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# mRNA Vaccine Platforms Targeting HIV 1 Envelope Glycoproteins: Current Progress and Future Directions

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## ABSTRACT

Human immunodeficiency virus type 1 remains a major global health challenge, with persistent transmission despite advances in antiretroviral therapy and preventive interventions. The viral envelope glycoproteins gp120 and gp41, organized as trimeric spikes on the virion surface, mediated host cell entry and represented the principal targets of neutralizing antibodies; however, extensive glycan shielding, conformational masking, and genetic variability historically hindered vaccine development. The purpose of this review was to critically evaluate current progress in mRNA vaccine platforms encoding HIV 1 envelope glycoproteins and to examine their potential to overcome longstanding immunological barriers. A structured narrative synthesis of recent preclinical and early clinical studies, integrated with advances in structural biology and molecular engineering, was undertaken to assess emerging evidence. Accumulating data indicated that mRNA platforms permitted precise encoding of stabilized envelope trimers, germline targeting constructs, and mosaic immunogens, resulting in improved antigen expression and enhanced induction of neutralizing antibody precursors in animal models and early human trials. Nevertheless, induction of broadly neutralizing antibodies with sufficient breadth and durability remained elusive. mRNA-based approaches provided unprecedented flexibility and translational promise for HIV vaccine design, yet required iterative immunogen optimization and rigorous clinical evaluation to achieve meaningful protective efficacy.

**Keywords:** HIV 1, mRNA vaccine, Envelope glycoprotein, Broadly neutralizing antibodies, Structural vaccinology.

## INTRODUCTION

Human immunodeficiency virus type 1 continues to impose a substantial global disease burden, with millions of individuals living with infection and significant numbers of new transmissions annually [1, 2]. Although combination antiretroviral therapy has transformed HIV infection into a manageable chronic condition, it does not eradicate latent reservoirs and requires lifelong adherence. Preventive strategies, including pre-exposure prophylaxis and behavioral interventions, have reduced incidence in some settings, yet a safe and effective vaccine remains the most sustainable solution for global control [3].

Vaccine development has been profoundly complicated by the extraordinary genetic diversity and immune evasion strategies of HIV 1 [4, 5]. The envelope glycoproteins gp120 and gp41 form trimeric spikes that mediate viral attachment to CD4 receptors and chemokine coreceptors [6]. These glycoproteins are heavily glycosylated and conformationally dynamic, masking conserved neutralization epitopes and enabling escape from antibody recognition. Traditional vaccine platforms using recombinant proteins, viral vectors, or DNA constructs have achieved limited success in eliciting broadly neutralizing antibodies capable of targeting diverse viral strains. The advent of mRNA vaccine technology has introduced new possibilities for precision antigen design, rapid iteration, and enhanced immunogenicity [7, 8]. By enabling in situ expression of structurally defined envelope immunogens, mRNA platforms can incorporate stabilized trimers, germline targeting constructs, and sequential immunization strategies designed to guide antibody maturation. This review examines the structural biology of HIV 1 envelope glycoproteins, the molecular principles underlying mRNA vaccine platforms, innovative design strategies for envelope immunogens, current preclinical and early clinical evidence, and the scientific and translational challenges

that remain. The purpose of this study is to critically assess whether mRNA-based approaches can meaningfully advance the quest for an effective HIV vaccine.

**Structural and Functional Biology of HIV 1 Envelope Glycoproteins**

The HIV 1 envelope spike is a trimeric complex composed of three gp120 surface subunits noncovalently associated with three gp41 transmembrane subunits [9]. Synthesized as a gp160 precursor, the protein undergoes cleavage to generate gp120 and gp41, which assemble into metastable trimers embedded within the viral membrane. This spike mediates sequential binding to the CD4 receptor and either CCR5 or CXCR4 coreceptors, triggering conformational rearrangements that enable membrane fusion.

A defining feature of gp120 is its dense glycan shield, comprising numerous N-linked glycans that obscure underlying peptide epitopes [10]. These glycans mimic host carbohydrate structures, reducing immunogenicity and shielding conserved functional regions. Moreover, the envelope trimer exhibits conformational plasticity, transitioning between closed, intermediate, and open states during receptor engagement. Many conserved neutralization epitopes are transiently exposed, limiting antibody access.

Despite these challenges, rare individuals develop broadly neutralizing antibodies that target conserved regions such as the CD4 binding site, the V1 V2 apex, the V3 glycan supersite, the gp120 gp41 interface, and the membrane proximal external region of gp41 [11]. Structural elucidation of these epitopes has informed rational immunogen design. Stabilized soluble trimers that maintain the prefusion closed conformation have been engineered to better mimic native spikes [12]. Understanding the structural and functional complexity of envelope glycoproteins is essential for vaccine development. Immunogens must faithfully present conserved epitopes while minimizing exposure of immunodominant but non-neutralizing regions. mRNA platforms offer the opportunity to encode such precisely engineered constructs for in vivo expression.

**Principles and Molecular Engineering of mRNA Vaccine Platforms**

mRNA vaccines function by delivering synthetic messenger RNA encoding a target antigen into host cells, where translation produces the antigen in situ [13]. The mRNA molecule typically includes a 5 prime cap, optimized untranslated regions, an open reading frame encoding the antigen, and a polyadenylated tail. Codon optimization enhances translational efficiency, while incorporation of modified nucleosides can reduce innate immune sensing and increase stability.

Lipid nanoparticle delivery systems protect mRNA from degradation and facilitate cellular uptake through endocytosis [14]. Ionizable lipids enable endosomal escape, releasing mRNA into the cytoplasm for translation. Fine-tuning of lipid composition influences biodistribution, reactogenicity, and magnitude of immune responses. Innate immune activation plays a dual role. Controlled stimulation of pattern recognition receptors promotes dendritic cell maturation and antigen presentation, enhancing adaptive immunity. Excessive activation, however, may impair translation and limit antigen production. Careful sequence engineering and purification processes are therefore critical.

For HIV vaccine development, mRNA platforms permit rapid iteration of complex envelope constructs without the need for protein purification [15]. Multiple immunogens can be encoded and administered sequentially to guide affinity maturation of B cell responses. Furthermore, in situ expression may better preserve conformational integrity compared with recombinant protein approaches. The biochemical precision afforded by mRNA technology aligns closely with the demands of structural vaccinology for HIV 1, where subtle conformational differences determine epitope exposure and immunogenicity.

**Design Strategies for mRNA-Encoded HIV-1 Envelope Immunogens**

A central objective in HIV vaccine research is the induction of broadly neutralizing antibodies capable of recognizing diverse viral strains. mRNA platforms have facilitated innovative design strategies aimed at this goal. Stabilized envelope trimers represent a foundational approach. Engineered modifications, including disulfide bonds and cavity-filling mutations, maintain the prefusion closed conformation, enhancing presentation of conserved epitopes [16]. Encoding such trimers via mRNA allows expression of membrane-anchored or soluble forms that more closely resemble native spikes.

Germline targeting strategies seek to activate rare naive B cells expressing precursors of broadly neutralizing antibodies. Immunogens are designed to bind with sufficient affinity to these germline receptors, initiating maturation pathways that can be guided through sequential immunization with progressively native like antigens [17]. mRNA technology is particularly suited for this iterative approach. Mosaic and consensus immunogens incorporate sequences from multiple viral clades to broaden immune recognition. Additionally, nanoparticle display systems encoded by mRNA can multimerize envelope antigens, enhancing B cell receptor cross-linking and immunogenicity.

Sequential immunization regimens delivered via mRNA offer flexibility in timing and composition, enabling adaptive vaccine strategies based on immunological readouts. Collectively, these approaches illustrate how mRNA platforms integrate structural insight with immunological engineering to address the unique challenges posed by HIV 1.

**Preclinical and Early Clinical Progress**

Preclinical studies in small animals and nonhuman primates have demonstrated that mRNA vaccines encoding stabilized envelope trimers can elicit binding antibodies and autologous neutralizing responses [18, 19]. Germline targeting constructs delivered via mRNA have successfully activated precursor B cells in engineered mouse models expressing human antibody genes.

In nonhuman primates, sequential mRNA immunization strategies have induced increasing breadth of neutralizing activity, although levels remain below those observed in naturally infected individuals who develop broadly neutralizing antibodies. Importantly, mRNA vaccination has been associated with robust germinal center responses, a prerequisite for affinity maturation.

Early phase clinical trials evaluating mRNA vaccines encoding HIV envelope immunogens have reported acceptable safety profiles and measurable immune responses [20]. Induction of neutralizing antibodies targeting specific epitopes has been observed, though breadth and potency remain limited. T cell responses have also been detected, contributing to potential supportive roles in antibody maturation. While these findings represent meaningful progress, no mRNA-based HIV vaccine has yet demonstrated protective efficacy in large-scale efficacy trials. Nonetheless, the ability to rapidly refine immunogen design and dosing schedules provides a dynamic framework for continued optimization.

**Scientific Barriers, Translational Challenges, and Future Directions**

Despite technological advances, formidable barriers remain. The extraordinary sequence diversity of HIV 1 necessitates induction of antibodies with exceptional breadth [21]. Viral mutation and glycan heterogeneity enable rapid escape from immune pressure. Immune imprinting from prior exposure may influence vaccine responsiveness in endemic populations. The induction of broadly neutralizing antibodies typically requires prolonged affinity maturation characterized by high levels of somatic hypermutation. Designing immunization regimens that reliably recapitulate this process in diverse human populations remains a central challenge.

Manufacturing scalability and global distribution must also be considered. Although mRNA platforms allow rapid production, ensuring stability and cold chain maintenance in resource-limited settings requires continued innovation [22, 23]. Regulatory evaluation of complex sequential immunization strategies may further complicate development pathways.

Future directions include integration of advanced structural modeling, systems immunology analyses, and artificial intelligence-guided immunogen optimization. Combination approaches incorporating T cell-based strategies or passive immunization may also enhance efficacy. A coordinated global effort linking basic science, clinical research, and public health implementation will be essential to translate promising laboratory advances into effective preventive vaccines.

## CONCLUSION

The pursuit of an effective HIV 1 vaccine has challenged the scientific community for decades, largely due to the structural complexity and immune evasion strategies of the viral envelope glycoproteins. mRNA vaccine platforms have introduced a transformative technological paradigm, enabling precise encoding of stabilized trimers, germline targeting constructs, and sequential immunization strategies informed by structural vaccinology. Preclinical studies and early human trials demonstrate encouraging immunogenicity and favorable safety profiles, underscoring the versatility and adaptability of this approach. Nevertheless, the induction of broadly neutralizing antibodies with sufficient breadth, potency, and durability to confer protection across diverse viral strains remains an unresolved objective. Substantial gaps persist in understanding optimal immunogen design, dosing regimens, and mechanisms governing long-term affinity maturation in heterogeneous populations. Translational challenges related to manufacturing, distribution, and regulatory oversight must also be addressed to ensure equitable global access. Sustained multidisciplinary collaboration integrating structural biology, immunology, clinical investigation, and global health policy is strongly recommended to accelerate the rational refinement and evaluation of mRNA vaccines targeting HIV 1 envelope glycoproteins.

## REFERENCES

1. Kaslow, R.A., Tang, J. 'James', Goepfert, P.A.: Human Immunodeficiency Virus Types 1 and 2: Global History, Occurrence, and Spread. In: Viral Infections of Humans. pp. 1–59. Springer, New York, NY (2024)
2. Obeagu, E.I., Alum, E.U., Obeagu, G.U.: Factors Associated with Prevalence of HIV among Youths: A Review of Africa Perspective. Madonna University journal of Medicine and Health Sciences ISSN: 2814-3035. 3, 13–18 (2023)
3. Odo, E.O., Igwe, M.C., Okwaja, P.R.: Revolutionizing HIV Prevention in Africa: Landmark Innovations that Transformed the Fight. IAA-JAS. 11, 1–12 (2024). https://doi.org/10.59298/IAAJAS/2024/1.3.5288
4. Habib, A., Liang, Y., Zhu, N.: Exosomes multifunctional roles in HIV-1: insight into the immune regulation, vaccine development and current progress in delivery system. Front. Immunol. 14, (2023). https://doi.org/10.3389/fimmu.2023.1249133

5. Boomgarden, A.C., Upadhyay, C.: Progress and Challenges in HIV-1 Vaccine Research: A Comprehensive Overview. Vaccines. 13, (2025). https://doi.org/10.3390/vaccines13020148
6. Shaik, M.M., Peng, H., Lu, J., Rits-Volloch, S., Xu, C., Liao, M., Chen, B.: Structural basis of coreceptor recognition by HIV-1 envelope spike. Nature. 565, 318–323 (2019). https://doi.org/10.1038/s41586-018-0804-9
7. Zhang, Y., Li, J., Wang, Z., Kuang, Y., Li, S., Wang, X.: Precision-engineered mRNA vaccines: antigen design, structural optimization, and programmable delivery for emerging pathogens. Animal Diseases. 5, 32 (2025). https://doi.org/10.1186/s44149-025-00186-7
8. Uti, D.E., Ugwu, O.P.-C., Alum, B.N.: Toward a cure - Advancing HIV/AIDs treatment modalities beyond antiretroviral therapy: A Review. Medicine (Baltimore). 103, e38768 (2024). https://doi.org/10.1097/MD.0000000000038768
9. Shaik, M.M., Peng, H., Lu, J., Rits-Volloch, S., Xu, C., Liao, M., Chen, B.: Structural basis of coreceptor recognition by HIV-1 envelope spike. Nature. 565, 318–323 (2019). https://doi.org/10.1038/s41586-018-0804-9
10. Doores, K.J.: The HIV glycan shield as a target for broadly neutralizing antibodies. The FEBS Journal. 282, 4679–4691 (2015). https://doi.org/10.1111/febs.13530
11. Mahomed, S.: Broadly neutralizing antibodies for HIV prevention: a comprehensive review and future perspectives. Clinical Microbiology Reviews. 37, e00152-22 (2024). https://doi.org/10.1128/cmr.00152-22
12. Riley, T.P., Chou, H.-T., Hu, R., Bzymek, K.P., Correia, A.R., Partin, A.C., Li, D., Gong, D., Wang, Z., Yu, X., Manzanillo, P., Garces, F.: Enhancing the Prefusion Conformational Stability of SARS-CoV-2 Spike Protein Through Structure-Guided Design. Front. Immunol. 12, (2021). https://doi.org/10.3389/fimmu.2021.660198
13. Wang, Y., Zhang, Z., Luo, J., Han, X., Wei, Y., Wei, X.: mRNA vaccine: a potential therapeutic strategy. Mol Cancer. 20, 33 (2021). https://doi.org/10.1186/s12943-021-01311-z
14. Wang, J., Chen, R., Xie, Y., Qin, X., Zhou, Y., Xu, C.: Endo/Lysosomal-Escapable Lipid Nanoparticle Platforms for Enhancing mRNA Delivery in Cancer Therapy. Pharmaceutics. 17, (2025). https://doi.org/10.3390/pharmaceutics17070803
15. Linares Fernández, S.: Optimising a mRNA Vaccine platform against HIV-1 : from the in vitro transcription design to envelope protein expression, https://theses.hal.science/tel-04185910, (2021)
16. Gonzalez, K.J., Yim, K.C., Blanco, J.C.G., Boukhvalova, M.S., Strauch, E.-M.: Systematic computer-aided disulfide design as a general strategy to stabilize prefusion class I fusion proteins. Front. Immunol. 15, (2024). https://doi.org/10.3389/fimmu.2024.1406929
17. Schmidt, A.G., Do, K.T., McCarthy, K.R., Kepler, T.B., Liao, H.-X., Moody, M.A., Haynes, B.F., Harrison, S.C.: Immunogenic Stimulus for Germline Precursors of Antibodies that Engage the Influenza Hemagglutinin Receptor-Binding Site. Cell Reports. 13, 2842–2850 (2015). https://doi.org/10.1016/j.celrep.2015.11.063
18. Ramezani-Rad, P., Cottrell, C.A., Marina-Zárate, E., Liguori, A., Landais, E., Torres, J.L., Myers, A., Lee, J.H., Baboo, S., Flynn, C., McKenney, K., Salcedo, E., Zhou, X., Kalyuzhniy, O., Georgeson, E., Phelps, N., Lu, D., Eskandarzadeh, S., Menis, S., Kubitz, M., Groschel, B., Alavi, N., Jackson, A.M., Lee, W.-H., Tran, A.S., Ben-Akiva, E., Kaczmarek Michaels, K., Diedrich, J.K., Enemuo, C.A., Lewis, V., Pradhan, A., Kasturi, S.P., Schiffner, T., Steichen, J.M., Carnathan, D.G., Himansu, S., Yates, J.R., Paulson, J.C., Ozorowski, G., Irvine, D.J., Silvestri, G., Sok, D., Ward, A.B., Crotty, S., Schief, W.R.: Vaccination with an mRNA-encoded membrane-bound HIV envelope trimer induces neutralizing antibodies in animal models. Science Translational Medicine. 17, eadw0721 (2025). https://doi.org/10.1126/scitranslmed.adw0721
19. Parks, K.R., Moodie, Z., Allen, M.A., Yen, C., Furch, B.D., MacPhee, K.J., Ozorowski, G., Heptinstall, J., Hahn, W.O., Zheng, Z., Lu, H., Grant, S., Domin, E., Duff, M.O., Seese, A., Marini-Macouzet, C., Ballweber-Fleming, L., Lee, W.-H., Cottrell, C.A., Liguori, A., Georgeson, E., Alavi, N., Kubitz, M., Phelps, N., Seaton, K.E., Cohen, K.W., Anderson, M.A., Mondal, K., Laufer, D.S., Kublin, J.G., Ward, A.B., Hyrien, O., De Rosa, S.C., Himansu, S., Leav, B., Reuter, C., Tomaras, G.D., Montefiori, D., Walsh, S.R., Frank, I., Sobieszczyk, M.E., Goepfert, P.A., Stephenson, K.E., Baden, L.R., Van Tieu, H., Keefer, M.C., Clark, J., Riddler, S.A., Schief, W.R., McElrath, M.J.: Vaccination with mRNA-encoded membrane-anchored HIV envelope trimers elicited tier 2 neutralizing antibodies in a phase 1 clinical trial. Science Translational Medicine. 17, eady6831 (2025). https://doi.org/10.1126/scitranslmed.ady6831
20. Leal, L., Guardo, A.C., Morón-López, S., Salgado, M., Mothe, B., Heirman, C., Pannus, P., Vanham, G., van den Ham, H.J., Gruters, R., Andeweg, A., Van Meirvenne, S., Pich, J., Arnaiz, J.A., Gatell, J.M., Brander, C., Thielemans, K., Martínez-Picado, J., Plana, M., García, F., Consortium, on behalf of the iHIVARNA: Phase I clinical trial of an intranodally administered mRNA-based therapeutic vaccine against HIV-1 infection. AIDS. 32, 2533 (2018). https://doi.org/10.1097/QAD.0000000000002026
21. Mahomed, S.: Broadly neutralizing antibodies for HIV prevention: a comprehensive review and future perspectives. Clinical Microbiology Reviews. 37, e00152-22 (2024). https://doi.org/10.1128/cmr.00152-22

22. Uddin, M.N., Roni, M.A.: Challenges of Storage and Stability of mRNA-Based COVID-19 Vaccines. Vaccines. 9, (2021). https://doi.org/10.3390/vaccines9091033
23. Ezenwaji, C.O., Alum, E.U., Ugwu, O.P.-C.: Bridging the gap: telemedicine as a solution for HIV care inequities in rural and vulnerable communities. International Journal for Equity in Health. 24, 205 (2025). https://doi.org/10.1186/s12939-025-02584-2

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