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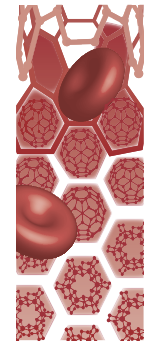
Nanomedicine



Nano drug-delivery systems for management of AIDS: liposomes, dendrimers, gold and silver nanoparticles

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AIDS causes increasing mortality every year. With advancements in nanomedicine, different nanomaterials (NMs) have been applied to treat AIDS and overcome its limitations. Among different NMs, nanoparticles (NPs) can act as nanocarriers due to their enhanced solubility, sustained release, targeting abilities and facilitation of drug–dose reductions. This review discusses recent advancements in therapeutics for AIDS/HIV using various NMs, mainly focused on three classifications: polymeric, liposomal and inorganic NMs. Polymeric dendrimers, polyethylenimine-NPs, poly(lactic-co-glycolic acid)-NPs, chitosan and the use of liposomal-based delivery systems and inorganic NPs, including gold and silver NPs, are explored. Recent advances, current challenges and future perspectives on the use of these NMs for better management of HIV/AIDS are also discussed.

Plain language summary: AIDS is a disease affecting many worldwide. Since it is difficult to cure AIDS, new therapies have been developed. Tiny materials called nanoparticles with promising features are used to carry different drugs to relevant organs in the body. There are various nanoparticles with different textures and shapes used in AIDS therapy. Branched nanoparticles, nanoparticles with repetitive building blocks and metal-based nanoparticles are three commonly used nanoparticles in AIDS treatment that are studied in this review. These tiny materials can find the exact place in the body to deliver drugs. They can also reduce the side effects of anti-AIDS drugs and help patients use fewer drugs while getting the same or better results.

Tweetable abstract: In this review, recent advances, current challenges and future perspectives in the use of liposomal-based delivery systems and inorganic nanoparticles (including gold and silver nanoparticles) for better management of HIV/AIDS are critically discussed.

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Keywords: antiretroviral therapy • liposomes • nano drug-delivery system • nanomedicine • polymeric and inorganic nanoparticles

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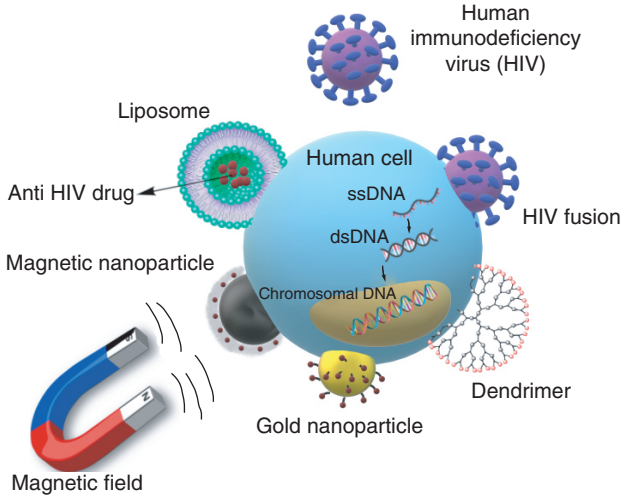
Graphical abstract:



AIDS is the regular loss of $CD4^+$ lymphocytes due to infection by HIV, which remains a public health problem worldwide [1]. The disease can transmit from one person to another through blood transfusion, drug injection and birth from infected mothers. This global disease was reported for the first time by the CDC in 1981 and identified in 1983. The virus is a lentivirus in the family *retroviridae*, subfamily *orthoretrovirinae* [2,3]. With a genome size of less than 10 kb and few genes, HIV-1 (which is the most significant cause of HIV infection worldwide) can simultaneously use cellular pathways and hide from the immune system [3,4]. The worldwide spread of HIV-1 also shows the virus actively facing innate, adapted and intrinsic immunities [5]. Currently, HIV infection and AIDS remain one of the most important epidemic diseases worldwide. According to WHO, approximately 38 million people had HIV at the end of 2019, with 81% of them being aware of their disease [6].

HIV: a T-cell attacker

The HIV genome encodes eight viral proteins that are critical for its life cycle. The HIV capsid, which is composed of the viral protein p24, encircles its single-stranded RNA. AIDS symptoms start with a decrease in the number of $CD4^+$ T-cells and an increase in p24 levels in the blood. In addition, the virus encodes Vif, Vpr, negative regulatory factor (Nef) and viral protease. Nef is one of its many virulence factors. The small-sided protein influences the human immune system, allowing the spread of the infection and, at the same time, the survival or replication of the pathogen, which is indispensable for HIV-1 replication. The virus also has an envelope glycoprotein (Env) at its surface. Env, which is formed by heterodimers of gp120 and gp41, is responsible for the virus binding to the human host cell receptor CD4 and its coreceptors (mainly CCR5 or CXCR4), resulting in viral entry into the target cells. Gp120 and gp41 are, therefore, considered the best targets for HIV vaccine endeavors [7,8]. HIV can only enter the host cells following the interaction between CD4 molecules on human cells and molecules on the virus surface. Gp120 molecules on the HIV surface initially attach to CD4; CCR5 and CXCR4 then help complete the process by making the attachment more effective, leading to disease progression (Supplementary Figure 1) [9].

Challenges in AIDS treatment

Despite highly active antiretroviral therapy (HAART) being effective in treating HIV patients and reducing morbidity and mortality rates, HIV infection remains a global concern. One of the most important ways of combating such a serious disease is the use of antiretroviral (ARV) drugs. Despite their serious side effects, they are reported to considerably increase the life span of HIV/AIDS patients. According to the National Health Service (NHS), ARV medications inhibit virus replication in the body, giving the immune system another chance to repair itself and prevent further damage. They play a critical role in the fight against HIV by inhibiting HIV protease, blocking HIV maturation, preventing HIV entry, disturbing reverse transcriptase and restraining integrase [10]. This is while most of the existing ARV drugs show undetectable delivery through the blood–brain barrier (BBB) [11]. In low-income countries, the main challenges remain the irregular or lack of access to drugs, poor drug adherence, drug

toxicities and drug–food or drug–drug interactions [12]. Moreover, due to HIV's quick adaptation and resistance rate, a combination of HIV drugs is usually needed. It is, therefore, vital to find novel ways to improve AIDS treatment.

Nanomedicine: a potential treatment for AIDS

Although there is no cure or vaccine for HIV/AIDS, nanomedicine has shown promising results for its diagnosis, prevention and treatment [13]. Nanomedicine is the use of nanomaterials (i.e., nanoparticles [NPs]) to improve drug delivery to targeted cells [14]. NPs are generally made of organic or inorganic materials with a size distribution of mostly under 100 nm. NPs are good candidates for drug delivery, inducing immunity and virus detection. There are different types of nanostructure materials, including nanotubes and nanofibers [15]. Thus far, nanomaterials such as dendrimers, liposomes, inorganic NPs and polymeric NPs have been used in HIV disease treatment, whereas quantum dots, carbon-based nanomaterials and metal nanoclusters are applied for diagnosis [11,16]. Nano-sized particles have the ability to solve various challenges in the detection and treatment of HIV. They increase the efficiency of drug delivery by releasing the drugs in the target organ or tissue and increasing the solubility of hydrophobic drugs. Very low concentrations of drugs are therefore needed when NPs are applied. The sustained release and lower toxicity of these drugs (compared with free drugs) are among other advantages of these particles. Antibodies immobilized on the surface of NPs can detect low amounts of antigens, improving the efficiency of diagnostic kits. In this review, the most commonly used NPs in HIV diagnosis and treatment, their mechanisms of action as well as pros and cons are discussed [17].

This review aims to elaborate on the most extensively used NPs in HIV therapy and investigate the recent studies and applications in this area. Polymeric, liposomal and inorganic NPs and their main subtypes are fully discussed, and the most recent studies in this area are investigated. In a novel manner, the similarities and relationships between different NPs are reviewed and visualized as concept maps. Furthermore, clinical/preclinical studies and US FDA-approved NP-based HIV drugs, along with the challenges facing the use NPs, are addressed in this review, which makes it comprehensive and critical compared with previously written articles in the field of HIV therapy. This article can help scientists to better investigate and compare useful NPs for future studies and clinical trials.

Nanomaterials applied for AIDS diagnosis & treatment

Polymeric NPs

Polymeric NPs can be synthesized from either the breakdown of previously synthesized polymers (top-down) or by polymerization of monomers (bottom-up) [18]. Dendrimers and chitosan-based NPs can also be subcategorized as polymeric NPs. With their size varying between 1 and 1000 nm, these particles can be loaded with active compounds entrapped within or decorated on their surface [19]. Polymeric NPs have great potential for targeted drug delivery. These NPs, such as polyethylenimine (PEI) and poly(lactic-co-glycolic acid) (PLGA) NPs, have great potential in delivering nucleic acid-based drugs due to their structure and surface charge. Some authors describe them as having great potential for improving physiochemical drug features. In fact, enhancing drug solubility and stability as well as achieving sustained drug release are the main goals for applying such particles. Using polymeric NPs is a promising strategy to level up the efficiency and safety of ARV treatments [20]. They can play an important role in detecting and blocking gp120, working as a viral mimic (HIV model), carrying siRNAs and ARV drugs, increasing the uptake of drugs and immune response and inhibiting HIV entry and cell-to-cell fusion. Some of these features are discussed further [20,21]. For instance, in recent studies, lipid-wrapped polymeric NPs were used as a virus-mimicking model in macrophages to observe the effect of core stiffness on NP uptake and intracellular fate [22]. Also, mono-sialodihexosylganglioside (GM3)-presenting lipid-coated polymer NPs that mimic HIV-1 particles in macrophages were applied as carriers for delivery and sustained release of two ARVs, rilpivirine and cabotegravir [23]. In the following sections, studies of different polymeric NPs like dendrimers, PEI, PLGA and chitosan NPs are discussed.

Dendrimers

Dendrimers are 3D branched nanopolymers containing a core, several branches and internal cavities. They are known as a subcategory of polymeric NPs despite their unique structure, as they can be prepared in different generations (layers) and be associated with polymeric molecules to obtain specific aims [24,25]. These particles have several functional groups that can attach to pharmaceutical and viral components during the vaccine design process, and their internal cavities have the ability to encapsulate anti-HIV drugs [26]. Dendrimer-based NPs have shown

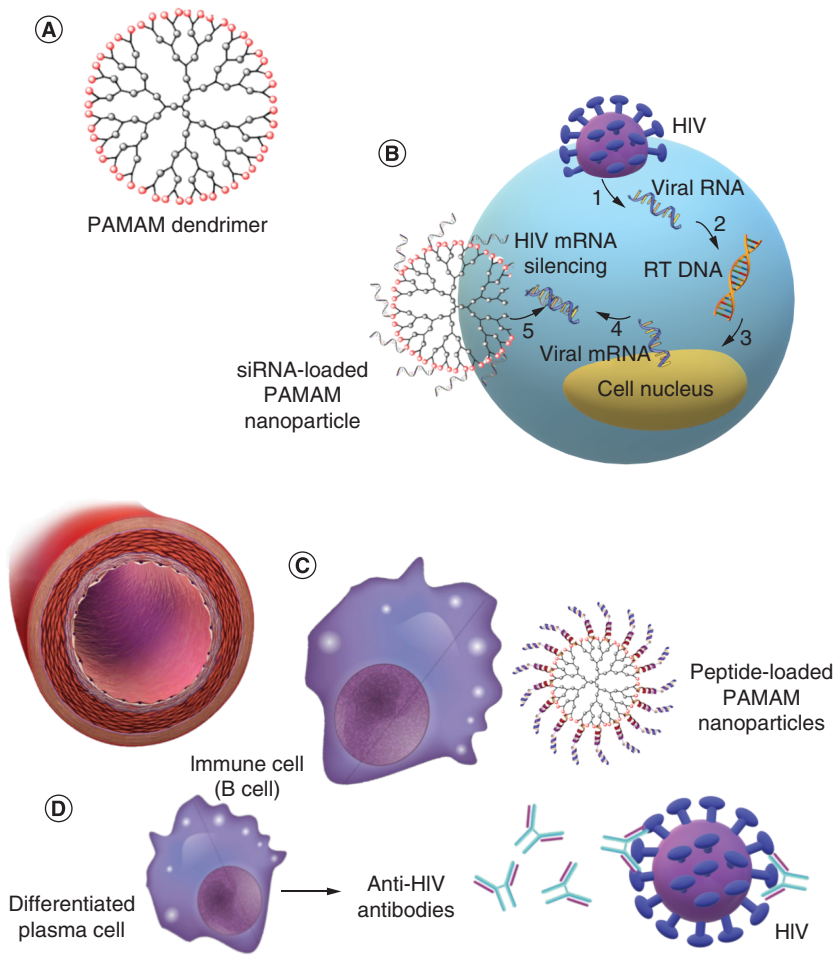


Figure 1. Applications and properties of dendrimer nanoparticles in HIV therapy. (A) PAMAM dendrimers, **(B)** siRNA-loaded PAMAM NPs that silence the HIV mRNA inside host cells to prevent HIV proliferation, **(C)** peptide-loaded PAMAM NPs that interact with immune cells and induce anti-HIV immune pathways and **(D)** induction of anti-HIV antibody production in plasma cells.
NP: Nanoparticle; PAMAM: Poly(amidoamine).

great potential in solving some of the problems with ARV therapy. For example, in the case of latent HIV infection in the $CD4^+$ T-cells that could not be solved by ARVs alone, polyanionic carbosilane dendrimers were used to reduce latent HIV-1 persistence [27]. Also, the use of dendrimers for efavirenz with a booster dose of ritonavir was helpful. This improved bioavailability and compensated for inadequate organ perfusion [28]. Another reason for the failure of most ARVs is the appearance of resistance. Studies on novel dendrimers helped researchers design new types of drugs that do not generate resistance mutations [29].

Poly(amidoamine) dendrimers

Poly(amidoamine) (PAMAM) is a branched-type dendrimer with a sphere-like shape and internal tree-like branching molecular architect (Figure 1A) [30]. It is mostly made of amides and amines [31,32]. In some studies, different generations of these molecules were designed as carriers, immunogens and adjuvants. PAMAMs are mainly used as recognizing or neutralizing agents against gp120 to stop HIV entry into $CD4^+$ cells [33].

In addition to blocking entry, PAMAM NPs can enhance the immune system against HIV. In another study, intranasal immunizing G4-PAMAM was used to multiply antibody responses against HIV-1 gp120 peptide epitopes in BALB/cJ mice [34]. The treatment improved IgA and IgG responses (anti-gp120), suggesting its potential to be used as an adjuvant. The fourth generation of PAMAM dendrimers (G4-PAMAM) is capable of increasing immunoglobulin levels; they are thus the most applied such NPs. In Rodríguez-Fonseca *et al.*'s study, two peptides were loaded on these particles to induce antibody production and neutralize gp-120 HIV type-1 (Figure 1C &

D) [35]. The authors concluded that these NPs can act as nanocarriers for immunogenic peptides. PEGylated PAMAM NPs can also be used as carriers. They can prolong drug release while increasing safety and reducing toxicity risks by enhancing the encapsulation of HIV drugs. Surface alternation using PEG can lower toxicity and raise the circulation time, resulting in the accumulation of dendrimers at the target sites [36].

Gene delivery is another method to combat HIV (Figure 1B), by targeting both viral and cellular transcripts without causing serious toxicity. Cationic PAMAM dendrimers can protect the body against viral-induced $CD4^+$ T-cell depletion by controlling the transcription process in a RAGhu mouse model through siRNA delivery [37].

To summarize, preventing HIV entrance to $CD4^+$ human cells, encapsulating anti-HIV drugs and peptides and cellular uptake enhancement are options by which PAMAM NPs are used in HIV treatment and delivery systems.

Poly(propyleneimine) dendrimers

Poly(propyleneimine) (PPI), an amine-terminated molecule, is another type of polymeric NP with a branched molecular structure and a discrete number of functional end groups [38,39]. PPI dendrimers as well as their modified forms have shown therapeutic effects. They have the potential to protect anti-HIV antisense oligonucleotides against nucleolytic digestion [40]. Interactions between anti-HIV antisense oligonucleotides and PPI have been monitored using dynamic light scattering and transmission electron microscopy. Zeta potential has been used to characterize various features of these NPs, confirming that the nature of the complex depends on the stoichiometry and concentration of DNA phosphate and dendrimer amines concentration as well as solvent properties and dynamics of mixing [41]. Their use might thus be challenging, as correct assessment of the stoichiometry of DNA phosphate, dendrimer amines and solvent properties is needed.

PPI-based NPs can be used as ARV drug carriers. Dendriplexes, anti-HIV oligonucleotides combined with PPI-Mal G4 (generation 4 PPI modified with maltose) and PPI-Mal III (maltotriose) G4 have the capability to self-assemble. These particles construct 1D and 3D nanostructures with therapeutic properties [42]. Again, gp120 detection plays an important role when it comes to PPI dendrimers. John *et al.* designed a novel HIV platform based on the detection of specific sequences of DNA and gp120 using G4-PPI/streptavidin. They characterized these particles using scanning electron microscopy, voltammetry and electrochemical impedance spectroscopy. In this platform, a single-stranded 5′-biotinylated probe DNA and B40 aptamer were used for DNA sequence and gp120 protein detection with great selectivity. The team also claimed that it can detect complementary DNA at picomolar concentrations. The detection and blocking of gp120 via PPI dendrimers can protect the cells against HIV and inhibit virus entry, respectively. Among different available PPI dendrimers, the fourth generation is more popular [43].

Other dendrimers

In various investigations, dendrimer NPs have been loaded with different types of drugs or antigens to achieve specific goals. Certain dendrimers have microbicide properties (even when not loaded with drug). They can stop HIV in various stages of infection including attachment, entry, latency and replication. One such dendrimer is SPL7013. It is potent against different strains of HIV, such as CXCR4-(X4) and CCR5-(R5). The complex uses a CXCR4 coreceptor to inhibit HIV entry [44]. In an *in silico* study, the ability of the dendrimer to attach to the gp120 binding site of $CD4^+$ cells and block gp120-CD4 formation was shown [45]. It was therefore concluded that the dendrimer can prevent the entrance of the virus. It is known that G2-S16 protects the cell against host cell infection through viral attachment and acting directly against the virus; however, Rodríguez-Izquierdo *et al.* studied the chance of resistance mutation in HIV model cell lines treated with G1-S4 or G2-S16 dendrimers. G1-S4 induced three mutations while G2-S16 caused none, making it a safe HIV-entry inhibitor [46]. The comparison of different generations of anionic dendrimers showed G1C (first generation with carboxylated terminal groups) and G1S (first generation with sulfonate terminal groups) to be capable of effectively blocking HIV-1 from entering the host cells. They were shown to have antiviral properties in both acidic and basic pH environments without causing any noticeable inflammation in the vaginal epithelium [47].

Tyssen *et al.* used the second (SPL7115) and fourth generation (SPL7013) of DNA dendrimers in an *in vivo* study to optimize their activity against HIV-1 and herpes simplex virus 2 (HSV-2). SPL7013 was shown to be more effective against HSV and inhibited cell-to-cell fusion by blocking the HIV-1 envelope [48]. SB105-A10-based HIV-1 dendrimers synthesized on a lysine core inhibited HIV-1 infection on peripheral blood mononuclear cells by interfering with the attachment of CXCR4 (X4) and CCR5 (R5) to host cells and their early replication [49]. To study latent HIV-1 persistence, G1-S4, G2-S16 and G3-S16 polyanionic carbosilane dendrimers were combined

with latency reversal agents showing a dramatic increase in GFP expression in model monocytes and reduced virus latency [50]. In another study, anti-HIV drugs loaded on the same NPs showed higher efficiency [51]. The second and third generations of polyanionic carbosilane dendrimers with metal cores showed anti-HIV-1 and anti-HIV-2 properties. Their cytotoxicity and antimicrobial features were evaluated in Briz *et al.*'s study using different anti-HIV drugs. The combination of anti-HIV drugs with dendrimer complexes has shown great synergistic effects against HIV.

To study the effects of X4-HIV-1 tropic cell-to-cell fusion, Guerrero-Beltran *et al.* investigated the TZM-bl, HEK-293T and HEK-293T cell lines with G1-S4, G2-S16 and G3-S16 dendrimers. They concluded the designed systems to be biocompatible and capable of inhibiting X4-HIV-1 infection. G2-S16 and G1-S4 noticeably decreased syncytia formation in HIV-1 Env-mediated cell-to-cell fusion models [52]. Carbosilane dendrimers are also reported to be able to inhibit viral infection at the entry step. They can inhibit the binding of the virus to the surface of target cells and impede membrane fusion by blocking gp120-CD4 interactions. In fact, polyanionic carbosilane dendrimers have the potential to prevent cell-to-cell HIV transmission [53].

To enhance the solubility and, consequently, cell uptake of the drug, Alfei *et al.* applied novel water-soluble NPs with low cytotoxicity. Thanks to their water solubility, few complexes permitted the drug to become bioavailable and they had a good pharmacokinetic profile [54]. As a result, they managed to solve the insolubility problem of ARV drugs. Nanocarriers are also used for drug cytotoxicity reduction while maintaining their ARV effects. Pargoo *et al.* developed a negatively charged nano-biopolymer linear globular G2 dendrimer loaded by two ARV drugs, lamivudine and efavirenz. Their study showed retroviral activity reduction without cell toxicity [55]. Different dendrimers used in HIV treatment are summarized in Table 1.

Poly(ethyleneimine)

PEI is a polymer containing repeating amine groups with carbon aliphatic CH_2CH_2 spacers. Three forms of PEI, linear, branched and dendritic have been reported [59]. PEI has several advantages, including high charge density, chain flexibility and low immune response, over other polycations such as L-lysine [60]. PEI NPs, when used as drug carriers, have also helped increase drug uptake, enhance immune responses and improve transfection. Due to the positive charge of PEI NPs, they are promising carriers for delivering different nucleic acid-based drugs and DNA vaccines, since they can be attached electrostatically. The more potent to transfecting cells, the more immune responses in the case of immunotherapy or vaccination will be earned [61,62]. Modified PEI with His-tag peptides in Hauptmann's study increased their uptake in dendritic cells (Figure 2A & B) [63]. The system also facilitated the interaction between NPs and immature dendritic cells. It was thus described as a promising nontoxic carrier for antigen delivery. In another attempt, mannosylated PEI was used to enhance *in vitro* transfection efficiency in dendritic cells compared with naked DNA [64]. The polymer was therefore suggested as a promising compound in DNA vaccines, directed at the anti-HIV immune response.

PEI can also play a significant role in gene and protein delivery. In one example, they were used to deliver siRNA to infected microglial cells in mice, aiming to inactivate suppression of Beclin-1, a host autophagic protein. In fact, siBeclin1 could lower HIV replication and HIV-induced inflammatory responses by activating phosphatidylinositol-3 kinase (PI3KCIII/Vps34) complexes that can facilitate autophagosome fusion with lysosomes. PEI polymers have also been used as carriers for suppressing RNAs and have shown potential in silencing the HIV-infected brain [65].

Magnetic silica nano-complexes coated with PEI were used by Hu *et al.* to enhance multilayer attachment to NPs. The system was able to detect HIV DNA by delivering the NPs containing virus cDNA [66]. In another attempt, PEG-PEI dendrimers loaded with nucleoside reverse transcriptase inhibitors and delivered to monocyte-derived macrophages harbored in the brain showed high efficiency in inhibiting HIV-1 at very low concentrations [67].

It is possible to stop viral replication by gene suppressors. Using PEG to form PEG-PEI/siRNA, Weber *et al.* targeted *Nef*, the HIV gene, and knocked it down by siRNA. The PEG-PEI/siRNA complex was used for stability enhancement and cytotoxicity reduction. The complex knocked down the expression of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), preventing HIV replication [68].

As previously described, increasing the solubility of hydrophobic anti-HIV drugs is one application of NPs. NPs coated with PEG are shown to have high suitability and low toxicity. PEGylated NPs, when used as siRNA carriers, have revealed promising potential in suppressing or knockdown of genes (like *GAPDH*) that mediate HIV replication. Similar to other NPs, they can be used as carriers of ARV drugs to achieve a more efficient delivery to the targeted organs. PEG dendrimers are also popular, accessible and commonly used in nanosystems [69].

Table 1. Dendrimers studied against HIV.

Type of nanocarrier	Targeted cells	Cargo	Results and effects	Ref.
PAMAM dendrimers				
Sialic acid-PAMAM glycodendrimers	–	–	Sulfo-6 stopped all four HIV-1 strains examined in the low micromolar range	[56]
G4-PAMAM-HIV peptide complexes	Ab-secreting plasma cell precursors	pPGT122: DIIGDIRQAH and pVRC03: DGGANNTSNETFR	Immunogenic and effective in mucous membrane via increasing IgG and IgA levels	[34,35]
PEGylated PAMAM dendrimers	–	Lamivudine	Controlled and prolonged drug release, reduced toxicity and improved drug loading capacity in PEGylated PAMAM	[36]
Cationic PAMAM dendrimers	RAGhu mouse model	siRNAs	System suppressed HIV-1 infection and preserved against virally induced $CD4^+$ cell depletion; inhibiting HIV-1 titers and accumulation of NPs in PBMCs	[57]
PPI dendrimers				
PPIG1-G4	–	Anti-HIV antisense oligonucleotides: SREV, ANTI TAR, GEM91	Improving drug delivery by protecting nucleic acid-based drugs via DNA folding	[41]
PPI-Mal G4 and PPI-Mal III G4 (modified PPI)	–	ANTI-TAR, GEM91, SREV	Focusing on comparative morphological assessment. Self-assemble of ANTI-TAR and GEM 91 into fibrils. On the contrary, SREV formed quadrilateral-like 3D nanostructures	[42]
G4-PPI/streptavidin	Sequence-specific DNA and gp120	–	Detection of cDNA at picomolar concentrations; Outstanding selectivity in the presence of noncomplementary and mismatch DNA	[43]
Other dendrimers				
SPL7013	TZM-bl	–	SPL7013 has HIV-1 virucidal properties against X4 and R5X4 but not R5 HIV-1 strains. Use of CXCR4 coreceptor for HIV entry inhibition	[58]
SPL7013-gp120-CD4	*In silico* study	–	Dendrimer competes with gp120 to attach to gp120 binding region of CD4	[45]
G2-S16 sulfonate dendrimer	MT-2	–	G1-S4 induced three mutations while G2-S16 caused none, making it a safe alternative as a HIV entry inhibitor	[46]
G1C, G2C, G3C G1S, G2S and G3S	TZM.bl	–	Blocks entry of HIV-1 strain by G1C and G1S. Antiviral properties in both acidic and basic pH with no noticeable inflammation	[47]
SPL7115 and SPL7013	MT-2	–	Inhibiting cell-to-cell fusion by blocking HIV-1 envelope; inhibition of viral entry with parallel potency against X4 and R5 HIV-1 strains	[48]
Peptide-derivatized SB105-A10 dendrimer	PBMCs and cervicovaginal histocultures	–	Interfering with attachment and replication of X4 and R5 strains of HIV	[49]
Polyanionic carbosilane dendrimers	J89GFP lymphocyte and THP89GFP MDMs	Bryostatin, romidepsin or panobinostat	Increased GFP expression in monocytes and reduced latency persistence of virus by combining NPs with LRAs	[50]
G2 and G3 anionic carbosilane dendrimers	PBMCs, TZM-bl, HeLa	Primary R5- and X4-HIV-2 isolates	Inhibits replication of HIV-2 at early stages before integration of virus DNA into human genome	[51]
Anionic carbosilane dendrimers	TZM-bl, HEK-293T, HEK-293T	–	Biocompatible system, X4-HIV-1 infection inhibition, decrease in syncytia formation by G1-S4	[52]
G3-S16 and G2-NF16	PBMDC, MDM, DC, HeLa MAGI P4.R5, TZM.bl	X4-HIV-1NL4.3 or R5-HIV-1NL (AD8)	Aimed at various protein targets of viral envelope and host cells; inhibition of HIV infection	[53]
Polycationic polyester-based amino acids-modified hydrophilic and amphiphilic dendrimers	SKOV-3 and MCF7	O-TC 1	Bioavailable with a proper pharmacokinetic profile drug; high solubility in water	[54]
Negatively charged nano-biopolymer linear globular G2 dendrimer	HEK293 T-cells	Lamivudine and efavirenz	Decreased retroviral activity without cell toxicity	[55]

BRY: Bryostatin; CD4: Cluster of differentiation 4, glycoprotein T-cell receptor; G1C: First generation with carboxylated terminal groups of dendrimers; G1S: First generation with sulfonate terminal groups of dendrimers; G4-PAMAM: Fourth generation of PAMAM dendrimers; gp120: Glycoprotein 120; PAMAM: Poly (amidoamine); PBMCs: Peripheral blood mononuclear cells; PNB: Panobinostat; PPI: Poly(propyleneimine) dendrimers; PPI-Mal G4: Generation 4 of poly(propyleneimine) modified with maltose; PPI-Mal III G4: Generation 4 of poly(propyleneimine) modified with maltose maltotriose; RMD: Romidepsin; SPL7013: G4 L-lysine dendrimer with DNAA surface groups; SPL7115: Second generation of L-lysine dendrimer with DNAA surface groups.

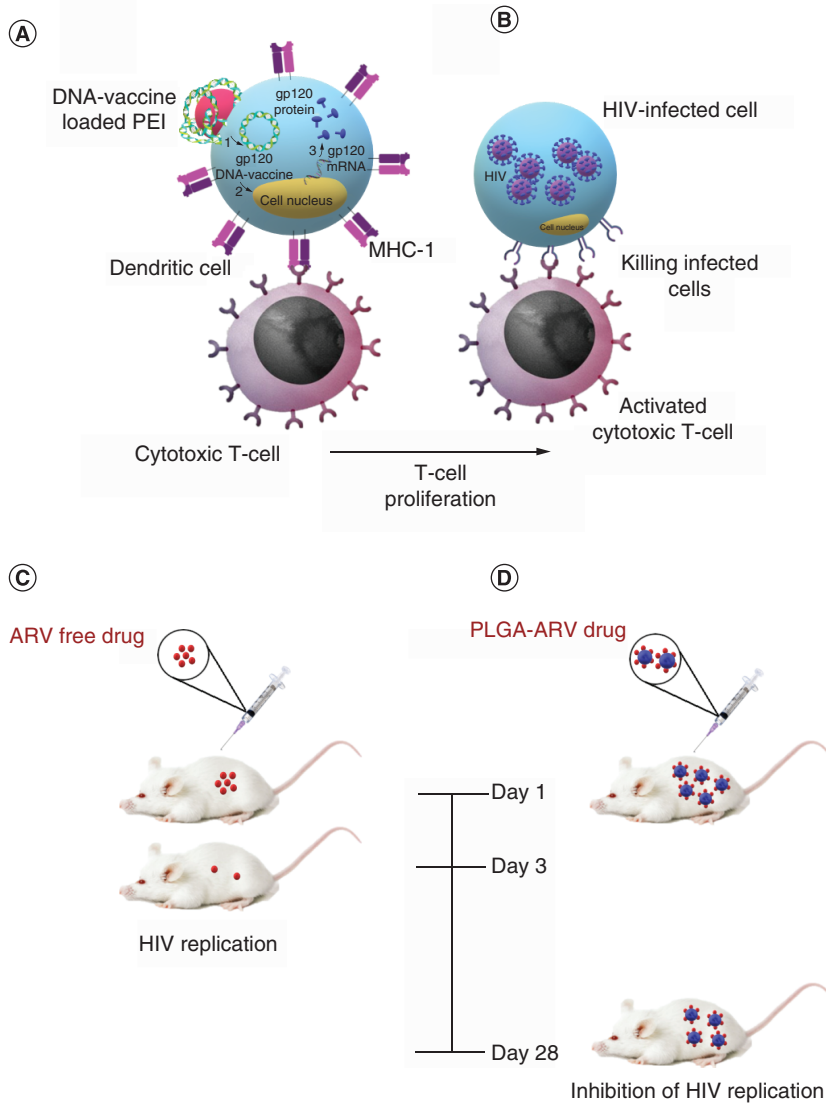


Figure 2. Applications and properties of polymeric nanoparticles in HIV therapy. (A) DNA-loaded PEI NP as a positively charged polymeric NP for DNA-vaccine transfection into dendritic cells; gp120 DNA-vaccine is translated to gp120 proteins inside dendritic cells and presents to $CD8^+$ T-cells (cytotoxic T-cells) through MHC-1 molecules. **(B)** After T-cell activation by dendritic cells, mature T-cells will proliferate and attack HIV-infected cells. **(C)** ARV free drug will circulate and be cleared in hu-CD3-NSG mice three days after injection. **(D)** PLGA-ARV polymeric NPs increase drug concentration in hu-CD3-NSG mice and delay its clearance until day 28.
ARV: Antiretroviral; NP: Nanoparticle; PEI: Poly(ethyleneimine); PLGA: Poly(lactic-co-glycolic acid).

Poly(lactic-co-glycolic acid)

PLGA is a copolymer produced by means of ring-opening copolymerization of two different monomers such as glycolic acid and lactic acid [70]. This polymer is broadly used as a carrier for several ARV drugs, antibodies and suppressing molecules. This is mainly because PLGA-based NPs have almost all the advantages of the previously discussed NPs, plus the capability to enhance binding to target cells. It can also help stop cell-to-cell transmission of the virus by enhancing the antiviral properties of ARV treatment and prolonging drug resistance at the target site.

Yang *et al.* compared the synergistic properties of two AVRs with PLGA as the carrier [71]. PLGA was loaded with griffithsin and dapivirine and showed strong synergistic properties against HIV-1 at a 1:1 ratio of IC_{50} values. The use of PLGA helped with the sustained release of drugs. Mandal *et al.* claimed that tenofovir alafenamide (TAF) and elvitegravi (EVG)-PLGA NPs could cause sustained protection in the mouse model of HIV [72]. They used

TAF and EVG via subcutaneous delivery due to their prevention effects. They concluded that their long-acting nanoformulation caused high-level suppression of vaginal HIV-1 infection among hu-CD3-NSG mice (Figure 2C & D).

The combination of ARV-NPs has shown a dramatic increase in the antiviral properties of the drug, reducing its needed dose. This confirms the synergistic effects of these particles compared with free drugs [73]. The particles can be used to detect and combat HIV. PLGA NPs coated with CD7 antibodies were also used to target T-cells [74]. The evaluation of pemetrexed showed that the scFvCD7 and scFvCD7-conjugated particles have a high binding affinity to A3.01 cells. PLGA NPs resulted in no cytotoxicity. In another attempt, elvitegravir was loaded on PLGA-based NPs to suppress HIV in infected monocytes [75]. The results revealed enhanced drug uptake by the monocyte U1 cell line and superior viral suppression for a long time period. Furthermore, PLGA NPs can prevent HIV transmission. The incorporation of HIV-1 inhibitor peptide with PLGA NPs covered with glycol-chitosan can lead to better NP mobility to reach the HIV transmission site in the vaginal epithelium [76]. The combination of PLGA and combination ARV NPs (cART NPs), when loaded with efavirenz, has shown promising results in minimal cell viability and effective inhibition of HIV transduction, both necessary to stop HIV replication [77]. PLGA-ARV NPs loaded with ritonavir, lopinavir and efavirenz were also used for sustained monthly drug release and were effective in inhibiting HIV-1 replication [78]. Similar to other polymeric NPs, PLGA dendrimers can prolong drug release, making the treatment more efficient. Using PEG-PLGA-based NPs loaded with efavirenz, Nunes *et al.* reported enhanced colorectal availability of EFV, prolonged drug residence at the lower colon and possibly increased protection from HIV transmission (Table 2) [79].

Chitosan

Chitosan is a linear polysaccharide made of randomly distributed D-glucosamine and N-acetyl-D-glucosamine units. It can be produced by treating the chitin shells of crustaceans with an alkaline substance [91]. Chitosan has recently gained great attention as an anticancer drug carrier because of its biocompatibility and biodegradability and simple preparation methods for drug-loaded NPs [92]. Chitosan can attach to anti-HIV drug-loaded NPs and control drug release while enhancing drug-loading efficacy. For instance, poly(lactic acid) (PLA)/chitosan loaded with lamivadine showed a lower rate of drug release in acidic pH. NPs based on PLA-chitosan are nontoxic in mouse fibroblast cells [80]. Chitosan-based NPs conjugated with tripolyphosphate are proper carriers for zidovudine. They provide continuous release of zidovudine *in vitro* and their physicochemical and biological features (specifically mucoadhesive properties) help with zidovudine delivery [81].

Adding chitosan to carbon nanotubes can help with the sustained release of tenofovir along with higher dispersibility and stability of the NPs in aqueous medium [93]. These NPs have also been used for food applications. Chitosan-based NPs loaded with dolutegravir were used as a food and milk admixture for children [83]. Chitosan can also increase the attachment of NPs to the target tissue. Chitosan-thioglycolic acid NPs loaded with tenofovir have shown high mucoadhesion properties when used as a noncytotoxic vaginal drug-delivery system. By increasing the NP diameter, the mucoadhesion properties of the particles were enhanced; the highest encapsulation efficiency belonged to the largest NPs [84].

By combining with other polymeric molecules, such as PEI and PLGA, chitosan can show additional features. The combination of chitosan and PEI enhanced siRNA delivery to model cell lines without causing any cytotoxicity or inducing apoptosis [85]. In another attempt, loading both hydrophobic and hydrophilic ARV treatments on PLGA chitosan-coated NPs resulted in an affordable and accessible nanoformulation (in resource-limited countries), which improved patient outcomes [86]. The sudden release of the second ARV drug (nevirapine) followed that of the first ARV drug (lamivudine), resulting in a promising method for HIV-1 treatment. The use of antibodies to modify chitosan NPs can result in the development of targeted nanodrug delivery systems and increase the drug concentration in the target area. In Gu *et al.*'s study, Ab-Cs-NPs could deliver siRNA across the BBB and inhibit HIV replication [94]. Saquinavir-loaded chitosan NPs were studied in Ramana's investigation [87]. High solution and great cell targeting efficiency was shown to effectively control the proliferation of the virus in T-cells.

Chitosan-based NPs have also shown great potential in treating viral diseases by reducing the side effects and toxicity of common drugs. By enhancing the antiviral efficiency of nucleoside reverse transcriptase inhibitors, Yang *et al.* reduced their side effects and prolonged drug release. They designed nano side monophosphate polymer coated with chitosan and evaluated its anti-HIV activity and cytotoxicity in the MT4 cell line. These particles can be used as prodrugs to improve treatment and reduce side effects [95]. In addition, the toxicity and side effects of p24 were observed when combined with chitosan-based NPs [89]. Loading tenofovir on the particles caused no

Table 2. Polymeric nanoparticles studied against HIV.

Type of nanocarrier	Targeted cells	Cargo	Results and effects	Ref.
PEI nanoparticles				
Ni(II)-nitrilo (triacetic acid)-modified PEI-maltose	iDCs	His6-Gp160, His6-P24 and His6-HIV-TAT	Increase in peptide, no toxicity in iDCs	[63]
man-PEI/DNA complex/AdV	DC 2.4 (murine DCs)	DNA complex/AdV (pVAX1-HIV gag plasmid vector)	Higher IgG2a titer, nonsignificant titers of IgG and IgG1, enhanced anti-HIV immune response with lower doses of drug	[64]
PEI-FITCsiRNA nanoplexes	Adult C57BL/6 J mice and primary human microglia	siRNA against *Beclin1* gene	Silencing *Beclin1* gene and lowering expression of targeted protein in brain tissues	[65]
Nano-γ-Fe2O3-coated magnetic nanospheres	–	–	Detecting target with high sensitivity; convenient, fast, capable of high anti-interference detecting methods	[66]
PEG-cl-(ss) PEI (NG1) and pluronic F68-cl-(ss) PEI (NG2)	MDMs	5′-TPs of antiviral nucleoside analogues	High efficiency of HIV-1 inhibition at very low concentrations of NTIRs	[67]
PLGA nanoparticles				
PLGA NPs	TZM-bl	Griffthsin and dapivirine	Sustained drug release, synergistic effects of the two drugs	[71]
PLGA-based TAF and EVG NPs	Hu-BLT and hu-CD34-NSG mouse model	TAF and EVG	Positive suppression of vaginal HIV-1 infection	[72]
ARV-PLGA-NP	TZM-bL	Maraviroc, etravirine, raltegravir	High antiviral properties. Reduced need for effective dosage and blocked virus transmission	[73]
ScFvCD7-PLGA/HDACi	A3.01-derived HIV infected cells, ACH2 and human PBMCs	PTX and DOX·HCl	More than 80% of binding ability on A3.01 cells, no cytotoxicity	[74]
PLGA-EVG	HIV-infected monocytic cell lines U1 and HIV-infected primary macrophages.	Elvitegravir	Concentration-dependent uptake of elvitegravir in monocytes, high suppression of virus compared with control for a long time period	[75]
NPsE2-FAM	Vaginal mucosa of swine	HIV-1 inhibitor peptide (E2)	Efficient inhibitory effects on HIV	[76]
PLGA-cART NPs	HeLa and H9 T	Efavirenz and boosted lopinavir	Minimal cell viability and effective inhibition of HIV transduction and replication	[77]
PLGA-fabricated AR NPs	BALB/c mice	Ritonavir, lopinavir, efavirenz	Sustained monthly treatment for AR drug delivery and inhibition of HIV-1 replication	[78]
PEG-PLGA NPs	Colorectal epithelial cell lines (Caco-2, HT29-MTX and SW480) and PBMCs	EFV	Enhanced colorectal availability of EFV, long drug presence at lower colon and possibly increased protection from HIV transmission	[79]
Chitosan NPs				
PLA/chitosan	Mouse fibroblast cell line	Lamivadine	Entrapping and protecting the drugs in acidic pH, sustained drug release in neutral pH	[80]
Chitosan-based nanoparticles	–	Zidovudine	By modulating the rate of loading and release of AZT through adjusting the AZT concentration, preparation conditions and molecular characteristics of chitosan	[81]
Multiwalled carbon nanotubes-chitosan	MCF7	Tenofovir	Controlling and enhancing drug loading, its high dispersibility and stability of NPs in aqueous medium, decrease *in vitro* cytotoxicity of carbon nano tubes	[82]
Cs-DTG NPs	C8166	Dolutegravir	Better therapeutic efficacy and lower cytotoxicity than pure drug, higher dissolution and minimal toxic effects	[83]
Chitosan-thioglycolic acid NPs	–	Tenofovir	Enhancement of mucoadhesion properties of the particles by increasing nanoparticle diameter	[84]
CsNPs	Macrophage RAW 264.7 and HEK293	Anti-HIV siRNA	Enhanced siRNA delivery, no cytotoxicity or apoptosis inducing effect	[85]
PLGA-CS-LMV NPs and PLGA-CS-NVP NPs	–	Lamivudine and nevirapine	Affordable and accessible. At the end of the burst of the first ARV (LMV), burst of the second ARV (NVP) happens, which is a promising method of HIV-1 infection	[86]
Ab-Cs-NPs	HIV-infected brain astrocytes	SiRNA	Improved cell accumulation and gene silencing efficiency of Ab-CS-NPs in astrocytes	[86]
Saquinavir-Cs	Jurkat and CEM-CCR5	Saquinavir	High solution efficiency and great cell targeting efficiency, great control on the virus proliferation in T-cells	[87]
Chitosan-O-isopropyl-50-O-d4T monophosphate	MT4	–	Reduced NRTI side effects and prolonged drug release	[88]
CS-NPs	Human lymphocytes	HIV-1 P24 protein-derived peptides	High encapsulation efficiency (>96%), controlled and sustained release of peptide drugs, reduced toxicity and side effects of loaded peptide	[89]
Chondroitin-sulfate nanoPECs	PBMCs	Tenofovir	Dose-dependent reduction of HIV-1, decreased IC_{50}	[90]

ART: Antiretroviral therapies; ARV: Anti-retroviral; ChonS: Chondroitin-sulfate; CS: Chitosan; CSNP: Chitosan-based nanoparticles; DOX·HCl: Doxorubicin hydrochloride; EFV: Efavirenz; ETR: Etravirine; iDC: Immature dendritic cells; LMV: Lamivudine; MDM: Monocyte-derived macrophages; MVC: Maraviroc; Ni-NTA-DG: Ni(II)-nitrilo (triacetic acid)-modified PEI-maltose; NP: Nanoparticle; NTIRs: Nucleoside reverse transcriptase Inhibitors; NVP: Nevirapine; PBMC: Peripheral blood mononuclear cell; PEI: Poly(ethyleneimine); PLA: Poly(lactic acid); PLGA: Poly(lactic-co-glycolic acid)/polylactic acid-polyglycolic acid; RAL: Raltegravir.

cytotoxicity to human peripheral blood. The reduction in HIV-1 infection was reported to be dose-dependent (Table 2) [90].

When it comes to biocompatible NPs, chitosan-based NPs are always a great choice for drug delivery. The use of chitosan enhances drug loading and drug-release rate [96]. As mentioned earlier, the attachment of NPs to target tissues is an important factor in increasing the chance of the exact delivery of the drug to the target tissue in the body. Chitosan-based NPs have shown great potential in this regard. Chitosan NPs also lower the toxicity of drugs and their side effects. PLGA dendrimers and chitosan NPs are both great options for drug delivery and both seem to be broadly used.

Nowadays, improvements in polymeric NPs have helped scientists overcome some of their drawbacks and develop some of their efforts as FDA-approved drugs [97]. Using multiple drugs for simultaneous delivery, application of conventional chemotherapeutics combined with other treatment modalities, delivery of drugs in association with photosensitizing agents, nucleic acids and antiangiogenic compounds can increase the efficacy of these systems and improve personalized therapy [98].

Supplementary Figure 2 illustrates a concept map to better review the effects of each polymeric NP on HIV treatment, pointing out those with similar therapeutic properties. For instance, PLGA, PAMAM and chitosan all prolong drug release; PLGA and PPI are both used as ARV drug carriers; chitosan inhibits the replication of HIV mediated by efficient delivery anti-HIV siRNAs while PEI acts via two sequential mechanisms, siRNAs delivery and knocking down *Nef*. PAMAM stops HIV entrance to the cells via binding to gp120, SPL7013 dendrimer using X4 and R5 HIV strains. G1C, G1S and carbosilane dendrimers, however, stop HIV entry directly.

Liposomes

The spherical vesicles commonly used for drug-delivery purposes are called liposomes, as they contain lipid bilayers [12]. Liposomes enhance the efficacy of drug release. Nayak *et al.* designed a novel system using liposomes in which low doses of NPs (under the WHO recommended dosage) helped with the sustained release of stavudine for up to 12 h while increasing their chances of reaching the reservoir sites (Figure 3A & B) [99]. Magneto-plasmonic liposomes containing tenofovir disoproxil fumarate released 59% of the loaded drug, increased its transmigration efficiency in the BBB and, finally, reduced viral replication through delivering the anti-HIV drug to HIV-infected cells using the guidance of triple-modal imaging [100]. There are ways to control and prevent HIV at the early stages of infection. Zhao *et al.* studied the targeting of the lymphatic system and the competency of the N15P nano-liposome system (naLipo-N15P) to block HIV entrance based on the antagonistic role of N15P against CXCR4 in HIV infection. It has shown promising results, such as an increase in the specific binding to CXCR4, facilitation of cell targeting, enhancement of anti-HIV properties and blocking of HIV infection [101].

Octyglyerol-loaded NPs were effective as a vaginal microbiocide against HIV. The system showed higher efficacy, better anti-HSV-1, HSV-2, and HIV activity and higher efficacy against *N. gonorrhoeae* than other groups. There are no reports of toxicity for the liposomal formulation or *lactobacilli* [102]. In another study, cell-derived liposomes with CCR5 molecules on their surface were shown to efficiently affect the infected cells, reducing the viability of the targeted cells (gp120-expressing HIV-infected cells) by 60% [103]. Therefore, liposomes can have different effects in terms of increasing or decreasing the toxicity response based on the design of the system.

A PEGylated niosomal formulation was introduced by Nikravesh *et al.* for tenofovir anti-HIV drug delivery. In this formulation, PEGylated niosomes were incorporated with TAT cell-penetrating peptide, which is the basic region of the *trans*-activating transcriptional activator protein from HIV-1 and is necessary for the replication of the virus. This nanoformulation increased cell entrance, enhanced the anti-HIV effect and improved the tenofovir release profile *in vitro* [104]. Lipid NPs can also be utilized to stabilize anti-HIV drugs. In work done by Chauhan *et al.*, two different combinations of anti-HIV drugs with fixed dosages were encapsulated in b-casein micelles. Further encapsulation in industrial microparticles of Eudragit® L100 could successfully prevent these drugs from enzymatic digestion. Such stabilizing nano-micelles can be used in the oral delivery of anti-HIV drugs (Figure 3C & D) [105]. Nanococrystallization of two ARV drugs was done by Witika *et al.* They cocrystallized lamivudine and zidovudine using sodium lauryl sulfate as an anionic detergent and α-tocopherol polyethylene glycol succinate 1000 as vitamin E derivatives. The results showed less cytotoxicity of the nanoformulation compared with the free drugs alone [106]. These NPs can be effective against HIV through changing amounts of cytokines. Kim *et al.* have shown HIV-1 suppression and latency reversion by decorating CpG motifs on the surface of uracil-decorated liposomes. CpG oligonucleotides activated dendritic and natural killer cells and also increased both IFN-1 and IFN-γ through toll-like receptor 9 (TLR9) activation. This phenomenon led to anti-HIV responses [107]. Liposomes not only are

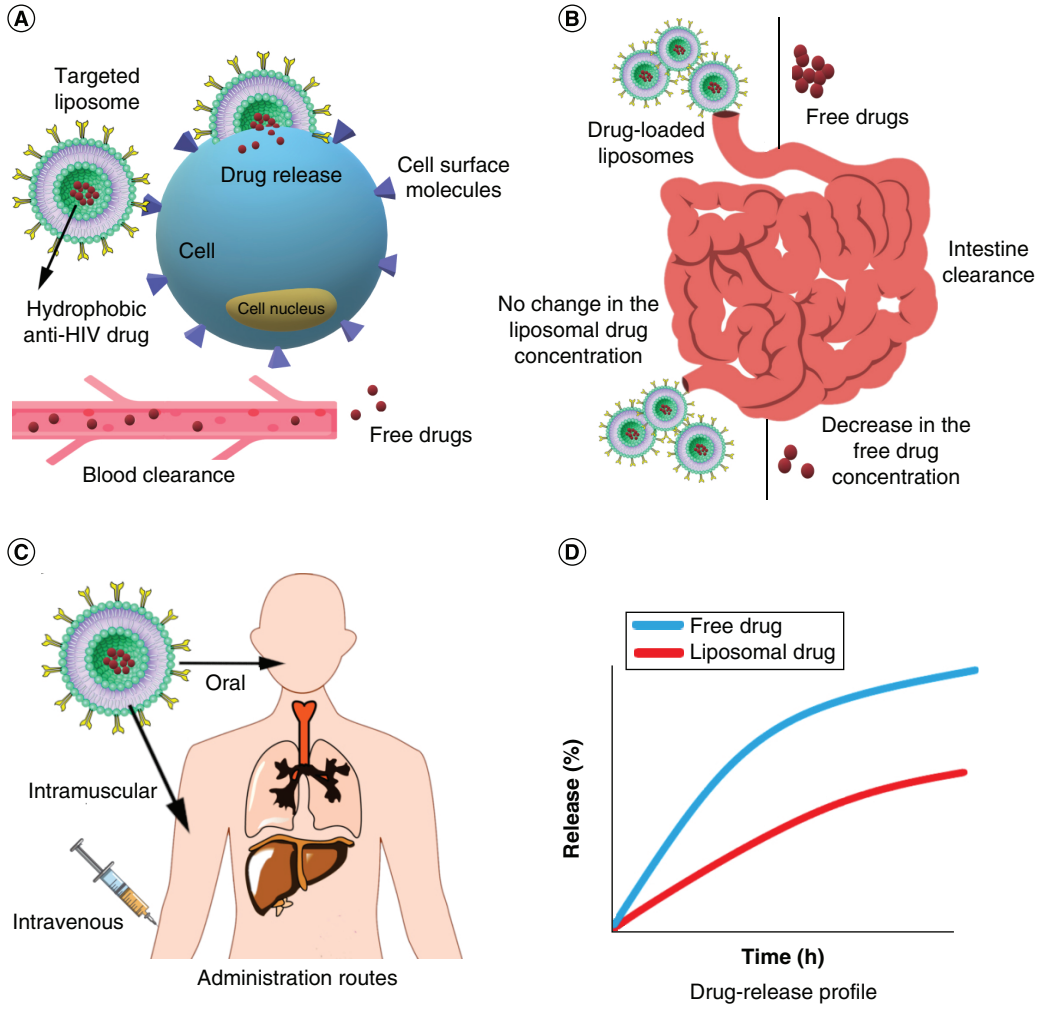


Figure 3. Applications and properties of liposomal nanoparticles in HIV therapy. (A) Targeted liposome NPs loaded with hydrophobic anti-HIV drugs increase the drug entrance into cells in two ways: more targeted and more concentrated drug delivery followed by less blood clearance. **(B)** Anti-HIV drugs' intestine enzyme degradation is much less, carrying in liposomal vehicles instead of being free delivered. **(C)** Different administration routes for liposomal formulations due to their stability and biocompatibility. **(D)** Comparison between drug-release profile of free and liposomal drugs.
NP: Nanoparticle.

used for ARV drug delivery but also are used as dual-loaded carriers. In research by Rojekar *et al.*, both etravirine as an ARV drug and selenium NPs (SeNPs) were used as cargo. Loading these two materials together enhanced the intracellular antioxidant and anti-HIV effects by synergic mechanisms. Liposomes were synthesized by solvent evaporation and SeNPs were captured as the core of the whole NP while etravirine was loaded in the lipid shell [108].

Liposome NPs can also be applied for detection purposes. A novel detection method was introduced by Zhuang's team. They designed liposome-based NPs with antibodies against HIV-p24 antigen (p24) on the surface and containing alkaline phosphatase (ALP). The particles could detect p24 by releasing ALP. Adding ascorbic acid 2-phosphate (AA-p) as substrate resulted in the production of ascorbic acid, increasing the photocurrent signals. This method increased detecting signals, showing high sensitivity in detecting the p24 antigen of HIV [109]. Damhorst *et al.* set up an electrical sensing technique for the detection of biological molecules using ion-encapsulating liposome particles. HIV detection was completed by measuring the number of certain ions released by the liposome (Table 3) [110].

Polymeric NPs include various types with different features. While they are mostly used for HIV treatment, liposome-based NPs are more efficient in HIV detection. Similar to chitosan NPs, liposomes are biocompatible.

Table 3. Liposome nanoparticles against HIV.

Type of nanocarrier	Targeted cells	Cargo	Results and effects	Ref.
SG-LP	Raw 264.7 macrophages	Stavudine	Sustained release of stavudine for up to 12 h; increased chance of reaching reservoir sites	[99]
Magneto-plasmonic liposomes	Human microglia cell line (CHME-5) and primary human astrocytes	Tenfovir	59% of drug release, increased transmigration efficiency in BBB and reduced in viral replication	[111]
NaLipo-N15P	PBMCs	–	Increase in specific binding to CXCR4, facilitated cell-targeting, enhanced anti-HIV properties and blocked HIV infection	[101]
OG liposomes	Vero and CV-1 cell model	Octylglycerol	Higher efficacy, better anti-HSV-1, HSV-2 and HIV activity, better efficacy against *N. gonorrhoeae* and no toxicity for the liposome against *lactobacilli*	[102]
Cell-derived liposomes	Namalwa or namalwa/ENV	Expressing CCR5	60% of viability reduction in targeted cells (gp120-expressing HIV-infected cells)	[103]
Lipid-modified uracil	U1	CpG motifs	Suppressing HIV-1 spreading and latency reversion	[107]
Lipid emulsion	JC53-bl (HeLa derivative)	Etravirine and SeNPs	Intracellular antioxidant and anti-HIV effects	[108]
ALP-Ls	–	Alkaline phosphatase	Improved signal detection and high sensitivity in detecting p24 antigen of HIV	[109]
Ion-encapsulating dipalmitoyl phosphatidylcholine liposomes	–	Ion	No need for bulky and high-cost optical equipment; proper point of care tool and easy to use for detecting different pathogens	[110]
PEGylated noisome	HeLa and HEK-293 T-cells	Tenofovir and TAT peptide	Improved tenofovir release profile and lowered anti-Scr HIV effect	[104]
b-Casein micelles	–	Tipranavir-efavirenz and darunavir-efavirenz-ritonavir	Enhanced oral delivery of anti-HIV drugs combinations; protected drugs against enzymatic degradation	[105]
Nanococrystals	HeLa	Lamivudine and zidovudine	Less cytotoxicity than free drugs	[106]

ALP: Alkaline phosphatase; bCN: b-Casein; CCR5 (CD195): HIV-co-receptor; CXCR4 (CD184): HIV-co-receptor; EFV: Efavirenz; gp120: Glycoprotein 120; HSV-2: Herpes simplex virus 2; naLipo-N15P: Nano-liposome system; OG: Octyglyerol; PBMC: Peripheral blood mononuclear cell; RTV: Ritonavir, SeNP: Selenium nanoparticle; TPV: Tipranavir.

By adding antibodies against HIV antigen on the surface of liposomes, these NPs can detect the virus and show specific signals by releasing enzymes or dyes. From among polymeric NPs, PLGA dendrimers and chitosan NPs are the most used NPs in HIV treatment. Also, liposome-based NPs can be used as vaccine candidates or in HIV detection.

Some liposome nanoformulations, like doxil, have made their way to FDA approval. Microfluidic methods have also facilitated the large-scale production of liposomes with uniform size and consistent physicochemical properties. Today, antibody engineering has made multiple targeting possible, which can lead to precise selection in targeting genetically distinct tumor cells, immune cells and cancer stem cells, decreasing the risk of adverse side effects [112].

Inorganic NPs

Inorganic NPs are synthetic particles used for different gene and protein delivery in the field of HIV treatment. They mostly consist of metal and metal oxide NPs in sub-100 nm diameters. Despite some concerns about their safety and accumulation in some organs, especially in high doses, they are considered safe and controllable NPs with good modification properties. Gold, silver, iron oxide (magnetic NPs) [113], zinc, nickle copper [114] and silica [115] are some of the inorganic NPs used in HIV treatment. Gold (Au) and silver (Ag) NPs are explained here as they are most common ones [116]. Figure 4 shows different mechanisms through which metal NPs inhibit microbial agents.

Gold NPs

AuNPs are versatile metal NPs, known as exciting candidates for diagnosis, as reported in many articles in the last decade [117,118]. This is mainly due to their unique optical and structural properties. AuNPs have increasingly been applied as an imaging tool or even for drug-delivery or therapeutic purposes (Figure 4A) [119,120]. As previously mentioned, despite the advantages of ARV therapies or combinational therapy in improving the quality of life of HIV-positive individuals through targeting the viral replication tactics and suppressing infection, some drawbacks, such as multidrug resistance and insufficient cellular uptake and pharmacokinetic disorders have made researchers look for novel drug-delivery systems. Remarkable size-dependent characteristics of AuNPs, such as their ability to cross the BBB, deep penetration and multivalency or ease of functionalization, which allow AuNPs to bind

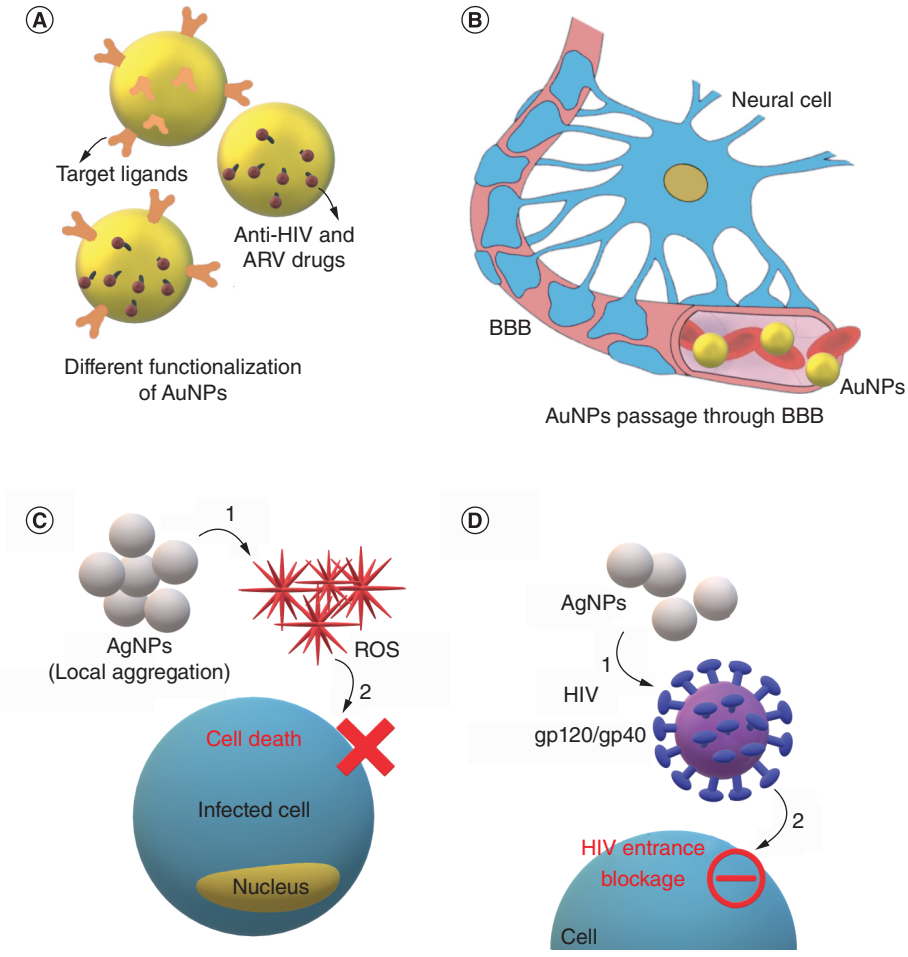


Figure 4. Applications and properties of metal nanoparticles in HIV therapy. (A) Inorganic NPs (AuNPs and AgNPs) loaded with anti-HIV drugs. **(B)** AuNPs passage through BBB as a promising drug-delivery vehicle. **(C)** Local aggregation of AgNPs causes reactive oxygen species formation and, subsequently, HIV-infected cell death. **(D)** AgNPs have antiviral effects through an unknown mechanism by affecting gp120 and gp40 HIV surface molecules.
AgNP: Silver nanoparticle; AuNP: Gold nanoparticle; BBB: Blood–brain barrier; NP: Nanoparticle; ROS: Reactive oxygen species.

with a wide range of biomolecules and chemical groups and lower toxicity, have turned AuNPs into a promising drug-delivery tool (Figure 4B) [121–124].

Many studies have demonstrated the synergistic effects of AuNPs with antiviral drugs in developing the ARV medications effective on various pathways, such as replication blockage or viral cycle, viral entry, retrotranscription, integration and maturation. As an example, viral inhibition happens by suppressing the pivotal enzymes in the replication step like integrase inhibitors (raltegravir, peptide or small molecules), RTase (abacavir and lamivudine) and also those hampering virus entry (gp120 blockage agents). Researchers have demonstrated that using a particular hexapeptide, known as an anti-integrase, can affect the conformational changes in the active site of the integrase enzyme that led to hampering the enzyme's activity. On the other hand, antiviral drugs have some drawbacks, such as the inability to enter cells or high degradation, which limit their effectiveness. Some studies have shown that AuNPs are able to improve the pharmaceutical characteristics of drugs and the biostability of peptides against protease activities. The antagonistic interactions with cell receptors underlie the metallic NPs' antiviral effects. The interaction of the virus's surface components with ligands and proteins of the cellular membrane is what allows the virus to enter and adhere to host cells, which is what causes the viral infection. So, the best strategy for designing antiviral medication might be to interfere with the interactions, which will stop the virus from adhering to cells and entering them [125].

Table 4. Inorganic nanoparticles against HIV.

Inorganic nanoparticles				
Gold NPs				
Type of nanocarrier	**Targeted cells**	**Cargo**	**Results and effects**	**Ref.**
AuNPs-galectin1 nanocomplex	CHME-5/HIV (HIV-transfected human microglial cell cultures)	Galectin 1	AuNP binding to gelactin-1 to increase the bioavailability and neurotherapeutic potential	[119]
Peptide-functionalized AuNPs	TZM-bl	Peptide bonded with hexa-peptide	Peptide-mediated inhibition of integrase	[128]
Glucose-coated gold NPs	TZM-bl-infected	Raltegravir	Multifunctional drug-delivery system to enhance integrase inhibitory effects	[129]
Dendronized AuNPs	TZM.bl cell line (HeLa, CD4 overexpressed, derivatives)	AuNPs bonded with polyanionic dendrons	Increased antiviral activity of dendrones through occupying binding sites of gp120 associated with targeted cell entry	[130]
PEGylated AuNPs	HIV seropositive patient peripheral blood mononuclear cells	–	Pegylated AuNPs act as an entry inhibitor rather than a virus neutralizer	[132]
β-diketo acid-coated AuNPs	*In vitro* study	Surface-grafted β-diketo acid to the AuNPs	Enhanced inhibitory effect of HIV-1 integrase catalytic activities vs free DKA ligands	[133]
Aptamers functionalized AuNPs	HEK 293T	RT1t49 (Aptpol) and ODN 93 (AptRH)-functinalized AuNPs	Great potential as HIV-1 RT inhibitor	[134]
Efaverinz-AuNP-loaded mannosylated niosomes	HeLa-R5-HIV-1Ba-L virus	AuNPs–EFV coloaded in noisome gel carrier	AuNP and EFV synergistic effects in inhibiting HIV dissemination in PBMCs host cells	[135]
Silver NPs				
AgNPs	HeLa-CD4-LTR-β-gal cells, MT-2 cells, HL2/3 cells, H9 cells, TZM-bl cells	AgNPs coated with PVP	AgNPs inhibit HIV-1 infection through preventing virus entrance to the target cells	[136]
AgNPs	U373-MAGI-CXCR4$_{CEM}$ cells	AgNPs with four monoclonal antibodies	Increased neutralizing potency of ABs when combined with AgNPs	[137]
AgNPs	cMAGI cells	AgNPs coated with PVP	AgNP binds to gp120 to inhibit HIV-1 entrance	[138]

AgNP: Silver nanoparticle; AuNP: Gold nanoparticle; CD4: Cluster of differentiation 4, glycoprotein T-cell receptor; DKA: β-diketo acid; EFV: Efavirenz; gp120: Glycoprotein 120; ODN: Antisense oligonucleotide; PBMC: Peripheral blood mononuclear cell; PVP: Poly(N-vinyl-2-pyrrolidone).

In research done by Kesarkar and colleagues, the anti-HIV activity of NPs was investigated. They worked on p-24 antigen inhibition by *in vitro* ELISA assay as an indication. The results suggested that AuNPs were more effective entry inhibitors than neutralizing agents. The complexity of viral structure could make it difficult to comprehend how NPs interact with dangerous viruses [126]. Some studies have also shown AuNPs and PEGylated AuNPs to have the potential to fight viruses and can thus be used as virus-neutralizing agents (Table 4) [127–132].

Silver NPs

AgNPs have been used as both antibacterial and antiviral elements in subcytotoxic concentrations for a long time, especially by producing reactive oxygen species (ROS; Figure 4C). As for HIV, AgNPs bind to gp120 and gp41 and hamper virus entrance through CD4-dependent viral binding process (Figure 4D) [139]. Some AgNP-based HIV-associated therapeutic products have obtained FDA approval [69,140]. Furthermore, AgNPs are more efficient than silver ions in their antibacterial and antiviral potencies. The difference in the oxidation number of AgNPs (Ag^0) and silver ions (Ag^{+1}) makes AgNPs about 12-times more efficient in antibacterial applications. Although AgNPs negatively affect HIV-entrance, silver ions may influence the postentry levels of the HIV cycle in cells due to their electron donation ability [136]. Table 4 shows studies done on AgNPs in HIV treatment.

Nowadays, inorganic NPs such as AuNPs have been applied as contrast agents in bioimaging and radiotherapy. They have shown higher loading efficiency and targeted delivery and more efficient drug release [141]. However, there are several challenges that must be overcome. Despite presenting broad and efficient virus inhibition in both *in vitro* and *in vivo* models, accumulation of the Au and AgNPs in some organs like the liver and spleen is still challenging. Furthermore, the preservation of antiviral particle activity when binding to the virus is a significant issue. These problems must be solved in future studies [142].

Supplementary Figure 3 illustrates a concept map representing the effects of various liposomal and inorganic NPs in HIV treatment, displaying their similarities in therapeutic effects. This concept map helps summarize the concept, showing the cause and effect of different NPs in a single view. For instance, liposomes and AuNPs both have

BBB transmigration capabilities; the liposomes prevent the entrance of HIV to the cells in two ways: attachment to gp120 and/or enhancing site-directed delivery. AgNPs do this by hampering the entrance mechanisms.

FDA-approved drugs based on nanodelivery systems

According to the guidelines of the US Department of Health and Human Services, 47 FDA-approved drugs exist for HIV treatment, none of which are NP-based [143]. Despite the absence of any approved nano-based drugs for AIDS, three approved nano-based drugs for HIV-related diseases are explained (Supplementary Table 1). Since the immune system of AIDS patients is under attack, diseases such as certain cancers and infections are more probable in these individuals. As a result, it is important to discover drugs to treat such HIV-related diseases.

Kaposi's sarcoma is a cancer caused by human herpesvirus 8 (HHV-8). Patients infected with HIV are at a high risk developing Kaposi's sarcoma. It is the second most prevalent tumor disease in HIV-positive patients in the United States and sub-Saharan Africa [144]. Doxil caelyx and DaunoXome are two drugs delivered by liposomal NPs to treat this disease. Doxorubicin and daunorubicin are the two cargos used in this regard, respectively [145]. Cryptococcal meningitis is a fungal infection mostly reported in patients suffering from immunodeficiency diseases like AIDS [127]. It is the reason for more than 100,000 deaths among HIV-positive patients worldwide [146]. AmBisome is a liposome NP-based drug that carries amphotericin B to treat HIV patients with cryptococcal meningitis [145].

Conclusion

HIV treatment has been a challenge in past decades. Recently, various NP-based treatment methods have been developed to improve the management of these patients. This is while antiviral drugs are still considered the most efficient HIV treatment option, despite their serious side effects, poor drug adherence, toxicity and unwanted interactions with other drugs. Therefore, stopping HIV from entering the body seems the safest option to stop the disease. Most NPs act in this very manner. This is while only NPs with negative charge can pass the skin barrier. It is therefore vital to keep the concentration of NPs' charge high enough to achieve the desired effects. PAMAM, Ag, liposomes and SLP7013 NPs are reported to inhibit the virus from entering the cells and also its proliferation. Early detection and neutralization of the virus are other effective ways to stop HIV before it damages the host cells. Again, PAMAM, AuNPs and AgNPs are shown to be efficient in this regard. The use of PLGA and PPI NPs in infected cells can enhance targeted ARV drug delivery. It is important to ensure these NPs do not cause toxicity in the cells. Some NPs can induce oxidative stress while others have antioxidative properties and thus are safer [147,148]. NPs such as AUNPs can be toxic at high concentrations. Thus, safer NPs like selenium NPs have gained more attention [149].

Toxicology, insufficient effectiveness and undesirable pharmacokinetics are frequently cited causes of phase I and phase II clinical trial failures. In a broader view, the drug leakage and limited capacity of loading in liposomes and hydrophobicity-dependent delivery of drugs delivered by micelles are other causes of their failure. Moreover, scale-up challenges for the industrial production of NPs, the probable toxicity of polymeric and inorganic NPs and inorganic NP accumulation in biological organs are other challenges facing the usage of NPs in HIV treatment. Also, physicochemical-dependent variability of NPs' behaviors like clearance, biodistribution and biocompatibility have been reported in studies that remained unanswered [150]. As a result, additional research must be conducted to address such concerns in the clinical and preclinical phases, followed by the feasibility of large-scale production in later steps.

Future perspective

The nanodelivery approach has been applied by some pharmaceutical companies to develop an effective vaccine against HIV. In this regard, ModernaTX, Inc. started a clinical trial for the first HIV mRNA vaccine in September 2021 [151]. Since mRNA vaccines have shown promising results for the SARS-CoV-2 virus as their first application, many are hopeful that an HIV mRNA vaccine can help defeat AIDS. According to recent developments, for oral administration of ARV medications, a variety of nanomedicine approaches are being investigated. Solid drug NP formulations are one of the current methods for enhancing the bioavailability of medicines that are poorly water-soluble and were recently used to create solid drug NPs of efavirenz compared with the normal Sustiva® product. Since 2011, rilpivirine, a non-nucleoside reverse transcriptase inhibitor, has been offered for oral dosing. Rilpivirine has been recently nanoformulated to create a long-acting injectable format. Rilpivirine concentrations were detected for up to two months in rats and six months in dogs after being injected subcutaneously or intramuscularly [152].

Recently, lopinavir solid drug NPs that have been pro-ethanol-free for pediatric administration have also been prepared in mono- and combinational-drug formulations [153].

In the case of anti-HIV nanodrugs, two recent preclinical cases have been investigated. A research group at Creighton University in 2018 and 2019 demonstrated the clinical effects of PLGA-bicteravir complex and PLGA-tenofovir@elvitegravir@emtricitabine complex. The clinical achievements revealed reliable outcomes including long-acting effects and lower toxicity of the noted drug-delivery system [154]. Also, in the most recent clinical study, long-acting injectable formats of cabotegravir and rilpivirine, using injectable NPs, are being studied in phase III (NCT02951052) [155]. Despite the amazing reported effects of NPs on HIV, most studies have remained theoretical and were never commercialized. This is because many factors should be taken into account before the NP is used in HIV treatment. For instance, changes in the NP size can change its features considerably. This suggests that more research on NPs and their characteristics are needed before these treatments are used in clinical practice.

Executive summary

Background

- AIDS is a worldwide disease with a high incidence rate.
- HIV infects the $CD4^+$ lymphocytes of humans.
- AIDS is transmitted between humans by biological fluids.
- The HIV genome is single-stranded RNA.
- HIV has eight viral proteins.
- Two of the main HIV proteins responsible for host-cell binding are gp120 and gp41.
- Using antiretroviral drugs is the main AIDS therapy component.
- The disadvantages of using antiretroviral drugs are their safety issues and poor permeability across the blood–brain barrier.
- Nanotechnology is helping AIDS therapy fin terms of better safety and blood circulation and longer life span in HIV patients.
- Nanoparticles (NPs) are made of organic or inorganic materials with a size distribution of mostly $<$100 nm.
- NPs are widely used in drug and gene delivery.
- Nano drug-delivery systems have advantages like low toxicity, ease of functionalization, high circulation rate, decrease drug dosage and high-efficiency drug/gene delivery.

Nanomaterials applied for AIDS diagnosis & treatment

- Dendrimers, polyethylenimine (PEI), poly(lactic-co-glycolic acid) (PLGA) and chitosan are examples of the mostly used polymeric NPs in HIV therapy.
- Polymeric NPs enhance drug solubility and stability and achieve sustained drug release.
- Chitosan inhibits the replication of HIV, mediated by efficient delivery anti-HIV siRNAs.
- Poly(amidoamine) (PAMAM) stops HIV entrance to the cells via binding to gp120 protein.
- PLGA, PAMAM and chitosan all prolong drug release.

Dendrimers

- Dendrimers are branched NPs with a high capacity to load drugs.
- Polyanionic carbosilane dendrimers are used to reduce latent HIV-1 persistence.
- PAMAM NPs can enhance the immune system against HIV.
- PEGylated PAMAM NPs can enhance the encapsulation of HIV drugs.
- Poly(propyleneimine) (PPI) NPs protect anti-HIV antisense oligonucleotides against nucleolytic digestion.
- PPI-based NPs can be used as antiretroviral drug carriers.
- Dendrimer-based anti-HIV drugs can stop HIV in various stages of infection including attachment, entry, latency and replication.
- G2-S16 dendrimers protect the cell against host cell infection through viral attachment.
- PEI has several advantages, including high charge density, chain flexibility and low immune response.
- PEI is an important polymeric NP used in anti-HIV gene and drug delivery.
- PLGA is a polymeric NP capable of increasing drug circulation in the body.
- PLGA loaded with griffithsin and dapivirine has strong synergistic properties against HIV-1.
- Chitosan has recently gained great attention as a nano drug carrier because of its biocompatibility and biodegradability.
- Chitosan can be used for sustained release of drugs.

Liposomes

- Liposomes enhance the efficacy of drug release.
- By adding antibodies against HIV antigen on the surface of liposomes, these NPs can detect the virus.
- Liposomes have good bioavailability and biocompatibility.
- Liposome-based drugs have less clearance and enzymatic degradation.
- Liposomes can be administered in different ways including oral, subcutaneous and intravenous routes.

Inorganic NPs
- Inorganic NPs can be easily surface-modified.
- Despite some concerns about inorganic NPs' safety and accumulation in some organs, especially in high doses, they are considered safe and controllable.
- Gold NPs have the ability to cross the blood–brain barrier.
- Local aggregation of silver NPs causes reactive oxygen species formation and, subsequently, HIV-infected cell death.
- Silver NPs are more efficient than silver ions in their antibacterial and antiviral potencies.
- Gold NPs have great optical, physical and structural properties.
- Gold NPs can be used in anti-HIV targeted drug delivery.
- Silver NPs have antibacterial and antiviral properties.

US FDA-approved drugs based on nanodelivery systems
- There are 47 FDA-approved drugs for HIV treatment.
- There are three approved nano-based drugs for HIV-related diseases.
- Nanodrug delivery has good potential for future FDA-approved anti-HIV drugs.

Conclusion
- NP-based treatment methods can help address challenges in HIV therapy.
- Stopping HIV from entering the body seems the safest option to stop the disease.
- PLGA and PPI NPs can enhance targeted antiretroviral drug delivery in HIV-infected cells.
- Toxicity and tissue accumulation of some NPs must be considered when used as drug-delivery agents.

Future perspective
- There are new and increasing clinical trials of NPs as drug carriers.
- Solid drug NP formulations are one of the current methods for enhancing the bioavailability of medicines that are poorly water-soluble.
- Investigation of NPs' surface properties is important for their safety and biological functions.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/nnm-2022-0248

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