Recent Development on HIV Variants and HIV Vaccine

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ABSTRACT

Human immunodeficiency virus (HIV) is a virus from the Retrovirus family that attacks human immune cells, especially T lymphocytes. The increasing number of HIV cases requires a more effective preventive measure; among others, through vaccination. Although it has been about 40 years, there is no HIV vaccine yet. It can be because of many variations of HIV, and each country has its own dominant HIV variant. In addition, the ability of HIV to evade immune responses, high mutation rates, and limited experimental animals add to the difficulties in developing effective vaccines. As of May 2022, 16 vaccines have undergone phase I/II clinical trials. Among HIV vaccines that have already undergone phase III clinical trials, only RV 144 vaccine gave promising results, with efficacy reaching 31.2%. The development of the HIV vaccine continues to obtain a safe and effective HIV vaccine.

Keywords: *Human immunodeficiency virus,* HIV vaccine, HIV variant

ABSTRAK

Human immunodeficiency virus (HIV) merupakan virus dari famili *Retrovirus* yang menyerang sel imun manusia, terutama limfosit T. Kasus infeksi HIV yang terus meningkat, membutuhkan tindakan pencegahan yang lebih efektif antara lain dengan vaksin HIV. Namun, meskipun sudah sekitar 40 tahun, belum ada vaksin HIV yang diedarkan. Hal ini bisa karena banyaknya variasi HIV serta tiap negara memiliki varian HIV dominan yang berbeda. Selain itu, kemampuan HIV menghindari respons imun, laju mutasi yang tinggi, ditambah dengan keterbatasan hewan coba, menyulitkan pembuatan vaksin. Hingga bulan Mei 2022 terdapat 16 vaksin yang tengah menjalani uji klinis fase I/II. Di antara vaksin HIV yang sudah pernah menjalani uji klinis fase III, hanya vaksin RV 144 yang memberikan hasil menjanjikan, yakni efikasi mencapai 31,2%. Perkembangan vaksin HIV terus berlanjut untuk mendapatkan vaksin HIV yang aman dan efektif. **Ridwan Balatif, Fadlan Hafizh Harahap, Isni Dhiyah Almira. Perkembangan Varian HIV dan Vaksin HIV**

Kata kunci: *Human immunodeficiency virus*, vaksin HIV, varian HIV

INTRODUCTION

HIV infection continues to be a global health problem. Until now, no country has declared itself free from HIV infection. HIV infection can disrupt various aspects, such as the economy, health, and education.[1]

Various efforts have been made to overcome HIV infection, such as developing drugs to creating an HIV vaccine. Although HIV was discovered about 40 years ago, there has not been a single HIV vaccine approved in the broader community.[2] This article aims to add insight into the latest information on HIV variants and the development of HIV vaccines.

HIV

HIV is a virus that attacks the immune system or the body's immunity, especially T-CD4 lymphocyte cells. The immunity of infected individuals will gradually be decreased, resulting in more susceptibility to opportunistic infections, such as tuberculosis, fungal infections, parasites, viruses, and some types of cancer that people with a healthy immune can usually be overcome system.[3] Acquired immunodeficiency syndrome (AIDS) can be interpreted as a collection of symptoms or diseases caused by decreased immunity due to HIV virus infection.[4]

HIV is still one of the severe challenges in global public health. Until the end of 2020, 37.7 million people were infected with HIV worldwide; 36 million cases occurred in adults, with more women (53%) than men (47%) affected. Around 650,000 people death in worldwide from AIDS-related diseases in 2021.[5] In Indonesia, new cases of HIV infection from January-March 2021 reached 7650 patients, with a total of 427,021 cases of HIV infection in March 2021, mainly in the 25-49 year age group (70,7%) and men (62%).[6]

The HIV epidemic is not only had an impact on individual health but also on households, communities, and the development and economic growth of a country due to increased medical costs and decreased productivity. Although various effective prevention and treatment efforts have been carried out, it is still not evenly distributed, and it is still challenging to reduce cases. Difficulties in accessing health services, differences in

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treatment, stigma, and discrimination have proven to be significant barriers to this process.[7,8]

HIV MORPHOLOGY AND DIVERSITY

HIV is a virus from the Retroviridae family. There are two subfamilies Retroviridae namely Orthoretrovirinae and Spumaretrovirinae. The Orthoretrovirinae subfamily has several generation, one of which is Lentivirus. HIV belongs to the Lentivirus (Lenti-slow).[9] Lentivirus is characterized by a slow onset of disease, can cause immunosuppression, and with a cylindrical nucleocapsid nucleus.[10,11]

HIV has a spherical shape, 80-100 nm in diameter, enveloped, has a reverse transcriptase (RT), and diploid positive-sense linear ss-RNA.10,11 There are two types of HIV circulating globally, namely HIV-1 and HIV-2 (**Table 1**). HIV-1 is further divided into four groups, namely M, N, O, and P12-14; while HIV-2 is divided into nine groups, namely A-I.[12,13]

Previously, HIV-1 group M was divided into nine subtypes, A-D, F-H, J, and K, but in 2020 a new subtype, subtype L, was established.[20] Globally, from 2010-2015, subtype C became the most common subtype (46,6%).[21] The diversity of sequencing between subtypes reaches 17%-35%, depending on the subtype and region of the genome examined.[22,23] Subtype A is further divided into six subtypes namely A1, A2, A3, A4, A6, A7; subtype D is divided into three subtypes: D1-D3; and subtype F is divided into two: F1 and F2 subtypes.[24] In 2021, another new A8 subtype was discovered. The intragroup variation of A8 reached 4.0%-7.4%, while the genetic variation between A8 and other subtypes reached 8.1%-19.0%, depending on the subtypes and genome regions examined. Especially for the A5 subtype, no pure form or prototype was found, even though this A5 subtype is still classified as CRF26_A5U.[25]

When a person is infected with two or more subtypes of HIV-1, the virus can recombine its genome and form new recombinations. If new recombination spreads to three or more individuals who are not epidemiologically related, this recombinant is known as circulating recombinant form (CRF). In contrast to CRF, a unique recombinant form (URF) is applied if it is only found in an individual infected with more than one subtype.[22] Based on an update from the Los Alamos National Laboratory HIV database, 118 CRFs have been found in HIV-1 worldwide.[25]

The CRF and URF subtypes accounted for approximately 16.7% and 6.6% of cases of HIV infection globally in 2010-2015, respectively. HIV infection in Southeast Asia is dominated by the subtype CRF01_AE (72.8%).[21] The

Table 1. Differences between HIV-1 and HIV-2

Differences	HIV-1	HIV-2	Reference
Virus Origin	Simian immunodeficiency virus (SIV) from chimpanzee	SIV from *sooty mangabey*	13,14
Dominant Group	M	A and B	12,13,15
Location	All over the world	Predominantly in West Africa	13,15
Median Time Required to Develop AIDS	Faster (6,2 years)	Slow (14,3 years)	16
Perinatal Transmission	Higher (15-30%)	Low (1-5%)	17,18
CD4 Decrease Rate per Year	Higher (0,9%)	Low (0,4%)	16
Average CD4 Percentage at the Time of AIDS	Low (8,2%)	Higher (18,2%)	16
Mortality Rate	High (1,86-3,5 times)	Low	16,19

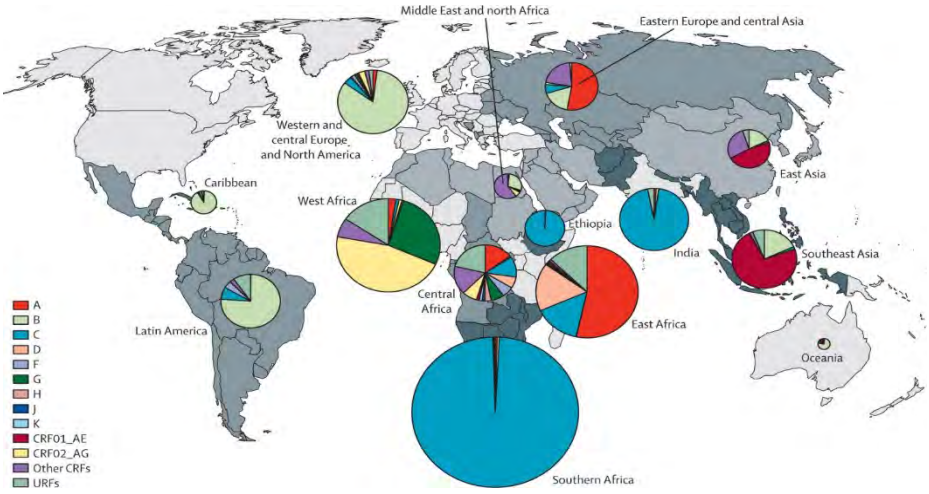

Figure 1. Regional distribution of HIV-1, CRF, and URF subtypes, 2010-2015.[23]

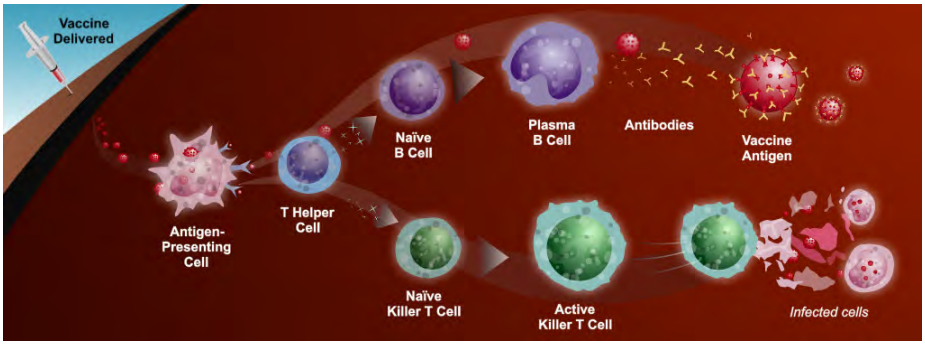

Figure 2. The mechanism of action of vaccines induces an immune response
Source: https://historyofvaccines.org/activities/how-vaccines-work

distribution of HIV-1 subtypes between regions can be seen in **Figure 1**. In Indonesia, the subtypes that dominate cases of HIV-1 infection are CRF01_AE (81.9%) and subtype B (12.4%).[27]

Each cycle of HIV replication can produce one mutation per genome. Four factors can cause the high mutation rate:[23]

1. The activity of the RT enzyme that results in the accumulation of transcription errors and HIV does not have the 3'à5' exonuclease enzyme that can repair genetic material.
2. High viral replication rate
3. The tendency of viruses to recombine during replication
4. Stress from host immunity

Basics of Vaccine

One of the most significant scientific achievements in history was the discovery of vaccines and their impact on spreading infectious diseases. The history of modern vaccination was first started in 1796 by Edward Jenner, a doctor in England. He observed that milkmaids exposed to cowpox (cowpox) had only mild symptoms and were protected from deadly smallpox. Jenner's discovery ushered in a new era of modern vaccines, and the term "vaccination" (Vacca = cow in Latin) emerged.[28]

Nearly 100 years after Jenner, Louis Pasteur produced a rabies vaccine in the 1880s, which marked the beginning of the development of new vaccines that, by the mid-twentieth century, vaccines for various diseases (such as diphtheria, pertussis, and typhoid) had been developed in the form of pathogens that inactivated or toxoid vaccines.[29]

Vaccines, like natural infections, act by initiating an innate immune response, which in turn activates an antigen-specific adaptive immune response **(Figure 2)**. Innate immunity is the first line of defense against pathogens that have entered the body which is formed within a few hours but is not specific for a particular pathogen and has no memory. Adaptive immunity provides a second line of defense, generally in the later stages of infection, characterized by a variety of lymphocytes and antibodies capable of recognizing and killing nearly all pathogens known to the immune system. Each pathogen (or vaccine) expresses antigens that induce cellular y immunity by activating a subset of T lymphocytes and humoral immunity by stimulating B lymphocytes to produce specific antibodies. After the elimination of the pathogen, the adaptive immune system forms an immunological memory, which includes the basis of long-term protection and the aim of vaccination. It is characterized by persistent antibodies and memory cells that can be rapidly reactivated upon subsequent

Table 2. Summary of vaccine clinical trials over the last 3 years.[48]

Candidate	Phase	Starting Date	Country	Description
mRNA-1644 (eOD-GT8 60 mer)	I	May 2022	South Africa, Rwanda	mRNA-based vaccine Trial name: IAVI G003 Target: 18 participants In phase I (IAVI G001) in 48 participants, 97% of participants were detected to have VRC01-class IgG B cells (neutralizing antibody precursors) – results have not been peer-reviewed.[52]
CH505TF	I	May 2022	United States of America	Protein subunit vaccine (gp120) Trial name: HVTN 300 Target: 12 participants In addition to receiving the CH505TF ch trimer vaccine, participants also received adjuvants in the form of 3M-052-AF (imidazoquinoline) and aluminum hydroxide.
BG505 MD39.3 mRNA BG505 MD39.3 gp151 mRNA BG505 MD39.3 gp151 CD4KO mRNA	Open label	Feb 2022	United States of America	mRNA-based vaccine Trial name: HVTN 302 Target: 108 participants
mRNA-1644 (eOD-GT8 60 mer) mRNA-1644 v2-Core (Core-g28v2 60 mer)	I	Nov 2021	United States of America	mRNA-based vaccine Trial name: IAVI G002 Target: 56 participants
Vaccine combination DNA-HIV-PT123 and AIDSVAX DNA-HIV-PT123 and CN54gp140 + MVA and CN54gp140	IIb	Jan 2020	Uganda, South Africa, United Republic of Tanzania, Mozambique	Vaccine combination Trial name: PV1/PrEPVacc Target: 1668 participants In a phase I trial of 132 participants, it was found that administration of the DNA vaccine significantly increased the response of CD4 T cells to the HIV envelope, and no serious side effects were reported.[53]
Ad26.Mos4.HIV,gp140	III	Oct 2019	United States of America, Argentina, Italy, Mexico, Peru, Poland, Spain	Viral-vector vaccine (adenovirus) Trial name: HVTN 706/ HPX 3002 Mosaico Target: 3900 participants In the Phase IIb trial on 2637 women, the vaccine efficacy reached 25.2% and there were no serious side effects due to the vaccine.[54]

exposure to the same pathogen.[30]

Vaccines can be divided into several types but work on the same principle. The types of vaccines now available are: live attenuated vaccines, e.g., measles/mumps/rubella and chickenpox; inactivated vaccines, for example, polio and diphtheria/ tetanus /pertussis; recombinant vaccines, e.g., HPV and hepatitis B vaccines, subunit vaccines; toxoid vaccine; mRNA vaccines; and viral vector vaccines.[30,31] Characteristics of an ideal vaccine include its ability to provide lifelong immunity, protection against all pathogenic variants, rapid and effective response in the body, immunogenicity in all age groups, protection even with a single dose, the potential for adverse reactions minimal, good tolerability, and cost effective.[32]

DEVELOPMENT OF HIV VACCINES

There are still many obstacles to developing an effective and safe HIV vaccine.

- The first obstacle is the extensive variety of HIV genetics. This genetic variation occurs due to mutation. This mutation changes the structure of the envelope (*env*) of the virus. Unfortunately, this *env* is the target of neutralizing antibodies. Furthermore, in specific populations, i.e., in Africa, around 10%-20% are infected with two or more HIV subtypes.[33,34] The second obstacle is the ability of HIV to evade the immune system. The mechanism presumably stems from the power of HIV to trigger RNA mutations through the methylation process. This methylation process occurs when HIV uses the enzyme 2'-O-methyltransferase to modify its RNA so that it is not recognized by host immune cells.[35] Another mechanism to evade the immune system is through the ability to move from between cells[36] and decrease the expression of major histocompatibility complex (MHC)-I through the Nef protein in viruses.[37]
- Other obstacles include a shortage of experimental animals and limited funding or interest from the pharmaceutical industry.[34]

Despite many obstacles, research is still ongoing to create a safe and effective HIV vaccine. Around 1984, Margaret Heckler stated that a vaccine would be available for testing in about two years.[38] In 1987, Zagurym, *et al*, experimented using a vaccinia vector expressing gp160. Zagury himself carried out this experiment; the result was that neutralizing antibodies were detectable but not sufficient to fight HIV infection.[39] After the first HIV vaccination study, various HIV vaccine studies overgrew regarding the type of vaccine used and increasingly better research methodology (pre-clinical and clinical tests).

However, many HIV vaccines did not give satisfactory results after clinical trials.[40-46] Several vaccine candidates have gone through phase III clinical trials,[44-46] but only clinical trial RV 144 provides sufficient efficacy for HIV prevention.[47,48] RV 144 trial used vaccine candidate ALVAC-HIV (vCP1521) with AIDSVAX B/E booster in Thailand. This trial offers new hope in HIV vaccine research. Approximately 31.2% efficacy was obtained from the phase III clinical trial.[47] The RV 144 clinical trial was also known to protect several HIV subtypes such as subtypes A, B, C, and CRF01_AE.[49]

Based on an update from The Global Advocacy for HIV Prevention (AVAC) until May 2022, there are 16 HIV vaccines currently undergoing clinical trials, most of which are in phase I/ II clinical trials.[48] There are only two vaccines currently undergoing phase III clinical trials, namely clinical trials with the names HVTN 706/HPX3002 Mosaico and HVTN 702.50 The HVTN 702 test has been discontinued due to no satisfactory efficacy (incidence rate of vaccine vs. placebo group: 3.4 vs. 3.3 per 100 person-years).[49] Although finished, participants in the trial were followed up.[48] A summary of the progress of clinical trials of vaccines over the past three years is shown in **Table 2.**

CONCLUSION

HIV is a virus that attacks the immune system. There are still two known types of HIV, namely HIV-1 and HIV-2. AIDS is a collection of symptoms or diseases caused by decreased immunity due to infection with HIV. Developing an effective and safe HIV vaccine still has several obstacles, including the wide variation of HIV genetics, the ability of HIV to evade the immune system, the shortage of experimental animals, and limited funding or interest from the pharmaceutical industry. However, research to create a safe and effective HIV vaccine continues. Based on the latest update from The Global Advocacy for HIV Prevention (AVAC) in May 2016, there are 16 HIV vaccines currently undergoing clinical trials, of which two are undergoing phase III clinical trials.

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