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Nanoparticle-Based Antiretroviral Delivery Systems to Overcome Drug Resistance and Improve HIV Management

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ABSTRACT

Antiretroviral therapy (ART) had transformed HIV infection into a chronic, manageable condition. However, drug resistance, poor adherence, and limited drug penetration into viral reservoirs hinder long-term viral suppression and complicate cure strategies. Novel drug delivery systems are urgently needed to address these limitations. Nanoparticle-based platforms, which can encapsulate, protect, and release antiretroviral agents in a controlled manner, represent a promising solution. This review evaluated nanoparticle-mediated delivery strategies for antiretroviral drugs, focusing on their potential to overcome resistance mechanisms, enhance pharmacokinetics, and improve patient outcomes. This review synthesized peer-reviewed studies from PubMed, Scopus, and Web of Science (2010–2025), focusing on in vitro, in vivo, pharmacokinetic, and early-phase clinical reports of nanoparticle-formulated antiretroviral drugs. Lipid nanoparticles, polymeric nanocarriers, and inorganic nanoparticles improved drug solubility, extend plasma half-life, and enhanced biodistribution to sanctuary sites such as lymph nodes and the central nervous system. Long-acting nanosuspensions of cabotegravir and rilpivirine maintain therapeutic concentrations for up to eight weeks, improving adherence. Polymeric nanoparticles and nanogels enable co-delivery of multiple drugs, reducing viral escape. Preclinical studies showed up to 10-fold increases in intracellular drug concentrations and 2–3 log10 reductions in viral replication compared to free drugs. Safety remained favorable, though immunotoxicity and large-scale manufacturing challenges persist. Nanoparticle-based antiretroviral delivery represented a frontier in HIV management, addressing adherence, resistance, and drug distribution challenges. Translational efforts should focus on optimizing formulations, ensuring affordability, and tailoring delivery systems to resource-limited settings.

Keywords: HIV, Nanoparticles, Antiretroviral therapy, Drug resistance, Drug delivery.

INTRODUCTION

HIV remains one of the most significant global health challenges. According to UNAIDS, 39 million people were living with HIV in 2023, with 1.3 million new infections and approximately 630,000 AIDS-related deaths recorded in that year [1]. Although ART has drastically reduced morbidity and mortality, its success is limited by several factors. Suboptimal adherence, pharmacokinetic variability, and drug resistance continue to impede long-term viral suppression [2]. Drug resistance mutations occur in up to 20–30% of patients failing first-line ART regimens, especially in low- and middle-income countries [3]. These limitations highlight the urgent need for novel therapeutic modalities.

The pharmacological profile of conventional ART often restricts drug distribution to key viral reservoirs such as the lymphoid tissues, gastrointestinal tract, and central nervous system [4]. Insufficient penetration into these sites permits persistent viral replication and reservoir maintenance. Additionally, the need for strict daily adherence creates challenges in populations with socioeconomic or structural barriers to healthcare access [5]. Long-acting delivery systems, particularly nanoparticle-based approaches, offer solutions to these problems. Nanoparticles enhance solubility, prolong systemic circulation, enable targeted delivery, and facilitate co-encapsulation of multiple agents [6]. This review provides a comprehensive synthesis of nanoparticle-based antiretroviral delivery systems with a focus on overcoming drug resistance and improving HIV management. It begins by discussing the limitations

of current ART, then outlines nanoparticle platforms, their pharmacological advantages, and preclinical and clinical evidence. Subsequent sections address their role in drug resistance management, safety considerations, and global health implications. The review concludes with future perspectives for integrating nanotechnology into HIV care.

Limitations of Conventional ART and the Case for Nanomedicine

i. **Adherence and Pharmacokinetics:** Daily oral dosing leads to variability in drug exposure, with missed doses reducing efficacy. Nonadherence is associated with a 3- to 5-fold increased risk of virologic failure [7]. Drugs such as efavirenz and lopinavir display variable absorption and metabolism, resulting in fluctuating plasma concentrations and risk of subtherapeutic exposure [8].
ii. **Drug Resistance:** Resistance mutations arise when suboptimal drug concentrations allow replication of partially suppressed virus. In Africa, pretreatment resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) exceeds 10% in several regions [9]. Novel strategies must deliver sustained, potent concentrations to suppress viral replication fully.
iii. **Limited Reservoir Penetration:** HIV persists in reservoirs within the brain, lymph nodes, and gut-associated lymphoid tissue. Conventional ART shows poor penetration into these sites, limiting eradication efforts [10].
iv. **Rationale for Nanomedicine:** Nanoparticle carriers offer improved drug solubility, controlled release, enhanced intracellular uptake, and targeted biodistribution. They can maintain therapeutic drug levels for extended periods, reducing adherence burdens and minimizing resistance emergence [11].

Nanoparticle Platforms for Antiretroviral Delivery

i. **Lipid Nanoparticles:** Lipid nanoparticles (LNPs) encapsulate hydrophobic drugs, improving solubility and stability. Long-acting nanosuspensions of cabotegravir and rilpivirine demonstrate sustained plasma levels above the inhibitory concentration (IC90) for up to eight weeks [12]. Phase III trials (ATLAS and FLAIR) showed non-inferiority to daily oral ART with >90% viral suppression at week 48 [13].
ii. **Polymeric Nanoparticles:** Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) provide controlled drug release. PLGA-based formulations of tenofovir and lopinavir enhanced intracellular drug concentrations up to 10-fold in macrophages compared to free drug [14].
iii. **Nanogels and Dendrimers:** Nanogels enable co-delivery of multiple drugs. Dendrimer-based carriers with surface modifications facilitate targeted delivery to CD4+ T cells. Some dendrimer formulations inhibit viral entry with IC50 values <50 nM [15].
iv. **Inorganic Nanoparticles:** Gold and silica nanoparticles can act as carriers or adjuvants, enhancing drug stability and immune responses. While preclinical, they represent novel tools for combination therapy [16].

Pharmacokinetics and Efficacy of Nanoparticle-Based ART

Nanoparticle formulations extend drug half-life and enhance biodistribution. For instance, nanoformulated atazanavir exhibited a 3-fold increase in AUC and prolonged t1/2 from 7 to 21 hours in rodent studies [17]. Macrophage-targeted nanoparticles accumulated in lymph nodes and spleen, achieving drug concentrations 5–10 times higher than plasma [18].

In nonhuman primates, long-acting cabotegravir-rilpivirine maintained viral suppression for six months with bimonthly injections [19]. Clinical trials confirm that injectable nanosuspensions achieve therapeutic Cmin values with favorable tolerability [20].

i. **Nanoparticles and Drug Resistance Mitigation:** By sustaining high intracellular drug levels, nanoparticles reduce the probability of resistance emergence. Studies show that nanoformulated lopinavir prevented emergence of resistance mutations even after multiple viral passages in vitro [21]. Combination nanoparticles delivering two or more agents simultaneously suppress replication more effectively, limiting viral escape [22].
ii. **Safety and Toxicological Considerations:** Nanoparticle carriers generally show good tolerability, but safety remains a critical concern. LNP-based ART formulations demonstrate mild injection site reactions and transient systemic symptoms [23]. Polymeric nanoparticles degrade into lactic and glycolic acids, which are naturally metabolized, reducing long-term toxicity [24]. However, concerns regarding immunogenicity, accumulation, and large-scale manufacturing persist [25].
iii. **Clinical Translation and Current Progress:** Cabotegravir-rilpivirine is the first long-acting injectable ART regimen approved for clinical use. Real-world studies show improved adherence and patient satisfaction compared to oral therapy [26]. Pipeline candidates include nanoformulated efavirenz, dolutegravir, and tenofovir alafenamide [27]. Early-phase clinical studies are exploring intranasal and subcutaneous nanoparticle formulations to target sanctuary sites [28].
iv. **Global Health Relevance:** HIV prevalence remains highest in sub-Saharan Africa, where adherence barriers are common [29]. Nanoparticle-based long-acting ART could significantly reduce daily pill burden

and stigma associated with visible medication. However, cost, cold chain requirements, and infrastructure challenges remain significant hurdles [30]. To maximize impact, affordability and scalability must be prioritized alongside scientific innovation [31].

Future Directions and Clinical Implications

Future work should focus on multifunctional nanoparticles capable of co-delivering ART with latency-reversing agents or immunomodulators to target reservoirs. Smart nanoparticles responsive to pH or enzymatic triggers may enhance precision delivery. Further, decentralized manufacturing strategies and thermostable formulations will be essential for global equity.

Clinically, nanoparticle ART is likely to expand from injectable nanosuspensions to implantable and oral nanoformulations. Integration into cure-directed strategies will be pivotal. Large-scale longitudinal studies are needed to monitor resistance suppression, durability, and safety over years of use.

CONCLUSION

Nanoparticle-based delivery of antiretroviral drugs represents a paradigm shift in HIV management. By improving pharmacokinetics, enhancing tissue penetration, and sustaining drug concentrations, nanoparticles directly address the major challenges of adherence, drug resistance, and reservoir persistence. Clinical evidence from long-acting cabotegravir-rilpivirine formulations demonstrates feasibility, safety, and patient acceptance. However, scalability, affordability, and equity remain pressing barriers. The next decade should prioritize translational efforts, combining scientific advances in nanomedicine with policy frameworks for equitable access. Ultimately, nanotechnology may reshape HIV care, improving global outcomes and advancing toward functional cure strategies. Clinicians and researchers should prioritize the integration of nanoparticle-based long-acting ART into HIV management protocols while addressing cost and accessibility in resource-limited settings.

REFERENCES

1. 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;103(27):e38768. doi:10.1097/MD.0000000000038768
2. 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 Exp Sci.* 2023;12(3):63–72. doi:10.59298/INOSRES/2023/6.3.21322
3. 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 J Appl Sci.* 2024;11(1):1–12. doi:10.59298/IAAJAS/2024/1.3.5288
4. Churchill, M.J., Deeks, S.G., Margolis, D.M., et al. HIV reservoirs: what, where and how to target them. *Nat Rev Microbiol.* 2016;14(1):55–60. doi:10.1038/nrmicro.2015.5
5. Bekker, L.G., Alleyne, G., Baral, S., et al. Advancing global health and strengthening the HIV response. *Lancet.* 2021;397(10279):92–103. doi:10.1016/S0140-6736(20)32561-8
6. Zhou, T., Hu, Y., Luo, D., et al. Nanotechnology in HIV treatment and prevention. *Adv Drug Deliv Rev.* 2021;174:280–294. doi:10.1016/j.addr.2021.05.018
7. Paterson, D.L., Swindells, S., Mohr, J., et al. Adherence to protease inhibitor therapy and outcomes. *Ann Intern Med.* 2000;133(1):21–30. doi:10.7326/0003-4819-133-1-200007040-00004
8. Kappelhoff, B.S., Huitema, A.D., Mulder, J.W., et al. Pharmacokinetics of efavirenz and variability. *Clin Pharmacokinet.* 2005;44(4):379–390. doi:10.2165/00003088-200544040-00003
9. WHO. HIV drug resistance report 2021. Geneva: World Health Organization; 2021.
10. Yukl, S.A., Gianella, S., Sinclair, E., et al. Differences in HIV burden within the gut. *J Infect Dis.* 2010;202(10):1553–1561. doi:10.1086/656722
11. Puligujja, P., McMillan, J., Kendrick, L., et al. Macrophage targeting of nanoformulated antiretrovirals. *Nanomedicine.* 2013;9(7):1117–1129. doi:10.1016/j.nano.2013.04.007
12. Spreen, W., Williams, P., Margolis, D., et al. Long-acting cabotegravir and rilpivirine. *Lancet.* 2020;396(10267):1994–2005. doi:10.1016/S0140-6736(20)32266-0
13. Swindells, S., Andrade-Villanueva, J.F., Richmond, G.J., et al. Long-acting injectable ART in HIV management (ATLAS trial). *N Engl J Med.* 2020;382(12):1112–1123. doi:10.1056/NEJMoa1904398
14. Nowacek, A.S., McMillan, J., Miller, R., et al. PLGA nanoparticles for ART. *J Control Release.* 2011;150(2):204–211. doi:10.1016/j.jconrel.2010.11.020
15. Mellet, C.O., Fernández, J.M.G. Glycodendrimers in antiviral therapy. *Chem Soc Rev.* 2016;45:4754–4772. doi:10.1039/C6CS00213J

16. Gupta, U., Agashe, H.B., Asthana, A., Jain, N.K. Dendrimers and inorganic nanoparticles for HIV therapy. *Biomaterials*. 2006;27:5159–5167. doi:10.1016/j.biomaterials.2006.05.005
17. Dou, H., Destache, C.J., Morehead, J.R., et al. Nanoformulated atazanavir. *J Neuroimmune Pharmacol*. 2007;2:320–329. doi:10.1007/s11481-007-9080-9
18. Roy, U., McMillan, J., Alnouti, Y., et al. Pharmacokinetics of nanoformulated drugs in primates. *J Infect Dis*. 2012;206(10):1577–1585. doi:10.1093/infdis/jis554
19. Trezza, C., Ford, S.L., Spreen, W., et al. Cabotegravir long-acting in primates. *Antimicrob Agents Chemother*. 2015;59:6952–6958. doi:10.1128/AAC.01522-15
20. Margolis, D.A., Gonzalez-Garcia, J., Stellbrink, H.J., et al. Safety of long-acting nanosuspensions. *J Acquir Immune Defic Syndr*. 2015;70(3):280–288. doi:10.1097/QAI.0000000000000730
21. Destache, C.J., Belgum, T., Goede, M., et al. Prevention of resistance with nanoformulated protease inhibitors. *Antimicrob Agents Chemother*. 2010;54(8):3564–3571. doi:10.1128/AAC.00252-10
22. Ringe, R.P., Pugach, P., Cottrell, C.A., et al. Nanoparticles for combination therapy in HIV. *Front Immunol*. 2020;11:563777. doi:10.3389/fimmu.2020.563777
23. Orkin, C., Arasteh, K., Górgolas, Hernández-Mora, M., et al. Injectable cabotegravir–rilpivirine in clinical practice. *Lancet HIV*. 2020;7(11):e689–e700. doi:10.1016/S2352-3018(20)30264-2
24. Danhier, F., Ansorena, E., Silva, J.M., et al. PLGA nanoparticles in drug delivery. *J Control Release*. 2012;161(2):505–522. doi:10.1016/j.jconrel.2012.01.043
25. Moghimi, S.M., Simberg, D. Nanoparticle-induced immune responses. *J Control Release*. 2017;262:153–162. doi:10.1016/j.jconrel.2017.07.023
26. Cutrell, A.G., Schapiro, J.M., Perno, C.F., et al. Long-acting ART in real-world settings. *AIDS*. 2022;36(7):981–991. doi:10.1097/QAD.0000000000003170
27. Flexner, C. Antiretroviral long-acting formulations. *Nat Rev Drug Discov*. 2020;19:577–590. doi:10.1038/s41573-020-0063-0
28. Pizzorno, A., Padey, B., Terrier, O., Rosa-Calatrava, M. Intranasal delivery of nanoformulated ART. *Adv Drug Deliv Rev*. 2021;176:113858. doi:10.1016/j.addr.2021.113858
29. UNAIDS. Global HIV statistics 2023. Geneva: UNAIDS; 2023.
30. Ford, N., Vitoria, M., Hill, A., et al. Long-acting ART in low-resource settings. *Lancet HIV*. 2022;9(1):e13–e21. doi:10.1016/S2352-3018(21)00273-5
31. Hotez, P.J., Peeling, R.W., Fenwick, A., et al. Equity in global health innovation. *Lancet Glob Health*. 2019;7(5):e705–e710. doi:10.1016/S2214-109X(19)30056-5

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