International Journal of Multidisciplinary Research and Development
www.allsubjectjournal.com
Online ISSN: 2349-4182, Print ISSN: 2349-5979
Received: 30-04-2022, Accepted: 16-05-2022, Published: 31-05-2022
Volume 9, Issue 5, 2022, Page No. 122-129

Challenges and possible solutions for HIV vaccine development

Attul Singh[1], Girija Kumari[1], Vikram Singh[2*]
[1] Department of Clinical Research, Amity Medical School, Amity University Haryana, Amity Education Valley Gurugram, Panchgaon, Manesar, Haryana, India
[2] Department of Medical Laboratory Technology, Amity Medical School, Amity University Haryana, Amity Education Valley Gurugram, Panchgaon, Manesar, Haryana, India

Abstract
Since the first case of HIV was detected, scientists throughout the globe have focused their attention towards developing a vaccine that is not only able to prevent infections related to HIV but also save lives of people already infected with it. The search for a vaccine is in works since late '80s, but there has not been any ground breaking progress in the respective field. Issues in funding, loss of scientists' interest and failure to generate a solid data in support of HIV vaccine development have always been the obstructions which need to be removed and a lot of work needs to be done to develop an effective and affordable vaccine to completely eradicate the virus. This article will review the various challenges being faced by the scientists in developing vaccine, the mechanism of newly made vaccines, their trials and possible outcomes we can expect based on the scientific studies going on in various parts of the world.

Keywords: HIV, AIDS, retrovirus, ZDV, HAART

Introduction

Human Immuno-deficiency Virus, or commonly known as HIV, is a retrovirus, originally derived from lentiviruses, member of Retroviridae family and is the etiological agent of Acquired Immune Deficiency Syndrome or abbreviated as AIDS. The first ever known case of HIV infection was reported in 1981, in an article which was published in the *Mortality and Morbidity weekly report* of United States' Centre of Disease Control and Prevention (CDC). The published article described that the infection was reportedly seen in homosexual men or gay men and was initially misidentified as pneumocystis and/or Kaposi sarcoma infections. After a couple of years of extensive research on the newly identified infection and this new outbreak, scientists named Luc Montagnier and Robert Gallo were the first to scientifically prove that the emerging cases were associated with a new retrovirus and was afterwards known as HIV. As time passed, more time and resources were poured in the research and as more data was collected, eventually first-ever HIV diagnostic test kits were developed. The licensing of first serological test kit was done in 1985.

Over the next few years, widespread diagnosis of AIDS and its screening on a large scale has helped researchers to understand the spread and infectiousness of this newly discovered virus and to initiate a response as quickly as possible on a global level to tackle the pandemic. A promising way to counter it was the development of first anti-HIV vaccine, AZT or Zidovudine in 1987. The vaccine when used with other anti-retroviral drugs gave the best results in protection in the preliminary testing and it changed the direction of pandemic and somewhat helped to cease the outbreak.

In the past, HIV has become a worldwide issue and has spread throughout, infecting more than 40 million people with the maximum number of cases from Asian and African subcontinent, and more than 20 million people dead because of it. United Nations Programme on HIV/AIDS (UNAIDS) has predicted that each year, some 5 million fresh cases of HIV are going to be detected on a global scale but due to the clinical advancements in the field of detection, diagnosis and prevention of the virus, the rate will be reduced to around 2 million cases per year which gives a rate of more than 50 percent. Contrary to some popular beliefs, the HIV epidemic is surely not under control of us, and it continues to spread which are, to some extent, true. And as of today, finding a cure and developing an effective anti-HIV vaccine remains the utmost priority of the scientists. Anti-HIV vaccine development remains one of the most difficult challenges in the field of biomedical research. Ron Desrosiers has commented on *Nature Medicine* that, our struggle to develop a new HIV vaccine can easily be compared to mythical punishment of Sisyphus, by which we are condemned by the gods to just roll a rock up to the top of a tall mountain for eternity.

As we confront the challenges coming across in search of an effective and affordable HIV vaccine, there are numerous frustrating challenges to deal with and even with some people, who live in the doubt that whether any HIV vaccine can ever be developed and whether the leading scientists can develop a way to tackle this ongoing silent epidemic with their new interventions. Hurdles Faced in Developing a Vaccine Among all the other

retroviruses discovered and their infections been cured, HIV is the notorious of them all. Time and again, scientists have found out that HIV is really a difficult infectious agent for which a vaccine cannot be developed as easy as it was for other viruses. To develop and prepare a vaccine against HIV, researchers are scratching their head as HIV exhibits some very different and unique characters such as a very high mutation rate which makes it difficult to find out the viral genome. Also, HIV can avoid the host cell's immune response and can remain latent for years due to which, the onset of symptoms is delayed, and it makes diagnosis of AIDS a challenging task to perform. When the virus is in a latent stage, it just rests silently in the body and remains integrated in the DNA of host cell. However, recent studies, clinical evidence, development of newer gene expression systems, replica models, study of pathogenesis, etc have provided us with enough proofs that an effective HIV vaccine development is possible, but it comes with a great price.

Speaking about price, getting adequate funding from reputed organizations also remains one of the many challenges faced during the development of an effective HIV vaccine. Funding as we know it, is a culture when the research groups appeal to the major regulatory authorities and organizations to help them financially so as to boost the rate of study and research towards finding a solid cure in minimum time and getting the world rid of a global epidemic. But getting funds is a lot more complicated than simply just announcing grant of funds. The fund providers throughout the world have a major responsibility to decide and make their minds about whether the funding can aid in the product development just by the applied research or more in pouring of knowledge is required in order to advance to the next step. After deciding the work that needs to be done, the funders or what we commonly call them, sponsors, need to attract some bright minded and skilled scientists to cover the vaccine development stages.

In today's world, what most of the people think is that just after a huge sum of money is received for funding of vaccine development from a pretty rich and wealthy stakeholder, the process of vaccine development starts, and the disease is cured immediately as soon as the proposed vaccine is developed and is made available for use. But this is not what basically happens. Even after several decades, and after numerous sponsors have invested millions of dollars in vaccine research and development, the quest of HIV vaccine development has not reached any milestone and the road to a safe and effective vaccine is still not so clear for a permanent cure. Sometimes it appears that in developing a vaccine, progress is done and just after few years the vaccine can be launched, but as the process comes to a successful end, the market becomes so uncertain and unpredictable that the scientific team of researchers developing the vaccine do not feel motivated anymore and do not wish to complete what they started, also not applying further for funding. What they assume to be the problem, is lack of basic appraisal from peers and not feeling motivated enough to dedicate their crucial time in developing something that is not even in demand in the market. In certain cases where the conditions get too unfavourable, the plan to develop vaccine is so unclear and blurry that the companies, funding organizations and the team of scientists who are working on vaccine development won't start doing any research-oriented task until the academic scholars and scientific authors of a few reputed institutions or the government appointed scientists have paved a way for them. Therefore, the funding agencies or the individuals providing fund have a major responsibility to recruit only the best and skilled scientists in the relevant field and to recruit such people who can provide positive results in minimum time because it is not important to just be the best, being efficient is also considered crucial for vaccine development and as the market is booming with competition, sooner or later, some 2 or 3 potential cure or products become available in the market which makes the customers confused and making it difficult to make their mind about which treatment to prefer over which a framework was designed in order to make a fixed set of procedures to follow in order to develop a vaccine. This involves observation of individuals who have been previously infected by HIV and have successfully recovered by the help of their own immune system. Just for a thought, if those kinds of curative immune responses can be generated by the vaccines administered even before the person gets exposed to the causative pathogen, the severity and the impact of the disease would be diminished slowly and eventually disease will be prevented. Therefore, the analysis of the immune responses gathered from the recovered people can establish a possibility of developing an effective vaccine against the infection. This can be guided by the quality of the immune responses, specificity of the epitopes and the titre quantity. The vaccine developers then tend to apply a small number of previously used practical strategies which are well-established, such as use of attenuated, whole-killed pathogen and other methodologies of surface protein analysis which have been used for years in the basic research and have been eventually added to the list of vector-based medicines in the coming times. A proper vaccine development, in all cases, is a very lengthy process which undoubtedly is complex and which can easily take 2-5 years depending on many factors like location, availability of resources, demands, no. of personnel working for development of vaccine, etc which is clearly not a task a single man could perform.

In addition to get the funding from the stakeholders, other challenges are also there which are faced while developing a vaccine which obstructs the scientists to proceed ahead. These hurdles might include a limited access to the samples of HIV infected individuals to work with and getting hold of sophisticated and specialized instruments and materials, and as we are progressing in a completely new field, the reference reagents and their standards are also hard to produce. Also are the challenges which are outside the area of expertise of investigators, such as studies in non-human primates' studies, manufacturing as per the compliance of cGMP, toxicology studies reports required by the regulatory authorities and the clinical trials that need to be conducted in support of the newly developed vaccine.

To understand the overlapping nature of the funding strategies, we need to have a look at Error! Reference source not found.. At the beginning stages of HIV vaccine development, the entire work of researching and providing scientific matter was left on the private sector, because it was thought to be purely applied research and there was nothing much to intervene from the major players.

Hence, the first products developed were actually made by small start-up biotech companies and were achieved with private funding. A company named MicroGeneSys, at that time, worked on a viral envelope subunit (gp160) which was called VaxSyn, created in a baculovirus-insect cell system and another company which was formed by Dr. Jonas Salk worked on a new, "whole-killed" product intended to be used as a therapeutic vaccine, Remmune. These developed vaccine products have made some progress as far as Phase II of the clinical trials, but in the mid '90s, they seem to have failed. At the same time, two more gp120 envelope protein vaccine candidates were under development as well by some other private companies named Chiron and Genentech. They, asked NIH to provide a large scale funding to proceed to Phase III trials but many scientists lost hope that a simple protein might serve as a cure and will be able to be developed in an effective vaccine due to which, NIH declined funding and the research stopped.

In 1996, Levine committee: a high-level review team made some recommendations for NIH to manage HIV/AIDS research funds. And the most important recommendation was that NIH should put more of their efforts in understanding the relationship between the HIV and its interaction with the host cell's immune system to make NIH-sponsored AIDS vaccine and to proceed in that way even though sometimes it might need them to go back to the basics.

In 2003, nearly after two decades of discovery of this retrovirus and with no treatment whatsoever, a policy article was published by a group of 24 internationally known scientists and in that article; they called for a "Global HIV Vaccine Enterprise". They called, among many other things, establishment of multiple research and development centres for HIV vaccine development, which would be self-contained and would advance the development of HIV vaccine.

The therapeutic experiments and interventions made so far consisted of treatment with drugs and therapeutic vaccines. Preventive interventions included prophylactic vaccines which somehow were thought to reduce the risk of infection in the uninfected individuals. But sadly, none of those were able to cease the epidemic. To inhibit the viral activity, a number of vaccines and drugs were developed. Zidovudine (ZDV) was the drug that has been extensively used and has shown success only in extending the survival time of AIDS patients. However, in early-stage cases, the drug proved to slow down the disease progression but did not improve overall survival time.

Some other anti-HIV drugs have also been used in the trials namely, Didanosine (ddI) and Zalcitabine (ddC) and were tested in comparison with ZDV. In certain cases, these drugs proved to be effective, but with respect to AIDS cure, these drugs were not even close and the testing on the drugs came to a halt.

One of the main reasons of HIV vaccine failures is the extremely high cost of treatment and care. In United States itself, it is estimated that on an average HIV infected person, the cost of treatment is approximately $119,000 calculated from the time of infection till the death of the person. Likewise, in the developing countries, where the economies go up and down and are never stable to support the common man, the cost of such treatments of HIV/AIDS infected individual can skyrocket even more and is not affordable, in any way. The developing countries also suffer from poor hygiene, lack of education & past history of being epicentre of global pandemics, which makes it more obvious that a vaccine against this deadly infection is more than required.

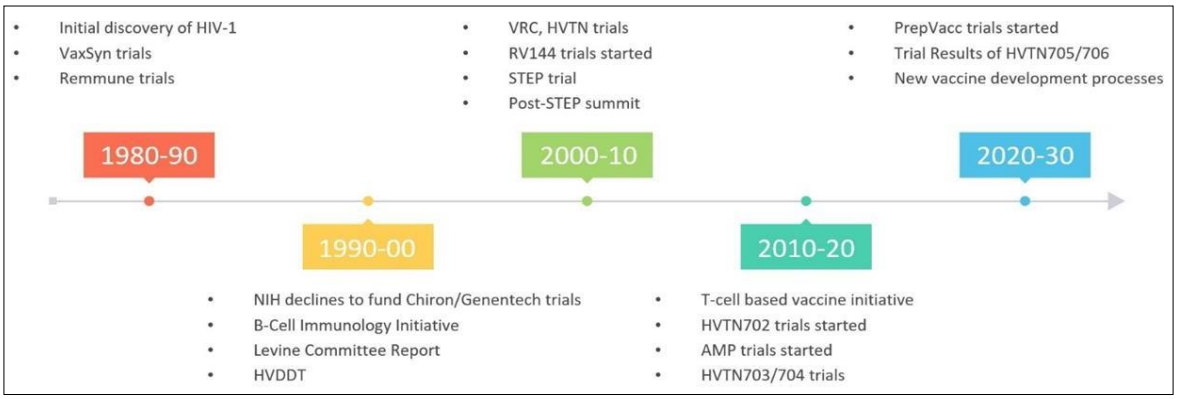

Fig 1

Uncertainties in HIV Vaccine Development

In developing a effective HIV vaccine, there are a lot of unpredicted issues and uncertain outcomes which may serve as barriers in reaching to a global HIV vaccine development mission. Among a lot of issues, few are described here.

Firstly, there are questions which are arising and those deal with the perfect and appropriate composition of the vaccine. Under testing drugs like ddI and ddC both were entirely based on gp120 viral envelope protein. Several other clinical trials were based on recombinant subunits of virus as well as some vaccines were based on the live

attenuated viruses. These approaches are not based on fixed composition and all other possibilities are undergoing testing in preclinical phases and lab studies.

Secondly, questions are there about how a vaccine should be introduced in the body and how it will stimulate the immune system to produce an effective immune response. The evaluations are required in the vaccines which correspond to enhancement in magnitude, breadth, and duration of the observed immune response.

Third, there is uncertainty in determining the components of the immune system to be targeted. Such type of stimulus is needed to be provided which will result in long lasting immune response even after getting a single dose of vaccine. Studies need to be conducted to determine whether to stimulate humoral immune system to get humoral immunity or cell-mediated immune response after dose administration.

Fourth, is again a major concern which relates to how to achieve protection against a wide variety of HIV strains. As it is evident that HIV exhibits a wide variety of genetic variation and mutation i.e. new strains are being discovered at every step and developing a common vaccine to protect the individuals from the variety of strains is most important. Some vaccines, when in testing, have shown protection against numerous strains like those used in making the vaccine, very little success is reported in protection against the "wild" strains of HIV present worldwide and to which, most of the people are exposed.

Fifth, are the safety concerns regarding the vaccine and its administration in infected and the population not exposed to HIV infection. Fears are there with regards to the vaccine that whether the vaccine, instead of suppressing the symptoms and treating the infection, might increase the susceptibility to infection or also can worsen the condition of a person infected with HIV.

To be precise and clear, the HIV infections acquired by the individuals can be prevented. Statistically speaking, most of the HIV infections seen worldwide are associated with high- risk-behaviours such as homosexual activities, sharing of used needles, poor hygiene, exchange of body fluids, etc. Control on these things and using non-vaccine interventions can help reduce the HIV-transmission and save a lot of people from getting infected with this deadly virus. All the interventions lead to a common goal, which is to develop an ideal vaccine which is best, effective, and fast in its action so that the HIV infected individuals at their advanced stage might also get some relief and hope to be cured.

Goals of Vaccine Research

In the times when global efforts are being made to develop a safe and effective HIV vaccine, it is very important to know about how an ideal vaccine should be developed and what features it has to possess in order to give the best outcome in minimum time possible. All the studies and trials and interventions have a common goal, which is to develop a vaccine which can save lives of people or at the minimum, provide some benefit to the people who already have contracted infection from HIV, even after getting vaccinated.

An ideal vaccine could have the ability to protect an individual who has got HIV but keep him away from being infected. In other words, the vaccine should be able to produce sterilizing immunity to the individual who, even after acquiring the virus, will remain protected from infection and let the virus remain in latent stage and without showing any signs or symptoms of AIDS. The immunity thus generated will not destroy the virus but surely will be effective to protect the health of the person. An ideal vaccine should also allow the person to seroconvert and in doing so, not let the person gets chronic infection. The vaccine should readily prevent any transient infection and even if the vaccine is not capable of preventing chronic infection, it must delay the onset of symptoms and prolong the life of the infected individual.

Undoubtedly, there are weaknesses with the use of such vaccines providing sterilizing immunity and preventing transient infection, and thus, other endpoints are to be determined. *Surrogate markers* are one of the options to consider.

Surrogate markers are in fact the measures of the biological activity and are meant to substitute for the measures of efficacy, where the effects on efficacy endpoints unequivocally display the tangible benefits to the subject or participant. These measures of biological activity are determined in the individuals over a much shorter period duration as compared to the measures of efficacy. However, some serious issues are noted too while using surrogate markers.

An example of the use of surrogate markers is provided by CD4 lymphocyte counts which were used as surrogates in HIV/AIDS related clinical trials. CD4 counts, even though predicted the time to death in the natural history setting, the changes induced by interventions in CD4 counts are not predictive of the survival time in AIDS patients. CD4 count, hence, is a surrogate which is not as effective as an ideal surrogate.

In current scenario, the function of Cytotoxic T-lymphocytes (CTL) is measured by the assays such as IFN-ɣ enzyme-linked immunospot assay (Elispot) and intra-cellular staining (ICS) using flow cytometry. Even though the Elispot assay is sensitive, solid and a cost cutting method of rapid antigen- specific CTL screening and antigen mapping, it does not provide any sound evidence regarding the immune response and only helps to measure the production of single effector molecule, IFN-ɣ. On the other hand, ICS correlates better in the multi-parameter format and can easily provide more information about specific T- lymphocytes, their functional profiles and maturational phenotype, as this technique of ICS is used along with flow cytometry which undoubtedly, is the best method to be used in cytological evaluations.

Several reports have this stated that the IFN-ɣ is not always associated with the replication control and its examination will alter the total anti-HIV-1 specific $CD4^+$ lymphocytes. The production of IFN-ɣ is seen in early phases of the immune response but the secretion decreases with increasing antigenic clearance.

In pre-clinical studies, when the T-cell based vaccine candidates were being tested for the control of virus load in test subjects, the maximum response was against the Gag antigen, which in turn, induced IL-2 and IFN-ɣ responses and other substantial proliferative responses as they were recorded by Elispot methods. On the other hand, Env gene analyses showed somewhat weaker IL-2 and IFN-ɣ responses, but a substantial IL-4 response was seen in Elispot assays. Pre-existing immunity to AdHu5, which is naturally found in humans, has changed the vaccine induced T-cells pattern. In such models, frequencies of transgene specific T-cells were seen more in spleen than in the circulation but were high exceptionally in livers when they got vaccinated with AdHu5 vectors or vectors from Chimpanzee adenovirus. The increasing scarcity of Indian rhesus monkeys is a sign to call for developing AIDS models using other substitutes which are Chinese rhesus monkeys. These animal models need knowledge of MHC genotype by doing detailed analysis. More clinical trials are needed because it is difficult to predict as to how the pre- existing immunity would affect the HIV-1 infection outcome.

Possibilities of Developing a Vaccine against HIV

Development of anti-HIV vaccines is, without any doubt, a challenge to the scientists because of its ability to mutate and recombine, create latent infection by combining with host DNA and avoid body's immune response. Despite the challenges and difficulties, a path to develop an effective vaccine against HIV is being carved out of the uncertainties at each step going forward. Scientists and the highly skilled professionals working on the vaccine development are making advancements and finding out new features as well as defining characters in research of HIV vaccine. For example - the people, who are highly exposed to HIV and yet remain uninfected, are known as the "elite controllers", who technically can control the HIV replication and its prevalence throughout the world. These elite controllers are able to keep the virus viable since the past decades and that too without any highly active anti-retroviral therapy (HAART). Immune system of such individuals gives solid evidence and enough motivation to the researchers that even though there are uncertainties, the development of HIV vaccine is possible.

As it is known that vaccine's main aim is to produce antibodies, a HIV vaccine which is able to produce cytotoxic and memory T-cells is under progress that might be able to hold HIV away from infecting newer people by limiting its replication in host body and thereby preserving the system of an individual. In the same regards, several groups of people have been tested to demonstrate that the effective immune response can neutralise HIV infection before it even reaches T-cell of the host. Another group of researchers is working on characterising about how to delay the onset of symptoms of AIDS post HIV infection in the infected individuals and making people less susceptible based on their genetic design.

These studies along with many more, hold promises to provide what is required by the world the most, an effective HIV vaccine which provides protection from HIV and create similar immune responses against HIV so that the replica can be traced, and treatment can be made easier.

USAID (United States Agency for International Development) is an agency working with a main motive of developing globally relevant HIV vaccine. In addition to their five decades of experience in international development and field presence in over 100 nations, USAID has been an expert in clinical trial design and also conducting the studies related to HIV and its other disciplines such as immunology, virology, product development, pharmaceutical regulatory affairs, ethics, gender issues, etc. USAID's vast partnership in prevention of HIV, care and treatment of HIV infected individuals gives a hope that the world might get its first highly active anti-retroviral therapy in the form of a vaccine, working strongly against HIV infection. Since 2001, USAID has contributed more than $134 million to help research organizations discover HIV vaccine and currently, USAID is providing an annual funding of around $28 million in HIV vaccine Research and Development.

IAVI (International AIDS Vaccine Initiative) is also a non-profit organization currently acting as an unofficial and virtual pharmaceutical company to boost and speed up the development of HIV vaccine and clinical trials related to it. IAVI facilitates collaborations among various US based universities, government and private sector groups and also provide analyses of important issues coming in between the road to develop a global HIV vaccine such as regulatory issues, licensing issues, normal lab values, new strategies and preparation of manufacture of HIV vaccine along with its distribution once they are proven effective. USAID has been constantly backing up IAVI to strengthen the Clinical trials capacity in the developing countries so that there can be advancements in development of novel vaccine, analyzing policies and future issues in HIV vaccine related aspects.

Current Scenario and Future of a Potential HIV Vaccine

In earlier times, researchers believed that developing vaccines that target envelope glycoprotein and neutralizing antibodies would suffice in protection from HIV. The first ever experimental immunization was carried out by Zagury and colleagues in 1986 in Congo, in which the vaccine aimed to neutralize gp160 envelope glycoprotein. The effects produced were weak and other interventions were combined to give a boost in immune response to get satisfactory results. Following this impeccable intervention, over 250 trials all over the world were carried out, with most of them being safety and efficacy trials i.e., Phase I and II trials. Around 140 of them were in US with several other trials being conducted in African nations and in Thailand. The major clinical trials performed to get a HIV vaccine are shown in Table 1 below: Over the years, the use of broadly neutralizing antibodies (bNAbs) in human trials as a possible vaccine candidate has gained researchers' interest and as a result, Antibody Mediated Prevention studies (AMP Studies) are being conducted to test the safety and efficacy of a bNAb, VRC01, and to check whether it can prevent the infection from HIV in homosexual men as well as men who perform sex with heterosexual women.

Table 1: List of documented HIV trials

Vaccine Name	Year of Trial	Location	Target Population	Components	Immune Response
VaxSyn	1987	Canada	Adults (72)	HIV rgp160 protein	Detection of neutralizing antibodies
HIVAC-1e	1988	USA	Men (35)	Recombinant vaccinia virus	No protection
Vax004	1998-02	North America	Women (300)	AIDSVAX B/B gp120	No protection
Vax003	1999-03	Thailand	Adults (2545)	AIDSVAX B/E gp120	No protection
HVTN 505	2009-13	USA	Men and Transgender men (2504)	DNA encoding *gag, pol, nef, env* and Ad5 vaccine	No protection
STEP/ HVTN 502	2004-07	North America, Caribbean South America, Australia	Men having sex with other men (3000)	MRKAd5 HIV-1 *gag/pol/nef* vaccine	No protection
HVTN 503	2003-07	South Africa	Adults (801)	rAd5 (*gag/pol/nef*)	No protection
RV144	2003-09	Thailand	Adults at-risk (16402)	ALVAC HIV and AIDSVAX B/E vaccine	IgG antibody seen
HVTN 305	2012-17	Thailand	Adults (162)	ALVAC HIV and AIDSVAX B/E vaccine	No protection
HVTN 306	2013-20	Thailand	Adults (360)	ALVAC HIV and AIDSVAX B/E vaccine	No protection
HVTN 097	2012-13	South Africa	Black Africans (100)	ALVAC HIV and AIDSVAX B/E vaccine	$CD4^+$ T-cells seen
HVTN 100	2015-18	South Africa	Adults (252)	ALVAC HIV and gp120/MF59 vaccine	$CD4^+$ T-cells and gp120 binding
HVTN 702	2016-20	South Africa	Adults (5400)	ALVAC HIV and gp120/MF59 vaccine	No protection

HVTN703/HPTN 081 Phase 2b Study

This recent clinical trial is a phase 2b randomized, controlled, double-blind study conducted in sub-Saharan Africa. Started in May 2016, it aimed to assess safety, tolerability, and efficacy of VRC01 in preventing the infection in healthy uninfected sexually active women. Around 1900 HIV-uninfected women were enrolled with ages ranging from 18-50 yrs. and were divided in groups in a 1:1:1 ratio and given IV infusion of 10mg/kg VRC01 (low), 30mg/kg VRC01 (high) and placebo

HVTN704/HPTN 085 Phase 2b Study

This clinical trial is yet another VRC01 safety and efficacy trial aiming to prevent HIV-1 infection in healthy men and transgender men who have sex with men. Commenced in March 2016, study saw the enrolment of 2701 HIV-uninfected transgender men and heterosexual men in Brazil, Switzerland, Peru and United States.

Similar to HVTN703, participants here too were distributed in 3 groups in 1:1:1 ratio and were given IV infusion of 10mg/kg VRC01 (low dose), 30mg/kg VRC01 (high dose) and placebo every 8 weeks to identify properties of VRC01 such as optimal concentration of antibodies and effector functions.

HVTN 705/HPX2008 Phase 2b Trial (Imbokodo Study)

This ongoing study is multicentric, randomized, controlled, double-blinded efficacy trial being conducted at 24 sites in 5 sub-Saharan African countries. A total of 2600 healthy, HIV-uninfected sexually active women were enrolled, aged 18-35 years. Study that commenced in Nov 2017 is expected to be completed by May 2022 and aims to evaluate safety, efficacy and tolerability of a regimen for prevention of HIV infection.

The regimen is consisting of a tetravalent adenovirus vector vaccine which is, Ad26.Mos4.HIV and Al-PO_4 adjuvanted clade C gp140 and Mosaic gp140 protein vaccine.

Participants randomly assigned in 1:1 group received intramuscular (IM) injections of the Ad26.Mos4.HIV at month 0 and 3, followed by IM injections combined with Ad26.Mos4.HIV Al-PO_4 adjuvanted clade C gp140 at months 6 and 12 and control group would get IM injections of placebo. The participants will be assessed for safety, efficacy, and Adverse Events (AEs) post administration along with immunogenicity and genomic sequences of viral isolates from both the groups.

HVTN 706/HPX3002 Mosaico Phase 3 Trial

Another ongoing clinical trial is the Mosaico trial, which is multicentric, randomized, controlled, double-blind phase 3 trial. Started in Oct 2019, it is undergoing in Europe, North America, and South America. Study is being done on the Ad26.Mos4.HIV and adjuvanted clade C gp140 and Mosaic gp140 protein vaccine. Expected to be completed by Sep 2023, 3800 participants aged 18-60 years who were healthy, HIV-uninfected transgender men and homosexual men, were enrolled. Study aimed to ensure safety, efficacy, and detection of severe AEs along with the frequency of humoral as well as cell—mediated immune responses.

PrepVacc Phase 2b Trial

Finally, this is another clinical trial carried out currently which is multicentric, randomized, controlled, double-blinded in phase 2b. This is being conducted in Mozambique, South Africa, Uganda and Tanzania. This study is

being done to check the efficacy of combination of two regimens (DNA/AIDSVAX and DNA/CN54gp140+ MVA/CN54gp140) with PrEP (PrEPVacc).

In the study commenced in Jan 2020 and going to finish by Mar 2023, 1668, healthy, non-HIV infected participants aged 18-40 were enrolled and divided equally in 6 groups (Group A, B, C, D, E, and G). The goal is to determine whether the vaccine will lead to decrease in the

Table 2: Ongoing HIV Vaccine trials spread of HIV infection post immunization and will there be any AEs associated with the combined regimen administration. Refer to Table 2 for a summarised overview.

Vaccine Name	Year of Trial	Location	Target Population	Components
HVTN 703	2016-20	Sub-Saharan Africa	Women (1900)	VRC01 neutralizing monoclonal antibodies
HVTN 704	2016-20	Switzerland, Peru, Brazil, United States	Men and Transgender people (2701)	VRC01 neutralizing monoclonal antibodies
HVTN 705	2017-22	Sub-Saharan Africa	Women (2600)	Ad26.Mos4.HIV and adj. clade C gp140, Mosaic gp140 protein
HVTN 706	2019-23	North America, South America, Europe	Men having sex with men and Transgender people (3800)	Ad26.Mos4.HIV and adj. clade C gp140, Mosaic gp140 protein
PrepVacc	2020-23	Tanzania, Uganda, Mozambique, South Africa	Men and Women (1668)	DNA/AIDSVAX and DNA/CN54gp140 + MVA/CN54gp140 and PrEP

Conclusion

Over three decades, the quest of developing an effective vaccine against HIV infection has never been easy because of unpredictable situations like random genetic mutation and decade-long latency in the host body but the human will to succeed and improve public health has never let them down and sooner or later, some scientific breakthroughs are seen which time and again have proved that there is a tremendous possibility of achieving the unachievable. The search of a perfect HIV vaccine is underway, and a lot of organizations have come forward to volunteer, to provide funding and to support in vaccine development. Years of extensive research and numerous model designs, safety and efficacy trials and unlimited failures have provided enough motivation to the scientists and researchers to constantly search for a preventive vaccine, if not a cure, for the HIV infection. This silent epidemic has been with the mankind for ages and needs to be removed completely from existence so that this world can be declared free from HIV/AIDS.

References

1. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J *et al*. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science,1983:220:868-871.
2. Bekker LG, Tatoud R, Dabis F, Feinberg M, Kaleebu P, Marovich M *et al*. The complex challenges of HIV vaccine development require renewed and expanded global commitment. Lancet,2020:395:384-8. doi: 10.1016/S0140-6736(19)32682-0
3. Bolognesi DP. The immune response to HIV: implications for vaccine development. Semin. Immunol,1993:5:203-14.
4. Braun MM, Heyward WL, Curran JW. The global epidemiology of HIV infection and aids. Ann Rev Microbiol,1990:44:555-577.
5. Center for Disease Control Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men New York City and California. MMWR Morb Mortal Wkly Rep,1981:30:305-308.
6. ClinicalTrials.gov. A Combination Efficacy Study in Africa of Two DNAMVA-Env Protein or DNA-Env Protein HIV-1 Vaccine Regimens with PrEP (PrEPVacc)
7. ClinicalTrials.gov. A Study to Assess the Efficacy of a Heterologous Prime/ Boost Vaccine Regimen of Ad26.Mos4.HIV and Aluminum Phosphate-Adjuvanted Clade C gp140 in Preventing Human Immunodeficiency Virus (HIV) -1 Infection in Women in Sub-Saharan Africa
8. ClinicalTrials.gov A Study of Heterologous Vaccine Regimen of Adenovirus Serotype 26 Mosaic4 Human Immunodeficiency Virus (Ad26.Mos4.HIV), Adjuvanted Clade C gp140 and Mosaic gp140 to Prevent HIV-1 Infection Among Cis-gender Men and Transgender Individuals Who Have Sex with Cisgender Men and/or Transgender Individuals (MOSAICO).

9. ClinicalTrials.gov. Evaluating the Safety and Efficacy of the VRC01 Antibody in Reducing Acquisition of HIV-1 Infection in Women.
10. Cohen J. Jitters jeopardize AIDS vaccine trials. Science,1993:262:980-81.
11. Cohen J. The HIV Vaccine Paradox. Science,1994:264:1072-1074.
12. de Gruttola V, Wulfsohn M, Fischl MA, Tsiatis A. Modeling the relationship between survival and CD4 lymphocytes in patients with AIDS and AIDS related complex. AIDS,1993:6:359-365.
13. Desrosiers RC. Prospects for an AIDS vaccine. Nature Med,2004:10:221-223.
14. Esparza J. A brief history of the global effort to develop a preventive HIV vaccine. Vaccine,2013:31:350-18. doi: 10.1016/j.vaccine.2013.05.018
15. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A doubleblind, placebo-controlled trial. New Engl. 1. Med,1987:3:1:7:185-91.
16. Fleming TR. Surrogate markers in AIDS and clinical trials. Stat. Med,1994:13:1423-35.
17. Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science,1984:224:500-503.
18. Gilbert PB, Juraska M, deCamp AC, Karuna S, Edupuganti S, Mgodi N et al. Basis and Statistical Design of the Passive HIV-1 Antibody Mediated Prevention (AMP) Test-of-Concept Efficacy Trials. Stat Commun Infect Dis,2017:9:1-45. doi: 10.1515/scid-2016-0001
19. Hamilton 10, Hartigan PM, Simberkoff MS, Day PL, Diamond GR et al. A controlled trial of early versus late treatment with zidovudine in symptomatic human immunodeficiency virus infection. Results of the Veterans Affairs Cooperative StUdy. New Engl. J. Med,1992:326:437-43.
20. Hellinger FJ. The lifetime cost of treating a person with HIV. J. Am. Med. Assoc,1993:270:474-78.
21. Kahn JO, Lagakos SW, Richman DO, Cross A, Pettinelli C et al. A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. The NIAID AIDS Clinical Trials Group. New Engl. 1. Med,199:327:581-87.
22. Klausner RD, Fauci AS, Corey L, Nabel GJ, Gayle H, Berkley S et al. The need for a global HIV vaccine enterprise. Science,2003:300:2036-2039.
23. Kleiner K. Back to Basics for AIDS Research. New Scientist, 1996.
24. Krim M, Ward DE. The emergence and early years of the HIV/AIDS epidemic. In: Ward DE, The AmFAR AIDS handbook: The complete guide to understanding HIV and AIDS. WW Norton, New York, Chapter, 1999.
25. Larsen D. The march of dimes and polio: Lessons in vaccine advocacy for health educators. Am. J. Health Ed,2012:43:47-54.
26. Levine AM, Groshen S. Allen J, Munson KM, Carlo DJ, Daigle AE et al. Initial studies on active immunization of HIV-infected subjects using a gp120-depleted HIV-1 Immunogen: Long-term follow-up. J. Acquir. Immune Defic. Syndromes Hum. Retrovirol,1996:11:351-364.
27. Mascola JR, Mathieson BJ, Zack PM, Walker MC, Halstead SB, Burke DS. Summary report: workshop on the potential risks of antibody-dependent enhancement in human HlV vaccine trials. AIDS Res. Hum. Retroviruses,1993:9:1175-84.
28. McCoy Tatsis N, Korioth-Schmltz B et al. The effect of pre-existing immunity to antigens of adenovirus of the human serotype 5 on immune responses of nonhuman primates to vaccine regimens based on human or chimpanzee-derived adenovirus vectors. J Virol,2007:81(12):6594-6604.
29. McGhee JR, Kiyono H. Effective mucosal immunity. Current concepts for vaccine delivery and immune response analysis. Int. J. Technol. Assess. Health Care,1994:10:93-106.
30. Morris L, Mkhize NN. Prospects for passive immunity to prevent HIV infection. PLoS Med,2017:14:e1002436. doi: 10.1371 /journal.pmed. 1002436
31. Rappuoli R, Bottomley MJ, D'Oro U, Finco O, De Gregorio E. Reverse vaccinology 2.0: Human immunology instructs vaccine antigen design. J. Exp. Med,2016:213:469-481.
32. Schaper et al. Annu. Rev. Public Health statistical issues in the design of HIV vaccine trials,1995:103:83:14-74.
33. Stover J et al. Can we reverse the HIV/AIDS pandemic with an expanded response. Lancet,2002:360:73-77.
34. Thorner AR, Barouch DH. HIV-1 Vaccine Development: Progress and Prospects. Curr Infect Dis Rep,2007:9(1):71-75.
35. USAID/Global Health, Pathways of discovery: HIV vaccine research and development, 2008.
36. Vaccine Research Program, Division of AIDS, National Institute of Allergy, and Infectious Diseases, 5601 Fishers Lane, Rm 9C20B, Bethesda, MD 20892-9829, USA, 2020.
37. Walker MC, Fast PE. Clinical trials of candidate AIDS vaccines. AIDS 8: S2 13-36 (Suppl. 1), 1994.
38. Wang HB, Mo QH, Yang Z. HIV vaccine research: the challenge and the way forward. J Immunol Res,2015:503978. doi: 10.1155/2015/503978
39. Zagury D, Leonard R, Fouchard M, Reveil B, Bernard J, Ittele D et al. Immunization against AIDS in humans. Nature,1987:326:249-50. doi: 10.1038/326249a0