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Therapeutic mRNA Vaccines for HIV: Immune Restoration and Viral Control in Advanced Disease

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ABSTRACT

Despite advances in antiretroviral therapy (ART), individuals with advanced HIV disease continue to face significant challenges related to immune dysfunction and persistent viral reservoirs. Therapeutic messenger RNA (mRNA) vaccines have emerged as a promising intervention aimed at restoring immune competence and achieving sustained viral control beyond the capabilities of ART. These vaccines are engineered to encode HIV-specific antigens and immunomodulatory molecules, stimulating robust cytotoxic T lymphocyte responses while reversing T-cell exhaustion. Unlike prophylactic vaccines, therapeutic mRNA constructs are designed to engage dysfunctional immunity, reprogram host immune responses, and potentially target latent viral reservoirs. Key innovations, such as self-amplifying RNA, codon optimization, and lipid nanoparticle (LNP) delivery systems, enhance the stability, potency, and specificity of the immune response. Preclinical studies and early-phase clinical trials demonstrate promising results in reducing viral rebound and improving immune activation in advanced disease settings. In this review, a narrative methodology was employed to synthesize findings from experimental models, vaccine trials, and immunopathological studies. Despite existing challenges, including viral diversity, immune senescence, and delivery constraints, therapeutic mRNA vaccines hold significant potential as components of functional cure strategies. Their integration into comprehensive HIV treatment paradigms may offer a transformative path toward durable viral suppression, particularly in populations where ART alone fails to fully restore immune function.

Keywords: Therapeutic mRNA vaccines, Advanced HIV disease, Immune restoration, Viral reservoir control, Cytotoxic T lymphocyte responses.

INTRODUCTION

Despite significant strides in antiretroviral therapy (ART), the Human Immunodeficiency Virus (HIV) continues to challenge global public health, especially in individuals presenting with advanced disease characterized by high viral load and profound CD4+ T-cell depletion [1, 2]. While ART effectively suppresses viral replication and prolongs life expectancy, it falls short in eradicating viral reservoirs or fully restoring immune competence in many late-stage patients [3]. Consequently, attention has shifted toward adjunctive immunotherapeutic strategies that can bolster endogenous immune control and reduce long-term viral persistence.

Among these emerging strategies, therapeutic messenger RNA (mRNA) vaccines have garnered substantial interest [4]. Unlike conventional prophylactic vaccines, therapeutic mRNA vaccines aim to reprogram host immunity to recognize and eliminate HIV-infected cells, thereby restoring immune surveillance and facilitating durable viral control [5]. mRNA vaccine platforms, made prominent by their success against SARS-CoV-2, offer multiple advantages: rapid development, scalability, safety, and the ability to encode multiple antigens or immunomodulatory elements [6].

In the context of HIV, therapeutic mRNA vaccines are designed to elicit robust cytotoxic T lymphocyte (CTL) responses and modulate immune checkpoints, targeting viral reservoirs that persist despite ART [7]. Early-phase

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clinical trials and preclinical studies suggest that these vaccines may enhance T-cell function, reduce immune exhaustion, and contribute to viral rebound control upon ART interruption.

This review provides a comprehensive analysis of therapeutic mRNA vaccines for HIV, with a focus on their role in immune restoration and viral control in advanced disease. It examines the immunopathogenesis of late-stage HIV, the mechanisms of mRNA vaccine action, the design of HIV-specific mRNA constructs, and clinical outcomes to date. Finally, it discusses challenges, such as immune escape and delivery barriers, and considers the broader implications of this technology in HIV cure research and functional remission paradigms.

Immunopathogenesis of Advanced HIV and the Rationale for Therapeutic Vaccination

Advanced HIV disease is typified by systemic immune dysfunction, marked depletion of CD4+ T cells, expansion of regulatory T cells (Tregs), chronic immune activation, and heightened susceptibility to opportunistic infections [8]. This immunological milieu creates a hostile environment for traditional vaccine-induced responses and hampers the host's ability to contain viral replication once ART is withdrawn. A significant challenge in advanced disease is the establishment of latent viral reservoirs within long-lived immune cells, particularly central memory CD4+ T cells [9]. These reservoirs remain transcriptionally silent under ART but can reactivate upon treatment cessation, leading to viral rebound. Moreover, persistent antigenic stimulation results in T-cell exhaustion, characterized by the upregulation of inhibitory receptors such as PD-1, TIM-3, and LAG-3, further impairing effective cytotoxic responses. Therapeutic vaccination in this setting is aimed at restoring immune effector function by reinvigorating cytotoxic CD8+ T cells and promoting the clearance of infected cells [10]. Unlike prophylactic approaches, therapeutic vaccines must overcome immune suppression and reprogram existing dysfunctional immunity. This makes mRNA-based vaccines particularly appealing, as they can be engineered to not only express viral antigens but also include immunostimulatory sequences and checkpoint blockade elements.

Restoring immune competence in late-stage HIV, therefore, demands a vaccine platform that is flexible, potent, and capable of inducing both broad and deep immune responses, criteria that mRNA vaccines are uniquely positioned to fulfill.

Mechanism of Action of mRNA Vaccines in HIV Therapeutics

Therapeutic mRNA vaccines function by introducing synthetic mRNA encoding one or more HIV antigens into host cells, typically dendritic cells (DCs), to elicit antigen-specific adaptive immune responses [11]. Once inside the cytoplasm, the mRNA is translated into HIV proteins, which are then processed and presented via major histocompatibility complex (MHC) class I and II pathways. This presentation activates antigen-specific CD8+ and CD4+ T cells, enhancing cellular immunity and aiding in the identification and destruction of infected cells.

The non-integrating, transient nature of mRNA avoids the risks associated with DNA-based platforms, such as insertional mutagenesis. Additionally, the use of chemically modified nucleosides reduces the innate immune sensing of exogenous RNA, improving translation efficiency and minimizing systemic inflammation. Innovative mRNA vaccine constructs now incorporate self-amplifying RNA (saRNA) for sustained antigen expression, as well as adjuvants such as toll-like receptor (TLR) agonists to further boost immunogenicity [12]. Moreover, co-delivery of mRNA encoding immune checkpoint inhibitors or cytokines (e.g., IL-12, GM-CSF) is being explored to recondition the exhausted immune microenvironment in advanced HIV disease. Lipid nanoparticle (LNP) formulations have emerged as the gold standard for mRNA delivery, offering efficient cellular uptake, targeted delivery to antigen-presenting cells, and protection of mRNA from degradation [13]. Some vaccine strategies are also exploring ex vivo loading of autologous DCs with HIV-encoded mRNA, followed by reinfusion into the patient, offering personalized cellular immunotherapy. Through these mechanisms, therapeutic mRNA vaccines aim not only to stimulate immune responses but to modulate immune dysfunction, an essential goal in restoring control over HIV in individuals with advanced disease.

Design and Optimization of HIV-Specific mRNA Constructs

The success of therapeutic mRNA vaccines hinges on the careful design of antigenic constructs that can stimulate a broad and effective immune response against diverse HIV strains [14, 15]. Unlike traditional vaccines that rely on full-length viral proteins, mRNA vaccines enable modular construction, allowing for the encoding of conserved viral epitopes, such as those from Gag, Pol, and Nef proteins, which are less prone to mutation. Codon optimization enhances the translation of the encoded antigen, while untranslated regions (UTRs) and poly(A) tails improve mRNA stability and translational efficiency [16, 17]. Inclusion of modified nucleosides such as pseudouridine reduces innate immune activation and improves tolerability. Additionally, efforts are being made to incorporate multiepitope mosaics artificially designed sequences representing multiple global HIV variants into a single mRNA strand to maximize breadth of response. To address viral escape, some constructs are designed to encode mutant-specific neoantigens targeting resistance-associated mutations. Others include non-structural viral proteins expressed during the early stages of infection, increasing the likelihood of recognizing reactivated latently infected cells. Recent innovations also explore bifunctional mRNA constructs co-encoding both HIV antigens and therapeutic

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agents like checkpoint inhibitors or immunostimulatory cytokines. These multi-functional constructs aim to directly reverse immune exhaustion while simultaneously inducing antigen-specific responses. In sum, mRNA construct design for therapeutic HIV vaccines involves a synergy of antigen selection, immunoengineering, and delivery science to ensure robust and targeted immune activation in the complex setting of advanced disease.

Clinical and Preclinical Evidence of mRNA Vaccines in Advanced HIV

Although therapeutic mRNA vaccines for HIV are still in early developmental stages, a growing body of preclinical and clinical data supports their potential efficacy, particularly in individuals with advanced disease. In animal models, therapeutic mRNA vaccines have demonstrated the ability to elicit polyfunctional T-cell responses, reduce viral loads, and delay viral rebound following ART interruption [18]. For example, macaque studies using LNP-formulated saRNA encoding Gag and Pol proteins have shown durable expansion of HIV-specific cytotoxic T lymphocytes and partial control of viral replication [19, 20]. Human trials are in their nascent phases. The HIVACAT T cell Immunogen (HTI) mRNA vaccine is under investigation for its capacity to induce T-cell responses against conserved HIV regions. Preliminary data from ex vivo studies suggest that mRNA-transfected DCs can enhance antigen-specific T-cell proliferation and cytokine production in cells derived from ART-treated individuals. Another promising approach is the combination of mRNA vaccination with latency-reversing agents (LRAs) [21]. This "kick and kill" strategy involves reactivating latent virus (kick) and then using the immune system, primed by therapeutic vaccination (kill), to clear reactivated infected cells. Such regimens could be particularly relevant in individuals with large, stable reservoirs due to late ART initiation. Furthermore, therapeutic mRNA vaccines are being investigated as part of analytical treatment interruption (ATI) protocols, where ART is temporarily halted to evaluate vaccine-induced immune control. Preliminary findings indicate that vaccinated individuals experience delayed viral rebound and lower peak viremia during ATI. Though more large-scale, randomized controlled trials are needed, early results offer hope that mRNA vaccines could become a critical component of HIV cure strategies, especially in those with compromised immunity.

Challenges, Limitations, and Future Directions

Despite their promise, therapeutic mRNA vaccines for HIV face several scientific and logistical hurdles, particularly in individuals with advanced disease. First, immune exhaustion and T-cell senescence in late-stage patients may limit vaccine responsiveness [22]. Even with optimized antigen presentation, restoring functional cytotoxicity in a chronically inflamed, immunosuppressed environment remains a formidable challenge. Overcoming this may require combining mRNA vaccines with adjunctive therapies such as checkpoint inhibitors, cytokine support, or therapeutic apheresis. Second, HIV genetic variability poses another challenge. While multivalent mRNA designs attempt to address this, ongoing viral evolution, particularly in untreated individuals, necessitates constant surveillance and iterative vaccine design. Third, delivery barriers remain a concern. Although LNPs have improved delivery efficiency, tissue-specific targeting and dose optimization are still areas of active research. Moreover, repeated dosing may trigger innate immune responses against LNP components, leading to reduced efficacy or adverse reactions.

Cost and manufacturing scalability, particularly in low- and middle-income countries where advanced HIV is most prevalent, also present critical obstacles. Global partnerships and technology transfer will be essential to ensure equitable access. Looking ahead, combining mRNA vaccines with other immunotherapeutic modalities such as therapeutic monoclonal antibodies, CAR-T cells, or CRISPR-based reservoir editing may yield synergistic outcomes. Integrating mRNA vaccination into comprehensive treatment frameworks could shift the paradigm from lifelong ART to functional remission or viral eradication.

CONCLUSION

Therapeutic mRNA vaccines represent a novel and potentially transformative strategy for immune restoration and viral control in individuals with advanced HIV disease. Their ability to encode customized, multi-epitope antigens and immunomodulatory agents positions them uniquely to overcome the immunological barriers that hinder traditional interventions in late-stage infection. By enhancing cytotoxic T-cell responses, reversing immune exhaustion, and targeting latent reservoirs, mRNA vaccines could address the unmet need for durable viral suppression beyond ART. While preliminary clinical and preclinical evidence is promising, significant challenges remain, ranging from antigenic diversity and immune senescence to delivery and manufacturing hurdles. Nevertheless, ongoing research efforts, coupled with innovations in mRNA engineering and nanotechnology, are rapidly advancing the feasibility of this approach. In the broader context of HIV cure research, therapeutic mRNA vaccines could serve as both standalone immunotherapies and components of multi-modal strategies aimed at functional remission. Particularly in settings where ART alone is insufficient for immune reconstitution, mRNA-based therapeutics offer a compelling, adaptable, and precision-targeted solution. As the field matures, it will be essential to validate these technologies in diverse populations and clinical scenarios, ensuring that future HIV treatment paradigms are not only scientifically effective but also globally accessible and equitable.

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REFERENCES

1. Alum, E.U., Uti, D.E., Ugwu, O.P.C., Alum, B.N.: Toward a cure - Advancing HIV/AIDs treatment modalities beyond antiretroviral therapy: A Review. Medicine (United States). 103, e38768 (2024). https://doi.org/10.1097/MD.0000000000038768
2. Obeagu, E.I., Obeagu, G.U., Odo, E.O., Igwe, M.C., Ugwu, O.P.-C., Alum, E.U., Okwaja, P.R.: Revolutionizing HIV Prevention in Africa: Landmark Innovations that Transformed the Fight. IAA Journal of Applied Sciences. 11, 1–12 (2024). https://doi.org/10.59298/IAAJAS/2024/1.3.5288
3. Madu, C.V., Aloh, H.E., Ugwu, O.P.C., Obeagu, E.I., Uti, D.E., Egba, S.I., et al. The price of progress: Assessing the financial costs of HIV/AIDS management in East Africa. Medicine (Baltimore). 2025 May 2;104(18):e42300. doi: 10.1097/MD.0000000000042300. PMID: 40324279; PMCID: PMC12055164.
4. Prakash, S., Kumar, M.: The Hidden Enemy Within: Uncovering the Secrets of HIV Tissues Reservoirs and Current mRNA Vaccine Development. Curr HIV Res. 22, 73–81 (2024). https://doi.org/10.2174/011570162X301593240409072840/CITE/REFWORKS
5. Esteban, I., Pastor-Quiñones, C., Usero, L., Plana, M., García, F., Leal, L.: In the Era of mRNA Vaccines, Is There Any Hope for HIV Functional Cure? Viruses 2021, Vol. 13, Page 501. 13, 501 (2021). https://doi.org/10.3390/V13030501
6. Pardi, N., Krammer, F.: mRNA vaccines for infectious diseases — advances, challenges and opportunities. Nature Reviews Drug Discovery 2024 23:11. 23, 838–861 (2024). https://doi.org/10.1038/s41573-024-01042-y
7. Esteban, I., Pastor-Quiñones, C., Usero, L., Plana, M., García, F., Leal, L.: In the Era of mRNA Vaccines, Is There Any Hope for HIV Functional Cure? Viruses 2021, Vol. 13, Page 501. 13, 501 (2021). https://doi.org/10.3390/V13030501
8. Okoye, A.A., Picker, L.J.: CD4+ T-cell depletion in HIV infection: mechanisms of immunological failure. Immunol Rev. 254, 54–64 (2013). https://doi.org/10.1111/IMR.12066
9. Alum, E.U., Ugwu, O.P.-C., Obeagu, E.I., Aja, P. M.: Reducing HIV Infection Rate in Women: A Catalyst to reducing HIV Infection pervasiveness in Africa. (2023). https://doi.org/10.58538/IJIAR/2048
10. Barili, V., Vecchi, A., Rossi, M., Montali, I., Tiezzi, C., Penna, A., Laccabue, D., Missale, G., Fisicaro, P., Boni, C.: Unraveling the Multifaceted Nature of CD8 T Cell Exhaustion Provides the Molecular Basis for Therapeutic T Cell Reconstitution in Chronic Hepatitis B and C. Cells 2021, Vol. 10, Page 2563. 10, 2563 (2021). https://doi.org/10.3390/CELLS10102563
11. Van Gulck, E., Vlieghe, E., Vekemans, M., Van Tendeloo, V.F.I., Van De Velde, A., Smits, E., Anguille, S., Cools, N., Goossens, H., Mertens, L., De Haes, W., Wong, J., Florence, E., Vanham, G., Berneman, Z.N.: MRNA-based dendritic cell vaccination induces potent antiviral T-cell responses in HIV-1-infected patients. AIDS. 26, (2012). https://doi.org/10.1097/QAD.0B013E32834F33E8
12. Tregoning, J.S., Stirling, D.C., Wang, Z., Flight, K.E., Brown, J.C., Blakney, A.K., McKay, P.F., Cunliffe, R.F., Murugaiah, V., Fox, C.B., Beattie, M., Tam, Y.K., Johansson, C., Shattock, R.J.: Formulation, inflammation, and RNA sensing impact the immunogenicity of self-amplifying RNA vaccines. Mol Ther Nucleic Acids. 31, 29–42 (2023). https://doi.org/10.1016/j.omtn.2022.11.024
13. Zong, Y., Lin, Y., Wei, T., Cheng, Q.: Lipid Nanoparticle (LNP) Enables mRNA Delivery for Cancer Therapy. Advanced Materials. 35, 2303261 (2023). https://doi.org/10.1002/ADMA.202303261;WEBSITE:WEBSITE:ADVANCED;CTYPE:STRING:JOURNAL
14. Chaudhary, N., Weissman, D., Whitehead, K.A.: mRNA vaccines for infectious diseases: principles, delivery and clinical translation. Nature Reviews Drug Discovery 2021 20:11. 20, 817–838 (2021). https://doi.org/10.1038/s41573-021-00283-5
15. Omidi, Y., Pourseif, M.M., Ansari, R.A., Barar, J.: Design and development of mRNA and self-amplifying mRNA vaccine nanoformulations. Nanomedicine. 19, 2699–2725 (2024). https://doi.org/10.1080/17435889.2024.2419815;REQUESTEDJOURNAL:JOURNAL:INNM20;WGROUP:STRING:PUBLICATION
16. Wu, Q., Bazzini, A.A.: Translation and mRNA Stability Control. Annu Rev Biochem. 92, 227–245 (2023). https://doi.org/10.1146/ANNUREV-BIOCHEM-052621-091808/CITE/REFWORKS
17. Kim, S.C., Sekhon, S.S., Shin, W.R., Ahn, G., Cho, B.K., Ahn, J.Y., Kim, Y.H.: Modifications of mRNA vaccine structural elements for improving mRNA stability and translation efficiency. Mol Cell Toxicol. 18, 1–8 (2022). https://doi.org/10.1007/S13273-021-00171-4/METRICS
18. Usero, L., Leal, L., Gómez, C.E., Miralles, L., Aurrecoechea, E., Esteban, I., Torres, B., Inciarte, A., Perdiguero, B., Esteban, M., García, F., Plana, M.: The Combination of an mRNA Immunogen, a TLR7

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Agonist and a PD1 Blocking Agent Enhances In-Vitro HIV T-Cell Immune Responses. Vaccines (Basel). 11, 286 (2023). https://doi.org/10.3390/VACCINES11020286/S1

19. Rappaport, A.R., Bekerman, E., Boucher, G.R., Sung, J., Carr, B., Corzo, C.A., Larson, H., Kachura, M.A., Scallan, C.D., Geleziunas, R., SenGupta, D., Jooss, K.: Differential shaping of T cell responses elicited by heterologous ChAd68/self-amplifying mRNA SIV vaccine in macaques in combination with αCTLA4, αPD-1, or FLT3R agonist. The Journal of Immunology. 214, 489–501 (2025). https://doi.org/10.1093/JIMMUN/VKAE052
20. Valentin, A., Bergamaschi, C., Rosati, M., Angel, M., Burns, R., Agarwal, M., Gergen, J., Petsch, B., Oostvogels, L., Loeliger, E., Chew, K.W., Deeks, S.G., Mullins, J.I., Pavlakis, G.N., Felber, B.K.: Comparative immunogenicity of an mRNA/LNP and a DNA vaccine targeting HIV gag conserved elements in macaques. Front Immunol. 13, 945706 (2022). https://doi.org/10.3389/FIMMU.2022.945706/XML/NLM
21. Cevaal, P.M., Kan, S., Fisher, B.M., Moso, M.A., Tan, A., Liu, H., Ali, A., Tanaka, K., Shepherd, R.A., Kim, Y., Ong, J., Furtado, D.L., Holz, M., Purcell, D.F.J., Casan, J.M.L., Payne, T., Zhao, W., Fareh, M., McMahon, J.H., Deeks, S.G., Hoh, R., Telwatte, S., Pouton, C.W., Johnston, A.P.R., Caruso, F., Symons, J., Lewin, S.R., Roche, M.: Efficient mRNA delivery to resting T cells to reverse HIV latency. Nature Communications 2025 16:1. 16, 1–12 (2025). https://doi.org/10.1038/s41467-025-60001-2
22. Pawelec, G.: Is there a positive side to T cell exhaustion? Front Immunol. 10, 432816 (2019). https://doi.org/10.3389/FIMMU.2019.00111/BIBTEX

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