Advances in HIV Research: Mechanisms, Transmission Routes, and Emerging Therapeutic Strategies

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Abstract. Recently significant progress has been made towards the goal of achieving a cure for AIDS, but there is still a long way to go. This essay comprehensively reviews the latest advancements in HIV/AIDS research, emphasizing the virus's mechanisms of action, transmission routes, and emerging therapeutic strategies. HIV, a retrovirus that targets CD4+ T cells, continues to pose a significant global health challenge. The essay provides an overview of the HIV life cycle, highlighting the roles of viral envelope proteins and single-cell sequencing technology in understanding its intricate mechanisms, and discusses the progression of HIV from initial infection to AIDS, highlighting the ability of the virus to integrate into the host genome and evade the immune system. In addition, the paper analyzes HIV transmission routes, mainly sexual contact, blood contact, and mother-to-child transmission, and explores emerging treatment strategies, including gene-editing technologies such as CRISPR-Cas9, immunotherapy and cell therapies such as broadly neutralizing antibodies (bNAbs), HSCT, and vaccine development. While a cure remains elusive, these advancements offer hope for the future eradication of HIV/AIDS as a global health threat.

Keywords: HIV; AIDS; gene editing; CRISPR-Cas9; immunotherapy; transmission routes.

1. Introduction

HIV is a retrovirus that targets and destroys the immune system's CD4+ T cells, leading to the development of Acquired Immune Deficiency Syndrome (AIDS) [1]. Since it was first reported in 1981, AIDS has become a major global public health challenge.

In the realm of HIV/AIDS research, recent years have witnessed remarkable progress towards the goal of a cure. In February 2023, a remarkable case was reported from the University Hospital Düsseldorf in Germany. A 53-year-old male patient, known as the "Düsseldorf Patient," achieved a functional cure of HIV following a hematopoietic stem cell transplant. This patient, who had been battling both HIV and cancer, underwent a transplant using stem cells from a donor. The cells had a rare genetic mutation that confers natural resistance to HIV. After the transplant, the patient's HIV viral load remained undetectable for an extended period, marking him as the fifth person globally to be confirmed as cured of HIV through this approach.

This year, a 60-year-old German man who had no detectable HIV after a stem cell transplant in 2015 could become the seventh person in the world to be successfully cured of HIV. Compared with the previous six cases of cured AIDS patients, they were all cured of AIDS and blood cancer patients through stem cell transplantation. These results imply that stem cell transplantation is a workable therapeutic alternative, and this idea can be applied to future research to investigate safer treatment choices.

2. HIV Mechanisms of Action

HIV's intricate life cycle comprises several pivotal stages, including attachment to host cells, entry, reverse transcription, into the host genome, and replication.

2.1. Attachment and entry

Each stage contributes significantly to the virus's persistence and pathogenesis. Beginning with the attachment to host cells, HIV specifically targets CD4+ T cells [2], which are crucial components of the immune system. This process is facilitated by viral envelope proteins, particularly gp120, which interacts with the CD4 receptor on the surface of the host cell. Following initial attachment, a conformational change in gp120 enables the binding of a co-receptor, typically CCR5 or CXCR4 [3], facilitating the fusion of the viral and cellular membranes and allowing entry of the viral core into the host cell.

2.2. Reverse transcription

Once inside, HIV undergoes reverse transcription, a unique feature of retroviruses. This process involves the conversion of the virus's RNA genome into DNA, mediated by viral enzymes such as reverse transcriptase.

2.3. Integration

The DNA is then transported into the host cell's nucleus, where it integrates into the host genome. This integration forms a stable "virus library," ensuring the virus's persistence within the host and allowing it to evade immune clearance, even during periods of immune suppression.

2.4. Replication

With its genome now embedded within the host's DNA, HIV can commence replication. This involves the transcription of viral genes, the synthesis of viral proteins and RNA, and the assembly of new virions within the host cell. Ultimately, these virions are released from the infected cell, either by lysis or exocytosis, and go on to infect other cells, perpetuating the cycle of infection.

In recent years, advances in single-cell sequencing technology have shed light on the unique surface proteins expressed by HIV-infected cells. These proteins not only distinguish infected from uninfected cells but also provide new therapeutic targets for intervention [4]. By disrupting any of these critical steps in the virus's life cycle, researchers aim to develop more effective strategies for preventing, controlling, and ultimately eradicating HIV infection.

3. Development of HIV

In general, when infected with HIV for the first time, the infected person will enter the incubation period ranging from months to decades after an acute infection period of about 2 to 4 weeks. As the virus attacks, the body's immune system is destroyed. The onset period is mainly manifested as a variety of opportunistic infections, and finally enters the terminal stage of AIDS.

3.1. Acute infection period

During the acute infection phase, the HIV viral load explosively increases in the infected person's body, successfully activating the body's immune system. Then the body will produce various specific antibodies against HIV proteins. At this time, the human immune system can fight HIV infection through specific immune and non-specific immune responses. In a short period of time, the body's specific cellular immunity can rapidly suppress HIV that is constantly replicating.

3.2. Incubation period

However, due to the characteristics of retroviruses, HIV will integrate its own genetic material into the host cell. Once the reverse transcription process is completed, HIV builds a very stable "virus library" in the human body.Therefore, when the function of the human immune system is perfect, the HIV virus library can remain latent for a long time and cannot be completely eliminated by the human immune system. The incubation period of HIV infection is also known as the "asymptomatic period".

At this stage, most people with HIV do not have particularly obvious symptoms of discomfort, almost like normal people.

3.3. Terminal stage

When the immune system is continuously damaged and the normal immune function of the human body is suppressed, the HIV virus reservoir will be activated, and the virus will begin to replicate in large numbers. Over time, as HIV continues to replicate in the infected person's body, the body's CD4+T cells and CD8+T cells will be consumed. In the end, the HIV virus in the human body constantly consumes human immune cells, increasing the burden on the human immune system. Even to the late stage of AIDS disease, the normal cellular immune function of the human body will be completely destroyed.

4. Modes of Transmission

HIV primarily propagates through four distinct modes of transmission: sexual intercourse, direct blood contact, perinatal transmission from mother to child, and, albeit less frequently discussed in isolation, shared use of contaminated needles or equipment during intravenous drug use. While these primary routes of transmission are well-documented and widely recognized, contemporary research endeavors have delved deeper into elucidating the intricate dynamics of HIV spread within populations.

Specifically, scientists have intensified their focus on assessing the effectiveness of various intervention strategies in mitigating the epidemic's burden. For instance, groundbreaking studies have meticulously analyzed the profound impact of preventive measures like pre-exposure prophylaxis (PrEP), which involves administering antiretroviral medications to HIV-negative individuals at high risk of acquiring the virus, and antiretroviral therapy (ART) for those already infected, in significantly reducing transmission rates [5]. These interventions, when coupled with comprehensive education programs and access to timely testing, have emerged as potent tools in the global fight against HIV/AIDS.

Moreover, research is also exploring the role of social determinants of health, such as poverty, stigma, and discrimination, in shaping the epidemiology of HIV transmission. By addressing these underlying factors, policymakers and healthcare providers aim to create an environment conducive to reducing new infections and improving the overall health outcomes of those living with HIV.

5. Emerging Therapeutic Strategies

5.1. Gene Editing Technologies

The advent of gene editing technologies, notably CRISPR-Cas9, has marked a significant milestone in HIV research. Researchers at the University of Amsterdam have recently showcased the remarkable achievement of eradicating HIV genetic material from infected cells using this innovative approach. By precisely targeting and excising the HIV DNA from CD4+ T cells, the primary target of HIV infection, CRISPR-Cas9 offers a glimmer of hope towards achieving a potential cure for this devastating disease [6].

Nevertheless, the translation of this promising laboratory result into clinical practice faces formidable challenges. Among them, the risk of off-target effects, where CRISPR-Cas9 mistakenly edits unintended regions of the genome, poses a significant concern [7]. Additionally, long-term safety considerations, including potential immunogenic responses and unforeseen consequences on cell function and human health, must be rigorously evaluated before widespread application. Addressing these challenges through further research and refinement of the technology is crucial to harnessing the full potential of CRISPR-Cas9 in the fight against HIV.

5.2. Immunotherapy and Antibody-Based Therapies

Immunotherapy, particularly the utilization of broadly neutralizing antibodies (bNAbs), has emerged as a promising therapeutic frontier in the battle against HIV. These powerful antibodies exhibit remarkable capabilities in neutralizing a broad spectrum of HIV strains, thereby impeding the virus's replication in infected individuals. The efficacy of bNAbs stems from their ability to recognize and bind to conserved regions of the viral envelope, effectively blocking viral entry into host cells. Multiple studies have demonstrated the potential of bNAbs to significantly reduce viral loads and control disease progression in HIV-positive patients [8].

The application of bNAbs in immunotherapy holds significant promise for both treatment and prevention strategies. As prophylactic agents, they could potentially prevent HIV acquisition in high-risk populations. The ongoing research efforts aimed at optimizing bNAbs for improved potency, breadth, and durability of action underscore their potential to revolutionize HIV management.

5.3. Cell Therapies

Cell therapies, particularly those involving hematopoietic stem cell transplantation (HSCT), have shown promise in eliminating HIV [9]. While HSCT is currently limited by its high cost, complexity, and potential risks [10], it represents a potential treatment strategy. Ongoing research is aimed at perfecting and improving these treatments to make them more widely available.

5.4. Vaccine Development

HIV vaccine development has been a challenging endeavor due to the virus's high mutation rate and ability to evade the immune system. In particular, germline targeting strategies have emerged as a promising direction, aiming to elicit an immune response that targets conserved regions of the virus, making it less susceptible to mutations [11]. Additionally, the use of mRNA-lipid nanoparticles as vaccine delivery systems has shown immense potential in stimulating the production of broadly neutralizing antibodies (bNAbs). These antibodies hold great promise as they can effectively neutralize a broad spectrum of HIV strains, offering a ray of hope for the development of an effective HIV vaccine [12].

6. Conclusion

Ongoing HIV/AIDS research efforts have made significant progress in understanding the mechanism of the virus, its transmission routes and potential treatment strategies. While a cure for HIV remains elusive, applications of gene editing technology, immunotherapy, antibody-based therapies, cell therapies and vaccine development offer hope for the future. As research continues to develop, it is hoped that these advances will eventually lead to the eradication of HIV/AIDS as a global health threat.

Reference

[1] Assawinchaichote, W. , and S. Junhom. "Infection System with Dual Drug Dosages via an LMI Approach." (2011).

[2] Kanyalkar, Meena , et al. "Conformational study of fragments of envelope proteins (gp120: 254-274 and gp41: 519-541) of HIV-1 by NMR and MD simulations. " Journal of Peptide Science 10.6(2004):363–380.

[3] Deng L. Transition of two major conformational states of HIV-1 gp120. 2019. Yunnan University.

[4] Sun, Weiwei. , et al. "Phenotypic signatures of immune selection in HIV-1 reservoir cells." Nature (2023).

[5] Liying, Wang , M. Timothy R. , and Jane M., SimoniFlorence, NambiLylianne, NakabugoJoseph, KibuukaDorothy, ThomasIngrid T., KatzErika,FeutzKatherine K., ThomasNorma C., WareMonique A., WyattHerbert, KadamaAndrew, MujugiraRenee, Heffron. "Behavioral Modeling and its Association with PrEP and ART Use in Ugandan HIV-Serodifferent Couples." AIDS and behavior 28.5(2024):1719-1730.

[6] Huang, Z et al. “Current application of CRISPR/Cas9 gene-editing technique to eradication of HIV/AIDS.” Gene therapy vol. 24,7 (2017): 377-384.

[7] Newton Matthew D, et al. "DNA stretching induces Cas9 off-target activity.." Nature structural & molecular biology 26.3(2019):185-192.

[8] Jannifer Jasmin Thavarajah, Bo Langhoff Hønge, and Christian Morberg Wejse. "The Use of Broadly Neutralizing Antibodies (bNAbs) in HIV-1 Treatment and Prevention.." Viruses 16.6(2024):911-911.

[9] Bryant, Adam , and S. Milliken . "Successful reduced-intensity conditioning allogeneic HSCT for HIV-related primary effusion lymphoma. " Biology of Blood and Marrow Transplantation 14. 5(2008):601-602.

[10] G. D. P. E. S. C. M. D. Souza, et al. "Epidemiological characterization of patients submitted to hematopoietic stem cell transplantation at a reference center in Curitiba, Paraná, Brazil, 2011-2015." ABCS Health Sciences 43(2018).

[11] Schiffner, T., Phung, I., Ray, R. et al. Vaccination induces broadly neutralizing antibody precursors to HIV gp41. Nat Immunol 25, 1073–1082 (2024).

[12] Chaudhary Namit, Weissman Drew, and Whitehead Kathryn A. "mRNA vaccines for infectious diseases: principles, delivery and clinical translation.." Nature reviews. Drug discovery 20.11(2021):817-838.