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Review Article

Current strategies to boost immunity in patients who receive AIDS vaccines*

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Abstract

We have not exhausted all strategies to develop an effective AIDS vaccine. We are continually learning more about the human immunodeficiency virus (HIV), different types of vaccines appear every day and we are also learning how to use the immune system itself to our benefit. This review describes three strategies that have been cited in medical journals to boost immunity in patients who receive any of the existing AIDS vaccines and describes their potential use both separately and jointly. These strategies are: 1) the administration of thyroid hormones; 2) the use of the immune system itself; and 3) identifying natural defenses against HIV.

Introduction

Despite international efforts, an effective vaccine against AIDS has not yet been discovered. Twenty years have passed since Margaret Heckler, U.S. Secretary of Health and Human Services, and more than 10 years since former U.S. President Clinton predicted that we would have an effective AIDS vaccine and we still have not achieved this (1).

The AIDS epidemic continues to be alarming and there is therefore a great need for an effective vaccine that will achieve permanent immunity against the human immunodeficiency virus (HIV). A total of 4.3 million new cases of AIDS were reported during the year 2006 and 2.9 million deaths worldwide; as of March 2007, more than 65 million people had been infected with AIDS and approximately 25 million people had died due to infection caused by HIV. The most alarming fact is that 40% of new cases of infection due to HIV are among young people between 15 and 24 years of age (2). It is estimated that 14,000 new infections due to HIV occur every day worldwide (3).

HIV is a very complex virus, is extremely effective in avoiding the immune system and the strategies to achieve effective immunity through vaccination must also be very complex. An effective AIDS vaccine must condition an adequate immune response in order to establish complete protection against HIV (3-5).

The huge diversity of different variants of HIV represents an obstacle to the development of an effective vaccine. It is thought that more genetic variants of HIV exist in a single infected individual than types of flu virus in the world (6). Also, HIV is capable of constant evolution and of escaping the neutralizing response of antibodies produced by the immune system (7). The principal HIV antigen determinant is a portion of the third variable region of the external protein gp120 (8). The great heterogeneity of the virus is a factor that has determined that the vertical transmission of the virus from mother to fetus does not always occur (9). We are thus facing a virus with a great ability to mutate, which is also reflected in its capacity to generate resistance to antiretroviral drugs in the short term (10).

Infections due to HIV do not present the same characteristics as other viral infections we have managed to control through vaccination (11). An effective AIDS vaccine must be capable of inducing long-term, preferably indefinite, neutralizing antibodies and it must also stimulate $CD4^+$ helper T-cells and $CD8^+$ cytotoxic T-cells (12). The HIV virus has managed to evade all immunological responses, and therefore the strategies used to develop effective immunity through the application of an AIDS vaccine will necessarily require a high degree of ingenuity.

Available AIDS vaccines

A number of vaccines with different characteristics have been manufactured with the aim of preventing AIDS. HIV envelope proteins have been used, principally gp120. Live viral vectors and polyvalent vaccines (13)

*This work is dedicated to the memory of a great man, Jose Bucay, my grandfather.

have been prepared. Naked HIV DNA has been administered, which has resulted in the development of some immunity (12). Vectors such as the adenovirus have been added to vaccines in order to induce a cytotoxic T-lymphocyte response (1). CD40 lymphocyte receptors have been added to the vaccines (14) and various adjuvants have been incorporated into the vaccines (15), including recombinant proteins (16), cytokines and T-cell co-stimulatory molecules (17). Vaccines with multiple recombinant proteins have recently been applied to healthy individuals (18). AIDS vaccines have been administered directly through mucous membranes to evaluate the immunity generated (19) and different vaccines have been applied together with other microorganisms, such as *Leishmania* (20) and Bacillus Calmette-Guerin (BCG) (21). Efforts to find an effective vaccine have been truly exhaustive.

Strategies to boost immunity in patients receiving AIDS vaccines

Three strategies to boost immunity in patients receiving any of the existing AIDS vaccines have been published at the international level and may be tested individually or jointly: 1) the administration of thyroid hormones together with the vaccine; 2) the stimulation of the immune system itself; and 3) the identification of natural defenses against HIV.

Why choose thyroid hormones to stimulate the immune system to boost the immunity induced by AIDS vaccines? Thyroid hormones have the intrinsic capacity to directly activate different types of leukocytes, including T- and B-lymphocytes, and they participate in the release of various cytokines and the production of antibodies (22). Moreover, the immune system itself is able to induce the release of thyroid hormones (23). Also, AIDS patients frequently present abnormalities in thyroid function test results (24). Therefore, patients receiving thyroid hormones will benefit at the endocrinological level and the hormones will also directly stimulate their immune system to enhance the immunity induced by the AIDS vaccine.

How can we stimulate the immune system to enhance the immunity induced by AIDS vaccines? Various strategies have been used to directly stimulate the immune system, both as a treatment for AIDS patients and as adjuvants for AIDS vaccines. Anti-HIV human polyclonal (25) and neutralizing monoclonal antibodies (26) have been administered; autologous antibodies (27) and hyperimmune globulins (28) have also been used; and gene transport units with viral proteins (29) and dendritic cell-based vaccines (30) have been used to stimulate the immune system. The objective for the future will be to revisit these strategies and use them in conjunction with others, such as the concomitant use of thyroid hormones, in order to achieve the final objective of boosting immunity in patients receiving AIDS vaccines.

What constitutes a natural defense against HIV and how can we get patients to express it? There are three types of individuals who, despite being in contact with HIV, have some type of natural defense against AIDS and do not develop the illness: long-term nonprogressors (LTNPs) who remain asymptomatic for 15 years or more (31); highly exposed, persistently seronegative subjects (HEPS) (32); and children of mothers seropositive for AIDS who are not infected during pregnancy. Only 15-35% of pregnant women with AIDS vertically transmit the virus to their children (33), while the remaining children do not develop infection due to HIV. We therefore need to identify the natural defense against AIDS in these children, as well as in the LTNPs and HEPS (34), and discover how to get an individual to express this defense in order to achieve natural immunity or boost the immunity induced by an AIDS vaccines. This natural defense could be a humoral factor the LNTPs and HEPS have (35), such as in seronegative newborn children of HIV-seropositive mothers (36), or it could be an innate or acquired structural modification of the leukocyte receivers, including CCR2-CCR5 receptors (37), the IL-4 receptor (38) or major histocompatibility complex (MHC) receptors (39).

Discussion

HIV is a very complex virus, but the human mind is much more complex. A large number of AIDS vaccines have already been developed, and the final obstacle is managing to get the immune system to express and produce permanent immunity against HIV through the application of vaccines. This brief review describes several strategies that may be of great use in research projects that focus on achieving the immunity necessary in order for AIDS vaccines to be effective. If universal immunization against AIDS is possible and if the immune system can develop immunity against HIV through the application of a vaccine, then the future will be promising.

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