

HIV Vaccine Development: Current Scenario and Future Prospects

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Abstract

The search for a preventive vaccine that can halt the global pandemic is the ultimate goal of HIV research. Development of a vaccine against HIV-1 has been plagued by many insurmountable challenges. Different vaccine concepts have been tested to overcome these challenges. Experimental vaccines that showed promise in preclinical studies were advanced into clinical trials. Yet, human trials proved to be a huge disappointment until the results of the RV144 trial in Thailand. This trial not only provided the first evidence of a modest efficacy, but also valuable insights on the possible immunologic correlates of vaccine protection. Currently, the HIV vaccine research landscape has been rejuvenated by two major developments. On one hand, there has been a resurgence of interest in T cell-based vaccines with the promising results obtained using a recombinant cytomegalovirus vector vaccine. On the other hand, the discovery of more than a hundred broadly neutralizing antibodies from cohorts of HIV-infected individuals has led to the development of antibody-based preventive vaccines. Innovations in the design of vaccines, vaccination strategies and clinical trial programs will be necessary to accelerate the search for a prophylactic HIV vaccine. This article reviews the current status of HIV vaccine research and provides a roadmap to future efforts in vaccine development.

Keywords: HIV; Prevention; Vaccines; T cell-based vaccines; Antibody-based vaccines; Clinical trials

Introduction

More than thirty years have elapsed since Human Immunodeficiency virus (HIV) was first identified as the cause of acquired immunodeficiency syndrome (AIDS) [1]. AIDS continues to be a global public health challenge and it is estimated that more than 70 million people have been infected with HIV and more than half of these individuals including children have died from AIDS. Epidemiological studies indicate that new HIV infections are currently either on a decline or have stabilized in many nations of the world including sub-Saharan Africa which is at the epicentre of this pandemic and India which is home to the third-largest population of people living with HIV [2]. This decline can be attributed to a significant increase in easier access to AIDS therapy at the global level along with effective prevention efforts among key target groups [3-6]. In addition, the fact that during the natural course an epidemic usually peaks before declining to stable levels is also a contributory factor.

Recent studies have succeeded in elucidating many of the complexities involved in the host immune response to HIV infection. Yet, neither a complete cure nor a protective vaccine has been found and new infections continue to occur at the rate of approximately 7000 people per day.

The Need for An Anti-HIV Vaccine

The first milestone in the fight against HIV was the introduction of anti-retroviral therapy (ART) to treat AIDS. Since then there have been major advances in both, the treatment and prevention of HIV/AIDS. Pre-exposure prophylaxis [7-10] and the use of ART for prevention have positively impacted the available prevention options. In fact, current evidence strongly supports early initiation of ART, as it not only improves the health of infected individuals but also reduces the risk of HIV transmission [11-13]. Yet, ART has its limitations as it cannot fully restore the immune system and there is a need for life-long treatment as HIV persists indefinitely in latent reservoirs of the infected individuals [14,15]. Furthermore, there are problems with adherence and the retention in care of the HIV-infected individuals. Hence the development of a safe, effective and affordable vaccine continues to be

a priority and will be vital in the long term to control the transmission of HIV and its eradication.

Scientific Challenges in the Development of a Globally Effective HIV Vaccine

One of the major challenges in the development of an anti-HIV vaccine is that the immune correlates of protection against HIV infection in humans are still not clearly defined. In fact, the mechanism by which an HIV vaccine will be able to provide protection has not yet been elucidated. Vaccines designed to prevent various infectious diseases in the past have been successful in generating protective immune responses similar to those that occur during natural infection. However, the absence of natural immunity against the virus has proved to be a major stumbling block in the development of a vaccine against HIV. It appears that an effective vaccine will have to elicit an immune response which is significantly different from that which occurs during the course of a natural infection [16].

Another barrier in the development of a vaccine targeting HIV has been the extraordinary sequence diversity exhibited by the virus and its ability to continually evolve in order to escape the host immune response. In particular, Group M of HIV-1 has nine distinct subtypes and different circulating recombinant forms worldwide. The amino acid sequence of the Env region of this virus can exhibit up to 20% diversity within a subtype and up to 35% diversity between subtypes [17]. It is a matter of great concern that a vaccine derived from a particular clade may not provide protection against all other clades and this may prove to be an insurmountable hurdle in the design of a globally effective anti-HIV vaccine.

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Received September 12, 2016; Accepted October 06, 2016; Published October 13, 2016

Citation: Ajbani SP (2016) HIV Vaccine Development: Current Scenario and Future Prospects. J AIDS Clin Res 7: 626. doi: [10.4172/2155-6113.1000626](https://doi.org/10.4172/2155-6113.1000626)

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Another major obstacle to HIV vaccine development has been the lack of suitable animal models which can be used to predict human response to vaccines [18]. HIV-1 only infects chimpanzees in nature but they do not develop human-like AIDS disease. Although HIV does not infect monkeys, a closely related virus, Simian immunodeficiency virus (SIV) can establish a productive infection in monkeys which recapitulates HIV pathogenesis seen in humans. However, due to differences in the envelope (Env) region of HIV-1 and SIV replication-competent chimeric SIV/HIV constructs called SHIV have been engineered which can infect cynomolgous and rhesus monkeys. SIV or SHIV/non-human primates (NHPs) are the models of choice for the preclinical testing of HIV/AIDS vaccines. However, the prevention observed in the NHPs has not been duplicated in human trials. Thus NHPs are not very reliable models for predicting HIV vaccine efficacy in humans. Yet, in the absence of any other suitable alternative, NHPs are still used for preclinical research on HIV vaccines.

The Search for an HIV Vaccine

The search for a vaccine against HIV has not been as easy as anticipated in the early 1990s. To date more than 30 vaccine candidates have been developed yet the world still does not have an anti-HIV vaccine. Traditional vaccination approaches involving the use of attenuated and inactivated virus were the first to be tested in NHPs but due to reasons of biosafety and a possible danger of reversion to pathogenicity could not be advanced to human clinical trials [19].

Apart from safety, HIV-1 vaccine development has been guided by the principles of stimulating either sterilizing immunity or cellular immunity or preferably both against the virus. It is strongly believed that an effective HIV vaccine will have to elicit both broadly reactive neutralizing antibodies as well as CD4+ and CD8+ T cell responses to confer protection [20]. Additionally, adjuvants and vectors capable of triggering innate immunity may be required to improve the quality of the adaptive immune responses. Over the years several vaccine candidates have been developed based on these guiding principles.

The candidate vaccines which were able to elicit varying levels of protective immunity in NHPs during preclinical studies were then advanced to human clinical trials [21,22] and evaluated either alone or in combination in a homologous/heterologous prime-boost approach. They include HIV-1 protein subunit vaccines, peptide vaccines, plasmid DNA vaccines, HIV-1 viral-like particle vaccines and recombinant vaccines constructed from viral vectors such as poxvirus, adenovirus, adeno-associated virus and alphavirus. Some of the candidate vaccines have been administered along with different adjuvant formulations [23,24]. The recombinant vaccines have utilized HIV genes either in their native form or as fusion constructs which have been codon-

optimized or modified in various ways for generating potent immune responses [25-28]. Furthermore, many of the recombinant viral vectors have been tested either in the replication-competent or replication-incompetent modality as HIV vaccines (Table 1).

Most of the vaccine candidates which exhibited potential in Phase I and Phase II trials either failed to show protection or exhibited an increased risk for HIV-1 acquisition in Phase IIB/III trials. They include the recombinant HIV-1 envelope gp120 based bivalent sub-unit vaccines namely AIDSVAX B/E with alum evaluated in the Vax003 trial [29] and AIDSVAX B/B with alum evaluated in the Vax004 trial [30] and the replication-incompetent adenovirus serotype 5 (Ad5) vectored HIV-1 trivalent vaccine evaluated in two different trials namely the Step trial and HIV Vaccine Trials Network (HVTN) Phambili trial [31,32].

The first evidence of vaccine induced protection was provided by the RV144 Phase III trial, which was conducted in Thailand and involved the use of two immunogens (the canary pox-vectored ALVAC-HIV prime and AIDSVAX gp120 B/E subunit vaccine boost) which had failed when used separately [33]. Results of this trial showed that although protection occurred early after vaccination the vaccine efficacy appeared to diminish over time from 60% after one year to 31% after three years. Though this vaccine was not approved for use in the general population, the RV144 trial has been instrumental in providing unique insights on the potential immunological correlates of vaccine protection. They include the absence of neutralizing antibodies and cytotoxic T cells, the presence of a clear correlation between protection and non-neutralising antibodies against the V1V2 region and the probable role of antibody-dependent cell-mediated cytotoxicity (ADCC) as a mechanism of protection [34-36].

Current Status of HIV Vaccine Research Landscape

Currently many novel vaccine strategies are being explored that have the potential to significantly advance HIV vaccine development. One such exciting area has been the construction and evaluation of cytomegalovirus (CMV)-based replication-competent vectors for antigen delivery. A RhCMV-based vaccine expressing SIV antigens demonstrated robust CD8+ T cell responses which correlated with protection in about 50-60% of the rhesus macaques irrespective of the route of challenge (intra-rectal/intra-vaginal). Furthermore, no viral rebound was observed after the removal of CD8+ T cells *in vivo* [37,38] and compared to the conventional SIV-specific T cell responses, vaccination with the RhCMV/SIV vector stimulated an atypical CD8+ T cell response which was predominantly MHC class II restricted [39]. As these vectors did not stimulate any antibody response they have rekindled interest in T cell-based vaccines. Although encouraging it remains to be seen whether these results can be duplicated in humans.

Preclinical/Clinical trial	Type of virus	Viral vector used for antigen delivery	Replication characteristic
Phase III trial (RV 144) Phase II trial Phase II trial NHP studies	Poxvirus	Canary pox (ALVAC) Modified Vaccine Ankara (MVA) NYVAC NYVAC- KC	Deficient Deficient Deficient Competent
Phase IIb trial (STEP, Phambili and HVTN 505) Phase I trial Phase I trial Phase II trial	Adenovirus	Adenovirus Serotype 5 Adenovirus Serotype 26 Adenovirus Serotype 35 Chimp adenovirus	Deficient Deficient Deficient Deficient
NHP studies (Expected to enter Phase I trial in 2017)	Cytomegalovirus	Rh Cytomegalovirus (RhCMV)	Competent

Table 1: Different replication-competent/deficient viral vectors used in HIV Vaccine trials.

The recombinant CMV-based HIV vaccines developed by the Louis Picker group are expected to enter Phase I human trials in 2017.

Induction of broadly neutralizing antibodies (bnAbs) by active immunization is an alternate strategy which is also being currently explored. The bnAbs directed towards the Env of HIV-1 are rare since they are found only in a small percentage of infected individuals. Only about approximately 20% of the infected individuals can produce truly cross-reactive potent bnAbs capable of neutralizing a wide variety of viral strains 2-3 years post-infection. Furthermore, the development of bnAbs in infected individuals requires extensive somatic hypermutations in order to achieve the binding specificities appropriate for neutralizing different viral strains [40]. Stimulation of the correct sequence of somatic hypermutations by a series of antigens/envelope proteins in active immunization regimens could induce broadly reactive neutralizing antibodies capable of effectively neutralizing different viral variants. Though promising, it is nevertheless, an extremely complex and difficult process to induce these bnAbs as many levels of somatic hypermutations are needed over many years. Meanwhile, the virus continues to evolve by developing new and resistant mutations [41-43]. Additionally, there are concerns that some of these potent bnAbs may be either poly-reactive or auto-reactive and therefore may be clonally deleted to prevent autoimmunity.

A candidate vaccine capable of inducing bnAbs against most circulating strains of HIV has been elusive. Neutralization of Env on HIV-1 has been impeded due to a number of factors such as its remarkable antigenic diversity, concealment of critical epitopes by heavy glycosylation and the fact that antibodies continue to evolve as a result of extensive somatic hypermutations [21,44-47]. But recently the successful stabilization of the Env trimer in a soluble form has enabled its use as an immunogen [48-51]. The trimeric Env has a greater potential to generate antibodies that will recognize the functional spike of HIV and neutralize the virus. It remains to be seen whether the entire trimer or specifically engineered partial regions of Env or a combination of both will be required to stimulate the difficult-to-induce B cell lineages. Two experimental vaccines, BG505 SOSIP and engineered gp120 variants have shown potential to stimulate intermediate antibodies and not the mature forms [48]. Currently, many regions of HIV-1 Env are being explored as targets for stimulating bnAbs and include gp120 CD4/CCR5 receptors/CXCR4 coreceptors, the V1/V2 variable loops, membrane proximal external region (MPER) of gp41 and some exposed glycans [52,53].

Furthermore, the isolation of more than a hundred bnAbs from cohorts of HIV-1 infected individuals has paved the way for the development of antibody-based HIV vaccines. Studies involving the passive transfer of bnAbs in nonhuman primates have been promising. Suppression of viremia in infected monkeys and prevention of viral acquisition in uninfected monkeys was observed in these studies [54-56]. Moreover marked suppression of HIV production in viral reservoirs by bnAbs has also been detected in *ex vivo* studies [57]. Although the ability of bnAbs to prevent infection in humans is still not known, studies have shown decrease in the levels of circulating virus after administration of bnAbs [58].

A trial called HVTN 703 which is currently underway in South Africa is based on passive immunisation with preformed antibodies. This proof-of-concept Phase IIb trial, also called the AMP (antibody-mediated protection) Study, is designed to prove whether a preformed antibody VRC01 can prevent HIV infection in humans. The outcome of this trial is also expected to reveal the dose of antibody needed to protect humans from HIV infection. VRC01 is a broadly neutralizing antibody

which has been cloned from an antibody-producing cell isolated from an HIV-infected individual. Administration of VRC01 has been found to be safe in humans in Phase I trials and has demonstrated its ability to prevent infection in NHP studies.

Another major Phase III efficacy trial in South Africa has been designed to build on the RV144 trial with the aim to not only replicates the partial protection observed in Thailand but if possible to surpass it. This trial called HVTN 702 is going to be initiated in November 2016 and is based on the classical approach of eliciting T cell immunity [59]. The HVTN 702 vaccine regimen consists of two experimental subtype C vaccines tailored to match the viral strains circulating in Southern Africa. These vaccines include a canary pox-based vaccine (ALVAC-HIV) prime and a bivalent gp120 protein subunit vaccine boost which is formulated with the adjuvant MF59. The vaccine candidates will be administered in 5 injections over a period of 12 months in an attempt to increase the magnitude and duration of vaccine-elicited immune responses as compared to the RV144 trial. The appearance of V1V2 binding antibodies in greater than 50% of the vaccinated individuals and the presence of HIV-1-specific helper T cell responses will serve as the benchmarks for evaluating the efficacy of this active immunization strategy. If the vaccine is found to be safe and able to reduce the number of infections by at least 50% it may be considered suitable for use in the general population.

The results from the HVTN 702 and HVTN 703 trials will be out in 2020 and 2022, respectively and are expected to be instrumental in generating an increased understanding of the requirements of an effective HIV vaccine which can decimate this virus. Yet, it may take years or even decades before a vaccine is licensed for use in the general population.

Roadmap to Future Efforts in Vaccine Development

The development of a safe and effective HIV-1 vaccine remains one of the highest research priorities to create a world without AIDS. Although an effective prophylactic vaccine still remains elusive, the results of the RV144 trial have reenergized the HIV-1 vaccine landscape. The lessons learnt from this trial are currently being applied by scientists not only to develop modified and possibly more effective vaccine candidates but also to guide future vaccine trial protocols. The ability to express the native Env trimer of HIV-1 as a recombinant protein has also been a major step forward in vaccine design and development. Furthermore, the results of some of the novel vaccine candidates in the non-human primate models have been quite encouraging. Evaluations of these novel immunogens in human trials, an increased understanding of immune pathways which lead to the generation of effective antibodies and the availability of modern tools to study the intricacies of the B cell response have the potential to further transform the field of HIV vaccine development.

However, there are many areas of concern that will have to be addressed on a priority basis. One major concern is whether the immune correlates of vaccine protection derived from the RV144 trial can be applied to other modalities of vaccines and diverse subtypes. Furthermore, although results obtained in NHP models are still used to guide HIV-1 vaccine research there is an urgent need to develop new animal models which can more accurately predict human immune responses. Adjuvant formulations which can enhance the humoral immune response and facilitate antigen dose sparing may also play a significant role in the design of a successful vaccine. Evaluation of diverse vaccine concepts and vaccination regimens in an accelerated and dynamic human vaccine trials program will clearly result in

greater success in developing the vaccine. Greater investment in the development of infrastructure in countries which are experiencing the major brunt of the HIV/AIDS epidemic will also be essential to bring us closer to an effective vaccine. The bottom line is that there is an urgent need to explore strategies to design a truly global prophylactic vaccine which can address the extensive viral diversity and provide protection against all circulating strains. Discovery of a preventive vaccine to end the AIDS epidemic in the near foreseeable future can be possible by a truly unified global level comprehensive response involving all the stakeholders including researchers, clinicians, epidemiologists, national and international HIV/AIDS organisations, governments, local communities and the drug development industry.

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Citation: Ajbani SP (2016) HIV Vaccine Development: Current Scenario and Future Prospects. J AIDS Clin Res 7: 626. doi: [10.4172/2155-6113.1000626](https://doi.org/10.4172/2155-6113.1000626)

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