INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

GENE THERAPY FOR HIV: A REVOLUTIONARY APPROACH TOWARDS A CURE

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ARTICLE INFO

Article history
Received 09/08/2023
Available online
31/08/2023

Keywords
Gene Editing,
Gene Silencing,
Gene Modification,
Immune Cell Engineering,
Augmentation.

ABSTRACT

Human Immunodeficiency Virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) continue to pose a significant global health burden, demanding novel strategies to combat this devastating pandemic. Gene therapy, a cutting-edge therapeutic approach, has emerged as a promising avenue for revolutionizing the treatment landscape by offering a potential cure for HIV and AIDS. This review article provides a comprehensive analysis of the advancements made in gene therapy research, highlighting the diverse modalities employed and their efficacy in combating HIV infection. From traditional gene editing tools, such as zinc finger nucleases and transcription activator-like effector nucleases, to the breakthrough CRISPR-Cas9 system, this appraisal delves into the gene editing technologies employed to target and manipulate the HIV genome. Additionally, the versatile approaches utilized in gene therapy, including gene augmentation, gene silencing, and immune cell engineering, are explored in the context of HIV and AIDS treatment. Furthermore, we addressed ethical considerations associated with this revolutionary approach. By providing a comprehensive overview of the current state of gene therapy for HIV and AIDS, this review aims to inspire further research and foster the development of curative strategies, paving the way towards an eventual cure for this global health crisis.

DOI NO: 10.5281/zenodo.8307643

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*Please cite this article in press as **Seetharam Gude** et al. Gene Therapy for HIV: A Revolutionary Approach towards A Cure. Indo American Journal of Pharmaceutical Research.2023:13(08).*

INTRODUCTION

Human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) constitute a range of medical conditions resulting from the infection caused by the human immunodeficiency virus (HIV), a retrovirus. Subsequent to the initial infection, an individual may not exhibit any noticeable symptoms or may undergo a short-lived period of flu-like illness which can persist for multiple days. Generally, following this initial phase, a protracted incubation period ensues, characterized by the absence of symptoms, during which the virus undergoes silent replication and gradually weakens the immune system. If the infection progresses, it progressively impairs the immune system, thereby heightening the susceptibility to common infections such as tuberculosis, as well as other opportunistic infections and infrequent tumors in individuals with normal immune functionality. These latter symptoms of infection are commonly referred to as acquired immunodeficiency syndrome (AIDS). Typically, this stage is also accompanied by unintentional weight loss, as the body's ability to absorb and utilize nutrients becomes compromised. It is crucial to bear in mind that while HIV/AIDS is a grave and potentially life-threatening condition, individuals can lead long and meaningful lives with appropriate medical care and treatment.

Unprotected sexual contact (including anal and vaginal sex), contaminated hypodermic needles or blood transfusions, and maternal transmission during pregnancy, delivery, and breastfeeding are the primary methods by which HIV is transmitted. There are certain bodily fluids that do not transmit the virus, including saliva, sweat, and tears.**[1-3]**

Virology:

As the name implies, HIV is a retrovirus that is mainly responsible for infecting components of the human immune system such as CD4+ T cells, macrophages, and dendritic cells. It directly and indirectly destroys CD4+ T cells.

HIV is a member of the genus *Lentivirus*, part of the family *Retroviridae*. Lentiviruses are single-stranded, positive-sense, enveloped RNA viruses that infect many mammal species. They cause long-duration illnesses with a long incubation period. Upon entry into the target cell, the viral RNA genome is converted into double-stranded DNA by a virally encoded reverse transcriptase. The viral DNA is then integrated into the cellular DNA by a virally encoded integrase and host co-factors. This integration may enable the virus to become latent, avoiding detection by the immune system. Alternatively, the virus may replicate by transcribing new RNA genomes and viral proteins, which are released from the cell as new virus particles.[**4-6]**

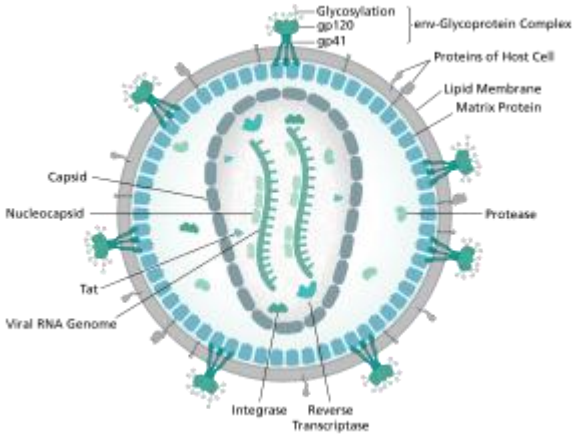

Fig-1: Structure of HIV virion.

pathophysiology:

HIV virion particularly targets CD4+ T cells, which play a crucial role in coordinating the body's immune response. The pathophysiology of HIV involves a series of complex interactions between the virus and the immune system, leading to the progressive deterioration of immune function and the development of acquired immunodeficiency syndrome (AIDS).

1. ***Transmission*:** HIV can be transmitted through various routes, including sexual contact, sharing needles or syringes, mother-to-child during childbirth or breastfeeding, and exposure to infected blood. Once the virus enters the body, it seeks out target cells, predominantly CD4+ T cells, macrophages, and dendritic cells.
2. ***Viral Replication*:** HIV enters target cells by binding to specific receptors on their surface, primarily the CD4 receptor and a co-receptor (CCR5 or CXCR4). Upon entry, the virus releases its genetic material, which is in the form of RNA, into the host cell. The viral RNA is then reverse transcribed into DNA by the enzyme reverse transcriptase. The newly synthesized viral DNA integrates into the host cell's genome, becoming a permanent part of the cell.
3. ***Destruction of CD4+ T Cells*:** As HIV replicates within the host cells, it leads to their destruction. The virus kills CD4+ T cells directly through viral-induced cell death and indirectly by causing immune responses that trigger cell death pathways. This continuous depletion of CD4+ T cells weakens the immune system's ability to mount an effective defense against infections and diseases.
4. ***Chronic Immune Activation and Inflammation*:** HIV infection triggers chronic immune activation and inflammation in the body. The immune system responds to the presence of the virus by releasing inflammatory molecules and activating immune cells. However, this persistent immune activation leads to increased production of cytokines, which can damage healthy tissues and organs and contribute to the progression of HIV disease.
5. ***Impaired Immune Function*:** As the number of CD4+ T cells declines, the immune system becomes increasingly compromised. The body's ability to mount an effective immune response against opportunistic infections and malignancies is severely impaired. Individuals with advanced HIV infection may experience recurrent infections, opportunistic infections, and certain types of cancers, which are hallmarks of AIDS.
6. ***Development of AIDS*:** Acquired Immunodeficiency Syndrome (AIDS) is the advanced stage of HIV infection. It is characterized by severe immune suppression and the occurrence of opportunistic infections and malignancies. The progression to AIDS is typically defined by a significant decline in CD4+ T cell count or the development of specific AIDS-defining conditions, such as Kaposi's sarcoma, Pneumocystis pneumonia, or cytomegalovirus infection.

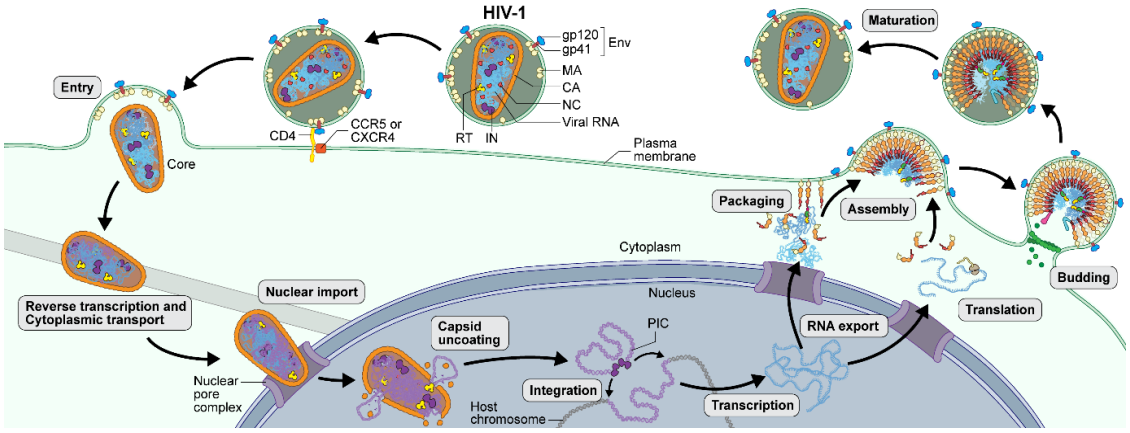

Fig-2: Life Cycle of HIV virion.

Traditional treatment approaches, such as antiretroviral therapy (ART), have significantly improved the quality of life for individuals living with HIV. However, a complete cure has remained elusive. In recent years, gene therapy has emerged as a promising avenue for treating HIV and potentially eradicating the virus altogether.

Understanding gene therapy:

Gene therapy is a therapeutic approach that aims to treat or prevent diseases by modifying the genetic material within a person's cells. It involves introducing, altering, or silencing genes to correct genetic disorders, enhance immune responses, or inhibit the progression of diseases. Gene therapy holds great promise for treating a wide range of conditions, including inherited disorders, cancer, viral infections, and neurological diseases.

Types of Gene Therapy:

***Gene Replacement Therapy*:**

This approach is used to correct genetic mutations by introducing a functional copy of the defective gene into the patient's cells. The therapeutic gene is typically delivered using viral vectors or non-viral methods. Viral vectors, such as retroviruses, lentiviruses, adenoviruses, and adeno-associated viruses (AAVs), are modified to carry the therapeutic gene into the target cells. Once inside the cells, the therapeutic gene is integrated into the genome, allowing the production of functional proteins.

***Gene Augmentation Therapy*:**

Gene augmentation therapy involves introducing additional copies of a functional gene into the patient's cells to compensate for the deficient or mutated gene. This approach is commonly used in inherited disorders caused by the loss or dysfunction of a particular gene. By increasing the expression of the functional gene, the therapy aims to restore normal cellular function and alleviate disease symptoms.

1. ***Gene Suppression Therapy*:** Gene suppression therapy, also known as gene silencing, aims to inhibit the expression of disease-causing genes or specific viral genes. It is particularly relevant for conditions in which overexpression or abnormal activity of a gene contributes to the disease process. Two commonly used approaches in gene suppression therapy are RNA interference (RNAi) and antisense oligonucleotides (ASOs). RNAi involves the introduction of small RNA molecules, called small interfering RNAs (siRNAs), which target and degrade specific messenger RNA (mRNA) molecules, preventing the production of the corresponding protein. ASOs, on the other hand, are short DNA or RNA molecules that bind to specific mRNA molecules, blocking their translation or causing their degradation.
2. ***Genome Editing*:** Genome editing techniques enable precise modifications of the genetic material within cells. The most widely used genome editing tool is the CRISPR-Cas9 system, which utilizes a guide RNA (gRNA) to direct the Cas9 enzyme to a specific location in the genome. Cas9 then introduces double-stranded breaks at the target site, triggering the cell's DNA repair mechanisms. This allows for gene insertions, deletions, or replacements, effectively editing the genome. Other genome editing tools, such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), operate through similar principles but use different DNA-binding domains to target specific sequences.
3. ***Cell Therapy*:** Cell-based gene therapy involves modifying a patient's cells outside the body and then reintroducing them back into the patient. One prominent example is chimeric antigen receptor (CAR) T-cell therapy, which harnesses the power of the patient's own immune cells to target and destroy cancer cells. In this therapy, T cells are extracted from the patient, modified to express a CAR specific to the cancer cells, and then reinfused into the patient. The CAR allows the T cells to recognize and eliminate cancer cells more effectively.

Gene editing tools for targeting the HIV genome:

Advanced gene editing tools have revolutionized the field of gene therapy for targeting the HIV genome. Among these tools, the CRISPR-Cas9 system has garnered significant attention and demonstrated great potential. Here is a detailed explanation of advanced gene editing tools for targeting the HIV genome:

CRISPR-Cas9 System:

The CRISPR-Cas9 system is a revolutionary gene editing tool that has transformed the field of genetic research and holds immense potential for therapeutic applications. It is derived from a naturally occurring bacterial defense mechanism against viral infections

a. CRISPR: CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is a unique DNA sequence found in the genomes of bacteria and archaea. It acts as an adaptive immune system, allowing these organisms to defend against viral infections. The CRISPR region consists of repeated sequences interspersed with short viral or foreign DNA fragments known as spacers.

b. *Cas Proteins*: Cas (CRISPR-associated) proteins are essential components of the CRISPR system. They act as molecular scissors capable of cutting DNA. Cas proteins work in conjunction with the CRISPR RNA (crRNA) to identify and cleave specific DNA sequences.

c. *Guide RNA (gRNA)*: In the CRISPR-Cas9 system, a single-guide RNA (sgRNA) is used, which combines both the CRISPR RNA (crRNA) and the trans-activating CRISPR RNA (tracrRNA) into a single molecule. The gRNA serves as a guide to direct the Cas9 enzyme to the target DNA sequence.

d. *Cas9 Nuclease*: Cas9 is the most widely used nuclease in the CRISPR system. It acts as a pair of molecular scissors capable of creating double-strand breaks (DSBs) at specific target sites within the genome. The Cas9 protein consists of two nuclease domains that cut the two strands of DNA, creating a DSB.

e. *Recognition and Cleavage*: To initiate the gene editing process, the gRNA binds to a specific DNA sequence complementary to the target site within the genome. The gRNA contains a 20-nucleotide sequence known as the target sequence, which directs the Cas9 nuclease to the precise location for DNA cleavage.

f. *Double-Strand Break Repair*: After the Cas9 nuclease generates a DSB, the cell's natural DNA repair mechanisms come into play. Two primary repair pathways are involved:

Non-Homologous End Joining (NHEJ): NHEJ is an error-prone repair mechanism that directly re-joins the broken DNA ends. This often leads to small insertions or deletions (indels) at the target site. These indels can disrupt the functionality of the targeted gene or introduce frameshift mutations.

Homology-Directed Repair (HDR): HDR is a more precise repair mechanism that uses an exogenous DNA template as a repair template. This template contains the desired genetic modification. When introduced alongside the CRISPR-Cas9 system, HDR allows for precise DNA modifications, such as gene insertions, gene deletions, or gene corrections.

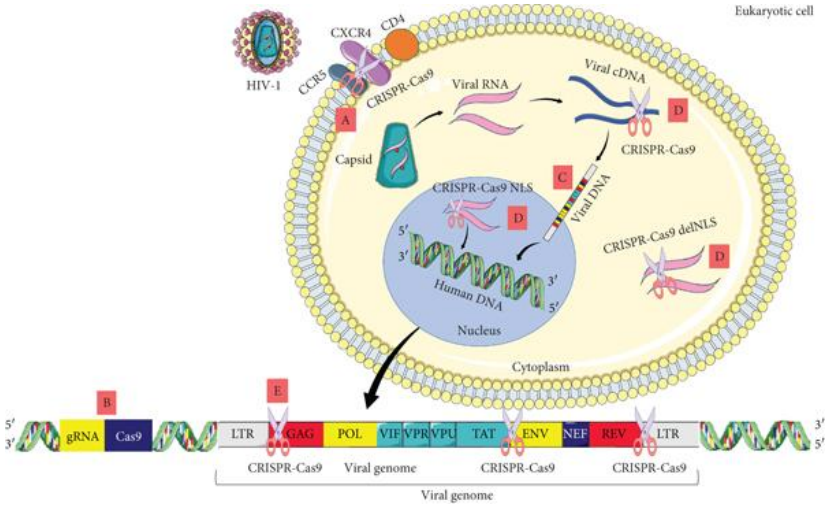

Fig-3: Overview of the CRISPR-Cas strategy to interfere on the HIV-1 infection cycle.

A: The use of the CRISPR-Cas system in several types of cells for introducing mutations that affect the CCR5 and/or CXCR4 receptors; B:A: Cas and gRNA stable expression from the host cell genome inhibit virus-cell invasion, reverse transcription, and integration; C:gRNAs can be targeted to a variety of sites within the HIV-1 genome, including LTR, gag, pol, tat, and rev to inhibit viral replication; D:the transduction of Cas9-NLS and gRNA into the R and U5 regions of the Long Terminal Repeat before the viral DNA is integrated into the host DNA; E: the rupture of the proviral genome from latent reservoirs, targeting the LTR region in particular or other viral genes, thereby modulating several HIV-1 characteristics and its ability to infect.[7]

Zinc Finger Nucleases (ZFNs):

Zinc finger nucleases are engineered proteins that consist of a DNA-binding domain and a nuclease domain. The DNA-binding domain is designed to recognize and bind to specific DNA sequences within the HIV genome, while the nuclease domain introduces DSBs at the targeted site. Similar to CRISPR-Cas9, the DSBs can be repaired by NHEJ or HDR, leading to targeted disruption or modification of viral genes.

Transcription Activator-Like Effector Nucleases (TALENs):

Transcription activator-like effector nucleases are another type of engineered proteins used for gene editing. TALENs are composed of a DNA-binding domain derived from transcription activator-like effectors (TALEs) and a nuclease domain. The DNA-binding domain can be customized to recognize specific sequences within the HIV genome, while the nuclease domain induces DSBs. Repair of the DSBs through NHEJ or HDR enables precise editing of viral genes.

Prime Editing:

Prime editing is a recently developed gene editing technique that expands the capabilities of CRISPR-Cas9. It allows for precise modifications of the HIV genome without requiring DSBs. Prime editing utilizes a modified Cas9 protein fused with a reverse transcriptase enzyme and an engineered gRNA containing a prime editing guide. The prime editing guide directs the reverse transcriptase to copy the desired edit from a synthetic RNA template and precisely inserts it into the HIV genome. This technique offers the potential for more precise and efficient editing with fewer off-target effects.

Mechanisms of gene therapy for HIV and AIDS:

Mechanisms of gene therapy for HIV and AIDS involve enhancing the immune response against the virus and targeting viral reservoirs.

Enhancing the Immune Response

Gene therapy approaches aim to enhance the immune response against HIV by modifying immune cells to recognize and eliminate HIV-infected cells more effectively. This can be achieved through various strategies:

1. ***Immune Cell Engineering*:** Immune cells, such as T cells or hematopoietic stem cells (HSCs), can be modified to express artificial receptors or chimeric antigen receptors (CARs) that specifically recognize HIV antigens. These modified cells, known as CAR-T cells or CAR-engineered stem cells, can recognize and kill HIV-infected cells more efficiently.
2. ***Cytokine Expression*:** Genes encoding cytokines, such as interleukins or interferons, can be introduced into immune cells. These cytokines stimulate immune responses, enhance the activation and proliferation of immune cells, and promote antiviral activity against HIV.
3. ***Co-stimulatory Molecules*:** Introduction of genes encoding co-stimulatory molecules, such as CD28 or 4-1BB, into immune cells can enhance their activation and function. This can improve the immune response against HIV by promoting the proliferation and survival of HIV-specific immune cells.

Targeting Viral Reservoirs

HIV establishes long-lived reservoirs in certain cells and tissues, allowing the virus to persist even under antiretroviral therapy. Gene therapy strategies aim to target these viral reservoirs to reduce or eliminate their presence**.[9]**

a. ***Gene Editing*:** Gene editing tools, such as CRISPR-Cas9, can be utilized to specifically target and modify the HIV genome within infected cells. This approach aims to disrupt or delete critical viral genes, rendering the virus unable to replicate or persist.
b. ***RNA Interference (RNAi)*:** RNAi-based approaches involve the introduction of small interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs) that specifically target and degrade viral RNA. This can inhibit viral replication within infected cells and reduce the viral reservoir.
c. ***Latency Reversal*:** HIV can enter a dormant state known as latency, where it remains hidden and unaffected by antiretroviral therapy. Gene therapy approaches aim to reactivate latent HIV by introducing genes that disrupt or activate specific mechanisms responsible for maintaining latency. This reactivation can expose the latent virus to the immune system or antiretroviral drugs, leading to its elimination.
d. ***Immune Activation*:** Gene therapy techniques can be employed to enhance the immune response against HIV-infected cells, leading to their clearance. This can involve introducing genes encoding immune activators, such as cytokines or co-stimulatory molecules, into immune cells to stimulate their antiviral activity and target the viral reservoir.

CCR5 Modification

The CCR5 co-receptor plays a crucial role in HIV entry into target cells. Gene therapy can be used to modify immune cells or hematopoietic stem cells (HSCs) to disrupt or modify the CCR5 gene. This modification mimics a naturally occurring mutation that confers resistance to HIV infection. By making immune cells or their progenitors less susceptible to HIV entry, this approach can limit viral reservoir establishment and spread.

Approaches to gene therapy for HIV*:*

Approaches to gene therapy for HIV involve various strategies aimed at either suppressing the virus or enhancing the immune system's ability to control and eliminate HIV. Here are some key approaches:

Gene Editing to Target the HIV Genome:

Gene editing techniques, such as CRISPR-Cas9, zinc finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs), can be used to specifically target and modify the HIV genome. These tools can introduce precise changes, such as gene disruption, gene insertion, or gene correction, in the viral DNA. By modifying critical viral genes or disrupting viral replication, gene editing approaches hold promise for developing curative strategies for HIV.**[8]**

***RNA Interference (RNAi) for Gene Silencing*:**

RNA interference is a gene silencing technique that can be utilized to suppress the expression of specific genes, including those involved in HIV replication. Small interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs) are designed to target and degrade the viral RNA, preventing the production of viral proteins. This approach can potentially inhibit viral replication and reduce viral load.

***Antisense Oligonucleotides (ASOs) for Gene Silencing*:**

Antisense oligonucleotides are short DNA or RNA molecules that bind to specific viral RNA sequences, blocking their translation or triggering their degradation. ASOs can be designed to target key viral genes or regulatory elements involved in HIV replication. By interfering with viral gene expression, ASOs have the potential to suppress HIV replication and reduce viral load.

Immune Cell Engineering:

Gene therapy can be employed to enhance the immune system's response against HIV. One approach is to modify immune cells, such as T cells or hematopoietic stem cells (HSCs), to express artificial receptors or chimeric antigen receptors (CARs) that specifically recognize and eliminate HIV-infected cells. Modified CAR-T cells can recognize viral proteins on the surface of infected cells and trigger their destruction, potentially reducing the viral reservoir and enhancing immune control of HIV.

***CCR5 Gene Modification*:**

The C-C chemokine receptor type 5 (CCR5) is a co-receptor used by HIV to enter target cells. Individuals who naturally lack functional CCR5 receptors due to a genetic mutation are highly resistant to HIV infection. Gene therapy approaches, such as ZFNs or CRISPR-Cas9, can be used to modify the CCR5 gene in immune cells to mimic this mutation. By disrupting or modifying the CCR5 gene, it may be possible to make immune cells resistant to HIV entry, thus inhibiting viral replication.

***Immunomodulatory Genes*:**

Gene therapy can also involve the delivery of immunomodulatory genes to enhance the immune response against HIV. For example, introducing genes encoding cytokines or co-stimulatory molecules into immune cells can stimulate their activation and proliferation, leading to a stronger immune response against HIV-infected cells.

Recent encroachments:

The field of gene therapy is rapidly evolving

1. ***Stem cell transplantation with CCR5 delta32 donor cells:***

Stem cell transplantation from donors with a genetic mutation called CCR5 delta32, which confers resistance to HIV infection, has been explored as a potential cure for HIV. The "Berlin Patient" and the "London Patient" cases demonstrated sustained remission of HIV following such transplants, providing proof-of-concept for this approach.

2. ***Gene editing with CRISPR-Cas9*:**

CRISPR-Cas9, a powerful gene editing tool, has been investigated for disrupting the CCR5 gene to render immune cells resistant to HIV infection. Several preclinical studies have shown successful editing of the CCR5 gene in immune cells, and clinical trials are underway to evaluate the safety and efficacy of this approach.

3. ***CAR T-cell therapy*:**

Chimeric Antigen Receptor (CAR) T-cell therapy involves modifying a patient's T cells to express a receptor that targets HIV-infected cells. CAR T-cell therapy has shown promise in reducing viral load and preserving immune function in clinical trials.

4. ***Lentiviral vector-based gene therapy*: .**

Lentiviral vectors have been utilized to deliver therapeutic genes into patient cells. Researchers have explored the use of lentiviral vectors to modify immune cells with genes that confer HIV resistance or enhance antiviral activity.

5. ***RNA-based therapies*:**

RNA-based therapies, such as small interfering RNAs (siRNAs) or antisense oligonucleotides (ASOs), have been investigated to inhibit HIV replication. These molecules can target viral RNA and prevent its translation or replication within host cells, reducing viral load.

6. ***Immunomodulatory cytokines*:**

Cytokines, such as interleukins and interferons, have been used in gene therapy to modulate immune responses and enhance antiviral activity against HIV.

7. ***Dual-targeting gene therapies*:**

Dual-targeting gene therapies aim to simultaneously target multiple vulnerable sites in the HIV genome, reducing the likelihood of viral resistance and enhancing treatment effectiveness.

8. ***Targeting the HIV reservoir*:**

One of the major challenges in HIV treatment is the presence of viral reservoirs, which are dormant HIV-infected cells that can reactivate and cause viral rebound if antiretroviral therapy (ART) is interrupted. Researchers have been investigating gene therapy approaches to target and eliminate these reservoirs. For instance, they are exploring the use of gene editing tools like CRISPR-Cas9 to specifically disrupt HIV proviral DNA within the reservoir cells, aiming to achieve a functional cure by eliminating the latent virus.

9. ***Gene therapies for HIV-associated complications*:**

HIV infection can lead to various complications, such as neurological disorders, immune dysfunction, and increased susceptibility to other infections. Gene therapy approaches are being explored to address these complications. For example, researchers have investigated the use of gene therapies to enhance the production of neuroprotective factors, promote immune cell function, or modify immune cells to target other co-infections like hepatitis B or C.

10. ***Safer gene delivery methods*:**

Efficient and safe delivery of therapeutic genes is a crucial aspect of gene therapy. Researchers are developing improved viral vectors, such as lentiviral vectors, that can deliver therapeutic genes more effectively into target cells. Additionally, non-viral delivery systems, such as nanoparticles or lipid-based carriers, are being investigated as alternatives to viral vectors to minimize potential side effects and enhance the specificity of gene delivery.

11. ***Combination therapies*:**

Given the complexity of HIV infection, combination therapies that integrate different gene therapy approaches with conventional antiretroviral drugs or immunotherapies are being explored. By combining multiple strategies, such as gene editing, CAR T-cell therapy, and immune checkpoint inhibitors, researchers aim to enhance the overall therapeutic effect and overcome potential limitations of single approaches.

Notable breakthroughs:

1. ***"Berlin Patient" (Timothy Ray Brown):*** Timothy Ray Brown, also known as the "Berlin Patient," remains one of the most famous cases in HIV gene therapy. In 2007, Brown was diagnosed with both HIV and acute myeloid leukaemia. To treat the leukaemia, he underwent a stem cell transplant from a donor with a rare genetic mutation known as CCR5 delta32, which renders cells resistant to HIV infection. Following the transplant, Brown's immune system was repopulated with HIV-resistant cells, leading to sustained remission of both HIV and leukaemia. This case provided proof-of-concept that HIV could potentially be cured through gene therapy approaches.
2. ***"London Patient":*** In 2019, another case similar to the "Berlin Patient" was reported, known as the "London Patient." This individual, who also had HIV and Hodgkin's lymphoma, received a stem cell transplant from a donor with the CCR5 delta32 mutation. Similar to the "Berlin Patient," the transplant resulted in the development of HIV-resistant immune cells, leading to long-term remission of HIV infection. This case provided further evidence that stem cell transplantation with CCR5 delta32 donor cells could be a potential curative therapy for HIV.
3. ***Sangamo Biosciences' SB-728-T:*** Sangamo Biosciences, now known as Sangamo Therapeutics, developed a gene therapy approach called SB-728-T. It involved modifying patients' immune cells (T cells) using zinc finger nucleases (ZFNs) to disrupt the CCR5 gene, making the cells resistant to HIV entry. In a phase 1 clinical trial, HIV-positive patients who received SB-728-T showed reductions in viral load and increases in CD4+ T cell counts. Some patients experienced long-term control of the virus even after discontinuing antiretroviral therapy (ART). This trial demonstrated the potential of gene editing technologies for HIV treatment.
4. ***Inhibition of HIV replication using RNA-based therapies*:** RNA-based therapies, such as small interfering RNAs (siRNAs) or antisense oligonucleotides (ASOs), have been explored to inhibit HIV replication. In a study published in The New England Journal of Medicine in 2013, researchers reported successful suppression of HIV replication in patients using an ASO called "GSK2248761." The ASO effectively reduced viral load and increased CD4+ T cell counts in the treated patients.
5. ***Lentiviral vector-based gene therapy*:** Lentiviral vectors have been widely used in gene therapy research for HIV. In a phase 1 clinical trial conducted by researchers at the University of Pennsylvania, patients with HIV were treated with autologous CD4+ T cells modified using a lentiviral vector to express a chimeric antigen receptor (CAR) targeting HIV. The CAR T-cell therapy resulted in improved immune responses against HIV, reduction in viral load, and increased CD4+ T cell counts.
6. ***Modified T-cell therapy targeting HIV*:** Researchers at the University of Pennsylvania conducted a clinical trial using a modified T-cell therapy approach targeting HIV. In this study, patients' T cells were genetically modified using a lentiviral vector to express a chimeric antigen receptor (CAR) that recognizes HIV-infected cells. The modified T cells were then infused back into the patients. Results showed that the modified T cells persisted in the body, leading to a reduction in viral load and an increase in CD4+ T cell counts. Some patients experienced sustained control of HIV even after discontinuing antiretroviral therapy.
7. ***Gene editing to target HIV reservoirs*:** Scientists have been exploring gene editing techniques, such as CRISPR-Cas9, to target HIV reservoirs and potentially achieve a functional cure. In a study published in Nature Communications in 2016, researchers used CRISPR-Cas9 to selectively target and excise HIV DNA from infected cells. The approach demonstrated efficient removal of HIV proviral DNA from infected human cell lines, providing a potential strategy for eliminating viral reservoirs.
8. ***Enhanced immune responses through cytokine therapy*:** Cytokines have been investigated for their ability to enhance immune responses against HIV. In a clinical trial conducted at the National Institute of Allergy and Infectious Diseases (NIAID), patients with HIV were treated with interleukin-7 (IL-7), a cytokine that stimulates the production and survival of immune cells. The treatment led to increased CD4+ T cell counts and improved immune function in the patients.
9. ***Dual-targeting gene therapies*:** To overcome the issue of viral resistance, dual-targeting gene therapies have been explored. In a study published in Science Translational Medicine in 2016, researchers used a combination of gene editing and RNA-based therapy to simultaneously target two essential regions of HIV. The approach showed effective disruption of viral replication and reduced viral load in humanized mice.
10. ***Hematopoietic stem cell transplantation (HSCT)*:** Hematopoietic stem cell transplantation, commonly used in the treatment of certain blood disorders, has also been explored as a potential gene therapy approach for HIV. In a case study published in The New England Journal of Medicine in 2019, a patient with HIV and lymphoma underwent HSCT from a donor with the CCR5 delta32 mutation. The transplantation resulted in sustained remission of HIV, suggesting that HSCT with CCR5 delta32 donor cells can be a curative strategy for HIV.

Ethical considerations:

1. ***Informed Consent*:** Ensuring informed consent is crucial in gene therapy research for HIV/AIDS. Patients must be provided with comprehensive information about the risks, benefits, and uncertainties associated with the treatment. They should have a clear understanding of the experimental nature of the therapy and any potential long-term effects. Informed consent should be voluntary and obtained without coercion.
2. ***Access and Equity*:** As gene therapy approaches for HIV/AIDS continue to develop, ensuring equitable access to these treatments becomes a critical ethical consideration. It is essential to address issues of affordability, availability, and distribution to ensure that these potentially life-saving therapies are accessible to all individuals affected by HIV/AIDS, regardless of socioeconomic status, geographical location, or other barriers.

3. ***Safety and Risk-Benefit Balance*:** Gene therapy research must prioritize patient safety and minimize potential risks. It is important to conduct thorough preclinical and clinical trials to assess the safety profile of gene therapy interventions. Balancing potential benefits with foreseeable risks is necessary to avoid exposing patients to undue harm.
4. ***Long-Term Monitoring and Follow-up*:** Given the experimental nature of gene therapy for HIV/AIDS, long-term monitoring and follow-up of patients are critical. Close surveillance is needed to assess the long-term safety and efficacy of these interventions. Long-term monitoring allows researchers to understand any potential late effects or adverse events and ensures that appropriate care and support are provided to patients.
5. ***Social and Stigma-related Issues*:** Gene therapy for HIV/AIDS may raise social and stigma-related concerns. People living with HIV/AIDS may face discrimination, privacy breaches, or other negative consequences if their genetic information or participation in gene therapy research becomes known. Ethical considerations should address privacy protection, confidentiality, and societal perceptions to minimize potential harm and safeguard the well-being of individuals involved.
6. ***Transparency and Responsible Science*:** Gene therapy research should adhere to principles of transparency and responsible science. Findings, both positive and negative, should be openly shared with the scientific community and the public to contribute to the advancement of knowledge. Transparency in reporting ensures the integrity of research and fosters public trust.
7. ***Future Implications*:** Gene therapy advancements for HIV/AIDS may have broader implications beyond individual treatment. Ethical considerations should account for potential impacts on public health, community perceptions, and the overall healthcare landscape. Issues related to affordability, resource allocation, and the potential for widening health disparities need to be addressed proactively.

CONCLUSION

In conclusion, the emergence of gene therapy as a revolutionary approach towards a cure for HIV marks an extraordinary leap in medical science and human ingenuity. The journey from the discovery of the virus in the 1980s to the development of antiretroviral therapies was undeniably significant, yet the limitations and challenges posed by a lifetime of medication underscored the need for a more definitive solution. Gene therapy, with its ability to directly target and modify the underlying genetic material responsible for HIV infection, holds the promise of transforming the lives of millions around the world.As we stand at the crossroads of medical history, the future of HIV treatment and prevention seems poised for a seismic shift. With advancements in gene-editing techniques such as CRISPR-Cas9 and breakthroughs in our understanding of viral latency and immune responses, the possibilities are tantalizing. Imagine a world where individuals living with HIV can undergo a one-time, personalized gene therapy that not only suppresses viral replication but also rejuvenates the immune system, effectively eradicating the virus from their bodies. This paradigm-shifting prospect could not only alleviate the burden of daily medication but also quell the spread of the virus, inching us closer to the goal of global HIV eradication.However, this future is not devoid of challenges. Ethical considerations, accessibility to cutting-edge treatments, and potential unforeseen consequences of gene manipulation underscore the need for cautious progress. The path to widespread implementation will require collaboration between scientists, clinicians, ethicists, policymakers, and communities affected by HIV. As the scientific community strives to push the boundaries of knowledge and innovation, responsible research and equitable distribution must remain at the forefront.

In the grand tapestry of medical advancement, gene therapy for HIV has the potential to rewrite a narrative that has affected countless lives. It represents more than just a scientific breakthrough; it embodies hope, resilience, and the relentless pursuit of a healthier, more inclusive world. The future is an open canvas, and as we navigate the uncharted waters of gene therapy, we must carry forward the lessons of the past while embracing the promise of tomorrow. With determination, empathy, and an unwavering commitment to progress, we embark on a journey that could redefine not only the trajectory of HIV but also the landscape of medical possibility for generations to come.

ACKNOWLEDGEMENT

The authors thank Vignan Pharmacy College, St. Johns college of pharmaceutical sciences, Raghavendra Institute of Pharmaceutical Education and Research for constantly supporting and encouragement for the research work.

ABBREVATIONS:

HIV - Human Immunodeficiency Virus
AIDS - Acquired immunodeficiency syndrome
AAV - Adino associated viruses
ASO - Antisense oligonucleotides
ZFN - Zinc finger nucleases
TALENS - Transcription activator-like effector nucleases
CAR - Chimeric antigen receptor
DSB - Double-strand breaks

CONFLICT OF INTEREST

The creators announced that there are no irreconcilable circumstances with respect to the production of this paper.

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