Nanoparticle-Based Immunoengineered Approaches for Combating HIV

Allan Bowen, Elizabeth E. Sweeney and Rohan Fernandes

1 The George Washington Cancer Center, The George Washington University, Washington, DC, United States, 2 Department of Medicine, The George Washington University, Washington, DC, United States

Highly active antiretroviral therapy (HAART) serves as an effective strategy to combat HIV infections by suppressing viral replication in patients with HIV/AIDS. However, HAART does not provide HIV/AIDS patients with a sterilizing or functional cure, and introduces several deleterious comorbidities. Moreover, the virus is able to persist within latent reservoirs, both undetected by the immune system and unaffected by HAART, increasing the risk of a viral rebound. The field of immunoengineering, which utilizes varied bioengineering approaches to interact with the immune system and potentiate its therapeutic effects against HIV, is being increasingly investigated in HIV cure research. In particular, nanoparticle-based immunoengineered approaches are especially attractive because they offer advantages including the improved delivery and functionality of classical HIV drugs such as antiretrovirals and experimental drugs such as latency-reversing agents (LRAs), among others. Here, we present and discuss the current state of the field in nanoparticle-based immunoengineering approaches for an HIV cure. Specifically, we discuss nanoparticle-based methods for improving HAART as well as latency reversal, developing vaccines, targeting viral fusion, enhancing gene editing approaches, improving adoptively transferred immune-cell mediated reservoir clearance, and other therapeutic and prevention approaches. Although nanoparticle-based immunoengineered approaches are currently at the stage of preclinical testing, the promising findings obtained in these studies demonstrate the potential of this emerging field for developing an HIV cure.

Keywords: HIV cure strategies, immunoengineering, nanoparticles, immune activation, HAART (highly active antiretroviral therapy), combination therapy for HIV, latency reversing agents

INTRODUCTION

Approximately 37 million people worldwide are living with HIV for which there is no practical cure (1). There are two main types of the virus: HIV-1 and HIV-2. HIV-1, which is the focus of cure strategies discussed in this paper, is more prevalent and pathogenic, and primarily infects CD4+ T helper cells (2). Other cell populations susceptible to HIV-1 include dendritic cells, macrophages, microglia, and astrocytes although the mechanisms of infection for these cell types are not yet fully understood (3–8). HAART is an effective treatment regimen for HIV-1 (9), however, it allows the virus to remain viable and does not provide a sterilizing or functional cure in patients. Further HAART causes several deleterious comorbidities (10, 11). Since HAART targets the HIV-1
replication cycle, HIV-1 evades targeting by undergoing latency (12, 13). Latent HIV-1 reservoirs are also able to go undetected by the immune system, which increases the risk of a viral rebound. Another confounding factor is the lack of unique surface markers on latently infected cells, which has hindered the development of strategies to generate total viral clearance or permanent latency (14–16). This challenge is supported by the fact that there have been only two well-documented cases wherein patients have experienced total HIV-1 viral clearance. This suggests that it is extremely rare for individuals to adequately control HIV-1 without a sustained antiretroviral treatment regimen (17, 18). Hence, there is an urgent need for novel HIV cure strategies.

The field of immunoengineering encompasses a broad variety of bioengineering approaches and technologies to manipulate the immune system. A notable component of these approaches involves engineered biomaterials including nanoparticles, polymeric scaffolds, and hydrogels to engage the immune system to fight disease, and represents an attractive strategy for developing a cure for HIV-1 (19–21). While numerous nanoparticle-based immunoengineered approaches have been successfully applied in the field of cancer immunotherapy (22–26), fewer studies have utilized these promising benefits for an HIV cure. The goal of this mini-review is to familiarize the reader with the field of nanoparticle-based immunoengineering approaches for an HIV cure. In particular, we focus on the use of nanoparticles to enhance HAART, latency reversal, vaccination strategies, gene editing, cell therapies, among others (Figure 1). We highlight both immune-mediated strategies (e.g., nanoparticles in conjunction with adoptive cell transfer) and those targeting endogenous immune cells involved in HIV (e.g., nanovaccines). For a comprehensive discussion on the use of nanoparticles for treating HIV/AIDS in the context of nanoparticles classes, formulation, and their use in drug delivery, we direct the readers to several published reviews in the literature (27–29).

**NANOPARTICLES EXHIBIT BENEFICIAL PROPERTIES FOR IMMUNOENGINEERING CURES FOR HIV-1**

Nanoparticle sizes range from ∼1 to 100 nm (30). On account of their sizes, nanoparticle-based therapies can easily be administered by varied techniques (i.e., intravenously, subcutaneously, intraperitoneally) and penetrate body barriers (31). Related to their sizes and pertinent to HIV cure strategies, nanoparticles accumulate in lymphoid tissue and lymphatic organs (32), the sites of anatomical HIV reservoirs (33, 34) when parenterally injected (especially when injected intradermally, subcutaneously, and/or intramuscularly). Additionally, because nanoparticles have a large surface area-to-volume ratio, diverse molecules such as drug payloads, immunological adjuvants, and targeting ligands can be bioconjugated to their surface (35), which can then be trafficked to sites of latent HIV reservoirs. Nanoparticles can also be synthesized in the form of depots/reservoirs that encapsulate and release therapeutic drugs or immunomodulatory agents (36), allowing for their improved bioavailability and sustained release kinetics in an HIV cure setting. In the following sections, we review various examples of nanoparticles used for immunoengineering HIV cures.

**Nanoparticles for Improving HAART**

HAART can successfully inactivate HIV-1, however the virus is able to persist within latent lymphoid, gut, and CNS reservoirs (5–8). This requires patients to remain adherent to the HAART regimen for the duration of their lifetime to prevent viral rebound (9). Since nanoparticles facilitate the sustained release of drugs, a group of researchers have developed a long-acting slow-effective release antiretroviral therapy (termed “LASER ART”), which utilizes nanoparticles for controlled release of HAART agents, thereby improving regimen adherence (37, 38). In a recent study, the same group of researchers demonstrated that a nanocrystallized product of lamivudine, a nucleoside reverse transcriptase inhibitor (NM23TC), maintained antiretroviral activity in HIV-1-infected monocyte-derived macrophages after viral challenge for up to 30 days. NM23TC was taken up by a nanocrystallized product of lamivudine, a nucleoside reverse transcriptase inhibitor (NM23TC), sustained antiretroviral activity in HIV-1-infected monocyte-derived macrophages after viral challenge for up to 30 days. NM23TC was taken up by HIV-1-infected monocyte-derived macrophages and remained in high prodrug concentration in whole blood for 30 days after a single dose. In addition, at day 28, M23TC, a metabolized version of lamivudine, was detected at high levels in the liver, lymph nodes, and spleen (39), suggesting that this nanoplateform may improve delivery of the drug to HIV-1 niches. Other groups have also developed nanoparticles for improving HAART (40–43) (Table 1).

**Nanoparticles for Improving Latency Reversal**

Latency-reversing agents (LRAs) are able to reactivate viral replication. LRAs are used in “shock and kill” treatment approaches, wherein the LRA-elicited viral replication is coupled...
### TABLE 1 | Nanoparticle-based immunoengineering approaches for HIV/AIDS.

| Nanoparticle class                      | Key findings                                                                 | References |
|-----------------------------------------|------------------------------------------------------------------------------|------------|
| **NANOPARTICLES FOR IMPROVING HAART**  |                                                                               |            |
| Poloxamer-based nanoparticles           | LASER ART (also known as nanoART) nanoparticles for controlled release of | (37–40)    |
| Lipid nanoparticle                      | Lipid-drug nanoparticles exhibited 5-fold increased bioavailability of HAART drugs in lymph nodes, and markedly increased sustained release over the course of 7 days | (41)       |
| PLGA/pluronic nanoparticle              | Nanof ormulation of HAART drugs demonstrate greater bioavailability in plasma and absorption in various tissues over the course of 14 days | (42)       |
| Lactoferrin nanoparticle                | First-line nano formulated HAART drugs exhibited 4-fold increase in bioavailability and an increase in anti-HIV activity compared to soluble agents | (43)       |
| **NANOPARTICLES FOR IMPROVING LATENCY REVERSAL** |                                                                               |            |
| Lipid nanoparticle                      | LRA and protease inhibitor encapsulated within nanoparticle reversed latency and prevented HIV-1 viral spread | (44)       |
| Lipid-coated PLGA nanoparticle          | Co-administration of LRA:s-individually encapsulated within nanoparticles exhibited synergistic induction of HIV-1 mRNA levels at low cytotoxicity | (45)       |
| Iron oxide nanoparticle                 | LRA and vorinostat-loaded nanoparticle penetrated BBB, reversed HIV-1 latency and exhibited anti viral efficacy in astrocytes. | (46)       |
| PLG/PEG nanoparticle                    | LRA and protease inhibitor encapsulated within PLGA-PEG nanoparticles reversed latency and inhibited viral spread | (47)       |
| **NANOVACCINES**                       |                                                                               |            |
| PLGA nanoparticle                       | Encapsulating TLR-agonist improved HIV-1 vaccine immunogenicity and decrease required dose for immunogenic effect | (48)       |
| Lumazine synthase- and ferritin-based nanoparticles | Antigens encapsulated within nanoparticles were trafficked within germinal centers promoting a potent immunogenic response | (49)       |
| Polyetheroxylamine mannose/DNA/ glucose nanoparticle | DermaVir nanof ormulation delivered HIV-1 antigen to Langerhans cells, which matured into Dendritic cells, mounting an immune response | (50)       |
| eOD-GT8 nanoparticle                    | Engineered outer domain (eOD)-60 mer nanoparticle exhibited sufficient precursor native B cell binding for bNAb production | (51)       |
| Liposome nanoparticle                   | Clade C-derived trimers decorated on liposomal surface induced enhanced germinal center and bNAb responses compared to soluble trimers | (52)       |
| Ferritin nanoparticle                   | Consensus-derived Env trimers conjugated to nanoparticles induced greater bNAb targeting of apex trimers of in vivo models | (53)       |
| Protein nanoparticle                    | Nanomaterial presenting SOSIP trimer increased B-cell activation and induced greater bNAb titers against Tier-1A viral strains | (54)       |
| Liposome nanoparticle                   | Vaccination with liposomes formulated with HIV envelope protein elicits bNAb targeting and neutralization | (55)       |
| (Continued)                             |                                                                               |            |
| **NANOPARTICLES FOR TARGETING HIV VIRAL FUSION TO IMMUNE CELLS** |                                                                               |            |
| Silver nanoparticle                     | Silver nanoparticles exert anti-HIV activity through gp120 binding in various viral strains | (57)       |
| Poly (acrylate)-based nanoparticle      | Hydrophobic nanoparticle impedes amyloid fiber structure, thereby disrupting HIV-1 trafficking to its target cell | (58)       |
| PLGA nanoparticle                       | Nanoparticles coated with a T-cell membrane were able to serve as a “decoy” for HIV-1 binding, resulting in viral suppression | (59)       |
| Extracellular vesicles                  | Extracellular vesicles (EVs) released by Lactobacillus inhibited HIV-1 viral attachment and entry to target cells | (60)       |
| Extracellular vesicles                  | EVs isolated from semen inhibited HIV-1 regardless of donor infection status; EVs from ART-treated subjects inhibited HIV-1 in vivo | (61)       |

### TABLE 1 | Continued

| Nanoparticle class                      | Key findings                                                                 | References |
|-----------------------------------------|------------------------------------------------------------------------------|------------|
| Ferritin nanoparticle                   | HIV antigens are presented on nanoparticles in native trimeric structure as a tool for vaccine development | (56)       |
| **NANOPARTICLES TO ENHANCE GENE EDITING APPROACHES** |                                                                               |            |
| Gold nanoparticles                      | Au-nanoparticles can mediate CRISPR-Cas9 components to target cells with higher efficiency and lower cytotoxicity | (62)       |
| Poloxamer-based nanoparticles           | LASER ART combined with CRISPR/Cas9 eliminated HIV-1 in a small subset of mice | (63)       |
| **NANOPARTICLES TO ENHANCE CLEARANCE BY ADOPTIVELY TRANSFERRED IMMUNE CELLS** |                                                                               |            |
| PLGA nanoparticles                      | Nanoparticles encapsulating neutralizing antibody and LRA improved NK cell effector function toward J-Lat cells compared to free agents | (64)       |
| Lipid nanoparticle                      | IL-15-loaded nanocapsules conjugated to HIV-1-specific CTLs improved elimination of infected cells | (65)       |
| **OTHER THERAPIES**                     |                                                                               |            |
| PEG-b-PR co-polymer nanoparticles       | STING agonist nanof ormulation reversed HIV-1 immune evasion mechanism | (66)       |
| Quantum dots                            | Graphene quantum dots mediated HIV-1 viral suppression | (67)       |
| Nanodiamonds                            | Eflavirenz-nanodiamond conjugation improved bioavailability and blood brain barrier penetration | (68)       |
| Gold nanoparticles                      | Gold conjugated with HIV integrase inhibitors could penetrate the BBB and exert antiviral efficacy in targeted HIV-1-infected microglial cells | (69)       |
| PLGA nanoparticles                      | FTC-loaded nanoparticles exhibited greater bioavailability and lower IC50 compared to soluble agents | (70)       |
| PLGA nanoparticles                      | TDF-loaded nanoparticles in thermosensitive gel conferred 100% protection from HIV-1 strains within 24 h time period and had no detectable viral levels in plasma throughout 4 weeks period | (71)       |
| Cellulose acetate phthalate nanoparticles | DTG-loaded nanoparticles in thermosensitive gel were uptaken into vaginal epithelial cells with low cytotoxicity | (72)       |
to the actions of HIV-1 cell-specific cytotoxic agents or immune-mediated clearance (73). Several classes of molecules and macromolecules have been used as LRAs including protein kinase C (PKC) agonists, histone deacetylase inhibitors, and cytokines, and their mechanisms of latency reversal are well-described. For example, PKC agonists function via the NF-KB pathway. Activated PKC isoforms downregulate the inhibitor IKB, thereby releasing the transcription factor NF-KB, which translocates into the nucleus, and binds to the HIV-1 proviral long terminal repeats, thereby mediating viral transcription (74). Similar to HAART, nanoparticles have been utilized to improve the delivery of LRAs (Table 1). In one study, Kovochich et al. encapsulated bryostatin, a potent PKC agonist (75) and neflinvar, an HIV-1 protease inhibitor, into nanoparticles. Their nanoparticle targeted CD4+ cells in a peripheral blood mononuclear cells (PBMC) culture, activated latent virus, and inhibited viral spread (76). In a more recent study, Cao et al. synthesized hybrid lipid-coated PLGA nanocarriers that incorporated diverse LRAs. These lipid-coated nanoparticles could selectively activate CD4+ T cells in nonhuman primate PBMCs as well as in murine lymph nodes with substantially reduced toxicity (44). Despite the fact that it is currently impossible to identify and target every HIV-1-infected cell in the latent reservoir (45), the ability of nanoparticles and nanocarriers to traffic and deliver LRAs to sites of latent HIV reservoirs can maximize their therapeutic benefit, and serve as an important component of successful shock and kill cure regimens. Other examples of nanoparticles for improving latency reversal appear in Table 1 (46, 47).

Nanovaccines

Traditional vaccines for HIV-1 have been difficult to develop, and clinical trials using HIV-1 vaccines have demonstrated poor efficacy (77, 78). Vaccines fail for several reasons including poor delivery to dendritic cells, reversion of a live attenuated virus to its virulent form, or if the vaccine is too weak to facilitate an immune response (68). Consequently, an ideal vaccine should be clinically safe, stable, and capable of inducing a potent immune response (79). Nanoparticles have been shown to overcome these limitations (80) by protecting antigens from proteolytic enzymes, promoting antigen uptake and processing by antigen-presenting cells (APCs), in addition to being biocompatible and biodegradable (81). Several groups have leveraged favorable properties of nanoparticles to develop nanovaccines for HIV-1 (Table 1).

One effective strategy is utilizing nanovaccines to activate dendritic cells (DCs), which in turn cause T cell activation (82). To this end, Rostami et al. decorated antigens onto the surface of nanoparticles to facilitate greater interaction with the APCs due to the high surface area to volume ratio of the nanoparticles (48). Specifically, a flagellin molecule sequence derived from Pseudomonas aeruginosa (FLIC), a toll-like receptor 5 agonist, was conjugated to an HIV-1 p24-NeF peptide, and encapsulated within PLGA nanoparticles. The FLIC-p24-NeF-encapsulated nanoparticle elicited higher levels of lymphocyte proliferation and cytotoxic T cell activity compared to controls (48), suggesting its potential use in an HIV-1 vaccination strategy. In a more recently study by Tokatlian et al., nanoparticles encapsulating HIV-1 antigens were observe to localize to the lymph nodes more than corresponding soluble antigen counterparts, and remained localized there for up to 4 weeks (49). In another study, Lori et al. showed that their nanoparticle “DermaVir” could administer HIV-1 antigens to Langerhans cells, which resulted in a potent immunogenic response (50). DermaVir is currently undergoing a phase 3 clinical trial evaluation based on excellent responses observed in Phase I/II clinical trials (83). Together, these studies along with others summarized in Table 1 (51-56), clearly suggest the importance of nanovaccines for treating HIV-1.

Nanoparticles Targeting HIV Viral Fusion to Immune Cells

Targeting the HIV replication cycle by inhibiting the ability of HIV-1 to fuse and/or enter a target cell has been the focus of several published studies (Table 1). Fusion or entry inhibition leads to inhibition of viral activity and viral cytotoxicity. In one approach, Lara et al. showed that silver nanoparticles are antiviral and prophylactic against HIV-1 fusion to target cells (57). Silver nanoparticles exert anti-HIV activity at an early stage of viral replication, likely as a virucidal agent or as an inhibitor of viral entry. Silver nanoparticles bind to gp120 in a manner that prevents CD4-dependent virion binding, fusion, and infectivity, acting as an effective virucidal agent against cell-free and cell-associated virus. Further, silver nanoparticles inhibit post-entry stages of the HIV-1 life cycle (57).

Another approach utilized semen-derived enhancer of viral infection (SEVI), which is a type of amyloid fibril present in human semen that enhances HIV-1 infection of target cells by capturing HIV-1 virions, resulting in increased viral fusion (84). SEVI serves as a mediator for HIV-1 viral attachment due to its highly cationic nature (84, 85). In their study, Sheik et al., synthesized a hydrophobic polymeric nanoparticle to reduce SEVI fibril-mediated infection (58). The hydrophobicity of the nanoparticle interferes with Aβ amyloid structure, forming amorphous aggregates, thereby disrupting the amyloid HIV-1 trafficking protein to target cells (86-88). Thus, the hydrophobic nanoparticles were able to reduce HIV-1 virion binding affinity toward their target cells (58).

Biomimicry approaches, such as plasma membrane-coated nanoparticles, represent a unique strategy to target a variety of human pathologies (89). A pivotal study showed the efficacy of coating a nanoparticle with a cell membrane to imitate and model endogenous cell activity. HIV-1 infection begins when an exposed HIV-1 surface protein, gp120, interacts with CD4 receptor and chemokine receptor type 5 (CCR5) co-receptor on target cells (90). Wei et al. coated polymeric nanoparticles with a CD4+ T cell membrane, causing the modified membrane-coated nanoparticle to preferentially interact with HIV-1. This preferential binding ultimately neutralized HIV-1 viral activity in PBMCs in vitro (59), illustrating the potential of biomimicking nanoparticle approaches to reduce HIV-1 viral spread by blocking viral fusion to T cells.

Unlike synthetic nanoparticles, extracellular vesicles (EVs) are naturally occurring nanoscale structures that carry cargo (e.g., proteins, lipids, nucleic acids) and can be released from
both healthy and apoptotic cells (91). Recently, Palomino et al. discovered that EVs released by Lactobacillus in the healthy vaginal microbiota prevented HIV-1 attachment to target cells and thereby inhibited HIV-1 infection (60). In a recent study by Welch et al., EVs extracted from semen inhibited HIV-1 in vitro regardless of HIV infection status of the donor, while EVs extracted from the blood and semen of ART-treated subjects inhibited HIV-1 in vivo (61). These studies suggest a potential avenue for bacterial and/or EV-based treatment strategies in preventing HIV-1 viral spread.

**Nanoparticles to Enhance Gene Editing Approaches**

Gene therapy technologies have been explored for HIV-1 cure strategies (Table 1). Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (CRISPR-Cas9) is a gene editing platform wherein genes can be added, removed, or altered at given genetic loci (92). CRISPR-Cas9 is a faster and more efficient technique than other genetic editing platforms using other viral vectors or the Cre-Lox system, although current CRISPR-Cas9 delivery techniques use electroporation to facilitate DNA entry into living cells, which is difficult to control and can generate cytotoxicity (92, 93). Previously, gene-editing tools have knocked out CCR5 in CD4+ T cells to block HIV-1 viral entry (94, 95). However, gold nanoparticles (AuNPs) have a unique ability to safely deliver CRISPR-Cas9 components to their targets (96). AuNPs have large surface area to volume ratios and are biocompatible with low toxicity (5). Shahbazi et al. developed AuNPs with layer-by-layer surface conjugation of CRISPR components (AuNP/CRISPR), targeting two locations within the hematopoietic stem and progenitor cell (HSPC) genome, CCR5 and the gamma-globin gene promoter. Genetic deficiency in CCR5 is linked to HIV-1 resistance through the elimination of viral anchoring and entry through its CCR5 co-receptor (62, 97). AuNP/CRISPR was able to penetrate into CD34+ hematopoietic cell line, which is difficult to transfect. At micromolar concentrations, AuNP/CRISPR exhibited an overall low amount of gene editing and homologous directed repair (HDR) at the CCR5 and the gamma-globin promoter locus. This demonstrates that AuNP/CRISPR functioned with low efficacy. However, genetic editing and HDR via AuNP/CRISPR was higher than the electroporation-driven process. This suggests that AuNP/CRISPR could be effective in delivering gene editing for HIV-1 therapy (62).

With the promising innovations of LASER ART and CRISPR-Cas9, Dash et al. combined the two methodologies to evaluate a potentially synergistic functionality. Two of seven HIV-1-infected mice that received LASER ART followed by subsequent AAVs-CRISPR-Cas9 treatment targeting a fragment of the HIV-1 genome were cured of viral rebound and experienced a restoration of their CD4+ T cells, suggesting HIV-1 regression/elimination (63). Additionally, HIV-1 RNA levels diminished to undetectable levels in the plasma, spleen, liver, gut, and brain in the cured mice. Further, naïve humanized mice that were challenged with adoptively transferred cells isolated from the cured mice showed no detectable HIV-1 viral loads. This study demonstrates the possibility of eliminating HIV-1 in plasma and infectious tissues through this novel combination approach (63).

**Nanoparticles to Enhance Clearance by Adoptively Transferred Immune Cells**

Recent studies show promising effects of cell therapies for treating HIV-1 (98–100). Here, autologous or allogenic immune cells are transferred to the patient after *ex vivo* expansion and/or modification to clear HIV-1 infected cells. Nanoparticles may offer the ability to enhance the ability of immune cells to target and kill target cells in the context of HIV-1. In their study, Sweeney et al. generated a PLGA nanoplatform that co-encapsulated an LRA and a target cell-specific antibody to improve NK cell effector function in an *in vitro* cell model of latent HIV-1 (64). The nanoplatform was able to increase NK cell cytotoxicity of the target cells, thereby illustrating an example of nanoparticles enhancing immune cell function in the context of latent HIV-1 (64). In another studies, Jones et al. demonstrated that cytotoxic T lymphocytes (CTLs) were made more potent by conjugating drug-loaded lipid nanoparticles to their surface (65). HIV-1-specific CTLs were able to specifically target HIV-1-infected cells and deliver the nanoparticle-encapsulated payload (65).

**Other Focus Areas**

### Nanoparticles to Boost Innate Immunity

HIV-1, like many other viruses, has evolved mechanisms to evade or disrupt immune surveillance. Therefore, one strategy to eliminate HIV-1 viral load is to reverse immune evasion. HIV-1 typically inhibits the cGAS-STING pathway that normally functions via cGAMP binding to STING on the endoplasmic reticulum resulting in an IFN-1-mediated antiviral response (66, 101, 102). pH-sensitive polymeric nanoparticles were engineered to deliver a STING agonist to counteract HIV-1 immune evasion via the cGAS-STING pathway. These STING agonist-nanoparticles demonstrated potent antiretroviral activity for up to 12 days (66).

### Nanoparticles to Inhibit HIV-1 Reverse Transcriptase Activity

Quantum dots are biocompatible semiconductor crystal nanoparticles with low toxicity that have been used for biosensing, image contrast, and drug delivery (103, 104). These nanomaterials are attractive due to their intrinsic antiviral activity and thus, their potential as inhibitors of HIV-1. In a proof-of-concept study by Iannazzo et al., a reverse transcriptase inhibitor (RTI; CH499) was readily conjugated onto the surface of the graphene quantum dots (GQDs) via intrinsic functional groups (67). The conjugated GQD product (GQD-CH499) achieved remarkable anti-reverse transcriptase and cellular anti-HIV-1 activities compared to the free drug alone. This additive improvement may be the result of the GQDs’ intrinsic structure, where the polycarboxylation group could mediate the inhibition of HIV-1 reverse transcriptase through viral fusion (67), suggesting the potential of GQDs in treatment for HIV-1.

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Nanoparticles to Enhance Blood Brain Barrier Penetration

Aside from persistent HIV-1 in CD4$^+$ helper T cells, HIV-1 may also persist in microglial cells, which are the resident macrophages of the CNS (6). These cells may confer HAART resistance, perpetuate HIV-1 infection in peripheral tissues, and are critical in the development of HIV-1 associated neurocognitive diseases (105). The brain poses an anatomical barrier, where there is low drug penetration by virtue of the blood brain barrier (BBB). Therefore, there is a need to develop ways to penetrate the BBB to target persistent HIV-1 in microglial cells (6, 105). Nanodiamonds are ~10 nm diamonds which are known for their inexpensive production, surface modifications, and low cytotoxic profile. In the context of HIV-1, Roy et al. complexed efavirenz (EFV), an effective non-nucleoside RTI, to a nanodiamond to effectively improve the poor bioavailability of EFV (ND-EFV) (68). ND-EFV allowed for sustained release of EFV in a BBB model in vitro. In addition, ND-EFV was effective in controlling HIV-1 replication for 7 days, where the EFV alone drug was able to inhibit HIV-1 for 5 days (68). Similarly, gold nanoparticles have also been used through the BBB. Garrido et al. showed that gold nanoparticles conjugated with HIV integrase inhibitors could penetrate the BBB with antiviral efficacy, providing another nanoplatform for targeting HIV-1-infected microglial cells (69).

Nanoparticles for Prophylactic HIV-1 Prevention

Another application of nanoparticles is in improving pre-exposure prophylaxis (PrEP), which provides a ~90% effective approach to prevent HIV-1 infection but requires daily oral administration (106). PrEP comprises tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), two nucleoside RTIs that have low half-lives and require high dosing, thereby increasing the risk of adverse effects (107). Mandal et al. encapsulated FTC within PLGA nanoparticles (FTC-NPs), and demonstrated improved bioavailability of FTC with significantly lower inhibitory concentration (IC$_{50}$) than free FTC in vitro (70). Alternatively, Destache et al. loaded TDF into PLGA nanoparticles (TDF-NPs), and subsequently incorporated them within a thermosensitive vaginal gel (71). Mice challenged with two strains of HIV-1 and treated with the TDF-NP gel were 100% protected against the virus with no detectable viral plasma load (71), suggesting the efficacy of sustained release of TDF by nanoparticles via vaginal administration to prevent HIV-1 infection. In another study, Mandal et al. encapsulated dolutegravir (DTG), an integrase strand transfer inhibitor, within nanoparticles made from cellulose acetate phthalate, a pH-sensitive polymer that intrinsically inhibits HIV-1 entry into its target cells (DTG-CAP-NPs) (72). Similarly to above, DTG-CAP-NPs were incorporated into a thermosensitive vaginal gel. Vaginal epithelial cells were able to take up DTG-CAP-NPs, where they persisted for up to 7 days with low cytotoxicity (72). These studies demonstrate the potential of nanoparticles for use in HIV-1 preventative strategies, including enhancing PrEP.

CONCLUSION

Here, we have reviewed the field of nanoparticle-based immunoengineered approaches toward an HIV-1 cure. We highlighted the potential and use of nanoparticles to facilitate and improve the delivery, bioavailability, and/or functionality of HAART, LRAs, vaccines, gene-editing approaches, and other therapeutic or preventative strategies. The innovative advances described herein demonstrate the potential of the field of nanoparticle-based immunoengineering in treating and preventing HIV-1.

AUTHOR CONTRIBUTIONS

AB, ES, and RF all participated in the writing and the preparation of the manuscript, and approved it for publication.

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