Project On

A review of the current status of the vaccine for the Human immune deficiency virus (HIV)

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Submitted By

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APPROVAL

This project, A review on the most recent research article, an evaluation of the HIV vaccine, submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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CERTIFICATE

This is to certify that the results of the investigation that are embodied in this project are original and have not been submitted before in substance for any degree of this University. The entire present work submitted as a project work for the partial fulfillment of the degree of Bachelors of pharmacy, is based on the result of author's (Md. Fahim Shahariyar, Id: 183-29-1339) own investigation.

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DECLARATION

I hereby announce that I am carrying out this thesis study under the supervision of "**Mr. Md. Mominur Rahman** (Lecturer)**"**, Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Impartial Compliance with the Bachelor of Pharmacy Degree Requirement (B. Pharm). This project, I declare, is my original work. I also state that neither this project nor any part thereof has been submitted for the Bachelor award or any degree elsewhere.

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Md. Fahim Shahariyar

Author

DEDICATION

I dedicate this work to my parents and to my teachers and my friends who stand by my side at my lowest situation.

ABSTRACT

There are two different types of lentiviruses that cause human immunodeficiency, both of which may infect humans. Acquired immunodeficiency syndrome (AIDS) is a condition in which the immune system progressively fails, enabling malignancies and life-threatening opportunistic infections to develop. It is caused by a combination of factors, including HIV infection, autoimmune illness, and a weakened immune system. The present status of the HIV vaccine is my primary motivation for doing this research. The investigation starts with a study of the relevant literature. For the purpose of this research, around thirty publications are analyzed. Finding relevant literature for this investigation was intended to be done via the use of Google Scholar, PubMed, and a variety of other websites. All of the information gathered is from the years 2000 to 2022. During the years 2000–2003, protein was used as the delivery vehicle for the CladeB/B-Env immunogen. Subsequently, during the years 2005–2007, CladeB-Gag/Pol immunogen was evaluated; however, the results did not demonstrate any effectiveness. In the combination immunogen CladeB-Gag/Pol CladeB/B-Env trial that took place between 2003 and 2009, the vaccination efficacy after 42 months was determined to be 31.2%.

Keywords: HIV, Pharmacological, Vaccine, Drug.

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Introduction

1.1. Vaccine

Vaccines are biological preparations used to actively develop immunity to certain infectious diseases. Vaccines include a substance that is meant to resemble the disease-causing germ; this ingredient is often taken from a weakened or dead strain of bacteria, a toxin generated by the bacterium, or a surface protein from the bacterium. Because of this molecule, the immune system is boosted. Vaccine method shown in Fig. 01 that first neutralizes the substance and then wipes out any linked germs the body meets in the future. Vaccines have the potential to both heal preexisting conditions and protect against future illnesses caused by "wild" viruses (to fight a disease that has already occurred, such as cancer). [2-5] Certain immunizations provide permanent sterile immunity, making them superior to others in their ability to prevent infections. The process of administering a vaccine to a human being is known as vaccination. Diseases like smallpox, polio, measles, and tetanus have been brought under control in large swaths of the world because vaccination is the most efficient technique of preventing their spread. The safety and effectiveness of vaccines have been extensively researched and verified, with examples being those used to prevent influenza, human papillomavirus, and chickenpox. According to the World Health Organization (WHO), there are now 25 vaccinations available for potentially fatal illnesses. Lady Mary Wortley Montagu, as mentioned in the preceding paragraph [9], introduced smallpox vaccine to Britain from Turkey in 1721. Vaccine and vaccination are both derived from the Latin word for "cowpox," Variolae vaccine. In addition to coining the term "vaccination," Edward Jenner is mostly credited for developing the idea of vaccinations and developing the first vaccine. In his work Inquiry into the Variolae vaccine, published in 1798, Using the protective properties of the cowpox vaccine against smallpox, Edward Jenner coined the phrase "herd immunity." To further acknowledge Jenner's contributions, French scientist Louis Pasteur suggested expanding the terms in 1881 to encompass the emerging field of preventative immunizations. [12] Vaccology is the scientific study of vaccines and the process by which new vaccines are created and introduced to the public.

History of vaccine

Before cowpox material was used in vaccinations, humans were protected against smallpox by a method known as "deliberate variolation" (heterotypic immunization). About the eleventh century, traditional Chinese texts first mentioned using variolation to treat smallpox. [13] There has to be more research done on this topic right now. Variation was first used, according to historical records, in China somewhere in the fourteenth century. Powdered smallpox material, mostly scabs, was blasted into the nose as part of the "nasal insufflation" procedure. The insufflation methods utilized by the Chinese in the 16th and 17th centuries were diverse. [14]: 60 In 1700, Martin Lister, a Chinese-based employee of the East India Company, informed Clopton Havers and him about the Chinese inoculation process, and the two of them subsequently reported it to London's Royal Society. [15] Mary Wortley Montagu, after seeing a variolation in Turkey in 1721, variolated her 4-year-old daughter in front of the Royal Court physicians in England. By the year's end, Charles Maitland had six prisoners at London's Newgate Prison participate in a carefully observed experiment in variolation. Because of the positive results of the experiment, the royal family's support of variolation has received a lot of attention. However, in 1783, just three days after receiving the immunization, British Prince Octavius tragically passed away. James Phipps, age 8, had no adverse reactions after receiving a smallpox immunization. Jenner had cowpox from a milkmaid who had touched infectious pus. [16] Jenner stated that his vaccine, introduced in 1798, was safe for both children and adults and could be transmitted from arm to arm, thereby decreasing reliance on an unpredictable supply from sick cows. Due to the vaccine's limited in vitro shelf life of 12 days, the Spanish Balmis smallpox vaccination expedition adopted the arm-to-arm distribution method to convey the vaccine to Spain's colonies in Mexico and the Philippines. Animal pox was used. [17] Since the cowpox vaccine was more secure, smallpox immunization was outlawed in England in 1840, despite the fact that the illness was still present at the time. Louis Pasteur, based on Jenner's prior work, introduced vaccines for chicken cholera and anthrax in the 1880s, raising vaccinations to a matter of national pride. Laws mandating vaccines were enacted, and a countrywide vaccination campaign was implemented. In 1931, researchers Alice Miles Woodruff and Ernest Goodpasture discovered that the fowlpox virus could replicate in the embryo of a chicken egg. As time went on, researchers stopped focusing on improving viral culture in eggs in favor of examining alternative virus production methods. Eggs were used for virus propagation in both the yellow fever vaccine (discovered in 1935) and the seasonal flu

vaccine (developed in the 1950s) (developed in 1945). When it comes to vaccines before 1959, eggs were the method of choice for viral propagation. Developmental media and cell culture have since taken their place. [18] The twentieth century witnessed the invention and widespread use of various vaccines, including those against diphtheria, measles, mumps, and rubella. The eradication of smallpox in the 1960s and 1970s and the discovery of a vaccine against polio in the 1950s were other crucial steps forward. Some of the most effective vaccinations of the twentieth century were developed by Maurice Hilleman. Some individuals may now take vaccines for granted because of how prevalent they have become. A number of important diseases for which vaccines are needed, such as herpes simplex, malaria, gonorrhea, and HIV/AIDS, lack adequate protection. [19-20]

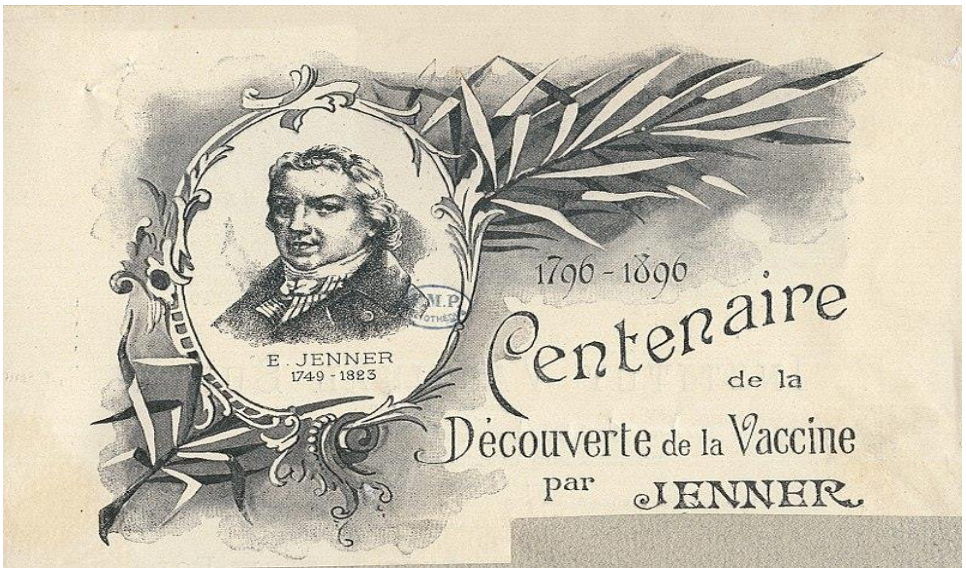

Fig 02: French print in 1896 marking the centenary of Jenner's vaccine

1.2. Different Types of Vaccines

Scientists created the first human viral vaccines using attenuated or weakened strains to generate an immune response without actually making the recipient sick. Scientists looked to cowpox, a poxvirus that is genetically related to smallpox but seldom causes serious disease on its own, to develop a vaccine against smallpox. Rabies virus was the first disease to be attenuated in a lab in order to develop a vaccine for humans. Scientists use a large toolkit of methods while developing vaccines. Toxins produced by bacteria, rather than the bacteria themselves, are the true pathogens in bacterial infections, hence components may take the form of inactivated or dead organisms or viruses, toxin fragments, or even merely pathogen fragments (this includes both subunit and conjugate vaccines). Live, attenuated vaccines are now recommended for protection against measles, mumps, and rubella (via the combination MMR vaccine), varicella (chickenpox), and influenza in the United States (in the nasal spray version of the seasonal flu vaccine). Live and attenuated vaccines are recommended as part of the treatment plan. Each kind of vaccine has its own unique set of requirements. Below, we'll go into further depth about each distinct kind of immunization. [21]

Attenuated Live Vaccines

There are a number of ways to develop attenuated vaccines. Common methods involve seeding cell cultures or animal embryos with the pathogenic virus (typically chick embryos). For instance, the virus is grown in a cell culture of embryonic chicks. Every time the virus is passaged, its ability to reproduce in chick cells improves at the cost of its ability to replicate in human cells. Many vaccine viruses need the production of approximately 200 separate embryos or cell cultures. Due to its reduced ability to multiply in human cells, the attenuated virus has potential as a vaccine. The virus undergoes a series of mutations whenever it is transferred to a person from a non-human host, making it recognizable by the immune system but unable to replicate efficiently inside the human body. The resulting vaccine virus lacks the ability to multiply to the point where it causes sickness, yet it may still elicit a protective immune response. [22] Vaccines raise valid concerns that the virus might revert to a form that causes disease. Vaccine viruses can undergo mutations during internal replication, which could result in a more dangerous strain of the virus. Due of the low reproductive potential of the vaccine virus, this is very improbable. However, the potential for mutations was taken into consideration during the development of an attenuated immunization. The oral polio vaccine (OPV) is a live inoculation that is swallowed rather than injected, and its mutation rate is low.

Paralyzing polio is extremely uncommon, but outbreaks can occur if the vaccine virus undergoes a virulent mutation. As a result, the inactivated polio vaccine (IPV) has replaced the oral polio vaccine (OPV) on the United States Recommended Childhood Immunization Schedule (IPV) because the protective effects of a live, attenuated vaccine last much longer. [23]

Killed or Inactivated Vaccines

An inactivated vaccine is an option if you are uneasy about receiving a live, attenuated one. Scientists often utilize heat or chemicals like formaldehyde or formalin to render a disease dormant while developing vaccines in this category. The infectious agent's reproductive ability is eliminated while it remains "intact," making it easily identifiable by the immune system. Since viruses are not often thought of as living entities, vaccines against them are sometimes referred to as "inactivated" rather than "killed" [24]. Once a virus has been eliminated or made latent, it cannot revert to a more dangerous form that might cause illness (as discussed above with live, attenuated vaccines). Vaccines on the United States's recommended vaccination schedule include those that are either lethal or inactivated, such as the inactivated polio vaccine and the seasonal influenza vaccine. However, they often only provide short-term protection and need several injections of the same vaccine in order to achieve long-term immunity. A Recommended Vaccination Schedule for Children (injectable).

Toxoids

In other cases, the sickness is not caused by the bacteria themselves but rather by a toxin they secrete. In the case of tetanus, for instance, the Clostridium tetani bacterium is not responsible for the onset of tetanus itself, but rather for the creation of the neurotoxin tetanospasmin. By rendering the symptom-causing toxin inert, it becomes feasible to create vaccines against this virus. This may be accomplished in a few different ways, the most common being the use of a chemical like formalin or heat, both of which are also used to kill or inactivate organisms or viruses before they are incorporated into dead or inactivated vaccinations. Vaccines containing toxoids are created from inactive forms of toxins. Toxoids are classified separately from "killed" or "inactivated" vaccines because they include an inactivated toxin rather than live germs or viruses.

Subunit and Conjugate Vaccines

Both subunit vaccinations and conjugate vaccines use just fragments of the whole virus or bacteria to provide protection. In order to elicit an immune response from the body, subunit vaccinations only display a small portion of the full-length pathogen. It's possible to do this with only one disease-related protein serving as the antigen. Subunit vaccinations include flu shots and acellular pertussis inoculations. Subunit vaccines are another kind that might be developed through genetic engineering. Inserting the gene for a vaccine protein into a different virus or into cultured vaccine-making cells may generate the protein needed for vaccination. Proteins for vaccines are generated either while the carrier virus is replicating or after the producing cell has completed its metabolic processes. By encouraging the immune system to produce antibodies against the targeted pathogen, the recombinant vaccine produced via this technology is very effective. The United States presently use a recombinant vaccine to defend against Hepatitis B. Genetic engineering has been used to generate a number of vaccines, including one that protects against human papillomavirus (HPV). A lower number of HPV strains are covered by one vaccine compared to four covered by the other vaccine. Each vaccination only uses a single viral protein from each type of HPV. These proteins lead to the creation of VLPs (viral-like particles) when they are expressed. These VLPs are non-pathogenic because they lack the infectious genes. Although they may not be able to completely prevent HPV infection, they do give some protection by stimulating the immune system. Conjugate vaccines, like recombinant vaccines, are created by joining two separate substances. Conjugate vaccines, on the other hand, include pieces of bacterial cell walls. Coatings like this are chemically bonded to a carrier protein to create a vaccine. However, the immune system will react strongly to the carrier protein, not the "piece" of bacteria that is supplied. Although the bacterial fragment does not pose a threat on its own, it may do so when fused to a carrier protein. Pneumococcal vaccines, used to prevent disease in children, are now manufactured with this method.

mRNA Vaccines

The United States and other countries across the world rushed to develop a SARS-CoV-2 vaccine in 2020, when the COVID-19 pandemic was already well under way. In "Operation Warpspeed," the United States government spent billions of dollars researching, developing, and commercializing a vaccine. Clinical trials of the vaccine would have been conducted next under normal circumstances (i.e., phase I, phase II, phase III, etc.). As a result of the public

health crisis, vaccine studies had to be expedited (phases I, II, and III simultaneously). By the end of 2020, two emergency vaccinations based on messenger RNA will have been approved for use in the United States. (We'll get into the nuts and bolts of getting approval for a third viral vector-based vaccination in the following part.) mRNA is encapsulated in lipid (fat) spheres using this method. Vaccine mRNA is made accessible to immune system cells after intravenous immunization. The encoded protein is generated by the cell and has structural similarities to the "spike" protein found on the surface of coronaviruses. The protein is released to other immune cells, where it sets off an immune response that searches for and kills coronaviruses producing that spike protein, along with any infected host cells.

Viral Vector

As early as 2021, the United States may provide a third immunization against the COVID-19 pandemic. A simian adenovirus was used to generate the vaccine, with much of its genome deleted so that space could be made for the messenger RNA needed to code for a coronavirus spike protein. Since simian adenovirus is now known to cause illness, mRNA vaccines and other viral vectors incorporate the virus' genetic material into the immune system through injection. An immune response is initiated when an immune cell produces a spike protein [25,26].

1.3.HIV

Human immunodeficiency viruses, or HIVs, are members of the retrovirus family Lentiviruses. As AIDS progresses, the immune system gradually weakens, placing the patient at risk for potentially fatal opportunistic infections and malignancies. Without treatment, a person infected with HIV has a 9 to 11 years life expectancy. [27] This is conditional on the subtype being addressed. [28] HIV is often transmitted by intimate or casual contact with infected blood, pre-ejaculate, sperm, or vaginal secretions. A mother may pass the virus to her unborn child via non-sexual means such as during pregnancy, birth, through exposure to blood or vaginal fluid, and through breast milk. [29-31] Different fluids may be tested for the presence of free HIV particles or HIV inside infected immune cells. Research on same- and opposite-sex couples has indicated that if the HIV-positive partner maintains a viral load below the detection threshold, then engaging in sexual activity without the use of a condom is safe. [32] CD4+ T cells (helper T cells), macrophages, and dendritic cells are only few of the primary immune cell types that HIV attacks. Multiple mechanisms, such as pyroptosis of abortively infected T cells, apoptosis of uninfected bystander cells, direct viral killing of infected cells,

and killing of infected CD4+ T cells by CD8+ cytotoxic lymphocytes that recognize infected cells [33], contribute to the low CD4+ T cell counts that are characteristic of HIV infection. If CD4+ T cell levels drop below a certain threshold, cell-mediated immunity is lost and the body becomes more vulnerable to opportunistic infections [34], which may contribute to the development of AIDS.

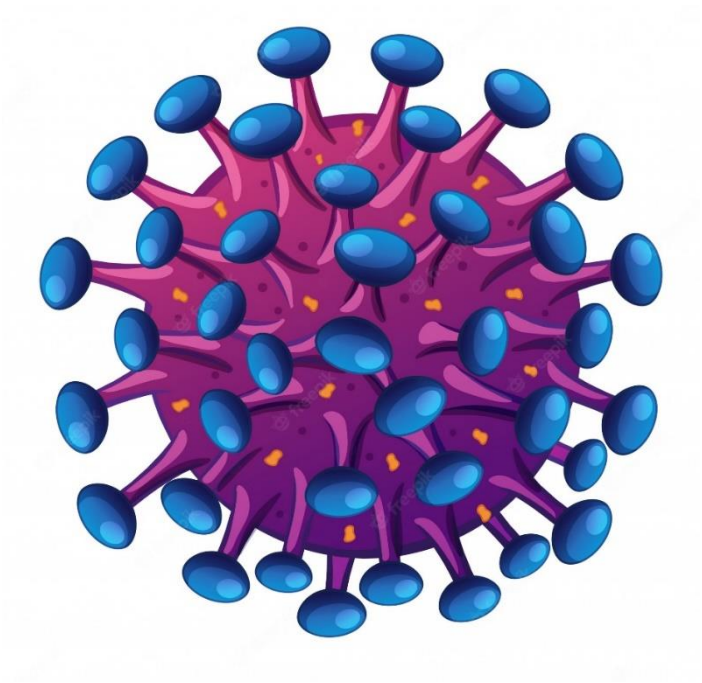

Fig 03: HIV

1.4. Major types of HIV

HIV-1

The HIV-1 subtype is the primary topic of this article since it is the most widely distributed and lethal strain of the virus. Every year, there are around 2 million new cases of the virus. [35] According to studies, HIV-1 may be divided into a primary subgroup (Group M) and one or more subgroups (Group N, O, and maybe even P). Each cluster is thought to have been caused by a different SIV transmission from human to human (but subtypes within a group are not). There are 39 open reading frames (ORFs) in the HIV-1 complete genome sequence across all six reading frames (RFs),[36] however only a small number of them are actually used by the virus.

Group M

More than 90% of HIV/AIDS cases are attributable to infection with HIV-1 group M, thus the "major" designation. Before 1960, HIV, the pandemic virus, was discovered at Léopoldville, then a part of Belgian Congo but today the capital of the Democratic Republic of the Congo (DRC), now known as Kinshasa (DRC). [37] This infectious illness was first discovered in chimpanzees and is caused by the SIVcpz virus. Additional subclades within the M group have been given letters according to the new categorization scheme. There are also CRFs, or "circulating recombinant forms," which are the offspring of recombination between viruses of different subtypes; these CRFs are also given a number. CRF12 BF is an example of a recombinant between subtypes B and F.

- ✓ Subtype A has been mostly concentrated in eastern Africa.
- ✓ Except in Japan and Australia, subtype B is the most prevalent kind worldwide (see) And studies show that subtype B is the most common in the MENA area.
- ✓ In 1964, it might have been introduced to Haiti by Haitian experts who had visited Kinshasa.
- ✓ Subtype C is the most common and is found mostly in Southern Africa, Eastern Africa, India, Nepal, and a few areas of China.
- ✓ "Subtype D" only occurs in the central and eastern areas of Africa.
- ✓ It has been determined that the correct designation for the strain previously known as subtype E is subtype CRF01 AE.
- ✓ This suggests that the original, single E strain is no longer extant, but its hybrid offspring is still there to prove its existence.
- ✓ Subtype F is found in Eastern Europe, Central Africa, and South America.
- ✓ The subtype G endemic zones are located throughout central Europe and Africa (and the CRF02 AG).
- ✓ It has been confirmed that subtype H is endemic solely to Central Africa.
- ✓ The "complex" recombination of several subtypes has resulted in the renaming of the strain formerly known as Subtype I to CRF04 cpx.
- ✓ Subtype J is mostly distributed in the Caribbean and North, Central, and West Africa.
- ✓ Subtype K has a very specific distribution, occurring exclusively in the Democratic Republic of the Congo and Cameroon.
- ✓ Subtype L has only been documented in the Democratic Republic of the Congo (DRC).

- ✓ The Kinshasa subtypes spread across the DRC through the country's railroads and waterways.

There are more subtypes within these groups, such as A1 and A2 or F1 and F2. To be cited. It was determined in 2015 that the recombinant subtype A/D/G strain CRF19 with a subtype D protease was responsible for the rapid spread of AIDS in Cuba. Because new species are certain to be found, this is by no means an exhaustive or final tally.

Group N

The letter N stands for "not M" or "not O." The HIV-1 variant strain YBF380 was discovered and recovered in 1998 by a Franco-Cameroonian partnership; it originated in a Cameroonian lady who had died of AIDS in 1995. Testing revealed that the YBF380 variation was in fact a novel HIV-1 strain; it reacted to testing with an envelope antigen from SIVcpz rather than Group M or Group O. Less than twenty instances of Group N infection have been reported since 2015. [41]

Group O

The O ("Outlier") group consists of around 100,000 individuals who are confined to West-Central Africa. Cameroon is thought to have the highest prevalence of Group O HIV, with 2% of all HIV-positive samples being from that country in research conducted in 1997. The SIVgor virus originally infected gorillas but has now jumped to humans (rather than the more common source, SIVcpz). [42] Concerns were raised since the group was invisible to early HIV-1 test kits. More accurate HIV testing can now distinguish between Group O and Group N infection.

Group P

A simian immunodeficiency virus (SIV) identified in wild gorillas (SIVgor) in 2009 was reported to be more closely related to the SIVs seen in chimpanzees (SIVcpz). In 2004, a Cameroonian lady residing in France was diagnosed with HIV-1, and researchers there later obtained the virus from her. However, until further human cases are uncovered, the researchers claimed that this sequence fit the criteria for a new Group P. [43]

HIV-2

Outside of Africa, however, HIV-2 is relatively unknown. HIV-2 was first identified in 1985 by a team led by Senegalese scientist Souleymane Mboup and his colleagues. The first incidence in the United States was reported in 1987. A Portuguese man who was being treated

at the London Hospital for Tropical Diseases in 1987 was the first person to be diagnosed with HIV-2. It is believed that he caught the illness when he was living in Guinea-Bissau between 1956 and 1966. His pathology report said he had cryptosporidium and enterovirus infection, but in 1987 his stored serum was tested and HIV-2 was found to be present [44]. Multiple HIV-1 testing kits may be used to detect HIV-2. Since 2010, eight distinct subtypes of HIV-2 have emerged (A to H). Only A and B travelled the globe at warp speed. While the original outbreak of Group A originated in West Africa, the virus has now spread to other parts of the globe, including Angola, Mozambique, Brazil, India, Europe, and the United States. While HIV-2 has a global reach, Group B HIV is confined mostly to West Africa. [45] While HIV-2 is exclusively found in West Africa, everyone who has had any kind of bodily fluid exchange with a West African, even casual encounters, should be tested for the virus if they develop HIV symptoms (i.e., needle sharing, sexual contact, etc.). [46] Located in the forests of Littoral West Africa, the sooty mangabey (Cercocebus atys atys) is endemic to a simian immunodeficiency virus (SIVsmm) that is very similar to the human immunodeficiency virus (HIV) (HIV-2). Phylogenetic study shows that the SIVsmm found in the sooty mangabeys of the Tai Forest in western Ivory Coast is most closely linked to the two strains of HIV-2 that have spread significantly in humans (HIV-2 groups A and B). [47] Six more HIV-2 subtypes, each of which has only ever been diagnosed in a single patient, have been discovered. Everything from sooty mangabeys to humans seems to have a common ancestry with these illnesses. Groups C and D were found in two Liberians, Groups E and F in two Sierra Leoneans, and Groups G and H in two Ivoirians. There is strong genetic evidence linking these HIV-2 strains to SIVsmm strains from sooty mangabeys in the same country as the human infection, indicating that humans are the ultimate host for these viruses. [48]

1.5.HIV Vaccines

Outside of Africa, however, HIV-2 is relatively unknown. HIV-2 was first identified in 1985 by a team led by Senegalese scientist Souleymane Mboup and his colleagues. The first incidence in the United States was reported in 1987. A Portuguese man who was being treated at the London Hospital for Tropical Diseases in 1987 was the first person to be diagnosed with HIV-2. It is believed that he caught the illness when he was living in Guinea-Bissau between 1956 and 1966. His pathology report said he had cryptosporidium and enterovirus infection, but in 1987 his stored serum was tested and HIV-2 was found to be present [44]. Multiple HIV-1 testing kits may be used to detect HIV-2. Since 2010, eight distinct subtypes of HIV-2 have emerged (A to H). Only A and B travelled the globe at warp speed. While the original outbreak

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B-cell immunogens

After more than a decade of research and development, clinical trials are underway for novel HIV vaccine candidates based on immunogens that are intended to trigger B cells of the immune system to make broadly neutralizing antibodies (bnAbs) against the virus. The vaccines rely on immunogens that are engineered to elicit a response from the body's B cells. Inspiration for this area of study came in 2009 with the identification of hitherto uncharacterized powerful bnAbs in large cohorts of HIV-positive individuals. [50-51] With the discovery of these antibodies, the field of HIV vaccine development entered a new era. By studying how bnAbs interact with the virus and destroy it in the lab, researchers have found multiple weak places on the HIV outermost protein, HIV Envelope, or Env, which is the target of all bnAbs. These gaps in the envelope protein of HIV were therefore identified. Immunogens for vaccines have been created using this data. Furthermore, the importance of engaging with the early B-cell populations that expressed germline antigen receptors was highlighted by a thorough understanding of the mechanism by which bnAbs change over time in HIV-infected individuals. A bnAb response may originate from germline B cells. Germline targeting refers

to the present effort by scientists to evoke these germline B cells by sequentially delivering a set of HIV vaccine immunogens tailored particularly for this aim. [52]

HIV trimer

In this animation, the trimer (gray) of HIV's outer Envelope protein cycles through many different conformations. The trimer is encased in a thick layer of sugar molecules (in purple) that do not activate the immune system. The immune system has a hard time producing broadly-effective antibodies because the large percentage of the trimer's surface area not coated in sugars is very variable (in red and yellow). IAVI's use of a photograph by Sergey Menis In a Phase I clinical study, IAVI and its collaborators found that the first of these customized immunogens, EOD-GT8 60mer, was able to make contact with the intended germline B cells. Collaborators of IAVI are investigating whether a second synthetic immunogen (Core-g28-v2 60mer) can further direct responses primed by EOD-GT8 60mer toward the production of bnAbs. IAVI G002 is a follow-up Phase I clinical study that includes these examinations. This is an important part of the complex and time-consuming process required to produce bnAbs. In this clinical research, Moderna's messenger RNA (mRNA) technology is being used to administer both immunogens. Starting in May 2022, participants in the IAVI G003 clinical trial will be asked to inject themselves with EOD-GT8 60mer using Moderna's mRNA platform in an effort to determine whether or not this method of immunization can elicit the same immune responses in Africans as were seen in the earlier IAVI G001 study. Another scientific advance that prompted the invention of immunogens for producing bnAbs was a better knowledge of the structure of Env [53]. These immunogens were developed to elicit virus-neutralizing antibodies in the immune system. Stabilizing and understanding Env in unprecedented depth has been limited for decades by the protein's instability, but recent advances have enabled scientists to overcome this obstacle. Researchers have developed vaccine immunogens that mimic the actual structure of Env, and they are now testing these products in humans. Research and clinical testing of some of these so-called native-like trimers are being funded by IAVI. Two sites in the United States and one in Kenya are conducting a Phase I clinical study of a candidate dubbed BG505 SOSIP.664 gp140, adjuvanted.

T-cell immunogens

Research into immunization techniques whose overarching goal is to elicit highly efficient and widely reactive antiviral T-cell responses against HIV is being supported by IAVI. The worldwide variety of HIV has inspired the creation of some of the most promising T-cell

immunogens now in the works. One of these approaches, the use of a so-called conserved HIV immunogen, is now in the clinical development stage, and it is receiving funding assistance from IAVI. This strategy involves combining viral epitopes, or parts of the virus, that are shared by the vast majority of the many different strains of HIV now in circulation. Through its clinical research partners, IAVI is also directing the development and assessment of next-generation T-cell immunogens. The VISTA scientific initiative, coordinated by African researchers at IAVI, is carrying out this work. The VISTA consortia are also investigating the mechanisms through which a small percentage of HIV-infected people, known as elite controllers, are able to manage the virus on their own. Infected people that fall into this category are called "elite controllers."

Innovative HIV vaccine technologies

The Institute for the Advancement of Vaccines and Immunization (IAVI) focuses its research efforts on developing vaccine technologies that can efficiently and effectively transport immunogens into the body. Therefore, IAVI and its partners are investigating two potential technologies for this purpose. The vesicular stomatitis virus serves as a primary research subject for the International Association for the Study of Viral Vectors (IAVI) due to its usefulness as a model for investigating the use of a replicating viral vector (VSV). A recombinant VSV vector containing an HIV Envelope gene is now undergoing preclinical testing. The HIV gene put into the rVSV vector has clinical promise, albeit it is currently only utilized for prophylactic immunization. IAVI is developing rVSV-vectored vaccine candidates for a variety of diseases, including Lassa fever, Marburg virus disease, Ebola Sudan virus disease, and COVID-19. IAVI is also looking at mRNA for its potential in vaccine delivery (mRNA). Proteins, which are generated in the cells following instructions from messenger RNA, are essential for the various bodily processes. Safely induces cells to produce a SARS-CoV-2 protein that triggers an immune response that provides protection against SARS; it was first used in authorized COVID-19 vaccines. IAVI and the biotechnology firm Moderna are conducting clinical trials termed IAVI G002 and IAVI G003 to investigate the use of messenger RNA (mRNA) for transporting HIV antigens and stimulating targeted immune responses.

1.6.HIV vaccine development

The potential exists for an HIV vaccine to serve either as a preventative or a curative vaccination. This would suggest that it would either prevent new cases of HIV infection or effectively treat those who already have the virus. Many believe that a vaccine against HIV would either stimulate an immune response in the recipient (known as "active vaccination") or include antibodies already effective against HIV (passive vaccination approach). [54] Two different active vaccination regimens, RV 144 and Imbokodo, were shown to be effective in preventing HIV infection in clinical studies. However, the benefit accrued by a minority and did not last for long. These factors are why no effective HIV vaccines are currently available.

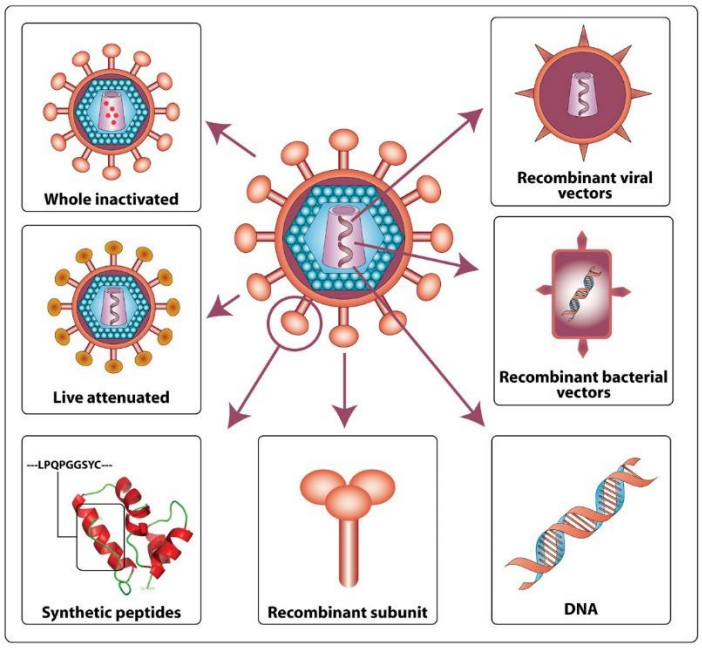

Fig 04: HIV vaccine development

1.7. Clinical trials

Several possible vaccines are in different stages of clinical testing.

Phase I: Most early efforts have concentrated on inhibiting the viral envelope protein. There have been at least 13 potential envelopes for gp120 and gp160. In the United States, the AIDS Vaccine Evaluation Group conducted the vast majority of these studies. Since gp41/gp160 are more difficult to produce and initially offered no evident benefit over gp120 forms, researchers

focused their efforts on gp120 instead. They have been used extensively in a wide variety of people groups, where they have been shown to be both safe and effective in boosting the immune system. Almost everyone who receives one develops neutralizing antibodies, although CD8+ cytotoxic T cells are very infrequently triggered by them (CTL). The production of neutralizing antibodies from envelope preparations derived from mammals has been more successful than that from yeast and bacteria. Getting and maintaining the high anti-gp120 antibody titers necessary to neutralize HIV exposure proved challenging, despite the fact that vaccination required many "booster" injections. [55] Given the availability of several recombinant canarypox vectors, recent research has shown promising findings that might be generalized to additional viral vectors. The number of volunteers with detectable CTL has grown more than if the dosage of the viral vector was increased simply because additional genes and epitopes have been added to the canarypox vectors. Volunteers' CTLs were effective in eliminating primary HIV isolates from their PBMNCs. These results imply that generated CTLs may have important physiologic consequences. Not all participants had the same experience, but some did have cells that could destroy HIV-infected cells from different clades. The canarypox vector is the first potential HIV vaccine to elicit cross-clade functional CTL responses. Beginning in the first few months of 1999, volunteers from Uganda participated in the first phase I trial of the potential vaccine on the African continent. The number of volunteers in Uganda who had CTL that can combat the A and D subtypes of HIV, which are the most frequent in Uganda, was tallied. Using a canarypox vector called ALVAC and a gp120 protein customized for the subtype C HIV that is widespread in sub-Saharan Africa, together with an adjuvant called MF59, a Phase I experiment called HVTN 100 was conducted in South Africa in 2015. Immune responses were rapid and robust in those who received the vaccination series, and the series was well tolerated. Peptides, lipopeptides, DNA, an attenuated Salmonella vector, p24, etc. are some of the other methods that have advanced to phase I trials in healthy persons. Vaccine candidates are being sought for in particular those induce cytotoxic T-cell responses in the majority of recipients, potent mucosal immune responses, and neutralizing antibodies that are effective against a broad spectrum of HIV main isolates. In 2011, researchers from Madrid's National Biotech Centre presented the results of a Phase I clinical study of a novel MVA-B vaccine. A majority of healthy vaccination recipients (92%), however, did develop an immunity. [56] Phase I clinical trial data for SAV001, a lethal whole-HIV-1 vaccine, was released to the public in 2016. The chemical and physical components of HIV employed in the vaccine were destroyed by the radiation. The 2012 Canadian study demonstrated its safety and the production of HIV-1 antibodies. Antibodies against gp120 and

p24 rose by 8 and 64 fold, respectively, following vaccination, according to Dr. Chil-Yong Kang of Western University's Schulich School of Medicine & Dentistry in Canada, who developed this vaccine. In 2021, researchers aim to test their "env-gag VLP mRNA platform" in a Phase 1 clinical trial for an mRNA vaccine against HIV. This is due to the positive results from the vaccine's use in primates and mice. [56] On January 17, 2022, IAVI and Moderna launched a phase I study of an mRNA-based HIV vaccine. On March 14, 2022, the NIH website announced, "NIH initiates clinical study of three mRNA HIV vaccines." The primary study will conclude in July 2023.

Vaccines to protect against HIV in Phase II

The V520 HIV vaccine, a recombinant Adenovirus-5, was tested in two Phase 2b trials (Phambili and STEP). The STEP research, a phase II clinical trial of a novel HIV vaccine, enlisted 3,000 patients from around the Americas, South America, the Caribbean, and Australia on December 13, 2004. [57] The research was funded in part by the NIH's National Institute of Allergy and Infectious Diseases (NIAID) and the pharmaceutical business Merck & Co. V520 was developed by Merck to enhance cellular immunity against HIV, prompting the body to produce T cells that destroy HIV-infected cells. This vaccination has been shown to be safe in preliminary, smaller-scale studies, with no adverse effects seen. Half or more of those who were vaccinated against HIV showed evidence of cellular immune responses. [58] V520 is infected with a less potent form of the adenovirus that contains three HIV genes (of subtype B) (gag, pol, and nef). In the regions where the research was conducted, HIV subtype B predominated. Adenoviruses are a major factor in upper respiratory tract infections like the common cold. There is no risk of HIV transmission or respiratory infection to test subjects since the vaccine is a weakened adenovirus containing just three HIV genes. Since it seemed that receiving the V520 vaccination increased the risk of HIV infection for certain patients, the experiment was slated to stop in September 2007. The fact that many individuals have been exposed to adenovirus previously means that they already have antibodies that target the recombinant virus. In contrast, a rapid immune response may be expected with many of the other viral vectors utilized in HIV vaccines, such as adenovirus vectors. Because of this, a T cell response to the inserted antigen is more difficult to develop (HIV antigens) Following the trial's findings, researchers reevaluated their approach to creating vaccines. HVTN 505, a phase IIb trial that started in 2009 but was terminated in 2013 due to its lack of relevance, began in 2009. Some HIV-infected persons, but not all, produce antibodies that may stop the virus from multiplying. People with this condition have gone decades without experiencing any

symptoms. Scientists have developed monoclonal antibodies that might one day be used to kill a broad variety of viruses. Clinical studies of passive immunization, using these antibodies, are now underway. [59] In May of 2016, the Human Vaccine Studies Network (HVTN) began two AMP trials with antibodies. In this study, researchers tested a monoclonal antibody for the first time in phase IIb trials for HIV prophylaxis. VRC01, a monoclonal antibody that targets the CD4 binding site, was not effective in preventing HIV infection in two separate studies, HVTN 703 and HVTN 704. The HVTN 705/Imbokodo phase IIb study was initiated in 2017 by Janssen and the HVTN to evaluate the mosaic vector vaccine Ad26.Mos4.HIV and the aluminum phosphate-adjuvanted Clade C gp140 vaccines, both of which are designed to provide protection against all known HIV subtypes. According to the National Institutes of Health (NIH), there was no statistically significant reduction in HIV infection in the Imbokodo Phase 2b research. Clinical studies for Cuba's Terevac-VIH vaccine were completed in 2018 and the vaccine is now in the next, more advanced stage of research, which is expected to be completed in 2019. Therapeutic HIV vaccines Biosantech developed a vaccine called Tat Oyi that attacks the tat protein in HIV. In a double-blind Phase I/II experiment in France, 48 HIV-positive patients who had achieved viral suppression with Highly Active Antiretroviral Therapy and had received the intradermal Tat Oyi vaccination were asked to discontinue taking antiretrovirals.

Vaccines to protect against HIV in Phase III

There are currently no Phase III candidates for passive HIV vaccines, however there are for active HIV vaccines. VaxGen announced the failure of its AIDSVAX B/E vaccine in North America in February 2003. The company cited a lack of a statistically meaningful decrease in the number of HIV-positive patients in the trial group as the reason for their conclusion. The RV 144 vaccination study in Thailand, in which ALVAC and AIDSVAX B/E participated, demonstrated that the vaccine was effective in protecting against HIV. AIDSVAX B/E and ALVAC were developed to combat the virus by targeting the gp120 envelope protein. The research included 16,395 individuals who did not have HIV. Of them, 8198 were given a sham therapy and 8197 were given two investigational vaccinations that target HIV types B and E, which are prevalent in Thailand. Participants were given HIV testing every six months for a whole three years. After three years, those who received the vaccination had a 30% reduced chance of contracting HIV than those who received the placebo. After accounting for the seven participants (two in the placebo group and five in the vaccination group) who were HIV-positive before receiving the vaccine, the difference shrank to 26%. [60] Individuals who

developed IgG antibodies against the V2 loop of the HIV outer envelope were 43% less likely to get HIV in the RV 144 study. However, those who produced IgA antibodies were 54% more likely to get HIV than those who did not (but not worse than placebo). Viral samples collected from vaccinated individuals showed mutations in the V2 region. The monkeys who developed antibodies against this area after receiving a SIV vaccination were more resistant to the virus. This suggests that developing vaccines that elicit an IgG response to the V2 loop will be a primary goal of future studies. The ALVAC/gp120/MF59 vaccines tested in the phase IIb-III trial HVTN 702/"Uhambo" in South Africa in 2020 were shown to be safe and cause no damage, however they did not prevent the spread of HIV. Uhambo vaccinations began in late 2016, and they will end in early 2020. [61] An HVTN 706/"Mosaico" phase III trial of the Ad26.Mos4.HIV plus adjuvanted clade C gp140 vaccine regimen will begin in 2020. An adenovirus vector vaccine and a protein vaccine make up the course of treatment. Adenovirus vector vaccines are developed to provide protection against a wide variety of HIV strains. [62] There are currently no therapeutic HIV vaccine candidates in phase 3 clinical trials.

1.8.Future work

Some research suggests that those infected with HIV and GB virus C (GBV-C), commonly known as hepatitis G virus, have a better prognosis than those without GBV-C. Patients may have additional differences, however. The potential for GBV-C to aid in the creation of an HIV vaccine in the near future has been noted [63]. Human studies on the efficacy of live attenuated vaccines against HIV have not been conducted, despite their shown efficacy against illnesses such as polio, measles, and rotavirus. The potential safety risk of the virus reverting back to its live form has prevented further clinical development of a live attenuated HIV-1 vaccine to this day. New strategies are being explored in the quest to create a safe and effective live attenuated HIV-1 vaccine. Such as the creation of a genetically modified strain of HIV in which the virus's codons (a sequence of three nucleotides that constitute genetic code) have been altered to depend on an artificial amino acid for correct protein translation, allowing the virus to properly multiply. Genetic engineering was used to change the virus's genetic coding. Because humans can't produce this amino acid, the virus can't reproduce and spread. [64]

1.9. Difficulties in development

As soon as it was established that HIV was the causative agent of AIDS, in 1984, U.S. Secretary of Health and Human Services Margaret Heckler predicted that a vaccine would be on the market within two years. [65] While it was possible to prevent HIV infection by training the adaptive immune system to identify viral envelope proteins, this did not work. A number of factors set an HIV vaccine different from the classic vaccinations that have traditionally been used to protect against disease. But nearly no one with AIDS survives the illness and recovers. Vaccines often provide protection against specific illnesses rather than infections themselves. It takes HIV a very long time to go from a latent state to an active one, which is when it causes AIDS. The most potent vaccinations are those that use either whole-killed or live-attenuated organisms. As utilizing a live retrovirus in a vaccine poses safety issues, it is important that HIV-1 be kept alive to maintain its antigenicity.

Fig 05: AIDS symbol

HIV structure

HIV structure cycle

The viral envelope has a greater variety of epitopes than those of many other viruses. Additionally, glycosylation, trimerization, and receptor-induced conformational changes in the gp120 protein obscure its functionally essential epitopes, making it difficult to block with neutralizing antibodies.

Most previously developed vaccinations have failed due to the following:

To start, HIV itself is constantly evolving. The virus population in an infected person typically changes so that it can evade the two main parts of the adaptive immune system, humoral

immunity (which is mediated by antibodies) and cellular immunity, because the virus can respond quickly to the selective pressures put on it by the immune system (which is mediated by T cells). Second, the HIV isolates themselves vary greatly from one another. There are several genetically distinct subtypes of HIV. So, it's important for any vaccination to elicit immune responses that are sufficiently broad to include this variation. Vaccines that don't protect against everything generally won't function. Since eliciting a robust antibody response is challenging, researchers have been attempting to develop a vaccine that stimulates the production of cytotoxic T-lymphocytes. It is also possible to create a single peptide consisting of the least variable components of all HIV strains currently in existence, which would be another method of dealing with the issue. [66]

Animal model

Baby chimpanzees at Tchimpounga Sanctuary (Republic of the Congo) The macaque, a kind of monkey, is the species of choice for testing vaccinations. Monkeys may be injected with SIV or the hybrid virus SHIV for scientific study. Vaccination was formerly an effective method of creating neutralizing antibodies, but this strategy has failed because it is so difficult to create antibodies that can inhibit the activity of heterologous main HIV isolates. Chimpanzees and macaques exposed to a similar virus were protected by vaccinations based on the viral envelope. Nonetheless, clinical experiments showed that persons inoculated with identical components still acquired HIV-1 when exposed to the virus. It may be challenging to employ an animal model for SIV due to the fact that it differs from HIV in many ways. It's important to remember that the animal model has both positive and negative aspects. A novel animal model has been developed to study how HIV manifests in humans. Activated CD4+ T cell death in mice has resulted in a generalized immune response, providing researchers with new tools to study HIV's behavior. [67] Studies conducted using a cytomegalovirus (CMV)-based SIV vaccine have demonstrated that it may prevent the transmission of the virus in monkeys, thanks to funding from the National Institute of Allergy and Infectious Diseases (NIAID). While a virus may reproduce and spread within days after infection, it can take weeks for a vaccination to activate T cells and send them to places where viruses are reproducing. Scientists speculated that vaccinations designed to maintain the functionality of effector memory T cells may halt viral replication before it took hold. [68-69]

1.10. How does the HIV vaccine work?

Those who are not HIV-positive are the ones who get a prophylactic HIV vaccination in the hopes of protecting them from contracting the virus in the future. The immunization primes the immune system to identify and attack the HIV virus in the event that the infection ever enters the body.

The purpose of my studies

HIV is a virus that hurts the immune system of the body. AIDS can happen if HIV is not treated.

At the moment, there is no good way to treat it. Once someone has HIV, they will always have it.

My aim of this study,

- To see the current condition of HIV in the world.
- To overview the current treatment of HIV.
- To see the current HIV vaccine program.
- To open a new area of higher studies.

Methodology

3.1. Introduction:

A literature review leads the examination. Around 30 papers are reviewed for this study.

3.2. Research Design:

This exploration was planned through google scholar, PubMed, and many other websites to find literature.

3.3. Method of Data Analysis:

After an assortment of information, all information was checked for precision and internal consistency to deny missing or clashing data, and those were discarded. Information investigation was done through Microsoft's dominant refreshed rendition. All collected information is from 2000 to 2022.

3.4. Ethical Considerations

Before beginning the information assortment, educated verbal permission was taken from the investigation members. The obscurity of the respondents was kept private, and study subjects were educated that they could have the option to leave the program.

Result & Discussion

4.1. The HIV vaccine efficacy trial

Immunogen	Delivery vehicle	Trial timeline	Result
CladeB/B-Env	Protein	2000-2003	No Vaccine Efficacy
CladeB-Gag/Pol	Ad5	2005-2007	No Vaccine Efficacy
CladeB-Gag/Pol CladeB/B-Env	Canary Pox protein	2003-2009	31.2% vaccine efficacy at 42 months.

Table 1: The HIV vaccine efficacy trial

Protein was used as the delivery vehicle for CladeB/B-Env immunogen trials in 2000–2003; trials of CladeB-Gag/Pol immunogen occurred in 2005–2007, but yielded no positive results. The combination immunogen CladeB-Gag/Pol CladeB/B-Env research from 2003-2009 [70] found a vaccination efficacy of 31.2% at 42 months.

4.2. HIV vaccine trials and immune response

Vaccine trial	Immune response	Result
VaxSyn	Neutralizing antibodies were detected	No vaccine efficacy
HVAC-1e	The vaccine was unable to confer protection against HIV	No vaccine efficacy
Vax004	The vaccine was unable to confer protection against HIV	No vaccine efficacy
HVTN505	The vaccine was unable to prevent infection or decrease viral load in vaccinated volunteers	No vaccine efficacy

Table 02: HIV vaccine trials and immune response.

According to reviews of numerous studies, VaxSyn, HVAC-1e, Vax004, and HVTN505 are the vaccines now being tested, and their immunogenicity and immune response are less stable [71].

4.3. Efficacy of RV144 vaccine efficacy rate

The RV144 human efficacy trial was a large-scale study that was completed in the summer of 2009 in Thailand. With these results, the first Phase III trial has shown promising effectiveness in preventing new HIV infections, although to a lesser extent. This study provides the first evidence that a vaccine to prevent HIV infection is feasible. A Canarypox vector harboring three synthetic HIV genes was used in the vaccination regimen tested in Thailand.

The number of new HIV-1 infections dropped by 31% during the trial of the RV144 vaccine. Boosted levels of antibodies that bind to the V1V2 region of the HIV Envelope (Env) were linked with a successful vaccine [72, 73].

4.4. Selected prophylactic HIV vaccine trials

Vaccine Trial	***Vaccine Immunogen***	***Efficacy***
Phase-III VAX003	AIDSVAX gp120 B/E Subtype-B MN & CRF01_AE	No efficacy vaccine
Phase-III VAX004	AIDSVAX gp120 B/B Subtype-B MN & GNE8	No efficacy
Phase-IIb HVTN 502	Ad5-gag/pol/nef Subtype B	Negative efficacy
Phase-IIb HVTN 503	Ad5-gag/pol/nef Subtype B	Negative efficacy

Table 03: Selected prophylactic HIV vaccine trials.

Several nations have applied for preventative HIV vaccines, including Phase-III VAX003, Phase-III VAX004, Phase-IIb HVTN 502, and Phase-IIb HVTN 503, but no efficacy has been demonstrated [74].

Conclusion

The body's defenses are attacked by the human immunodeficiency virus (HIV). If left untreated, the HIV virus that causes AIDS might worsen (acquired immunodeficiency syndrome). Since neither a vaccine nor a medication exist, there is presently no cure for HIV infection. The development of one is being studied by scientists.

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