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EDITORIAL

HIV/AIDS Vaccines

How long must humanity wait?

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كم من الوقت يجب على البشرية أن تنتظر؟

علي بن عبد الله الجابري

Over forty million people are infected with the human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), and more than 95% of these infected individuals are in the developing countries. The prevalence levels for this virus will continue to rise globally. The HIV/AIDS pandemic is the most devastating global public health crisis since the great plagues of the middle-ages with approximately fifteen thousand new HIV infections and ten thousand deaths due to AIDS every day and approximately 3.1 million total deaths due to AIDS.[1] Historically, vaccines have proven to be the most effective weapon in our fight against infectious diseases such as small pox, polio, measles and yellow fever. HIV vaccines are our best hope to end the HIV pandemic. Although successful vaccines have been developed for the common childhood diseases, the development of a vaccine against the AIDS virus is a much greater challenge.

The best way to stop the spread of the disease and the suffering of AIDS patients is by the development of successful vaccines to prevent infection with HIV and delay or stop progression to AIDS. It is now two decades and a half since HIV was first discovered and researchers have spent millions of Riyals (Omani currency; 1 Riyal = 2.6 US$) looking for possible candidates as vaccines, but what is the outcome of this research? It seems the discovery of a licensed and globally accessible HIV/AIDS vaccine is still years away, the question that arises is: how soon are we going to see a successful HIV/AIDS vaccine? More realistically, how long are we going to wait for such a vaccine? In this article, I will very briefly touch on the scientific hurdles that have impeded the search for an effective AIDS vaccine and discuss novel research approaches to accelerate its progress.

Despite important progression in the understanding of HIV pathogenesis[2] and HIV/AIDS virus compared to any other viral disease, why are we still not able to produce an effective or even partially effective HIV/AIDS vaccine? The answer to this question lies in understanding how the virus evades the immune system. First, HIV disables the very cells that are responsible for fighting it. Second, HIV is able to integrate its viral genome into the chromosome of the infected cells and therefore hide from recognition by the immune response for many years. Third, HIV is able to conceal the protein components that can induce protective immune responses and therefore presents itself to the body in a way that makes it difficult for the immune system to respond effectively. Fourth, HIV is genetically diverse and rapidly changing, particularly its outer envelope, and this allows the virus to evade most of the natural and protective immune mechanisms that the immune system is able to make. As soon as HIV infection becomes established, HIV continues to mu-

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Table 1: ***Examples of HIV vaccine strategies***

Subunit vaccines (a structural piece of HIV such as the envelope or a core protein)
Live vector vaccines (a live bacterium or virus modified to carry genes that encode HIV proteins).
Peptides (small pieces of HIV proteins).
Fusion protein vaccines (two proteins merged together).
DNA vaccines (direct injection of HIV-DNA sequences).
Vaccine combinations such as the prime-boost strategy

tate genetically and many variants may arise within an infected person. Therefore, investigators need to know the significance of strain variation within the individuals and among the populations when developing an effective HIV/AIDS vaccine.

The most logical approach for designing an effective HIV/AIDS vaccine is to identify which immune responses are most protective against this virus infection and to construct a vaccine that is able to stimulate these protective responses. Of the two main types of immune responses, the humoral immune response mainly uses antibodies to protect against a cell-free virus, whereas the cell mediated immune response is essential for body defense when the virus is hidden inside the cells. Although earlier vaccine research focused primarily on vaccines that elicited antibodies, it is now generally believed that both arms of the immune response are required in order to control and prevent HIV infection. Moreover, much attention has recently been directed towards vaccines that induce good innate (natural) immune responses particularly dendritic cells and toll-like receptors which play an important role in inducing and modulating the adoptive immune responses.[3]

The most practical goal for an HIV vaccine is to prevent HIV transmission rather than preventing infection with the virus. Experts believe a vaccine is the only way to eradicate HIV/AIDS because the most common modes of transmission, sexual contact, injection drug use and mother-to-child transmission at childbirth or breast-feeding are impossible to eliminate completely. The main characteristics of a desirable HIV vaccine are: safety, simple administration as well as affordable cost, long lasting immunity and effective against all HIV subtypes. To develop such an HIV/AIDS vaccine there is a need for team work in fundamental basic research; preclinical screening for active candidates and appropriate animal model followed by product development, manufacturing, and clinical research.[3]

Currently, there are more promising vaccine candidates being tested than ever before. Vaccine candidates are being constructed based on isolates from different regions of the world, and several research groups are testing a cocktail or a mixture of different viral components from different isolates of HIV. In addition, to optimize the immune responses, new vaccine strategies are being tested [Table 1].

The most current HIV vaccine candidates focus on producing cytotoxic CD4+ T cells, which attack HIV-infected cells in the body; such vaccines might not prevent an HIV-negative person from contracting the virus, but would delay HIV from progressing to AIDS and prevent transmission to others. Another challenge in vaccine research is that HIV strains vary among people and regions. Vaccine trial participants are chosen based on health standards for industrialized nations and many people in developing countries are not healthy enough to participate in such trials.[4] Vaccine-induced antibodies that interfere with viral entry are the protective correlate of most existing prophylactic vaccines; however, for highly variable viruses such as HIV-1, the ability to elicit broadly neutralizing antibody responses through vaccination has proven to be extremely difficult. The major targets for HIV-1 neutralizing antibodies are the viral envelope glycoprotein trimers on the surface of the virus that mediate receptor binding and virus entry. HIV-1 has evolved many mechanisms on the surface of envelope glycoproteins to evade antibody-mediated neutralization, including

the masking of conserved regions by glycan, quaternary protein interactions and the presence of immunodominant variable elements. The primary challenge in the development of an HIV-1 vaccine that elicits broadly neutralizing antibodies therefore lies in the design of suitable envelope glycoprotein immunogens that circumvent these barriers.[5]

Individuals who are infected with HIV but remain healthy and keep viral replication in check may offer some hope for guiding the design of an effective HIV vaccine.[6] Some of these long-term survivors make a very small amount of antibody, which, when isolated, can neutralize HIV from patient isolates. Further, those antibodies can neutralize viruses from many different patient isolates, which is necessary for an AIDS vaccine that will be effective against a broad spectrum of HIV strains. Unfortunately, even these antibodies may not be the whole answer. Tests of cells in culture indicate that the antibodies must be present at surprisingly high concentrations to block HIV entry into cells effectively.

Many researchers continue to look into developing a live, attenuated HIV vaccine despite safety concerns. Because such a vaccine would closely mimic active HIV, it should theoretically be effective at inducing cellular immunity, antibody-based immunity and perhaps-other unknown modes of protection. By systematically deleting genes critical for HIV replication, scientists hope to develop a variant of the virus that can elicit a strong immune response without giving rise to AIDS.[4] It also is hoped that vaccines may give the body an immunological 'head start' by priming the immune system to attack HIV as soon as it appears, rather than taking time to initiate a defense from scratch.

As the pathogenesis of HIV infection has become better understood, investigators have realized that if the virus can be kept at low concentrations in the blood, an infected person may never progress to AIDS.[7] This insight is encouraging because it suggests that even a partially effective vaccine could be valuable in limiting the amount of virus in patients, thus potentially reducing virus infectiousness and the AIDS symptoms.

The multitude of scientists searching for successful AIDS vaccines will require appropriate funding and ample time. Funding is now improving, but because of the above difficulties we may not see a vaccine in near future.[8] Governments need to cooperate to break barriers, reduce the stigma associated with HIV/AIDS, encourage HIV testing, provide support for people with HIV/AIDS and allocate appropriate funding to institutes that work for the development of HIV/AIDS vaccines. The development of appropriate antiviral therapy and reconstructing the damaged immune system are two approaches, both of which require significant financial support. For developing countries, educating the public on preventative measures is the first step in preventing and reducing the spread of HIV/AIDS. Treating those infected with HIV or who have AIDS is also, of course, critical, but the real hope for the future lies in developing a successful vaccine.

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