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International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Advances in Nanoparticle-Based Drug Delivery for HIV/AIDS Treatment: A Review

Gowhar Bashir[1], Tanya Sharma[2] .

[1]Student at Mewar University
[2]Assistant professor at Mewar University
Email: lonegowhar71@gmail.com

ABSTRACT

HIV/AIDS treatment and prevention have progressed significantly using combination antiretroviral therapies (cART). Challenges such as bioavailability, adherence, systemic toxicity, and above all remaining viral reservoirs clearly remain. Nanoparticle drug delivery systems have been developed and promise to overcome such limitations, providing targeted control and sustained release of therapeutic agents. This review has captured the current development in nanoparticle technologies applied for HIV/AIDS treatment, types of nanoparticles and their delivery mechanisms along with pharmacokinetic enhancement and toxicity reduction. New research and clinical trials are discussed, such as long-acting formulations and nanotechnology-based PrEPs. This article reviews some of the insufficiencies in clinical translation and gives prospective future avenues such as nanotechnology combined with gene therapy and vaccine development. However, these applications, with the current gap in knowledge and the advancement of nanomedicine, could prove transformative in achieving better management and possible curative application of HIV/AIDS therapies.

Keywords: HIV/AIDS, Nanoparticles, Drug Delivery Systems, Antiretroviral Therapy, Long-Acting Formulations, Targeted Delivery, Pre-Exposure Prophylaxis, Nanomedicine, Viral Reservoirs, Gene Therapy

Introduction

Though HIV has for more than 30 years remained a global health issue, it has still left millions in its wake throughout the world. Though ART has turned HIV from a fatal disease into a manageable chronic condition, it has its own limitations: poor bioavailability, lifelong adherence, systemic toxicity, and inability to optimally target latent viral reservoirs [1]. Such limitations impose a dire need for novel approaches in drug delivery for the enhancement of treatment efficacy with a minimized side effect profile.

Nanoparticle-based drug delivery systems are positive alternatives to surmount obstacles that are confronted in treating HIV through conventional means. These nanoparticles as carriers allow for targeted delivery, controlled drug release, enhanced pharmacokinetics, and crossing biological barriers such as the blood-brain barrier-an important aspect for targeting central nervous system reservoirs of HIV [2]. In addition to that, nanoparticles can encapsulate different therapeutic agents, thus allowing for combination therapy on a single platform to address viral resistance [3].

Nanotechnology has now grown to develop various nanocarrier systems, regarding lipid-based nanoparticles, polymeric nanoparticles, dendrimers, metallic nanoparticles, and nanogels. The The unique properties of each enhance drug solubility, stability, and cellular uptake [4]. Preclinical and early clinical evaluation have rendered a perspective to show that these nanocarriers significantly can improve ART outcomes by reducing dosing frequency, thus improving adherence by the patients [5].

The purpose of this review is to provide an updated overview of the current progress made in nanoparticle-based drug delivery for the treatment of HIV/AIDS. It will address different nanocarrier platforms, the mechanisms of action, ongoing investigations and clinical advancements, and the challenges that remain in translating these technologies into extensive clinical usage.

Nanoparticles in Drug Delivery

Nanoparticles are engineered materials of a variety of their own kind that have dimensions on the nanometer scale, 1 to 100 nm, and have unique physicochemical properties besides being the best suited for drug delivery application. Its small size and large surface area-to-volume ratio allow them to serve maximally with biological membranes: by solubilizing hydrophobic drugs and making them available for use and being functional wherever intended for targeted delivery. Their versatile design allows for the synthesis of nanoparticles into different forms, such as liposomes, polymeric particles, dendrimers, or metallic structures that will be focused on optimizing drug stability and release kinetics [6].

For example, they could be devised for unique physiological conditions such as pH alteration, temperature variation, or enzyme activity in the environment of the target disease when combined with therapeutic agents; those made for such applications may encapsulate them for premises against their premature degradation and mediate release to the site of action. These targeted releases have their specific applications, especially in chronic diseases where precise location of the drug is a requirement, for its therapeutic effectiveness and low side effects delivery [7].

In this regard, treatment for people living with HIV/AIDS has great prospects using nanoparticles; that is, surpassing the challenges posed by conventional antiretroviral therapy. These can be designed to cross physiological barriers such as those in the blood-brain barrier, enabling the delivery of antiretroviral medicines to sanctuary sites of virus persistence. Additionally, the nanoparticle system can facilitate the co-administration of several medicines, which is critical in viral resistance and achieving the desired steady state of the therapeutic level. Hence, nanoparticle-designed systems may place the needed transformation in HIV/AIDS treatment based on improved drug bioavailability and dosing frequency reduction [8, 9].

Delivery Mechanisms

Nanoparticle targeting and controlled drug-delivery systems for the treatment of HIV/AIDS allow precise control over the manner, place, and time when therapeutic agents are released. These systems utilize several delivery mechanisms to enhance drug localization, intracellular uptake, and sustained release, all of which are important components in successfully segregating the virus from its latent reservoirs. Passive targeting through the enhanced permeability and retention (EPR) effect allows for the accumulation of nanoparticles within leaky vascular areas; for example, in inflamed lymphoid tissues, which are common areas for HIV replication [10]. Active targeting may be achieved by surface modifications of nanoparticles decorated with ligands, such as antibodies or oligopeptides or aptamers, whereby the ligands then bind selectively to their specific receptors on HIV-infected cells or immune cells, such as CD4+ T cells and macrophages [3].

Once taken up by the target cells via receptor-mediated endocytosis or through other uptake pathways, the nanoparticles can circumvent traditional cellular barriers and achieve release of antiretroviral drugs directly in the cytoplasm and/or even the nucleus. Various systems combine such release capabilities with pH- or enzyme-sensitive materials that release their drug payload in response to the acidic environment found intracellularly or in the presence of specific enzymes, thereby controlling drug release with exquisite temporal resolution [11]. Such deregulatory mechanisms are particularly necessary for targeting latent HIV reservoirs that are often privy to standard therapies only through cellular or anatomical barriers.

Furthermore, nanoparticles enable the delivery of therapeutic agents into the body in a controlled and sustained manner, thereby reducing frequent dosing. Long-acting nanoformulations, such as those being designed for cabotegravir and rilpivirine, can keep therapeutic levels of the drug for weeks or even months after a single dose [12]. Controlled release will ultimately lead to better adherence for the therapeutic agent and less variability in plasma drug concentration, which in turn will help prevent the emergence of drug-resistant strains of the virus.

Apart from systemic delivery routes, nanoparticles can also be engineered for localized or mucosal delivery. For example, intravaginal or intrarectal nanoformulations are being developed for pre-exposure prophylaxis (PrEP) and microbicides for site-specific protection against HIV transmission at mucosal surfaces [13]. Such a variety of delivery strategies makes nanoparticles an excellent weapon in the fight against HIV/AIDS from both therapeutic and preventive angles.

Types of Nanoparticles

Nanoparticles can be classified into several categories in terms of structures, compositions, and functionalities, along with promising advantages in enhancing the pharmacological profile and targeting the antiretroviral drugs toward the virus. Such nanocarriers may generally be classified into lipidic, polymeric, dendrimeric, metallic, and hybrid systems.

Lipid-based nanoparticles: Lipid nanoparticles include liposomes and solid lipid nanoparticles (SLNs), which are the most researched compositions for treating HIV disease. Liposomes are vesicles with phospholipid bilayers that may entrap either hydrophilic or lipophilic drugs. Among these advantages are improved drug solubility and reduced systemic toxicity. In HIV treatment, the use of liposomal dosage forms has extended to delivering zidovudine and saquinavir to MPS, such as macrophages that serve as reservoirs for virus infection [14]. SLNs also have other advantages regarding physical stability and controlled release of drugs, which makes them suitable for long-acting delivery [15].

Polymeric nanoparticles: Among other previously described classes, polymeric nanoparticles are, again, an eminent group, generally made of biocompatible and biodegradable polymers such as PLGA (poly(lactic-co-glycolic acid)) and chitosan. These systems allow precise control of drug loading, kinetics of the release, and surface modification for active targeting. Polymeric nanoparticles were also used to deliver protease inhibitors and reverse transcriptase inhibitors but without sacrificing the cellular uptake and bioavailability. Specially designed for targeting HIV-infected cells and reducing off-target effects, they carry a lot of weight [16].

Dendrimers: Dendrimers are extremely branched and tree-like macromolecules possessing well-defined structure and surface functionalities. Their multivalent property makes them useful for simultaneous drug loading and targeting. Within AIDS/HIV, dendrimers have added promise as not just carriers but as antiviral agents themselves through their ability to hinder attachments and fusion processes by a virus. Thus, for instance, these polyanionic dendrimers exhibit inhibitory activity against HIV-1 as they encounter the viral envelope [17].

Metallic nanoparticles: Literature is surveying the metallic nanoparticles such as gold or silver nanoparticles; they are not only being studied for their antiviral applications but also for serving as drug carriers. If gold nanoparticles are conjugated with antiretroviral agents and targeting ligands, they will be able to provide a fine delivery of target-infected cells. On the other hand, silver nanoparticles have a property of inherent antiviral activity, which disrupts viral membranes and inhibits replication. Cytotoxicity, however, needs to be monitored minutely while formulating [18].

Hybrid and nanogel systems: Hybrid systems and nanogels combine features derived from more than one type of nanoparticle for improved performance. For example, crosslinked, hydrophilic polymer networks-nanogels-provide high drug-loading capability, responsiveness to environmentally dependent stimuli, e.g., pH or even temperature, and.

Nanoparticles do have a lot of diverse structure, composition, and properties when it comes to drug delivery for HIV/AIDS. But it is even more interesting that each such type of nanoparticle offers exclusive merits in upgrading the pharmacological profile of the antiretroviral drug with more effective targeting to the virus. Nanocarriers could generally be categorized into lipidic, polymeric, dendrimeric, metallic, and hybrid systems.

Research and Clinical Progress

Accelerated research and clinical development of nanoparticle-based drug delivery systems for HIV/AIDS treatment have been marching on for over 20 years. Nanocarriers have been shown through both preclinical studies in animal models and in vitro systems to increase pharmacokinetics, bioavailability, and tissue distribution of antiretroviral drugs. For example, research using poly (lactic-co-glycolic acid) (PLGA) nanoparticles loaded with ritonavir and lopinavir has reported better accumulation in HIV reservoir sites like lymph nodes and the brain, resulting in longer viral suppression versus conventional formulations [20]. Similarly, slow-release SLNs now carrying zidovudine have demonstrated drug retention and cellular uptake increased in HIVs for macrophages, wherein they play a significant role in pathogenesis [21].

Various nanomedicine platforms are now in the early phases of clinical trial development, including, among others, those targeting long-acting injections. One notable An An example is is cabotegravir and rilpivirine nanosuspension formulation, both antiretroviral agents with a long- Acting treatment indication for HIV-1 infection. Administered intramuscularly once every four or eight weeks, these formulations have demonstrated non-inferiority to daily oral regimens in large-scale clinical trials, such as the FLAIR and ATLAS studies [22]. These successes signify potential advancements of nanoparticles in optimizing patient adherence, decreasing pill burden, and minimizing drug-resistant strain emergence.

Beyond that, in addition to treatment, the other areas of nanoparticle work are being extended by prevention strategies such as pre-exposure prophylaxis (PrEP) and mucosal immunization. Vaginal and rectal nanogel formulations with either tenofovir or dapivirine incorporated are seeking to test efficacy against sexual transmission of HIV through topical microbicides. Some of these products have entered human studies, and preliminary results have been positive as to safety and tolerability and mucosal drug concentrations [23]. Additional uses include nanocarriers as vaccine adjuvants and antigen delivery systems for improved immune responses for a possible HIV vaccine [24].

However, challenges remain regarding scalability with production reproducibility and regulatory compliance for clinical translation. Nevertheless, the consistent preclinical and early clinical evidence continues to develop an optimism in the field. The integration of nanotechnology with the other newest emerging platforms, such as gene editing and immunotherapy, might accelerate as well into productive progress toward durable HIV remission or functional cure [25].

Challenges and Limitations

Although they hold great promise in HIV/AIDS treatment, there are still barriers that inhibit their full-scale clinical application. Biocompatibility and toxicity are among these issues. Certain nanoparticles produce cytotoxic effects, oxidative stress, or immune reactions, especially upon long-term or repeated exposure; thus, most metallic and non-biodegradable nanoparticles tend to be implicated in inducing these effects. Safety would be another outstanding challenge if non-target tissue accumulation posed a concern, as it would require exhaustive toxicological assessments to be performed before clinical translation. Efficacy and safety remain two of the primary barriers to the advanced stages of development.

Another limitation is scalability and reproducibility. Although nanoparticle formulations are very effective in the laboratory, achieving them in large-scale, affordable production is invariably complex. Variants as slight as minor changes in particle size, surface charge, or drug loading may give a different performance profile. The technical challenge that remains for industrial production and global distribution, especially in resource-poor regions where the prevalence of HIV/AIDS is highest.

From regulatory and clinical perspectives, nanomedicines ' approval process is indeed more complicated than that of conventional drugs. Often, regulatory agencies adopt no standardized frameworks for evaluation of nanoparticle-based therapies; thus, mired in ambiguity are the estimated times for the development of those therapies and additional costs. Moreover, monitoring of new endpoints such as biodistribution of nanoparticles and long-term toxicity during clinical trials on nanomedicines will have to be more rigorous than in standard drug trials [28].

Besides, another critical limitation is that targeting latent HIV reservoirs is a challenge. Even when nanoparticles provide access to improved drug delivery to so-called sanctuary sites like the brain and lymph nodes, their complete eradication continues to prove elusive. Most latently infected cells are not replicating, harboring integrated viral DNA, and still pose a significant barrier to curing the infection. The goal of research on nanoparticles is to develop them so that they can deliver both latency-reversing agents and antiretroviral drugs, but this is still in progress and is rather complex [29].

Finally, patient-specific factors such as genetic variation, immune status, or co-infections could affect the nanoparticles' uptake and therapeutic outcomes. Personalized nanomedicine is still futuristic and will necessitate advances in biomarker discoveries and individualized treatment design for its application in HIV management [30].

Future Directions

Promising future applications of nanoparticles for drug delivery applications in HIV/AIDS treatment are being researched today to overcome limitations and attain new therapeutics. A strong focus would be the manufacture of multifunctional, stimuli-responsive nanoparticles, with several combinations of agents, that include combination doses of antiretrovirals and latency-reversing agents. Such systems could mediate the "shock and kill" strategy whereby latent reactivation of HIV is followed by its eradication by effector cells via a single delivery platform [31]. Developments in materials science have allowed the design of smart nanoparticles that respond to environmental signals—for example, acidity, temperature, or enzymatic activity—for controlled and site-specific drug release mediated by [32].

Integration with gene-editing technologies such as CRISPR/Cas9 represents yet another exciting frontier. Nanoparticles can act as non-viral vectors for safely delivering gene-editing tools to HIV-infected cells for excising proviral DNA or disrupting host co-receptors like CCR5. That said, the convergence of various approaches might bring the field closer to achieving a functional cure [33]. Further, hybrid systems for co-delivering gene therapies and conventional antiretrovirals are being developed to maximize therapeutic effect while minimizing off-target effects [34].

Long-acting and implantable nanomedicines are also emerging topics. These innovations may permit the delivery of therapeutic levels of drugs over the course of months or during an entire year through biodegradable polymer matrices and in-situ forming implants. This results in better adherence and accessibility, especially in resourceful settings where daily oral therapy may be challenging [35]. Nanotechnology-based PrEP strategies that combine sustained drug delivery with mucosal protection are an ideal research area to enhance preventive efficacy [36].

Nanoparticles being developed for vaccine manufacture also deliver HIV antigens and adjuvants mimicking the viral architecture, enhancing immune recognition and response. Such approaches would overcome earlier hurdles associated with HIV vaccines in trials by building stronger and longer-lasting immunity over time [37]. In addition, personalized nanomedicine, based on genomics and biomarkers, is likely to offer the opportunity to more accurately tailor future nanoparticle formulations to individual patients [38].

All this brings hope, but continued interdisciplinary synergy, investment, and a regulatory environment that evolves with science will be necessary to realize advances. Yet, the increased integration between nanotechnology and the disciplines of virology, immunology, and bioengineering makes this an area leading the charge in transformative HIV/AIDS therapy.

Conclusion

Nanoparticle-based drug delivery systems threaten to become a major transforming approach in the ongoing fight against HIV/AIDS, presenting treatment and preventative options to old-time problems. Such nanoparticles may serve to enhance drug solubility, bioavailability, and targeting theorems; thus, enhancing therapeutic efficacy with reduced toxicity and dosing frequency. Several classes of nanoparticles-from lipid-based carriers to polymeric particles and dendrimers to hybrid systems-have been studied for their potential in overcoming physiological barriers to effectively target viral reservoirs. Thus, their successful utilization in HIV management would be promising.

This situation considered research and early clinical developments on long-acting injectables like cabotegravir and rilpivirine, demonstrates the plausible integration of nanotechnology into conventional HIV therapy. But safety concerns, manufacturing scalability, regulatory hurdles, and the current issue of latent viral reservoirs would need to be overcome. Furthermore, patients' peculiarities as well as cost-effectiveness would be relevant to the widespread use of such technologies, particularly in resource-limited settings.

So far, the future of nanoparticle-based HIV treatment is bright due in part to the ongoing innovations in smart-drug delivery systems, gene editing, vaccine design, and personalized nanomedicine; such developments will not only maximize existing therapies but will also be a key player toward functional cures and far better modalities of prevention. Hence, with augmented cross-cutting collaborations and regulatory support, nanoparticles are likely to be a key focus in the next generation of management of HIV/AIDS.

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