Why don’t we have an HIV vaccine?

Infectious diseases and the vaccines that can prevent them are the sources of some of the biggest science headlines in the past few years. Experts caution that it could be three years or more before we have a vaccine for Zika virus as fears mount over the risks for pregnant women. To the relief of global health officials, the latest Ebola vaccine trial was successful and is now moving into large-scale production even as the epidemic slowly grinds to a halt in West Africa. A recent outbreak of measles prompts pleas for parents to give the incredibly effective and safe MMR vaccine to their children. Vaccines, it seems, are all around us, and illnesses like diphtheria and whooping cough have faded from the public consciousness. Yet when it comes to HIV/AIDS, one of the most widespread epidemics in human history, one of the most effective public health interventions is missing from the toolbox. If we have been able to tackle some of the most pernicious illnesses by vaccination campaigns, why does HIV continue to elude us? Why do we still not have a vaccine that can prevent HIV infection?

In the early years of the epidemic, it was thought that development of an HIV vaccine would be straightforward once the virus was identified as the causative agent behind AIDS. In fact, the United States Secretary of Health and Human Services declared in 1984 that a vaccine would be available two years after the discovery of the virus. Yet when that time elapsed, and elapsed again, we were only marginally closer to an effective vaccine. As of 2016, there have been over 50 different HIV vaccine candidates tested, with only one showing partial efficacy – not good enough to manufacture and distribute worldwide. The failure to produce an HIV vaccine is not the result of neglect or lack of effort – 570 million pounds were spent on AIDS vaccine research and development in 2014, and thousands of research groups across the world are studying the virus in hopes of designing a more effective vaccine. But why is it so difficult? Despite being a small and relatively new virus, HIV is much more complicated than anyone imagined when it burst onto the global landscape in the early 1980s. The virus has a formidable set of defences that get the better of the human immune system’s ability to control and eliminate infection, and though it has been studied extensively for the last 40 years, it continues to challenge scientists as much as ancient diseases such as tuberculosis and cancer.

The first vaccines were derived based on a series of observations that, once infected, people were somehow protected from future illness with the same disease. If you managed to survive smallpox, or yellow fever, you did not have to worry about being infected again. This principle of a memory immune response that can fight off future infections is one of the hallmarks of vaccinology. How can we apply this principle to HIV, when most people, even when on the best treatments, will have to take anti-HIV drugs for the rest of their lives to prevent the virus from coming back? Only one person has ever been cured of HIV, via two specialised bone marrow transplants - a painful, expensive process that is impossible to offer to the 35 million people currently infected. What then? Two groups of people offer possible avenues for training the immune system to prevent HIV infection and AIDS. First, there are a small number of people who,  

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2 https://www.niaid.nih.gov/topics/hivaids/understanding/prevention/Pages/clinicalStudies.aspx
Despite multiple exposures to HIV, never get infected. What is special about their immune systems or other factors that give them protection? Second, another group of people do get infected with HIV, but never get sick and develop AIDS. What clues to controlling infection and preventing illness do their immune systems hold? Fortunately, researchers have identified groups of these rare individuals around the world and are intensely studying them (with their consent, of course) to understand what we need to do to create an HIV vaccine. The hope is that if we better understand the rare, natural cases of good immune defences against HIV, we can try and re-create those using vaccines so that healthy individuals can mimic these specialised defences and be protected.

One of HIV’s key defence mechanisms is that it has the ability to evolve on a scale that dwarfs human evolution. Humans pick up a few new mutations in their genetic code each generation, which may or may not be helpful and passed on to the next generation. Each new generation of HIV is “born” in about two days, and quirks of the virus reproduction cycle means that it can introduce many more changes to its genome, giving each new generation of viruses a wide variety of new tools to evade the immune system. It is also a battle of one vs. many: an individual person has to fight off billions of viruses that are constantly changing and adapting to the attacks of the human immune system. While most people are infected by a single virus, that “founder virus” rapidly reproduces and diversifies, with billions of copies of virus circulating throughout the body within a few weeks of infection. Not all the viruses need to survive, and indeed many do not and are removed by various defence mechanisms throughout the human body. However, as long as a few survive (remember, it only takes one virus to infect a new host!), it can keep evolving and spreading. HIV also uses one of the host’s own defences against it, crippling our ability to respond to infection by infecting and killing the very defensive cells we need to fight back. HIV does not infect all human cells – it targets a specific type of cell that is involved in the immune system and is responsible for defending against invading viruses, bacteria, and other infections. These cells, called CD4 T cells, are a critical line of defence in any infection, and by infecting and killing them, HIV cripples the immune system and prevents it from fighting back. In fact, HIV often infects activated CD4 T cells, who migrate from the site of infection to the “battle stations” of the immune system, where there are millions more CD4 T cells – which means more targets for infection, which means fewer healthy cells to try and fight off infection. By crippling the immune system early on, HIV can establish itself as a lifelong presence in its infected host. A good vaccine could prevent this massive infection and loss of CD4 T cells and provide a robust defence against the few remaining viruses.

How does HIV’s diversity and rapid evolution help it evade the immune system? The surface of the virus is decorated with molecules called glycans that are constantly changing and prevent the immune system from learning how to recognize the virus. Your immune system works well when it can recognize the same feature on a virus, so it can make thousands of copies of the cells that recognize and kill anything with that feature. HIV adapts to this, however, by disguising the essential parts of the virus with an ever-changing array of glycans, so each time the immune response learns to target one, it changes and the immune system can no longer recognize that target. Glycans can shift with each generation of the virus; meaning within a few days, what used to be a good immune response is no longer effective. This is one of the greatest challenges in designing a vaccine – what do you train the immune system to recognize when the virus is constantly changing? The key lies in the discovery of broadly neutralising antibodies, immune molecules that can recognize many different viruses (broad) and can effectively
eliminate them (neutralisation). Roughly 20% of people who are infected with HIV will, late in infection, spontaneously develop broadly neutralising antibodies – as though years of the immune system fighting the virus have finally trained it to recognize a wide array of viral defences. Unfortunately, this usually comes too late to be able to completely eliminate all of viruses. But what if we trained the body to develop these special broadly neutralising antibodies before infection, so that it was prepared to fight off any HIV it comes in contact with, no matter what glycans are on the surface? One of the major goals of an HIV vaccine is to create these broadly neutralising antibodies in people before they are infected, so that no matter how much the virus mutates, they have the ability to recognize and kill it.

Examples of people who never get infected despite many exposures to HIV, others who never get sick even after being infected for years, and the discovery of potent defence mechanisms that can kill nearly every virus they come in contact with: these are just some of the reasons that HIV researchers are confident that we will develop an HIV vaccine. There are many things we still do not understand about the development of immune memory, how the immune system learns to recognise dangerous invaders, and why some vaccines last a lifetime and some require regular “booster” doses. What if we can develop a way to produce the broadly neutralising antibodies in people before they are exposed to HIV, and they could fight off infection? What if we figure out why some people are infected but do not get sick, and use those tools in engineering a vaccine? What if the human immune system, which we understood so poorly only a century ago, is capable of more than we ever imagined? We know that these questions have answers, it just takes patience, rigorous scientific research, and a touch of luck to find them out. The other good news is that in a quest for an HIV vaccine, we are also developing the tools and knowledge that informs our development of other vaccines. In the Zika and Ebola epidemics, scientists had a jump start on designing vaccines because of the technologies and discoveries from studying HIV – and the lessons we learn from testing the vaccines for these and other diseases will help inform future HIV studies.

In the quest for an HIV vaccine, we have learned so much about the human immune system. We have made great strides in understanding a virus and a disease that we were unaware of half a century ago. The burgeoning fields of cancer immunology and cancer vaccines are helped by the understanding of the immune system generated by AIDS researchers, and insights into Ebola and Zika vaccines may provide new keys to HIV scientists. Developing an HIV vaccine is difficult and expensive, of that there is no doubt. But the potential to save millions of lives, whether in the next five years or twenty-five years, makes the effort worth it. In science what seems impossible is often found to be merely improbable, then entirely likely, then so commonplace that we assume that it was always known. Smallpox was one of the greatest scourges in history, yet now has been eliminated completely except for a few vials in a freezer, deep under lock and key. Imagine what we can do in these modern times, with all the tools of 21st century science available to us and expanding every day. We can look to the past to see the impossible accomplished, so let us try again to do what seems impossible, or now merely improbable.