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A comprehensive journey through AIDS: History, development, and treatment

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Abstract. Acquired immune deficiency syndrome (AIDS) is a disease that attacks the human immune system. From its first discovery to modern investigations about this disease and the viruses that cause it, AIDS went through the process of being viewed as deadly and mysterious to controllable and preventable. By studying the mechanism of human immunodeficiency virus (HIV) and discovering the route of transmission of AIDS, the danger of this disease is gradually controlled by pills and therapies. The HIV life cycle has been uncoded and people found ways to target the specific steps to hinder HIV replication. Antiretroviral therapies are invented and gradually perfected to control the infection of AIDS. Nevertheless, a specific cure and any form of vaccine for AIDS has still not been found by humans. Several modern cases exhibited possible solutions to HIV infection while bringing more controversies and investigations. This review summarized the history and development of AIDS studies and its treatment, to possible future methods that could completely cure this disease.

Keywords: AIDS, HIV, Antiretroviral Therapy, AIDS Treatment.

1. Introduction

The emergence and persistence of acquired immunodeficiency syndrome (AIDS) over the past four decades have marked one of the most challenging and transformative chapters in the history of medicine and public health. This devastating disease, caused by the Human Immunodeficiency Virus (HIV), has had profound global implications, affecting millions of lives and reshaping healthcare policies, societal attitudes, and research priorities. In this comprehensive review, we embark on a journey through the annals of the history, development, and treatment of AIDS. Our exploration seeks to illuminate the multifaceted aspects of this epidemic, from its initial appearance in the early 1980s to the present day, where remarkable progress in treatment and prevention strategies has emerged.

We begin by tracing the historical roots of the AIDS epidemic, shedding light on its mysterious origins and rapid spread. This section delves into the early years of uncertainty and fear, recounting the challenges faced by healthcare professionals, activists, and affected communities as they grappled with an elusive and deadly virus. The subsequent portion of our review delves into the evolution of scientific understanding regarding HIV and AIDS. We chronicle the groundbreaking discoveries in virology, immunology, and epidemiology that have shaped our comprehension of this virus, from its mode of transmission to its impact on the immune system. One of the most remarkable aspects of the AIDS story is the evolution of treatment strategies. We examine the development of antiretroviral therapies, from the early, rudimentary attempts to the sophisticated and life-saving regimens available today. While

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significant progress has been made, AIDS continues to pose challenges. We discuss the difficulties and drawbacks of modern antiretroviral therapies, how they lead to the side effects that patients are enduring, and possible solutions to the problems people are facing. Additionally, we explore the journey toward the cure of HIV through bone marrow transplantation and gene editing.

As we navigate this disease, we aim to provide a comprehensive and up-to-date overview of the history, scientific developments, and treatment options surrounding AIDS. By exploring the remarkable progress and persistent challenges in the battle against HIV/AIDS, we hope to contribute to the collective knowledge and ongoing efforts to bring an end to this global health crisis.

2. History

The earliest discovery of AIDS traces back to 1981 when the case of five gay men found infected by a rare lung disease named *Pneumocystis* Pneumonia was reported by the US Center for Disease Control (CDC). Later that year several cases of unusual malignant disease were reported in America, and each case, the patients turned out to be gay men. Thus, AIDS was initially referred to by the public as "gay cancer," until similar symptoms of severe immune deficiency were discovered among female sexual counterparts of male infectors. In 1982, the CDC used the term acquired immune deficiency syndrome for the first time in the report and defined the disease as one that leads to diminished resistance in patients for unknown causes [1]. The cause of AIDS was found in 1983. The virus was named HIV, and its origin was traced to primates like chimpanzees in Africa. Hamilton et al examined the similarities between the genome of HIV-1, HIV-2, and simian immunodeficiency viruses (SIVs), and doubted that the virus was ingested by humans when hunting primates and later transported to the US [2]. A diagnostic blood test was produced to detect AIDS infection. The transmission of AIDS was at first identified through sexual contact, making gay and lesbian populations especially susceptible to the disease. Then patients get infected through contaminated blood sources was discovered in 1984. Now people found out that HIV can be transmitted through sexual contact, mother to baby, and sharing needles, allowing people to be cautious in preventing the infection of AIDS. The development of AIDS treatment will be mentioned below.

3. Discovery of HIV and AIDS

3.1. The Structure of HIV

HIV is classified as a retrovirus, utilizing RNA as the genetic material, and has two strands of viral RNA. CD4+ cells, which are important in human humoral and cellular immune responses, are the main target of HIV. The genome of HIV consists of nine genes, with the three typical retroviral genes *gag*, *pol*, *env*, and six regulatory genes (*tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu*) [3]. *Gag* codes for the structural protein capsid, matrix, and nucleocapsid; *pol* codes for the functional enzymes reverse transcriptase, protease, and integrase; and *env* codes for glycoproteins gp120 and gp41 [4]. In the regulatory genes, *tat* is responsible for improving proviral transcription; *rev* regulates the transportation of viral mRNAs into the host cell's cytoplasm; other genes are considered "accessory" since they do not play irreplaceable roles during viral replication, but facilitate the virus to invade cells and overcome antiretroviral cellular factor [3]. The viral structures coded by the genome allow the virus to infect cells efficiently, protein capsid and nucleocapsid protect the genetic information of the virus. The enzymes carry out the steps during the invasion and replication of the virus. The glycoproteins gp120 and gp41 help the virus bind to CCR5 receptors on the host cell and fuse into the cell membrane [4].

3.2. The HIV Life Cycle

The HIV life cycle could be roughly divided into three parts: entry, expression, and budding [5]. For a clearer explanation, the three parts could be further classified into seven steps: 1. Binding, 2. Fusion (entry), 3. Reverse transcription, 4. Integration, 5. Replication (expression), 6. Assembly, 7. Binding (binding). During the entry phase, the gp120 glycoprotein binds to the CCR5 receptor on the surface of CD4+ cells to gain entry for the virion. The gp41 glycoprotein helps the protein capsid of the virus to

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fuse with the cell membrane, releasing the inner nucleocapsid into the cytoplasm [4]. After entering the host cell, HIV starts its replication. The viral RNA and enzymes covered in the nucleocapsid are released. The reverse transcriptase reverse transcribes the viral RNA into viral DNA. This conversion allows viral DNA to enter the cell nucleus through the nuclear pore complex and be integrated into the cell's genetic material by integrase. Viral DNA then gains control of the cell and can turn it into a viral-producing factory. After transcribing the viral DNA, the machinery of the host cell will produce long strands of viral proteins that are later used as the building block of new viruses. Those materials are assembled into new, immature HIV after being transported to the surface of the cell. At this point, the viruses are not infectious yet. New HIV buds out of the host cell. Within the virus, protease cuts the long chain of viral proteins, creating mature HIV[3, 5]. Because the replication cycle of HIV is complicated, the blocking of any of the steps above results in failure to produce new viruses. Based on this central idea, scholars invent medication against HIV infection.

4. Treatments

4.1. The Development of Antiretroviral Therapies

Antiretroviral therapies are drugs targeting retroviruses, usually by inhibiting the process of the replication cycle of the viruses. Belonging to the retrovirus group, HIV could also be controlled by antiretroviral medication. The first drug proven to be effective against HIV is azidothymidine (AZT). It was first developed as an anti-cancer drug, but instead of curing cancer, it was later used for treating AIDS [6]. AZT is a kind of nucleoside reverse transcriptase inhibitor (NRTI), which blocks the reverse transcription step in the HIV life cycle, forbidding the virus to reverse transcribe its viral RNA. Fischl et al have conducted an experiment investigating the efficacy of AZT toward AIDS patients. They measured the CD4+ cell count in the patient's blood as an indicator of the strength of their immune system. Their results indicated that patients taking AZT had higher CD4+ cell counts compared to the placebo group, and the cell counts gradually increased after a longer time taking AZT, proving that AZT is effective against HIV replication [7].

Although AZT was initially effective in controlling AIDS, the high mutation rate of the viral genome made the virus develop resistance against this drug. Therefore, scientists started to explore new drugs, such as other NRTIs, to treat AIDS. In the early 1990s, data showed that the combination of AZT and another NRTI, zalcitabine, was more effective than using AZT alone [6]. This finding boosts the use of combination therapy in treating AIDS. People start to apply different combinations of NRTIs to prevent the development of drug resistance.

The major advance in AIDS treatment came in 1996. Researchers found that the combination of three drugs could suppress HIV replication to a minimal extent in a durable manner [6]. This triple-drug therapy, also known as highly active antiretroviral therapy (HAART), is the treatment for AIDS that people continue to use now. People realized that more effective treatment of AIDS is possible, and started to consider the initiation and decision of a more complex treatment based on various factors like viral pathogenesis and antiretroviral resistance patterns [8]. At this stage, the treatment of AIDS became more specified and could be adjusted based on the patient's reaction after starting the therapy. More drugs are also identified to be effective against HIV replication and later approved to be used in HAART. By the early 2000s, the type of drugs has increased from NRTI combinations to the combination of NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) [9]. In modern HAART, six different types of inhibitors are applied, including NRTIs, NNRTIs, PIs, Integrase strand transfer inhibitors (INSTIs), fusion inhibitors (FIs), and chemokine receptor antagonists (CCR5 antagonists) [10]. They target the steps of reverse transcription, budding, integration, fusion, and binding in the HIV replication cycle, respectively. The combinations of these drugs could maintain the viral load in the patient's body to a very small amount for their whole life, giving AIDS patients a chance to survive and live as normal people.

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4.2. Side Effects and Drawbacks

HAART is a savior for AIDS patients, but there are still difficulties and challenges people need to face when taking the therapy. The most common and severe problem patients are encountering is the side effects of antiretroviral drugs. They possibly damage or affect some body functions while they are suppressing AIDS. NRTIs and NNRTIs are known for mitochondrial toxicity. They inhibit mitochondrial DNA polymerase as well as terminate the HIV DNA chain, causing an impaired synthesis of mitochondrial enzymes that make ATP by oxidative phosphorylation [11]. Hypersensitivity is another complication that could be triggered by multiple types of antiretroviral drugs, resulting in symptoms like rashes or fever. The cause of hypersensitivity remains unknown, and scientists suggest that it could be related to immune activation and cytokines [11]. Hepatitis could also be caused by taking HAART, which is suspected to be related to improved immune response [11]. Plenty of side effects are also related to specific drugs under a type, such as efavirenz causing central nervous system effects and indinavir causing renal tubule obstructions due to low water solubility [10, 11]. HAART leads to many kinds of side effects, some of them with explanations and some of them with unknown causes. Patients need to withstand them on their path of fighting AIDS.

Another difficulty that patients have to overcome is the adherence to the therapy. HAART is composed of three drugs with complex dosing and timing, and people receiving the treatment need to take the pills for their whole life. The routine could be interrupted by various causes, leading to a decreased efficiency of the treatment. Patient factors that could affect adherence to the therapy include active substance abuse, sexual contact, youth, depression, lower level of education, etc [12]. The side effects as mentioned above also obstruct patients from constantly taking their medication. Without constant adherence to medication, the effect of the therapy could be reduced, therefore discouraging the patients from accepting the dosing. To help patients to adhere to the treatment, alarm devices, and medical support and reminders have been provided to them [12]. Future solution to the adherence problem has focused on the duration of drug effects and reducing the problem of missing doses [12].

5. Cases and Attempts for Curing HIV

5.1. The Berlin Patient

Timothy Ray Brown, known as “The Berlin Patient,” is the first and only human cured of HIV now. After testing positive for HIV in 1995, he began living with the virus and taking antiretroviral drugs for 11 years. In 2006, he learned that he had developed acute myeloid leukemia, which has no known relationship with AIDS and HAART [13]. To fight this cancer, Brown received chemotherapy that destroyed his original immune system [13]. The chemotherapy failed and his treatment shifted to bone marrow transplants, another common treatment for myeloid leukemia, and received his first transplant in 2007. When he received this transplant, he stopped taking the antiretroviral treatment, which should be devastating to his AIDS infection. However, after this treatment, researchers found his blood carrying a very small amount of viral load and those viruses are ineffective in self-replication [13]. In 2008, Brown’s leukemia returned, and he received a second bone marrow transplant. Then Brown had lived his life 8 years without HIV and 7 years without leukemia.

In the case of the Berlin Patient, the real factor that allowed Brown to get rid of his AIDS as well as leukemia remains known. Several possibilities have been published regarding this result. Scientists found out that Brown’s bone marrow donor had a rare mutation in his CCR5 gene, which the CCR5 receptor on his cells could not normally function [13]. As mentioned above, HIV initiates its infection mainly through binding with the CCR5 receptor on the surface of CD4+ cells, and this gene crippling the function of the CCR5 receptor might block the pathway for the virus to enter the cell. Another explanation for the result is the process of the graft versus host disease, whereas Brown’s new immune system established after transplantation attacks the remains of the old one, which could get rid of the virus [13]. Nevertheless, according to the result of the monkey experiment conducted by Guido Silvestri’s team, the possibilities could not steadily recreate the result of curing HIV and could not be applied to human patients [13]. More investigations regarding the Berlin Patients need to be conducted.

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5.2. The Mississippi Baby

The Mississippi Baby was born to an HIV-1-infected mother. Since the mother had not received parental antiviral treatment, the infant tested positive for the virus in the blood and started to be treated. The treatment was stopped at 18 months against the medical advice and revealed no sign of rebound in viremia [14]. This result raised the expectation that early therapy could prevent the establishment of a stable viral reservoir in infants [14]. However, 27 months later after the interruption of the treatment, viral load rebounds in the infant's blood. Scholars attributed the revival of infection to a group of extremely stable CD4+ cells that carried latent provirus [14]. After cellular activation, those proviruses could bud from host cells, forming mature viruses that can replicate. There are also other cases of viral rebound after the intended cure, bringing insights into the major target of finding the latent reservoir. If latent reservoirs could be detected and regularly monitored in the patients, it is possible off therapy for a period and turn to monitoring for future cure strategies [14].

5.3. Lulu and Nana

In 2018, the gene-edited babies Lulu and Nana became international news, bringing scientific debate and media speculation around the feasibility and moral concerns about this practice. The girls were born to an HIV-1 positive father, thus suspected to carry the virus from their birth. He Jiankui, the scientist who conducted this process, claimed in his interview that he had used CRISPR, the Cas9 genome-editing tool, to disable the CCR5 gene of the girls and provide them with HIV resistance [8]. He also mentioned that the twins are now healthy and living with their parents, with DNA sequencing showing that the editing has only affected the target gene [15]. However, since his results were not verified and published, many scientists suspect underlying negative effects on the health of the girls and whether the editing worked [15][16]. Arguments including humanitarian suspects, lack of experience and investigations, and unnecessary action that could cause extra harm were posed to doubt this practice. Later investigations into the results showed that the editing did take place, but none of them provided effective resistance to their girls against HIV [16]. Lulu received deletion for 15 base pairs on the targeted gene, but only for one in two copies of the CCR5 gene, which means with one normal gene she still possesses normal CCR5 receptors; Nana had bases added for one copy and deleted for another, but there is a chance that she would be "genetic mosaic" and has unaffected cells with normal CCR5 [16]. The results are discouraging to further research regarding this practice, but it enlightened one of the paths for future cures of AIDS. More things need to be considered when applying gene-edition to embryos, and any breakthrough would be significant yet controversial in both gene-editing and HIV treatment fields.

6. Conclusions

The history of fighting AIDS is not remote yet rough, testing human resilience, scientific innovation, and the power of collective action. From the pathologic investigation and analysis of HIV, the development of antiretroviral drugs and HAART, to modern attempts that people try to cure AIDS, understanding has built up over time and effort about this mysterious disease. As the infections could be controlled by HAART, AIDS is now far from as fatal as it was initially discovered. Though an immunization or a real cure has still not been found, the HAART is gradually being perfected and several cases have shed light on new paths for finding the cure. Eventually, people could completely control this disease and end this global health crisis.

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