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# The Prospect of an HIV Vaccine – a Review of Recent Research

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**Abstract**

*Human immunodeficiency virus, HIV, causes a progressive decline in humans' immune system, leading to development of AIDS. According to the World Health Organization, approximately 36.7 million people are living with HIV in the world, and more than 1 million people died in 2019. Vaccination is one effective method of stopping HIV from spreading around the world. So far, no effective vaccine against HIV has been found. Research teams are conducting 40 trials worldwide to find a vaccine against HIV. The nature of the virus, which is primarily characterized by an extremely high genetic variability, is a significant obstacle to vaccine development. The* RV144 *clinical trial has become a precursor to the use, and further development of biology system approaches for the correlation of infection risk. Analyzing the virus, which involved studying HIV genetic sequences, breakthrough infections, vaccine components, and observed functional immune relationships, helped scientists develop associations and differences that might be indicative of protection against the virus. The* RV144 *and RV217 clinical trials, which hypothesized that a vaccine could induce host immunity, are still speculation. Vaccines are adapted to current approaches to ensure that study participant are exposed to HIV antigens in a variety of ways to elicit mixed immune responses i.e., humoral, cellular, and innate arms of the host immune system using heterologous vaccines to induce non-specific immunity. HIV vaccine clinical trials are significant to humanity. Epidemiological data make us aware of the great problem we are dealing with. The medical experiment* RV144 *shows that it is possible to obtain a vaccine. We must hope that the nearest future in HIV prevention is an effective and safe vaccine.*

**Key words:** *HIV vaccine, RV 144*

## Introduction

Human immunodeficiency virus, HIV – so far, two types of this virus have been known: HIV-1 and HIV-2. HIV causes a progressive decline in humans' immune system, leading to the development of AIDS. According to the World Health Organization, approximately 36.7 million people are living with HIV in the world, and more than 1 million people died in 2019. The most significant number of people living with active infection are in Sub-Saharan Africa, about 25.7 million, in Western and Central Europe, about 2.5 million [1]. According to the National Institute of Hygiene, in Poland, from the implementation of the research from 1985 to December 31, 2019, HIV infection was found in 25.544 people, 3.768 AIDS cases were reported; 1.429 sick people died [2]. From the beginning of 2017, there were nearly 10.000 patients under antiretroviral treatment in Poland [3]. People access to medical services and antiretroviral therapies vary considerably across the world. Third world countries cannot afford the cost of antiretroviral treatments for most patients. The U.S. President's Global AIDS Relief Program (PEPFAR) and heroic efforts to curb the HIV pandemic are still insufficient to equalize the opportunities for treatment [4]. Economic barriers, totalitarian political systems, and an uneducated society keep HIV a death sentence in some parts of the world rather than a chronic disease that can be controlled through antiretroviral therapy.

Vaccination is one effective method of stopping HIV from spreading around the world. So far, no effective vaccine against HIV has been found. Research teams are conducting 40 trials worldwide to find a vaccine against HIV. A review of the literature and research will bring closer the current state of knowledge on the invention of the HIV vaccine.

## The essence of the problem with the invention of a vaccine against HIV

Research teams around the world are trying to get an effective HIV vaccine; this discovery would become one of the most important events of

the 21st century. Therefore the financial outlays and social expectations are huge. The central aspect is that humans do not develop natural protective immunity to HIV infection. Except for rabies, vaccines only exist for diseases for which there is specific immunity. There are people in the world who remain infected with HIV but do not develop clinical disease symptoms for a long time, and this is a tiny group of people called "elite controllers". Unfortunately, the overwhelming majority, as many as 99% of people, are not able to control the infection themselves, in the absence of treatment [5]. Elite controllers, however, still produce the virus and suffer the consequences of inflammation. Another problem in the invention of a vaccine is the absence of a specific response. It remains the immune, cellular, and antibody functions, which are poorly understood. Since the host immune response to HIV is incapable of completely eradicating the virus, developing a vaccine to elicit an effective immune response presents a particular challenge since a natural infection does not provide any blueprint for vaccine design.

The nature of the virus is a significant obstacle to vaccine development. It is primarily characterized by an extremely high genetic variability. Modeling studies demonstrate that the virus is sufficiently variable to obstruct the typical host development of broadly neutralizing antibody responses that require extensive somatic mutation in the immunoglobulin gene locus and deviation in immune tolerance mechanisms [6]. The virus is so flexible that, thanks to its ability to evade Tc cell responses, many forms of the virus can survive, not necessarily in a single variant.

Scientists cite HIV latencies as another significant problem in vaccine development. The human immunodeficiency virus genetically integrates into the host's chromosomes. Recent studies show that HIV latency may be related to how at least some variants of the virus are made. The infected cell is most often re-infected with multiple options of the virus, allowing genetically recombinant forms to emerge in reactivated mutant infections [7]. Host cells containing the reactivated ones are relatively rare in the presence of an antigen. They are, therefore, relatively insensitive to antibody-dependent cellular cytotoxicity (ADCC) and other forms

of immune surveillance. Attempts to develop an effective HIV vaccine on a global scale have evolved. To date, only six clinical trials have been conducted with the efficacy of the vaccine. Scientists focused on monomeric HIV envelope proteins, combined with canarypox viral vectors and adeno-induced HIV genes, either alone or in combination with HIV DNA [8]. Due to well-founded safety concerns, no methods based on viral attenuation or virion inactivation were included in clinical trials. Historically, the technique that has been effective and best known for vaccine development for many years has been eliminated.

**A review of the most promising studies**

The clinical study "RV144", which was conducted in Thailand on more than sixteen thousand men and women randomly assigned to receive placebo or a combination of canarypox vector vaccine (ALVAC-HIV vCP1521) and recombinant HIV glycoprotein 120 (gp120) product of B and E subtypes (AIDSVAX B / E) in 2003-2009, has demonstrated potential protection against HIV. So far, this is the only study that has shown the effectiveness of the vaccine. By excluding people infected with HIV at the beginning of the clinical trial, the vaccine proved to be effective at the level of 31.2% at three years after the primary injection. From a global point of view, this is not satisfactory effectiveness. However, scientists already have a starting point, and further work is more than likely. The protective effect six months after the primary vaccination series was 60.5%; unfortunately, this effect quickly diminished [9]. Vaccinations affected viral load following infection or CD4 + T cell counts in people with breakthrough HIV infection. Immunological markers related to the protective effect of the vaccine have been identified. The extensive collaboration of international laboratories has shown in HIV-infected and tested individuals the strongest association providing protection for IgG antibodies against the variable regions of the HIV 1 and 2 envelope (V1V2) – IgG3 in particular – and low serum IgA antibodies [10]. This allows us to look to the future with optimism. Phase II of the clinical trial "RV144"

arouses widespread emotions among the public due to the expectation of even better vaccine effectiveness [11]. Phase II focuses primarily on the efficiency in the various conditions of the existence of the virus and its subtypes.

The "RV144" clinical trial has become a precursor to the use, and further development of biology systems approaches for the correlation of infection risk. By analyzing the virus, which involved studying HIV genetic sequences, breakthrough infections, vaccine components, and observed functional immune relationships, it helped scientists develop associations and differences that might be indicative of protection against the virus [12]. Further exploratory studies around the world following the presentation of the analysis of the clinical experiment "RV144" reflect the multilateral investigative approaches, and the use of potential vaccine "products" for further clinical trials in other subtypes, such as subtype C in South Africa [13].

Another approach by scientists to fight HIV is to try without a vaccine. The story of how the immune system can partially or more fully control HIV is complex and, in a sense, has been told backward, starting with artificially induced immunity from vaccine research, rather than on a real understanding of HIV infection as it has been established. Decades of experience with HIV patients passed before the acute course of the infection was properly understood. The observational study "RV217" is a prospective analysis of patients at high risk of infection in East Africa and Thailand. 2.300 patients were recruited for the study. The acute phase of the disease was noted in 5% of respondents. A maximum viral load was achieved after approximately 30 days, and a positive "EIA" test was achieved after 14 days. Up to the time of peak viral load, N.K. cells responded variable; The B cells initially dropped and then returned to normal. CD8 + T cells, CD4 + T cells decreased and remained inversely proportional to the viral load [14, 15]. This information is beneficial for developing an HIV vaccine strategy in several ways. Like many other viral syndromes, the human immunodeficiency virus fills most of its distribution in host tissues during the first two weeks. The diverse effect on the population

of B and T cells is still unclear about the importance of innate immunity. HIV causes less symptomatic acute disease (and therefore less inflammation throughout the body) than previously thought and stabilizes fairly quickly. Consequently, a neutralizing antibody available during log virus expansion would be a useful, but potentially insufficient, control mechanism. Scientists believe that key here will be primarily antibody-mediated non-neutralizing functions – and possibly innate effector functions.

The "RV144" and "RV217" clinical trials, which hypothesized that a vaccine could induce host immunity, are still speculation. Vaccines are adapted to current approaches to ensure that study participant are exposed to HIV antigens in a variety of ways to elicit mixed immune responses i.e., humoral, cellular, and innate arms of the host immune system using heterologous vaccines to induce non-specific immunity. Researchers' current efforts are focused on designing immunogens that would elicit a sustained and broad neutralizing antibody response against HIV. The number of monoclonal antibodies capable of extensively neutralizing anti-HIV activity is increasing exponentially thanks to the currently dominant molecular techniques for their recovery from HIV infected patients. Monoclonal antibodies, i.e., PGT121, VRC01, and VRC03, have been observed in cellular assays to inhibit CD4 + T cell insertion by latent viruses from chronically infected individuals. PGT121 and VRC01 antibodies were used in preclinical studies in acute phase infected king macaques with SIVs virus to reduce both viral load and viral DNA associated with cells [16]. It is not possible to cause such a reaction through active vaccination in humans at this point. Still, their use for HIV prevention and control by passive immunization is currently being tested in several clinical trials, which would provide evidence why they would likely work in active immunization. Researchers continue to search based on their observations of virus neutralization for the real antibody and antigen.

## Ongoing research into an HIV vaccine

Table. 1 Clinical trials HIV vaccine, own study [14]

| Country | Substance | Title of study | Type of Study | Phase | NCT number |
|---|---|---|---|---|---|
| US | N/A | A T Cell-based HIV Vaccine | Observational | N/A | NCT02389595 |
| Thailand | AIDSVAX B/E | Study of Immune Responses Induced by an HIV Vaccine | Interventional double blind | 2 | NCT01933685 |
| South Africa | ALVAC-HIV (vCP2438) and Bivalent Subtype C gp120/MF59 | Pivotal Phase 2b/3 ALVAC/Bivalent gp120/MF59 HIV Vaccine Prevention Safety and Efficacy Study in South Africa | Interventional | 2b/3 | NCT02968849 |
| US | (A, B, C, A/E)/gag (C) DNA Vaccine, gp120 (A, B, C, A/E) Protein Vaccine, GLA-SE adjuvant | Evaluating the Safety and Immunogenicity of Env (A, B, C, A/E) /Gag (C) DNA and gp120 (A, B, C, A/E) Protein/GLA-SE HIV Vaccines, Given Individually or Co-administered, in Healthy, HIV-1-Uninfected Adults | Interventional double blind | N/A | NCT03409276 |
| US | a1DC + inactivated whole autologous HIV, a1DC + conserved HIV peptides, a1DC + no antigen, pgDC + inactivated whole autologous HIV, pgDC + conserved HIV peptides, pgDC + no antigen | Comparison of Dendritic Cell-Based Therapeutic Vaccine Strategies for HIV Functional Cure (DC-HIV04) | Interventional double blind | 1 | NCT03758625 |
| Germany | N/A | HIV and STIs Clinical Study in Germany | Observational | | NCT03884816 |

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| Thailand | ALVAC-HIV, AIDSVAX B/E, ALVAC-HIV Placebo, AIDSVAX B/E Placebo | Study of Late Boost Strategies for HIV--Uninfected Participants From Protocol RV 144 | Interventional double blind | 2 | NCT01435135 |
| US | PENNVAX-GP, INO-6145, INO-9012, CELLECTRA® 2000 | Therapeutic Vaccination in Treated HIV Disease | Interventional | 1/2 | NCT03606213 |
| France, Hungary, Italy, Poland, Spain | N/A | Prospective Observational Cohort HIV & STI Study in Europe | Observational | N/A | NCT03866759 |
| US | Ad4-Env145NFL, Ad4-Env150KN, VRC-HIVRGP096--00-VP (Trimer 4571) with alum | Safety and Immunogenicity of Ad4--HIV Envelope Vaccine Vectors in Healthy Volunteers | Interventional | 1 | NCT03878121 |
| US | p4CE1/2 pDNA Vaccine, p55^gag pDNA Vaccine, IL-12 pDNA Adjuvant | Evaluating the Safety and Immunogenicity of pDNA Vaccines Expressing HIV M Group p24^Gag Conserved Elements and/or p55^Gag, Administered With IL-12 pDNA by Intramuscular Electroporation, in Healthy, HIV-Uninfected Adults (HVTN 119) | Interventional | 1 | NCT03181789 |
| Brazil | Yellow Fever vaccination (17 DD Biomanguinhos) | Immunogenicity and Safety of the Yellow Fever Vaccine in HIV-Infected Individuals (YF-HIV) | Interventional | 4 | NCT03132311 |
| Taiwan | Vaqta Injectable Product | Effectiveness of Booster With 1 or 2 Doses of HAV Vaccine Among HIV-Infected Patients | Interventional | 4 | NCT03855176 |
| Taiwan | Engerix-B | Hepatitis B Virus Vaccination in HIV-Positive Patients and Individuals at High Risk for HIV Infection | Interventional | 4 | NCT03854630 |

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| US | p24CE1/2 pDNA vaccine, p24CE1/2 pDNA vaccine admixed with full--length p55^gag pDNA vaccine, Full-length p55^gag pDNA vaccine | HIV-1-Gag Conserved-Element DNA Vaccine as Therapeutic Vaccination in HIV-Infected Persons With Viral Suppression on Antiretroviral Therapy | Interventional | 1/2 | NCT03560258 |
| Spain | HPV9v | A Clinical Trial to Evaluate the Immunogenicity of the Nonavalent Vaccine Against Human Papillomavirus in Men Infected by HIV Who Have Sex With Men. GESIDA 10017 (GESIDA10017) | Interventional | 4 | NCT03626467 |
| Belgium | HPV vaccine genotype | Vaccination Against Human Papillomavirus (HPV) With the 9-Valent Vaccine in HIV--Positive Women (the Papillon Study) (Papillon) | Interventional | 4 | NCT03391921 |
| Netherlands | ConM SOSIP.v7 gp140, adjuvanted with MPLA liposomes | Amsterdam UMC Clinical Trial With a Native-like HIV-1 Envelope Vaccine (ACTHIVE-001) | Interventional | 1 | NCT03961438 |
| US | Prevnar-13 | Impact of HIV-1 and Aging on Mucosal Vaccine Responses | Interventional | 4 | NCT03729778 |
| US | eOD-GT8 60mer + AS01B/ DPBS sucrose/IM, DPBS Sucrose | A Phase I Trial to Evaluate the Safety and Immunogenicity of eOD-GT8 60mer Vaccine, Adjuvanted | Interventional | 1 | NCT03547245 |

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| Spain | Vaccine + extension of the ATI period, Placebo + extension of the ATI period | Study to Assess the Safety and Durability of Viral Control Beyond 24 Weeks of Analytical Treatment Interruption After the Administration of Candidate HIV-1 Vaccines DNA.HTI, MVA.HTI and ChAdOx1.HTI or Placebo in Early Treated HIV-1 Positive Individuals (ATI Extension of AELIX-002 Study) | Interventional double blind | 1 | NCT04385875 |
| US | AIDSVAX® B/E | Evaluating HIV-1 Neutralization Antibody Breadth in Response to HIV gp120 Protein Vaccine in HIV-Uninfected Adults With Quiescent Systemic Lupus Erythematosus | Interventional | 1 | NCT03618056 |
| Malawi, Mozambique, South Africa, Zambia, Zimbawe | Ad26.Mos4.HIV, Clade C gp140 | A Study to Assess the Efficacy of a Heterologous Prime/Boost Vaccine Regimen of Ad26.Mos4.HIV and Aluminum Phosphate-Adjuvanted Clade C gp140 in Preventing Human Immunodeficiency Virus (HIV) -1 Infection in Women in Sub-Saharan Africa | Interventional | 2 | NCT03060629 |
| Spain | Human Papillomavirus 9-valent Vaccine, Recombinant | Immunogenicity and Safety of a 9-Valent Human Papillomavirus Vaccine in HIV-positive Women (9-VPH-MVIH) | Interventional | 4 | NCT04270773 |
| France | Additional blood sampling | Study on the Response to Tetanus Vaccination of People Living With HIV (VACTE-VIH) | Interventional | N/A | NCT03853681 |
| US | N/A | Immunogenicity of Novel H1N1 Vaccination Among HIV-Infected Compared to HIV-Uninfected Persons | Observational | N/A | NCT00996970 |

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| France | N/A | Influenza Vaccination in Patients Living With HIV in the Northern Region (VACCI-GRIPPE) | Observational | N/A | NCT04402684 |
| Brazil | CYD Dengue Vaccine, Placebo (NaCl 0.9%) vaccine group | Safety and Immunogenicity of a Tetravalent Dengue Vaccine in HIV-Positive Adults | Interventional | 2 | NCT02741128 |
| Sub-Saharan Africa | Recombinant Human Papillomavirus Nonavalent Vaccine | HPV Vaccine Therapy in Reducing High-Grade Cervical Lesions in Patients With HIV and HPV (COVENANT) | Interventional | 3 | NCT03284866 |
| Spain | ChAdOx1.HTI, MVA.HTI, GS-9620 | Safety, Tolerability and Immunogenicity of MVA.HTI and ChAdOx1.HTI With Vesatolimod in HIV-1-positive Patients (AELIX-003) | Interventional double blind | 2 | NCT04364035 |
| US | HIVAX, saline solution | Safety and Immunogenicity of HIVAX in HIV-1 Infected Subjects (GCHT01) | Interventional | 1 | NCT01428596 |
| Spain | DNA.HTI 0.5mL, MVA.HTI 0.5mL, DDDMM, ChAdOx1.HTI 0.5mL, MVA.HTI 0.5mL | Safety and Immunogenicity Study of DNA.HTI, MVA.HTI and ChAdOx1.HTI in HIV-1-Positive Patients (AELIX-002) | Interventional duble blind | 1 | NCT03204617 |
| Moldova | N/A | Immune Response to BCG Vaccination in Neonates Born to HIV and LTBI Infected and Non-infected Mothers (IMMUNEO) | Observational | N/A | NCT03383211 |
| US | p24CE DNA prime (p24CE/IL-12), IL-12 adjuvanted DNA boost (p24CE plus p55gag) | Combinatorial Therapy to Induce an HIV Remission | Interventional | 1/2 | NCT04357821 |

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| Argetina, Brazil, Italy, Mexico, Peru, Poland, Spain, US | Ad26.Mos4.HIV, Clade C gp140 | A Study of Heterologous Vaccine Regimen of Adenovirus Serotype 26 Mosaic4 Human Immunodeficiency Virus(Ad26.Mos4.HIV), Adjuvanted Clade C gp140 and Mosaic gp140 to Prevent HIV-1 Infection Among Cis-gender Men and Transgender Individuals Who Have Sex With Cis-gender Men and/or Transgender Individuals (MOSAICO) | Interventional triple blind | 3 | NCT03964415 |
| South Africa | ChAdOx1 nCoV-19 | COVID-19 Vaccine (ChAdOx1 nCoV-19) Trial in South African Adults With and Without HIV-infection | Interventional oduble blind | 1/2 | NCT04444674 |
| UK | Engerix B, Fendrix | A Pilot Study Comparing the Immunogenicity of Fendrix vs. Double-dose Engerix B in HIV-infected Non-responders to Standard Hepatitis B Vaccination Courses | Interventional | 2/3 | NCT02434848 |
| Thailand | Rabies vaccine | Immune Responses After a Four-site Intradermal Rabies Booster Vaccination in HIV--Infected Adults | Observational | N/A | NCT02547727 |
| Thailand | ALVAC-HIVAIDSVAX B/EALVAC--HIV Placebo, AIDSVAX B/E Placebo | Study of Boosting Strategies After Vaccination With ALVAC-HIV and AIDSVAX® B/E | Interventional double blind | 2 | NCT01931358 |

## Conclusion

HIV vaccine clinical trials are significant to humanity. Epidemiological data make us aware of the great problem we are dealing with. The medical experiment "RV144" shows that it is possible to obtain a vaccine. There is still a lot of work ahead of researchers to get an entirely safe and effective vaccine. Thanks to continuous investment, scientists can conduct further clinical trials in populations most at risk of HIV infection. HIV vaccine research has become an innovative mechanism for vaccine research, as demonstrated by a variety of vaccine vector products used in the study of other pathogens. The invention of the HIV vaccine is no longer a dream but a reality that scientists scrupulously pursue. We must hope that the nearest future in HIV prevention is an effective and safe vaccine.

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