responses. It soon became clear that this was virally induced immunosuppression. At the time that identification of the virus was announced by the U.S. Secretary of Health and Human Services Margaret Heckler in 1984, it was also suggested that an effective vaccine would be available within two years. Now almost 40 years later that goal remains elusive.

In view of the rapid development of a number of vaccines against the SARS-CoV-2 virus, the question has been asked, why we are still awaiting an HIV vaccine?

Mortality in HIV has been dropping, related to the development of antiviral agents. These agents do not cure the disease but are able to prevent the manifestations and improve outcomes. Ideally, to control the HIV/AIDS pandemic, the world needs an effective vaccine.

Unique difficulties with HIV vaccine development

In trying to understand the difficulties in producing such a vaccine, one must first remember that the HIV virus is quite unique, in that no one spontaneously recovers from the infection. With other viral infections, even severe infections such as smallpox, people will recover fully from the virus and subsequently will have immunity that can be lifelong. In developing a vaccine, scientists conventionally have tried to mimic the human immune response. This, of course, is not possible with HIV as the human immune response is inadequate and incapable of neutralising the virus.

Scientists are left with trying to stimulate antibody and cellular responses that would potentially be effective in combating the infection. This is made more complicated by the fact that the HIV virus mutates rapidly and is also covered with a sugar molecule layer, which essentially hides the surface of the virus from the immune system. Other problems associated with the development of the vaccine include the lack of correlates of protective immunity. This means there aren't any easily identifiable antibodies or cellular responses that would predict that the vaccine would be effective. Finally, we do not have an animal model that will reliably predict vaccine efficacy in humans. The virus infects T lymphocytes, cells that are normally used to fight infection, leading to an impaired immune response. There is only a narrow window to prevent infection and consequent immune deficiency.

Many vaccines work to attenuate infection, but in the case of HIV the goal must be to prevent infection and block the virus at an early stage of exposure.

One of the reasons the COVID vaccine programme proceeded so rapidly was the huge financial resource that was made available. I think it is fair to say that HIV vaccine research has

been impacted by the fact that those infected are often part of marginalised or stigmatised groups, and certainly early in the epidemic there was limited funding commitment for HIV research.

HIV vaccine experience

Despite the difficulties there has been ongoing research over many years aimed at developing an effective vaccine. Unfortunately, early trials failed to show evidence of immune responses or protection, and to complicate matters, in some trials, those who received the vaccine, had a higher incidence of HIV infection.

For example, the so-called STEP trial, using an adenovirus vector vaccine which had been modified to contain HIV genes, not only proved ineffective but seemed to increase the risk of infection, particularly in men.[2] A second trial, in Phambili, South Africa was discontinued after six months. The participants were then advised whether they had received active vaccine or placebo. Follow-up studies found that those who had received the vaccine were significantly more likely to be infected. One hypothesis for this is that the vaccine attenuated immune responses because of previous exposure to adenovirus. It is also possible that there was a social explanation, in that most of the infections occurred after the blinding had been broken.[3]

The RV144 study conducted in Thailand initially held out some hope. The study demonstrated a 31.2% efficacy in preventing infection. The trial used a canarypox virus which had been modified to carry the genetic instruction for some HIV proteins.[4] The cells then produce the HIV antigens, which induce an immune response in the host. Subjects received a total of six injections. While this trial only showed modest efficacy, it was encouraging and prompted the establishment of Pox Protein Public-Private Partnership (P5).

This partnership combined vaccines from Sanofi and GlaxoSmithKline, which included sub-Saharan African strains for testing in a population at high risk of infection. In phase 1 and 2 trials, the vaccine demonstrated safety and induced good cellular and humoral responses. In the phase 2b-3 trial, known as HVTN 702 (Uhambo), over 5000 adults were randomised to receive the vaccine or placebo. The results were published this year and disappointingly showed no efficacy. HIV was diagnosed in 138 participants in the vaccine group and 133 in the placebo group.[5]

Further disappointment has recently come with the negative results from the Imbokodo study. This study used a vaccine engineered by Johnson & Johnson using a viral vector platform similar to their successful COVID-19 vaccine. It enrolled 2,600 women in southern Africa who were at high risk of HIV infection. A repeated dosing regime was used, combined with soluble protein at the third and fourth visit. Unfortunately, the vaccine efficacy was only 25.2%.[6] A companion study called Mosaico[7], including men who have sex with men and transgender people, will continue in the Americas and Europe but using a different mix of soluble proteins.

Current studies building on research findings

The RV144 study, apart from showing some degree of efficacy, seemed to indicate that for protection to occur, antibody responses were important. The concept of broadly neutralising antibodies (bNAbs) is not new. These antibodies target sites on the virus that are important for establishing infection and do not vary much between different HIV virus strains. They were first identified in a small group of HIV infected patients known as “elite controllers”. The challenge is to trigger this type of antibody as a vaccine response.

A combination of T cell response and bNAbs will probably be required to induce an adequate immune response to prevent HIV infection. The current COVID pandemic has brought new vaccine platforms into clinical use. The mRNA vaccines from Moderna and Pfizer BioNTech have demonstrated excellent efficacy both in terms of antibody responses and clinical protection against COVID-19. This platform is now being investigated for HIV vaccine development. Moderna has partnered with IAVI and Scripps Research to develop an mRNA vaccine expressing an immunogen capable of stimulating bnAbs. The phase 1 trial is expected to be completed by May 2023. Initial trial results are encouraging, with 97% of participants triggering specific B cells potentially capable of producing bNAbs. This approach is known as germline targeting.[8]

Conclusion

Because of the complex nature of the HIV virus, attempts to develop a vaccine have so far been disappointing. In the process, scientists have learnt and continue to learn much about the virus and the potential approach that will need to be used to develop a successful vaccine. This will certainly require a multistep approach but almost 40 years after starting the process there is cautious optimism that the end is in sight.

On 1 December 2021, WHO is calling on global leaders and citizens to rally to confront the inequalities that drive AIDS and to reach people who are currently not receiving essential HIV services. Find out more at: World Aids Day 2021

About the author

John O'Brien *is a specialist physician and pulmonologist. In 2016 he joined Gen Re full-time as the Chief Medical Officer (CMO) for the Global Underwriting and Research & Development department. He is now the CMO for the CUSAC segment covering Canada, UK, Ireland, Southern Africa, Australia and New Zealand, and continues to support the R&D department.*

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Endnotes

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