Journal of Cell Science & Therapy

Asif and Irshad, J Cell Sci Ther 2017, 8:2
DOI: 10.4172/2157-7013. 1000265

Review Article Open Access

Efficacy Trials and Progress of HIV Vaccines

Daud Faran Asif[1*], **and Irshad M**[2]

[1]*Department of Biochemistry and Biotechnology, University of Gujrat, Pakistan*

[2]*Department of Biotechnology, University of Gujrat, Gujrat, Pakistan*

[*]**Corresponding author:** Daud Faran Asif, BS. Hons Student, Department of Biochemistry and Biotechnology, University of Gujrat, Pakistan, Tel: 92533643112; E-mail: Daudfaranasif@gmail.com

Rec date: Mar 18, 2017; **Acc date**: Apr 01, 2017; **Pub date:** Apr 04, 2017

Abstract

Discovery of HIV as causative agent of AIDS let 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 HTLVIIIB. 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
HTVN 505	2009-2015	IIb	DNA plasmid (gag/pollneflenv) +rAD5 (gag/pollen)	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 Phambili/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 anit-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 adjutants 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.

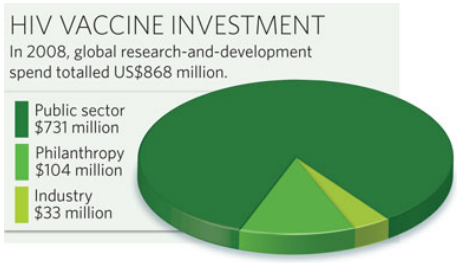

Figure 1: Therapeutic vaccine: A functional cure.

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 Lampur 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	Bionor 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.

References

1. Gallo RC, Montagnier L (1987) The chronology of AIDS research. Nature 326: 435-436.
2. Esparza J (2013) What has 30 years of HIV vaccine research taught us? Vaccines 1: 513-526.
3. Day TA, Kublin J (2013) Lesson learned from HIV vaccine clinical efficacy trials.Curr HIV Res 11: 441-449.
4. Abdool KQ, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, et al. (2010) Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV in fection in women. Science 329: 1168-74.

5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, et al. (2010) Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 363: 2587-2599.
6. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, et al. (2011) Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 365: 493-505.
7. Esparza J, Bhamarapravti N (2000) Accelerating the development and future availability of HIV-1 vaccines: Why, when, where, and how? Lancet 355: 2061-2066.
8. Esparza J, Osmanov S (2000) Current issues in HIV vaccine development. J Health Manag 2: 245-255.
9. Esparza J, Heyward WL, Osmanov S (1996) HIV vaccine research: From basic science to human trials. AIDS 10: S123-S132.
10. Esparza J (2001) An HIV vaccine: How and when? Bull World Health Org 79: 1133-1137.
11. Picker LJ, Hansen SG, Lifson JD (2012) New paradigms for HIV/AIDS vaccine development. Annu Rev Med 63: 95-111.
12. Zagury D, Sala€un JJ, Bernard J, Dechazal L, Goussard B (1988) Immunization against the human immunodeficiency virus in Zaire. Med Trop (Mars) 48: 417-423.
13. Esparza J (2013) A brief history of the global effort to develop a preventive HIV vaccine. Vaccine 31: 3502-3518.
14. Excler JL, Tomaras GD, Russell ND (2013) Novel directions in HIV-1vaccines revealed from clinical trials. Curr Opin HIV AIDS 8: 420-430.
15. The Math of Hiv. IAVI REPORT 17. Accessed on 03 April 2017.
16. Beena V, Choudhary K, Rajeev R, Sivakumar R, Heera R (2013) Human immunodeficiency virus vaccine an update. J Oral Maxillofac Pathol 17: 76-81.
17. Saunders KO, Rudicell RS, Nabel GJ (2012) The design and evaluation of HIV-1 vaccines. AIDS 26: 1293-1302.
18. Lema D, Garcia A, Sanctis B (2014) HIV vaccines: A brief overview. Scand J Immunol 80: 1-11.
19. Approaches to the development of broadly protective HIV vaccines: Challenges posed by the genetic, biological and antigenic variability of HIV-1. Report from a meeting of the WHO-UNAIDS Vaccine Advisory Committee, Geneva, 21-23 February 2000. AIDS, 2001, 15: W1-W25.
20. A Timeline of HIV Vaccine Research. The First 20 Years: 1984-2003. Very Well. Accessed on 04 April, 2017.
21. Coffin J, Haase A, Levy JA, Montagnier L, Oroszlan S, et al. (1986) What to call the AIDS virus? Nature 321: 10
22. Keefer MC, Graham BS, McElrath MJ, Matthews TJ, Stablein DM, et al. (1996) Safety and immunogenicity of Env 2-3, a human immunodeficiency virus type 1 candidate vaccine, in combination with a novel adjuvant, MTPPE/MF59 NIAID AIDS Vaccine Evaluation Group. AIDS Res Hum Retroviruses 12: 683-693.
23. Belshe RB, Clements ML, Dolin R, Graham BS, McElrath J, et al. (1993) Safety and immunogenicity of a fully glycosylated recombinant gp160 human immunodeficiency virus type 1 vaccine in subjects at low risk of infection. National Institute of Allergy and Infectious Diseases AIDS Vaccine EvaluationGroup Network. J Infect Dis 168: 1387-1395.
24. Gorse GJ, Patel GB, Newman FK, Belshe RB, Berman PW, et al. (1996) Antibody to native human immunodeficiency virus type1envelopeglycoproteinsinducedby IIIB and MN recombinant gp120 vaccines The NIAID AIDS vaccine evaluation group. Clin Diagn Lab Immunol 3: 378-386.
25. Graham BS, Keefer MC, McElrath MJ, Gorse GJ, Schwartz DH, et al. (1996) Safety and immunogenicity of a candidate HIV-1 vaccine in healthyadults: recombinant glycoprotein (rgp) A randomized, double-blind trial NIAID AIDS Vaccine Evaluation Group. Ann Intern Med 125: 270-279.
26. McElrath MJ, Corey L, Montefiori D, Wolff M, Schwartz D, et al. (2000) Aphase II study of two HIV type 1 envelope vaccines, comparing their immunogenicity in populations at risk for acquiring HIV type 1 infection. AIDS Vaccine Evaluation Group. AIDS Res Hum Retroviruses 16: 907-919.
27. Thomas P (2001) Big Shot: Passion Politics, and the Struggle for an AIDS Vaccine Public Affairs, New York 515 p.
28. Flynn NM, Forthal DN, Harro CD, Judson FN, Mayer KH (2005) Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis 191: 654-665.
29. Pitisuttithum P, Gilbert P, Gurwith M, Heyward W, Martin M, et al. (2006) Randomized, Double-Blind, Placebo-Controlled Efficacy Trial of a Bivalent Recombinant Glycoprotein 120 HIV-1 Vaccine among Injection Drug Users in Bangkok, Thailand. J Infect Dis 194: 1661-171.
30. Gilbert PB, Peterson ML, Follmann D, Hudgens MG, Francis DP, et al. (2005) Correlation between immunologic responses to a recombinant glycoprotein 120 vaccine and incidence of HIV-1 infection in a phase 3 HIV-1 preventive vaccine trial. J Infect Dis 191: 666-6 77.
31. Forthal DN, Gilbert PB, Landucci G, Phan T (2007) Recombinant gp120 vaccine-induced antibodies inhibit clinical strains of HIV-1 in the presence of Fc receptor-bearing effector cells and correlate inversely with HIV infection rate. J Immunol 178: 6596-6603.
32. Mascola JR, Stiegler G, VanCott TC, Katinger H, Carpenter CB, et al. (2000) Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. Nat Med 6: 207-210.
33. Gilbert P, Wang M, Wrin T, Petropoulos C, Gurwith M, et al. (2010) Magnitude and breadth of a nonprotective neutralizing antibody response in an efficacy trial of a candidate HIV-1 gp120 vaccine. J Infect Dis 202: 595-605.
34. Burton DR, Desrosiers RC, Doms RW, Feinberg MB, Gallo RC, et al. (2004) Public health. A sound rationale needed for phase III HIV-1 vaccine trials. Science 303: 316.
35. McNeil JG, Johnston MI, Birx DL, Tramont EC, et al. (2004) HIV Vaccine Trial Justified. Science 303: 961.
36. Pérez-Losada M, Posada D, Arenas M, Jobes DV, Sinangil F (2009) Ethnic differences in the adaptation rate of HIV gp120 from a vaccine trial. Retrovirology 6: 67.
37. Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, et al. (2008) Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): A double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet 372: 1881-1893.
38. Gray GE, Allen M, Moodie Z, Churchyard G, Bekker LG, et al. (2011) Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: A double-blind, randomised, placebo-controlled test-of-concept phase 2B study. Lancet Infect Dis.
39. Duerr A, Huang Y, Buchbinder S, Coombs RW, Sanchez J, et al. (2012) Extended follow-up confirms early vaccine-enhanced risk of HIV acquisition and demonstrates waning effect over time among participants in a randomized trial of recombinant adenovirus HIV vaccine (Step Study). J Infect Dis 206: 258-266.
40. Fauci AS, Johnston MI, Dieffenbach CW, Burton DR, Hammer SM, et al. (2008) HIV vaccine research: tThe way forward. Science 321: 530-532.
41. Hutnick NA, Carnathan DG, Dubey SA, Makedonas G, Cox KS, et al. (2009) Baseline Ad5 serostatus does not predict Ad5 HIV vaccine-induced expansion of adenovirus-specific CD4+ T cells. Nat Med 15: 876-878.
42. Gray G, Buchbinder S, Duerr A (2010) Overview of STEP and Phambili trial results: two phase IIb test of-concept studies investigating the efficacy of MRK adenovirus type 5 gag/pol/nef subtype B HIV vaccine. Curr Opin HIV AIDS 5: 357-361.
43. Koblin BA, Mayer KH, Noonan E, Wang CY, Marmor M, et al. (2012) Sexual risk behaviors, circumcision status and pre-existing immunity to adenovirus type 5 among men who have sex with men participating in a randomized HIV-1 vaccine efficacy trial: Step Study. J Acquir Immune Defic Syndr 60: 405-413
44. Curlin ME, Cassis-Ghavami F, Magaret AS, Spies GA, Duerr A, et al. (2011) Serological immunity to adenovirus serotype 5 is not associated with risk of HIV infection: a case-control study. AIDS 25: 153-158.

45. Benlahrech A, Harris J, Meiser A, Papagatsias T, Hornig J, et al. (2009) Adenovirus vector vaccination induces expansion of memory CD4 T cells with a mucosal homing phenotype that are readily susceptible to HIV-1. Proc Natl Acad Sci U S A 106: 19940-19945.
46. Perreau M, Pantaleo G, Kremer EJ (2008) Activation of a dendritic cell-T cell axis by Ad5 immune complexes creates an improved environment for replication of HIV in T cells. J Exp Med 205: 2717-2725.
47. O'Brien KL, Liu J, King SL, Sun YH, Schmitz JE, et al. (2009) Adenovirus-specific immunity after immunization with an Ad5 HIV-1 vaccine candidate in humans. Nat Med 15: 873-875.
48. Qureshi H, Ma ZM, Huang Y, Hodge G, Thomas MA, et al. (2012) Low-dose penile SIVmac251 exposure of rhesus macaques infected with adenovirus type 5 (Ad5) and then immunized with a replication-defective Ad5-based SIV gag/pol/nef vaccine recapitulates the results of the phase IIb step trial of a similar HIV-1 vaccine. J Virol 86: 2239-2250.
49. Perreau M, Welles HC, Pellaton C, Gjoksi B, Potin L, et al. (2012) The number of TLR9Agonist motifs in the adenovirus genome correlates with induction of dc maturation by adenovirus immune complexes. J Virol.
50. Michael NL (2012) Rare serotype adenoviral vectors for HIV vaccine development. J Clin Invest 122: 25-27.
51. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, et al. (2009) Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. N Eng J Med 361: 2209-2220.
52. Lifson JD, Haigwood NL (2012) Lessons in nonhuman primate models for AIDS vaccine research: from minefields to milestones. Cold Spring Harb Perspect Med 2: a007310.
53. Michael NL (2010) Correlates of immunity: RV144-lessons learned. AIDS Vaccine 2010 conference, Atlanta.
54. Reynolds MR, Weiler AM, Piaskowski SM, Piatak M Jr, Robertson HT, et al. (2012) A trivalent recombinant Ad5 gag/pol/nef vaccine fails to protect rhesus macaques from infection or control virus replication after a limiting-dose heterologous SIV challenge. Vaccine 30: 4465-4475.
55. Ojo-Amaize E, Nishanian PG, Heitjan DF, Rezai A, Esmail I, et al. (1989) Serum and effector-cell antibody-dependent cellular cytotoxicity (ADCC) activity remains high during human immunodeficiency virus (HIV) disease progression. J Clin Immunol 9: 454-461.
56. Ferrari G, Pollara J, Kozink D, Harms T, Drinker M, et al. (2011) A HIV-1 gp120 envelope human monoclonal antibody that recognizes a C1 conformational epitope mediates potent ADCC activity and defines a common ADCC epitope in human HIV-1 serum. J Virol 85: 7029-7036.
57. Buchbinder S, Mehrotra D, Duerr A, Fitzgerald DW, Mogg R, et al. (2008) Efficacy assessement of a cell-mediated immunity HIV-1 vaccine(the step study): A double-blind randomized, placebo controlled, test of concept trial. Lancet 373: 1881-1893.
58. Rolland M, Tovanabutra S, Decamp AC, Frahm N, Gilbert PB, et al. (2011) Genetic impact of vaccination on breakthrough HIV-1 sequences from the STEP trial. Nat Med 17: 366-371.
59. Churchyard GJ, Morgan C, Adams E, Hural J, Graham BS, (2011) et al. A phase IIA randomized clinical trial of a multiclade HIV-1 DNA prime followed by a multiclade rAd5 HIV-1 vaccine boost in healthy adults (HVTN204). PLoS ONE 6: e21225.
60. James GK, Cecilia MA, Tracey DA, Peter GB, Steve SG, et al. (2012) HIV vaccine trials network: Activities and achievements of the first decade and beyond. Clin Invest 2: 245-254.
61. Kim SC, Becker S, Dieffenbach C, Hanewall BS, Hankins C, et al. (2010) Planning for pre-exposure prophylaxis to prevent HIV transmission: Challenges and opportunities. J Int AIDS Soc 13: 24
62. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, et al. (2009) Vaccinationwith ALVAC and AIDSVAX to prevent HIV-1 infection inThailand. N Engl J Med 361: 2209-2220.
63. HIV Vaccine Trial in Thai Adults (2014) ClinicalTrials.gov. Accessed on April 3, 2017.
64. Kim JH, Rerks-Ngarm S, Excler JL, Michael NL (2010) HIV vaccines: lessons learned and the way forward. Curr Opin HIV AIDS 5: 428-434.
65. Gilbert PB, Berger JO, Stablein D, Becker S, Essex M, et al. (2011) Statistical Interpretation of the RV144 HIV Vaccine Efficacy Trial in Thailand: A Case Study for Statistical Issues in Efficacy Trials. J Infect Dis 203: 969-975.
66. Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, et al. (2012) Immunecorrelates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med 366: 1275- 1286.
67. Plotkin SA (2008) Vaccines: Correlates of vaccine-induced immunity. Clin Infect Dis 47: 401-409.
68. Plotkin SA (2010) Correlates of protection induced by vaccination. Clin Vaccine Immunol 17: 1055-1065.
69. Rerks-Ngarm S, Paris RM, Chunsutthiwat S, Premsri N, Namwat C, et al. (2012) Extended evaluation of the virologic, immunologic, and clinical course of volunteers who acquired HIV-1 infection in a phase III vaccine trial of ALVAC-HIV and AIDSVAX(R) B/E. J Infect Dis 207: 1195-1205.
70. Souza MS, Ratto-Kim S, Chuenarom W, Schuetz A, Chantakulkij S, et al. (2012) The Thai phase III trial (RV144) vaccine regimen induces T cell responses that preferentially target epitopes within the V2 region of HIV-1 envelope. J Immunol 188: 5166-5176.
71. Qin L, Gilbert PB, Corey L, McElrath MJ, Self SG (2007) A framework for assessing immunological correlates of protection in vaccine trials. J Infect Dis 196: 1304-1312.
72. Plotkin SA, Gilbert PB (2012) Nomenclature for immune correlates of protection after vaccination. Clin Infect Dis 54: 1615-1617.
73. Montefiori DC, Karnasuta C, Huang Y, Ahmed H, Gilbert P, et al. (2012) Magnitude and breadth of the neutralizing antibody response in the RV144 and Vax003 HIV-1 vaccine efficacy trials. J Infect Dis 206: 431-441.
74. Paris R, Bejrachandra S, Thongcharoen P, Nitayaphan S, Pitisuttithum P, et al. (2012) HLA class II restriction of HIV-1 clade-specific neutralizing antibody responses in ethnic Thai recipients of the RV144 prime-boost vaccine combination of ALVACHIV and AIDSVAX ® B/E. Vaccine 30: 832-836.
75. Hertz T, Gartland A, Janes H, Li S, Fong Y, et al. (2012) T-cell based sieve analysis ties HLA A*02 to vaccine efficacy and IgA-C1 immune correlate in RV144 Thai trial. Retrovirology 9: O61.
76. Karasavvas N, Billings E, Rao M, Williams C, Zolla-Pazner S, et al. (2012) The Thai phase III HIV Type 1 vaccine trial (RV144) regimen induces antibodies that target conserved regions within the V2 loop of gp120. AIDS Res Hum Retroviruses 28: 1444-1457.
77. Robb ML, Rerks-Ngarm S, Nitayaphan S, Pitisuttithum P, Kaewkungwal J, et al. (2012) Risk behaviour and time as covariates for efficacy of the HIV vaccine regimen ALVAC-HIV (vCP1521) and AIDSVAX B/E: A post-hoc analysis of the Thai phase 3 efficacy trial RV 144. Lancet Infect Dis 12: 531-537.
78. Gilbert P, Self S, Rao M, Naficy A, Clemens J (2001) Sieve analysis: Methods for assessing from vaccine trial data how vaccine efficacy varies with genotypic and phenotypic pathogen variation. J Clin Epidemiol 54: 68-85.
79. Gilbert PB, McKeague IW, Sun Y (2008) The 2-sample problem for failure rates depending on a continuous mark: An application to vaccine efficacy. Biostatistics 9: 263-276.
80. Rolland M, Edlefsen PT, Larsen BB, Tovanabutra S, Sanders-Buell E, et al. (2012) Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2. Nature.
81. The-RV144-trial. Aidsmap. Accessed on 04 April, 2017.
82. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, et al. (2009) Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. Science 326: 285-289.
83. Wu X, Yang ZY, Li Y, Hogerkorp CM, Schief WR, et al. (2010) Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. Science 329: 856-861.
84. Walker LM, Huber M, Doores KJ, Falkowska E, Pejchal R, et al. (2011) Broad neutralization coverage of HIV by multiple highly potent antibodies. Nature 477: 466-470.

85. Bonsignori M, Montefiori DC, Wu X, Chen X, Hwang KK, et al. (2012) Two distinct broadly neutralizing antibody specificities of different clonal lineages in a single HIV-1-infected donor: implications for vaccine design. J Virol 86: 4688-4692.

86. Kuritzkes DR, Jacobson J, Powderly WG, Godofsky E, DeJesus E, et al. (2004) Antiretroviral activity of the anti-CD4 monoclonal antibody TNX-355 in patients infected with HIV type 1. J Infect Dis 189: 286-291.

87. Jacobson JM, Kuritzkes DR, Godofsky E, DeJesus E, Larson JA, et al. (2009) Safety, pharmacokinetics, and antiretroviral activity of multiple doses of ibalizumab (formerly TNX-355), an anti-CD4 monoclonal antibody, in human immunodeficiency virus type 1-infected adults. Antimicrob Agents Chemother 53: 450-457.

88. Kalams SA, Parker SD, Elizaga M, Metch B, Edupuganti S, et al. (2013) Safety and Comparative Immunogenicity of an HIV-1 DNA Vaccine in Combination with Plasmid Interleukin 12 and Impact of Intramuscular Electroporation for Delivery. J Infect Dis 208: 818-829.

89. Barouch DH, Kik SV, Weverling GJ, Dilan R, King SL, et al. (2011) International seroepidemiology of adenovirus serotypes 5, 26, 35, and 48 in pediatric and adult populations. Vaccine 29: 5203-5209.

90. Goepfert PA, Elizaga ML, Sato A, Qin L, Cardinali M, et al. (2011) Phase 1 safety and immunogenicity testing of DNA and recombinant modified vaccinia ankara vaccines expressing HIV-1 virus-like particles. J Infect Dis 203: 610-619.

91. Riedmann EM (2014) GeoVax expands its HIV/AIDS vaccine program. Hum Vaccin. Hum Vaccin 7(6): 596.

92. Day TA, Kublin JG (2013) Lessons Learned from HIV Vaccine Clinical Efficacy Trials. Curr HIV Res 2013;11(6): 441-449.

93. Rose NF, Marx PA, Luckay A, Nixon DF, Moretto WJ, et al. (2001) An effective AIDS vaccine based on live attenuated vesicular stomatitis virus recombinants. Cell 106: 539-549.

94. Sacha JB, Chung C, Rakasz EG, Spencer SP, Jonas AK, et al. (2007) Gag-specific CD8+ T lymphocytes recognize infected cells before AIDS-virus integration and viral protein expression. J Immunol 178: 2746-2754.

95. Cooper D, Wright KJ, Calderon PC, Guo M, Nasar F, et al. (2008) Attenuation of recombinant vesicular stomatitis virus-human immunodeficiency virus type 1 vaccine vectors by gene translocations and g gene truncation reduces neurovirulence and enhances immunogenicity in mice. J Virol. 82: 207-219.

96. Fischer W, Perkins S, Theiler J, Bhattacharya T, Yusim K, et al. (2007) Polyvalent vaccines for optimal coverage of potential T-cell epitopes in global HIV-1 variants. Nat Med 13: 100-106.

97. Santra S, Korber BT, Muldoon M, Barouch DH, Nabel GJ, et al. (2008) A centralized gene-based HIV-1 vaccine elicits broad cross-clade cellular immune responses in rhesus monkeys. Proc Natl Acad Sci USA 105: 10489-10494.

98. Day T, Morgan C, Kublin (2013) Will mosaic vaccine immunogens expand immune response breadth to rival HIV-1 strain diversity? Clin Invest 3: 413-415.

99. Wu Y, Marsh JW (2001) Selective transcription and modulation of resting T cell activity by preintegrated HIV DNA. Science 293: 1503-1506.

100. Jordan A, Defechereux P, Verdin E (2001) The site of HIV-1 integration in the human genome determines basal transcriptional activity and response to Tat transactivation. EMBO J 20: 1726-1738.

101. Lin X, Irwin D, Kanazawa S, Huang L, Romeo J, et al. (2003) Transcriptional profiles of latent human immunodeficiency virus in infected individuals: Effects of Tat on the host and reservoir. J Virol 77: 8227-8236.

102. Altfeld MA, Livingston B, Reshamwala N, Nguyen PT, Addo MM, et al. (2001) Identification of novel HLA-A2-restricted human immunodeficiency virus type 1-specific cytotoxic T-lymphocyte epitopes predicted by the HLA-A2 super type peptide-binding motif. J Virol 75: 1301-1311.

103. Munier CM, Andersen CR, Kelleher AD (2011) HIV vaccines: Progress to date.Drugs. 71: 387-414.

104. Ensoli B, Bellino S, Tripiciano A, Longo O, Francavilla V, et al. (2010) Therapeutic immunization with HIV-1 Tat reduces immune activation and loss of regulatory T-cells and improves immune function in subjects on HAART. PLoS ONE 5: e13540.

105. Reynolds MR, Weiler AM, Weisgrau KL, Piaskowski SM, Furlott JR, et al. (2008) Macaques vaccinated with live-attenuated SIV control replication of heterologous virus. J Exp Med 205: 2537-2550.

106. Baba TW, Jeong YS, Pennick D, Bronson R, Greene MF, et al. (1995) Pathogenicity of live, attenuated SIV after mucosal infection of neonatal macaques. Science 267: 1820-1825.

107. Baba TW, Liska V, Khimani AH, Ray NB, Dailey PJ, et al. (1999) Live attenuated, multiply deleted simian immunodeficiency virus causes AIDS in infant and adult macaques. Nat Med 5: 194-203.

108. Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S (2000) Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 × 10(6)/L CD4 cell counts: A randomized controlled trial. JAMA 284: 2193-2202.

109. Kim JH, Excler JL, Michael NL (2015) Lessons from the RV144 Thai phase III HIV-1 vaccine trial and the search for correlates of protection. Annu Rev Med 66: 423-437.

110. Hansen SG, Vieville C, Whizin N, Coyne-Johnson L, Siess DC, et al. (2009) Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. Nature Med 15: 293-299.

111. Virgin HW, Walker BD (2010) Immunology and the elusive AIDS vaccine. Nature 464: 224-231.

112. Haase AT (2010) Targeting early infection to prevent HIV-1 mucosal transmission. Nature 464: 217-223.

113. Pancera M, Majeed S, Banb YEA, Chena L, Huang CC, et al. (2010) Structure of HIV-1 gp120 with gp41-interactive region reveals layered envelope architecture and basis of conformational mobility. Proc. Natl Acad Sci USA 107: 1166-1171.

114. Chen L1, Kwon YD, Zhou T, Wu X, O'Dell S, et al. (2009) Structural basis of immune evasion at the site of CD4 attachment on HIV-1 gp120. Science. 20;326(5956): 1123-1127.

115. Stamatatos L, Morris L, Burton DR, Mascola JR (2009) Neutralizing antibodies generated during natural HIV-1 infection: Good news for an HIV-1 vaccine? Nature Med 15: 866-870.

116. HIV Vaccines and microbicides resource tracking working group adapting to realities: Trends in HIV prevention research funding (July 2009).

117. Kulkosky J, Bray S (2006) HAART-persistent HIV-1 latent reservoirs: Their origin, mechanisms of stability and potential strategies for eradication. Curr HIV Res 4: 199-208.

118. Haynes BF, Gilbert PB, McElrath MJ, Zolla-Pazner S, Tomaras GD, et al. (2012) Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med 366: 1275-1286.

119. Allers K, Hutter G, Hofmann J, Loddenkemper C, Rieger K, et al. (2011) Evidence for the cure of HIV infection by CCR5Delta32/Delta32 stem cell transplantation. Blood 117: 2791-2799.

120. Hütter G, Nowak D, Mossner M, Ganepola S, Müssig A, et al. (2009) Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med 360: 692.

121. Hocqueloux L, Prazuck T, Avettand-Fenoel V, Lafeuillade A, Cardon B, et al. (2010) Longterm immunovirologic control following antiretroviral therapy interruption in patients treated at the time of primary HIV-1 infection. AIDS 24: 1598-1601.

122. http://www.genticel.com/technology/therapeutic-vaccines.html

123. Markowitz M, Jin X, Hurley A, Simon V, Ramratnam B, et al. (2002) Discontinuation of antiretroviral therapy commenced early during the course of human immunodeficiency virus type 1 infection, with or without adjunctive vaccination. J Infect Dis 186: 634 -643.

124. MacGregor RR, Ginsberg R, Ugen KE, Baine Y, Kang CU, et al. (2002) T-cell responses induced in normal volunteers immunized with a DNA-based vaccine containing HIV-1 env and rev. AIDS 16: 2137-2143.

125. MacGregor RR, Boyer JD, Ciccarelli RB, Ginsberg RS, Weiner DB (2000) Safety and immune responses to a DNA-based human immunodeficiency virus (HIV) type I env/rev vaccine in HIV-infected recipients: Follow-up data. J Infect Dis 181: 406.

126. Schooley RT, Spino C, Kuritzkes D, Walker BD, Valentine FA, et al. (2000) Two double-blinded, randomized, comparative trials of 4 human immunodeficiency virus type 1 (HIV-1) envelope vaccines in HIV-1-infected individuals across a spectrum of disease severity: AIDS Clinical Trials Groups 209 and 214. J Infect Dis 182: 1357-1364.

127. Smith D, Gow I, Colebunders R, Weller I, Tchamouroff S, et al. (2001) Therapeutic vaccination (p24-VLP) of patients with advanced HIV-1 infection in the pre-HAART era does not alter CD4 cell decline. HIV Med 2: 272-275.

128. Trauger RJ, Daigle AE, Giermakowska W, Moss RB, Jensen F, et al. (1995) Safety and immunogenicity of a gp120-depleted, inactivated HIV-1 immunogen: Results of a double-blind, adjuvant controlled trial. J Acquir Immune Defic Syndr Hum Retrovirol 2: S74-S82.

129. Eron JJ, Ashby MA, Giordano MF, Chernow M, Reiter WM, et al. (1996) Randomised trial of MNrgp120 HIV-1 vaccine in symptomless HIV-1 infection. Lancet 348: 1547-1551.

130. Sandström E, Wahren B (1999) Therapeutic immunisation with recombinant gp160 in HIV-1 infection: A randomised double-blind placebo-controlled trial. Nordic VAC-04 Study Group. Lancet 353: 1735-1742.

131. Peters BS, Cheingsong-Popov R, Callow D, Foxall R, Patou G, et al. (1997) A pilot phase II study of the safety and immunogenicity of HIV p17/p24:VLP (p24-VLP) in asymptomatic HIV seropositive subjects. J Infect 35: 231-235.

132. MacGregor RR, Boyer JD, Ugen KE, Lacy KE, Gluckman SJ, et al. (1998) First human trial of a DNA-based vaccine for treatment of human immunodeficiency virus type 1 infection: Safety and host response. J Infect Dis 178: 92-100.

133. Robbins GK, Addo MM, Troung H, Rathod A, Habeeb K, et al. (2003) Augmentation of HIV-1-specific T helper cell responses in chronic HIV-1 infection by therapeutic immunization. AIDS 17: 1121-1126.

134. Lederman MM, Douek DC (2003) Sometimes help may not be enough. AIDS 17: 1249-1251.

135. Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S (2000) Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 x 10(6)/L CD4 cell counts: A randomized controlled trial. JAMA 284: 2193-2202.

136. Vardas E, Stanescu I, Leinonen M, Ellefsen K, Pantaleo G, et al. (2012) Indicators of therapeutic effect in FIT-06, a Phase II trial of a DNA vaccine, GTU(®)-Multi-HIVB, in untreated HIV-1 infected subjects. Vaccine 30: 4046-4054.

137. Rockstroh JK, Pantaleo G, Pollard R, et al. (2011) A phase II, randomized, double-blind, multicenter, immunogenicity study of Vacc-4x versus placebo in patients infected with HIV-1 who have maintained an adequate response to ART (Abstract #TULBPE028). Poster session presented at: 6th IAS Conference on HIV Pathogenesis. Treatment Prevention 17-20.

138. Preventive technologies, research toward a cure, and immune-based and gene therapies. HIV Treatment Bulletin. Accessed on 04 April 2017.

139. National Institute of Allergy and Infectious Diseases (U.S.) (Press Release). NIH-sponsored HIV vaccine trial launches in South Africa. 2015 February 18.

140. NIH-Sponsored HIV Vaccine Trial Launches in South Africa. HIV/AIDS News. Accessed on 04 April 2017.

141. Scientists-just-set-their-sights-on-a-new-target-for-a-hiv-vaccine. sciencealert. Accessed on 04 April 2017.