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Effectiveness of Exosome-Delivered siRNA Therapy Versus Broadly Neutralizing Antibodies on HIV Viral Load Suppression: A Review

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ABSTRACT

HIV continues to pose significant global health challenges, with antiretroviral therapy (ART) providing effective viral suppression but failing to eliminate latent reservoirs. To address this limitation, recent research has explored novel therapeutic strategies, such as exosome-delivered small interfering RNA (siRNA) and broadly neutralizing antibodies (bNAbs), both of which aim to achieve more durable viral control or a functional cure. This review was conducted to compare the mechanisms, clinical effectiveness, and translational potential of these two emerging therapies in reducing HIV viral load in individuals receiving or transitioning from ART. A narrative review methodology was used, synthesizing relevant peer-reviewed literature published between 2010 and 2025 across preclinical and clinical settings. Findings show that exosome-delivered siRNA offers targeted gene silencing with high specificity and reduced toxicity, although current evidence remains limited to experimental models. In contrast, bNAbs have demonstrated significant reductions in viral load and delayed rebound in clinical trials, particularly when used in combination or sequential dosing strategies. Despite their potential, both therapies face limitations, including delivery challenges, the risk of viral resistance, and concerns regarding scalability. In contrast, while bNAbs are closer to clinical application, exosome-based siRNA therapy holds considerable promise and warrants further investigation. A combinatory or personalized approach may represent the most viable pathway toward functional HIV remission.

Keywords: HIV viral suppression, Exosome therapy, siRNA delivery, Broadly neutralizing antibodies, Functional HIV cure.

INTRODUCTION

HIV infection remains one of the most challenging viral diseases to manage and eradicate, primarily due to its integration into host genomes and the rapid mutation rate of its viral envelope [1, 2]. Although the widespread implementation of antiretroviral therapy (ART) has significantly reduced HIV-related morbidity and mortality, it does not eradicate the virus [3, 4]. Long-term adherence, the risk of drug resistance, and viral rebound upon treatment interruption have driven the search for alternative and adjunctive therapeutic strategies. Two such promising avenues are exosome-delivered small interfering RNA (siRNA) therapy and broadly neutralizing antibodies (bNAbs). These novel interventions have gained attention for their potential to reduce viral load and possibly contribute to a functional cure.

siRNA therapy utilizes short RNA sequences that specifically target and silence viral mRNA, inhibiting replication at the post-transcriptional level [5, 6]. The major challenge lies in effective delivery to target cells. Exosomes, which are naturally occurring extracellular vesicles, have emerged as ideal carriers due to their biocompatibility, low immunogenicity, and ability to cross biological barriers. Exosome-encapsulated siRNA offers a promising solution for systemic delivery, potentially enabling selective knockdown of HIV gene expression in infected cells [7, 8].

In contrast, bNAbs are immunoglobulins that recognize and neutralize diverse strains of HIV by targeting conserved regions of the envelope glycoprotein [9]. These antibodies can block viral entry, facilitate immune clearance of infected cells, and have shown prolonged viral suppression in clinical trials when used alone or in combination with ART. This review critically compares the mechanisms, preclinical and clinical outcomes, safety profiles, and translational feasibility of exosome-delivered siRNA and bNAb therapies. It evaluates their relative effectiveness in suppressing HIV viral load and their roles in next-generation HIV therapeutics. The aim is to determine the extent to which each strategy may complement or replace traditional ART in the pursuit of durable virologic control or cure.

HIV Pathogenesis and the Need for Novel Therapeutics

HIV primarily targets CD4+ T lymphocytes, resulting in progressive immune suppression [10]. The virus integrates into the host genome, forming a latent reservoir that remains undetectable by immune surveillance and unaffected by ART. Although ART blocks replication at various stages of the viral lifecycle, it does not target the integrated provirus or eliminate infected cells.

Persistent low-level viral replication, immune activation, and inflammation underlie ongoing tissue damage and comorbidities in treated individuals. Furthermore, the need for lifelong adherence and the emergence of drug-resistant strains contribute to treatment fatigue and failure. As a result, innovative therapies are being developed to reduce or eliminate viral reservoirs, control replication independently of ART, and enhance host immune responses. Among these approaches, gene-silencing technologies such as siRNA and immune-based interventions like bNAbs have demonstrated considerable preclinical efficacy [11]. The delivery platform and immune engagement mechanisms, however, determine their practical impact in vivo.

Mechanism and Application of Exosome-Delivered siRNA Therapy

Small interfering RNAs are short double-stranded RNA molecules that harness the endogenous RNA interference pathway [12]. Once inside the cytoplasm, siRNAs are incorporated into the RNA-induced silencing complex (RISC), where they bind complementary sequences on target mRNA and induce degradation, effectively silencing gene expression. In HIV, siRNAs have been designed to target essential viral genes such as gag, pol, tat, and rev, or host dependency factors such as CCR5 [13]. Targeting viral genes can reduce replication, while silencing host factors can prevent entry or assembly.

One of the major challenges in siRNA therapy is achieving efficient and selective delivery to HIV-infected cells [14]. Naked siRNA is unstable in the bloodstream and prone to rapid degradation by nucleases. Exosomes provide a physiologically compatible delivery vehicle that enhances the stability, cellular uptake, and tissue penetration of therapeutic siRNA. Exosomes are small vesicles (30–150 nm) secreted by many cell types and capable of carrying nucleic acids, proteins, and lipids [15, 16]. Their lipid bilayer protects siRNA from degradation, and their surface markers enable tissue-specific uptake. Exosome-mediated delivery can be engineered by modifying donor cells to express targeting ligands or by loading siRNA via electroporation, transfection, or passive incubation.

Preclinical studies have shown that exosome-delivered HIV-specific siRNAs reduce viral replication in vitro and in animal models. For example, exosomes loaded with siRNA targeting tat or rev resulted in a marked reduction of viral RNA and protein expression in CD4+ T cells and monocytes [17]. However, this therapeutic approach is still in the experimental stage, with limited human data. Further optimization is needed to enhance loading efficiency, targeting specificity, and scalability for clinical translation.

Mechanism and Application of Broadly Neutralizing Antibodies (bNAbs)

Broadly neutralizing antibodies represent a class of immunoglobulins that bind to conserved epitopes on the HIV envelope protein (Env), particularly gp120 and gp41 [18]. These regions are functionally important for viral entry and are less subject to mutational escape. bNAbs prevent infection by blocking the attachment of HIV to CD4+ receptors or by interfering with fusion to the host membrane. Beyond neutralization, bNAbs mediate antibody-dependent cellular cytotoxicity (ADCC), complement activation, and phagocytosis, enhancing clearance of infected cells. Some bNAbs also exert immunomodulatory effects, promoting the expansion of HIV-specific T cell responses. Several bNAbs have been isolated from long-term non-progressors and elite controllers, including VRC01, 3BNC117, and 10-1074 [19, 20]. These antibodies have demonstrated potent in vitro neutralization breadth and have entered phase I and II clinical trials. Clinical studies show that a single infusion of bNAbs can significantly reduce plasma HIV RNA levels in ART-naive and ART-suppressed individuals. In a landmark study, administration of 3BNC117 led to a 1.5 log10 reduction in viral load, while combination therapy with 3BNC117 and 10-1074 delayed viral rebound after treatment interruption.

Unlike ART, bNAbs offer the advantage of immune engagement, longer half-lives, and the potential for intermittent dosing. However, the emergence of resistant viral strains remains a concern, necessitating the use of bNAb cocktails or engineered multispecific antibodies.

Comparative Efficacy in Viral Load Suppression

Both exosome-delivered siRNA and bNAbs aim to reduce HIV replication, albeit through distinct mechanisms [21]. siRNA directly inhibits gene expression at the post-transcriptional level, while bNAbs block entry and enhance immune-mediated clearance. In preclinical studies, exosome-encapsulated siRNA has shown a significant reduction in viral RNA and protein levels in HIV-infected cell cultures. In murine models with humanized immune systems, systemic administration of exosome-siRNA resulted in decreased viremia and reduced HIV gene expression in target tissues. However, the effect is transient, and repeat dosing is often required.

In contrast, bNAbs have produced robust reductions in viral load in human subjects [22]. For instance, VRC01 achieved temporary suppression in approximately 30 percent of recipients, while combination bNAb therapy delayed rebound for several weeks post-ART interruption in most participants. Direct comparisons are difficult due to the lack of head-to-head trials. Nevertheless, current evidence suggests that bNAbs achieve more immediate and measurable reductions in viral load in vivo, whereas exosome-siRNA therapy is promising but remains confined to early-stage investigations.

Both strategies face challenges in durability and viral escape. For siRNA, mutations in the target sequence may prevent binding, while bNAbs may be rendered ineffective by envelope glycan shielding or mutational escape. Accordingly, a combination of multiple siRNAs or bNAbs targeting distinct epitopes may be necessary for sustained suppression.

Safety and Immunogenicity

Safety profiles are a critical consideration in the development of any new therapeutic modality. Exosomes, being endogenous to the body, are generally considered safe and non-immunogenic. They exhibit low toxicity and minimal inflammatory responses, especially when derived from autologous cells. However, standardization of production, purification, and quality control remains a challenge in ensuring reproducibility and safety. siRNAs themselves can induce off-target gene silencing and innate immune activation through toll-like receptors if not properly designed. Chemical modification of siRNA and careful sequence selection can minimize these risks.

bNAbs have demonstrated favorable safety in human trials, with most adverse events being mild and infusion-related [23]. However, repeat dosing may elicit anti-drug antibodies that neutralize efficacy or trigger hypersensitivity reactions. Engineering Fc regions and using fully humanized antibodies can reduce immunogenicity. In terms of organ toxicity, neither modality has shown significant long-term adverse effects in animal studies or early-phase human trials. Nonetheless, larger studies are needed to assess long-term outcomes and interactions with ART or other immunotherapies.

Delivery and Translational Potential

Delivery is a major differentiator between these therapies. Exosome-based siRNA therapy benefits from the biological compatibility and natural trafficking properties of exosomes [24]. These vesicles can cross biological barriers, including the blood-brain barrier, and target tissue-resident HIV reservoirs such as the central nervous system and lymphoid organs. However, production and loading methods are still under refinement. Achieving high encapsulation efficiency, consistent batch quality, and targeted delivery remains a barrier to widespread application. Additionally, regulatory frameworks for exosome-based therapies are still evolving.

On the other hand, bNAbs can be delivered via intravenous infusion, subcutaneous injection, or even through gene therapy vectors encoding antibody genes. Their half-lives can be extended using Fc engineering, allowing dosing intervals of several weeks or even months. Several bNAbs are now being tested in combination with long-acting ART or latency-reversing agents, expanding their utility in functional cure strategies. Manufacturing processes are well established for monoclonal antibodies, and scalability is feasible with current biopharmaceutical infrastructure. In practical terms, bNAbs are closer to clinical application, while exosome-siRNA therapy requires more foundational research to address formulation, targeting, and delivery challenges.

Future Directions and Combination Strategies

While both strategies hold promise, their optimal utility may lie in combination with other modalities. Exosome-siRNA can be used alongside ART to suppress residual replication or in latency reversal strategies to block reactivated transcription. It may also be engineered to deliver immunostimulatory cargo, combining gene silencing with immune activation.

bNAbs are increasingly being combined with other immunotherapies, such as therapeutic vaccines and immune checkpoint inhibitors [25, 26]. The use of trispecific antibodies and engineered variants with enhanced effector functions are in advanced stages of development.

In the long term, the integration of RNA-based silencing, antibody-mediated immunity, and latency-targeting strategies may converge into multipronged therapeutic regimens. These regimens could be tailored to viral genotypes, host immune status, and reservoir size, supporting personalized HIV treatment and cure approaches.

CONCLUSION

The search for alternatives to lifelong ART has brought exosome-delivered siRNA therapy and broadly neutralizing antibodies to the forefront of HIV research. Both offer unique mechanisms of viral control with the potential to reduce dependence on conventional therapy. Exosome-based siRNA therapy holds great promise due to its precision in silencing viral genes and its compatibility with natural biological pathways. However, its clinical application is limited by challenges in delivery efficiency, scalability, and a lack of human trial data. Broadly neutralizing antibodies, by contrast, have demonstrated potent viral suppression in clinical settings and provide the added benefit of immune-mediated clearance of infected cells. Their safety, tolerability, and compatibility with existing treatment protocols make them highly promising candidates for near-term clinical integration. While neither therapy is sufficient as a standalone cure, each contributes valuable tools to the evolving HIV therapeutic arsenal. Their strengths may be maximized through rational combination strategies that exploit both molecular precision and immune engagement. Ongoing research must focus on optimizing delivery systems, minimizing resistance, and conducting robust clinical trials to establish long-term efficacy. Ultimately, these innovative therapies bring us closer to a future in which durable viral suppression or functional cure is achievable beyond the confines of lifelong ART.

REFERENCES

1. Tough, R.H., McLaren, P.J.: Interaction of the host and viral genome and their influence on HIV disease. Front Genet. 10, 430537 (2019). https://doi.org/10.3389/FGENE.2018.00720/BIBTEX
2. 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
3. Obeagu, E.I., Obeagu, G.U., Alum, E.U., Ugwu, O.P.-C.: Comprehensive Review of Antiretroviral Therapy Effects on Red Blood Cells in HIV Patients. INOSR Experimental Sciences. 12, 63–72 (2023). https://doi.org/10.59298/INOSRES/2023/6.3.21322
4. Madu, C.V., Aloh, H.E., 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.
5. Adeola, A., O.: Treatment of Influenza: Prospects of Post-transcriptional Gene Silencing Through Synthetic siRNAs. http://www.xiahepublishing.com/. 2, 1–11 (2017). https://doi.org/10.14218/ERHM.2016.00013
6. Lam, J.K.W., Chow, M.Y.T., Zhang, Y., Leung, S.W.S.: siRNA versus miRNA as therapeutics for gene silencing. Mol Ther Nucleic Acids. 4, e252 (2015). https://doi.org/10.1038/MTNA.2015.23/ASSET/3E144955-8C1C-4A2B-8627-08CEFBB8E76A/MAIN.ASSETS/GR3.JPG
7. Gorshkov, A., Purvinsh, L., Brodskaia, A., Vasin, A.: Exosomes as Natural Nanocarriers for RNA-Based Therapy and Prophylaxis. Nanomaterials 2022, Vol. 12, Page 524. 12, 524 (2022). https://doi.org/10.3390/NANO12030524
8. Liang, Y., Iqbal, Z., Lu, J., Wang, J., Zhang, H., Chen, X., Duan, L., Xia, J.: Cell-derived nanovesicle-mediated drug delivery to the brain: Principles and strategies for vesicle engineering. Molecular Therapy. 31, 1207–1224 (2023). https://doi.org/10.1016/J.YMTHE.2022.10.008/ASSET/4BF6C5ED-3A00-4261-926A-7EB9C428DF80/MAIN.ASSETS/GR2.JPG
9. Burton, D.R., Hangartner, L.: Broadly Neutralizing Antibodies to HIV and Their Role in Vaccine Design. Annu Rev Immunol. 34, 635–659 (2016). https://doi.org/10.1146/ANNUREV-IMMUNOL-041015-055515/CITE/REFWORKS
10. 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. PMID: 38968496.
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. Ranasinghe, P., Addison, M.L., Dear, J.W., Webb, D.J.: Small interfering RNA: Discovery, pharmacology and clinical development—An introductory review. Br J Pharmacol. 180, 2697–2720 (2023). https://doi.org/10.1111/BPH.15972
13. Mishra, V., Kesharwani, P., Jain, N.K.: siRNA nanotherapeutics: a Trojan horse approach against HIV. Drug Discov Today. 19, 1913–1920 (2014). https://doi.org/10.1016/J.DRUDIS.2014.09.019
14. 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

15. Alzhrani, G.N., Alanazi, S.T., Alsharif, S.Y., Albalawi, A.M., Alsharif, A.A., Abdel-Maksoud, M.S., Elsherbiny, N.: Exosomes: Isolation, characterization, and biomedical applications. Cell Biol Int. 45, 1807–1831 (2021). https://doi.org/10.1002/CBIN.11620;WGROUP:STRING:PUBLICATION
16. Boriachek, K., Islam, M.N., Möller, A., Salomon, C., Nguyen, N.T., Hossain, M.S.A., Yamauchi, Y., Shiddiky, M.J.A.: Biological Functions and Current Advances in Isolation and Detection Strategies for Exosome Nanovesicles. Small. 14, 1702153 (2018). https://doi.org/10.1002/SMLL.201702153
17. HIV Latency, A., Malatesta, M., Boschi, F., Carton, F., Andre, M., Nair, M., Raymond, A.D.: HIV Latency and Nanomedicine Strategies for Anti-HIV Treatment and Eradication. Biomedicines 2023, Vol. 11, Page 617. 11, 617 (2023). https://doi.org/10.3390/BIOMEDICINES11020617
18. Klasse, P.J., Sanders, R.W., Ward, A.B., Wilson, I.A., Moore, J.P.: The HIV-1 envelope glycoprotein: structure, function and interactions with neutralizing antibodies. Nat Rev Microbiol. 1–19 (2025). https://doi.org/10.1038/S41579-025-01206-6;SUBJMETA=2557,326,596,631;KWRD=VIROLOGY,VIRUS
19. Thavarajah, J.J., Hønge, B.L., Wejse, C.M.: The Use of Broadly Neutralizing Antibodies (bNAbs) in HIV-1 Treatment and Prevention. Viruses 2024, Vol. 16, Page 911. 16, 911 (2024). https://doi.org/10.3390/V16060911
20. Mahomed, S.: Broadly neutralizing antibodies for HIV prevention: a comprehensive review and future perspectives. Clin Microbiol Rev. 37, (2024). https://doi.org/10.1128/CMR.00152-22/SUPPL_FILE/CMR.00152-22-S0001.XLSX
21. QIU, Y., MA, J., ZENG, Y.: Therapeutic Potential of Anti-HIV RNA-loaded Exosomes. Biomedical and Environmental Sciences. 31, 215–226 (2018). https://doi.org/10.3967/BES2018.027
22. Thavarajah, J.J., Hønge, B.L., Wejse, C.M.: The Use of Broadly Neutralizing Antibodies (bNAbs) in HIV-1 Treatment and Prevention. Viruses 2024, Vol. 16, Page 911. 16, 911 (2024). https://doi.org/10.3390/V16060911
23. Mahomed, S.: Broadly neutralizing antibodies for HIV prevention: a comprehensive review and future perspectives. Clin Microbiol Rev. 37, (2024). https://doi.org/10.1128/CMR.00152-22/SUPPL_FILE/CMR.00152-22-S0001.XLSX
24. Gorshkov, A., Purvinsh, L., Brodskaia, A., Vasin, A.: Exosomes as Natural Nanocarriers for RNA-Based Therapy and Prophylaxis. Nanomaterials 2022, Vol. 12, Page 524. 12, 524 (2022). https://doi.org/10.3390/NANO12030524
25. Thavarajah, J.J., Hønge, B.L., Wejse, C.M.: The Use of Broadly Neutralizing Antibodies (bNAbs) in HIV-1 Treatment and Prevention. Viruses 2024, Vol. 16, Page 911. 16, 911 (2024). https://doi.org/10.3390/V16060911
26. Kapoor, A., Tan, C.S.: Immunotherapeutics to Treat HIV in the Central Nervous System. Curr HIV/AIDS Rep. 17, 499–506 (2020). https://doi.org/10.1007/S11904-020-00519-W/METRICS

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