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HIV VACCINETRIALS AND FUTURE PROSPECTS

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Abstract

Despite having made rapid progress in this field of HIV vaccination research in the past few years, a treatment for the deadly HIV-AIDS is still the dream of many. Human immunodeficiency virus [HIV]being the sole cause for this disease, is a rapidly mutating virus which targets the T lymphocyte cells and thereby brings down the hosts immune system. There are specific antibodies synthesized in vivo that are transiently effective against the virus but, as the disease progresses the helper cells are destroyed by the virus with which the antibody secretion also halts. Several studies are carried out that aims at curing the disease. Recombinant vaccines are the focus at present where viral vectors with HIV antigens are used to trigger the immune response in the host and provide immunity from HIV. The vaccine research is making some strong progress recently mainly due to the success of the RV144 trial. The various clinical trials that were carried out lackedefficacy like AIDSVAX trials, Step trials, and Phambili, while a few were stopped midway like HVTN505. HVTN 100 trial which is currently being carried out in South Africa is the next phase of the famous RV-144 trial and is expected to procurebetter results than RV144. With a lot of money being spent on the best brains of the decade, a cure for HIV isa certain in the future.

Keywords: HIV mutation, Recombinant vaccines, RV144, Vaccination trials

Introduction

HIV was at first identified in 1983. It is a type of lentivirus and belongs to the family of retroviridae. It is known to attack the immune system of humans, thereby making the body more susceptible to other diseases. A patient infected with this virus thus suffers from a wide range of diseases and hence, this condition is referred to as a syndrome i.e. acquired immunodeficiency syndrome [AIDS].The initial stages of HIV infection are similar to influenza-like illness followed by a prolonged period without any symptoms [dormant period]. As the disease progresses, it interferes with the immune system making the host much more susceptible to opportunistic infections like tuberculosis, herpes and

may more.AIDS has already proved to be a catastrophic disease, causing amenace to mankind since the past 30 years and yet the cure for this seems so far away. The pathogen responsible for acquiring this disease is HIV. The casualties for this disease is staggering with almost 78 million people having been infected with HIV and about 39 million people dead since the beginning of this pandemic (http://www.avert.org/about-avert.htm).Currently, the worst affected part of the world by this HIV is the Sub-Saharan region(http://www.avert.org/about-avert.htm.). HIV is not like any other typical virus, it is around 120 nm in diameter and roughly spherical. It has an outer lipid layer which contains receptors for binding to CD4+ T cells. The receptors precursorsare known as gp160 (Glycoprotein 160). This gp160 is later processed to gp120 and gp41(1). The virus contains two copies of non-covalently linked, unspliced, positive –sense single stranded RNA as shown in figure 1. Both RNA copies are enclosed in a conical capsid which also consists of a viral protein p24. The RNA is 9749 nucleotide long and has a 5'cap [Gppp], a 3'polyA tail and several open reading frames [ORFs]. The single-stranded RNA is tightly bound to p7 nucleocapsid proteins, late assembly protein p6, and enzymes essential to the development of the virion such as reverse transcriptase and integrase. Lysine tRNA is the primer of the magnesium-dependent reverse transcriptase. The nucleocapsid associates itself with the genomic RNA [one molecule per hexamer] and protects the RNA from digestion by nucleases. Also enclosed within the virion particle are Vif, Vpr, Nef, and viral protease. The viral protein p17 present in the matrix of the virus surrounds the capsid thereby enhancing the virus particle's integrity(http://www.avert.org/about-avert.htm).

Majorly there are two types of HIV i.e. HIV-1 and HIV-2. HIV -1 is found in the global population while, HIV-2 is mainly localized to South Africa (http://www.avert.org/about-avert.htm),(2).HIV-1 has been found to have originated from chimpanzees. The SIVcpz strain found in these organisms are very similar to the HIV-1 that is seen in humans(3). HIV-2 comes from sooty mangabey monkeys. These are similar to the SIVsmm strain found these monkeys. HIV-2 is very rare and also less infectious than HIV-1. Hence, it is localized only to a few regions like the countries of West Africa: Mali, Mauritania, Nigeria and Sierra Leone(4). In 2008, a total of $ 868 million (US) was spent on research and development of HIV vaccines (5)(http://www.hivresourcetracking.org).

VACCINE PURSUITS FOR HIV

There has been various vaccination strategies developed to help counter the virus, by aiding in prevention of the occurrence of the disease [preventive vaccines] or by helping in the treatment of the pre-existing disease [treatment vaccines].We prefer the use of vaccines to curb HIV mainly because of the fact that it is more cost effective and

would be safer than to design treatment methods. The fear of inducing possible resistance to the virus against the treatment drug because of its repeated usage also has prompted the researchers to focus more on vaccine development. The vaccines may be designed to contain: a) whole-inactivated HIV; b) a synthetic peptide that can elicit an immune response against the virus; c) recombinant viral vector that carry pieces of HIV; d) Pieces of DNA of the virus; e) broadly neutralizing antibodies; f) virus-like particles that have the same shape as HIV but changed on the inside; g) live-attenuated / weakened HIV; h) recombinant sub-unit that is, a HIV protein made in a lab. Among these, only a few of the strategies has been implemented in the production of vaccines and they include the following:

a. Direct administration of bNAbs (Broadly neutralizing Antibodies)

In recent years, it has been found out that after the primary infection of the virus in the host, roughly around 20% of the infected individuals start developing certain antibodies which haveweak neutralizing effects on the HIV virus(6). These types of antibodies are referred to as bNAbs[Broadly neutralizing antibodies]. The production of these antibodies, however, requires the exposure to a largerviral load (http://www.treatmentactiongroup.org/tagline/2015/spring/hiv-cure-and-vaccine-within-next-15-years). At the same time, the production of these antibodies induces a strain on the virus causing it to mutate constantly. As the disease progresses, the bNAbs tend to decrease in amounts due to the depletion of CD4+ T cells which play a prominent role in activating the immune system (7). Certain ex-vivo studies have shown that these bNAbs decrease the expression of virus in the viral reservoirs. In-vivo studies conducted show decreased virus in circulation in the presence of bNAbs(8). There are studies where people tried to mass synthesize these bNAbs against the Env protein of HIV and in turn trying to neutralize the virus but, the high mutation frequency of the virus protected it from the Abs (9).

b. Subunit vaccines

Subunit vaccines are composed of certain proteins which act as antigens on entering the host. This stimulates the body to synthesize certain antibodies to counter the antigen. These antibodies build up in the body in turn protecting the body from the subsequent viral attacks. The trials conducted by VaxGen mainly employed this vaccination strategy and they designed the vaccine with gp120 protein as the antigen (10).

c. Recombinant vector vaccines

These vaccines have viral vectors which are modified to express HIV-1 gag, pol, pro and gp120like antigens which prepare the body to fight against the disease by inducing the synthesis of certain antibodies against the expressed antigens (11, 12). Most of the promising trials used this technique but, dealt with synthesizing different antigens of

varying concentrations. There are several viral vectors that have been used to carry out this method. The commonest vectors include Canarypox virus, Sendai virus,adenovirus, and lentivirus. The famous RV-144 trial used Canarypox virus to express HIV antigens(12). HVTN505 also employed this technique wherein the adenovirus vector was subjected to express a wide range of antigens. Step study trial and HVTN503 [Phambili trial] employed this strategy wherein MRKAd5 viral vectorswere used to express gag, pol and nef(13, 14).

d. Interleukin mediated vaccines

This is the current area being explored with the hope of formulating a successful vaccine. Here, an expression plasmid with interleukin-2 gene is administered along with an HIV-1 DNA vaccine(15). A study involved administration of both the vaccine and the expression plasmid in a cationic liposome into a mice. The result was that there was a significant decrease in the IgG1/IgG2a ratio in the serum and there was an increased production of IL-2 and INF-γ while IL-4 levels secreted by re-stimulated immune lymphoid cells also decreased(15-18).

Clinical Trials

A very few vaccine designs have been successful and have proceeded to clinical trials, themajority haven't been able to come up come with goodcompetence. Some of the major trials that took place for evaluating the potency were:

1. AIDSVAX trials

It was carried out by VaxGen which is a California-based company. The vaccine was designed to include monomeric HIV-1 Env gp120 protein which would elicit antibodies against the gp120 envelope protein of the virus thereby, helping to counter the virus (19).At first,two bivalent vaccines were designed and were tested separately. The first of the vaccines was a bivalent, recombinantHIV-1 subtype B called AIDSVAXB/B. The phase III trial of this vaccine was carried out extensively in US, Netherlands and Porto Rico(20, 21). The volunteers recruited mainly included men having sex with men [MSM]and women at high risk(22). A total of 1,679 participantswere administered the placebo while, 3,330 were administered the vaccine. The trial concludedby the end of 2002 and the result was announced in Feb 2003, which confirmed that the trials were ineffective. Despite the ineffectiveness, the analysis revealed certain specific groups of people like the Asians and the African Americans developed higher amounts of antibodies than the whites and Hispanics. The authorities claimed that the vaccine showed a possible efficacy of 78% in the African American population and 67% in Asian and other minorities. In addition, many questioned the p-value [significance value] of the statistical analysis(20, 21) (http://www.aidsmap.com/The-AIDSVAX-trials/page/2027990/).

The second vaccine tested was a bivalent, recombinant HIV-1 subtype B/Ecalled AIDSVAX B/E. It was subjected to phase III trials in Thailand where in the drug users were recruited for the trial. Nevertheless, the vaccine was neither successful in aiding HIV-1 prevention nor reducing the disease progression. Even though both these gp120 based vaccines failed, it was used as a booster in the RV-144 trial.

2. Step study trial

Step study trialtried to control the infection through cell-mediated immune responses by inhibiting the viral replication and reducing the early plasma HIV-1 levels. This was a proof of concept, double-blind, placebo-controlled, randomizedphase IIb trial conducted by Merck and the National Institutes of Health(19). It washeld in 34 sites i.e. in North America, South America, Caribbean and Australia.

Around 3000 volunteersas shown in Table .1were enrolled at the beginning of the study majorly consisting of men having sex with men [MSM], heterosexual men and women (22). On further screening, 1484 patients were administered with three 1.0mL intramuscular injections ofMerck Trivalent Adenovirus Serotype 5 HIV-1 gag/pol/nef Ad5 [MRKAd5 HIV-1 gag/pol/nef] vaccine on day1, week 4 and week 26 while, 1495 other participants were administered with three 1.0mL intramuscular placebo injectionson the same days as the vaccines were administered, after random selection(https://clinicaltrials.gov/ct2/show/results/NCT00095576?term=NCT00095576&rank=1).

The hazard ratio [vaccine/placebo]for recipients who were Adenovirus 5 seropositive (Ad5) and uncircumcised was higher when compared to the recipients who were Ad5 seronegative and circumcised. The study concluded that cell-mediated immunity did not help in preventing HIV-1 infection and this led to the study being discontinued in the early stages as it met thepre-specified futility boundaries. The trial paper containing the results and analysis was published in 2008(13).

3. Phambili Trial

This vaccination trial aimed at inducing T cell mediated immune response which would decrease the viral load after infection or provide complete or partial immunity from HIV-1 infection. The complete phase II-b trial was carried out in South Africa in 2007, wheresubtype C of HIV is the predominant one.

A total of 1428 participantsinvolving heterosexual men and women were screened at the beginning of the trial, out of which 801 were selected for the next step of the trial. Out of 801, 400 were assigned to receive a vaccine while the remaining 401 were assigned to receive a placebo which was nothing but 1 mL solution of the vaccine diluent with no Ad5 vector. The vaccine administered wasMRKAd5 HIV-1 gag/pol/nef subtype B vaccine and the dosage was 1·5

$\times 10^{10}$ adenovirus genomes per mL(14).For vaccine efficacy and safety analysis, 400 recruits from the vaccination pool were evaluatedof which 93 were included for the testing of vaccine immunogenicity which was done through ELISPOT assay. Similarly, 400 from the placebo pool were included for vaccine efficacy analysis, 401 were included for safety analysis of which 93 for ELISPOTassay.

The results showed no signs of efficacy which might have been because of the short interruption during the process which occurred due to the temporary suspension of enrollment and vaccination of this trial due to the failure of the Step study trial.

4. *RV144 Trial or the Thai trial*

This was the first HIV clinical trial to express vaccine efficacy. This was a phase III trial conducted in Thailand on 16,402 men and women between the ages of 18 and 30 as depicted in Table.2(12). Thevaccination strategy of the trial was to induce the synthesis of antibodies as well as to enhance the T-cell mediated immunity. It had two components i.e. the vaccine and the booster. The vaccine is referred to as ALVAC-HIV and the booster referred to as the AIDSVAX B/E. The ALVAC-HIV was a recombinant Canarypox vaccine which was engineered to express HIV-1 gag and pro and CR01_AE (subtype E)HIV-1 gp120 linked to the transmembrane anchoring portion of gp41.AIDSVAX B/E consisted of subtype E envelope from the HIV-1 strain A244 and a subtype B envelope from the HIV-1 MN produced in Chinese hamster ovary cell lines. A placebo for the vaccine was also used as a control. The vaccine was administered at baseline, 4 weeks, 12 weeks and 24 weeks, while the booster was administered onthe 12th week and 24th week.

The study initially started off by recruiting 26,676 volunteers who were regarded as community-risk population(22) but, after multiple stages of screening, only 8197 received the vaccine while another 8198 received a placebo. During the course of administration, another 2021 were excluded from vaccine pool and 1832 from the placebo pool because of reasons like receiving alow dosage of drugs, receiving doses outside the time frame, dosage errors, age restrictions and HIV infections. Further, during analysis, 15 patients were further excluded from vaccination pool and 24 from the placebo pool.

The results of the analysiswere published in 2009 and it was observedthat the vaccine neither influenced the viremia nor the CD4+ T-cell count in patients who were subsequently diagnosed with HIV. The final conclusion was that the trialshowed a 31.2% efficacy at 42 months(12) (http://www.treatmentactiongroup.org/tagline/2015/spring/hiv-cure-and-vaccine-within-next-15-years), (www.niaid.nih.gov/news/newsreleases/2015/Pages/HVTN100.aspx).

5. *HVTN505*

It was launched in 2009 and was initially designed to decrease viral load in the volunteers. Before they actually started the clinical trials, they used a vaccine similar to HVTN 505 and used them on rhesus macaques to treat simian immunodeficiency virus (SIV). The results showed that half of the treated rhesus macaques, developed immunity towards SIV(23). It involved the use of a DNA adenovirus 5-vectored vaccine which encodes for epitopes fromHIV clade B Gag, Pol, and Nef, and Env from HIV clade A, B, C, followed by a booster in the form of Ad5 vector-based vaccine candidate encoding clade B Gag-Pol fusion protein and Env glycoproteins from clades A, B, C(23). The vaccination was given at weeks 0, 4 and 8 while, the booster was given on week 24.

This HVTN 505 was a large scale, proof of concept study of a product developed by the Vaccine Research Center (VRC). Thephase IIbtrial consisted of 2,496 participants who were HIV-1 uninfected, adenovirus type 5 seronegative, circumcised men who have sex with men (MSM)(24). Out of those recruited, 1,251 subjects were given the vaccine and 1,245 were administered the placebo. The subjects were monitored for upto 2 years and the hazard ratio was calculated at the end of it, the value was 1.25. The vaccination trials were discontinued shortly after that and the information regarding the drug administered i.e. vaccine or a placebo was revealed to the patients on April of 2013. The main reason for aborting the study was that the results obtained after preliminary studies showed very low levels of efficacy (www.fredhutch.org/en/labs/vaccine-and-infectious-disease/news/publication- spotlight /hvtn_505_ phase_2b hiv_vaccine_trial.html). Some studies performed later on, on the individuals, showed that this vaccine elicited the production of a few antibodies which were referred to as polyreactivesince they recognized HIV as well as microbes which are a part of the intestinal microbiome. This polyreactivity decreased the effectiveness of the antibodies and inturn couldn't prove to be as effective as expected (www.niaid.nih.gov/news-events/hvtn-505-vaccine-induced-antibodies-nonspecific-hiv).

6. HVTN 100

This was the current trial being carried out while writing this paper in South Africa which is one of the worst affected countries in the world by this HIV (www.niaid.nih.gov/news/newsreleases/2015/Pages/HVTN100.aspx). This trial was started in 2015 and the results are expected to be drawn in the year 2017. The vaccine being used is based on the one used in RV144 but, are made more specific to the Clade C subtype of HIV, which is widespread type in southern Africa (http://www.aids2016.org/Media-Centre/The-Latest/Press-Releases/ArticleID/62/New-vigour-in-HIV-vaccine-research-evident-at-AIDS-2016). The trial also involves an adjuvant, to enhance the body's immune response. It

involved the participation of 252 people, 210 of whom were administered the vaccine while, 42 of them got the placebo. The results obtained has exceeded everyone's expectations and its interim results have prompted the start of the phase III efficacy trial named as HVTN 702 (http://www.hvtn.org/en/community/community-compass/current-issue/cc-current-article2.html).

Apart from the above trials, P5 developmental track trials [ALVAC/gp120, MF59 adjuvant], P5 research track trials [various combinations of ALVAC, NYVAC, gp120 protein, DNA and adjuvants], RV144 follow-on trials [ALVAC/AIDSVAX], Janssen Ad26 trials [AD26], VRC01 and 3BNC117are still under clinical trial and testing for various mosaic based products. Vaccine using replicating virus such as Sendai virus and Tiantan replicating vector has shown promising results in phase trials in terms of efficacy and safety.

Current Research

The process of finding out a cure for HIV is turning out to be a daunting task. Even though there are few methods by which the condition can be controlled, they are not involved in decreasing the viral load in itself. In order to completely curb the HIV infection rates, a cure or a vaccine that can decrease the viral load should be formulated. The CD4+ T cell activation has proved to be an effective technique which has the ability to control the viral load. By activating the HIV-specific CD4+ T cells, the CD8 cells with higher efficiency in combating the virus is produced and also effective B cell responses. This is supported by compelling evidence obtained from in vivo experiments (25). This mechanism is being used currently in certain therapies like combination therapy where two different drugs are administered in which one activates the CD4+ T cells and the other activates the virus present in its dormant stage. So, the activated helper cells aid in inducing the action of HIV-specific CD8 T cells. Drugs like disulfiram and SAHA are administered which brings the virus out of its dormant stage(26, 27). After this drug administration, the presence of HIV can be looked for by screening methods.Even c-ART (combination anti-retroviral therapy) can be used to effectively control the viral spread. Apart from this, they are also trying to mass produce BNAbs that are specific to the Env proteins which in turn can be used for vaccinations(7). There have been studies which clearly show that increased levels of IgG3 and IgAantibodies specific to V1V2 region of gp120 and decreased Env-specific antibodies in the blood reduces the risk of being infected with HIV(28-30).

Significant progress has also been made in RNA-i guided HIV therapy. They are trying to target the surface receptors of CD4+ T cells which prevent the HIV attack on the T cells and thereby on the immune system itself. This method has found success but not too significant that it can be considered to treat the disease(31). HIV-1 Virus-like particles

(VLP) are being looked at as the next potential candidate that can be used to prevent HIV infection. These VLP's have functional Env spikes on their membrane and hence can elicit host's immune response. Since these are non-infectious, non-replicating genome-lessvirions, the safety aspects are also covered. These are used in tandem with dendritic cells (DC) which are capable of capturing these VLP's and are presented by both MHC class I and class II molecules. There has been the development of four vaccines for different diseases by using this VLP concept and a few are currently in clinical trials(32).

Another relatively new concept called mucosal immunization is being looked into for exciting prospects to cure HIV. Mucosae is the first line of defense against the virus and it has been identified that cytotoxic T lymphocytes (CTL's) are effective in recognizing low concentrations of antigens. Hence, attempts are being made to enhance the activity of these CTL's in the mucosae and in turn counter the virus from the very beginning(33-35). There are reports of vaccines being developed to target this mechanism which inhibits IL-13 activity which leads to enhanced action of CD8+ T cells(33, 36). Recently, certain advances have been noticed in the development of certain suppositories referred to as microbicides. Microbicides are substances that could be used in the vagina or the rectum to prevent the occurrence of HIV.

Few clinical trials like Ring study and Aspire studies have been carried out to test its efficacy. The results were positive but modest.This are yet to be released to the public and still requires a few more years of research (www.aids.gov/hiv-aids-basics/prevention/prevention-research/microbicides/). All these methods face the same problem i.e. the high frequency of mutation of the HIV virus. These mutations are enhancedby the reverse transcriptase enzyme present in the virus. So, a method which has the ability to deal with the rapid mutations of the virus has a better chance of being able to cure the disease.

Conclusion

There is still no treatment method present that can cure/prevent the occurrence of this challenging disease. There are pre-exposure prophylactic (PrEP) treatment methods which helps prevent HIV infection in unaffected individuals but, needs to be taken very frequently (http://www.cdc.gov/hiv/basics/prep.html). The presence of ART helps people to live a longer life by inhibiting the growth of the virus.

The RV144 trial though didn't offer significant results, gave a glimmer of hope to the scientific community to come out with new improved strategies. It has been discovered that a certain percentage of theCaucasian population with CCR5 Δ32 mutation showed resistance towards HIV. This was because of the fact that the mutation caused knockout

of the CCR5 receptor, which plays an important role in HIV entry(37). This finding led to the cure of an HIV-infected patient now referred to as the "Berlin patient"(38) (www.fredhutch.org/en/news/center-news/2015/08/hiv-cure-conference-cautious-optimism.html) wherein, they used stem cell transplantation therapy from a donor who was CCR5 Δ32 mutated.

This led to the complete cure of his HIV infection. But, every patient cannot be cured by this procedure since it is difficult to find a donor with the required mutation and also faces compatibility issues between the donor and the patient. The infection can be inhibited significantly if the individual starts undergoing c-ART as soon as he is infected. This has been proved by the Visconti cohort trial were the 14 patients showed extremely low levels of the viral load after taking c-ART soon after they were infected [10 weeks], for 3 years continuous(39).These are certainly some positive signs through which the scientists can ardor from and continue their work towards finding a vaccine/cure for HIV.

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