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VACCINE DEVELOPMENT STRATEGIES, PROGRESSES AND CHALLENGES FOR HUMAN IMMUNODEFICIENCY VIRUS (HIV): A REVIEW

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ABSTRACT

Human immunodeficiency virus is classified under the *Retroviridae* family and identified as a causative agent of acquired immunodeficiency syndrome (AIDS).Since Human immunodeficiency virus (HIV) is identified as causative agent of AIDS, about 39 million people have been died and 78 million people have been infected worldwide. Despite tremendous efforts are being made to develop successful diagnosis, treatment and prevention methods, and to develop HIV vaccine the effort remains great challenge for researchers, due to extreme genetic variability of the virus. Even though vaccination of HIV is the most promising, cost effective and feasible intervention strategy to control and eradicate HIV disease route and transmission, still now we are struggling to find an elusive vaccine after thirty years and disappointing results are recorded from previous clinical trials, except the promising RV144 HIV vaccine which is phase III clinical trial with the modest vaccine efficacy. The contribution of this study is to reveal the challenges to found potent HIV vaccine during the last decades, significant lessons learnt about the basic virology, pathogenesis, immunology, HIV/AIDS treatment and HIV infection prevention and significant findings and clinical trials progresses which are currently open the way to some extent to hope that HIV vaccine development is possible.

Contribution/Originality: The contribution of this study is to reveal the challenges to found potent HIV vaccine during the last decades, significant lessons learnt about the basic virology, pathogenesis, immunology, HIV/AIDS treatment and HIV infection prevention and significant findings and clinical trials progresses which are currently open the way to some extent to hope that HIV vaccine development is possible.

1. ACQUIRED IMMUNODEFICIENCY SYNDROME

Human immunodeficiency virus is a catagorised under the *Lenti virus* genus, *Retroviridae* family and has identified as a causative agent of acquired immunodeficiency syndrome (Requejo, 2005). Extreme genetic variability is one of the most outstanding properties of the virus (Esteves *et al.*, 2002) which can be attributed to the HIV reverse transcriptase (RT) high mismatch error rate without a proof reading capacity, rapid turnover rate of the *in vivo* viral replication, selection pressures due to therapeutic agents and recombination events during replication (Kandathil *et al.*, 2005). Such extreme variability nature of the virus genetic material has significant implications in the diagnosis, treatment and prevention of the disease (Sahni and Nagendra, 2004). AIDS continues to spread unchecked starting its first documentation in 1981 (Kandathil *et al.*, 2005) and now in Africa it is the primary cause

of death and the fourth cause of death worldwide (Piot *et al*., 2001; Sahni and Nagendra, 2004). Since the first identification and characterization of the disease, 78 million people have been infected with the virus and 39 million people have beendied from AIDS (UNAIDS, 2014). As reported by UNAIDS (2016) 2.1 million new HIV infections are estimated to occur adding up the number of people living with HIV to a total of 36.7 million, worldwide in 2015 alone.

Mainly there are two *types of HIV*, causing acquired immunodeficiency syndrome, called human immunodeficiency virus type one (HIV-1) and human immunodeficiency virus type two (HIV-2) (Kandathil *et al*., 2005). The majority of the infection worldwide is caused by the HIV-1 virus, while HIV-2 is only restricted to some regions of Western and Central Africa (Requejo, 2006). Historically, United States and Europe are the first paces where HIV-1 virus is isolated and characterized for the first time (Hamel *et al*., 2007). However, it is believed that HIV-1 is originated in West Central Africa and transmitted via cross-species transmission mechanism from chimpanzees to human (Esbjörnsson *et al*., 2011).

2. HIV VACCINE DEVELOPMENT

Many people believed that an effective vaccine against AIDS would rapidly be developed when HIV was discovered as the causative agent of AIDS (Esparza, 2001) even though we are still struggling to develop an elusive vaccine after 30 years (Esparza, 2013).The challenges for HIV vaccine development are due to the absence of information about HIV/AIDS protection immunological correlation; the virus genetic variability; and the absence of ideal model animals (Esparza, 2001). In addition, HIV/AIDS virus-induced immune response does not possess the ability to prevent re-infection and slowing down the progression to disease, due to the ability of HIV virus to escape the host immune system (Asif and Irshad, 2017). Despite of the challenges to found potent HIV vaccine, over the past decades significant progress has been made in basic virology, pathogenesis, immunology, HIV/AIDS treatment and HIV infection prevention using antiretroviral drugs in a prophylactic manner (Shattock *et al*., 2011). Among such significant progresses, a phase III prime-boost RV144 trial is the best illustration in HIV/ AIDS vaccine development history (Rerks-Ngarm *et al*., 2009).

Usually to describe products which are designed to prevent individuals from getting a disease, the term vaccine is used (Idoko and Isa, 2005). Vaccine is the most cost effective health interventions to eradicate killer diseases such as HIV/AIDS. Even though HIV has been proven to be difficult for vaccination against, because of the virus extreme genetic mutation rate and its capability to escape from the immune responses (Joseph *et al*., 2006) an HIV vaccine is the most feasible and promising strategy to control HIV disease route and transmission mechanism (Duerr *et al*., 2006). This is due to the fact that vaccination is able to completely prevent infection and clinical disease progression by blocking infection and providing sterilizing immunity (Barouch, 2008). Therefore, safe, effective and affordable HIV vaccine designing and development is a critical global health priority to control the HIV pandemic (Chandran *et al*., 2002).

The HIV /AIDS virus genetic diversity and high genetic mutation rate create a plethora of constantly changing antigens (Kwong *et al*., 2012). The inaccurate viral enzymatic replication resulted in ongoing production of mutant virions, even genetic diversity is generated in a single HIV infected individual, which significantly complicates an HIV vaccine development process (Letvin, 2002) and brings a major setback in vaccine designing and identification of antigen presentation and delivery systems, capable of rapidly eliciting both the humoral and cellular components of the immune system that evoke strong and sustained immunity against different isolates of virus (Trovato *et al*., 2012). As a result of such complex challenges, there is no any licensed effective HIV vaccine up to date (Joseph *et al*., 2006).

Even though several vaccine development approaches have been tested to evoke anti-HIV immune responses by seating a goal to generate preventive HIV vaccine which illicit both broadly reactive humoral and cellular immunity against HIV in the host before exposure to the virus (Sahni and Nagendra, 2004) there is not any

potential candidate HIV-vaccine that has been found effective to prevent HIV infection since the identification of HIV as a causative agent of AIDS (Joseph *et al*., 2006) up to now.

However, there are a few promising neutralizing antibodies that have been developed against HIV-1 enveloping proteins which are proved to be highly effective to neutralize different viral strains in vitro (Xiao *et al*., 2001). The most encouraging result was reported in September 2009 for a vaccine with an estimated efficacy of 31.2% (Rerks-Ngarm *et al*., 2009).

3. STRATEGIES FOR HIV VACCINE DEVELOPMENT

An important aspect of vaccine designing is to decide which parts of the organism, virus or antigen can induce immune response (Spearman, 2006) which depends on an understanding of the disease agent pathogenicity and the immunological response of the host. Now a day's rapid advancement in a number of new technologies has simplified the development of new vaccines by reducing the timescale for vaccine development and assisting the identification of new target molecules. However, in case of HIV/AIDS viral replication process and pathogenesis of AIDS elucidate unique property which may not be amenable to control by immune responses evoked by traditional vaccine modalities; as evidenced by experiments done on nonhuman primates which bear out that inactivated virus vaccines, live attenuated virus vaccines and recombinant protein vaccines are ineffective in preventing HIV infection (Letvin, 2002). In fact, an ideal AIDS vaccine should have potential to prevent the viral transmission through mucosal and parenteral route and should be administered in single dose with an excellent safety profile; after vaccination it should have long lived effect of protection for many years with a minimal cost of vaccination and the ability to induce protection against the infection caused by diverse viral isolates (Sahni and Nagendra, 2004). Since the identification of HIV as causative agent of AIDS, scientists have tried different vaccine development methods to design such a vaccine that addresses all the challenges posed by the HIV virus. However, the road to develop a broad and effective HIV vaccine is not a straight line.

4. DNA VACCINES AGAINST HIV

The most recent advancement in vaccine development involves direct administration of DNA molecules which code for immunogenic antigens to tissues that are capable to take the DNA molecules and express the foreign antigen to evoke an effective immune response (Arnon and Ben-Yedidia, 2003). Most of such vaccines are found to be safe and to induce immune responses in model animals (Chin'ombe and Ruhanya, 2015). Different HIV surface proteins can be made DNA vaccine using recombinant DNA technology. The DNA vaccines expressing HIV-1 gp160 and rev, used to immunize chimpanzees, have raised enhanced virus-specific immune responses (Puls and Emery, 2006). In phase I vaccine trial which can express HIV-I recombinant gpI60 (rgpI60), the vaccine is found to induced the production of IgA serum antibodies and anti-envelope glycoprotein IgG in all the vaccinated volunteers (Curse *et al*., 1995). In the same way, successive immunization of mice with DNA and modified vaccinia virus Ankara (MVA) vaccines which express an immunogen called HIVA, consist of a consensus clade A gag p24/p17 and clade A-derived CTL epitopes, can induce strong T cells-mediated immunity for 155 days (Hanke *et al*., 2002). In a native Tat protein based phase I HIV vaccine trial, the vaccine is found to be able to induce Tat-specific T helper (Th-1 and Th-2) cell responses (Longo *et al*., 2009). In another phase I clinical trial which is conducted in Spain to study the effect of recombinant MVA-B, expressing the fused Gag-Pol-Nef (GPN) polyprotein and monomeric gp120, the trial evoke specific T cell response in the majority (92.3%) of the immunized volunteers (Gómez *et al*., 2011). Such research findings become a promising forwards when replication-competent Sendai virus (SeV)–Gag HIV-1 vaccine is found to be able to primed functional and durable HIV-specific T-cell responses and boosted antibody responses (Nyombayire *et al*., 2017). Besides to this, neutralization-sensitive strains of HIV can be neutraliz by DNA prime, recombinant oligomeric Env protein boost regimen (Spearman *et al*., 2015).

5. RECOMBINANT VIRAL VECTORS AS HIV VACCINE

Genetically modified viruses (GMVs) are being increasingly used as live vaccine vectors (Evans *et al*., 1999). In another way the tissue culture passage of viruses can also mutate many viruses by maintaining their infectious capacity but lose their pathogenic potential (Daniel *et al*., 1992). Genetically modified vectors, expressing one or more HIV genes, are among the most promising HIV candidate vaccines (Johnston and Flores, 2001). Currently, different viral vectors such as attenuated poxvirus vectors and recombinant adenoviral vectors become a potential candidate in HIV vaccine development (Zhang *et al*., 2007; Choi and Chang, 2013). Most effective T cell responses against HIV in non-human primate (NHP) model has been approved to be evoked by recombinant serotype 5 adenoviral vector (Ad5) vaccine (Duerr *et al*., 2006).

Recombinant canarypox live vector which expresses the hybrid HIV-1 gpl60 and gp41 genes containing gpl20 sequences from MN isolates and gp41 sequences from HIV-1 LAI isolates has been proved to rose neutralizing antibodies against homologous HIV-1 MN strains (Pialoux *et al*., 1995). The safety profiles of these live vectors are excellent and can elicit HIV-specific immune responses (Zhang *et al*., 2007). Another Clade-B'/C-based HIV-1 candidate vaccine trial which expresses env, gag, pol, nef, and tat in a MVA viral vector, the vaccine is found to be well-tolerated and elicit durable humoral and cellular immune responses (Vasan *et al*., 2010). The research findings result found by Gudmundsdotter *et al*. (2009); Afolabi *et al*. (2013) and Joachim *et al*. (2015) suggest that recombinant Modified Vaccinia Ankara (MVA) can be used to induce immune responses against HIV-1 in humans even though the general concerns over the safety of using live attenuated HIV vaccines which are insurmountable obstacle to extend this approach to human trials (Johnson and Mathieson, 2000).

6. ATTENUATED HIV VACCINES

Viruses such as HIV can be attenuated using genetic engineering modern tools to introduce mutations or deletions in specific viral genes which are expected to confer immunogenicity without causing AIDS (Chinombe and Ruhanya, 2015). Live attenuated HIV vaccines can be enough effective to provide protection against wild-type strains infection (Blower *et al*., 2001). The magnitude of $CD8^+$ and $CD4^+$ SIV specific T cells induced by live attenuated virus (LAV) vaccination showed promising outcome after pathogenic viral challenge (Watkins, 2012). Simian immunodeficiency viruse strains with Nef-deletion have shown promising immune protection against pathogenic SIV in rhesus macaques (Sahni and Nagendra, 2004; Girard *et al*., 2006). Non-pathogenic HIV-1 strain that contains deletions in the Nef gene and U3 region of the long-terminal repeat has found to have the potential to evok protection against HIV (Dale and Kent, 2000). However, as the attenuated strain could cause AIDS in some vaccinated individuals live attenuated HIV vaccines may not be completely safe (Blower *et al*., 2001). The approach of designing and developing an HIV vaccine by attenuating the viral particles is flawed (Letvin, 2002) because naturally attenuated HIV mutants have found to progress to AIDS in human subjects infected with such types of strains (Learmont *et al*., 1999).

7. CURRENT PROGRESSES AND CHALLENGES IN THE WAY FOR HIV VACCINE DEVELOPMENT

Even though RV144 trial is the only vaccine trial against HIV-1 to show high degree of efficiency (Shin, 2016) there are more than 187 separate HIV-1 vaccine clinical trials conducted since 1987 (O'Connell *et al*., 2012). Since 1985, there have been at least five Phase III efficacy trials of candidate HIV-1 vaccines, even if all trials were total failures, except RV144 trial in Thailand which elicited a mediocre 31.2% protection (Karasavvas *et al*., 2012; Girard, 2015). RV144 is the only HIV vaccine that has been proved to have modest efficacy (Tanuma, 2014). Such promising success of HIV-1 vaccine clinical trial, conducted in Thailand, offers an optimism that a protective HIV-1 vaccine is not impossibility, rather it showed that vaccination against HIV could provide modest protection for HIV infection (Yu *et al*., 2012). In addition to the promising scientific progress observed in RV144 clinical trials, the

identification of broadly neutralizing monoclonal antibodies, like VRC01 with more than 90% neutralizing capacity of natural HIV-1 isolates (Kwong *et al*., 2012) and the promising result observed from passively administered b12 broadly reactive neutralizing antibodies (b12 bnAbs) to provide adequate protection against simian-human immunodeficiency virus huge doses inoculated into rhesus macaques (Hessell *et al*., 2009). This revealed new opportunities for HIV vaccine development. The DNA/adenovirus becomes promising approach as this approach has stimulated most cross-reactive T-cell immunity (Emini, 2002). Early-phase human clinical trials with recombinant FPV and MVA HIV constructs are also ongoing (Letvin, 2005).

Despite of these major progresses have been made to understand the scientific basis for HIV vaccine development and the rapid expansion of HIV vaccine candidates in terms of number and type, we are still in struggle to develop potent HIV vaccine up to date (Duerr *et al*., 2006; Esparza, 2013). This is due to the virus extraordinary sequence diversity and its ability to continually evolve in order to escape the host immune response and the lack of clearly defined the immune protection mechanism against HIV infection (Ajbani, 2016).

AIDSVAX is the first HIV vaccine to reach a phase III efficacy trial, but has not shown the potential to eradicate HIV (Frisch and Robson, 2011). The failure of an antibody-based HIV vaccine approach led researchers to attempt protection against HIV by cellular immune responses, as observations both in simians and humans had shown that $CD8^+$ T-cell responses were critical to control viral replication (Idoko and Isa, 2005). Current efforts in the development of HIV vaccines are hampered by high genetic variability of the virus driven by the error-prone reverse transcriptase and lack of clear immune correlates of protection in humans (Barouch, 2008).

8. CONCLUSIONS AND THE WAY FORWARD

HIV vaccine development has proven to be difficult in view of the tremendous genetic variability nature of the virus; the absence of significant information on the immunological protection mechanism against HIV; and the lack of good animal models. Despite of these setbacks in the last decades, the development of exciting new technologies, the great promise obtained from RV144 clinical trial and the recent identification of broadly neutralizing HIV-1 antibodies enable us to approach HIV vaccine development in ways that were previously unanticipated. In the past clinical trials have shown that vaccine elicited cellular or humoral responses have been found insufficient to control transmission and infection. The prime-boost HIV vaccine, RV144 which demonstrated an efficacy of 31.2%, showed hope for the future and can be serve as a proof that an effective HIV vaccine is possible. Understanding the unique challenges in the development of HIV vaccine is the major key in creating breakthroughs and to come to a solution. Therefore, most probably vaccines that elicited both cellular and humoral responses will be an effective HIV vaccine. For this achievement, different vaccine designing and development strategy combinations should be re-evaluated.

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