Eduvest – Journal of Universal Studies
Volume 4 Number 9, September, 2024
p- ISSN 2775-3735- e-ISSN 2775-3727

THE LATEST DEVELOPMENTS IN HIV VACCINES

I Ketut Agus Somia[1], Gerry Setiawan[2]
[1,2] Fakultas Kedokteran, Universitas Udayana, Indonesia
Email: agus.somia@unud.ac.id, gerrysetiawanlay@gmail.com

ABSTRACT

Medical knowledge of HIV and AIDS is rapidly evolving, leading to increased understanding of the disease, its immunology, and clinical manifestations. Antiretroviral therapy has provided a means of controlling but not curing the disease. However, new challenges are emerging. A vaccine is one prevention tool that remains elusive. Research over the past 40 years illustrates how difficult it is to induce effective immunity against this virus. Progress of vaccine development has been hindered by the extensive genetic variability of HIV, our limited understanding of immune responses required to protect against HIV acquisition, and funding issues. Since the beginning of HIV vaccine development, it is worth noting that there have been many advances and innovations to make HIV vaccine more effective and safer.

KEYWORDS *HIV, vaccine, history of HIV vaccines, HIV vaccine development*

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection and Acquired Immunodeficiency Syndrome (AIDS) cases continue to increase and become a global health problem. Globally, there are approximately 39 million people living with HIV infection by the end of 2022. Of these 39 million people, 37.5 million are adults (15-49 years old) with HIV, and the remaining 1.5 million are children <15 years old. WHO reports that by 2022, 630,000 people will die from HIV-related diseases (WHO, 2023b). At the Southeast Asian level, the prevalence of HIV-infected people based on WHO data in 2018 was 3.8 million (WHO, 2023a). HIV infection is certainly also a challenge for Indonesia because it is one of the countries with HIV cases that have not decreased every year. The prevalence of HIV in Indonesia is recorded at around 640,000 people. The overall HIV prevalence is around 0.3% with an annual incidence of 46,659 (in 2018), 50,282 (in 2019), and 41,397 (in 2020) (Merati et al., 2021). Based on data from the Ministry of Health in 2016, there was a decreasing trend in AIDS-related mortality rate from 2004 (13.66%) to 2016 (0.57%) (Indonesia., 2016).

How to cite: I Ketut Agus Somia, Gerry Setiawan. (2024). The Latest Developments In Hiv Vaccines. Journal Eduvest. *4*(9): 8118-8131
E-ISSN: 2775-3727
Published by: https://greenpublisher.id/

Although the mortality rate due to AIDS in Indonesia is reported to have decreased, the number of incidents of HIV infection has not decreased significantly, so this is certainly still a big challenge to overcome. One of the efforts that can be a hope in overcoming this is the HIV vaccine. HIV vaccines are believed to have great utility in infection prevention efforts and can even function as therapeutic vaccines. However, HIV vaccine development still faces many challenges. These challenges include the high genetic variability of HIV, the low immune response that occurs after the vaccine is given, the lack of understanding of immunity, and of course, cost. There have been some promising studies, but unfortunately, they have not yet yielded the expected results. HIV vaccines are developed with various approaches, namely protein-based vaccines, peptide-based vaccines, DNA-based vaccines, viral vector-based vaccines, *broadly neutralizing antibodies* (bNAbs) based vaccines and finally *messenger ribonucleic acid* (mRNA) based vaccines. Although there are many challenges in vaccine development, the hope to develop safe and effective vaccines remains by studying the results of previous research over the past 40 years as well as the emergence of several new technologies in vaccine development (Development, 2022; Larijani et al., 2019).

As HIV vaccine development efforts continue in the world, the authors believe that we, as a society, should follow or, if possible, participate in these developments. The literature review entitled "Recent Developments in HIV Vaccines" was prepared with the aim of providing readers with information on the principles of approach, results, and obstacles in the development of HIV vaccines to date. Reflecting on the case of the Covid-19 pandemic that has passed, when the Covid-19 vaccine was circulated in Indonesia, there were several groups who refused to even believe in the truth and effectiveness of the Covid-19 vaccine. Therefore, the author hopes that this literature review can provide good information to readers about the latest developments in the HIV vaccine, so that events such as the Covid-19 vaccine do not occur again in the HIV vaccine. Hopefully, when a safe and effective HIV vaccine is found in the future and can be widely circulated, the Indonesian people can quickly accept the existence of this HIV vaccine and not hesitate and fear or even refuse to obtain it.

Human Immunodeficiency Virus **(HIV)**

The *human immunodeficiency virus* (HIV) is thought to have originated in Kinshasa in the Republic of Congo before 1920 when HIV was transmitted from chimpanzees to humans. Until around the 1980s, it was unknown how many people were infected with HIV or had *Acquired Immune Deficiency Syndrome* (AIDS) (Tatoud et al., 2021).

There are two main types of HIV, HIV-1 and HIV-2. HIV-1 has four groups divided by phylogenetics, namely groups M (*main*), O (*outlier*), N (non-M, non-O), and P, which is a genetically unique HIV *strain*. Group M HIV-1 has spread to all regions of the world and it is the virus responsible for the global HIV pandemic. Group O infections are rare and limited to people living in Central Africa. Group N and P infections are less common and are only found in Cameroon (Bennett & Blaser, 2015)(Bertels et al., 2018).

HIV measures 100 nm in diameter and has a capsule surrounding its RNA genome. HIV viral RNA contains Gag, Pol and Env genes, which encode important viral proteins typical for retroviruses. The *gag* gene encodes structural core and matrix proteins (p24, p7, p6, p17), the env gene encodes gp120 and gp41 glycoproteins that reside on the viral envelope useful for binding to the CD4 receptor. In addition, various enzymes required for the HIV replication cycle such as reverse transcriptase, integrase and protease are regulated by the *pol* gene. In addition, the HIV genome also contains six regulatory genes (tat, rev, nef, vpr, vpu, and vif) that facilitate viral replication and evasion from the host immune system (Khalid et al., 2021).

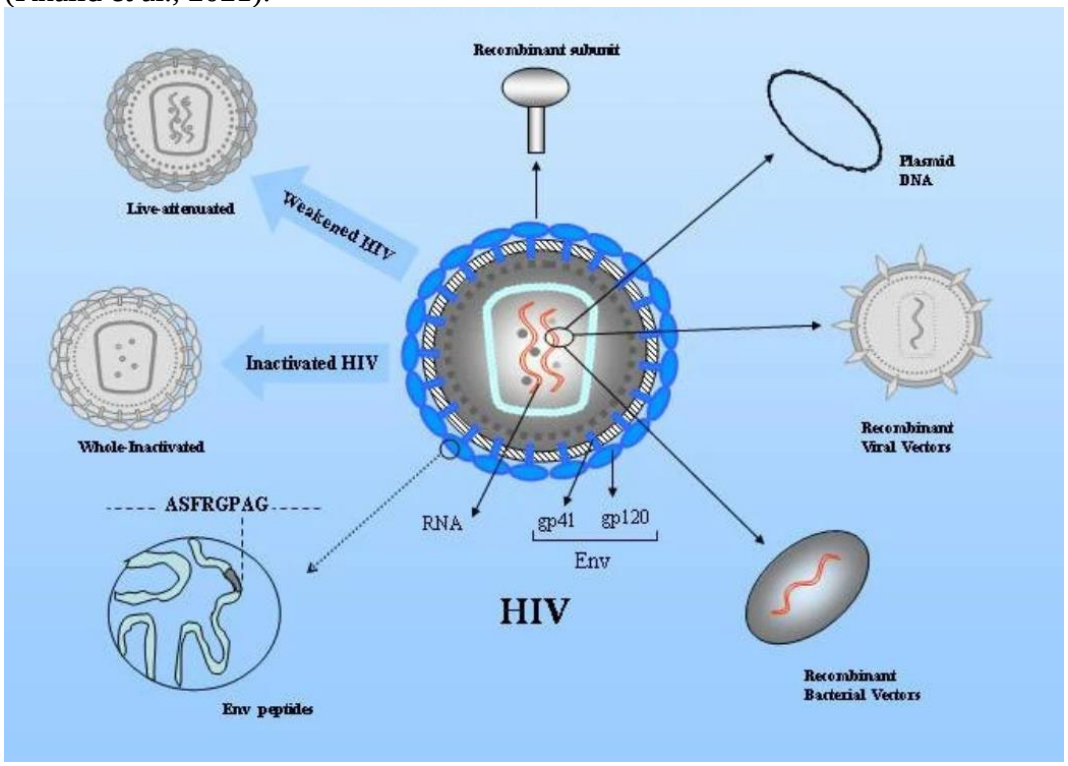


Image 1. Structure of the HIV virus which is the target of HIV Vaccine Development

RESEARCH METHOD

This study used a literature review method to explore the latest developments in HIV vaccine development. The review aimed to collect and analyze existing scientific literature, including clinical trial results and experimental findings related to various HIV vaccine approaches. The various vaccine platforms reviewed include protein-based vaccines, peptides, DNA, viral vectors, broadly neutralizing antibodies (bNAbs), and mRNA-based vaccines. The main data sources used were articles from peer-reviewed scientific journals, clinical trial reports, and data from global health organizations such as the World Health Organization (WHO) and the National Institute of Allergy and Infectious Diseases (NIAID). Inclusion criteria for

literature selection were studies discussing clinical and pre-clinical trials of HIV vaccines and papers describing challenges in vaccine development.

The data collection process involved searching for articles through online databases such as PubMed, Google Scholar, and institutional repositories using specific keywords such as "HIV vaccine development," "bNAbs vaccine," and "mRNA vaccine for HIV." The collected data were then qualitatively analyzed using a thematic approach, where each study was grouped based on the type of vaccine platform. The results of the studies were analyzed to evaluate the effectiveness of the immune response, the safety profile, as well as the obstacles faced in vaccine development.

RESULT AND DISCUSSION

Hiv Vaccine

Vaccines, in general, are specially prepared antigens that are introduced to the *host* with the aim of providing immunity against a specific disease. Vaccines contain one or more immunogens that resemble the microorganisms that cause a particular disease and are generally derived from attenuated or inactivated infectious agents or only their toxins, or use one of their surface proteins (Shapiro, 2020).

HIV Vaccine Development Approach

There are several types of HIV vaccine approaches in the research process, such as DNA vaccines, peptides, proteins, and others.

1. Protein-based vaccines

The principle of protein-based vaccines is to introduce recombinant proteins from a specific infectious agent to the host immune system so as to elicit the desired immune response. Over the past few decades, HIV vaccine trials have included almost all viral products, specifically proteins within the virus, with the aim of triggering cellular immunity to viral proteins. These viral proteins include Gag, HIV structural units, RT, Int and Pol, catalytic units, *Trans-Activator of Transcription* (TAT) regulatory viral products, and regulatory factors (Nef, vif, Vpu, Vpr). Unfortunately, none of them have been proven to be practically effective.

The first reported HIV vaccine was researched in 1987. VaxSyn, a protein-based vaccine produced by MicroGeneSys, became the first vaccine for HIV. VaxSyn works on the *envelope* protein gp160. VaxSyn then continued to phase 2 clinical trials but unfortunately was declared ineffective in producing antibodies that could provide protection. Furthermore, there are two vaccines based on the gp120 protein, namely VAX004 and VAX003. The VAX004 vaccine underwent efficacy trials starting in 1998 in the United States while VAX003 underwent efficacy trials in Thailand, but unfortunately these two vaccines have also not succeeded in demonstrating the ability to prevent HIV infection (Ng'uni et al., 2020).

One of the other protein-based vaccine developments is the GSK *Biological HIV Vaccine* which is designed as a therapeutic vaccine. This vaccine study aimed

to assess the efficacy and safety of a fusion protein (p24-RT-Nef-p17) on viral load reduction in HIV-1 infected adult patients who were not taking ART. Again, results from the vaccine study showed that the vaccine had no effect on HIV-1 viral load, CD4+ T-cell count, delayed ART initiation, or prevention of HIV-1-related clinical events.

Another study used Tat protein as a base, with the aim of assessing the immunogenicity, safety and therapeutic effects of the HIV-1 Tat vaccine in HIV-1-infected volunteers who did not have anti-Tat antibodies. Results after 48 weeks showed that the Tat vaccine was safe, immunogenic and also able to reduce persistent immune system disorders despite ART therapy. The vaccine also induced anti-Tat antibodies in the majority of patients (79%). These results suggest that Tat immunization is an effective intervention to improve ART efficacy. In addition to this study, there are two other Tat protein-based studies, namely Tat Oyi and TUTI-16. The Tat Oyi study provided safe results and successfully reduced HIV RNA and DNA. The TUTI-16 study was also safe and immunogenic but had no effect on HIV control after ART termination. However, despite these promising results, the Tat protein-based vaccine has not been able to control HIV relapse after ART termination.

2. Peptide-based vaccines

Peptide-based vaccines are specific vaccines using short chains of specific amino acids from pathogen antigens. Immune responses can be triggered directly against sub-immunodominant epitopes. Moreover, several *strains* and different life cycle phases can be targeted with the use of multi-epitopes. The production of peptides is considered easier, simpler and faster compared to protein-based vaccines. The use of peptides is also cost-effective using the *Solid Phase Peptide Synthesis* (SPPS) approach. In addition, this type of vaccine is generally water-soluble and can withstand simple storage conditions. Another advantage of peptide antigens is that they have very little chance of inducing an autoimmune or allergic response.

Vacc-4x is a peptide-based vaccine developed in 2007. Vacc-4x, is one of four synthetic peptide-based vaccines designed with the aim of inducing and sustaining a cellular immune response against HIV. These peptides consist of a portion derived from the HIV p24 *gag* protein. The study was a *multinational double-blind* study that administered the vaccine to ART-treated patients. There was a significant difference in viral load at week 48 and week 52 between the Vacc-4x and placebo groups. The study also reported an increase in viral counts again after ART cessation, but the placebo group showed a viral titer that was three times higher than the group that received the vaccine. The vaccine showed immunogenic results and was effective in inducing proliferative responses in CD4 and CD8 T cell populations (Fidler et al., 2020).

3. DNA-based vaccines

DNA vaccines or plasmids, are composed of small pieces of DNA. DNA plasmid antigens have the potential to induce humoral and cellular immune responses against the virus. When a target cell is infused with a DNA vaccine, the

encoded protein will become a major *histocompatibility complex* (MHC). There are several DNA vaccine trials that have been conducted, namely Ad26, MAG pDNA and PENNVAX-B (Gag, Pol, Env) + *electroporation*. The Ad26 vaccine study used type 26 adenovirus vectors that had the Gag, Pol, Env genes inserted in the hope of eliciting an immune response but unfortunately the results of this vaccine study were not reported. Research on the development of DNA-based vaccines for HIV has been ongoing since 1994. The MAG (multi-antigen) pDNA study used Gag, Pol, Nef, Tat, Vif, and Env genes with or without interleukin-12. This DNA vaccine consists of two main plasmids. The results of the MAG vaccine study in 2015 showed that this vaccine can trigger CD4+ responses but cannot trigger CD8+ T cell responses.

The PENNVAX-B vaccine study with a similar concept showed quite good results in that in addition to being safe and well received, the vaccine successfully generated T cell responses to at least one of the three antigens (Gag, Pol, Env). The vaccine also showed important results in inducing CD8 T cell responses, which are important in the management of chronic HIV infection.

4. Viral vector-based vaccines

Viral vectors are used in vaccine development from the ability of the virus to infect host cells. These viral vectors can facilitate vaccine production as they can induce a cytotoxic T cell response through intracellular antigen expression, which will lead to the elimination of virus-infected cells. However, there are safety issues with this type of vaccine, such as its expression being achieved by viral integration and this is thought to pose a risk of malignancy. Another obstacle is the presence of pre-existing immunity to the viral vector due to previous exposure and the development of neutralizing antibodies that may decrease vaccine efficacy. Adenoviruses are the most widely used vectors due to their potential to induce immune responses to foreign antigens.

As time went on, a more complex approach was thought of for the creation of an HIV vaccine. In the same year, HIVAC-1e, the second viral recombinant vaccine, was developed. This vaccine underwent phase 1 clinical trials in the United States and a T cell response was obtained in the study subjects, but the response was only temporary so that antibodies could not be formed and the protective function against HIV was not obtained. ALVAC-HIV was developed in 1993 and was the first HIV vector-based vaccine.

In later developments, vaccines were targeted to stimulate T cells. Early studies that examined T cells were the HVTN 502 test (1993) and Phambili/HVTN 503 which was a vaccine with a viral vector. The final results of this study in 2008 showed that the immune response did not protect subjects from HIV. In addition, STEP/HVTN was launched in 2004 and is classified as a viral lineage vaccine.

Several vector-based vaccines have been tested, including ChAdV63.HIVcons + MVA.HIVconsv, HIVAX, and JS7 DNA + MVA62B. In phase I trials, the ChAdV63.HIVcons + MVA.HIVconsv vaccine was reported to be safe, immunogenic, and could affect existing immune responses. However, in a phase 2 study conducted by Fidler and colleagues, the vaccine, which was intended as a therapeutic vaccine in combination with ART (Arunachalam et al., 2020),

failed to show significant benefits when compared to therapeutic efforts in HIV patients using ART alone. The HIVAX research vaccine examined a lentivirus vector-based vaccine administered to subjects already receiving ARVs, based on the results of a phase I study, the vaccine studied was reported to be safe, triggered CD4 and CD8 T cell responses, and also surpassed pre-existing immune responses. The JS7 DNA + MVA62B vaccine in phase I trials also showed quite good results. The vaccine successfully triggered CD8 responses without any sign of decline.

Table 1. Research on viral vector vaccines. (Arunachalam et al., 2020)

Research	Phase	Results	Recent developments
ChAdV63.HIVcons + MVA.HIVconsv	II	No significant benefit of therapeutic vaccines combined with ART compared with ART alone	2020
HIVAX	I	Safe, can elicit strong CD4 and CD8 T responses, beyond existing immune responses	2017
JS7 DNA + MVA62B	I	Successfully elicits a CD8 response and shows no sign of decline.	2017

5. *Broadly Neutralizing Antibodies* (bNAbs) based vaccines

Broadly neutralizing antibodies (bNAbs) are a type of antibody that can recognize and neutralize various subtypes of the HIV virus. 20 - 30% of individuals who contract HIV infection produce bNAbs 2 - 4 years post infection. The development of bNAbs vaccines for HIV has been longstanding and continues. bNAbs work by binding to the Env protein on HIV which is a protein required by the virus to bind to the host T cell CD4 receptor. nNAbs were first identified in the late 1990s, and since then, researchers have been working to understand how they work and how to stimulate their production through vaccination. Vaccine targets are leading to the emergence of *broadly neutralizing antibodies* (bNAbs) that can neutralize the majority of HIV strains. 2009 saw the first bNAbs vaccine with a study showing that a combination of bNAbs could protect monkeys from an HIV-like virus. This finding increased interest in the development of a bNAb vaccine for humans. In 2015, researchers reported success in stimulating the production of bNAbs in mice using immunogens targeting *germline* precursors. Since then, several clinical trials have been conducted to test the safety and effectiveness of bNAb vaccines in humans (Fortner & Bucur, 2022; Roark et al., 2021).

The bNAbs vaccine works by presenting a series of immunogens to the immune system that target the *germline* precursors of bNAbs, which are forms of antibodies that are not fully mature and have not undergone the necessary mutations to be effective against HIV. By targeting these precursors, the vaccine aims to enable the immune system to recognize and respond to HIV and produce bNAbs. Once produced, the bNAbs will bind to the HIV envelope glycoprotein, preventing

the virus from entering and infecting the host cell. Unlike traditional vaccines that only recognize certain types of the virus, bNAbs can recognize and neutralize different types of HIV subtypes, making it a promising approach to HIV prevention and treatment. However, the development of an effective bNAbs vaccine for humans is still ongoing, and more research is needed to improve the effectiveness of this vaccine (Maruggi et al., 2019).

One method to generate bNAbs is by using molecules that resemble Env. Injection of molecules that resemble *Env* proteins is expected to stimulate the production of bNAbs. One example of a vaccine that uses this concept is BG505.SOSIP.664 gp140, which is currently in phase 1 trials. Another method that can be used is to use HIV nanoparticles for *germline-targeting*. This method uses nanoparticles designed to resemble *Env* gp120 which aims to activate B cell precursors which then when mature can produce bNAbs. The third method is to use a B cell *lineage* vaccine by injecting it several times. The first injection uses the initial Env protein and then the next injection is done using the evolved Env protein so that this method is expected to trigger B cells to form bNAbs. Vaccine trials using this method are currently in phase I.

6. *Messenger Ribonucleic Acid* (mRNA) based vaccine

The COVID-19 pandemic in 2020 accelerated the development of mRNA vaccines, with Pfizer-BioNTech and Moderna successfully developing and obtaining emergency use authorization for their COVID-19 mRNA vaccines within one year of the start of the pandemic. These vaccines have shown high levels of efficacy in clinical trials and have been administered to millions of people around the world. Overall, the history of mRNA vaccines spans several decades, with significant advances in mRNA vaccine technology and development occurring in the last two decades, culminating in the development and successful use of COVID-19 mRNA vaccines.13 The rapid development of mRNA-based COVID-19 vaccines has also influenced HIV vaccines. The first RNA-based vaccine study was the IAVIG002 vaccine in 2021. Then in 2022, there was an mRNA 320 vaccine. Currently, clinical trials regarding mRNA are still ongoing.

The mechanism of action of mRNA vaccines is to use *messenger* RNA to instruct cells to produce proteins that trigger an immune response. The mRNA is synthesized in the laboratory and then injected into the body, where it mimics a viral infection by utilizing host cells to translate the mRNA as the corresponding antigen and trigger a strong humoral and cellular immune response. Being completely synthetic, almost any mRNA sequence can be designed, synthesized and delivered as a vaccine to be tested in the human body in a short period of time. The host's natural immune system has the ability to detect and respond to viral RNA sequences, so mRNA vaccines can trigger efficient natural immune responses, including the production of chemicals and proteins such as interleukin-12 (IL-12) and tumor necrosis factor (TNF) at the injection site, which are essential for generating effective adaptive immune responses to the integrated antigen (Xu et al., 2020).

The use of mRNA vaccines to treat HIV is still in its early stages, namely pre-clinical and early clinical trials. Several pre-clinical studies have been conducted to

develop HIV mRNA vaccines, and the results show promising humoral and cellular immune responses. One approach being investigated is the use of mRNA vaccines in combination with latent reversal agents (LRAs) and blockade antibodies to target latent reservoirs and prevent the spread of the virus. Currently, a phase I/IIa clinical trial is underway to investigate this combination strategy in HIV-1 infected patients (Pardi et al., 2019).

Several studies have been initiated to research different types of mRNA vaccines against HIV. These studies are mainly conducted by the *National Institute of Allergy and Infectious Diseases* and the *International AIDS Vaccine Initiative* (IAVI). These studies were developed in collaboration with Moderna. In the HVTN302 study, healthy participants are injected with one of three mRNA vaccines intramuscularly at a dose of either 100 µg or 250 µg and then given *boosters* at the second and sixth months. The participants will have blood tests and fine needle biopsies of their lymph nodes.

Another study, IAVIG002 examined the efficacy of eOD-GT8 nanoparticles for *germline-targeting* using an mRNA approach. Healthy participants will be injected with mRNA-1644 first and then followed by mRNA-1644v2-Core to stimulate precursor B cells that will produce bNAbs. The results will be compared with participants injected with mRNA-1644 or mRNA-1644v2-Core alone.

Table 2. Vaccines - mRNA vaccines undergoing clinical trials

Research	Vaccines	Research sponsor	Phase	Participants
HVTN302	• BG505 MD39.3 mRNA, • BG505 MD39.3 gp151 mRNA, • BG505 MD39.3 gp151 CD4KO mRNA	*National Institute of Allergy and Infectious Diseases* (NIAID)	I	108 estimated participants, HIV negative, age 18 - 55
IAVIG002	• eOD-GT8 60mer mRNA Vaccine (mRNA-1644) Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core)	*International AIDS Vaccine Initiative* (IAVI)	I	56 estimated participants, HIV negative, age 18 - 50

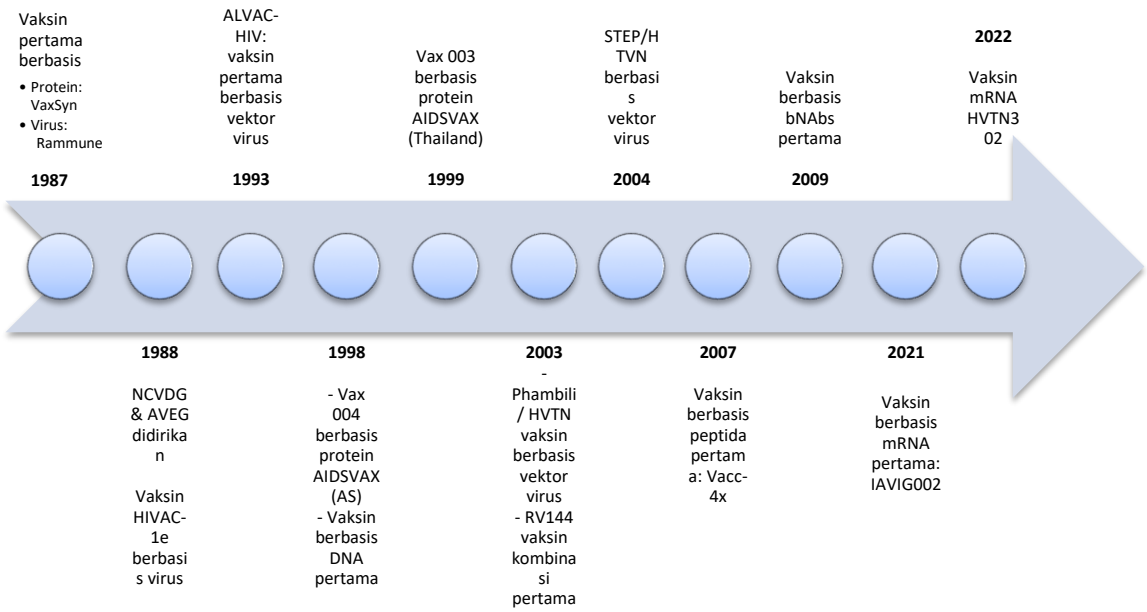
7. Combination-based vaccines

In combination-based vaccines there is a combination of 2 previously existing vaccines. One example is the RV144 vaccine which is a combination of ALVAC-HIV (vCP1521) which is a recombinant vaccine combined with the *canarypox* vector and AIDSVAX B/A which is a bivalent protein. In addition, there is the Ad26 mosaic vaccine developed by *Jannsen Pharmaceuticals* which is a combination of a viral vector (adenovirus serotype 26 or *modified vaccinia Ankara*), *boost protein* and other immunogen sequences. The vaccine focuses on stimulating T lymphocyte and antibody responses by incorporating the *envelope* into the vaccine design. Unfortunately, in the phase 3 MOSAICO study this vaccine failed to show meaningful efficacy (Kim et al., 2021).

RV144, the first combination vaccine studied since 2003 by the US Army and the Thai Ministry of *Health* supported by the *National Institutes of Health* (NIH), in its phase 3 study showed an efficacy of 60% at 12 months after vaccination but decreased to 31% 3.5 years after vaccination (Mdluli et al., 2020).

Vaccine Journey

The journey of HIV vaccines to date has not happened instantly but has gone through various stages. The *timeline of* HIV vaccine development based on when the research began can be seen in Figure 2.



HIV vaccine development *timeline*

The advantages and disadvantages of each HIV vaccine *platform* are summarized in Table 3.

Table 3 Advantages and disadvantages by HIV vaccine *platform*

(Hokello, Sharma, & Tyagi, 2021; Jones, Moody, & Thompson, 2020; Lee, Kumar, Jhan, & Bishop, 2018; Liu, Cao, Sun, & Li, 2020; Malonis, Lai, & Vergnolle, 2019)

HIV Vaccine Base	Disadvantages	Pros
Protein	Not likely to induce a strong or long-lasting immune response. Hampered by high genetic variability in HIV	Uses non-infectious parts of the virus. Safer compared to vaccines that use vaccines with viral vectors
Peptides	Generates weaker immune response compared to other *platforms*, may require additional *adjuvants* to increase immunogenicity Although it can target specific epitopes, HIV has high genetic variation, which may affect the efficacy of vaccines with this *platform*.	Small molecules so that they can generate immune responses to specific epitopes, especially to epitopes that have a low probability of mutation. Relatively low cost
DNA	The resulting immunity tends to be low compared to vaccines with other *platforms*.	Relatively easier to produce and can induce both humoral and cellular responses
Virus Vector	There is an increased risk of HIV infection in subjects who were previously *immunocompromised*.	Induces a strong and long-lasting immune response
bNAbs	It is still a complex and costly approach.	Can neutralize a wide variety of HIV *strains*, potentially providing a long protective effect
mRNA	The poor stability of the vaccine requires specialized storage. This vaccine can also induce a very strong immune response, which can potentially cause major side effects.	Can be designed and produced in a short period of time making it suitable for *emerging* disease management such as HIV Can induce humoral and cellular immune responses

Barriers

Barriers to HIV vaccine development from the biological field include the high mutation rate during viral replication. There are four major HIV groups with nine subtypes worldwide, no suitable animal models, and limited information on correlation with immune protection. The high mutation rate of HIV is due to the

error-prone *reverse transcriptase of* the virus, and it has been estimated that there are 1-10 mutations per genome per replication cycle. This mutation rate leads to changes in the capsule glycoprotein, which allows the virus to evade the immune system. Despite genetic diversity in the capsule glycoprotein, this structure remains the primary target of neutralizing antibodies. Another difficulty in developing a universal vaccine is that 10-20% of HIV-infected patients in some parts of Africa are infected with two or more viral variants (subtypes and recombinant forms) circulating in the area (Pitisuttithum & Marovich, 2020).

The lack of suitable animal models presented a barrier for researchers before the early 1990s. Chimpanzees, a species classified as *Non-Human Primates* (NHP), can contract HIV, but do not experience the same disease course as humans. This led the United States and Japan to separately develop SHIV, a *chimeric* virus with gag and pol genes from SIV and env genes from HIV, as it was a more pathogenically relevant model for HIV vaccine development. The current widely accepted standard animal model is the SHIV-infected macaque.

Researchers are also hampered by the lack of information on correlates of immune protection. This is due to the complex progression of HIV-1 infection, as the infection cannot be eliminated from the immune system. The virus has a *reservoir* in latent memory CD4+ T cells.

In addition to the above, another barrier to vaccine development is the lack of financial support, especially from the pharmaceutical industry. There is a gap between the resources and funding needed to develop an effective vaccine. Unfortunately, financial support for HIV vaccine research and development has been greatly reduced since 2010. About 85% of the funding comes from the US government and *the Bill & Melinda Gates Foundation*.

CONCLUSION

HIV is still a global health problem. Until now, HIV infection and AIDS continues to grow, but this development is also followed by the discovery and development of anti-retroviral drugs and HIV vaccines. These vaccine development approaches utilize immunologic approaches, however, they face challenges such as the extraordinary diversity and resistance of HIV, which will likely require a wide variety of immunologic approaches to obtain an effective vaccine. Efficacy trials are ongoing and advanced HIV vaccine approaches have resulted in new vaccine candidates. In this literature review of various HIV vaccine development approaches, *Broadly neutralizing antibodies* (bNAbs) and *messenger ribonucleic acid* (mRNA) based vaccines are the latest vaccine development approaches that have the opportunity to be the answer in one of the efforts to prevent HIV infection in the world.

REFERENCES

Arunachalam, P. S., Charles, T. P., Joag, V., Bollimpelli, V. S., Scott, M. K. D., Wimmers, F., Burton, S. L., Labranche, C. C., Petitdemange, C., & Gangadhara, S. (2020). T cell-inducing vaccine durably prevents mucosal SHIV infection even with lower neutralizing antibody titers. *Nature Medicine*,

26(6), 932–940.
Bennett, J. E., & Blaser, M. J. (2015). *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*.
Bertels, F., Marzel, A., Leventhal, G., Mitov, V., Fellay, J., Günthard, H. F., Böni, J., Yerly, S., Klimkait, T., & Aubert, V. (2018). Dissecting HIV virulence: heritability of setpoint viral load, CD4+ T-cell decline, and per-parasite pathogenicity. *Molecular Biology and Evolution*, *35*(1), 27–37.
Development, H. V. (2022). *NIH: National Institute of Allergy and Infectious Diseases. Accessed August 5, 2022. https://www.niaid.nih.gov/diseases-conditions/hiv-vaccine-development*.
Fidler, S., Stöhr, W., Pace, M., Dorrell, L., Lever, A., Pett, S., Kinloch-de Loes, S., Fox, J., Clarke, A., & Nelson, M. (2020). Antiretroviral therapy alone versus antiretroviral therapy with a kick and kill approach, on measures of the HIV reservoir in participants with recent HIV infection (the RIVER trial): a phase 2, randomised trial. *The Lancet*, *395*(10227), 888–898.
Fortner, A., & Bucur, O. (2022). mRNA-based vaccine technology for HIV. *Discoveries*, *10*(2).
Hokello, J., Sharma, A. L., & Tyagi, M. (2021). An update on the HIV DNA vaccine strategy. *Vaccines*, *9*(6), 605.
Indonesia., K. K. R. (2016). *Kajian Epidemiologi HIV Indonesia 2016. Published online 2017*.
Jones, L. D., Moody, M. A., & Thompson, A. B. (2020). Innovations in HIV-1 vaccine design. *Clinical Therapeutics*, *42*(3), 499–514.
Khalid, K., Padda, J., Khedr, A., Ismail, D., Zubair, U., Al-Ewaidat, O. A., Padda, S., Cooper, A. C., & Jean-Charles, G. (2021). HIV and messenger RNA (mRNA) vaccine. *Cureus*, *13*(7).
Kim, J., Vasan, S., Kim, J. H., & Ake, J. A. (2021). Current approaches to HIV vaccine development: a narrative review. *Journal of the International AIDS Society*, *24*, e25793.
Larijani, M. S., Ramezani, A., & Sadat, S. M. (2019). Updated studies on the development of HIV therapeutic vaccine. *Current HIV Research*, *17*(2), 75–84.
Lee, J., Kumar, S. A., Jhan, Y. Y., & Bishop, C. J. (2018). Engineering DNA vaccines against infectious diseases. *Acta Biomaterialia*, *80*, 31–47.
Liu, Y., Cao, W., Sun, M., & Li, T. (2020). Broadly neutralizing antibodies for HIV-1: efficacies, challenges and opportunities. *Emerging Microbes & Infections*, *9*(1), 194–206.
Malonis, R. J., Lai, J. R., & Vergnolle, O. (2019). Peptide-based vaccines: current progress and future challenges. *Chemical Reviews*, *120*(6), 3210–3229.
Maruggi, G., Zhang, C., Li, J., Ulmer, J. B., & Yu, D. (2019). mRNA as a transformative technology for vaccine development to control infectious diseases. *Molecular Therapy*, *27*(4), 757–772.
Mdluli, T., Jian, N., Slike, B., Paquin-Proulx, D., Donofrio, G., Alrubayyi, A., Gift, S., Grande, R., Bryson, M., & Lee, A. (2020). RV144 HIV-1 vaccination impacts post-infection antibody responses. *PLoS Pathogens*, *16*(12), e1009101.

Merati, T. P., Karyana, M., Tjitra, E., Kosasih, H., Aman, A. T., Alisjahbana, B., Lokida, D., Arlinda, D., Maldarelli, F., & Neal, A. (2021). Prevalence of HIV infection and resistance mutations in patients hospitalized for febrile illness in Indonesia. *The American Journal of Tropical Medicine and Hygiene*, *105*(4), 960.

Ng'uni, T., Chasara, C., & Ndhlovu, Z. M. (2020). Major scientific hurdles in HIV vaccine development: historical perspective and future directions. *Frontiers in Immunology*, *11*, 590780.

Pardi, N., LaBranche, C. C., Ferrari, G., Cain, D. W., Tombácz, I., Parks, R. J., Muramatsu, H., Mui, B. L., Tam, Y. K., & Karikó, K. (2019). Characterization of HIV-1 nucleoside-modified mRNA vaccines in rabbits and rhesus macaques. *Molecular Therapy-Nucleic Acids*, *15*, 36–47.

Pitisuttithum, P., & Marovich, M. A. (2020). Prophylactic HIV vaccine: vaccine regimens in clinical trials and potential challenges. *Expert Review of Vaccines*, *19*(2), 133–142.

Roark, R. S., Li, H., Williams, W. B., Chug, H., Mason, R. D., Gorman, J., Wang, S., Lee, F.-H., Rando, J., & Bonsignori, M. (2021). Recapitulation of HIV-1 Env-antibody coevolution in macaques leading to neutralization breadth. *Science*, *371*(6525), eabd2638.

Shapiro, S. Z. (2020). HIV vaccine development: 35 years of experimenting in the funding of biomedical research. *Viruses*, *12*(12), 1469.

Tatoud, R., Snow, W., & Esparza, J. (2021). A transformed global enterprise for an HIV vaccine. *African Journal of Reproduction and Gynaecological Endoscopy*, *24*(S7), e25822.

WHO. (2023a). *HIV. HIV/AIDS in the South-East Asia. Accessed October 4, 2023. https://www.who.int/southeastasia/health-topics/hiv-aids*.

WHO. (2023b). *HIV. The Global Health Observatory. Accessed October 4, 2023. https://www.who.int/data/gho/data/themes/hiv-aids*.

Xu, S., Yang, K., Li, R., & Zhang, L. (2020). mRNA vaccine era—mechanisms, drug platform and clinical prospection. *International Journal of Molecular Sciences*, *21*(18), 6582.