

The HIV Vaccine: Barriers and Breakthroughs

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The History of HIV

Human Immunodeficiency Virus (HIV) first came to the public's attention in 1981 when young, gay men in Los Angeles began dying from infections associated failing immune systems. By the end of the year, 270 gay men across the U.S. had developed immune deficiency, 121 of whom had died. On September 24, 1982, the CDC formally named the disease Acquired Immune Deficiency Syndrome (AIDS). The cause of HIV/AIDS transmission was not determined until March 4, 1983, when the U.S. Centers for Disease Control and Prevention (CDC) announced in its Morbidity and Mortality Weekly Report (MMWR) that Acquired Immune Deficiency Syndrome (AIDS) may be spread sexually or through contact with blood ("Timeline" 2011).

In 1984, Luc Montagnier of the Pasteur Institute, France, and Robert Gallo of the National Cancer Institute announced that they independently identified the retrovirus that caused AIDS. On April 23 of the same year, Margaret Heckler, the Secretary of the U.S. Department of Health and Human Services was infamously quoted saying she hoped "to have a vaccine ready for testing in two years." Now almost 30 years later, an effective vaccine has yet to be produced ("Timeline" 2011). It is important to emphasize that the HIV virus is deadly because it devastates the body's immune system, opening the door for fatal infections to take hold that eventually overwhelm the body.

HIV's Defenses

The main barrier to creating an effective vaccine for HIV is its high mutation rate. (This is the same reason the flu requires a new seasonal vaccine every year.) Vaccines historically rely on using a weakened (attenuated) or dead virus as an easy target for the immune system to identify, thus creating immunity. One of the issues with HIV is that it destroys the body's T4 lymphocyte cells, the very cells that identify targets for the immune system. In addition, HIV's gp120 surface proteins that a vaccine would target are hidden in the HIV virus. A vaccine would also have to address the high variation in strains of HIV that are specific to different regions of the world.

HIV is a retrovirus, which means it uses RNA, a less stable form of DNA, to replicate in host cells. RNA has a much higher rate of mutation than DNA because it lacks proofreading mechanisms that ensure no mistakes are made when it replicates. Whenever a mutation happens in HIV, it is permanent. For example, a single mutation can change HIV's outer structure just enough so that the body's immune system no longer recognizes the outer gp120 proteins of the virus. That means that as soon as the body's immune system begins to recognize and attack the virus, it can mutate and avoid detection again. And in an infected person, one billion new viruses can be produced per day. This means that there could be

multiple strains of virus present in the body at one time, all with different characteristics, and all attacking the immune system (Hunt, 2009).

HIV also targets receptors found on the outside of T4 lymphocytes (helper T cells), immune cells that identify targets for the immune system to attack. Loss of T4 helper lymphocytes leads to a general failure of the immune system (immunosuppression); therefore, infections that the body would normally defend itself against become fatal (Hunt, 2009). This process makes it difficult for a vaccine to invoke a large enough immune response from the body, when HIV is destroying the very cells needed by the body to destroy HIV.

A successful vaccine will have to overcome these challenges, and find a way to provide a means for the body to identify a broad range of HIV's gp120 proteins located on the outer coat of the HIV virus. This protein is what attaches to the receptors of helper T cells and gains access to the cell to replicate itself. The region of gp120 that attaches to these receptors is the key to providing an immune response because this region is the same across all the strains of HIV. The problem is that this region is hidden on the virus by mutable regions of HIV that shield it from the body's immune system (Hunt, 2009).

Another consideration in developing a successful HIV vaccine is the wide variety of HIV strains around the world. Most cases of HIV infection are due to the HIV-1 strain, which is deadlier than the HIV-2 strain that is found predominantly in West Africa. Each strain of HIV has different groups, each with several subtypes. For example, the main groups of HIV-1 are M, N, and O. HIV-1 main group (M) has been the most deadly, infecting 60 million and causing 25 million deaths, especially in sub-Saharan Africa. It also has 9 subtypes that are spread around the globe, with subtype B representing a majority of HIV-1 infections in Europe and the Americas. HIV's high degree of genetic diversity means that vaccines will likely need to be tailored to specific areas of the globe that have higher incidences of certain types of HIV (Hunt, 2009).

HIV Vaccine: Current State

The road to a broad, effective HIV vaccine is not a straight line. A vaccine has yet to be developed 30 years after the discovery of HIV, because it is unlike any virus we have encountered in the past, slowing the development process as we learn more about HIV and its replication cycle. (Even with a more straightforward virus, the vaccine development process as a whole is slow and deliberate to ensure safety and efficacy.) Scientists have tried many different methods to create a vaccine that addresses the challenges posed by the HIV virus. These methods include subunit vaccines, live attenuated vaccines, recombinant vector vaccines, and whole cell inactivated vaccines.

The first HIV vaccine tested in humans, AIDSVAX, was an example of a subunit vaccine, which used purified HIV gp120 surface proteins to provoke an immune response. The rapid mutation rate of HIV quickly changed the structure of these surface proteins rendering this vaccine ineffective. A vaccine that cannot adjust as fast as HIV has little hope to be successful against it. The likelihood of a subunit vaccine providing protection against a broad range of HIV strains is very low because of its genetic diversity (Tong, 2013).

Another strategy is using a live attenuated vaccine, which is made from a weakened HIV virus. This strategy has been effective with other vaccines, notably measles and mumps. Some scientists have genetically deleted the NEF gene in HIV, making it benign (Tong, 2013). Recent research shows that a live attenuated virus with the gene deletion has potential to be effective. However, although the risk is low, there is a possibility that the weakened strain with the gene deletion could revert to its original, virulent form (Hunt, 2009).

The dangers associated with using a live attenuated vaccine led some scientists to consider the strategy of using a recombinant vector vaccine. This type of vaccine inserts HIV genes into an attenuated vector (another bacterium or virus) that delivers and expresses the proteins of the HIV genes inside the body to stimulate immune response. A weakened adenovirus (which causes the common cold or sore throat) has commonly been used as an HIV vaccine candidate because of its specificity for human hosts and ability to enter the body (Tong, 2013).

Another possibility for a vaccine is using a whole cell inactivated vaccine, in which the ability of HIV to reproduce has been eliminated. This strategy had not been given much attention until recently, when Dr. Chil-Yong Kang at the University of Western Ontario announced the success of his team's vaccine in Phase 1 clinical trials. This vaccine uses a genetically modified killed whole virus HIV-1 that is chemically inactivated by radiation. Dr. Kang uses the NEF gene deletion to reduce HIV's virulence and radiation to inactivate its RNA genome. The vaccine is based on the HIV-1 subtype B group, which is found predominantly in Europe and the Americas. Even though it is based on that particular group, it can easily be adapted to other HIV types, if the vaccine is successful. The biggest challenge ahead for Dr. Kang is securing funding from a large multinational drug company with the funds necessary for Phase 2 and 3 human trials, which are estimated to cost \$100 million dollars (Kang, 2012).

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