Available online at www.ujpronline.com
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

REVIEW ARTICLE

A BRIEF OVERVIEW OF HIV TREATMENT STRATEGIES: A FOCUSED LOOK AT CHALLENGES AND OPPORTUNITIES

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Article Info:

Article History:
Received: 11 December 2024
Reviewed: 8 January 2025
Accepted: 20 February 2025
Published: 15 March 2025

Cite this article:
Eissa ME. A brief overview of hiv treatment strategies: A focused look at challenges and opportunities. Universal Journal of Pharmaceutical Research 2025; 10(1): 49-55.
http://doi.org/10.22270/ujpr.v10i1.1273

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Abstract

HIV continues to be a major global health concern, impacting millions. While antiretroviral therapy (ART) has dramatically improved outcomes, transforming HIV into a manageable chronic condition rather than a death sentence, a cure remains elusive. This mini-review examines the intricacies of HIV infection and explores novel curative strategies. Key challenges include the persistence of latent HIV reservoirs, where the virus lies dormant and undetectable and the emergence of drug resistance due to HIV's high mutation rate. Promising avenues of research include using Artificial Intelligence (AI) and Machine Learning (ML) to improve drug discovery and personalize treatment. Nanoparticles are being developed to deliver drugs directly to infected cells, improving effectiveness and minimizing side effects. Synthetic biology approaches, such as CAR-T and CAR-NK cells, aim to engineer immune cells to target and eliminate infected cells. Gut microbiome modulation is also being investigated as a way to boost immune response and reduce viral reservoirs. RNA interference (RNAi) uses siRNAs to suppress viral gene expression. Finally, therapeutic exosomes offer a new way to deliver antiviral agents to infected cells. These cutting-edge strategies offer hope for a functional or sterilizing cure. Further research and clinical trials are crucial to optimize these technologies and translate them into clinical practice, ultimately aiming to eliminate HIV and end the global epidemic.

Keywords: ART, Artificial Intelligence, CAR-T cells, HIV cure, Nanoparticles, RNA interference, synthetic biology.

INTRODUCTION

HIV continues to be a significant health concern on a global scale, impacting a large number of individuals across the world. Although considerable progress has been made in the field of medicine, the fight against HIV is still ongoing. The development and use of antiretroviral therapy (ART) has marked a turning point in the management of the disease, leading to substantial improvements in the well-being of people infected with HIV and changing the perception of the illness from a deadly one to a chronic condition that can be managed[1]. Nevertheless, ART is not a curative treatment for HIV. While it effectively reduces the amount of virus in the body by preventing it from replicating, it does not eliminate the virus entirely. This inability to completely remove HIV is largely attributed to the existence of hidden reservoirs of HIV-infected cells. In these cells, the virus can remain inactive, or latent, and is protected from both the body's immune responses and the effects of antiretroviral medications[2,3]. Additionally, the development of resistance to ART drugs remains a significant hurdle, complicating treatment regimens and threatening the long-term efficacy of ART[4,5].The persistence of latent HIV reservoirs is one of the most threatening challenges in the quest for a cure[2,3]. Unfortunately, these viral reservoirs form soon after infection and can remain even with extended antiretroviral therapy. While primarily located in resting memory CD4+ T cells, latent viruses can also be found in other cell types and various anatomical locations[6,7]. The processes involved in creating and sustaining these reservoirs are intricate and remain incompletely elucidated. However, it is clear that any strategy aimed at curing HIV must address these latent reservoirs. Drug resistance is another critical issue in HIV treatment. Because HIV mutates at a high rate, it can quickly change and become resistant to the medications used to treat it[5,8]. This can lead to treatment failure and necessitate changes in therapy, which can be costly and have significant side effects[5]. Multiple elements contribute to the rise of drug resistance, including not taking antiretroviral therapy (ART) consistently as prescribed, how easily the virus can genetically mutate to resist the medications being used, and whether the virus already

had resistance to the drugs before treatment began[6]. Addressing drug resistance requires a multifaceted approach, including the development of new drugs with higher barriers to resistance, improved adherence strategies and routine resistance testing. In addition to these challenges, there are several other factors that complicate the search for HIV cure. The virus's ability to integrate into the host genome allows it to persist for the lifetime of the infected cell[7]. The immune system's inability to recognize and eliminate these infected cells is another significant barrier. Furthermore, the diverse genetic variants of HIV and its ability to infect various cell types and tissues add layers of complexity to the problem. Despite these challenges, there is hope. Advances in the understanding of HIV biology and the body's defense mechanism to infection have led to the development of several promising strategies aimed at curing HIV[10]. These include "shock and kill" approaches, which aim to reactivate latent virus and then eliminate it, and "block and lock" strategies, which seek to permanently silence the virus[9-13]. Genetic engineering methods, including Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9 (CRISPR/Cas9), present a possible way to eliminate HIV by precisely targeting and removing viral DNA from infected cells[10-14]. Additionally, therapeutic vaccines and immune-based therapies are being explored to enhance the body's ability to control and eliminate the virus[11,15].This mini review will provide highlights into the complex nature of HIV infection, examining the mechanisms that allow the virus to persist and evade current therapies. It will also discuss the latest research and potential strategies for developing a cure, highlighting the progress made and the challenges that remain. By understanding the intricate interplay between HIV and the host immune system, strides can pave the way for innovative approaches that bring us closer to the ultimate goal of eradicating HIV.

The impact of Antiretroviral Therapy ART and exploring different strategies

Antiretroviral therapy, commonly referred to as ART, is a treatment regimen for HIV that involves the use of multiple medications. These medications work in synergy to impede the virus's replication process. By halting the reproduction of HIV, ART effectively diminishes the viral load in the body, thereby fortifying the immune system's functionality[1]. Antiretroviral therapy (ART) is not a cure for HIV, but it can greatly enhance the well-being and longevity of individuals affected by the virus[1,16]. Since its introduction, ART has significantly reduced HIV-related morbidity and mortality, improved the quality of life for millions of individuals and curtailed the transmission of the virus[1]. ART medications are categorized into several groups, such as Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Integrase Inhibitors, and Fusion Inhibitors. These medications work by interfering with different steps of the HIV life cycle. This action prevents the virus from multiplying and leads to a decrease in the amount of virus in the bloodstream; potentially reaching levels where it is no longer detectable[1]. The inhibition of viral replication halts the development of HIV into AIDS (Acquired Immunodeficiency Syndrome), a state marked by significant harm to the immune system and the emergence of opportunistic infections. The introduction of highly active antiretroviral therapy (HAART) in the mid-1990s marked a significant milestone, combining multiple antiretroviral drugs to enhance efficacy and reduce the likelihood of resistance development. One of the most profound impacts of ART is the dramatic increase in life expectancy for people living with HIV[16]. Before the advent of ART, HIV infection was often a death sentence, with individuals succumbing to AIDS-related complications within a few years of diagnosis[16]. Today, with consistent and effective ART, individuals with HIV can expect to live nearly as long as those without the virus. This extension of life expectancy has allowed people living with HIV to lead full, productive lives, contributing to society and pursuing personal goals. In addition to improving individual health outcomes, ART has played a crucial role in public health by reducing HIV transmission. When taken consistently, ART can lower the viral load to undetectable levels, a state known as viral suppression. Studies have shown that individuals with undetectable viral loads do not transmit the virus to their sexual partners, a concept encapsulated in the slogan "Undetectable = Untransmittable" (U=U)[17,18]. This has significant implications for HIV prevention strategies, emphasizing the importance of widespread access to ART and adherence to treatment regimens. Despite these successes, ART is not without its challenges. One of the primary issues is the persistence of latent HIV reservoirs. These reservoirs consist of cells where the virus remains dormant and undetectable by the immune system and antiretroviral drugs[2-3,7]. Even with prolonged ART, these reservoirs can reactivate, leading to viral rebound if treatment is interrupted[2-4]. Consistent, lifelong compliance with ART is required, which can create a substantial burden for both individuals managing their health and the healthcare systems that support them. A further major obstacle is the emergence of drug resistance. The human immunodeficiency virus's (HIV's) propensity for frequent mutations enables it to evolve quickly, potentially developing resistance to antiretroviral medications, especially when treatment regimens are followed inconsistently[5,8]. Drug-resistant strains of HIV can compromise the effectiveness of ART, necessitating the development of new drugs and treatment strategies[5]. This ongoing arms race between the virus and medical science underscores the need for continuous research and innovation in antiretroviral therapy. The side effects and long-term toxicity of ART also pose challenges[19]. While modern antiretroviral drugs are generally well-tolerated, they can still cause side effects ranging from mild gastrointestinal issues to more severe complications such as cardiovascular disease, liver toxicity and bone density loss[19]. Managing these side effects requires careful monitoring and, in some cases, switching to alternative medications, which can complicate

treatment plans. Looking to the future, the goal of ART extends beyond viral suppression to the ultimate aim of achieving a cure for HIV. Researchers are exploring various strategies to eradicate the virus, including "shock and kill" approaches that aim to activate and then eliminate latent reservoirs and "block and lock" strategies that seek to permanently silence the virus[9,12,13]. Advances in gene editing technologies, such as CRISPR/Cas9 where this system is derived from a natural defense mechanism found in bacteria, where it is used to protect against viral infections. By utilizing a guide RNA molecule, the CRISPR-Cas9 system can be directed to a specific DNA sequence, where the Cas9 enzyme cuts the DNA[10,14,20,21]. This allows scientists to remove, add or modify specific genes, opening up a wide range of possibilities in fields like medicine, agriculture and biotechnology. Additionally, therapeutic vaccines and immune-based therapies are being developed to enhance the body's ability to control and eliminate the virus[11,15]. At the end, while ART has had a transformative impact on the management of HIV, significant challenges remain. The persistence of latent reservoirs, the development of drug resistance and the side effects of long-term therapy highlight the need for ongoing research and innovation[2-5,7,8,19].

Challenges in Achieving a Cure for HIV: Latency, persistence and the development of resistance

HIV infection continues to be a significant global health challenge, despite significant advancements in treatment and management as stated earlier[1]. The ultimate goal of eradicating HIV remains elusive due to several complex and interrelated factors. One of the most significant barriers to curing HIV is the persistence of latent HIV reservoirs[1-4,7]. These reservoirs are established early in the infection and consist of a specific type of white blood cell where the virus becomes inactive, evading detection by the immune system and antiretroviral drugs[2-4]. Latent reservoirs are primarily found in resting memory helper T cells, but they can also reside in other cell types and anatomical sites, such as the brain and lymphoid tissues[4,7]. Several mechanisms contribute to the establishment and maintenance of HIV latency. Chromatin modifications play a crucial role, with histone modifications, including acetylation and methylation, altering the accessibility of the HIV provirus to transcriptional machinery. Additionally, DNA methylation can silence gene expression, including that of the HIV provirus. Transcriptional silencing further compounds this issue, as the availability of transcription factors necessary for viral gene expression is often limited in resting helper T cells. Moreover, certain viral and cellular negative regulatory elements can bind to the HIV genome to inhibit transcription. Post-transcriptional regulation is also significant; inefficient RNA splicing and impaired nuclear export can prevent effective viral gene expression, while microRNAs can target viral RNA, hindering translation. Host cell factors contribute to latency as well, as various host cellular proteins can interact with the HIV genome and interfere with its expression. Furthermore, certain cellular signaling pathways can influence the state of HIV latency, thereby affecting the overall latency of the virus. The reactivation of latent HIV reservoirs can lead to viral rebound if the compliance to ART schedule is compromised, necessitating lifelong adherence to treatment[8]. This reactivation can occur spontaneously or in response to certain stimuli, making it difficult to predict and control. Current research is focused on strategies to either eliminate these reservoirs or permanently silence the virus within them. Several stimuli can reactivate latent HIV from resting CD^4+ T cells. Cytokines play a significant role in this process, including Interleukin-2 (IL-2), which is produced by T cells and stimulates their growth and differentiation; Interleukin-7 (IL-7), which is involved in T cell development and survival; and Tumor Necrosis Factor-alpha (TNF-α), a cytokine that participates in inflammation and the body's defense mechanism. Additionally, other stimuli contributing to HIV reactivation include T-Cell Receptor (TCR) activation, where stimulation of the TCR can lead to cell activation and subsequent viral reactivation; Histone DeAcetylase inhibitors (HDACi), which can modify the structure of chromatin to make it more accessible to transcription factors, thereby promoting viral gene expression; and certain viral infections, such as influenza or CytoMegaloVirus (CMV), which can induce inflammation and trigger the reactivation of latent HIV[22]. In addition to the challenge of latent reservoirs, the development of drug resistance is a major obstacle in the fight against HIV. HIV has a high mutation rate, which allows it to rapidly evolve and develop resistance to antiretroviral drugs. This can compromise treatment leading to failure and mandate changes in therapy, which can be costly and have significant side effects. Drug resistance is influenced by several factors, including incomplete adherence to ART, the genetic barrier to resistance of the drugs used and the presence of pre-existing resistant virus[23-25]. Addressing drug resistance requires a multifaceted approach, including the development of new drugs with higher barriers to resistance, improved adherence strategies, and routine resistance testing. The high mutation rate of HIV also contributes to the genetic diversity of the virus, which complicates treatment and vaccine development[8]. This diversity allows the virus to adapt to different selective pressures, including host defenses and antiretroviral drugs. As a result, a single therapeutic approach is unlikely to be effective against all strains of HIV. This necessitates the development of combination therapies that can target multiple stages of the viral life cycle and reduce the likelihood of resistance development. Despite these challenges, there is hope for the future. Advances in the understanding of HIV biology and the host defense to infection have led to the development of several promising strategies aimed at curing HIV. Gene editing technologies, such as CRISPR/Cas9, offer the potential to excise HIV DNA from infected cells, providing a possible route to a functional cure[10,14,20,21,26]. While a fully effective HIV vaccine remains elusive, significant research efforts are underway to develop vaccines that can prevent or treat HIV infection[27,28]. The ideal HIV vaccine would induce

a robust and lasting immune response, which includes the production of neutralizing antibodies and cytotoxic T cells capable of effectively targeting and eliminating the virus[27]. There are two main types of HIV vaccines: preventive vaccines and therapeutic vaccines. Preventive vaccines are designed to prevent HIV infection in uninfected individuals, aiming to stimulate the immune system before exposure to the virus[29,30]. On the other hand, therapeutic vaccines are aimed at individuals already infected with HIV; their purpose is to boost the immune response to help control viral replication and potentially eliminate the virus from the body[29]. However, several challenges hinder the development of an effective HIV vaccine. One significant issue is viral variability; HIV is highly variable, making it difficult to create a vaccine that can targ*et al*l strains of the virus[8]. Additionally, HIV's ability to evade the immune response through rapid mutation and its capacity to infect immune cells complicate vaccine development. Furthermore, inducing a strong and sustained immune response against this complex virus presents a difficult problem[5, 23-25]. In addition to vaccine efforts, immune-based therapies aim to harness the body's immune system to combat HIV infection[1,3,9]. These therapies can be utilized alongside ART to improve treatment outcomes for individuals living with HIV. Several types of immune-based therapies have been explored. Monoclonal antibody therapy involves using monoclonal antibodies to specifically target proteins on the surface of HIV, neutralizing the virus and preventing it from infecting healthy cells.[11] Adoptive T cell therapy focuses on engineering T cells, a type of white blood cell, to recognize and destroy HIV-infected cells. Cytokine therapy leverages cytokines signaling molecules that regulate the immune response to enhance the immune system's ability to fight HIV. Collectively, these strategies hold promises for improving the management of HIV and advancing towards a potential cure[1,3,9].

Innovative and futuristic solutions for HIV treatment

The pursuit of an HIV cure has led researchers to explore a variety of innovative and unforeseen treatment strategies. Among these, several groundbreaking approaches have emerged, each offering unique mechanisms and pathways that could potentially lead to the eradication of HIV. The implementation of Artificial Intelligence and Machine Learning (ML) will be crucial in developing and accelerating discovery of new drugs[31,32]. Moreover, customization and personalization of the treatment system and plans case-by-case based on individual needs and patient situations can be explored and enhanced using appropriate algorithms[31,32]. One promising approach involves the use of therapeutic nanoparticles[33,34]. These nanoparticles can be engineered to deliver antiretroviral drugs directly to HIV-infected cells, enhancing the efficacy of the treatment and reducing systemic side effects[33,34]. The mechanism involves coating nanoparticles with ligands that specifically bind to receptors on the surface of HIV-infected cells. Once bound, the nanoparticles are internalized by the cells, where they release their drug payload. This targeted delivery system ensures that higher concentrations of the drug reach the infected cells, potentially overcoming issues related to the side effects, drug resistance and latency. Additionally, nanoparticles can be designed to carry multiple drugs, allowing for combination therapies that target different stages of the HIV life cycle[34].

Another innovative strategy is the use of synthetic biology to engineer immune cells that can better recognize and destroy HIV-infected cells[35,36]. This approach involves modifying T cells or natural killer (NK) cells to express chimeric antigen receptors (CARs) that specifically target HIV antigens. These CAR-T or CAR-NK cells are then expanded in the laboratory and infused back into the patient. The engineered cells can seek out and eliminate HIV-infected cells with high precision. The mechanism relies on the ability of CARs to bind to HIV antigens presented on the surface of infected cells, triggering a robust immune response that leads to the destruction of these cells. This approach has shown promise in preclinical studies and is currently being evaluated in clinical trials. A novel and less explored avenue in complementary medicine is the use of microbiome modulation to enhance the immune response against HIV[37,38]. The gut microbiome plays a crucial role in regulating the immune system and dysbiosis (an imbalance in the microbiome) has been linked to HIV progression. Researchers are investigating whether restoring a healthy microbiome through the use of probiotics, prebiotics or Fecal Microbiota Transplantation (FMT) can improve immune function and reduce HIV reservoirs. The mechanism involves promoting the growth of beneficial bacteria that can enhance gut barrier function, reduce inflammation and support the activity of HIV-specific immune cells. This approach is still in its early stages, but it offers a unique and potentially complementary strategy to existing treatments. Another unforeseen treatment strategy involves the use of RNA interference (RNAi) to silence HIV genes[39]. RNAi is a natural cellular process that can be harnessed to degrade specific mRNA molecules, preventing the production of viral proteins. Researchers are developing small interfering RNAs (siRNAs) that target essential HIV genes, such as those encoding the viral enzymes reverse transcriptase and integrase. These siRNAs can be delivered to infected cells using lipid nanoparticles or viral vectors. Once inside the cells, the siRNAs bind to their target mRNA, leading to its degradation and preventing the production of viral proteins. This approach has the potential to reduce viral replication and limit the establishment of new infections. In addition to these approaches, there is growing interest in the use of therapeutic exosomes[40,41]. Exosomes are small vesicles released by cells that can transfer proteins, lipids and nucleic acids between cells. Researchers are exploring the use of exosomes derived from HIV-resistant individuals or genetically engineered to carry antiviral molecules. These therapeutic exosomes can be administered to patients, where they can deliver their cargo to HIV-infected

cells, inhibiting viral replication and promoting immune responses. The mechanism involves the natural ability of exosomes to fuse with target cells and release their contents, providing a novel and potentially less invasive method of delivering therapeutic agents.In conclusion, the pursuit of an HIV cure has led to the development of several unforeseen and innovative treatment strategies[42-47,49,51-54]. Therapeutic nano-particles, synthetic biology approaches, microbiome modulation, RNA interference and therapeutic exosomes each offer unique mechanisms and pathways towards eradicating HIV[37,38,45]. While significant challenges remain, these approaches represent the cutting edge of HIV research and hold promise for achieving a functional or even sterilizing cure[41,46,48]. Continued research and clinical trials will be essential to refine these techniques and bring them closer to clinical application.

Nanorobotics represents a cutting-edge frontier in the treatment of HIV, offering a novel approach that could revolutionize how researchers manage and potentially cure the infection[48,55]. These microscopic robots, designed to perform precise tasks at the cellular and molecular levels, hold promise for addressing some of the most challenging aspects of HIV treatment, including targeted drug delivery, viral load reduction and even gene editing. One of the primary applications of nanorobotics in HIV treatment is the targeted delivery of antiretroviral drugs. Traditional drug delivery methods often result in systemic distribution, which can lead to side effects and reduced drug efficacy. Nanorobots can be engineered to recognize specific markers on the surface of HIV-infected cells. By binding to these markers, nanorobots can deliver their drug payloads directly to the infected cells, ensuring higher concentrations of the drug at the site of infection while minimizing systemic exposure[34, 51,52,56]. This targeted approach not only enhances the effectiveness of the treatment but also reduces the likelihood of the side effects and drug resistance developing, as the virus is less able to evade the concentrated attack. In addition to drug delivery, nanorobots can be utilized for real-time monitoring and diagnostics. These tiny machines can be equipped with sensors to detect the presence of HIV or measure viral load within the body. By providing continuous monitoring, nanorobots can offer valuable insights into the effectiveness of treatment regimens and the progression of the disease. This real-time data can help clinicians make more informed decisions about treatment adjustments, potentially improving patient outcomes[57]. Another innovative application of nanorobotics is in the realm of gene editing. Nanorobots can be designed to carry gene-editing tools, such as CRISPR/Cas9, directly to HIV-infected cells. Once inside the cells, these tools can excise the integrated HIV DNA from the host genome, effectively curing the infection at the cellular level[39,41,46,58]. This approach addresses one of the most significant challenges in HIV treatment: the persistence of latent reservoirs. By removing the viral DNA, nanorobots could potentially eliminate these reservoirs, paving the way for a functional cure. Furthermore, nanorobots can be engineered to perform immunomodulatory functions. They can be programmed to enhance the body's natural immune response against HIV by delivering immune-stimulating agents or by directly interacting with immune cells to boost their activity. For example, nanorobots could deliver cytokines or other signaling molecules that activate HIV-specific T cells, enhancing their ability to recognize and destroy infected cells[40,47,53,54]. This immunomodulatory approach could complement existing antiretroviral therapies and provide a more robust defense against the virus. The development of nanorobotics for HIV treatment is still in its early stages, but the potential benefits are immense. Researchers are exploring various materials and designs to optimize the functionality and safety of these nanomachines. Biocompatibility is a critical consideration, as nanorobots must be able to operate within the human body without eliciting adverse immune responses. Advances in nanotechnology and materials science are continually improving the design and performance of nanorobots, bringing us closer to their clinical application. Thus, nanorobotics offers a promising and innovative approach to HIV treatment. By enabling targeted drug delivery, real-time monitoring, gene editing and immunomodulation, nanorobots have the potential to overcome some of the most significant challenges in managing and curing HIV. As research progresses, these tiny machines could become a cornerstone of HIV therapy, transforming the landscape of treatment and bringing us closer to the ultimate goal of eradicating the virus.

CONCLUSIONS

The pursuit of an HIV cure has spurred diverse innovative strategies, each with unique mechanisms. Despite challenges like latency and drug resistance, advancements in gene editing, immunotherapy and novel delivery systems offer hope. A multifaceted approach is crucial, integrating therapeutic nanoparticles, synthetic biology, microbiome modulation, RNA interference and therapeutic exosomes. These target the virus and enhance immunity, offering a holistic approach. Synergies between these treatments, like combining gene editing with nanoparticles or microbiome modulation with immunotherapy, are promising. Personalized treatment and AI, especially ML, are also vital. Exploring the gut microbiome's role and restoring its health could enhance immune function and reduce inflammation. Therapeutic exosomes offer targeted, less invasive drug delivery. Nanorobotics also holds promise. While challenges remain, these innovative strategies offer unprecedented hope. Integrating multiple modalities, exploring new pathways and realizing synergistic effects mark a new frontier in HIV research, bringing us closer to eradication and impacting global health.

ACKNOWLEDGEMENTS

None to declare.

AUTHOR'S CONTRIBUTION

Eissa ME: conceived the idea, writing the manuscript, literature survey, formal analysis, critical review.

DATA AVAILABILITY

Upon request, the accompanying author can furnish the empirical data used to bolster the findings of the study.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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