

Efficacy Trials and Progress of HIV Vaccines

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Abstract

Discovery of HIV as causative agent of AIDS led to the belief that a vaccine for AIDS will be available shortly but was not that easy, and it took more than 30 years of hard laboratory and clinical work toward HIV vaccine development. Efficacy trials of RV144 and their results revealed that HIV vaccine is accomplishable. Clinical trials for developing bNAbs has monoclonal antibodies and to increase its half-life are also underway to achieve a proper HIV vaccine. In this review article, we see that how these efficacy trials are highlighting HIV vaccine concepts in clinical development. Therapeutic vaccines are proving to be a functional cure toward HIV treatment and progress is ongoing in such HIV vaccine development which will attack HIV before it fuses with cell and cause infection thus preventing AIDS. So, in near future it will be possible to cure HIV and bring an end to this epidemic.

Keywords: HIV vaccine; Clinical trials; AIDS; Efficacy trials of RV144

Introduction

When HIV (Human Immunodeficiency virus) was discovered and established as the causative agent of AIDS in 1983-1984 [1], the majority of people thought that vaccines against this HIV would be developed and applied rapidly. But, this was not going to happen in case of HIV as in AIDS, virus-induced immune response possesses no ability to prevent re-infection and also not capable of slowing down the progression to disease. The development of an HIV vaccine took almost 30 years of intense laboratory and clinical work. And because of this intense work, today we are closer to develop an HIV vaccine but, it is difficult to predict the time when we have the vaccine that possesses sufficient efficacy for implementation in public health programs [2].

Why HIV vaccine is needed?

To stop the spread of AIDS caused by HIV, we have to stop the occurrence of new HIV infections. For preventing new HIV infections from occurring, several preventive measures are applied, but these preventive measures have some shortcomings, e.g. although condom use and sterile needles have a strong impact, but they possess insufficient adherence and access that limit their impact [3]. Other preventive measures, including male circumcision, pre-prophylaxis (PreP) and Antiretroviral therapy (ART) [4-6] have encountered the same problems of limited access and adherence. Vaccination does not involve such problems so it is preferred over other preventive measures. Also, vaccination possesses the ability to eradicate the virus, because of this ability it has been the major goal to develop an HIV vaccine to prevent new infections from occurring [3]. In the past 33 years of the HIV pandemic, there has been monumental progress in the clinical management of HIV disease. Once considered a death sentence due to the inexorable decline in CD4 T cell number and function over time ultimately leading to AIDS, patients with HIV infection who have access to effective antiretroviral therapy (ART) now

have a near normal life expectancy. In the first 15-20 years of the pandemic, during a time when effective ART was unavailable or in its infancy, there was intense scientific interest and inquiry into molecular mechanisms of HIV replication, in order to develop effective drugs with which to inhibit HIV replication *in vivo*. In the past 15 years, multiple drugs in multiple classes have been developed and much has been learned about how best to use combinations of agents. Now it is possible, and even expected, that clinical viral suppression can be achieved, with consequent immune reconstitution. However, treated individuals still have excess morbidity and mortality when compared to uninfected persons, due largely to accelerated aging and age related diseases such as cardiovascular disease, metabolic syndrome solid organ malignancies, neurocognitive and functional decline and osteoporosis.

Development of an HIV Vaccine: A Difficult Challenge

The development of a safe and highly effective vaccine against HIV has been a difficult challenge because of the ability of HIV to escape host immune response. There are three main scientific challenges for the development of an HIV vaccine. These challenges include following [7-9]:

The immunological correlates of protection against HIV/AIDS are unknown

In most diseases that are prevented by vaccines, there is a correlation between the immune responses induced by vaccines and the protection against disease or infection. But in case of HIV virus in contrast to this correlation, broad range of immune responses is developed against HIV in people infected with this virus. These immune responses are not able to either eradicate the infection or to inhibit the progress towards AIDS [10]. The current development strategies of an HIV vaccine are directed at the induction of humoral and cellular immunity and these strategies, also involve the induction of both major types of immune responses (humoral and cellular). Although it is a difficult challenge, but it is not an impossible target to

achieve. There has been the evidence that the early stages of transmission of HIV are susceptible to intervention of immune response [11]. The first experiment involving the immunization of humans against HIV-I (a strain of HIV) begun in November 1986 involving a sufficient number of HIV healthy volunteers. In this experiment, vaccinia virus recombinant (V25) that expresses *gp160 env* at the surface of infected cells are applied. *gp160 env* are the determinants of HTLVIII_B. The results of this experiment showed that the immune response against HIV can be achieved in humans [12]. Following this experiment, almost more than 256 clinical trials (phase I and phase II) including over 44, 000 healthy volunteers have tested candidate vaccines against HIV [12-17]. Among these clinical trials, only six candidate vaccines have achieved clinical efficacy. These six vaccines include VAX004, VAX003, Phambali, HVTN505 and RV144 [18].

These earlier trials intended to target at the production of neutralizing antibodies but in these experiments, difficulties were reported with the immunogen. Then the focus of an HIV vaccines turned on to cytotoxic T-lymphocytes (CTLs) [12-17]. Because in immune system cytotoxic T-lymphocytes play a significant role in controlling the levels of virus during the natural infection of HIV. So, targeting CTLs has also been a preference for research and development of HIV vaccine [3]. The development of an HIV vaccine is a difficult challenge because of lengthy, time consuming and expensive clinical trials for testing HIV candidate vaccines. In spite of the difficult and enormous challenge, the recent success provides a way forward towards the development of vaccine against HIV [3] (Table 1).

HIV vaccine efficacy trial						
Trial Name	Trial duration	Phase type	Type of vaccine	Expected immune response	Outcome	
VAX004	1998-2003	III	rpg120 (clade B)	Humoral	No efficacy	
VAX003	1999-2003	III	rgp120 (clades B+E)	Humoral	No efficacy	
Step	2004-2007 (Stopped for possible enhancement in HIV acquisition)	IIb		Cellular	Enhanced HIV infection risk in uncircumcised men and MSM	
Phambili	2007	IIb	rAD5 (gag/pollnef)	Cellular	No efficacy	
RV 144	2003-2009	III	Canarypox (gag/pollnef)	Cellular along with humoral	31.2% efficacy	
HVTN 505	2009-2015	IIb	DNA plasmid (gag/pollneflenv) +rAD5 (gag/pollne)	Humoral as well as cellular	No efficacy	

Table 1: Illustrating the trials of different HIV vaccines and their outcomes [18; p3].

Presence of genetic variability in HIV

The genetic analysis of HIV strains that are isolated from different parts of the world has disclosed that many genes present in HIV display wide sequence heterogeneity specifically in the genes that encode viral envelope proteins gp120 and gp41. As a result of this heterogeneity, the strains of HIV-I are divided into groups and subtypes. Most of HIV infection are caused by viruses of HIV-I group M that is further divided into 9 subtypes from A-J. There is also a chance of generation of unique circulating recombinant forms (CRFs) as a result of recombination among viruses of different subtypes. Although, there is much knowledge about the genetic variability present in HIV strains but it is not clear about the relationship that is found between genetic variability and the vaccine induced protection against infection [10]. For example, it is unknown that whether the immunological types are defined by genetic subtypes or whether a separated vaccine has to be generated for each subtype. The answer to this question may be provided by the human trials with candidate vaccines that are constructed according to different genetic subtype [19].

The deficit of appropriate animal models

Many experimental HIV vaccines have produced different intensities of protection in non-human primate models involving Chimpanzees that are exposed with HIV and monkeys that are exposed to SIV; an analogous to HIV. The basic problem is that different experiment vaccines generate dissimilar results in these two models involving chimpanzees and monkeys. It is also not clear that the results from these models would predict vaccine induced protection in humans. Such information regarding vaccine induced protection will only result from trials involving humans.

Brief History of HIV vaccine development

This section provides summary of some of the key events in the history of development and research of HIV vaccines [2,20] (Table 2).

Efficacy trials-completed and ongoing

Clinical studies have provided effective completed yet important evidence as to which immune responses apply to a preventive HIV vaccine [21].

Sr. No	Year	Achievements
1	1984	Discovery of HIV-I
2	1986	Approval of first HIV-I vaccine for clinical trials
3	1989	Development of a simian immunodeficiency vaccine (SIV) that provide immunity in a small group of monkeys
4	1991	Beginning of Pasteur-Merieux Connaught's HIV vaccine program; Declaration of first experimental AIDS vaccine as safe vaccine
5	1992	Beginning of the first phase II trial of HIV vaccine; First therapeutic vaccine trial
6	1996	Phase III trials of the Salk vaccine in America and Thailand
7	1997	Completion of more than 95 vaccine trials
8	1998	Beginning of phase III trials of an HIV vaccine candidate AIDSVAX
9	2003	Failure of AIDSVAX trial in Thailand
10	2004	Beginning of STEP trial in United States
11	2007	Beginning of trial of Phambali in South Africa; Trials of Phambali and STEP are stopped due to lack of efficacy
12	2009	31.2% efficacy of RV144 is revealed; Beginning of trial of HVTN505
13	2013	Stopping of HVTN505 trials for lack of efficacy

Table 2: HIV vaccine development.

So far, three concepts were tested for efficacy in human: a gp120 envelope protein provokes antibodies [22-26], a vector H extract high levels of CTLs, and the combination of viral vector and special protein system i.e. (gp120) [27].

VAX003 / VAX004: The effectiveness of the first experiments divalent envelope protein (gp120), predominantly was tested in homosexual men [28], and drug addicts [29]. Although it did not notice any vaccine effectiveness (VE) in these two the Phase 3 trials, which were designed to detect the effectiveness of more than 30%, subset analysis revealed that the incidence of HIV infection was lower among those individuals with the persons having very quick antibody response [30,31]. Further analysis of antibodies was not that much satisfying to neutralize an antigen for preventing infection [32-34]. Thus, the area has been re-directed toward exciting vaccines for responses that may provide effective treatment against disease and combat the antigen in a better way [35,36] (Table 3).

Step Study

In general DNA plasmid and viral vectors was strategies for eliciting in the T cell responses. Ad5 Type adenovirus vaccine was used as it had strong CLT response (MtkAd5) and it proceeded to 2b phase in order to check the vaccine effectiveness that was >0. Merck and the HIV Vaccine.

Network trials (HVTN), the Americas and South Africa (step study / HVTN 502/023 and Merck Phambali/HVTN 503) conducted two different trials [37,38]. Both studies stopped at the start of September 2007, when the first step in the interim analysis of the study met vanity thresholds. Revealed analysis of available data later in the transient increase in the incidence of HIV infection among vaccinated individuals who were not circumcised and enjoys immunity from previous anti- Ad5 vectors [37,39].

With this failure and alarming evidence that the vaccine has boosted the acquisition of some of the participants, improve NHP models and research discovery has become the primary vaccine priority [40]. A large number of studies to determine behind the increase in the purchase price mechanism [41-47]. But this is yet to be determined conclusively. Studies of this phenomenon and continued to NHP has recently made significant progress. In one study, the investigators describe the new NHP model involving low dose challenges penis virus, which showed an increase in infection rates in conditions similar to those found in the study of step [48]. In another study, Perreau et al. Note that the immune complexes consisting of H tankers and neutralizing antibodies specific to effectively stimulate stem cells (DC) maturation and suggested that this may lead to more conducive to the spread of HIV in the port of entry conditions [49].

Sr No.	Features	VAX004 Study	VAX003 Study
1.	Transmission of HIV	Sexual	Through blood
2.	Number of volunteers	5400 (5100 MSM men + 300 women)	2500(IV Drug users including both men and women)
3.	Expected annual infection rate	1.50%	4.00%
4.	Follow up duration	36 months	
5.	Follow-up duration after infection	24months	
6.	Beginning date	Jun-98	Mar-99
7.	Full enrollment	Oct-99	Aug-00
8.	Completion of Analysis	Q1 2003	Q4 2003
9.	Sites of clinical trial	61	17

Table 3: The summary of the trial design of vaccines is given in following table.

In this way, preexisting Ad5 immunity, in the form of neutralizing antibodies, it has contributed to the increase in gain between the vaccine recipients. In a subsequent study found that the tanker derived from serological H patterns rare (i.e. Ad6, Ad26, AD35, Ad36, and vector Ad41) were less effective in bringing capital maturity and that this is associated with a number of TLR9 agonist motifs present in the genome vectors [50]. If confirmed, these results support the current efforts to develop a rare serotype vectors H [50].

At the same time, efforts to improve the NHP models for use in predicting the efficacy of the vaccine to the low-dose models of mucosal challenge that measure a decrease in gain instead of the progression of the disease [11,51,52]. It seems that these models to more closely resemble HIV-1 disease in humans, including the bottleneck membranes where it is moving only a few strains of the virus at the end of the day, and became the criteria for evaluating a candidate vaccine to protect against infection. In contrast to the NHP models used to develop a vaccine used in the study MrkAd5 step, a recent study using one of the latest models yielded similar results to those in step trial [53-58].

The study was step one of the first to evaluate the effects of a vaccine stimulates strong cellular immune responses to protect against HIV. Although the vaccine induced specific T-cell responses to HIV in more than 75% of the respondents fortified, it does not reduce the acquisition of HIV or viral loads after infection. However, the secondary study found that the vaccine did not affect the virus strains infect. Use study samples step, Roland et al. Study sieve analysis was conducted to compare the viral genome sequence in inflammatory breakthrough that occurred in vaccine recipients and placebo [58]. This study found that viruses that infect vaccine recipients were more likely to encode epitopes differ from those encoded in the vaccine. This indicates that the vaccine-induced T cell responses that had the effect of "screening" of some strains of the virus. The data represent the first evidence that a vaccine designed to induce T cell responses to immune pressure the virus.

HVTN 505: It led acquisitions to strengthen reported vaccine based on Ad5 in the study a step in the abolition of the trial of the effectiveness of large-scale (cradle 100) planned for the various recombinant containing Ad5 prime boost system. The vaccine was a

developed system by the Center for Vaccine Research (VRC) and the National Institute of Allergy and Infectious Diseases, and consists of the Prime Minister of DNA containing clade B gag, Paul, NEF, and gene env multiclade followed by Ad5 recombinant increase with matching Shut up, Paul, and include wildlife. And VRC recombinant Ad5 vectors differ materially from MrkAd5 vectors used in the study step. For example, because of the full E1 and E4 and E3 partial deletion of genes it does not produce a number of structural proteins which are present Ad5 goals by immunity Ad5. However, the cancellation paves 100 before recording. Then the involvement of many stakeholders, including the Institute of acquired immunodeficiency syndrome division (DAIDS) and the trial of members of the community site, to discuss the next steps vaccines HIV on the basis of Ad5. It was decided that the study of the system VRC DNA/rAd5 should start because of its ability to give valuable information, and safety and the results are promising immune system demonstrated in clinical trials early stage [59]. And it provided emergency, however, that the individuals who were not circumcised or have preexisting neutralizing antibodies for Ad5- who pretended to promote the acquisition of HIV virus in step would be excluded study. In addition, the results of the study step and potential risks of the Ad5 vector vaccine will be sent clearly to the participants as part of the pre-approval process. In June 2009, it opened HVTN 505 test to study the concept to evaluate the VRC system and transgender men who have sex with men. The trial was conducted by the HVTN, and the institute said the support of the international collaboration of scientists and educators with a large number of clinical trial sites in the United States and around the world [60]. It was recorded in 2504 in HVTN 505 participants from 21 locations in 19 cities in the United States. In April 2013, HVTN 505 vaccine was discontinued at the planned interim analysis, pointing out that this system was not effective in any prevention of infection by HIV or in reducing set point of viral load after infection.

RV144: Been reported encouraging results in September 2009 with the effectiveness of the vaccine is estimated at 31.2% [61-63]. This study, known as RV144, conducted by the US military research program in collaboration with several Thai institutions in more than 16,000 Thai associate with any particular danger in advance of HIV [64-66]. The system consists of a canarypox vector Prime Minister recombinant vaccine (ALVAC HIV, and Sanofi Pasteur) and boost the

protein gp120 (AIDSVAX B/E, Global Solutions for Infectious Diseases). This system was initially criticized based on its failure to bring either a strong CTL or neutralizing antibodies on a large scale (bNAb) responses [67,68]. Instead of the system raised in the first place CD4 cells in response+T and antibody specific binding of the envelopes. After a special analysis that higher efficiencies vaccine occurred in the first year after vaccination (VE~60%), and reductions in effectiveness over time correlated with antibody responses fell [62,68,69]. Although the antibody responses are more durable it can be preferred, and offers this observation further support to the reliability of the effectiveness observed. Evidence of the effectiveness of low-level trial RV144 has provided a unique opportunity to search for immunological risk associated with: the vaccine-induced immune responses that are associated with the risk of HIV-I collaborative effort a huge, through Bart Haynes led, has this goal, and succeeded in Two determining the risk associated to this study: envelopes variable region 1 and 2 (V1/V2) binding antibodies, and antibodies specific for IgA plasma envelopes [69]. These results indicate that antibodies V1/V2 may have contributed to the protection against HIV, and that high levels of IgA antibodies specific envelopes may interfere with the vaccine-induced protective responses. More specifically, the presence of high levels of IgA antibodies specific envelopes associated with the reduced effectiveness of the vaccine, but did not result in increased rates of infection for the vaccine recipients [29,69].

There is a need for more research to determine whether these immune responses to specific envelopes measure the degree of protection induced by the vaccine (which is linked to protection), or is it just a link with risk markers, such as exposure to infection [66-72]. One way to assess the credibility of the immune system is linked to the analysis of the HIV-infected participants in the test sequence using a sieve analysis method [73-79]. Because this approach to assess the impact of the vaccine from the viewpoint of viruses penetrating injury, because they represent the other side of the coin of the associated immune response. The sieve analysis was conducted targeting viruses penetrate RV144 found that the vaccine-induced differential gain of HIV-1 on the basis of viral sequences in the region that V2 [80]. These data support the hypothesis that linked the responses V1/V2 with the protection of the vaccine-induced. If confirmed, this is associated with other immune discovered in the future could be used to guide rationally iterative process to improve the efficacy of the vaccine.

The analysis provided is linked to a valuable contribution in this area: a reasonable and viable hypothesis to test the clinical efficacy observed in RV144. Many questions related to the development of a vaccine for HIV also raised. This approach will be effective in populations at high risk? Or against another virus strain with clade matching antigens? And it can be extended preventive responses after the first year of additional boosts protein? To address these and other questions related to confirm and to expand the results of the study RV144 issues is the main objective of the guideline pox protein partner public and private sectors (P5). And P5 is a novel collaboration between pharmaceutical companies and non-profit organization made up of the Bill and Melinda Gates Foundation, and the HVTN, the National Institute of Allergy and Infectious Diseases, Novartis Vaccines, Sanofi Pasteur, and the research of US HIV military HIV program (MHRP). Clinical trials, which plans the group's goal to improve the results of RV144 and prepare the path for the license for the vaccine in South Africa and Thailand.

ALVAC (R)-HIV, three HIV genes produced by Sanofi Pasteur Inc. (ENV, chip and use of viral vectors genetically engineered version pro).

Vector is ALVAC canarypox, an inert form of the influenza virus, cannot cause disease in humans or repeat. It has also been used in a test for cancer vaccines.

ALVAC (R)-HIV and AIDSVAX (R) compared to placebo in the mix between B and E reduce the incidence of HIV infection by 31.2%. This is likely to result in a low result meant the loss, but the confidence intervals for the estimate to reduce the extensive vulnerability, caused statistically significant ($P=0.039$, 95% CI 1.1% to 51.1%). It means 'real' vaccine efficacy is a 95% probability that lies somewhere between these limits there.

Seventy-four placebo recipients and individuals have been affected more than 51 HIV vaccine arm system. Vaccine affect the amount of virus in the blood system of volunteers became HIV infected during the study.

The results were a surprise to many. Said Colonel Nelson Michael, the United States Virus (MHRP) Military HIV Research Program organized a press conference after the director results in a call which provides 25% of the funds, \$ 119 million trial the most surprising aspect, perhaps appeared to be a great result and a protective effect of the vaccine produced no effect on viral load and balance among the injured.

"We are humbled by this result," he said. "This vaccine over their heads turned many of the basic assumptions in HIV research." He added that the trial showed that "the human animal and test tube experiments we trumps everything."

What happens with the two vaccines was pointed out Michael RV144 trial operation in two ways. Vaccine "prime", ALVAC, made a career canarypox virus genes of the human immune deficiency virus. The vaccines stimulate the cellular immune response is designed to provide this form. It does not prevent the initial infection, but scientific models-cytotoxic lymphocytes T (CTLs or CD8 cells) and the like, it would reduce the HIV viral load of HIV spread that slow or stop progress-some supporting data from studies with monkeys and AIDS [81].

Developmental study of HIV vaccine

Although analysis of RV144 suggests that protection from acquisition of HIV do not require bNAbs, but it is also accepted that vaccines having bNAbs are more effective. And these antibodies protect the individuals when they are at high risk. Investigators are also under study of the function of bNAbs and their development during the HIV-I infection. As a result, many bNAbs have been isolated from the patients who are chronically infected by HIV and also been under detailed study [80-91]. Although antigens which are performing the reaction of these antibodies have not been yet identified. But antibody properties have been identified that they are involve in neutralizing activity. Now researchers are working to develop these antibodies through vaccination. Meanwhile, many clinical trials are under discussion to develop powerful bNAbs as monoclonal antibodies. VRC01 is a monoclonal antibody which gets involved in clinical trials in 2013 [86]. After its safety and pharmacokinetics study, main objective is that to test the whether the bNAbs presence protect the infection from HIV. Further study of development is trying to increase the half-life of these antibodies or their alternative form to minimize the frequency of injection. Although there is need of some injections but this research is useful for some population which is at high risk and is uninfected. It is also useful as salvage therapy for those patients having infection which are drug resistant. This research is also effective

in phase 2 experiments of monoclonal antibody i.e. humanized anti-CD4, Ibalizumab which in combination with the effective therapy of patients which are infected with HIV [92,93]. In the research center of Diamond AIDS and foundation of Melinda and Bill Gates, Ibalizumab is under safety assessment in healthy uninfected HIV-I Adults during phase I trial experiment.

With the betterment in immunogenicity of plasmid product of DNA is under focus as these substances are easy to save and easy to manufacture.

This research has gain advancement from co-administration of cytokines with vaccines of DNA and from electroporation. In the recent study, stronger CD4+ and CD8+ responses of T-cells with a half dose vaccine is compared with the same vaccine but delivered intramuscularly and without any electroporation [93]. Now new techniques are working with the objective to made vaccines that develop immune responses on compartments of mucosa by providing the vaccines of DNA with chemokines of mucosa i.e. CCR10 ligands. CCR10 ligands are used in NHP working and CCL27 and CCL28 are used as adjuvants to promote antibody responses in mucosa and also improve the protection in SIV challenges of vagina as compared to the DNA separately.

A collection of new recombinant viral vectors are being studied with the combination of proteins and DNA products. These vectors involve those alternatives of adenovirus serotypes which have immunity which does preexist and it is less than that is for Ad5 in the global population [90]. As a result of different studies, future for alternative serotypes and for Ad5 is uncertain and under discussion. Different products of vectors including DNA vaccine Ankara (MVA) is now being in phase II experiments [91]. These are a few products of clade B which are being tested by more advanced techniques. The promising products of next generation involve cytokines GM-CSF co-expression has become enter in clinical assessment [92]. A new viral vector vesicular stomatitis is also under development. Now this vector is under safety by human study testing's [93-95]. In this year, some products of viral vectors that contains novel of consensus and mosaic antigen which are designed computationally are also under human testing [96,97]. NIAID, HVTN, vaccine immunology center of HIV/AIDS, National Los Alamos Laboratory, Switzerland foundation of IPPOX, foundation of Melinda and Bill Gates studied collaboratively to develop HVTN 099 [98]. This research also involves tests to check whether the consensus or mosaic inserts are dominant on inserts of virus transmitted for obtaining highest immune responses within the DNA prime context and regimens of NYVAC boost.

HVTN is also involved in studies of phase Ib. these studies desired to address the questions basic science and to develop new hypothesis of vaccination techniques and their collective responses of immunity. In these studies, the effect of antigen competition on magnitude and breath of T-cells study induced by vaccines is also under examination. In response to regimens of boost vaccine, immune responses of mucosa are also being examined in such studies. It is prescribed that wealth of knowledge on vaccine platform will be provided by early phase experiments which is applied on many infectious diseases and immunotherapeutic experiments.

A few students of HIV vaccine used therapeutic vaccines in patients which are HIV infected and now have enter in preventive pipelines of vaccine. An example of Regulatory protein of HIV-I which utilize vaccine is Tat. The expression of Tat protein is early phase of rebounding of virus and is involve in dispersion of virus [95-102]. The

resulted question of this study involves the use of immunogens in the form of recombinant type of adenovirus vectors [103]. T-1 alpha is a Tat based protein and now being developed by the center of National AIDS of the Italian ISS. Therapeutic vaccines of two phases 2 are now under experiments. In one trial, interim analysis of *ad hoc*, the immune function of HIV infected patient treated by ART had been improved [104-108]. As a result, this vaccine restores the immunity of infected peoples by the combination with ART. In phase I experiment of HIV-1, Tat protein when combine with Novartis which is an env protein is being used in healthy uninfected HIV-I participant.

Attenuated form of vaccine shows the strongest method to induce the protection in many NHP [109]. But in human testing, this research is ruled out due to safety [106,107]. Different methods are used to inactivate the virus in order to make it safe for human use in many instances. Remune was the first vaccine composed of inactivated purified virion gp120 surface striped and emulsified in adjuvants of incomplete form of Freund. Due to failure of the betterment of clinical results and time of progression of disease, phase III trial has been stopped [108].

The pre-specified immune correlates analysis showed that antibodies which are used against the gp120's region of V1V2 possesses an important role to protect from acquirement of HIV-1 and that envelope of plasma which is Env-specific IgA form of antibodies correlates directly with the risk [109].

Vaccines of viruses that are licensed to protect from diseases with the effect of immune system before it is exposed to pathogens. This provides antibody responses that involve in the prevention from infection, and responses of cells that focused to eliminate cells which are virally infected. Neutralizing antibodies, which are virus specific, binds with proteins on viral particle's surface and prevent their infection on host cells. Neutralizing antibodies destroys the cells which are infected by virus through the mechanism of cellular effectors [110-116]. Total global HIV vaccine investment for 2008 was US\$868 million (Figure 1) that is decrease 10% from 2007 [116]. But only 5% to 10% was concerned directly to solve the two major designed vaccine problems.

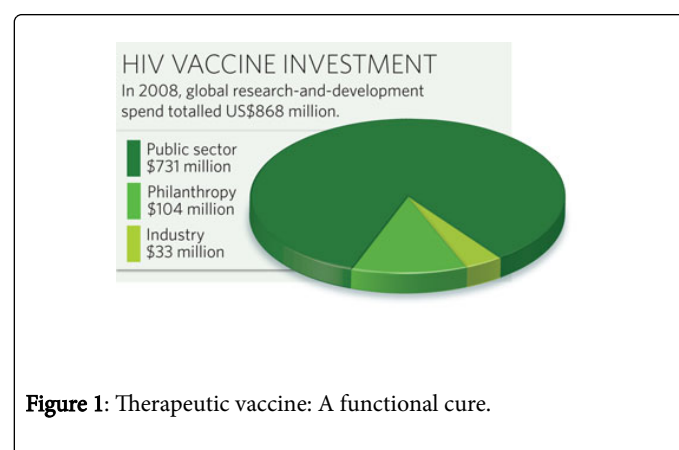


Figure 1: Therapeutic vaccine: A functional cure.

Very little work is done in testing and developing HIV therapeutic vaccine, because attempts to boost up immune system to eliminate viral load in body, have failed so far [117]. Before advent of new technologies, the only cure of HIV infected patients was to have CCR5Δ32/Δ32 stem cell transplantation [118-120]. As presented in 2013 AIDS society meeting held in Kuala Lumpur about 2 HIV infected patients when given bone marrow transplant to treat cancer it

was observed that their HIV might also have been cured because their ART (Ant-retroviral therapy) was stopped for 7 and 15 weeks and neither of them had HIV in their blood. Though bone marrow transplant is strong and effective way for treating HIV but possess risks due to which it does not have broad or widespread applications. Another way to treat HIV is to administer ART early after the infection, which leads to reduction in viral expansion and also preserves the immune response. So, this alternative can be a way to achieve a “Functional Cure” for HIV [121].

This kind of functional cure may have achieved in case of 2.5 years old child who was reported at conference on opportunistic infections and retroviruses, in 2013. Mother of that child had an HIV infection which was undiagnosed, so the child was given 3 drug ART right after birth. His ART was stopped after 18 months but despite that child remained healthy. ART early administration led to the success of that child's case but there is a catch that ART breaks in adults cause viral rebound meaning virus resurfaces in body after undetectable levels indicating that ART alone is not enough to achieve functional cure. It needs enhanced immune system which can be done by vaccination or therapeutic vaccine.

A therapeutic vaccine is different from conventional vaccine in a way that it is used for treatment not prevention of disease [122]. By

therapeutic vaccines immune system can be modulated for reduction in viral load. In the beginning many therapeutic vaccines like whole inactivated virus (RUMUNE) and recombinant protein (gp120) were used in clinical trials and they seemed to produce good results but it was seen that their capacity was limited to produce specific immune response against HIV so these results eventually became discouraging because there was no demonstration of constant immunogenicity and effect on viral load [123-135]. There are many HIV therapeutic vaccines in clinical trials like FIT biotech manufactured a DNA vaccine which was given to patients who were not on ART and this vaccine caused mild reduction in viral load in their blood [136]. Another peptide based vaccine Vacc-4x was manufactured by Bioner Pharma. Its *HOC* analysis in phase II clinical trials indicated decrease in viral load when ART was stopped or interrupted [137] (Table 4).

Results from these trials are suggesting that therapeutic vaccines are working better in absence of ART indicating that therapeutic vaccines might replace ART. Two candidate therapeutic vaccines are designed not to enhance immune system but to induce specific antibody responses to decrease ability of virus of causing dangerous effects.

Agent	Class/Type	Manufacturer (s)	Status
FIT-06, GTU-Multi HIV vaccine	DNA vaccine encoding complete sequences of HIV-1 clade B Rev, Nef, Tat, and p17/p24 proteins, and T-cell epitopes from Pol and Env proteins	FIT Biotech	Phase II
HIV-1 Tat vaccine	Tat protein vaccine	National AIDS Center at the National Institute of Health, Rome	Phase II
HIVAX	Replication-defective HIV-1 vector pseudotyped with VSV-G envelope	GeneCure Biotechnologies	Phase I
Vacc-4x	Synthetic peptides from the HIV-1 Gag p24 protein + adjuvant	Bioner Pharma	Phase IIb
VAC-3S	3S peptide from gp41	InnaVirVax	Phase I/IIa
DNA/MVA	DNA vaccine and an MVA vector encoding HIV-1 Gag and multiple CTL epitopes	Cobra Pharmaceuticals/IDT/University of Oxford/UK Medical Research Council	Phase I/II

Table 4: Therapeutic vaccines in clinical trials in 2013 [138].

Future of HIV Vaccination

Lessons learned from efficacy trials of HIV vaccines will ultimately lead towards a functional cure and prevention of HIV. As 31% efficacy was seen in RV144 trials but results from these trials revealed that in near future it might be possible to duplicate or even improve this efficacy up to 60% by using different combinations. For that trials are expected to start in 2017 and 2018 [139].

NIAID recently published in May 2016 that they have found new and strong targets for HIV vaccine to attack and eliminate the virus before it infects cells. This vaccine will attack 11 amino acid peptides which helps virus to fuse with cells and cause infection [140,141]. That time is not far when HIV vaccines will be the great tool in fighting the

tricky HIV beast. Now it only requires making better and broad HIV prevention packages along with HIV vaccines.

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