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The History, Current Status, and Future Challenges of HIV Vaccine Development

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Abstract. This paper reviews the history and current status of HIV vaccine development, analyzes recent research progress and challenges, and explores potential breakthroughs and future directions. Since peaking in 1997, the global incidence of HIV has declined, yet the number of infections and mortality rates remain high. HIV has a significant impact on individuals and societies, and its high variability and immune evasion mechanisms present substantial challenges for vaccine development. Current HIV vaccines include viral vector vaccines, DNA vaccines, protein vaccines, and mRNA vaccines, each facing unique scientific and technological challenges. Recent clinical trials of HIV vaccines have shown significant progress, but their efficacy and safety require further validation. Public trust in vaccines and prioritization strategies for high-risk populations pose social and ethical challenges in vaccine deployment. Future research will focus on novel vaccine technologies, innovative immunization strategies, and global collaboration and resource integration. Through continuous scientific efforts and international cooperation, it is anticipated that a successful HIV vaccine will eventually be created to manage and eliminate this worldwide epidemic.

Keywords: HIV vaccine, viral variability, immune escape, clinical trials, global cooperation.

1. Introduction

The HIV pandemic persists on a worldwide scale, affecting more than 34 million individuals who are presently carrying the human immunodeficiency virus (HIV). While HIV-1 accounts for the majority of infections, there are also reported cases of HIV-2 in select countries like Guinea-Bissau and Portugal. Despite many similarities between HIV-1 and HIV-2, important differences exist, including pathogenicity, immune control capabilities, and CD4 independence, providing valuable insights into the evolution, tropism, and pathogenesis of the viruses [1]. The capsid protein of HIV-1 is formed by processing the central domain of the Gag polyprotein, which after proteolytic cleavage becomes a discrete protein of 231 amino acids, forming the mature virus's characteristic conical core. Studies of the crystal structure of the HIV-1 capsid protein have revealed its detailed molecular conformation, aiding understanding of virus assembly and maturation mechanisms and providing a basis for developing anti-HIV treatment strategies [2].

The primary transmission routes of AIDS include bloodborne, sexual contact, and mother-to-child transmission, with sexual transmission being the most common. AIDS, in 1981, the emergence of HIV-1 was initially recognized when a distinctive set of symptoms surfaced among a small group of gay men in the United States. Other groups quickly reported cases of AIDS, including intravenous drug users and

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hemophiliacs. Shortly after the discovery of AIDS, similar symptoms were found in Asian rhesus monkeys, termed simian AIDS, and the related lentivirus, simian immunodeficiency virus (SIV), was identified. Further research revealed the existence of HIV-2 and established its close relationship with SIV [3]. HIV infection results in profound immunosuppression, predominantly impacting CD4+ T lymphocytes. The primary occurrence in HIV infection is the attachment of the viral envelope glycoprotein to the CD4 receptor, resulting in the contamination of CD4+ T cells and monocytes/macrophages. As the disease progresses, viral load increases in the peripheral blood. Current research is delving deeper into the mechanisms behind the increase in viral load from the asymptomatic stage to the advanced disease, identifying various factors that may influence HIV expression regulation, including mitogens, antigens, heterologous viruses, cytokines, and physical factors [4].

Despite some progress in HIV vaccine development, numerous challenges remain. Studies have shown that the high variability of the HIV virus and its immune escape mechanisms make vaccine development exceptionally difficult. Additionally, generating effective neutralizing antibodies and durable immune memory are key challenges in development. This study aims to provide a comprehensive overview of the history and current status of HIV vaccine development, analyze ongoing research progress and challenges, and explore potential future breakthroughs and directions. By detailing the development and clinical trial situations of different types of HIV vaccines, this paper seeks to provide valuable information and guidance for vaccine researchers, promoting further research and application of HIV vaccines. Through continuous scientific effort and international cooperation, it is hoped that an effective HIV vaccine will eventually be developed to control and ultimately eliminate this global pandemic.

2. Global HIV Incidence and Vaccine Development Progress

Based on the findings of the Global Burden of Disease Study (GBD 2015), the worldwide HIV infection rate reached its highest point in 1997, recording 3.3 million new cases (95% uncertainty interval: 3.1 million to 3.4 million). From 2005 onward, following a sharp drop between 1997 and 2005, the yearly occurrence rate has plateaued at around 2.6 million. The population affected by HIV/AIDS has been steadily climbing and hit 38.8 million in 2015. At the same time, the death toll from HIV/AIDS has been on a decreasing trend, dipping from a high of 1.8 million fatalities in 2005 to 1.2 million in 2015.While several countries have witnessed a decrease in HIV/AIDS-related deaths and the number of new infections each year, other nations have experienced a stagnation or even an increase in the rate of new infections annually [5].

HIV primarily harms individuals by suppressing the immune system, causing a variety of conditions, and ultimately may lead to death. It is highly infectious, affecting not only individuals but entire families. Family structures, economic situations, migration patterns, and life cycles are all impacted by HIV, creating widespread strain across communities [6]. AIDS mainly affects adults aged 20 to 45, who are the workforce of society. If this segment of the population is infected with HIV, it weakens societal productivity, affects economic growth, and reduces life expectancy.

In 1998, Vaxgen initiated the AIDSVax vaccine trial, aiming to induce neutralizing antibodies and elicit humoral immunity against HIV. However, the company announced in 2003 that the AIDSVax vaccine was ineffective. The only component of HIV that can induce an immune response in humans is the envelope glycoprotein on the virus surface; humoral immunity alone is insufficient for providing adequate immune protection against HIV infection. The second generation of HIV vaccines learned from this failure, incorporating HIV genes into Ad5 (replication-defective serotype 5 adenovirus), targeting cellular immunity and inducing cytotoxic T cells. However, human trials showed that this vaccine not only failed to prevent HIV infection but also increased the risk of infection.

The third generation of AIDS vaccines combines humoral and cellular immunity to combat HIV. The RV144 AIDS vaccine uses a prime-boost combination method to simultaneously induce antibody production and stimulate cytotoxic T cell generation, reducing infection risk by 60%. However, its protective efficacy declines over time, dropping to 31.2% by the third and a half year. Moreover, an interim analysis of the Step Trial (STEP trial) announced in 2007 showed that the recombinant AIDS

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vaccine based on a replication-defective serotype 5 adenovirus vector, HVTN502, also increased the risk of immune cells being infected by HIV after promoting immune cell attacks on HIV. The HVTN702 AIDS vaccine efficacy clinical trial was launched in South Africa in 2016 but ended in failure in 2020 [7].

3. Current Progress in HIV Vaccine Research

3.1. Existing Types of HIV Vaccines

With ongoing advances in the medical industry, existing HIV vaccines are primarily classified into four types: viral vector vaccines, DNA vaccines, protein vaccines, and mRNA vaccines. Developing vaccines that protect against intracellular pathogens like HIV-1 poses challenges, thus necessitating more rational vaccine design approaches in terms of epitope systematic design, use of immunogenic adjuvants, and selection of appropriate delivery platforms.Viral vectors, as a platform for vaccine development, are certainly endowed with adjuvant properties in the form of pathogen-associated molecular patterns such that they can elicit innate responses when engaged to specific pattern recognition receptors. Contrastingly, distinct viruses replicating from viral vectors could have selective cellular tropisms and unique innate or adaptive immune composition that may allow for preferential immunological memory against a particular pathogen. While that pre-existing immunity is an important factor in the choice of vector, a more complete knowledge of protective immunological mechanisms should have ultimate priority over selecting best vectors for vaccine antigen delivery. Viral vectors have thus far been used to deliver the following HIV vaccine candidates; non-replicating and replicating serotype 5 adenoviruses (Ad5), alternative serotypes of Adenovirus, poxviruses lymphocytic choriomeningitis viruses (LCMV) cytomegaloviruses (CMV) vesicular stomatitis virus also known as VSV and attenuated immunodeficiency viruses [8].

During the 1990s, the idea of DNA vaccination emerged when researchers noticed that injecting naked DNA into the muscles could stimulate the production of encoded antigens. Following this, Tang et al. illustrated that this approach could generate immune responses to the antigens produced. The fascination with DNA vaccines skyrocketed when researchers found that injecting DNA could trigger a strong enough immune response to shield mice and chickens from experimental strains of influenza virus. Indeed, vector-based DNA immunization offers a promising new strategy in the prevention of infectious diseases, distinguishing itself from traditional vaccines containing weakened pathogens or recombinant proteins, which are proven ineffective. Unlike naked DNA vaccines, this innovative approach shows great potential for combating such infections. While attenuated live vaccines and inactivated vaccines have proven effective for numerous diseases, there remain certain illnesses for which utilizing attenuated live pathogens could pose significant hazards. Notably, such vaccines may be harmful to individuals with compromised immune systems, including cancer patients undergoing chemotherapy, AIDS patients, newborns, or the elderly. Additionally, the risk of attenuated live viruses regaining virulence through mutation is a real danger. In the case of AIDS, the risk of regained virulence could be fatal and is therefore unacceptable. Interestingly, vector-based DNA vaccines can also induce robust and long-lasting cell-mediated and humoral immune responses without any of the risks associated with attenuated live vaccines. Recent HIV DNA vaccine research has primarily focused on using HIV-based lentiviral vectors for antigen delivery. Despite concerns about the safety of using HIV-based lentiviral vectors for vaccine delivery and gene transfer, HIV DNA vaccine inoculation strategies offer several advantages. In addition to being used to transfer HIV-specific target cells or in vivo gene therapy for HIV/AIDS infection, retrovirus vectors can be disguised as recombinant virus forms capable of infecting a variety of target cells, including nerve cells and cancer cells. Typically, DNA vaccines can be delivered through different routes, including intramuscular, subcutaneous and intradermal injections [9].

Recombinant protein vaccines stimulate the body to produce an immune response against HIV by mimicking proteins that enter host cells during the HIV-1 infection process. They are suitable for individuals with compromised immune functions, such as healthy individuals, those with

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immunodeficiencies, cancer patients, etc. Additionally, there is a protein recombinant vaccine, also known as GPV (human immunodeficiency virus type 4), which can stimulate the body to produce an immune response against HIV, suitable for minors but does not produce long-term immune protection after vaccination.

mRNA vaccines work by injecting mRNA molecules that encode HIV proteins, inducing the body to produce an immune response against these proteins to control virus replication, suitable for preventing HIV infection, especially in providing protection for uninfected individuals. Studies have shown that delivering initial and boost immunogens in the form of mRNA-LNP can generate lasting germinal centers (GC), somatic hypermutation, and antibody affinity maturation, indicating that mRNA-LNP may be an effective tool in HIV vaccine development. In summary, with technological advances and a deepening understanding of viral immune mechanisms, existing types of HIV vaccines are continually evolving, offering various potential solutions for effectively preventing and controlling HIV.

3.2. Candidate Vaccines That Have Entered Clinical Trial Phases

In recent years, clinical trials for HIV vaccines have made significant progress. The first clinical trial is the AELIX-002 project, a collaboration between Gilead and AELIX Therapeutics, which is a DNA+MVA prime, ChAd boost vaccine combination, and used in conjunction with Gilead's TLR-7 agonist Vesatolimod. Phase 1 clinical trial results (NCT03204617) were announced at last year's CROI conference. The study found that patients tolerated AELIX-002 well, with no severe adverse events (SAE), and showed immunogenicity in 97% of vaccine recipients (over a 2-fold increase in HIV-specific T cell responses compared to baseline).

The second clinical trial was conducted by researchers at NIAID's Immune Modulation Laboratory, testing a dual combination of bNAbs: 3BNC117 and 10-1074, targeting different parts of the HIV surface. Researchers conducted a Phase 1 trial from September 2018 to January 2021, finding that combined bNAb therapy could effectively suppress HIV for an extended period without antiretroviral therapy (ART), provided individuals did not harbor antibody-resistant viruses at the start of antibody therapy.

The third clinical trial was initiated on January 27, 2022, led by the renowned pharmaceutical company Moderna, conducting early clinical trials for an HIV mRNA vaccine. mRNA technology enables body cells to learn to produce proteins that trigger an immune response. Researchers have not only developed the vaccine but also an enhancer delivered through mRNA, a molecule capable of triggering an immune response. Researchers hope this process will induce specific white blood cells (i.e., B cells) to transform into broadly neutralizing antibodies to neutralize the virus [10]. These clinical trials represent the cutting-edge progress in HIV vaccine development, hoping to find effective methods to prevent and treat HIV infection through different technologies and strategies.

4. Main Challenges in HIV Vaccine Development

4.1. Scientific and Technological Challenges

As medical technology advances, the development of an HIV vaccine faces numerous scientific and technological challenges. Firstly, the high variability of the HIV virus presents significant difficulties for vaccine development. HIV is not a single virus but a collection of multiple viruses, complicating serological testing, vaccine research, and antiviral drug treatment. The virus exhibits significant genetic diversity, allowing some strains to evade existing serological tests, escape immune surveillance from natural infection or vaccination, and rapidly develop resistance to antiviral drugs. At least five subtypes of HIV-2 have been identified, with significant variation between and within subtypes of HIV-1 and HIV-2, even among viruses infecting the same patient. By comparing HIV DNA sequences, genetic variability within a subtype of HIV-1 can reach 20%, and variability between subtypes can be 30% or more [11].

Another major challenge is the difficulty in generating effective neutralizing antibodies. AIDS remains a major global health issue with high mortality and morbidity rates, necessitating an effective

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HIV vaccine. Controlling viral replication requires both humoral and cellular immune responses, so vaccine development should aim to produce broad and effective humoral and cellular immune responses. While several vaccine approaches have generated anti-HIV T cell responses in animals and humans, no strategy tested clinically so far has been able to induce a broad neutralizing antibody response against HIV. The presence of such antibodies could prevent infection or significantly reduce the number of infected cells, thereby delaying viral transmission and better controlling viral replication in infected hosts.

Establishing a long-lasting immune memory poses a significant challenge. Immune memory is characterized by its selectivity and preservation; following the initial infection, only a small subset of cells remains unchanged, poised to swiftly respond to reinfection. Memory T cells exhibit diversity in terms of their characteristics, functions, and locations within the body. Gaining insights into the cytokines and co-stimulatory signals that influence regulatory T cell differentiation and memory formation is crucial for manipulating vaccine responses effectively. By identifying the transcriptional programs and activation markers associated with protective memory responses, it becomes possible to predict the effectiveness of vaccines.

Currently, the strategies employed for targeted administration of vaccines and the incorporation of cytokines, chemokines, and immunomodulatory molecules are primarily based on empirical evidence. In the case of HIV-1 vaccines, this involves delivering plasmid DNA and recombinant viral vectors (both replicating and non-replicating) in vivo to express HIV-1 genes, cytokines, and chemokines. The utilization of recombinant viral vectors enhances immunogenicity by synergistically activating both innate immune responses and adaptive immunity. However, the interaction between antiviral (vector) immunity and the development of long-term memory against recombinant antigens remains unclear. While recombinant viral vectors can trigger local innate responses and enhance adaptive immune responses to recombinant antigens, potentially eliminating the need for adjuvants, further investigation is necessary to comprehend their role in inducing protective memory responses against HIV-1 infection [12].

4.2. Clinical and Regulatory Challenges

In the realm of HIV vaccine development, the effective design and execution of clinical trials pose significant obstacles. To expedite the clinical advancement of potential vaccines, numerous inventive trial designs have been suggested, aiming to enhance efficiency by reducing sample sizes or enabling quicker decision-making within clinical development plans while upholding essential operational characteristics and trial validity. These designs have long been employed in various domains, notably cancer research. Multi-arm trial designs facilitate the comparison between multiple active vaccine groups and a standard control group, thereby enhancing efficiency in terms of sample size.

Illustrations of different trial designs show examples of multi-arm and factorial designs, such as a design comparing three different vaccine strategies with a standard placebo group, evaluating vaccine strategies, another intervention, and a combination of both. These designs in HIV prevention trials may involve pre-exposure prophylaxis (PrEP) and drugs mobilizing the viral reservoir in treatment trials. Dual-arm group sequential designs and seamless adaptive designs are also used to advance trials seamlessly between phases, integrate trial arm selection, and make additional design adjustments.

In early preventative HIV vaccine trials in low-risk populations, the inclusion of a placebo group is controversial because HIV-specific immune responses can be close to zero. However, as vaccine strategies advance in the clinical development stage, randomized placebo groups become an essential part of head-to-head comparisons. The evaluation standards for safety and effectiveness are a significant hurdle in the development of vaccines. While experimental vaccines for simian immunodeficiency virus and HIV have shown promising results in inducing protective immunity in primates, we still need to establish the specific immune responses that provide protection. The genetic and antigenic variability of HIV also poses challenges for vaccine development. Although V3-specific neutralizing antibodies may be important, the immune response to HIV infection involves various cell-mediated responses against different viral proteins. Clinical trials involving twelve candidate vaccines conducted on HIV-negative

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individuals have demonstrated their tolerability and ability to induce neutralizing antibodies as well as diverse cell-mediated responses. Trials on four candidate vaccines with HIV-infected volunteers have shown safety and an enhancement of anti-HIV immune responses, although information regarding potential clinical benefits is yet to be obtained. The scientific community is currently discussing the criteria for initiating efficacy trials on preventive candidate vaccines, while collaboration between industrialized and developing countries, along with organizations like the World Health Organization, aims to identify suitable study populations and prepare accordingly for further research on HIV vaccines [13].

In terms of regulatory approval and market access, the HIV vaccine production industry has proposed several legal and regulatory approaches aimed at expanding access to new vaccines and considering public health perspectives. Key conclusions include the challenges of tiered or differential pricing, persuading policymakers and the public to accept the value of meeting the needs of low-income countries at lower prices without harming the profitability and new product development of manufacturers. Strengthening liability is considered crucial for facilitating access. Market exclusivity needs to be guaranteed through legislation in countries that incentivize innovators, but incentive measures are typically based on industrialized countries. Although low-income countries can prioritize health issues in their national budgets and effectively use aid, it is unrealistic to rely solely on these measures to fill the overall health gap. External assistance is needed to purchase new vaccines and strengthen health systems, and additional resources must be added to existing resources to achieve sustainable financing improvements. Dedicated health insurance can facilitate vaccination, but in low-income countries, people may not be able to obtain or afford such insurance. Rights programs such as the Children's Vaccine Initiative may accelerate the adoption of new vaccines and the availability of innovative revenues [14, 15].

The development of HIV vaccines presents significant social and ethical challenges due to the need for public acceptance and trust. While vaccines are widely recognized as crucial for public health, there has been a recent decline in public confidence towards them. This decrease in trust has been described by some experts as a critical situation. When it comes to deciding whether to accept vaccines, the public considers not only scientific and economic evidence but also psychological, sociocultural, and political factors. Policymakers and other decision-makers should fully comprehend and take into account these factors.

Public confidence in vaccines varies greatly, and establishing trust relies on comprehending the risks associated with vaccines, considering historical experiences, taking into account religious or political backgrounds, and acknowledging socioeconomic status. While it is crucial to provide accurate scientific evidence regarding the balance between risks and benefits of vaccines, this alone is insufficient to bridge the gap between current public confidence levels in vaccines and the level of trust required for adequate and sustained vaccine coverage. The vaccine community typically emphasizes rigorous evidence demonstrating the effectiveness and safety of new vaccines as well as the feasibility of technology and operations during their introduction. However, there is often a neglect for equally rigorous research aimed at understanding psychological, social, and political factors that influence public trust in vaccines [16].

Priority vaccination strategies for high-risk populations can effectively increase the uptake of HIV vaccines. High-risk groups include sex workers, injection drug users, and men who have sex with men, who are susceptible to HIV infection. Incorporating HIV vaccination into priority vaccination programs for high-risk populations, combined with HIV testing, can increase vaccination rates and encourage those who have not been vaccinated to undergo HIV testing. The implementation of this strategy can effectively increase the coverage and acceptance of HIV vaccination among high-risk populations, thereby reducing the risk of HIV transmission and protecting the health of high-risk groups.

Ethical review and informed consent are essential components of ensuring that the development, testing, and promotion of HIV vaccines follow ethical guidelines and protect individual rights. Independent ethics committees must review and approve the research and testing of HIV vaccines. These committees typically consist of physicians, scientists, legal experts, and community representatives,

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ensuring that research plans comply with ethical guidelines and legal requirements. The primary responsibility of ethics review committees is to ensure the reasonableness and scientific nature of the research design while protecting the rights and safety of participants. This includes ensuring that research risks are minimized, research purposes are clear, informed consent forms are lawful, and participant privacy and data protection are considered.

Before participating in any HIV vaccine research, researchers must thoroughly explain to participants the purpose, process, potential risks and benefits, and their rights and choices. This is an important means of protecting participants' autonomous decision-making and personal rights. Informed consent must be voluntary, without any form of pressure or coercion. Participants must have sufficient time and opportunity to consider whether to participate in the research, and they have the right to withdraw consent at any time without any penalty or loss. Ethical review and informed consent for HIV vaccines are not only important measures to respect participants' rights and protect their safety during the research process but also key steps to ensure the scientific nature and social acceptability of vaccine research. These measures comply with ethical standards and help increase public trust in vaccines, thereby promoting the successful development and widespread use of vaccines.

5. Future Directions and Potential Breakthroughs in HIV Vaccine Development

5.1. Novel Vaccine Technologies

In history, initial vaccines were developed using weakened or deactivated pathogens either as whole cells or fragments. Although these traditional vaccines were capable of inducing strong immune responses through humoral mechanisms, they necessitated simultaneous administration of antigens alongside adjuvants while only eliciting weak CD8+ T cell responses. Conversely, next-generation nano/microparticle-based vaccines offer notable advantages by effectively stimulating CD8+ T cell responses while serving as excellent carriers for proteins, adjuvants, and nucleic acids. These nano-carriers can be loaded with molecules that modulate immune responses by inducing various effector functions along with regulatory activities. Consequently making them ideal tools for reverse vaccination strategies targeting suppression of immune responses in autoimmune diseases. Polylactic-co-glycolic acid and liposomes are biocompatible materials approved by the U.S. Food and Drug Administration for clinical use in nano-particle-based vaccines. Moreover, the innovative vaccine candidate platforms based on extracellular vesicles have also been shown to effectively co-deliver antigens and adjuvants [17].

Due to the differences of HIV-1, the variation in viral subtypes across different geographic regions, developing an HIV-1 vaccine that can successfully induce and widely cross reactive humoral and cellular immune responses has always been a challenging goal. Researchers have designed three DNA vaccines named pJW4303-MEG1, pJW4303-MEG2, and pJW4303-MEG3, encoding highly conserved multiepitopes from the most prevalent HIV-1 subtypes in China, recognizable by the dominant HLA alleles in China. The protein encoded by pJW4303-MEG1 consists of a Th epitope from Env and multiple epitopes from Pol, Env, and Gag proteins, with GGGS linkers between epitopes. The epitope sequence of pJW4303-MEG2 differs but uses the same linkers; pJW4303-MEG3 has the same epitope sequence as pJW4303-MEG2 but uses AAY linkers. To evaluate immunogenicity, researchers immunized mice with these DNA vaccines intramuscularly. Results showed that both pJW4303-MEG1 and pJW4303-MEG2 vaccines induced effective humoral and cellular immune responses in immunized mice, whereas pJW4303-MEG3 failed to induce an immune response. These findings underscore the importance of epitope and linker sequences in designing epitope-based vaccines against HIV-1 and other viruses [18].

Currently, antiretroviral therapy (ART) remains the only reliable treatment to halt HIV-1 replication and prevent its progression to acquired immunodeficiency syndrome (AIDS). However, ART cannot eliminate latent integrated viruses, meaning HIV carriers need lifelong treatment and still face risks of opportunistic infections and treatment-related complications. Stopping ART leads to rapid viral resurgence in most HIV-1 carriers. To reduce the long-term hazards of HIV infection, researchers are

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exploring immune-based strategies, such as therapeutic vaccination, to enhance the host's immune response and thereby control HIV-1 replication without the need for ART.

5.2. Innovations in Immune Strategies

Broadly neutralizing antibodies (bnAbs) isolated from individuals infected with AIDS suggest that, despite their rarity and convoluted production process, the humoral immune system can generate effective anti-HIV antibody responses. Germline-targeting (GT) vaccines induce bnAbs through sequential immunization. This strategy is based on acquiring broad neutralizing antibodies (bnAbs) through multiple enhanced immunogens. However, driving B cell receptor (BCR) modifications further within germinal centers (GCs) remains a challenge due to the low efficiency of memory B cell recruitment to GCs and potential masking by serum antibodies induced epitopes.

HIV carriers reduce the viral load in their bodies by taking antiretroviral drugs, a therapy known as antiretroviral therapy (ART), which can reduce the viral load to undetectable levels. However, AIDS sufferers must undergo daily ART to minimize viral mutations and the possibility of developing drug resistance. Although ART can reduce viral levels to undetectable levels, it cannot completely eliminate the virus from the body, as HIV hides in immunoprivileged areas such as certain parts of lymphatic tissue, which are difficult for the immune system to access and clear. Killer T cells cannot traverse these reservoirs carrying the HIV virus, and continuous exposure to the virus drives cytotoxic T cells into an exhausted state, rendering them dysfunctional. These exhausted cytotoxic T cells display increased PD-1 proteins, which act to "turn off" their killing activity. One method to reverse cytotoxic T cell exhaustion is to block PD-1, but this does not enhance the immune system's response to the virus. In contrast, HIV vaccines can significantly boost immunity to the virus.

Most dendritic cell (DC)-based vaccine research focuses on T cell responses, with less emphasis on natural killer cells (NK cells), which play a crucial role in defending against viral infections and can directly clear infected cells. Human NK cells are divided into regulatory and cytotoxic subgroups, with multiple activation and inhibitory receptors, whose function depends on contact with and training by MHCI molecules. Trained NK cells play a significant role in immune responses and can indirectly lyse target cells through antibody-dependent cellular cytotoxicity, which is significant in HIV-1 infection and preventative vaccine trials. NK cells shape immune responses through bidirectional interactions with dendritic cells (DCs), functioning by killing immature DCs or stimulating mature DCs. Mature DCs play an important role in the immune response, also stimulating NK cells and inducing their migration, while the latter rapidly proliferate and produce interferon-γ. Thus, modulating the interactions between NK cells and dendritic cells presents a significant research value in immunotherapy.

5.3. Global Cooperation and Resource Integration

GlaxoSmithKline (GSK) and the International AIDS Vaccine Initiative (IAVI) announced plans to jointly develop an AIDS vaccine. This collaboration marks IAVI's first partnership with a major vaccine manufacturer to develop an anti-AIDS vaccine, with both parties collaborating on early-stage development of a new technology named "non-human primate adenovirus vaccine vector," a research outcome from the University of Pennsylvania. This technology uses non-infectious vaccine vectors to stimulate a unique immune response in humans to combat HIV. The University of Pennsylvania has granted GSK exclusive rights to use this technology. GSK and IAVI researchers will form a joint research and development team, with technology and funding provided by IAVI.

While the goal of the collaboration is to develop an AIDS vaccine suitable for global use, initial research phases will focus on HIV variants primarily spreading in the African region. After pre-clinical evaluation, GSK and IAVI plan to conduct Phase I clinical studies of the candidate vaccine and are committed to developing an affordable vaccine for developing countries as soon as possible. As a non-profit organization dedicated to AIDS vaccine development, IAVI has received support from multiple governments, groups, and companies, including the U.S. government, the European Union, the UK government, the Bill & Melinda Gates Foundation, the Rockefeller Foundation, the World Bank, and several major corporations.

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6. Conclusion

The high variability of the HIV virus poses significant challenges in developing effective vaccines. Since the discovery of HIV in the 1980s, vaccine research has been ongoing, but no breakthrough successes have yet been achieved. Most vaccine research focuses on preventing HIV infection, with relatively less attention given to vaccines that cure infected individuals. The main vaccine strategies include viral vector vaccines, DNA vaccines, protein vaccines, and mRNA vaccines. Immune escape, inconsistent clinical trial results, and the balance between safety and efficacy are the primary challenges at present. HIV's rapid mutation enables it to evade the host immune system's attacks, making it difficult for a single vaccine to cover all variants. Many vaccine candidates perform well in animal models but have been less effective in human clinical trials. Additionally, vaccines must ensure safety while providing sufficient protective effects, which is a critical issue that researchers need to balance. Future research may focus on combining multiple vaccine strategies to enhance immune response effects. Personalized vaccines based on host genetics and immune characteristics may become an important direction for future research. Moreover, extensive international cooperation is needed to accelerate the vaccine development process in response to the global HIV epidemic. Overall, although HIV vaccine research faces numerous difficulties, continuous scientific efforts and technological advancements offer hope for ultimately overcoming these challenges.

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