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The HIV VACCINE: Learning from Failure and Building on Success

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Abstract

An effective vaccine for acquired immune deficiency syndrome (AIDS) has eluded researchers since the identification of the HIV virus. There are many challenges in developing an effective HIV vaccine, including the lack of knowledge regarding the immune response to the virus and its diverse nature. Ethical concerns further complicate research. A recent phase III trial was performed in Thailand and showed that a significant reduction in HIV infection is possible. Pharmacists need to stay informed of these important breakthroughs in AIDS research in order to provide quality health information to patients in their community. This paper aims to evaluate the past failures and successes as well as explore the recent advancements towards finding a vaccine for HIV.

An estimated 33.4 million individuals worldwide are currently living with acquired immune deficiency syndrome (AIDS).¹ According to the Centers for Disease Control and Prevention, approximately 56,300 new cases of Human Immunodeficiency Virus (HIV) developed during 2006 in the United States alone.² A cure for this disease has puzzled and eluded researchers since the identification of the HIV virus in 1983. However, hope is on the horizon with the advances in research that could eventually lead to an effective HIV-1 vaccine. As one of the most accessible health care providers, pharmacists need to stay informed on these important breakthroughs in HIV/AIDS research in order to provide quality health information to patients in their community.

Background

Although there is currently no cure for HIV, there are several effective anti-retroviral treatments available. Commencement of therapy is recommended for all patients with a CD4⁺ count <350 cells/mm³ or in patients with an AIDS-defining illness (Pneumocystis pneumonia, Kaposi sarcoma, cryptococcosis, etc.). Goals of therapy currently include suppressing plasma HIV viral load, reducing HIV-associated morbidity and mortality, improving quality of life, restoring and preserving immunologic function, and preventing HIV transmission. The Department for Health and Human Services (DHHS) Panel recommends several preferred and alternative complex multi-drug regimens

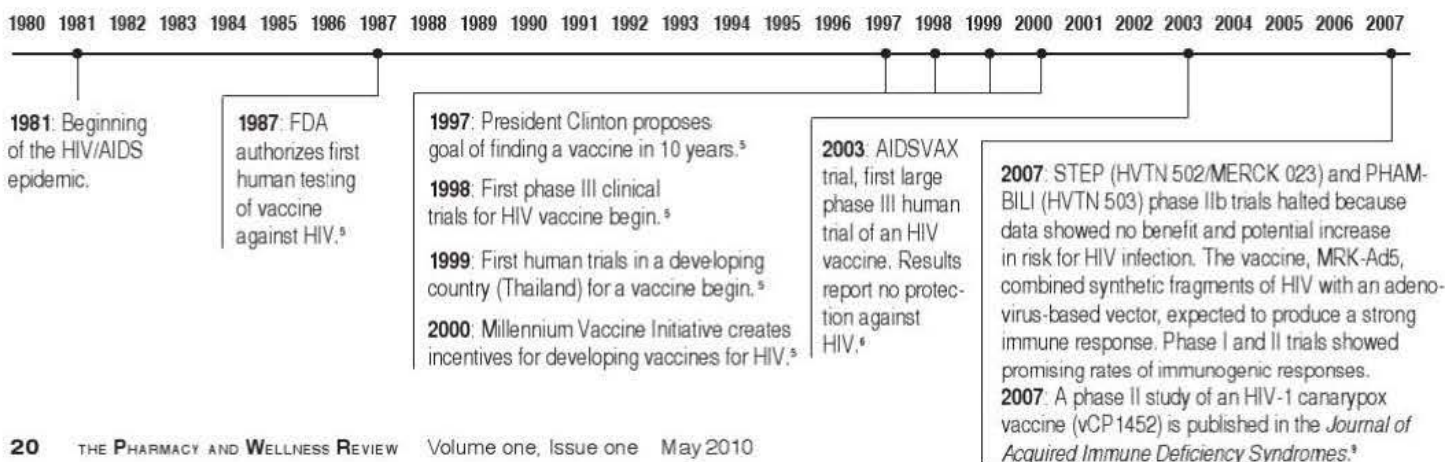
for HIV-positive patients. Treatment should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results and co-morbid conditions.³ Despite great improvements in disease management for HIV/AIDS, the "first-line therapy" is avoidance of infection in the first place. This has prompted interest in the development of an HIV vaccine.

The biggest challenge in developing an effective HIV vaccine is that the immune response to the HIV infection is not fully understood. Research is further complicated because the virus is extremely diverse and constantly changing. A successful vaccine would need to be effective against multiple forms of the virus. In many developing countries, the most common strain of the virus is wild-type or non-mutated, whereas in the U.S., medication-resistant HIV strains are of important concern. With a rise in the prevalence of HIV-2 and HIV-1/2 viral strains in the United States, development of successful vaccination formulations becomes even more difficult. Another obstacle in the development of a vaccine is the fact that people with HIV cannot fight off the virus, and mounting an immune response to a vaccine is necessary to prevent or reduce infection. Other major challenges include the inability to use attenuated viruses in humans, absence of a small animal model, and relatively little pharmaceutical interest.⁴ Although it seems there are many impossible barriers to overcome, learning from the previous mistakes and successful outcomes of prior research have already led to significant advances toward development of a successful vaccine.

Testing methods

HIV is an ever-elusive, ever-changing virus. It is important that the techniques and assays used in AIDS vaccine research improve as the virus changes. Canarypox is the vector of choice in developing a vaccine. It is an attenuated virus that can carry a large quantity of foreign genes and enter into human cells yet cannot grow or replicate within them. Interferon- γ enzyme-linked immunospot assays, or ELISpot assays, are newer assay technologies that allow detection of certain secreted cytokines at a single cell level. Qualitative enzyme-linked immunosorbent assays, or ELISAs,

HIV/AIDS Prevention-Vaccine Research Timeline:



are used to determine how many antibodies are in a certain sample or how much protein is bound to the antibodies. Chromium release assays are also frequently performed. This is accomplished by incubating infected cells in chromium, and then, as the cells die by CD8⁺ CTL induced apoptosis, the chromium is released from the cell and can be measured as an indicator of effective immune response. These various methods of data analyses are utilized in many current AIDS vaccine studies and are the methods of choice in the following three trial summaries.

Clinical trials

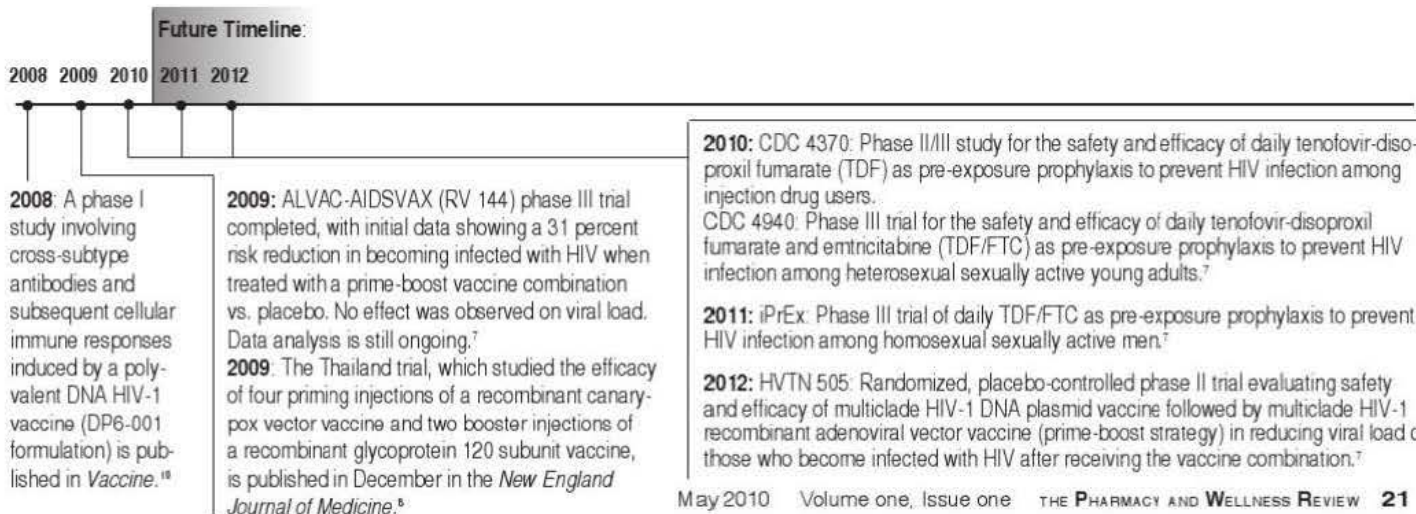
A phase III, community-based, randomized, multicenter, double-blind, placebo-controlled trial was performed in Thailand to assess the efficacy of four priming injections of a recombinant canarypox vector vaccine and two booster injections of a recombinant glycoprotein 120 subunit vaccine. A total of 16,395 healthy men and women were recruited for the study. Participants were monitored for HIV infection at the end of the six-month vaccination series and then every six months thereafter for three years. Adverse reactions to the vaccines were mild to moderate. The vaccine group had a statistically significant lower infection rate compared to placebo (efficacy 31.2%, $p < 0.04$). The study had an extremely large sample size and a long duration; however, it lacked correction for possible lifestyle, disease state or genetic differences. This trial showed that a statistically significant reduction in HIV infection is possible. Further studies must be performed to examine the individual parameters that could have led to such results.⁹

A double-blind, randomized, phase II trial was performed to assess the efficacy of HIV-1 canarypox vaccine candidate vCP1452 alone or in combination with rgp120 subunit protein. Healthy HIV-1-uninfected adults were recruited to participate. The vCP1452 alone was administered in the left arm to 120 participants, and protein rpg120 was administered in combination with vCP1452 to 120 participants in the right arm. The remaining 90 participants received placebo. Overall, vCP1452 and rpg120 were well tolerated. A significant immune mobilization could not be found in any of the four treatment groups with the various assay methods. This study was the first large, multicenter trial to test cell secretion via the ELISpot assay method. It was performed to determine if vCP1452 had a CD8⁺ CTL induction frequency of at least 30 percent; since this induction rate was not reached, plans for future vCP1452 trials were abandoned.⁹

A phase I clinical trial was conducted on HIV-1-specific immune responses in healthy adult volunteers that received the multi-gene, polyvalent, DNA prime-protein boost HIV-1 vaccine formulation DP6-001. HIV-1-negative adult volunteers of both genders were randomly assigned to either Group A or B, and once these participants had received the second protein boost and a safety review was conducted, enrollment in Group C was completed. There were a total of 27 volunteers. Groups A and B were administered 1.2 mg of DNA and at each vaccination site, and group C was given a much higher dose of 7.2 mg. Serum and PBMC samples were collected periodically throughout the study to measure antibody and cell-mediated immune (CMI) responses. Participants did not exhibit any serious adverse effects. Group C also demonstrated a higher CMI response than Groups A and B and still showed fairly high levels at the end of the trial ($p < 0.05$). Analyses showed that the antibodies were widely cross-reactive against a range of HIV-1 Env antigens and were able to neutralize pseudotyped viruses that expressed the primary Env antigens from several HIV-1 subtypes. Unfortunately, the trial experienced reactogenicity in Group C causing investigators to terminate the study early in that group. Overall, the data demonstrated that the DNA prime-protein boost immunization method is an effective way to generate humoral and CMI responses in humans. Moreover, the results showed that a polyvalent Env formulation could produce extensive immunogenicity against a wide range of HIV-1 viruses.¹⁰

Discussion

The Thailand trial was a critical breakthrough point in HIV/AIDS research because vaccine efficacy against the HIV virus has been established for the first time. Despite abandonment of the vCP1452 trial, it was still of importance because it was the first to utilize new assay techniques. According to researchers in the study using the DP6-001 vaccine, further studies need to be conducted to assess the structural basis for antibody and CMI cross reactivities. The arrangement of Env antigens should be enhanced in order to increase the strength of neutralizing activities against resistant viruses. Finally, before progressing to more in-depth human studies, the immunization schedule with adjuvant medication regimen needs to be improved to reduce immunogenicity of the DP6-001 formulation. Future trials should focus on determining the body's defense mechanisms against the HIV virus; this would allow for more specific vaccine targeting in order to improve immune system response.



While there is an obvious role for an HIV vaccine, there are many ethical concerns regarding the clinical efficacy testing. For some populations, vaccine administration may actually put individuals at a greater risk for developing the disease and/or may cause them to experience more rapid progression of the disease once infected; this was one of the reasons for halting Merck's clinical trial in 2007.¹¹ Another major ethical concern is that study participants may have false expectations upon receiving the vaccine. For instance, if trial participants believe they have developed immunity to the HIV virus resulting from vaccine administration, they may choose to participate in behaviors that could put them at a greater risk for developing HIV (illegal drug use, sexual practices, etc.).

Fortunately, evidence has indicated that subjects in previous trials have not engaged in behavioral disinhibition.¹² Most of these studies also take place in undeveloped countries, where the need for an HIV vaccine is greatest. However, because scientific and financial resources for the development of these vaccines come from developed countries, there is apprehension that the trials may not be conducted under stringent ethical and scientific standards. It is extremely important that all trial participants are educated about the risks associated with receiving the vaccine and informed that no vaccine has yet been clinically effective. If any of these issues are not addressed before trial initiation, the ethical conduct of the trial must be questioned.¹¹

Due to the fact that trials of a traditional model of vaccine have produced mixed results, some researchers have turned to more novel approaches in creating an HIV vaccine. For example, the Aaron Diamond AIDS Research Center has begun research with ibalizumab, a monoclonal antibody that can block viral entry into the CD4⁺ cell. Rather than boosting the immune system and preparing the body to fight infection like traditional vaccines, an ibalizumab vaccine would provide the body with all the defenses necessary to fight the infection.¹³

Conclusion

New and innovative ideas, combined with the knowledge from previous research, are vital to the growth and development of a successful vaccine for HIV. Despite the many obstacles, advances have been made, providing hope that someday HIV will no longer have the power to infect a staggering 56,300 American lives and millions more around the world each year.

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