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Impact of mRNA-Based Immune Modulators Versus Standard ART on Viral Reservoir Reduction in Treatment-Experienced HIV Adults: A Review

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ABSTRACT

Despite the success of standard antiretroviral therapy (ART) in achieving sustained viral suppression among people living with HIV, the persistence of latent viral reservoirs in resting CD4+ T cells remains a major barrier to cure. This review examined the emerging role of messenger RNA (mRNA)-based immune modulators as a novel therapeutic strategy to reduce the HIV reservoir in treatment-experienced adults. Unlike ART, which halts replication without affecting the latent pool, mRNA-based therapeutics are designed to induce targeted immune responses, reverse latency, or enhance the clearance of infected cells through the transient expression of immunostimulatory proteins. Promising preclinical and early-phase clinical studies have shown that mRNA platforms can enhance HIV-specific T cell responses and delay viral rebound following treatment interruption. However, evidence of direct reservoir reduction in humans was still limited, and challenges such as immune exhaustion, delivery logistics, and combination strategy design remained. This article employed a narrative review methodology, synthesizing findings from peer-reviewed studies published between 2010 and 2025 to compare the mechanistic and clinical impacts of mRNA-based immune modulators and standard ART. The review concluded that mRNA immune modulators may complement ART in curative efforts, particularly when used in combination with latency-reversing agents and immune-enhancing therapies.

Keywords: HIV reservoir, mRNA immune modulators, Antiretroviral therapy, Latency reversal, Treatment-experienced adults.

INTRODUCTION

Despite the advent and global scale-up of antiretroviral therapy (ART), HIV persists as a chronic infection largely due to the establishment of latent viral reservoirs that escape immune clearance and pharmacological suppression [1]. These reservoirs, formed early in infection and residing primarily in resting memory CD4+ T cells, present a formidable barrier to viral eradication [2, 3]. While ART effectively suppresses plasma viremia to undetectable levels, it fails to eliminate these latent reservoirs, necessitating lifelong therapy and posing risks of rebound upon treatment interruption.

Over the past two decades, research efforts have increasingly focused on novel strategies aimed at targeting and reducing the size and activity of these viral reservoirs. One promising approach involves the use of messenger RNA (mRNA)-based immune modulators [4, 5]. These modulators utilize synthetic mRNA platforms to transiently express immunologically active proteins or antigenic sequences designed to stimulate HIV-specific immunity, enhance immune recognition of infected cells, or reverse latency through immunotherapeutic mechanisms. Their emergence has coincided with technological advances in mRNA stability, delivery systems (notably lipid nanoparticles), and immunoengineering, as exemplified in mRNA vaccine development during the COVID-19 pandemic. In contrast, standard ART regimens, while highly effective in suppressing viral replication, do not influence the latent pool directly, nor do they prime the immune system to recognize and clear latently infected cells [6, 7]. Therefore, a comparative analysis of mRNA-based immune modulators and standard ART is critical to

understanding the translational potential of mRNA strategies in reservoir targeting, particularly in treatment-experienced adults who harbor long-standing and possibly more entrenched viral reservoirs. This review synthesizes the current scientific understanding of mRNA-based immune modulators, evaluates their mechanisms and clinical applications in comparison to standard ART, and critically assesses their impact on HIV viral reservoir reduction among treatment-experienced individuals. It also explores future directions, implementation challenges, and the implications of integrating such strategies into existing therapeutic frameworks.

Mechanisms of HIV Persistence and the Challenge of Viral Reservoirs

The persistence of HIV despite ART is largely attributed to the establishment of a latent reservoir, primarily within resting memory CD4+ T cells, although other cell types, such as macrophages and follicular dendritic cells, may also contribute [8, 9]. Latency is characterized by the integration of proviral DNA into the host genome without active transcription, allowing the virus to evade immune detection and ART, both of which target replicating virus.

Standard ART effectively halts replication but lacks any activity against cells harboring transcriptionally silent provirus [10, 11]. Interruption of ART typically results in rapid viral rebound due to the reactivation of these latent reservoirs. The magnitude and stability of the latent reservoir are major obstacles to HIV eradication and cure, and hence have become central targets in curative research.

Approaches to reduce or eliminate the viral reservoir have included latency-reversing agents (LRAs), immune checkpoint inhibitors, broadly neutralizing antibodies (bNAbs), therapeutic vaccines, and, more recently, mRNA-based immune modulators. These mRNA-based approaches aim to reprogram the host immune system or enhance antigen presentation to achieve immune-mediated clearance of reservoir cells.

Standard Antiretroviral Therapy (ART): Achievements and Limitations

ART comprises combinations of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, integrase strand transfer inhibitors (INSTIs), and entry inhibitors [12]. The principal goal of ART is to achieve and maintain viral suppression, restore immune function, and prevent disease progression and transmission [13, 14].

Despite its success in transforming HIV into a manageable chronic disease, ART must be taken continuously to sustain virologic control. Adherence challenges, drug resistance, long-term toxicities, and high healthcare costs remain persistent concerns, particularly in resource-limited settings. Moreover, ART exerts no effect on the size of the latent reservoir and provides no immunologic memory or enhanced clearance of infected cells.

Longitudinal studies have demonstrated that even among individuals with sustained virologic suppression for over a decade, the size of the latent reservoir decreases only minimally over time. Therefore, adjunctive strategies that can complement ART by directly targeting the reservoir or bolstering immune recognition are urgently needed.

mRNA-Based Immune Modulators: Concept and Mechanism of Action

mRNA-based immune modulators represent a class of therapeutics that utilize in vitro transcribed mRNA to express antigens or immunostimulatory molecules transiently in host cells [15]. These molecules can include HIV antigens, cytokines, costimulatory ligands, or chimeric constructs designed to enhance antigen presentation or induce latency reversal.

Key features of mRNA therapeutics include their non-integrating, non-replicating nature, rapid production scalability, and the ability to encode virtually any protein of interest [16]. When delivered via lipid nanoparticles (LNPs), mRNA is taken up by antigen-presenting cells (APCs), translated into protein, and presented via major histocompatibility complex (MHC) molecules to stimulate adaptive immune responses. Thus, mRNA-based immune modulators have a dual potential: to expose latent HIV through immune activation and to facilitate the clearance of infected cells via enhanced immune surveillance [17]. In the context of HIV, mRNA modulators are employed to either:

i. **Boost HIV-specific T cell responses**: By encoding HIV Gag, Pol, or Env antigens to prime or expand cytotoxic T lymphocyte responses.
ii. **Reverse latency**: By encoding immune-stimulatory cytokines (e.g., IL-15, IFN-α) or transcriptional activators that trigger latent provirus reactivation.
iii. **Induce immunomodulation**: Using checkpoint inhibitors (e.g., anti-PD-1) or costimulatory ligands to reinvigorate exhausted T cells.

Comparative Efficacy: mRNA Modulators Versus Standard ART in Viral Reservoir Reduction

Emerging clinical and preclinical studies have begun to shed light on the efficacy of mRNA-based immune modulators in targeting the HIV reservoir. In murine and non-human primate models, mRNA-based vaccines encoding HIV antigens have demonstrated the ability to elicit robust polyfunctional T cell responses, particularly when combined with adjuvants or immune checkpoint blockade [18, 19]. Notably, mRNA therapeutic platforms have shown early promise in inducing latency reversal, increasing cell-associated HIV RNA, and enhancing antigen

presentation without widespread T cell activation or systemic toxicity. In one study, mRNA encoding HIV Env protein delivered via LNPs in SIV-infected macaques led to a measurable reduction in the reservoir size, particularly when administered following ART-mediated viral suppression.

In contrast, standard ART, while effective in halting viral replication, does not reduce the size of the latent reservoir. Studies involving analytical treatment interruptions (ATIs) consistently show rapid rebound in patients maintained only on ART, irrespective of duration or viral suppression history. Importantly, recent pilot clinical trials involving treatment-experienced HIV-positive adults have tested mRNA vaccine candidates in combination with ART. Preliminary findings suggest that mRNA immunization enhances the breadth and magnitude of HIV-specific immune responses, and in some cases, delays time to viral rebound post-ART cessation, suggesting an indirect impact on reservoir activity or structure. However, quantitative reductions in the size of the inducible reservoir have not yet been definitively established in large-scale human trials. The lack of standardized assays to measure reservoir size and the heterogeneity in participant immune history pose additional challenges in comparing outcomes between ART and mRNA-based approaches.

Safety, Immunogenicity, and Implementation Considerations

Safety remains a paramount concern with any novel therapeutic platform. To date, mRNA-based immunotherapeutics have demonstrated favorable safety profiles in oncology and infectious disease contexts, including in therapeutic vaccines for cancer and prophylactic SARS-CoV-2 vaccines. Transient local and systemic reactogenicity is the most common side effect, typically resolving within days. In the context of HIV, mRNA strategies must be tailored to avoid overstimulation of the immune system, which may risk immune exhaustion or systemic inflammation [20]. Precision delivery systems, targeted antigen selection, and dose optimization are essential to maximizing therapeutic benefit while minimizing adverse effects.

From an implementation standpoint, the rapid scalability and flexibility of mRNA manufacturing offer a distinct advantage over protein- or viral vector-based immunotherapies. However, cold-chain requirements, cost of formulation, and the need for repeated dosing remain practical barriers, particularly in low-resource settings.

Furthermore, the immunologic history of treatment-experienced individuals, many of whom have undergone multiple ART regimens and harbor exhausted or senescent T cells, may limit the effectiveness of mRNA immune modulation. Thus, patient stratification based on immunophenotyping and reservoir characterization may be required to optimize therapeutic outcomes.

Future Directions and Combination Strategies

While current evidence supports the immunogenic potential of mRNA-based immune modulators, it is increasingly clear that a multipronged approach will be required to achieve meaningful reductions in the HIV reservoir. Strategies that combine mRNA immunotherapy with latency-reversing agents (LRAs) to induce viral expression, broadly neutralizing antibodies (bNAbs) to block new infection and enhance clearance, immune checkpoint inhibitors to restore T cell function, and gene-editing tools like CRISPR to excise proviral DNA are actively under investigation. Additionally, therapeutic timing (e.g., during ART suppression vs. treatment interruption), personalized immunotherapeutic design, and iterative booster regimens may influence the efficacy of mRNA interventions. The use of mRNA platforms to deliver personalized neoantigens derived from an individual's own proviral sequences represents a novel frontier in HIV immunotherapy [21].

Ongoing clinical trials are expected to clarify the role of mRNA immune modulators in cure-oriented strategies and whether they can be effectively integrated into ART-free remission protocols.

CONCLUSION

The persistent challenge of HIV viral reservoirs necessitates innovative therapeutic strategies beyond standard ART. mRNA-based immune modulators represent a promising and versatile class of interventions capable of enhancing host immune responses, reversing latency, and potentially reducing the size and stability of the latent reservoir. Unlike ART, which solely suppresses viral replication, mRNA therapeutics offer an active immunologic approach to target the reservoir directly. Preclinical data and early-phase clinical trials suggest that mRNA immune modulators can boost HIV-specific immunity and delay viral rebound post-ART, although definitive evidence of quantitative reservoir reduction remains limited. Importantly, these strategies are generally safe, customizable, and scalable, offering significant advantages in the evolving landscape of HIV cure research. However, several challenges persist, including immune exhaustion in treatment-experienced populations, the need for improved reservoir measurement techniques, and logistical issues in delivery and cost. Future efforts will likely focus on combination regimens that integrate mRNA-based strategies with other immunologic and gene-based tools. While standard ART remains the cornerstone of HIV treatment, mRNA-based immune modulators represent a compelling adjunctive strategy with the potential to shift the paradigm from lifelong viral suppression to functional cure or durable remission.

REFERENCES

1. Mr.S.R.P., -, Dr.A.A.: Nanostructured Lipid Carriers in HIV Therapy: Unlocking the Future of Long-Acting and Targeted Antiretroviral Delivery. IJSAT - International Journal on Science and Technology. 16, (2025). https://doi.org/10.71097/IJSAT.V16.I2.5597
2. 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
3. Li, K., Zhang, Q.: Eliminating the HIV tissue reservoir: current strategies and challenges. Infect Dis. 56, 165–182 (2024). https://doi.org/10.1080/23744235.2023.2298450;REQUESTEDJOURNAL:JOURNAL:INFD20
4. Wang, Y., Zhang, Z., Luo, J., Han, X., Wei, Y., Wei, X.: mRNA vaccine: a potential therapeutic strategy. Molecular Cancer 2021 20:1. 20, 1–23 (2021). https://doi.org/10.1186/S12943-021-01311-Z
5. Wadhwa, A., Aljabbari, A., Lokras, A., Foged, C., Thakur, A.: Opportunities and Challenges in the Delivery of mRNA-Based Vaccines. Pharmaceutics 2020, Vol. 12, Page 102. 12, 102 (2020). https://doi.org/10.3390/PHARMACEUTICS12020102
6. Alum, E. U., Uti, D. E., Ugwu, O. P., Alum, B. N. Toward a cure - Advancing HIV/AIDs treatment modalities beyond antiretroviral therapy: A Review. Medicine (Baltimore). 2024 Jul 5;103(27):e38768. doi: 10.1097/MD.0000000000038768.
7. Taye, M.A.: Drug Washout and Viral Rebound: Modeling HIV Reactivation Under ART Discontinuation. (2025)
8. Chen, J., Zhou, T., Zhang, Y., Luo, S., Chen, H., Chen, D., Li, C., Li, W.: The reservoir of latent HIV. Front Cell Infect Microbiol. 12, 945956 (2022). https://doi.org/10.3389/FCIMB.2022.945956/XML
9. Mzingwane, M.L., Tiemessen, C.T.: Mechanisms of HIV persistence in HIV reservoirs. Rev Med Virol. 27, e1924 (2017). https://doi.org/10.1002/RMV.1924
10. Sadowski, I., Hashemi, F.B.: Strategies to eradicate HIV from infected patients: elimination of latent provirus reservoirs. Cellular and Molecular Life Sciences 2019 76:18. 76, 3583–3600 (2019). https://doi.org/10.1007/S00018-019-03156-8
11. Schwarzer, R., Gramatica, A., Greene, W.C.: Reduce and Control: A Combinatorial Strategy for Achieving Sustained HIV Remissions in the Absence of Antiretroviral Therapy. Viruses 2020, Vol. 12, Page 188. 12, 188 (2020). https://doi.org/10.3390/V12020188
12. Foka, F.E.T., Mufhandu, H.T.: Current ARTs, Virologic Failure, and Implications for AIDS Management: A Systematic Review. Viruses 2023, Vol. 15, Page 1732. 15, 1732 (2023). https://doi.org/10.3390/V15081732
13. 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.
14. Ezenwaji, C.O., Alum, E.U. & Ugwu, O.PC. Bridging the gap: telemedicine as a solution for HIV care inequities in rural and vulnerable communities. Int J Equity Health **24**, 205 (2025). https://doi.org/10.1186/s12939-025-02584-2
15. Sahin, U., Karikó, K., Türeci, Ö.: mRNA-based therapeutics — developing a new class of drugs. Nature Reviews Drug Discovery 2014 13:10. 13, 759–780 (2014). https://doi.org/10.1038/nrd4278
16. 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
17. 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
18. 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
19. Zhang, Y., Jin, S., Zuo, Z., Liu, S., Xu, J., Yang, C., Wan, P., Xun, L., Luo, M., Yang, F., Chen, W., Song, Z., Qi, J.: Rational Design and Immunological Mechanisms of Circular RNA-Based Vaccines: Emerging Frontiers in Combating Pathogen Infection. Vaccines (Basel). 13, 563 (2025). https://doi.org/10.3390/VACCINES13060563/S1
20. Linares-Fernández, S., Lacroix, C., Exposito, J.Y., Verrier, B.: Tailoring mRNA Vaccine to Balance Innate/Adaptive Immune Response. Trends Mol Med. 26, 311–323 (2020).

https://doi.org/10.1016/J.MOLMED.2019.10.002/ATTACHMENT/ADB91320-EC2C-411A-9032-275CE59A919E/MMC1.MP4
21. Floudas, C.S., Sarkizova, S., Ceccarelli, M., Zheng, W.: Leveraging mRNA technology for antigen based immuno-oncology therapies. J Immunother Cancer. 13, e010569 (2025). https://doi.org/10.1136/JITC-2024-010569

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