REVIEW ARTICLE

Human immunodeficiency virus vaccine an update

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ABSTRACT

Since the discovery of acquired immuno deficiency syndrome (AIDS) in late1980s, the spread of human immunodeficiency virus (HIV) has reached pandemic proportions, representing a global developmental and public health threat. Finding of a safe, globally effective and affordable HIV vaccine offers the best hope for the future control of the disease pandemic. Significant progress has been made over the past years in the areas of basic virology, immunology, and pathogenesis of HIV/AIDS and the development of anti-retroviral drugs. However, the search for an HIV vaccine faces formidable scientific challenges related to the high genetic variability of the virus, the lack of immune correlates of protection, limitations with the existing animal models and logistical problems associated with the conduct of multiple clinical trials. Most of the vaccine approaches developed so far aim at inducing cell-mediated immune responses. Multiple vaccine concepts and vaccination strategies have been tested, including DNA vaccines, subunit vaccines, live vectored recombinant vaccines, various prime-boost vaccine combinations and vaccine based on broadly neutralizing human anti-HIV Antibody 2G12. This article reviews the state of the art in HIV vaccine research, summarizes the results obtained so far and discusses the challenges to be met in the development of a successful HIV vaccine.

Key words: **Acquired immuno deficiency syndrome, cell mediated immunity, human immunodeficiency virus vaccine**

INTRODUCTION

Acquired immuno deficiency syndrome (AIDS) was first reported in 1981, by Gottlieb *et al*., at University of California Medical Center.[1] In 1983, Barré-Sinoussiand Montagnier, isolated a new human T-lymphotropic retrovirus, later named as human immunodeficiency virus type 1 (HIV-1) which turned out to be one of the causative agents of AIDS. HIV/AIDS is one of the most important and preventable causes of morbidity, disability, mortality, and associated productivity loss and medical care cost, especially in the world's poorest countries.[2]

Vaccines are a proven cost-effective tool in fighting infectious diseases such as polio, smallpox, hepatitis B, yellow fever and a number of childhood illnesses. A safe, effective and accessible HIV vaccine would be the most economic among the various prevention strategies directed against the spread of HIV infection. In a number of modeling exercises, analysts have suggested that even a vaccine that is only partially effective could decisively lower the rate of new infections, thereby controlling the HIV epidemic. In the global effort to develop an HIV vaccine, more than 50 vaccine candidates are currently being studied in trials in 19 developed and developing countries and majority of them are in early stages of clinical trials. We have a long-way to go before a vaccine is identified, that is ready for large-scale production and distribution. When it is ready for large scale production, a "successful" HIV vaccine will probably have a demand more challenging than that of vaccines against childhood illnesses. Unlike most existing vaccines that are aimed at children on a "universal" basis, an HIV vaccine may be most appropriate for adolescents and adults, and from a public health perspective is likely to have the largest epidemiological impact when targeted at groups with the highest risk of getting infection, such as sex workers and intravenous drug users.

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/0973-029X.110741

REVIEW

Though anti-retroviral drugs could reduce the mortality of HIV-infected individuals, the high price and side effects of the current therapeutic drugs have not been beneficial for most AIDS patients. It is generally accepted that the development of a low priced and effective prophylactic AIDS vaccine is the only answer to stop the global pandemic.

Prophylactic vaccines

Prophylactic vaccine can broadly be classified into four major groups: Recombinant subunit proteins; synthetic peptides; recombinant viral vectors; and DNA vaccines.

In 1987, first time phase I trial of an HIV vaccine was conducted in USA. The vaccine consisted of an envelope protein, glycoprotein (gpl60), derived from the genetic material of HIV and produced in a Baculovirus -insect cell system. Although no significant toxic side effects have been known to occur at the doses tested, this vaccine was tested on only few participants. And the degree of protection conferred can only be assessed by a randomized trial.[3]

In 1989, the hopes for an HIV vaccine soared with the trial of a highly effective formalin-inactivated whole simian immune deficiency virus (SIV) vaccine which was known to confer protection in macaques with AIDS. This strategy was based on that the simian model for AIDS, which takes advantage of the similarities in viral composition and disease potential between SIV infection of rhesus macaques and HIV infection in humans. Immunization with a formalin-inactivated whole SIV vaccine potentiated with either alum and the Syntex adjuvant threonyl muramyl dipeptide (MDP) or MDP alone was done.[4] Their results demonstrated that a whole virus vaccine is highly effective in inducing immune responses that can protect against lentivirus infection and AIDS-like disease. However, 3 years later by Arthur *et al.*,[5] and simultaneously in 2003 by Natasha *et al*.,[6] it was found that the protective effect was mediated by antigens (such as human leucocytes antigen HLA and β2 microglobulin from the human cells which were used to grow the viral strain.

Genentech *et al*., in 1990, reported that recombinant gp120 subunit vaccine developed by them could induce protection in chimpanzees with HIV-1. In phase I and II trials, they confirmed the safety and immunogenicity. However, it failed to show reduction in HIV and thus was not able to become commercialized.[7,8]

A live attenuated SIV vaccine with a deletion in the negative factor gene was found to be efficient in treating AIDS of macaques by Ronald *et al*., in 1992. Unfortunately, 3 years later, Ruth Ruprecht found that this live attenuated vaccine had a safety issue in which the vaccine itself caused AIDS in neonatal macaques. Hence research into the development of a live attenuated vaccine was no longer carried out.[9]

Patterson *et al.*,[10] systematically investigated immunity elicited by multi-component vaccines delivered by replication-competent Ad5hr-SIV recombinants. They concluded that vaccine delivery via replication-competent live vectors, which can persistently infect new cells and continuously present low-level antigen, may be advantageous in overcoming competition among complex immunogens for immune recognition and that future vaccine design should focus on the effects of current multi-component vaccines on individual immune responses.

Studies of HIV vaccines in animal models suggest that it is difficult to induce complete protection from infection (sterilizing immunity) but that it is possible to reduce the viral load and to slow or prevent disease progression following infection. An excellent epidemiological model for the effects of a disease-modifying HIV vaccine that incorporates the intra host dynamics of infection, transmission rate and host mortality that depend on the viral load, the possible evolution and transmission of vaccine escape mutant viruses, a finite duration of vaccine protection, and possible changes in sexual behavior was developed by Devenport *et al.*,[11] and it was found that the extent of viral load reduction in vaccinated infected individuals (compared to unvaccinated individuals) is the key predictor of vaccine efficacy. Reductions in viral load of about 1 log10 copies ml^{-1} would be sufficient to significantly reduce HIV-associated mortality in the first 20 years after the introduction of vaccination. Surprisingly, their model suggests that the extent to which a vaccine slows disease progression and the rate of immunological escape of vaccine-induced immune responses have relatively little effect on the long-term outcome.

In previous trails, no consideration was given for vaccine against clades of HIV. In 2004, Karen[12] hypothesized that assembly of envelope cocktail vaccines will be probably necessary to represent the natural diversity of HIV-1, even within a single clade. Careful vaccine design may reveal a cocktail formulation which will be able to prevent virus infections in every world region, and to overcome the political and financial dilemmas associated with the production of clade, country or region-specific vaccines.

Considerable effort were put forward on evaluating live vector-based vaccine and plasmid DNA (pDNA) vaccine approaches for preventing HIV-1 infection both in animal model and human studies. Few trials testing prophylactic HIV-1 T-cell vaccines have also been published. Vaccines tested so far have included recombinant DNA, modified vaccinia Ankara (MVA), canary pox, and lipopeptides. Each study used different T-cell assays and applied different criteria to define the vaccine induced T-cell response. This, combined with the small numbers within each treatment group, makes it difficult to compare the immunogenicity of the regimens and establish the kinetics of the T-cell response induced following vaccination. In a study by Nilu *et al.*,[13] these problems were approached by measuring multiple functions of T-cells induced by vaccination and applying stringent criteria (determined from pre-vaccination and placebo data to define positive responders). In their double-blind randomized phase I trial, HIV-1 negative subjects received vaccines vectored by pDNA and MVA expressing HIV-1 p24/p17 gag linked to a string of CD8+ T-cell epitopes. They showed that a heterologous

prime boost regimen using DNA-and MVA-vectored vaccines can prime multifunctional HIV-1-specific T-cells capable of rapid proliferation in eight out of eight vaccine recipients; however, this vaccine strategy requires a little more polish to induce more durable and higher frequencies of HIV-1-specific CD8 T-cells. Clinical studies should focus on determining the longevity of the HIV-1-specific T-cell responses induced by DNA and MVA vaccination, developing novel delivery mechanisms and methods of adjuvanting of DNA vaccines, and partnering recombinant MVA with newly emerging and promising HIV-1 vaccine candidates.

Weaver *et al.*,[14] generated a synthetic group M consensus *env* gene (CON6) for induction of cross-subtype immune responses to overcome genomic diversity and reported a comparative study of T-cell responses to this and natural strain *env* immunogens in a murine model. Though, the limited major histocompatibility complex repertoire in inbred mice does not necessarily predict responses in nonhuman primates and humans, these results suggest that synthetic centralized *env* immunogens represent a promising approach for HIV-1vaccine design that merits further characterization.

In a review by Toma's *et al.,*[15] a candidate (HIV-1) vaccine focusing on T-cell induction, constructed as pTHr.HIVA DNA and MVA.HIVA, were delivered in a heterologous prime–boost regimen. These trials demonstrated that the pTHr. HIVA vaccine alone primed consistently weak CD4+ (mainly) and CD8+ T-cell response, and the MVA.HIVA vaccine delivered a consistent boost to both CD4+ and CD8+ T-cells, which was particularly strong in HIV-1-infected patients. Thus, whilst the search is on for ways to enhance T-cell priming, MVA is a useful boosting vector for human subunit genetic vaccines. Furthermore, by their clinical experience with the DNA- and MVA-vectored vaccines, they demonstrated that the perceived performance of a vaccine in humans is critically dependent on the trial design and assays employed to evaluate vaccine immunogenicity. The situation is not helped by the fact that simple correlates of protection against HIV-1 infection and/or progression to AIDS have not been identified.

A major challenge in HIV-1 vaccine development was to elicit potent and broadly neutralizing antibodies (bNAbs) that are effective against primary viral isolates. Previously, it was shown by Michel *et al.*,[16] that DNA prime-protein boost vaccination using HIV-1 gp120 antigens was more effective in eliciting neutralizing antibodies against primary HIV-1 isolates than was a recombinant gp120 protein-only vaccination approach. Later, they analyzed the difference in antibody specificities in rabbit sera elicited by these two immunization regimens using peptide enzyme-linked immunosorbent assay and a competitive virus capture assay. The study indicated that a DNA prime-protein boost regimen is more effective than a protein-alone vaccination approach in inducing antibodies that target two key neutralizing domains: The V3 loop and the CD4 binding site. Different profiles of antibody specificities provide insight into the mechanisms behind the elicitation of better neutralizing antibodies with the DNA prime-protein boost approach, and results supports the use of this approach to further optimize Env formulations for HIV vaccine development. Studies on larger samples are necessary to confirm consistency of these observed patterns.

Merck Co,[17] has reported in 2002 that replication-in competent adenoviral vaccine could elicit effective anti-viral T-cell immune response against simian human immunodeficiency virus (SHIV) (Pathogenic HIV-1 and SIV hybrid virus): Based on this positive result in monkeys, a clinical trial was done to evaluate the efficacy with almost 10,000 HIV-1 negative healthy volunteers. Disappointingly, in November 2007, it was announced that the vaccine was ineffective in lowering plasma viremia post infection and increased the risk of acquiring HIV-1 infection; therefore, further study on the vaccine was not pursued.[18]

Hessell *et al.*,[19] proved that developing an immunogen that elicits bNAbs is an elusive but important goal in HIV vaccine research, especially after the recent failure of the leading T-cell based HIV vaccine in human efficacy trials. Ability of 2G12 administered intravenously was investigated to protect against vaginal challenge of rhesus macaques with the chemokine receptors 5 (CCR5)-using SHIVSF162P3 vaccine. In contrasts, results showed strongly that the typically high titers observed for protection were confirmed by other neutralizing antibodies, including the bNAb b12. The results also raise the possibility that some epitopes on HIV may be better vaccine targets than others and support targeting the glycan shield of the envelope.

An attractive strategy for the development of an HIV vaccine was put forward by Elena *et al.*,[20] using viral vectors with a proven safety profile and an absence of pre-existing immunity in humans, such as New castle disease virus (NDV). Their results indicate that strategies directed towards increasing antigen expression by NDV resulted in enhanced immunogenicity and vaccine efficacy.

Four priming injections of a recombinant canarypox vector vaccine Administration of Live Canarypox Virus (ALVAC-HIV [vCP1521]) plus two booster injections of a recombinant gp120 subunit vaccine (AIDSVAX B/E) was evaluated in a community-based, randomized, multicenter, double-blind, placebo-controlled efficacy trial of a heterosexual population by Supachai *et al.*[21] It was concluded that ALVAC-HIV and AIDSVAX B/E vaccine regimen may reduce the risk of HIV infection in a community-based population with large heterosexual risk. Vaccination did not affect the viral load or CD4+ count in subjects with HIV infection. Although, the results show only a modest benefit, they offer insight for future research.

Therapeutic vaccines

Therapeutic vaccines are designed specifically for HIV positive people who have healthy immune systems. Therapeutic vaccine recipients must have strong immune systems for the vaccine to generate an effective anti-HIV immune response. Therefore, clinical trials of therapeutic vaccines are recruiting volunteers with CD4 counts greater than 250 cells/mm^3 and most studies require a CD4 count greater than 350 cells/mm^3. People with weaker immune systems may be unable to produce a good immune response to a therapeutic HIV vaccine, and are therefore not eligible for these trials. Furthermore, most of the trials require that therapeutic vaccine recipients continue taking anti-retroviral drugs during the study.

Although, multi-drug therapy has improved the prognosis for those infected by the virus, it has not eradicated the infection. Immunological therapies, including therapeutic vaccines, are needed to supplement drug therapy in the search for a 'functional cure' for HIV. Derma Vir (Genetic Immunity Kit, Budapest, Hungary and McLean, Virginia, USA), an experimental HIV/AIDS therapeutic vaccine, combines three key elements of rational therapeutic vaccine design: A single pDNA immunogen expressing 15 HIV antigens, a synthetic pDNA nanomedicine formulation and a dendritic cell-targeting topical-vaccine administration. Derma Vir's novel mechanism of action, natural transport by epidermal Langerhans cells to the lymph nodes to express the pDNA-encoded HIV antigens and induce precursor/memory T cells with high proliferation capacity, has been consistently demonstrated in mouse, rabbit, primate and human subjects. Safety, immunogenicity and preliminary efficacy of Derma Vir have been clinically demonstrated in HIV-infected human subjects. The Derma Vir technology platform for dendritic cell-based therapeutic vaccination might offer a new treatment paradigm for cancer and infectious diseases.[22]

Lisziewicz *et al*., in 2005 have tested Derma Vir alone and in combination with anti-retroviral drugs was tested in chronically SIV-infected macaques. Derma Vir provided virological, immunological and clinical benefit for SIV-infected macaques during chronic infection and AIDS. In combination with anti-retroviral drugs, Derma Vir augmented SIV-specific T-cell responses and enhanced control of viral load rebound during treatment interruptions. The results also indicated the feasibility of therapeutic immunization even in immune compromised hosts, and suggested that Derma Vir can complement anti-retroviral drugs to sustain suppression of HIV-1 replication.[23]

Shimada *et al*., assessed whether, a viral vector-based vaccine can be used as a therapeutic vaccine in SIV infected monkeys. The effect of vaccinating SIVmac239-infected rhesus monkeys with an SIV gag and gp120-expressing adeno virus vector vaccine and a MVA vaccine was explored while being treated with Antiretroviral therapy (ART). They suggested that vaccination can improve anti-viral cell-mediated and humoral immunity, which may contribute to controlling viral replication.[24]

It was concluded in a study published by Persaud *et al*., in 2011 that therapeutic immunization with MVA and Fowl pox-based HIV vaccines led to a transient increase in decay of latently infected CD4 T-cells. Further studies of therapeutic HIV vaccines may provide important insights into facilitating decay of the latent reservoir.[25]

Trumpfheller *et al*., in 2001 concluded in a study that dentritic cell targeted protein vaccines are a potential new vaccine platform, either alone or in combination with highly attenuated viral vectors, to induce integrated immune responses against microbial or cancer antigens, with improved ease of manufacturing and clinical use.[26]

Future prospectus

It was hypothesized that prophylactic HIV-1 vaccines would be most efficacious if they elicit a combination of adaptive humoral and T-cell responses.[27] The polymorphisms in CCR5, the major co-receptor for HIV, and CCL3 L1, a potent CCR5 ligand and HIV-suppressive chemokine, are determinants of HIV-AIDS susceptibility. Thus therapeutic vaccines directed towards reducing the infectivity of the host may play a role in halting epidemic spread. Further, CCL3 L1-CCR5 genotype may provide critical guidance for optimizing the design and evaluation of HIV-1 vaccine trials and prevention programs.[28] It was also demonstrated that the route and dose of DNA vaccines significantly impact the quality of immune responses, yielding important information for future vaccine design.[29]

Importantly, the success of any human vaccine trial should not be judged solely on short-term measures of how many infections were prevented in the vaccinated group. Rather than simply measuring HIV incidence in vaccines and controls, vaccine trials should also aim at closely monitoring viral loads of infected individuals in order to quantitate any reduction in viral load in vaccinated individuals**.**

CONCLUSION

There were five major vaccines introduced as possible treatments for AIDS: Killed vaccine, live-attenuated vaccine, subunit vaccine, vectored vaccine, and DNA vaccine. Among them, DNA vaccine is the most promising HIV vaccine, since it was the only one that could provide a safe and protective immunity against HIV. Despite the safety concerns of the live attenuated vaccine, it is currently the only vaccine that is capable of inducing a protective immunity. Hence, a vaccine that has similar qualities and which induces a strong response of the immune system similar to that of

the live attenuated vaccine is the most probable to become a successful AIDS vaccine. In order to develop an effective DNA vaccine, the vaccine candidate should be evaluated thoroughly in terms of protective immunity in a small number of volunteers before entering large-scale phase IIb~III efficacy trials. More importantly, even before considering any clinical trials in humans, the efficacy test should be evaluated in the appropriate SIV mac-rhesus macaque challenge model that closely resembles the human case. Though, we have a long way to go, at least all vaccines tested so far in humans have been found to be safe.

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How to cite this article: Beena VT, Choudhary K, Rajeev R, Sivakumar R, Heera R, Padmakumar SK. Human immunodeficiency virus vaccine an update. J Oral Maxillofac Pathol 2013;17:76-81.

Source of Support: Nil. **Conflict of Interest:** None declared.