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Review Article

Is there a Vaccine for HIV on the Horizon? What we've Learned thus Far from the Literature Review

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Abstract

AIDS and the human immunodeficiency virus (HIV) have risen to the status of main causes of death and disease morbidity in the developed world since their discovery in the early 1980s. In light of the first discovery and more than 78 million individuals have contracted the disease, and more than 39 million people have died from AIDS-related complications. Since the peak in 2005, AIDS-related mortality have decreased by 35 percent. There have been six human trials of HIV vaccine effectiveness. In spite of the fact that there are numerous effective prevention and treatment options, researchers have long been enthusiastic about HIV vaccine as the ultimate solution for HIV prevention and control. AIDS was found to be caused by HIV. It's been announced that an AIDS vaccine would be tested within two years by the United States' HHS Secretary Margaret Heckler.

Keywords: *AIDS; HIV-1; Six Human Trials; Future Directions; Challenges Faced*

Introduction

AIDS and the human immunodeficiency virus (HIV) have risen to the status of main causes of death and disease morbidity in the developed world since their discovery in the early 1980s. Around 35 million people were estimated to be infected with HIV in 2013 according to global estimates. In light of the first discovery and more than 78 million individuals have contracted the disease and more than 39 million people have died from AIDS-related complications. However, this disease's prevalence has decreased by 38% since 2001. In comparison to the 3.4 million new HIV infections in 2001, only 2.1 million people become infected in 2013. Since the peak in 2005, AIDS-related mortality have decreased by 35 percent. Between 2005 and 2013, AIDS-related deaths decreased from 2.4 million to 1.5 million. A chronic disease with decreasing incidence and rising prevalence, HIV infection has become more common with the introduction of antiretroviral drugs in the 1990s [1].

New HIV-1 infections continue to rise despite recent breakthroughs in HIV-1-prevention measures. If we are going to halt the AIDS pandemic by 2030, we need an effective HIV vaccine to stop new infections from occuring. There have been six human trials of HIV vaccine effectiveness. With a modest estimated vaccine efficacy of 31%, only one experiment - the RV144 Thai trial - has shown any evidence

of vaccination-mediated protection. There were various facets of vaccine-induced humoral immune responses in the RV144 study that contributed to a lower risk of infection, similar to most approved vaccines [2]. In spite of the fact that there are numerous effective prevention and treatment options, researchers have long been enthusiastic about HIV vaccine as the ultimate solution for HIV prevention and control [1].

History [3]

HIV vaccine research in the past.

1984

AIDS was found to be caused by HIV. It's been announced that an AIDS vaccine would be tested within two years by the United States' HHS Secretary Margaret Heckler.

1987

The NIH Clinical Center in Bethesda, Maryland, has begun the first clinical trial for an HIV vaccine. At the beginning of the study's first stage, 138 healthy, HIV-negative participants were recruited. The vaccine against the gp160 subunit was shown to have no significant side effects.

1988

An HIV vaccine clinical trials group, the first in the United States, began recruiting volunteers for its first experiment.

1992

The first HIV vaccine clinical trial in Phase 2 was launched by the NIAID. Volunteers in this study had a history of high-risk behaviour, such as injecting drugs, having several sexual partners, or having been infected with a sexually transmitted disease. Repeatedly, participants were warned about the dangers of HIV infection.

1998

It was reported that the first annual HIV Vaccine Awareness Day was held in honour of vaccine study volunteers. It was the beginning of the first large-scale HIV vaccination study. More than 5,400 people in North America and the Netherlands participated in a Phase 3 trial of AIDSVAX (VAX004) conducted by VaxGen.

1999

The first African HIV vaccine study was conducted in Uganda by the NIAID. This is the beginning of the first large-scale HIV vaccination experiment in a developing country. Over 2,500 people in Thailand have volunteered to take part in a Phase 3 trial of AIDSVAX (VAX003), which was started by VaxGen. Immunization activists Dale and Betty Bumpers had a special place in the heart of the new Vaccine Research Center (VRC).

2000

HVTN was created by the National Institutes of Allergy and Infectious Diseases to develop a preventive HIV vaccine by conducting clinical trials of vaccines in all stages of development. There were over 25 locations throughout the US, Africa, Asia, South America, and the Caribbean that were part of the network. It was in Uganda that the first African HIV vaccine study came to an end.

2003

RV144, a Phase 3 trial to investigate a new HIV vaccine technique known as "prime-boost," was launched jointly by the United States and the Royal Thai governments. Scientific American published an article in which it was suggested that the Global HIV Vaccine Enterprise should be established.

2004

In Phase 3 studies, neither of the VaxGen candidates provided HIV protection.

2007

For reasons of safety, both the Phase 2 Step and the Phambili trials were discontinued by the NIAID.

2009

In order to test the effectiveness of a "prime-boost" vaccine regimen designed by the VRC, the Phase 2 HVTN 505 trial was started. The vaccination combination showed a modest preventative benefit in people in the Phase 3 Thai Trial (RV144), according to the study's findings. For the first time, a comprehensive clinical research involving more than 16,000 volunteers demonstrated the efficacy of an investigational HIV vaccine.

2010

In the laboratory, VRC researchers discovered two powerful antibodies that effectively kill most HIV strains (VRC01 and VRC02). Pox-Protein Public-Private Partnership (P5), a worldwide team determined to improving on RV144's moderate success, was established.

2011

Protection against HIV became the primary endpoint of HVTN 505.

2012

Analyses of additional samples from RV144 shed light on the types of immune responses that may be required for a vaccine to work well.

2013

Due to ineffectiveness, the HVTN 505 immunisation programme was put on hold.

2015

The HVTN 100 project, which is a component of the P5 research effort, began in Phase 1/2 to examine the safety and immune response potential of an experimental HIV vaccination regimen based on the RV144 findings.

2016

Intravenous infusions of the antibody VRC01 are being tested to see if they are safe, acceptable, and effective for preventing HIV infection. (AMP Studies) They also sought to answer fundamental concerns about HIV prevention and vaccine development through the trials. P5's HVTN 702 is testing a new version of the RV144 HIV vaccine candidate to see if it is safe for adults in South Africa to receive it.

2017

Immune responses against a wide range of worldwide HIV strains were the focus of a Phase 2b proof-of-concept trial conducted by the NIAID with partners called Imbokodo or HVTN 705/HPX2008.

Advancement in the development of an active or passive HIV-1 vaccine [4]

Anti-HIV-1 antibodies of the first generation

Immunized guinea pigs had polyclonal antibodies that could neutralise many HIV-1 strains as early as 1990, but their neutralisation activity was restricted (Javaherian., *et al*. 1990). By phage display or the creation of immortalised B cell lines, further research has expanded on these discoveries to uncover antibodies from infected individuals with greater breadth and potency. There is a wide range of cross-clade neutralising breadth and efficacy among the first-generation MAbs to HIV-1, including b12, 2F5, 4E10 and 447-52D (Gorny., *et al*. 1992; Buchacher., *et al*. 1994; Burton., *et al*. 1994; Roben., *et al*. 1994; Trkola., *et al*. 1995, 1996; Stiegler., *et al*. 2001; Zwick., *et al*. 2001).

Cryopreservation of antibodies from a single cell

As a result of the widespread use of single-cell anti-HIV-1 antibody cloning methods, which were first introduced in 2008 and have since been utilised in a large number of other laboratories, researchers have discovered an entirely new generation of highly effective broadly neutralising antibodies, which has sparked renewed interest in developing both active and passive HIV-1 vaccines. Several findings were made as a result of this study, including why it is so difficult to induce anti-HIV-1 bNAbs and potential solutions to the problem techniques to developing vaccines

Genetically modified mice are being used to test HIV-1 vaccine concepts [4]

It is possible for a single B cell to have an extremely broad repertoire of naive B cells capable of responding to virtually any foreign antigen. That's because humoral immune responses to HIV-1 Env often entail the development of antibodies against multiple distinct epitopes, the great majority of which are strain specific or non-neutralizing (Dosenovic., *et al*. 2009). The complexity of such a reaction makes it difficult to assess, even if a diverse response spanning many different epitopes would be ideal in a vaccination regimen.

A cursory check at the material

Therapeutic Vaccination Expands and Improves the Function of the HIV-Specific Memory T-Cell Repertoire resulting in a safe and well tolerated vaccination, according to Casazza J P and colleagues [5]. Increased polyfunctionality and an expanded repertoire of HIV-specific CTLs were found following immunisation. Single-copy viral load and latent infection rates did not vary. Vaccination of patients with preexisting HIV-specific immunity increased the size, breadth and polyfunctionality of HIV-specific memory T-cell responses, but did not affect markers of viral control, the researchers concluded.

Shu J., *et al.* [6] compiled a database of 821 Chinese HIV isolates and 46 alleles of human leukocyte antigen (HLA) DR found in the Chinese community in order to build a vaccine that particularly targets the Chinese population. Bioinformatics was used to estimate a total of

20 possible HIV epitopes. With this combination, a theoretical 98.1 percent of the population is covered for both prevalent HIV genotypes and Chinese HLA-DR types. 'A vaccination targeting CD4+ T cells that is tailored to Chinese needs could be developed more quickly if this vaccine is put to the test experimentally.

Moodley N., *et al*. [7] examined the cost-effectiveness of implementing HIV vaccination services concurrently with current HIV management programmes. Cost effectiveness ratio (ICER) was US$ 43/QALY gained at the base vaccine cost of $12, with reduced vaccine costs yielding improved ICER values. When it came to vaccine-mediated protection and vaccination effectiveness, ICER was extremely sensitive. The results of this study show that ICER values would be improved by vaccinations with longer durations of protection and lower costs. It would be cost-effective to provide HIV vaccination services to adolescents in schools in addition to the present HIV prevention and treatment services provided.

HIV vaccine based on mRNA technology offers new hope [8]

mRNA vaccines for COVID-19 have proved nothing short of amazing in their ability to eradicate the disease. Whether or not this unique technology platform can be used to more complex problems. The work of finding a vaccine for HIV is now in progress with a lot of attention. Zhang., *et al.* preclinical work is published in Nature Medicine in this issue.

Studies on nonhuman monkeys to determine the statistical power of repeated low-dose challenge experiments were undertaken by Hudgens MG and colleagues [9]. A vaccination for the human immunodeficiency virus. There was investigation into the impact of various design characteristics on electrical power generation and consumption. For repeated low-dose experiments with 50 animals per arm, the power to detect a 50% reduction in the risk of infection after immunisation is often adequate, according to these results. The more challenges that animal is allowed to take, the higher its chance of becoming infected, and the greater the percentage of animals susceptible to infection.

Anti-HIV immune responses could be induced by Song X T and colleagues [10] using an alternate technique, blocking the body's natural defence mechanisms. Dendritic cells (DCs) can generate anti-HIV-1 immunity when suppressor of cytokine signalling (SOCS) 1 is silenced by small interfering RNA (siRNA), a critical negative regulator of the JAK/STAT pathway. Using SOCS1-silenced DCs, we were able to increase the number of HIV-1 Env-specific CD8+ cytotoxic T lymphocytes and CD4+ T helper cells in mice, as well as the production of antibodies. DCs that were silenced in the SOCS1 gene, however, were more resistant to HIV Env-mediated suppression while still producing HIV Env-specific antibody and T cell memory. Controlling the anti-HIV immune response is largely dependent on SOCS1-restricted signalling and DC production of proinflammatory cytokines such interleukin. Coimmunization using SOCS1 siRNA expressor DNA greatly enhances the potency of HIV DNA vaccine. Thus, the findings of this work show that SOCS1 acts as an antigen presentation attenuator to modulate both HIV-1-specific cellular and humoral responses. An attempt to induce HIV-specific T-cell and antibody responses by suppressing a host's antigen presentation attenuator has never been attempted before, which may provide a new and alternative avenue for the development of HIV vaccines.

Vaccine-induced antibodies may fade more quickly in HIV-infected people than in healthy ones, according to a study by Kerneis S., *et al* [11]. According to our research, those who originally responded well to immunisation have a gradual loss of immune response over time. To assess seroprotection 2 and 5 years after the last vaccination injection, researchers used a log binomial generalised linear model to simulate seroprotection decline across all of the studies they culled from the literature. In HIV-infected patients, the period of seroprotection was shorter, and existing standards would have led to a considerable proportion of patients losing their protective antibodies before a booster was recommended, according to our studies. As a result, we talk about the ramifications for these patients' ongoing antibody surveillance and revaccination schedules.

Antibodies that detect commensal microbial antigens may cross-react with a portion of the HIV envelope glycoprotein gp41, according to Cram J A., *et al* [12]. The role of the microbiota in influencing the immune response to HIV vaccines was studied by comparing the gut microbiota composition of participants in the HIV Vaccine Trials Network 096 clinical trial with their HIV-specific immune responses in response to vaccination with a DNA-prime, pox virus boost strategy designed to replicate the only efficacious HIV-vaccine trial. (RV144). Both baseline and post-vaccination levels of IgG antibodies to gp41 of the Con.6.gp120.B, ZM96.gp140 and gp70 B were found to have high levels of IgG antibodies to gp41. There were three clusters of family-level microbial taxa that were related with the CaseA V1-V2 antigens. There were numerous families in one cluster who had gp41-specific IgG responses that were favourably associated, and those who had vaccine-matched IgG responses that were negatively associated with gp120, gp140, and V1-V2-specific responses. Families in the second cluster had a negative association.

Positively correlated with gp41 and with gp120, gp140, and V1-V2 specific IgG responses microorganisms in a third cluster had no relation to any kind of immunological response. Although there was no significant correlation between baseline gp41 IgG levels and those following vaccination, this suggests that factors other than the microbiome may be contributing to differences in immune response. Sequence richness was positively linked with IgG, IgA, and CD4+ T cell responses to HIV-1 proteins specific for gp41, p24, pg140, and V1-V2, as well as gp41 and p24. Preliminary evidence suggests that the microbiota in the stomach is a major predictor of vaccination response, according to our findings.

A vaccine to prevent the spread of HIV has not yet been developed, according to Klatt NR., *et al* [13]. Mucosal immunity may be improved by modifying the microbiota through the use of probiotic treatment. SIV/HIV vaccination's immunogenicity and protective effectiveness are being studied to see if probiotic therapy can help. The HIV protein vaccine was administered intramuscularly with Adjuplex™ adjuvant to Rhesus macaques, who were also receiving daily oral Visbiome® probiotics during the study. Probiotics alone lowered the frequency of colonic CCR5+ and CCR6+ CD4+ T cell populations in the gastrointestinal tract. Using probiotics and SIV/HIV immunisation reduced CCR5+ CD4+ T cell frequencies in the colon similarly. The presence of SIV/HIV-specific T cells and antibodies in the peripheral blood of vaccinated mice was easily observed, but this reaction was not improved by probiotic treatment. The intrarectal challenge with a combination of probiotics and immunisation had no effect on the rectal SIV/HIV target populations or the rate of heterologous SHIV acquisition. Finally, post-infection viral dynamics were shown to be identical in all groups of patients. There were no vaccine-specific responses, despite the fact that probiotics were well-tolerated when given in conjunction with SIV/HIV vaccination. It has been greatly improved Microbiome modification methods must be improved in order to increase vaccination immunogenicity and boost protective immune responses in the mucosa.

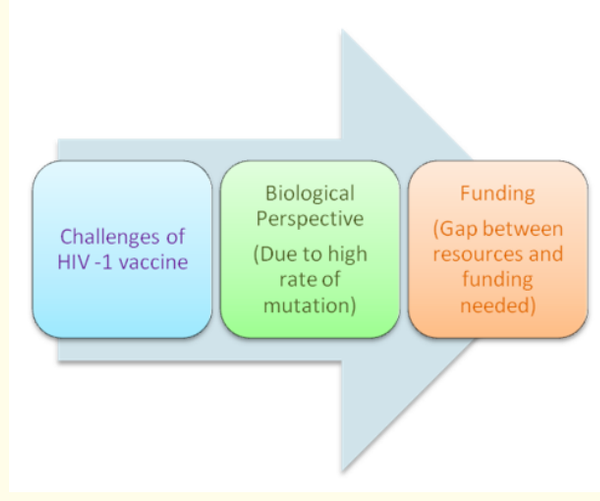

Figure 1

Future Directions

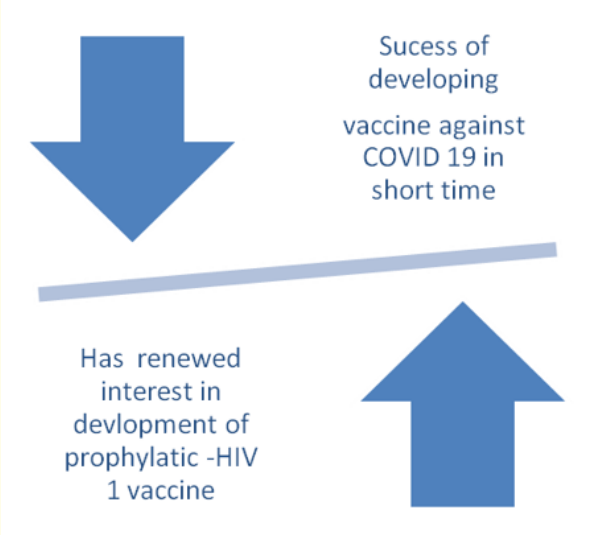

Figure 2

Conclusion

Whether or not this unique technology platform can be used to more complex problems. Zhang., *et al.* preclinical work is published in Nature Medicine. Studies on nonhuman monkeys to determine the statistical power of repeated low-dose challenge experiments were undertaken by Hudgens M.G. The more challenges that animal is allowed to take, the higher its chance of becoming infected, and the greater the percentage of animals susceptible to infection. DCs that were silenced in the SOCS1 gene, however, were more resistant to HIV Env-mediated suppression while still producing HIV Env-specific antibody and T cell memory. Thus, the findings of this work show that SOCS1 acts as antigen presentation attenuator to modulate both HIV-1-specific cellular and humoral responses.

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