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REVIEW

Recent Advances in Nanoparticle-Based Antiretroviral Drug Delivery Systems for HIV Treatment and Prevention: A Comprehensive Review

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Background: AIDS disease, caused by HIV, is a highly prevalent disease disturbing global health and swaying economic progress and social fidelity in the world.

Purpose: Eradication and cure of HIV infection has been a difficult assignment, and not many highly effective drugs and vaccines are available in the present scenario. Besides, the suboptimal adherence, toxicity, resistance to available drugs, and presence of several viral reservoirs make lifelong HIV infection treatment very challenging. Furthermore, a cure for HIV infection cannot be attained properly unless the latency issue is addressed and antiretroviral drug delivery to its specific cellular reservoir sites for an extended time is resolved. The advancement in nanotechnology could solve these issues with the formulation of advanced drugs in the nano-scale range. Currently, several nano-based architectures and formulations like nanoparticles (gold, silver, copper, and ruthenium) as nanocarriers, carbon nanotubes, liposomes, micelles, and polymer nanomaterials with superior solubility, sustained release, target specificity, long-duration delivery, and simplification of drug–dose reductions are developed which could act as effective HIV drugs/vaccine transporters in combination with available drugs and formulations. Several nano-based drug delivery approaches are suggested to target the CD4+ T cells, which are the primary target of HIV infection. While using nanoparticle-based drug delivery systems for HIV treatment, usually, three main strategies, such as the intracellular delivery of the anti-retroviral drugs by the polymeric nanoparticles, brain delivery of the anti-retroviral drugs by the polymeric nanoparticles, and use of the polymeric nanomaterials as an adjuvant for the HIV vaccines, are followed.

Conclusion: Though nanotechnology offers many advantages over the conventional system of medications, it also gives rise to many side effects and challenges that need to be rectified for its better application. This review discusses the status and limits of conventional drug treatment and the recent advancements and updated strategies in nano-therapeutics for HIV treatment and cures, along with the possible mechanism of action of nano-mediated drugs, clinical translational challenges, and prospects of advanced nano-drug delivery schemes in HIV prevention and management.

Keywords: nanoparticles, human immunodeficiency virus, nano carriers, drug delivery, antiretroviral drugs, nano formulations

Introduction

A highly prevalent disease, which has caused substantial illness and death during the last three decades, swaying economic growth and social stability worldwide, affecting global health, is commonly called AIDS, acquired immunodeficiency syndrome caused by the HIV (human immunodeficiency virus).[1,2] It continues to persist to date since its first case was reported in the year 1981.[3,4] As per the 2024 HIV Joint United Nations Programme epidemiological data, a projected 1.3 million people have acquired HIV in the year 2023, which is three times of what is targeted for 2025.[5] Usually, HIV is transmitted to the body by several pathways, such as sexual intercourse, from an HIV-infected mother to the child, and also by sharing of intravenous drug injection paraphernalia.[6]

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With the advancement in basic and translational research around the World and more significantly in the USA, several biomarkers associated with HIV and its development have been invented and documented.[7] Based on these HIV-related research, a substantial number of extremely effective oral antiretroviral drugs are permitted and are extensively used currently in combination with other formulations.[8] There are two injectable drugs (rilpivirine and cabotegravir) currently under clinical development for HIV infection.[9,10] However, the cure for HIV and AIDS remains indefinable to date due to a variety of factors.[11] HIV has a high mutation rate and eventually, it deceives the body's immune system, thereby infecting the patient. Further, the mono-drug treatments gave rise to drug-resistant viruses that ultimately led to therapeutic failure.[12] Besides, the use of several traditional HIV vaccines resulted in high side effects and other associated complications, such as a lack of target specificity and difficulties in penetrating the infected cells.[12] Furthermore, the traditional drugs, which exist currently, are only for oral or injectable purposes, and these are not always formed as the ideal formulation for each product.[13,14] Hence, as such, there has not been any significant advancement in the HIV vaccine research and development, and currently, only a few ongoing research studies have been reported, which are under different stages of clinical trials.[1] The most significant hindrance in the development of a highly effective HIV drug is that it should be targeted to the suppression of HIV reproduction without affecting the healthy cells.[1]

With the recent innovations in the field of nanotechnology and nanomedicine, various nanomaterials and nanoformulations have been developed to treat HIV infections and AIDS.[15] A literature search in various data bases like PubMed central and Web of Science, using the keyword, HIV drug delivery (nano), a total of 14,721 articles are published till today and among them, around 12, 651 articles are published during the last 10 years that includes, 11,415 journal articles, 1,195 articles are accepted manuscripts and 41 articles are preprints (https://pmc.ncbi.nlm.nih.gov/search/?term=HIV+drug+delivery+%28nano%29&sort=relevance). Furthermore, another keyword "nano HIV vaccine" resulted in a total of 11,162 articles published till today, and among them 9,892 articles were published during the last 10 years, with 8,926 published as journal articles, 833 accepted manuscripts, and 132 preprints (https://pmc.ncbi.nlm.nih.gov/search/?term=nano+HIV+vaccine). Nanomaterials, like dendritic polymers, polymer micelles, liposomes, and metal nanoparticles, have been reported previously to boost the potential of antiretroviral drugs in the deterrence, identification, and treatment of HIV.[16] It has proven to be a suitable approach to resolve the conventional HIV vaccine-related issues for HIV and AIDS management for three main reasons.[17] Firstly, nanotechnology research is capable of providing an enhanced system for the transmission of HIV vaccines and drugs, and better penetration capability of physiological barriers. Secondly, there are a number of nanoparticles that possess anti-viral properties and they can easily prohibit the replication of HIV in the body by entering and counteracting the virus and snooping with the virus accumulation. Lastly, these are less toxic in nature, which makes them suitable for formulating vaccines and drugs.[1] Besides, these nanomaterials can act as nanocarriers for various HIV drugs because of their improved solubility, controlled release capabilities, and target-specific abilities that enable lessening of the drug doses and targeting the drugs to the desired locations.[15] Furthermore, there are so many reasons to opt for nanoparticle-mediated HIV treatment and drug delivery currently. Protein and nucleic acid-related drugs require better carrier systems for target specificity and to increase their efficaciousness.[18] In such a scenario, the nanomaterials with a smaller size, larger surface area, and enhanced solubility and bioavailability properties could serve as a suitable carrier for HIV medications that can pass the blood-brain barrier (BlBrnBr), penetrate the pulmonary system, and be captivated via the tightened intersections of the endothelial cells in epithelial skin tissues.[19] Besides, nanoparticles are also engineered to exhibit several counterfeits of HIV-1 antigens, which could enhance the immune response and thus can diagnose and react effectively to the virus by prompting a strong antibody and T-cell response. Additionally, nanoparticles provide a harmless and active substitute to live-attenuated viruses, which are otherwise unsafe to use for an HIV-1 vaccine.[20] Recently, several long-acting nanoformulated HIV infection-targeted drugs have been tested for Phase I/II clinical trials.[21] Though the development of highly effective antiretroviral nano-based treatment methodology has extensively boosted the HIV treatment procedure, it also gave rise to many side effects (drug resistance, toxicity, etc) that need to be studied more. Moreover, the application of advanced nanotechnology in HIV treatment should put emphasis on these side effects for better results. Moreover, the acquiescence of various regulatory aspects of using nanotechnology in HIV treatment requires more clarification, and ethical reports should include the detailed guidelines of using HIV related drugs. In this review, the current status and limitations of

conventional HIV drugs, and advancements in the nano drug delivery strategy of HIV treatment and probable mechanisms of nano carrier action on the regulation of HIV infection, and their future directions are discussed.

Background -HIV and Its Pathogenesis

Human immunodeficiency virus, commonly known as HIV, belongs to the Lentivirus genus of the *Retroviridae* family.[22] The viruses share most of the morphological and biological characteristics and cause many long-term ailments with long expectancy in the infected mammals.[22,23] The HIV genome comprises 8 viral proteins essential for its development, and its protein capsid is made of p24viral protein enclosing its single-stranded RNA.[15] The HIV genome encodes various proteins like structural (3 nos)., envelope (2 nos)., accessory proteins (6 nos)., and enzymes (3 nos).[24,25] The HIV capsids are characteristically irregular cones made of capsid proteins that are dissimilar from regular icosahedral capsids.[24,25] HIV is spherical with a diameter of about 120 nm.[1] The lifecycle of HIV consists of 11 phases that includes binding (1), fusion (2), trafficking (3), nuclear import (4), reverse transcription (5), integration (6), transcription (7), translation (8), assembly (9), budding (10) and release/maturation (11) (Figure 1).[26] The figure shows that the initial stage starts with the integration of the virus with the host cell receptor (1) causing fusion of virus and discharge of the viral core to the cytoplasm of the host cell (2). Next, the viral core is transported to the cytoplasm (3) resulting in reverse transcription and nuclear import (4). Then the viral materials reach the nucleus where they move to the active chromatin along with uncoating and reverse transcribing (5). Next step is the integration process (6) followed by the viral gene transcription (7), and translation of the gene (8) into the Gag polyproteins, which assemble (9) and pinpoint to the host membrane, resulting in the development of a nascent virion (10). Then the viral protease enzyme chops the Gag polyprotein into its integral, useful proteins at the end of the HIV-1 lifecycle (11).[26] It can infect $CD4^+$ T cells, macrophages, and microglial cells, causing immunodeficiency.[1] There are two types of HIVs, HIV type 1 (HIV-1), commonly found globally, and HIV type 2 (HIV-2), mostly found in some areas of West Africa.[1] The HIV-1 virus is more contagious than the HIV-2.[1]

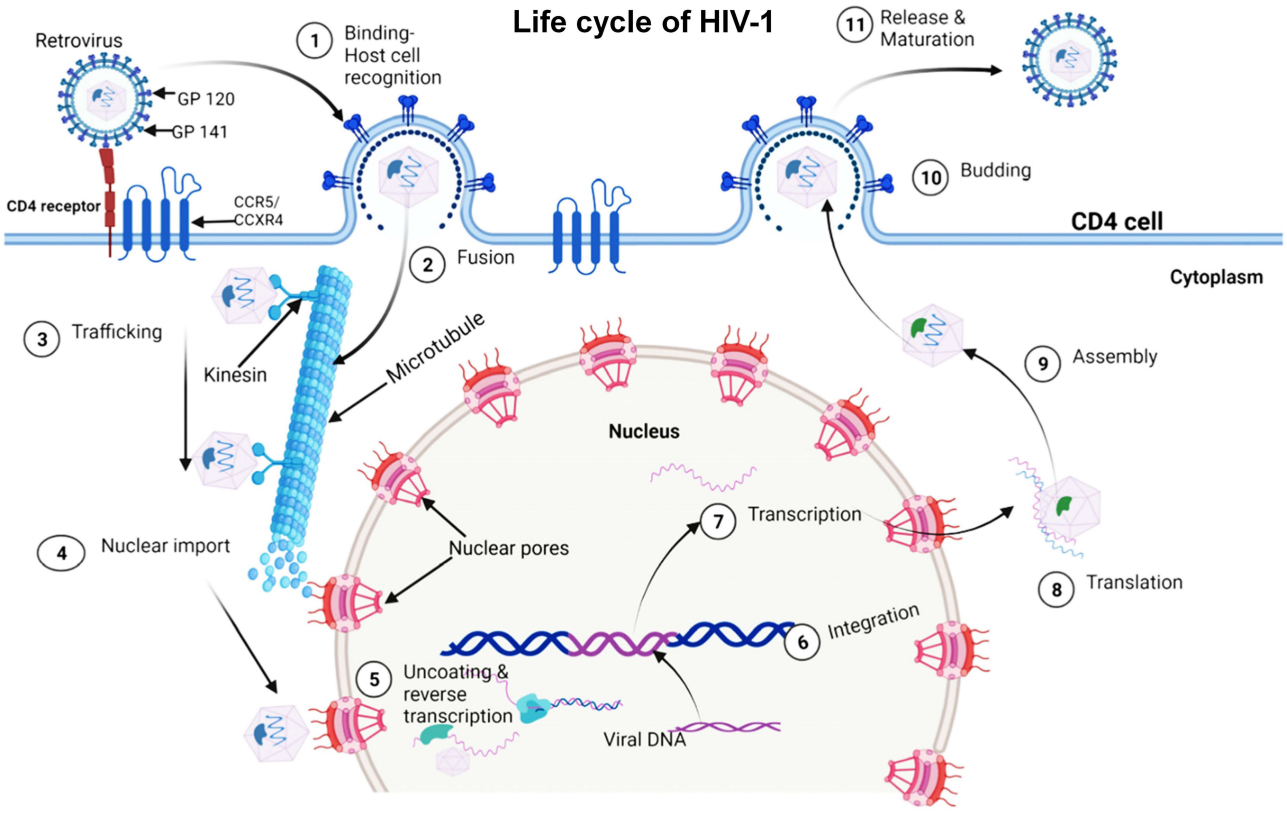

Figure 1 Schematic diagram showing the life cycle of HIV-1 in 11 phases. Reproduced from Masenga SK, Mweene BC, Luwaya E, Muchaili L, Chona M, Kirabo A. HIV–Host Cell Interactions. Cells. 2023; 12(10):1351. © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).[26]

Though AIDS is caused by the HIV-2 virus, the progression of the disease is slower than that of the HIV-1 virus and is usually less spread.[27,28]

The process of HIV infection can be summarized in six steps. The first step of the infection starts with the entering of the virus into the immune cells by adsorbing glycoproteins to cell target receptors. Next, the viral envelope is fused, and the HIV RNA molecule and diverse enzymes (integrase, protease, reverse transcriptase, and ribonuclease) are released in the cell.[1] The second step includes replication and transcription. In this step, the reverse transcriptase enzymes release the single-stranded RNA genome and duplicate it into a complementary DNA molecule.[1] In the third step, after the instructions were translated from the RNA to the DNA, the HIV attaches its DNA to the cell nucleus DNA.[1] In the fourth step, the recombination of the two RNA genomes of HIV occurred.[1] In the fifth step of the HIV viral cycle, the Env polyprotein (gp160) is conveyed to the Golgi complex by the endoplasmic reticulum, forming dual HIV envelope glycoproteins (gp41 and gp120), which enter the host cell membrane (Gp41) and anchor gp120 protein to the infected cell membrane.[1] In the last step, HIV transmits between the $CD4^+$ T cells and buds from a sick T cell and then infects another T cell by entering through the blood.[1]

Besides, HIV can also spread right from one sick T cell to another T cell through the process of virological synapse.[1] In the case of mucosal infection, the infected cells travel to the local lymph nodes, giving rise to the elevated number of HIVs in the naive T cells.[29] The viral infection is then quickly dispersed by the T cells to the lymphoid tissues associated with the bone marrow, intestine, and spleen.[30] In case of the HIV infections in the digestive system, there is a significant loss of $CD4^+$ and $CD8^+$ T cells that cannot recover fully by antiretroviral therapy.[31,32] In simple words, the occurrence of AIDS disease starts with the reduction of $CD4^+$ T-cells and inflation in the blood p24 levels.[15] Moreover, the virus encodes proteins like Vif, Vpr, Nef, and the viral protease enzymes.[15] The negative regulatory factor (Nef) is one of the virulence factors that affects the immune system of human beings by permitting the transmission of the infection, together with protecting and replicating the virus in the human body.[15] The viral glycoprotein formed by the gp120 and gp41 is accountable for virus binding to the host cell receptor (CD4) and its co-receptors (such as CCR5 or CXCR4), which facilitates the entry of the pathogen into the targeted cells.[15]

Current Situation and Restrictions of Conventional Drug Therapy and Treatment for HIV

Precise and speedy diagnosis of HIV significantly affects the clinical treatment of the disease.[16] Currently used traditional diagnostic approaches are mostly influenced by HIV antibody detection in the plasma or the serum by the most sophisticated techniques, such as the ELISA or Western blot assays.[16] Besides such an advancement in HIV diagnosis, there are many lacunae in the techniques, including false positive and false negative results caused by the reactions among the antigens and the samples.[16]

The HIV and AIDS treatment methods can be summarized into five different types. The first one is the use of blockers to halt the HIV binding to the target cells.[1] The second approach uses inhibitors that can inhibit the reverse transcriptase enzyme and the HIV precursor protease enzyme.[1] The third approach utilizes the inhibitors to hinder the expression of the HIV gene.[1] The fourth approach involves blockers to stop the assembly and release of HIV.[1] The fifth approach uses highly active antiretroviral therapy, most commonly called the HAART treatment, to kill the HIV completely.[1]

The ligand receptor and antibody-based HIV treatment are used that interfere with the entry of the virus into the patient's body or for providing therapeutic drugs to the infected cells, with antibodies aiming at the viral proteins and host cell receptors, and ligands aiming at definite cellular receptors on the infected cells.[33,34] The strategies for antibody treatment include neutralization of the antibodies that block the attachment of the virus and bispecific antibodies that involve the immune cells to kill the infected cells. While the ligand-based antibodies use ligands to bind to the receptors on the infected cells, thereby enhancing the drug delivery effects and decreasing the toxicity effects.[34,35] Several pre-clinical and clinical studies have been carried out recently on the development of therapeutic long-term effects on the immune control of HIV-1 when antiretroviral therapy is not available. Advancements in the chimeric antigen receptor technology and enhanced design established that potent HIV-1-specific T cells can be produced.[33] Continuing and strategic clinical trials of anti-HIV-1 chimeric antigen receptor cell therapy could provide further understanding into

the amount of antigen required to activate the cells, the role of C-C chemokine receptor type 5, the in vivo effectiveness, and determination of these reengineered chimeric antigen receptor cells, and their effect on escape mutants.[33]

The HAART treatment approach was suggested for the first time by a Taiwanese-American AIDS scientist, Dr. David Ho, in the year 1996.[36] The HAART treatment process involves the use of 3 or more antiretroviral drugs simultaneously directed towards the infected patient, including a nucleotide reverse transcriptase inhibitor, a protease inhibitor, fusion and entry inhibitors, a nucleoside reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor, and integrase inhibitors.[37,38] Based on the HIV lifecycle and their known molecular targets, a substantial number of highly effective, all FDA-approved HIV medications as of July 31, 2024, are presented in Table 1.[12,39,40] It shows the list of drug classes, their description, and the commercial name of the drug available in the market for use.

Table 1 List of All FDA-Approved HIV Medications

Drug Class	Description@	Name*
Nucleoside Reverse Transcriptase Inhibitors	These inhibitors block the reverse transcriptase enzyme, which is used by HIV to transform its RNA into DNA by the process of reverse transcription. This prevents the replication of HIV.	Abacavir (ABC; Ziagen)
		Emtricitabine (FTC; Emtriva)
		Lamivudine (3TC; Epivir)
		Tenofovir Alafenamide (TAF; Vemlidy)
		Tenofovir Disoproxil Fumarate (TDF; Viread)
		Zidovudine (AZT, ZDV; Retrovir)
Non-Nucleoside Reverse Transcriptase Inhibitors	These inhibitors bind to and block the HIV reverse transcriptase enzyme, which is used by the HIV to transform its RNA into DNA by the process of reverse transcription. This prevents the replication of HIV.	Doravirine (DOR; Pifeltro)
		Efavirenz (EFV; Sustiva)
		Etravirine (ETR; Intelence)
		Nevirapine (NVP; Viramune, Viramune XR [extended release])
		Rilpivirine (RPV; Edurant)
Protease Inhibitors	These inhibitors block the protease enzyme present in HIV and prevent the immature HIVs from becoming mature viruses that can infect other CD4 cells.	Atazanavir (ATV; Reyataz)
		Darunavir (DRV; Prezista)
		Fosamprenavir (FPV; Lexiva)
		Ritonavir (RTV; Norvir)
		Tipranavir (TPV; Aptivus)
Fusion Inhibitor	A fusion inhibitor blocks the HIV envelope from integrating with the host CD4 cell membrane by the process of fusion and prohibits HIV from entering the CD4 cell.	Enfuvirtide (T-20; Fuzeon)
CCR5 Antagonist	It blocks the CCR5 co-receptor on the surface of certain immune cells, such as CD4 cells, and prevents the entry of HIV into the cell.	Maraviroc (MVC; Selzentry)
Integrase Strand Transfer Inhibitors	It blocks the integrase enzyme that is used for the integration of HIV's viral DNA into the DNA of the host CD4 cell and prohibits the replication of the virus.	Cabotegravir (CAB; Vocabria)
		Dolutegravir (DTG; Tivicay)
		Raltegravir (RAL; Isentress, Isentress HD)
Attachment Inhibitor	It interferes with the early interaction between the gp120 protein on the HIV outer surface and the CD4 receptor on the host CD4 T cells and thus prohibits HIV from binding and entering CD4 cells.	Fostemsavir (FTR; Rukobia)
Post-Attachment Inhibitor	It binds to the CD4 receptor on a host CD4 cell and blocks HIV from attaching to the CCR5 and CXCR4 co-receptors and entering the cell.	Ibalizumab-uiyk (IBA; Trogarzo)

(*Continued*)

https://doi.org/10.2147/IJN.S540578

Table 1 (Continued).

Drug Class	Description[@]	Name*
Capsid Inhibitor	It interferes with the protein shell capsid of HIV that protects its useful genetic material and enzymes. It can affect the capsid at various stages of the HIV life cycle.	Lenacapavir (LEN; Sunlenca)
Pharmacokinetic Enhancer	It is used to boost the efficacy of another drug during the combination treatment of two drugs. It interferes with the breakdown of the other drug, which permits the drug to stay inside the body for a longer period at a greater concentration.	Cobicistat (COBI; Tybost)
Combination HIV Medications	It involves the regular use of HIV medications in combination, which includes three antiretroviral drugs from at least two different HIV drug classes.	Abacavir/Lamivudine (ABC/3TC; Epzicom)
		Abacavir/Dolutegravir/Lamivudine (ABC/DTG/3TC; Triumeq, Triumeq PD)
		Abacavir/Lamivudine/Zidovudine (ABC/3TC/ZDV; Trizivir)
		Atazanavir/Cobicistat (ATV/COBI; Evotaz)
		Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF; Biktarvy)
		Cabotegravir/Rilpivirine (CAB/RPV; Cabenuva)
		Darunavir/Cobicistat (DRV/COBI; Prezcobix)
		Darunavir/Cobicistat/Emtricitabine/Tenofovir Alefenamide (DRV/COBI/FTC/TAF; Symtuza)
		Dolutegravir/Lamivudine (DTG/3TC; Dovato)
		Dolutegravir/Rilpivirine (DTG/RPV; Juluca)
		Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF; Delstrigo)
		Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF; Atripla)
		Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate (EFV/3TC/TDF; Symfi, Symfi Lo)
		Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/COBI/FTC/TAF; Genvoya)
		Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF; Stribild)
		Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF; Odefsy)
		Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF; Complera)
		Emtricitabine/Tenofovir Alafenamide (FTC/TAF; Descovy)
		Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF; Truvada)
		Lamivudine/Tenofovir Disoproxil Fumarate (3TC/TDF; Cimduo)
		Lamivudine/Zidovudine (3TC/ZDV; Combivir)
		Lopinavir/Ritonavir (LPV/r; Kaletra)

Notes: [@]Descriptions data from Glossary of HIV/AIDS-Related Terms (https://clinicalinfo.hiv.gov/sites/default/files/glossary/Glossary-English_HIVinfo.pdf);[40] *With Brand Names and Abbreviations. Source: www.HIVinfo.NIH.gov.[40]

This HAART treatment process stabilizes the disease symptoms considerably, thereby extending the survival percentage of the patient to a greater rate.[37] While there has been substantial progress in these drug therapies, and it has contributed immensely towards the management of HIV infections, a number of limitations and issues always persist in patients, which are presented in the following figure (Figure 2). Usually, three types of issues are raised during the process of management of HIV, which includes the issue of long-acting and extended release resulting in non-compliance, fatigue due to taking so many drugs and failure of the treatment process; the issue of combination therapy resulting in gene mutation, resistance of multiple drugs and lower efficiency of the available drugs; and the targeting of virus reservoirs resulting in lack of target specificity and several side effects.[12] Unlike other viral infections, HIV is a specific type of retrovirus that targets the $CD4^+$ T cells, the main coordinators in the immune system of the body. The HAART treatment could not cure the patient completely, nor could it reduce the AIDS symptoms. It cannot eradicate HIV from the infected patients' body parts, specifically from the brain, intestine, kidney, liver, testis, and lymphoid tissues.[41] On the other hand, the HAART treatment is not able to eradicate the HIV-1 virus from resting in the blood $CD4^+$ T cells since the virus is already present in dormancy form at several sites in the patient's body.[42] It can trigger fresh infections in the tissues with less exposure to drugs, such as the brain and lymph nodes, between the administration of oral doses.[43] Despite the HAART treatment, the suppressed sick cells may seepage the viral immune response and continue to live for a longer time in the body and favorable conditions; these cells can reactivate and cause HIV infections again in the body.[44] In case of less drug exposure, the virus in the affected tissues could proliferate at lower concentrations and could enter the slow-replicating memory T cells' DNA, and vigorously-duplicating $CD4^+$ T cells.[43] Because of these properties, the memory $CD4^+$ T cells are deliberated as a precarious pool of latent HIV-1 proviral DNA.[44] The cost of HIV medication is too high considering the long-term use of the drugs. Several aftereffects of HIV drug use for a longer period, such as headache and dizziness, puffiness of the mouth, and injury to the liver and immune system, are reported.[41] Furthermore, there are some side effects like lipodystrophy, hyperlipidemia, and osteoporosis, which appear after months or years of taking the HIV medications.[41]

Complete removal of the HIV from the body of an infected patient is almost impossible due to the viral reservoirs such as the cellular (astrocytes, B-cells, T-cells, macrophages, dendritic cells, microglia, natural killer cells, monocytes, etc.) and tissue reservoirs (central nervous system, lungs, spleen, kidney, gut-associated lymphoid tissue, and reproductive organs, etc).[45] Besides, for the removal of the virus from these reservoirs, early diagnosis and therapy with a more effective bioavailability and drug delivery approach is required.[46] In the case of conventional vaccination methods, usually, a live or dead virus component is used as a vaccine for the development of antibodies in the injected person's body. However, this is not the case for HIV infection, as live HIV cannot be used since it is very virulent, and a dead virus does not retain the antigenicity that could trigger the body's immune system to develop antibodies.[47,48] Considering all these issues associated with the current HIV and AIDS treatment process, scientists have started looking for the most advanced medication and treatment procedures, which could be highly effective, reliable, less toxic, and above all, low-

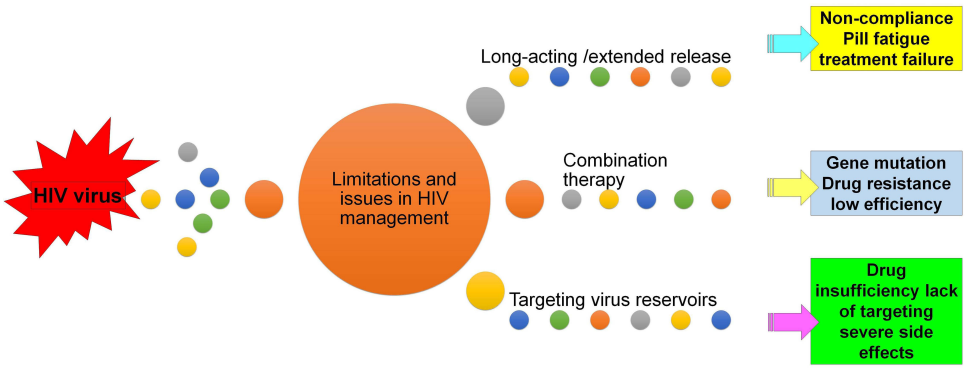

Figure 2 Limitations of HIV treatment. Adapted with permission from Gao Y, Kraft JC, Yu D, Ho RJ. Recent developments of nanotherapeutics for targeted and long-acting, combination HIV chemotherapy. Eur J Pharm Biopharm. 2019;138:75–91.[12]

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cost. In such a scenario, the advanced nanotechnology approach could prove to be effective, and an HIV vaccine can be formulated, or the most advanced AIDS treatment procedure can be designed.

NP in HIV Treatment and Diagnosis

Currently, the advancement in the field of nanotechnology and Nanomedicine has shown encouraging results in the diagnosis, eradication, and cure for the dreadful disease HIV and AIDS, particularly in the drug delivery and detection of virus.[18] The conventional systems of HIV drug delivery have a series of issues, such as low availability, limited targeting, site specificity, drug resistance, and inefficient drug release, and thus, maximum efficiency cannot be attained.[49] In such a case, an urgency in the development of modern scientific technology is required, which could solve the above issues and regulate the drugs for controlled drug delivery with maximum accuracy.[50] The controlled release of HIV drugs is very much crucial in the HIV/AIDS treatment since the maintenance of drug levels in plasma at a tenacious rate in the body for a prolonged period is the key to the success of these drugs. In addition, without the proficient delivery machinery, the whole HIV treatment process is much less effective. The idea of formulating nano-drugs is not new, and many nano-sized drug candidates such as nano-emulsions, colloidal nanoparticles have already been used in the pharma sectors.[12] Recently, research on advanced nano drug delivery systems has gained momentum for developing target and site-specific combination drugs to meet the current requirement in the HIV drug management and cure.[12] In addition, through the nanotechnology methodology, the nano-drug delivery of anti-retroviral drugs and target-specific delivery of drugs could impart better efficacy to HIV therapy.[1,2] In order to attain the target-specific nano drugs, it is important to surface-modify the drug-loaded nano-carrier with a targeting ligand with high specificity towards the chosen target, which will guarantee the entry of the carrier drug only into the preferred cells without affecting the adjacent non-targeted cells. Specific properties such as the physical nature, varying size, and suitable chemical properties of the nanoparticles have made them an effective tool for developing drug candidates in HIV treatment. Nanomaterials can be designed as per the requirement; they can be customized to different surface charges, nontoxic, biodegradable, etc., to make them target specific and cell-specific, and these characteristics add to amplified bioavailability of drugs and diminished peripheral toxicity and other side effects.[51,52] The nanoparticles are solid, colloidal particles of varying sizes (10 to 100 nm). It is ideal to dissolve, entangle, absorb, or attach a specific drug in the nanoparticle and reduce its size and properties to the nanometer scale.[44] Thus, the properties and efficiency of the drug candidate can be improved since the nanoparticles can protect against the degradation of drugs during storage and inside the body's fluid.[53] It can also be targeted to specific locations of the patient's body by modifying its surface charge with added ligands, surfactants, polymers, etc.[44,54] Further, the drug release capacity can also be improved by nanoencapsulation.[44,55] Drugs in sustained-release nanocarrier systems are able to decrease the metabolism and cellular efflux, thereby extending the retention of an adequate amount in the target cells.[12] Besides, the nano-drug delivery system is able to integrate medications with diverse physicochemical properties to fight against drug resistance.

Several types of nanomaterials (solid lipid nanoparticles, dendrimers, liposomes, nano-emulsion, carbon nanotubes, polymeric nanoparticles, micelles, and nano-mediated lipid carriers, etc.) are formulated to develop anti-HIV treatments and used as vaccine adjuvants for improving the defensive immune responses, etc.[2,47,56–59] Further, nanovector-mediated delivery of antiretroviral drugs has been reported to show positive outcomes in the treatment of HIV infections.[60,61] Apart from being used as a drug carrier system, nanomaterials (like gold, silver, copper, and ruthenium) and their derivatives of ligands have also been reported to possess anti-HIV effects by reversing the transcriptase inhibitor (atevirdine), and protease inhibitor (VX-950).[62] Some of the major nanomaterials used in the treatment of HIV are shown in Table 2.[2] The table shows the types of nano-carrier used, the therapeutic agents attached to the nanomaterial, the drug details such as the size and charge of the nanoparticle used, the drug loading percentage, in vitro/ in vivo efficacy of the drug, and its delivery route, along with the drug target and its effects. Taken together, all these benefits exhibited by the nanomaterials and nanocarrier drug delivery could enhance patient acquiescence and overall therapeutic consequences.

Strategies of Nanoparticles in the HIV Treatment

It is said that the nanotechnology-based HIV drug delivery methodology is only applicable either passively or actively on the reservoir sites of the virus to help in the elimination of the infection.[60] Besides, several nano-based drug delivery

Table 2 Major Nanomaterials Used in the HIV Treatment

S. No.	Nano Carriers	Therapeutic Agent	Drug Details	Therapeutic Target	Outcomes	Reference
1	Poly(lactide-*co*-glycolide)	Lamivudine	Drug loading %: dose of 10 mg/kg, delivery route: intravenous	Nucleoside/Nucleotide Reverse Transcriptase	Mannosylated-PLGA targeted effectively to the mannose receptors of macrophages	[63]
		Efavirenz	Particle size: 73 nm, drug loading %: 10.8%, in vitro/in vivo efficacy: Demonstrated a continuous in vitro release of efavirenz of 50% within the first 24 h, and delivery route: intravenous	Non-nucleoside Reverse Transcriptase	Enhanced bioavailability of the drug and rapidly permeating BBB	[64]
		Didanosine	Particle size: 679 nm (G5), surface charge: −11.2±0.37mV (zeta potential), drug loading %: 33.87% (G5), in vitro/in vivo efficacy: Didanosine was found to release from the experimental formulations over a extended time with 35% (G5) of drug release occurred in about 30 days, and delivery route: parenteral administration	Nucleoside/Nucleotide Reverse Transcriptase	Enhanced uptake of the drug encapsulated in PLGA nanoparticles by macrophages infected by HIV	[65]
2	Poly (L-lactic acid)	Zidovudine	Particle size: 328.1 ± 8.6 nm (PLA/PEG blend), surface charge: −6.5 ± 2.1 mV (zeta potential), drug loading % 160 μg mL^{-1}:, in vitro/in vivo efficacy: The greatest efficacy was obtained with poly(l-lactide) and poly(llactide)–poly(ethylene glycol) blend nanoparticles (mean half-life – 7.01 h), that displayed Zidovudine sustained release over 24 h, and delivery route: intranasal administration	Nucleoside/Nucleotide Reverse Transcriptase	Enhanced uptake of the drug encapsulated in PLA–PEG blend nanoparticles taken by the intranasal route	[66]
		Zidovudine	Particle size: 265.8 nm (poly(l-lactide) nanoparticles, surface charge: −20±1.2 mV (zeta potential), drug loading: 250 mg/mL, in vitro/in vivo efficacy: The poly (l-lactide) nanoparticles were more proficiently phagocytosed than poly(l-lactide) / poly(llactide)–poly(ethylene glycol) (1:0.25) blend ones., and delivery route: cell line study	Nucleoside/Nucleotide Reverse Transcriptase	Conventional PLA nanoparticles induced phagocytosis by macrophages efficiently than PLA–PEG blend	[67]
3	Poly(capro-lactone)	Saquinavir	Particle size: Saquinavir-Loaded poly(ethylene oxide)-modified poly(epsilon-caprolactone) nanoparticle of 271.0 nm, surface charge: −26.2 mV, drug loading %: 28 mg/mg (60%), in vitro/in vivo efficacy: Intracellular saquinavir concentrations when administered in the nanoparticle formulation were significantly higher than from aqueous solution, and delivery route: THP-1 human monocyte/macrophage cell line study	Protease	Enhanced uptake of saquinavir by monocyte/ macrophage cells	[68]
		Indinavir	Particle size: 211 nm, drug loading % efficiency: 76.26%, and delivery route: Caco-2 cells as a cellular mode)	Protease	Improvement in the uptake of orally administered drugs	[69]
		Lopinavir	Particle size: 320 nm, drug loading %: 17%, in vitro/in vivo efficacy: Encapsulation efficiency was 66%. Substantial decrease in lopinavir-loaded Polycaprolactone-based nanoparticles could be expected, as the drug entrapped in the Polycaprolactone matrix was unavailable for metabolism.	Protease	Enhanced oral bioavailability of the drug	[70]

(*Continued*)

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Table 2 (Continued).

S. No.	Nano Carriers	Therapeutic Agent	Drug Details	Therapeutic Target	Outcomes	Reference
4	Chitosan nanoparticles	Lamivudine	Chitosan nanoparticle was purchased commercially and loaded with Lamivudine, in vitro/in vivo efficacy: 0.1μM of Nano-Lamivudine was considered as the most effective dose of all, and delivery route: HEK293T cell line study	Nucleoside/Nucleotide Reverse Transcriptase	Reduction of viral load in HIV infected macrophages	[71]
		Tenofovir	Particle size: 602.43 nm, surface charge: 55.23 mV, drug loading %: 1.14%, in vitro/in vivo efficacy: The in vitro release, cytotoxicity assays, and mucoadhesive studies suggested that relatively large chitosan nanoparticles have the potential to be a controlled release, safe, and bioadhesive microbicide delivery system, and delivery route: cell line study	Nucleoside/Nucleotide Reverse Transcriptase	Prevention of HIV transmission by microbicide-loaded nanoparticles	[72]
		Saquinavir	Particle size: Saquinavir-loaded chitosan nanoparticles of 211 nm, surface charge: 24.4 mV, in vitro/in vivo efficacy: The saquinavir-loaded chitosan nanoparticles were found to exhibit superior potency than the free drug even in nanogram levels, and delivery route: human embryonic kidney HEK293T cell line study.	Protease	High efficiency in targeting the HIV infected cells and control of viral proliferation at the early stages	[73]
5	Carbosilane dendrimers	Zidovudine, Tenofovir, Efavirenz	In vitro/in vivo efficacy: The sulfated Carbosilane dendrimers (G3-S16) and naphthyl sulfonated Carbosilane dendrimers (G2-NF16) showed a synergistic or additive activity profile with zidovudine, efavirenz, and tenofovir in the majority of the combinations tested against the X4 and R5 tropic HIV-1 in cell lines, as well as in human primary cells, and delivery route: TZM-bl cell line HeLa cell line, C-X-C chemokine receptor type 4 X4-HIV-1_{NL4-3} and CCR5-tropic R5-HIV-$1_{NL(AD8)}$ virus strains.	Nucleoside/Nucleotide Reverse Transcriptase and Non-Nucleoside Reverse Transcriptase	Formulation increased the antiviral potency of the drugs	[74]
	Poly(propylene imine) dendrimers	Efavirenz	Entrapment efficiency of poly(propyleneimine) dendrimer (32.35%) to mannosylated poly(propyleneimine) dendrimer (47.4%) and t-Boc–glycine conjugated poly(propyleneimine) dendrimer (23.1%), in vitro/in vivo efficacy: Mannosylated poly(propyleneimine) dendrimers could be an active carrier system for targeted efavirenz delivery and probably other antiretroviral bio-actives, and delivery route: intracellular delivery.	Non-nucleoside reverse transcriptase	Reduction in viral load when compared with the free drug	[75]
6	Liposomes	Saquinavir	Particle size: 176.60 nm for Saquinavir loaded liposomes with PEG, surface charge: −35.50 mV (zeta potential), in vitro/in vivo efficacy: 14% of saquinavir was released from the PEGylated liposome in 30 min with complete drug release at 50 h of incubation, and delivery route: cell line study	Protease	Enhanced cellular uptake and exhibited good colloidal stability	[76]
		Efavirenz	Particle size: 411.10 nm for encapsulated efavirenz-loaded liposomes, surface charge: − 53.5.3 mV, in vitro/in vivo efficacy: Encapsulated efavirenz-loaded liposomes exhibited a comparatively measured encapsulated efavirenz release behavior that was comparable to the suspension profile of unencapsulated efavirenz.	Non-nucleoside reverse transcriptase	Enhanced targeted delivery to the infected lymphocytes	[77]
7	Ethosomes	Lamivudine	Particle size: 72 nm ethosomes with 60% ethanol, surface charge: –9.5 mV, % Entrapment Efficiency: 19.5%, in vitro/in vivo efficacy: The results of the imagining study specify that ethosomal formulation affected the normal histology of skin by generating lipid perturbation and enhancing the intercellular lipid lamellae space of the stratum corneum of the skin, and delivery route: skin permeation.	Nucleoside/Nucleotide Reverse Transcriptase	Efficiently crossed the skin compared to the free drug	[78]

8	Silver nanoparticles	–	Particle size: 2.48 nm, surface charge: 51.5 mV, in vitro/in vivo efficacy: HIV-1 protease and silver nanoparticles stay in a competitive relationship: the interaction rate between HIV-1 protease -peptide and silver nanoparticles-peptide is dissimilar, with the former being faster than the latter	Protease	Nontoxic and enhanced inhibition of HIV – 1 protease	[79]
		–	Particle size: 12 to 28 nm, in vitro/in vivo efficacy: HIV-1 Reverse Transcriptase was repressed by the silver nanoparticles with an IC_{50} value of 0.4 µg/mL, and delivery route: in vitro study using HIV Reverse Transcriptase	Reverse Transcriptase	Low doses of AgNPs showed high HIV inhibitory activity	[80]
9	Gold nanoparticles	Abacavir, Lamivudine	Particle size: 3 nm glucose-coated gold nanoparticles, drug loading %: around 10% of Abacavir and Lamivudine, in vitro/in vivo efficacy: The antiviral activity was confirmed by assessing the imitation of NL4-3 HIV strains in luciferase reporter infected cell line. The drugs were released from the glyconanoparticles in acidic conditions and were able to hinder viral replication in cellular assays with IC_{50} values of less than 10 µM, which is similar to the free drugs, and delivery route: cell line study.	Nucleoside/Nucleotide Reverse Transcriptase	Increased antiviral activity against HIV	[81]
		–	Particle size: 2 nm, in vitro/in vivo efficacy: 50% density of sulfated ligands on around 2 nm size nanoparticles is adequate to attain anti-HIV actions which are equivalent to those acquired with sulfated ligand-coated nanoparticles, and delivery route: MT-2 cell line study.	gp120	AuNPs bind with gp120 and inhibit HIV activity	[82]
10	Magnetoelectric nanoparticles	Zidovudine	Drug loading %: 24% after 3 h incubation, in vitro/in vivo efficacy: Owing to the intrinsic magnetoelectricity, these nanoparticles can pair with external magnetic fields with the electric forces in the drug–carrier bonds to allow distantly controlled delivery without using heat, and delivery route: In vitro experiments on HIV-infected human cells.	Nucleoside/Nucleotide Reverse Transcriptase	Upon applying the magnetic field externally, it crossed the BBB	[83]

Notes: The table was reproduced with permission from Soundararajan D, Ramana LN, Shankaran P, Krishnan UM. Nanoparticle-based strategies to target HIV-infected cells. Colloids Surf B. 2022;213:112405. (Source Table 1).[2] with more added information.

approaches are suggested to target the $CD4^+$ T cells, which are the primary target of HIV infection. Some of these remedial factors include antiviral siRNA or antiretroviral drugs targeted to $CD4^+$ T cells to avert the replication of HIV.[84] In the case of the nano-based drug delivery methodology, the immune response swayed by them usually depends on the potentiality of the vaccine, and the nanomaterial vaccine conjugates aid in target specificity.[85] Usually, three main strategies are followed while using nanoparticle-based drug delivery systems for HIV treatment, and these include the intracellular delivery of the anti-retroviral drugs by the polymeric nanoparticles; brain delivery of the anti-retroviral drugs by the polymeric nanoparticles, and use of the polymeric nanomaterials as an adjuvant for the HIV vaccines.[44]

The term, blood-brain barrier (BlBrnBr) is given to the obstruction caused between the blood capillary and the brain's interstitial fluid. It constitutes a basement membrane, endothelial cells, neuroglial membrane, and the projections of astrocytes. It hinders the passage of substances or drugs in the central nervous system (CNrS).[86–88] The BlBrnBr, along with its aftereffects, makes the treatment of neurological disorders a difficult affair.[89] Several viruses, including HIV, can easily cross this BlBrnBr endothelium by viral transcytosis and infect the CNrS. However, this barrier obstructs the entry of antiretroviral drugs into the infected site, thereby diminishing the treatment of HIV-associated neurocognitive disorders like neuroinflammation and brain damage in the infected person.[89–92] Nano-based drug delivery strategies could be effective in penetrating these BlBrnBr to deliver the drugs to the targeted sites and targeted cells, thereby enhancing the effect of the HIV drugs by many folds.[93] Specific versatile properties of nanoparticles (enormous surface-to-volume ratio, nanoscale range, external charge, etc. made them an effective nano-carrier for advanced drug delivery through the BlBrnBr to the CNrS.[94] Various modifications in the nanocarrier material properties can be made to make them target specific, for example, for targeting them to the CNrS, the surface coupling of specific molecules and ligands can be done so that they can pass through the BlBrnBr to reach the targeted HIV-reservoir locations.[95] Besides, another strategy is the transporter-mediated nano delivery of drugs that facilitates easy penetration of nanomaterials into the BlBrnBr on the principle of using transporters expressed on endothelial cells at the BlBrnBr by recognizing and binding to target antigens or receptors, which are well-expressed or subjectively expressed by specific cells or tissues.[93] Likewise, antiretroviral drugs attached to nanomaterials have been effectively used in treating HIV infection in the CNrS because of their target specificity and bioavailability properties.[96] Figure 3 demonstrates the entry of HIV into the brain interstitial area over the BlBrnBr to infect the microglia, causing HIV infection.[88] Later, the nano-based HIV drug (nano silver + highly active anti-retroviral drug) penetrates the BlBrnBr and cures the infected cells. It shows that nano-mediated antiretroviral drugs prove more effective by inhibiting HIV duplication with fewer neurocognitive illnesses.[88,97–99]

In a study by Endsley and Rodney,[84] the authors formulated a lipid nanoparticle targeting the $CD4^+$ cells and enclosed an anti-retroviral drug indinavir. The author concluded that the drug candidate could provide a selective binding to the $CD4^+$ cells by delivering the drugs to them, thereby improving the anti-HIV effect of the drug even in the dynamic washout conditions, also.[84] In another study, Soundararajan et al,[2] have discussed how a surface-altered gold nanoparticle conjugated with an antiretroviral medication provides binding sites to the free HIVs so that they cannot bind to the CD4 cells, thus preventing infection in patients (Figure 4).

Reports say that the nano co-crystal hydrogels (PF-127 hydrogels and chitosan) have effectively enhanced the bioavailability, lessened the use of the drugs, and extended dosing frequency.[16] A study by Kumar et al,[100] showed that a lactoferrin nanoparticle-loaded tripartite drug amalgamation of efavirenz, lamivudine, and zidovudine was helpful in enhancing the efficacy and decreasing toxicity in the infected patients. The author concluded that this nanoparticle drug combination could enhance the bioavailability of drugs with decreased side effects and tissue-related inflammation.[100] A similar study on the porous iron (III) carboxylates-based metal-organic frameworks displayed promising effects on the loading of busulfan- an alkylating agent widely used in chemotherapy, conferring the use of nanoparticles as nanocarriers in HIV-controlled drug delivery treatment.[101] In another study, Abadi et al,[102] showed that gold nanoparticles combined with the drug tenofovir displayed promising anti-HIV-1 and anti-HIV-1 protease activities. Similarly, Gong et al[103] developed a poloxamer-based nanoformulation loaded with elvitegravir- an antiretroviral drug and studied their biocompatibility, stability, protein corona, and cellular internalization pathway for its possible clinical interpretation. The author has also studied the effect of the drug combination on the BlBrnBr and suppression of HIV-1 infections.[103]

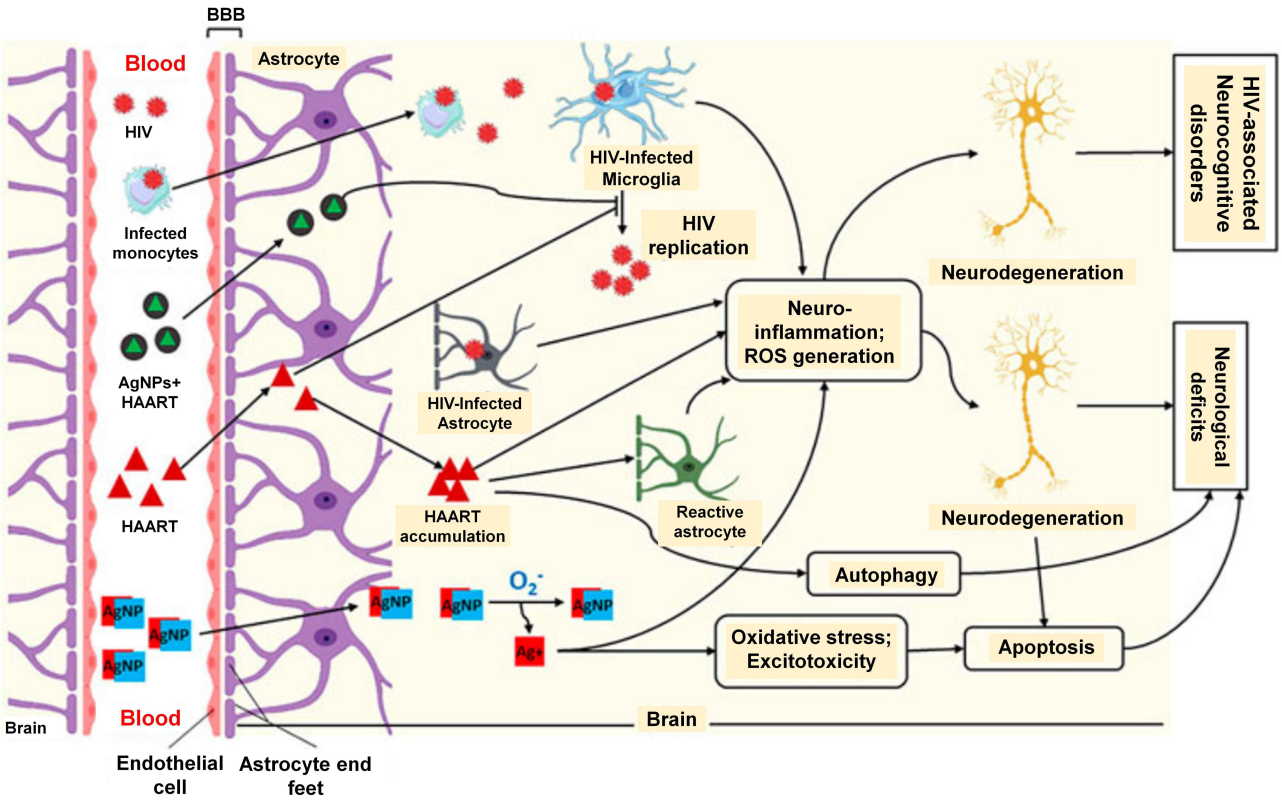

Figure 3 Nano-based antiretroviral drug therapy and its mechanism of action. Reproduced from Lawal SK, Olojede SO, Faborode OS, et al. Nanodelivery of antiretroviral drugs to nervous tissues. *Front Pharmacol.* 2022;13:1025160. © 2022 Lawal, Olojede, Faborode, Aladeyelu, Matshipi, Sulaiman, Naidu, Rennie and Azu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).[88]
Abbreviation: AgNPs, silver nanoparticles; HAART, Highly Active Antiretroviral Therapy; BBB, blood-brain barrier.

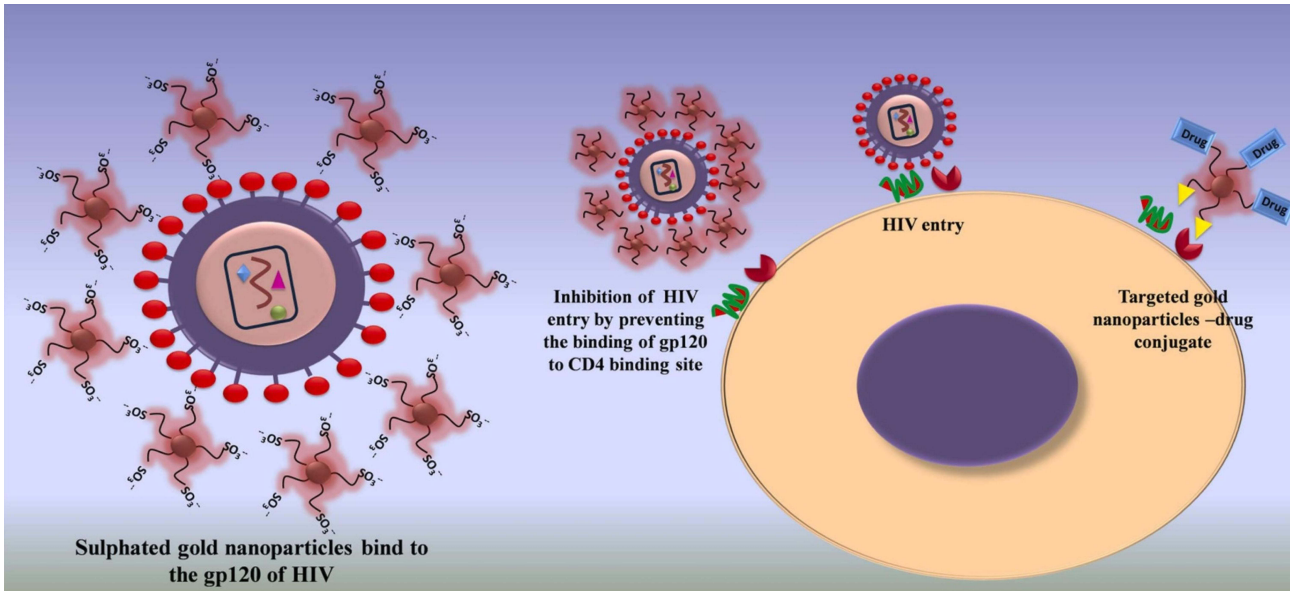

Figure 4 Schematic diagram showing the selective adherence properties of gold nanoparticles with HIV. Reproduced with permission from Soundararajan D, Ramana LN, Shankaran P, Krishnan UM. Nanoparticle-based strategies to target HIV-infected cells. Colloids Surf B. 2022;213:112405.[2]

Several applications of lipid-based nanomaterials in HIV treatment have been developed recently.[104–106] Lipid nanoparticles can deliver antiretroviral drugs effectively due to their ability to lower the toxicity of these drugs, and are easy to synthesize, offering functionalization abilities, targeted specificity, measured release of drugs, and improved

load capability.[104,105] In a review by Suriyarachchi and Katuwavila,[104] the authors have discussed the types of liposomal formulations used in the treatment of HIV/AIDS (Table 3). The table shows the different types of liposomes on the basis of their configuration and applications, the specific drugs loaded into the liposomes, and their significance in treating HIV.

Zhou et al[105] have discussed the application of lipid nanoparticles in the management of several diseases, including HIV. Rojekar et al[115] studied the designing of a nanostructured lipid carrier surface-modified with selenium nanoparticles and loaded with efavirenz, which displays synergistic targeting ability against HIV-1 infection, improves the intracellular antioxidant balance, and increases the effectiveness of long-term HIV therapy. Likewise, Joshy et al[116] synthesized a gelatin-modified hybrid polymeric lipid nanoparticle which could encapsulate the antiretroviral drug candidate, zidovudine, and provide a sustained release of the drug in the targeted site.[116] In a study by Bazargani et al,[117] the authors formed solid lipid nanoparticles with variable PEGylation levels (0–15% w/w of PEGylated lipid), co-encapsulated with Elvitegravir and Atazanavir as an integrase and protease inhibitor, respectively. This encapsulated nano-based drug candidate was able to overcome issues like enzymatic degradation in the nasal mucosa, low penetrability, and mucociliary clearance within the nasal cavity for the intranasal drug administration in HIV treatment.[117] Islam et al,[118] have developed a fostemsavir encapsulated lipid nanoparticle formulation that could prevent HIV-1 infection. This drug formulation was able to create a drug depot in the monocyte-derived macrophages that prolonged the drug's plasma residence time.[118]

The cell-penetrating peptides are the most important candidate in the adsorptive-mediated transcytosis mechanism that is used as the nanoparticle surface targeting elements. These ligands enable superior intracellular drug delivery by the process of endocytosis or by the creation of a transitory assembly with the cell membrane.[119] At present, the HIV-1 Tat peptide is among the best extensively verified cell-penetrating peptides.[120] Furthermore, these peptide ligands possess protein-transduction domain regions that can help pass through the biological membranes.[120] In the case of the BlBrnBr, the entry of the drug is not dependent on the transporters and receptor-mediated endocytosis; rather, it depends on the combination of β-galactosidase enzymes to Tat peptide.[121,122] Using a nanocarrier for the delivery of drugs has several benefits, such as controlled release of drugs, site and target specificity, enhanced solubility of a less soluble drug candidate, and enhanced bioavailability of the medication for an extended time with less toxicity.[123,124]

Similarly, in the case of HIV diagnosis, various nano-mediated biosensors are developed and tested. Hu et al,[125] developed a 3,4,9,10-perylene tetracarboxylic acid functionalized graphene sheets and decorated them with gold nanoparticles with an amine-terminated ionic liquid and tested them for the presence of the pol gene of HIV 1 in patients. In another study, Jia et al,[126] a bimetallic NiCo-based metal-organic framework pyrolyzed into an innovative complex encompassing $NiCo_2O_4$ spinel, CoO, and metallic Co/Ni nanoparticles entrenched with carbon nanotubes was used as a bio-platform for electrochemical biosensors for HIV-1 gene identification. Diao et al,[127] formulated a surface plasmon resonance (SPR) biosensing approach based on double-layer DNA tetrahedrons and dynamic entropy-driven chain shift reactions for the diagnosis of enzyme-free or label-free HIV.[127] Several biosensors are established for identifying HIV-1 proteases, including SPR and quartz crystal microbalances. Esseghaier et al,[128] have established a new sensing assay using a gold sensor for label-free recognition of HIV-1 protease, useful in the diagnosis of HIV-1 virus. Yang et al,[129] formulated a quick detection kit by conjugation of the HIV antigen gp41 and gp36, using a nano-immunomagnetic lateral method for detecting HIV. In another review study, Patil et al,[130] the authors have critically examined the potential of nanocarrier-based preparations, such as solid lipid nanoparticles, lipid nanoemulsions, supersaturated self-nanoemulsifying drug delivery systems, poly(lactic-co-glycolic acid) nanoparticles, and cubosomes, in elevating darunavir (a nonpeptidic protease inhibitor) pharmacokinetics in the antiretroviral treatment of HIV.

Possible Mechanism of Action of Nano-Mediated Drugs on HIV Treatment

The current HIV infection treatment has some drawbacks. Understanding the mechanism of actions of nanoparticle-mediated drug delivery and their effect on HIV treatment is of utmost importance to better apply the advanced technology effectively. Nanomaterials are used in HIV treatment in various ways, such as carriers for nano drug delivery, nanoformulations, etc., and hence it is essential to understand their mechanism of action. Some possible mechanisms of action of nano-mediated HIV treatment are discussed below.

Table 3 Different Types of Lipid-Based Nanoformulations Used in the HIV/AIDS Treatment

Main Types of Liposomes Based on Their Composition and Application	Liposome Type	Drug Loaded	Significance	Reference
Charged liposomes	Cationic liposomes	Sifuvirtide	Liposomes containing sifuvirtide showed effective delivery and concentration of the drug towards the viral and lipid raft vicinity.	[107]
Stealth stable liposomes	PEGylated liposomes	Saquinavir	The PEGylated liposomal delivery to mammalian cells in culture showed sustained release, with an encapsulation efficiency of about 33%. Lesser cytotoxicity was observed in the cell viability studies as compared with the non-PEGylated liposomes.	[76]
	PEGylated elastic liposomes	Zidovudine	Elastic liposomes increased the transdermal flux compared with the free drug. Elastic liposomes showed improved lymphatic accumulation of the drug.	[108]
	Polyunsaturated endoplasmic reticulum liposomes (PERLs)	Polyunsaturated fatty acids	PERLs showed greater activity by reducing intracellular cholesterol than lovastatin. Due to decrease plasma membrane cholesterol levels, the ability of the hepatitis C virus or The time it takes for HIV to establish an infection was found to decrease.	[109]
	Lyophilized liposomes	Zidovudine	When used to target the reticuloendothelial system, lyophilized liposomes containing different concentrations of egg and dipalmitoyl Phosphatidylcholine showed zero-order release.	[110]
Actively targeted liposomes	Mannosylated liposomes	Indinavir	The study used dimyristoyl phosphatidylethanolamine and βD-1 thiomannopyranoside residues in mannosylated liposomes loaded with indinavir to target the mononuclear phagocyte system. About 88.7% of these liposomes effectively ensnared targets, with significant levels of the drug reported in macrophage-rich regions.	[111]
	Liposome microbicide	Octyl glycerol	The liposome containing 1% Octyl glycerol and Phosphatidylcholine demonstrated superior efficacy compared with the conventional gel, with no observed toxicity in both ex vivo and in vivo testing.	[112]
	CCR5-conjugated cell derived liposomes	EDTA	Cell-derived liposomes incorporated with EDTA showed a 60% reduction in the viability of gp120-expressing cells as compared with control cells that do not express gp120.	[113]
	Magnetic liposomes	Azidothymidine 5' triphosphate	In an in vitro model, magnetic Azidothymidine 5' Triphosphate liposomes with cholesterol and phosphatidylcholine showed increased permeability across the blood–brain barrier when exposed to an external magnetic field.	[114]

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Nanocarriers Used in HIV Treatment

In recent times, the use of nanocarriers in HIV drug delivery has garnered much attention among scientists around the world. The use of nanocarriers in anti-retroviral drug delivery displayed particular advantages like target specificity, dose specificity, continuous drug discharge for extended time, enhanced stability, and lessened toxicity.[2] The nanocarriers are also able to penetrate the cellular and physiological barriers to reach the specific targeted tissues and cells in the infected person.[2] A patient's immune cells got infected by HIV because of their interaction with the gp120 HIV glycoproteins. However, several free HIVs not interacting with the immune cells undergo several mutations. Hence, targeting the infected cells with the antiretroviral drugs is much easier. Thus, many cellular components, such as chemokine receptors, CD4 proteins, carbohydrate-binding antigens, C-X-C chemokine receptor type-4 protein, etc., are explored for their possible targets in the nanocarrier-based HIV treatment process.[2,131,132] The designed nanocarriers carry the antiretroviral drugs to the targeted cells and inhibit the HIV enzymes at different HIV lifecycle stages.[133]

Various types of nanoparticle-related carrier systems have been developed for the delivery of multiple antiretroviral drugs to their specific locations.[12] It includes lipid-based nanocarrier systems like liposomes, which are formulated with coordinated lipid layers that can protect the attached drugs and make them biocompatible and biodegradable. The liposomes can hold both the hydrophilic and hydrophobic drugs in their phospholipid bilayer.[12] Another type is the ethosomes that contain alcohols and phospholipids at very high concentrations together with water molecules, that is used for transdermal delivery of antiretroviral drugs.[12] Some anti-HIV drugs are also covalently conjugated with polymers, encapsulated into polymeric nanoparticles, and used in HIV treatment.[12] Lactoferrin protein, a component of the body's immune system, is used as a carrier for HIV drugs.[100] In a study by Kuo and Su,[134] the authors studied the permeability of antiretroviral drugs such as tavudine, delavirdine, and saquinavir using polybutylcyanoacrylate nanoparticles, methyl-methacrylate-sulfopropylmethacrylate nanoparticles, and solid lipid nanoparticles as the carrier system across the in vitro BlBrnBr model.[95] In another study, some researchers have conjugated the Poly(l-lactic acid) nanoparticles with Tat peptide and explored their effect on the transport of ritonavir across the BlBrnBr and into the CNrS.[122,135] Besides, several inorganic nanoparticles like iron oxide nanoparticles, silver nanoparticles, gold nanoparticles, quantum dots, carbon nanotubes, silica dots, etc. are also tested for drug delivery abilities.[136] Some reports suggest that monocyte-derived macrophages are also used as nanocarriers for HIV drug delivery.[137] Many RNAi approaches in the treatment of HIV-1 infection using two different groups of approaches (RNA targeting via antisense and protein targeting via decoy or aptamers) based on the mechanism of action have been investigated recently.[138,139] However, in the case of HIV, the key challenge in the RNA-based therapy is the delivery of RNA to the targeted host cells since the latent reservoir is spread throughout the body, resulting in rapid removal of RNAs from circulation, and thus not easily taken up by cells, and are incompetent at endosome escape in the target cells.[140] To address these issues, a specific delivery system is required, which could avoid the renal clearance and pass these barriers and reach the target cells without any hindrance.[141] Currently, the manufacture of siRNAs and nanocarrier systems is a very multifaceted process and has been a major blockage in getting the treatments to the clinic due to issues in scalability and reproducibility. A new platform called the NanoAssemblr®, has been developed which could successful manufacture lipid based nanoparticles with reliable sizes and encapsulation of drugs.[142]

Nanomaterials Trigger an Immune Response

The application of cell-based therapies in HIV-1 treatment has been reported recently.[96,143,144] This type of treatment is based on the transfer of allogenic immune cells into the patients after ex vivo growth and/or alteration, to remove the HIV-1-infected cells.[96] Nanoparticles have been reported to improve the potentiality of the immune cells to target and destroy the HIV-1-infected cells. Basically, the nanobased immunomodulatory systems (NIMS) are categorized into 4 different groups, such as lipids and carbohydrate-based NIMS, polymeric nanoparticles, metallic nanomaterials (gold, silver, copper, carbon nanotubes, etc)., natural organic substances (rosmarinic acid, bilirubin, cell membrane-based nanoparticles), and hybrid immunomodulatory systems (protein-polymer, polymer-polymer, etc).[145] Figure 5, by Khatun et al,[145] shows the different types of nano-based immunomodulators used with their respective inherent properties and different types of compounds used to synthesize them. Here, the author has categorized the nano-based

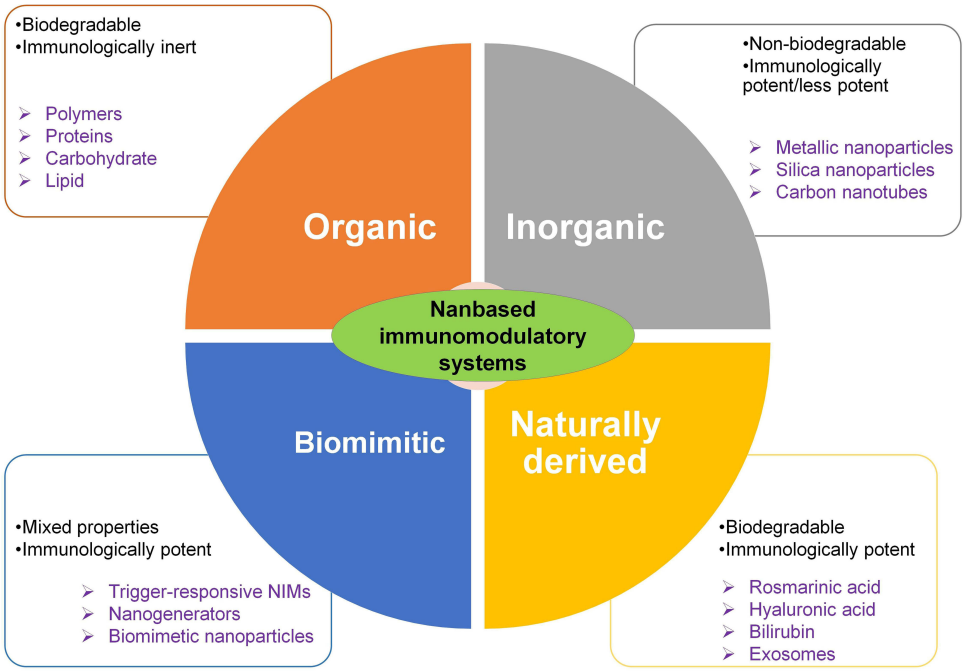

Figure 5 Different groups of nanobased immunomodulatory systems and their respective characteristics. Adapted with permission from Khatun S, Putta CL, Hak A, Rengan AK. Immunomodulatory nanosystems: an emerging strategy to combat viral infections. Biomaterials and Biosystems. 2023;9:100073. Copyright 2023, Elsevier.[145]

immunomodulatory systems into 4 groups named organic (containing polymers, lipids, carbohydrates, and proteins), inorganic (containing metallic nanoparticles, silica nanoparticles and carbon nanotubes), biomimetic (trigger-responsive nanobased immunomodulatory system, nano-generators, and biomimetic nanoparticles), and naturally derived (containing bilirubin, hyaluronic acid, rosmarinic acid, and exosomes).[145] The first group of polymeric nanoparticles operates with double potentiality as adjuvants and delivery materials for diversified payloads like antigens and co-adjuvants, and delivers them to the immune cells with continuous release, protecting the drug from an adverse environment. The second group of metallic nanoparticles has higher binding properties with specific functional groups and ligands that enhance their therapeutic properties. The third group assists the natural communication between the biological components and the nanoparticles mimicking the properties of the native cells. The fourth group showed synergistic effects with enhanced therapeutic properties.[145]

In a report by Sweeney et al,[146] the authors have developed a poly(lactic-co-glycolic acid) nanodepots that co-encapsulate the prostratin, a latency-reversing agent, and anti-CD25, a cell surface binding antibody, to improve the function of the primary NK cell against HIV.[146] The formulated nanomaterials increased the NK cell cytotoxicity of the target cells, which is a case of enhancement of the immune cell function concerning the HIV-1 infection.[146] In another study, the author validated that by conjugating lipid nanoparticle-based drugs to the surface of Cytotoxic T-Lymphocytes, their lytic mechanism can be designated to lyse the cell-bound drug carrier, delivering the discharge of drug cargo when exposed to the targeted cells.[147]

Furthermore, the HIV-1 virus has developed a methodology to disrupt the immune function of the body, and thus, to eradicate the HIV-1 infection from the body, its immune mechanism requires reestablishment. It is reported that the HIV-1 virus characteristically hinders the cGAS-STING pathway that usually functions via the cGAMP binding to STING on the endoplasmic reticulum, subsequently leading to an IFN-1-mediated antiviral response.[147,148] It is reported that pH-sensitive polymeric nanoparticles were able to deliver a STING agonist to offset the HIV-1 immune evasion via the cGAS-STING pathway and demonstrate promising antiretroviral activity.[147] In a study by Bahr et al,[149] it was reported that a synthetic derivative of muramyl dipeptide (a nucleotide-binding oligomerization domain-containing 2 agonist) named murabutide has completed the Phase II clinical trial, representing its clinical tolerance and effectiveness for

 https://doi.org/10.2147/IJN.S540578

enhancing the antiviral immunity in HIV-infected patients.[149] In another study, the author has prepared an ultra pH-sensitive cGAMP-loaded micelle named PC7A as an adjuvant for modulating the innate immune response in HIV and concluded that the formulation was able to affect the replication of two HIV-1 strains (IIIB and LAI) in the peripheral blood mononuclear cells.[150] In 2021, Astorga-Gamaza et al[151] have formulated a bispecific gold nanoparticle conjugated with anti-HIVgp120 and anti-human CD16 antibodies, which were able to enhance the contact between the natural killer cells and the HIV-expressing cells, thus triggering a cytotoxic response against the HIV-infected cells.[151] A schematic diagram shows how the nanoengagers decorated with anti-CD16 and anti-tumor antigen antibodies are able to target the tumor cells, triggering a cytotoxic response (Figure 6).[152] Applications of nanoengagers against the human immunodeficiency virus-infected cells can be explored in future studies.

Improved Cellular Uptake of HIV Vaccine

Using nanomaterials for antiretroviral drug delivery is very helpful for the targeted delivery of drugs to specific locations, such as to the cells associated with the HIV infection.[153] A study by Panyam et al,[154] has tested the effectiveness of two formulation doses of nanoparticle-based drugs (dexamethasone) for their cytoplasmic delivery to the intracellular locations. The author concluded that the drug interacts with the cytoplasmic receptors, forming a composite that is conveyed to the cell nucleus, triggering the initiation of definite genes responsible for cell proliferation. Loading the drug with nanoparticles like PLGA, PLA, etc., and controlling its release for a longer period enhances its antiproliferative effect for vascular muscle cells.[154]

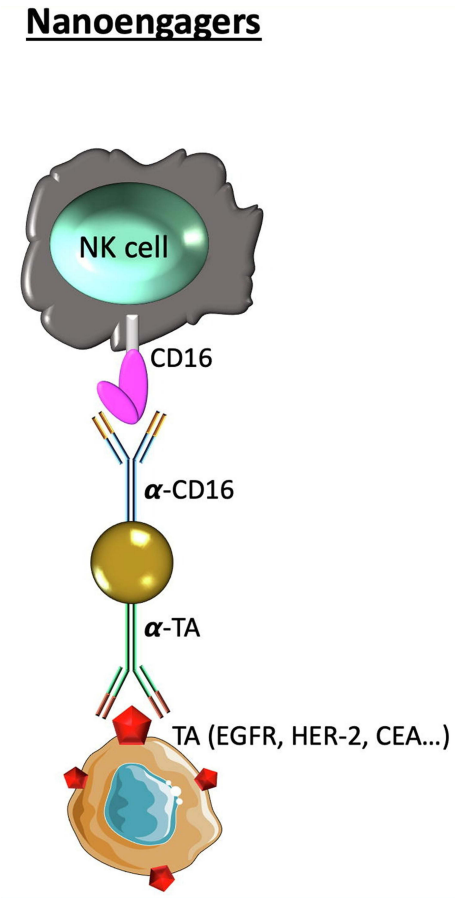

Figure 6 Schematic diagram showing the effect of nanoengagers against the tumor cells. Reproduced with permission from Mikelez-Alonso I, Magadán S, González-Fernández Á, Borrego F. Natural killer (NK) cell-based immunotherapies and the many faces of NK cell memory: A look into how nanoparticles enhance NK cell activity. *Adv Drug Deliv Rev*. 2021;176:113860. Copyright © 2021 Elsevier B.V. All rights reserved.[152]
Abbreviations: CD16, IgG Fc receptor (FcγRIIIa); α-CD16, antibody binding CD16; α-TA, antibody binding TA; TA, Tumor antigen; EGFR, Epidermal growth factor receptor; HER-2, human epidermal growth factor receptor 2; CEA, Carcinoembryonic antigen.

Improved Penetrability and Effectiveness of HIV Vaccine

Nanoparticle-mediated delivery of antiretroviral drugs increases the drug penetration capacity through the BlBrnBr.[155] Besides, through the use of nanomaterials, the amount of drug dose and its frequency are also reduced and controlled because of its target-specific properties, thereby decreasing the side effects of HIV drugs.[155] In an old report from 1993, the author compared the nanoparticle-mediated azidothymidine medication with only azidothymidine medication and found that liposomal-mediated azidothymidine medication displayed enhanced effect with very few side effects as compared with treatment with only azidothymidine medication in HIV patients.[156]

Nanotechnology and Gene Therapy

The use of gene therapy in HIV treatment has been explored recently. Nanoparticle-mediated gene therapy is introduced into the HIV-infected cells for treatment.[153] By application of gene therapy, progressive HIV infection can be prevented by continued meddling with the viral replication in the absence of chronic chemotherapy.[157] Earlier, Scientists used the gene-editing system to knock out the chemokine receptor type 5 in $CD4^+$ T cells, blocking HIV-1 virus entry.[158,159] With the advancement of nanotechnology, gold nanoparticles have been developed with surface conjugation of clustered regularly interspaced short palindromic repeats, which target the two locations within the hematopoietic stem and progenitor cell genome, chemokine receptor type 5 and the gamma-globin gene promoter.[96,160] Clustered regularly interspaced short palindromic repeats conjugated gold nanoparticles were able to enter the $CD34^+$ hematopoietic cell line, which is difficult to transfect. Finally, this conjugated particle was able to exhibit gene editing and homologous directed repair at the chemokine receptor type 5 and the gamma-globin promoter locus at a higher potential than the electroporation-driven process.[96,160]

In a study by Dash et al,[161] the authors have demonstrated the combined effect of two techniques to investigate the synergism in HIV treatment. The author showed that out of the seven tested mice, only two mice that received the sequential long-acting slow-effective release antiviral therapy followed by successive AAV9-based delivery of CRISPR-Cas9 treatment resulted in an undetectable amount of virus and integrated DNA. The portion of the HIV-1 genome was treated for viral return and saw a reestablishment of their $CD4^+$ T cells, signifying HIV-1 deterioration and abolition.[161] It has been reported that CRISPR-Cas9-mediated genome editing can hinder the various HIV-1 infection stages.[162] In a study by Hultquist et al,[163] the authors used CRISPR-Cas9 techniques for the mechanistic examination of the HIV host factors in $CD4^+$ T cells.[163] A number of factors, such as apolipoprotein B mRNA-editing enzyme and TRIM5α gene expression, could result in the host restriction against HIV infections, and the use of CRISPR-Cas9 technology could enhance these expressions and thus are useful in the anti-HIV therapies.[164,165]

Dendrimer siRNA on Suppression of HIV Replication

Unchanged dendrimers are reported as highly useful RNA interference regulator carriers.[166] Cationic triethanolamine-polyamidoamine dendrimers G5 are used to transport siRNA precursors (Dicer-substrate siRNAs), for multi-target elimination of HIV.[166] In a study by Zhou et al,[167] the authors assessed the in vivo effectiveness of mechanically bendable, cationic poly(amidoamine) dendrimers as a small interfering RNA (siRNA) delivery arrangement in a Rag2 (-)/-γc-/- (RAG-hu) humanized mouse model for HIV-1 infection.[167] The author concluded that the treatment of dendrimer-dsiRNA was able to inhibit the HIV-1 infection by several folds, followed by protection against the virus-induced $CD4^+$ T-cell exhaustion. Besides, the author also proved that the follow-up injections of the dendrimer-based dsRNA, when the infection resurfaced, led to a thorough eradication of the HIV-1 titers.[167] Besides, the NN16 dendrimers have been reported to be used effectively to deliver the siRNA that eliminates the important HIV-1 proteins (NEF, COX_2, GAG, and p24), with a reduction of the viral load from 35 to 60% in different cell lines under in vitro conditions.[168,169] Briz et al,[170] demonstrated the elimination effect of the HIV-1 contamination in the primary human peripheral blood mononuclear cells with a fourth-generation phosphorus dendrimer complexed with anti-NEF siRNA and reported effective virus repression with less toxicity.[170] Table 4 summarizes the dendrimer-centered siRNA gene delivery systems for HIV treatment.[166] The table shows the details of the target protein and the type of sRNA, the object it is targeted at, the dendrimer and dendrimer-based constructions, and their significant effects.

Table 4 Dendrimer-Based Gene Delivery Systems for siRNA Therapeutics in HIV Treatment

Target Protein/Type of Short RNA	Object	Dendrimer/Dendrimer-Based Construction	Effect	Ref.
Polyamidoamine dendrimers				
Cocktail of viral (HIV) Tat and Rev, lymphocytic CD4/TNPO3/dsiRNAs	T-cells and primary human PBMC	Triethanolamine-polyamidoamine dendrimers G5	Decrease of viral p24 expression by >50% and CD4 expression by 60–75%	[167]
	HIV-infected humanized Rag2 −/−γc−/− mouse model		Decrement of viral load up to 0% prevents $CD4^+$ T-cell level fall.	
CD4 (primary HIV receptor)/dsiRNA	Human hematopoietic $CD34^+$ stem cells	Amphiphilic triethanolamine-polyamidoamine dendron G3 bearing alkyl chain C18 in the focal point, decorated with arginine	Decrease of CD-4 mRNA by 60%	[171]
	Acute lymphoblastic leukemia T-cells (CCRF-CEM)	Amphiphilic Janus-type- triethanolamine-polyamidoamine dendrons bearing two alkyl chains	Decrease of CD4-mRNA by 55%, knockdown of CD4 protein expression by 80%	[172]
Cocktail of HIV-1 Tat/Rev (viral integrase)/dsiRNAs	PBMC $CD4^+$, hematopoietic stem cells $CD34^+$		Decrease of Tat/Rev mRNA level by 50–55%, inhibition of HIV replication in infected cells by 30–40%	
Delivery of siRNA by non-polyamidoamine dendrimer constructions				
Nef (necessary protein for HIV reproduction)/siRNA	$CD4^+$-lymphocytes	Carbosilane (CBS) G2, G3 dendrimers	HIV-1 reproduction inhibition in vitro by 35% (G2) and by 50% (G3)	[168]
	PBMCs	Phosphorous G4 dendrimer	HIV-1 reproduction inhibition by 60%	[170]
COX_2 (cyclooxygenase-2, stimulator of HIV propagation in the brain)/pool of four siRNA sequences	Astroglioma cells (U87MG)	NN-16 G2 (carbosilane dendrimer)	Decrease of COX_2 expression in HIV-infected cells to the level of uninfected cells	[173]
P24, NEF (HIV structural proteins)/siRNA			50% inhibition of HIV-1 propagation	[174]
P24, GAG1, NEF (HIV structural proteins)/cocktail of three siRNAs	T-cell lymphoma lymphoblasts (SupT1), primary PBMCs		35% inhibition of HIV-1 propagation	[169]

Note: Reproduced from Dzmitruk V, Apartsin E, Ihnatsyeu-Kachan A, Abashkin V, Shcharbin D, Bryszewska M. Dendrimers show promise for siRNA and microRNA therapeutics. Pharmaceutics. 2018;10(3):126. doi:10.3390/pharmaceutics10030126. © 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)[166]

Nanoparticle Methods for Targeting CD4$^+$ T Cells

In HIV contamination, the virus targets the CD4$^+$ T cells of the infected person. Hence, in order to eradicate the virus from the patient's body, an important strategy is to target these CD4$^+$ T cells, and a variety of nano-based systems are developed to deliver the drugs or antiviral siRNA to these CD4$^+$ T cells to hinder replication of HIV.[153] In a study by Campbell et al,[175] the authors examined the effectiveness of nano-mediated CD4$^+$ T cell membrane-coated nanoparticles encapsulated with DIABLO/SMAC mimetics to both deactivate HIV-1 and kill the HIV-1-infected resting CD4$^+$ T cells and macrophages. In another study, the author examined the synthesis of a novel lipid nanoparticle combined with protein kinase C activator bryostatin-2 and targeted them to the primary human CD4$^+$ T cells to activate them and motivate the production of latent virus from human T-cell lines under in vitro conditions and in a humanized mouse model under ex vivo conditions. Additionally, they demonstrated that these nano systems can also be loaded with the protease inhibitor nelfinavir, fabricating a particle that can activate the latent virus and inhibit the spread of the virus.[176] Tombacz et al,[177] demonstrated that the CD4-targeted mRNA- lipid nanoparticles can penetrate all T cell subtypes and targeted tissues (lymph nodes) passing through the BlBrnBr under in vivo conditions. This application enables the delivery of mRNA therapy and engineered genome editing enzymes to T cells for effective HIV treatment, by eliminating the HIV combined provirus from the genome of latently infected cells.[177] In a recent study by Cevaal et al[178] the authors have developed an mRNA-based lipid nanoparticle formulation (encapsulated with the HIV Tat protein, an activator of HIV transcription) with extraordinary strength to deliver mRNA to the resting CD4$^+$ T cells in the absence of cellular toxicity or activation. This drug was able to enhance the transcription of HIV in ex vivo CD4$^+$ T cells from people living with HIV.[178] It also allows the delivery of clustered regularly interspaced short palindromic repeats (CRISPR) stimulation mechanism to control both viral and host gene transcription.[178]

Nanoparticles Boost Permeation of Blood-Brain Barrier

Apart from the presence of HIV-1 in CD4$^+$ helper T cells, it is also present in the microglial cells of macrophages of the CNrS. It may resist the highly active antiretroviral treatment process or could spread the HIV-1 contamination in the adjacent tissues, which are important in the progression of the HIV-1 virus-linked neurocognitive ailments.[179,180]

BlBrnBr is a regular protective membrane mechanism of the body that guards the CNrS from entry of toxins and pathogens in the blood.[91,181,182] However, due to this natural barrier of the body, several CNrS-related ailments are difficult to treat, as most of the drugs and formulations are obstructed from entering the brain, leading to low therapeutic efficiency as well as intensified side effects due to the accumulation of these drugs in other organs and tissues.[91,181] It is important to formulate a mechanism to overcome the anatomical BlBrnBr and deliver the required drugs to the stubborn HIV-1 in microglial cells. Figure 7 shows the regulation strategies of the BlBrnBr and the process of brain-targeted drug delivery systems.[181] The figure discusses various mechanism of action of drugs crossing the BlBrnBr that occurs through the pathways of paracellular and transcellular diffusion, receptor-based, cell-based, transporter-based, and adsorptive-based transcytosis process (a). The different cell structures of the BlBrnBr include astrocytes, pericytes, junctions, endothelial cells, and capillary lumen (b). The transcytosis mechanism includes the stages like passive transcytosis, intranasal administration, ligand functionalization, membrane coating, and disruption of the BlBrnBr (c). Different types of engineered materials, such as liposomal formulation, polymeric materials, gold, carbon, and iron oxide, silica, and biomass-based materials, are used in the brain-targeted drug delivery (d).[181]

To penetrate the BlBrnBr, site-specific antiretroviral drugs combined with small-sized nanoparticles are formulated.[183] The nano-conjugated drugs can cross the BlBrnBr via transient pathways without compromising the neurological integrity, and concurrently preserve the innate healing effects of the original drug. Besides, another factor is the charge and surface moieties that can functionalize the nanoparticles to provide specificity to the targeted receptors.[91] A study by Gong et al,[103] demonstrated that PLGA-coated elvitegravir nanoparticles penetrate through the BlBrnBr system and efficiently suppress the replication of HIV, followed by a decrease of brain interface inflammation.[103] In another study, the authors formulated the surface-modified nanodiamonds conjugated to the efavirenz drug to cross the BlBrnBr system and display promising results. Besides, the inert, nontoxic carbon nanosystem helps in the retention of the drug at the CNrS for a longer time with no neuronal plasticity side effects.[184] Research by Kanazawa et al,[185] showed the formulation of a nose-to-brain delivery system joined with cell-penetrating peptide-modified nano-micelles that encompass polyethylene glycol–polycaprolactone

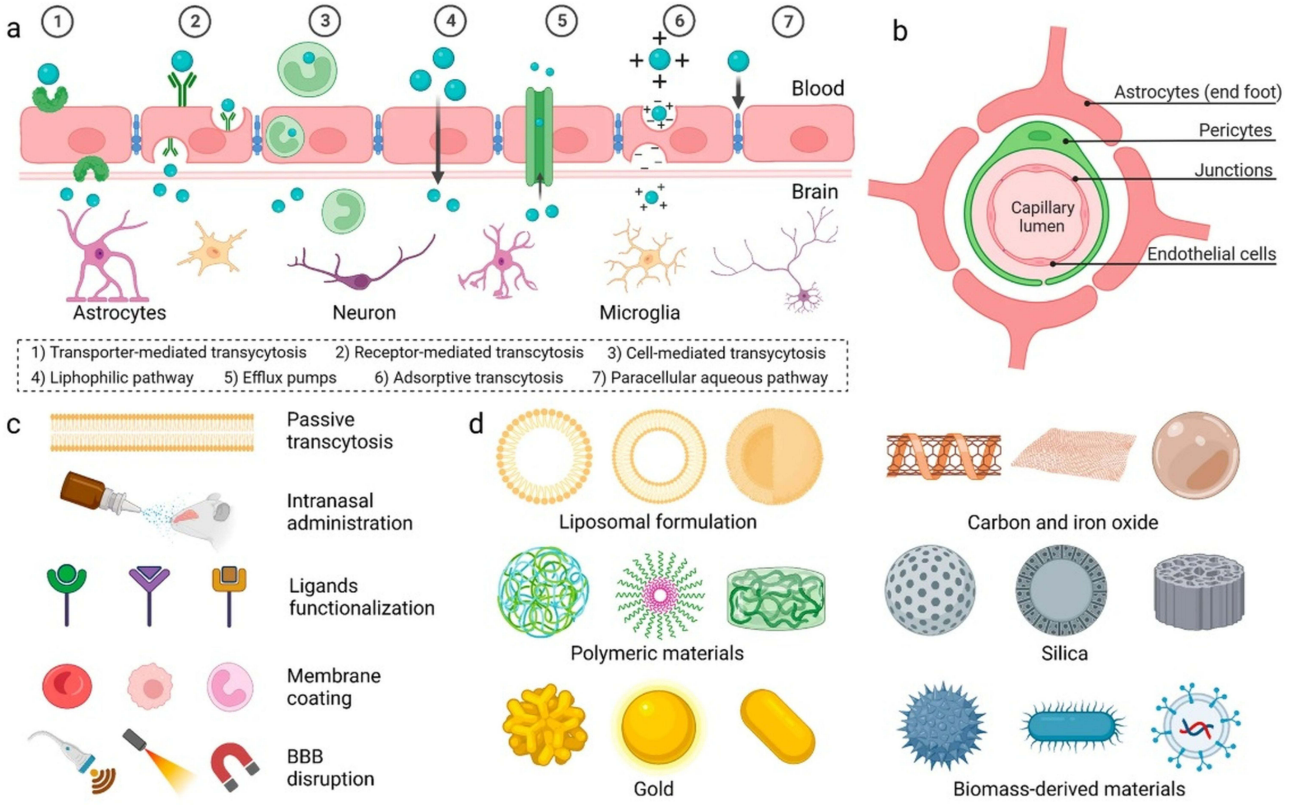

Figure 7 Brain blood barrier regulation Strategies and brain-targeted drug delivery. (**a**) Mechanism of crossing of the brain blood barrier; (**b**) structure of the brain blood barrier; (**c**) different non-invasive strategies for crossing the brain blood barrier; and (**d**) various engineered particles for targeted drug delivery. Reproduced from Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood–brain barrier: Structure, regulation and drug delivery. *Sig Transd Target Ther.* 2023;8(1):217. © The Author(s) 2023. Creative Commons Attribution 4.0 International License.[181]

copolymers conjugated with the cell-penetrating peptide (Tat) to expand the efficacy of the delivery of small interfering RNA to the brain. The author concluded that this system was able to transport the drug in a faster way along the olfactory and trigeminal nerve pathways because of its high permeation across the nasal mucosa.[185] This mechanism could be helpful in HIV treatment. Garrido et al,[186] revealed that HIV integrase inhibitors connected to gold nanoparticles can enter the BlBrnBr and exhibit improved antiviral effects.

Clinical Translational Challenges and Nano-Drug Delivery Prospects in HIV Management

Several studies have been developed on the uses of nanotechnology in the treatment of chronic and infectious diseases recently.[187] Largely, the advancement of nanotechnology in antiretroviral therapy is primarily in its initial clinical translation stage.[12] Recently, several long-acting nanoformulated HIV infection-targeted drugs have been tested for Phase I/II clinical trials.[21] Some of these nanomediated drugs are discussed below. A therapeutic vaccine called DermaVir (NCT00711230 and NCT00712530) patch (Genetic Immunity, Budapest, Hungary) has entered Phase II clinical trials.[188,189] The drug is in the form of a patch, and it includes mannosylated poly(ethyleneimine), glucose, and an HIV antigen-coding DNA plasmid, which are articulated into nanoparticles, and these nanodrugs are delivered to the epidermal cells, which then engulf the nanoparticles and evolve to produce an immune response.[21,190] It was reported that the drug was safe and tolerable by patients and could induce a long-term effect in the memory T cells, thereby reducing the load of HIV in the viral reservoirs.[21,190] Another drug, long-acting injectable nanoformulations combinations of rilpivirine and GSK1265744 (cabotegravir, an HIV-1 integrase strand transfer inhibitor and equivalent of dolutegravir) (NCT05697289, NCT06185452, NCT01467531) was reported to have progressed through clinical trials. This drug, GSK1265744 (NCT02178800),[191] has been detected in the plasma of patients at 48 weeks under phase II

clinical trial.[191] A carbomer gel (Vivagel® (NCT00740584)[192] (Starpharma, Melbourne, Australia)), containing a dendrimer (SPL7013) with inherent but unspecific antiviral activity, is another nano-microbicide drug under clinical trial phase.[192,193] SPL7013 contains naphthalene disulfonate-terminated polylisine branches adhered to a central benzhydrylamine amide group, and its outer sulfonate groups are accountable for interrelating with the viral gp120, which inactivates the HIV at submicromolar concentrations under in vitro conditions.[194] Its Phase I trials show positive results of Vivagel.[195,196] Besides, some more nanomediated antiretroviral drugs are also under development for HIV-1 treatments.[21] These include TMC278-LA (long-acting) with poloxamer 338 and d-a-tocopheryl polyethylene glycol under phase II clinical trials.[197] Enfuvirtide, a fusion inhibitor with iron oxide nanoparticles coated amphiphilic polymer under in vitro testing stage.[198]

A study by Mielke et al,[199] in Thailand on the RV144 trial, is the only HIV-1 vaccine trial that showed positive results. Here, the author demonstrated that a vaccine with computationally selected immunogens could maximize the coverage of the subtype C V1V2 region and is able to protect the NHPs from a heterologous SHIV challenge.[199] Another study by Shen et al,[200] studied the effect of breadth of the anti-V1V2 vaccine response on the broadening by including HIV-1 Env strains computationally designed to improve the subtype C V1V2 sequence diversity coverage.[200] Further, some more studies related to the RV144 trial are also reported in the clinicalTrial databases (NCT00337181, NCT03875209, NCT00223080, NCT03368053, NCT01435135, NCT01931358)(https://clinicaltrials.gov/expert-search?term=RV144%20trial). Apart from these, in a preclinical study by Zhang et al,[201] have demonstrated that a single-component, self-assembling protein nanoparticle (1c-SApNP) conjugated to BG505 uncleaved prefusion-optimized trimers to prompt the production of broadly neutralizing antibodies in mice, rabbits, and nonhuman primates.[201] Moreover, the author also reported that exact modification of the glycan could also enhance the response of the vaccine.[201] In some clinical studies like Leggat et al[202] and Cohen et al,[203] the researchers have formulated an outer domain germline that targets the version 8 (eOD-GT8) 60-mer nanoparticle, which can prim the VRC01-class HIV-1-specific B cells for production of broadly neutralizing Abs.[202] And they also discovered that the eOD-GT5 60-mer induced a CD4 T cell response, which proves the highly active immunogenic abilities of the nanoparticle-based vaccine.[203]

Sufficient information on residual virus sites and their impact on the virus return is just developing. It is important to focus on treatment measures for removing HIV from the body's residual location using various advanced nano-techniques, including targeted drugs and immune-therapeutics.[12] Though nanotechnology offers many advantages over the conventional system of medications, it also gives rise to a number of side effects and challenges that need to be rectified for its better application.[12,187] In a review by Huang et al,[187] the authors discussed such limitations and challenges faced by the nanotechnology-mediated HIV treatment process (Figure 8). Among them, one of the major challenges is to achieve target specificity during the drug delivery process. Due to specific biological barriers in the lungs and gastrointestinal tract, nano-mediated drug candidates are not able to achieve 100% targeted drug delivery.[187] Furthermore, there are certain challenges faced during the manufacture of nanomaterials and nanoformulations due to diverse physicochemical properties. And at last, the major challenge is the high cost of nano-mediated HIV treatment procedure, along with addressing various regulatory issues.[12,187]

The widespread applications of nanotechnology in HIV treatment have provided an upper hand in the treatment process. Nevertheless, it also gave rise to toxicity and safety issues, and some reports suggested that organs like kidneys, lungs, and liver, where there is speedy perfusion, are vulnerable to accumulation of nanoparticle traces leading to damage by cytotoxicity, oxidative stress, genotoxicity, and inflammation.[204–206] Some liposomal formulations have been evaluated clinically for their safety, acceptability, and effectiveness in patients with HIV/AIDS.[21,106,207] However, no liposomal formulations of antiretroviral therapy have received regulatory approval for their clinical use in HIV/AIDS treatment due to their several limitations, including stability, variability, biological barriers, high cost, toxicity, tissue specificity, and hurdles in their clinical translation.[106,208] Similarly, carrier-mediated targeted drug delivery encounters several hurdles such as selectivity, location specificity, stability of drug formulations, immune response, synthesis, large-scale production, regulatory obstacles, and patient inconsistency.[106] Furthermore, the natural barriers in the body, such as the blood barrier, immune system, and cell membrane blockage systems, act as hindrances for targeted drug delivery of nano-mediated drugs and thus sometimes affect the efficacy and target specificity of the nano-drugs.[187] Some studies

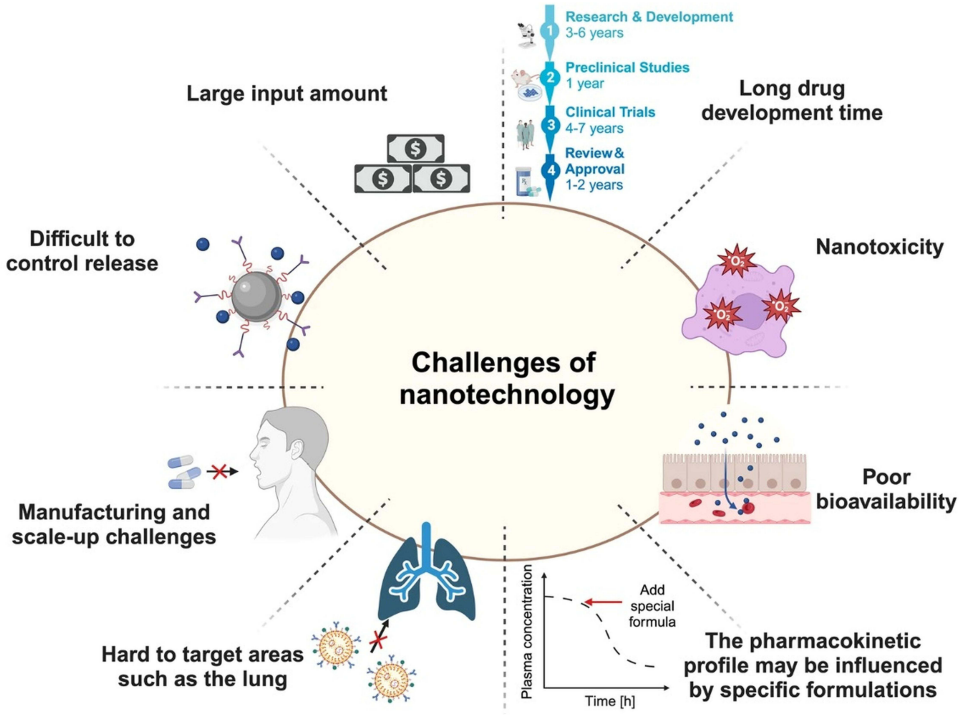

Figure 8 Major challenges faced by nanomediated drug delivery systems. Reproduced from Huang Y, Guo X, Wu Y, et al. Nanotechnology's frontier in combatting infectious and inflammatory diseases: prevention and treatment. *Signal Transduct Target Ther.* 2024;9(1):34. © The Author(s) 2024. Creative Commons Attribution 4.0 International License.[187]

showed that the efficient target-specific delivery of nano-mediated drugs is associated with the surface condition of the target site and delivery route.[209,210] In most of the drug delivery systems, the mononuclear phagocyte system is responsible for the fast clearance of several medication carriers, decreasing the time they spend in circulation and their therapeutic efficacy.[211] Recently, research has been undertaken to develop a stealth, such as polyethylene glycol coating, to evade immune detection.[211,212] However, challenges, such as the immunogenicity of these polyethylene glycol, are still unsolved. Another important factor is to maintain the consistency of the nanoparticles during their fabrication, repository, and application stage.[213,214] In addition, any change in its stability leads to a decrease in the efficacy of the nano-mediated drug delivery, affecting its long-term performance.[215] Besides, high cost and regulatory and ethical issues are some of the other challenges that have affected the widespread applications of nano-mediated drug delivery in HIV treatment.

Besides, the fate of nanocarrier systems, post-drug delivery in the HIV treatment, is another important issue that needs to be evaluated for enhancing the usability of the nano-based ATR medications. It is known that different types of carrier systems have different mechanisms for their drug release.[216] Some carriers can release the drugs to the targeted site at the site of the lesions without entering the cells, while other types of carrier systems directly interact with the cell membranes and discharge the drugs into the cytoplasm and do not enter the cells.[216] Further, some types of carrier systems directly enter the cells through various pathways and are then transported to the specific subcellular sites to deliver the drugs; in such a case, some drugs are degraded in one way while others escape the degradation.[216] In case of using the nanocarriers in the HIV treatment, the nanocarriers are designed to be degraded and cleared from the body after its purpose is achieved, however their fate depends on the type of nanocarrier used to deliver the drugs, such as lipid and polymeric nanocariers are usually degraded in the body and subsequently get out of the body through the fecal matter.[2,17,138] While some nanocarriers carrying long-term use drugs are usually coated with polyethylene glycol, they get accumulated at the targeted sites and remain there until all the drugs have been utilized by avoiding the immune response of the body.[217]

Advanced future application of gene therapy with CRISPR-Cas9 is promising for the clinical sciences and rapidly developing for its applications in therapy for human diseases.[218] Though the CRISPR-Cas9 technology is at its initial stage and is only used for patients with severe life-threatening diseases, most of its clinical trials are in the phase ½ stage and are mostly concerned with the safety and effectiveness of the genome editing in humans to boost the molecular processes involved in genome editing.[218] Besides, the therapeutic genome editing techniques are currently advancing to the ethical dubious variation in the human early stage embryo genome to protect from HIV infection.[219] Thus, there should be rules and regulations for the application of these advanced technologies. There are various substantial regulatory hurdles for the application of long-acting injectables and CRISPR-based genome editing therapies in HIV, concerning their long-term effects, immunogenicity, target-specific delivery, and safety.

A key advantage of nano-mediated drug delivery technology is that it can be connected with adjuvants, which could improve the body's immune response to an antigen by exciting the pro-inflammatory cytokines release.[220] A recent research demonstrated that the nano-based adjuvants can enhance the antibody production after the HIV-1 vaccination significantly.[221] Besides, the adjuvants are able to help in creating a more vigorous and long-lasting immune response in the patient's body.[220,222] Though these studies highlight the effectiveness of integrating adjuvants into the vaccination treatment,[220] using these formulations has contributed immensely to "vaccine hesitancy", due to some side effects such as body aches, inflammation of tissue, and fever in patients.[223,224]

Summary and Future Orientation of HIV Treatment

In the current scenario, the formulation of the HIV vaccine has not been fruitful. However, a number of continuous efforts in this field are presently going on around the World, and the application of nanotechnology is playing a major role in this process. Presently, numerous investigations are being undertaken using nanomaterials as potential HIV vaccine carriers or adjuvants. Moreover, these nano-based treatment processes have shown promising capabilities to develop the solubility, distribution, penetrability, consistency, and pharmacokinetics of HIV vaccines. Currently, many nanoparticles are used in the anti-retroviral drug delivery treatment process, and further, some of the nanomaterials, like inorganic nanoparticles, liposomes, dendrimers, carbon-based nanomaterials, and fullerenes, are reported to possess anti-HIV properties. The application of nanomaterials in the HIV treatment process (drugs, diagnosis, and carriers) could play a major role in solving the hurdles faced by conventional HIV treatment methods. Advances in the nanoparticle-based anti-retroviral drug delivery system that includes dendrimers, nanovesicles, liposomes, polymeric micelles, nanoemulsions, etc., deliver an efficient and better-targeted drug delivery with controlled pharmacokinetics and high therapeutic values. Presently, more research is focused on the study of HIV vaccine adjuvants using biocompatible and biodegradable nanomaterials. Several factors, such as the shape, size, physical and chemical properties, encapsulation effect of the nanocarriers, and variable circumstances in between the immune response of the experimental animal to that of humans, significantly prove the potential of nano-adjuvants and their exact mechanism of action. Besides, the cost-effectiveness of the nano-carrier drugs should also be evaluated for their better application in the HIV treatment process.

Recently, most of the sustained-release anti-HIV treatments are based on the optimization of their pharmaceutic and pharmacokinetics features in the preclinical models, and only the long-acting cabotegravir and rilpivirine treatments have advanced to the clinical trial stage in humans, and their acceptability is under investigation. Besides, there are a few nano-mediated drug formulations targeting HIV host cells, and more research in various nano combinations in the antiretroviral drug delivery treatment process needs to be explored. In 2021, a pharmaceutical company named ModernaTX, Inc. started a clinical trial for the first HIV mRNA vaccine. Besides, several nano-mediated antiretroviral oral drugs (efavirenz) have also been developed, tested, and compared with the normal Sustiva® product. Another drug, Rilpivirine, which was used as an oral drug, has been combined with nanoformulations to form a long-acting injectable format. A nano-mediated solid drug lopinavir that was pro-ethanol-free for pediatric treatment has been modified for mono and combinational drug preparations. Two more preclinical trials of nanoparticle-mediated HIV drug candidates were also developed by the research group at Creighton University in 2018 and 2019. Its results proved the clinical effectiveness of PLGA-bicteravir complex and PLGAtenofovir@ elvitegravir@emtricitabine complex in HIV treatment. In the future, advanced nanomaterials-based clinical research and treatment should focus more on several underlying issues, such as the physical and chemical characteristics of the nanoparticles, their toxicity and stability issues, as well as

their pharmacodynamics and pharmacokinetic models in a specific situation, and their association with various tissues and cells. Besides the HIV vaccine development, more advanced research is also focused on the development of anti-HIV drugs, antiretroviral candidates, and nucleic acid-based therapies. One of the major hurdles faced in the case of HIV treatment is the target specificity of the drugs to the remote reservoirs like the bone marrow, brain, testicles, and other cellular and subcellular locations. Though the development of highly effective antiretroviral treatment has extensively boosted HIV treatment, it also gave rise to many after-effects like drug resistance, toxicity, low drug penetrability, and lower bioavailability. In addition, the advanced nanomaterials-based HIV treatment should emphasize these hurdles for better results. The advanced application of nanotechnology in HIV prevention, treatment, and therapies might result in the emergence of more effective therapeutic mediations for fighting against the dreadful disease HIV AIDS. Besides, compliance of regulatory aspects of use of nanotechnology in HIV treatment is another topic that needs to be clarified, and ethical reports should include detailed guidelines for using HIV related drugs. Furthermore, the convergence of AI technology with nanoscience should be explored for further improvement in targeted drug delivery mechanisms. The synergy between AI technology and nanoscience could catalyze the enhancement of highly tailored and specific targeted drug delivery treatments. These nano-carrier-based drug delivery signifies an exemplary shift in medicine, offering extraordinary prospects to develop patient health and well-being on a universal scale.

Abbreviations

AIDS, Acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; CD4+ T cells, helper T cells; BlBrnBr, blood-brain barrier; RNA, Ribonucleic acid; DNA, Deoxyribonucleic acid; Vif, Viral Infectivity Factor; Vpr, Viral Protein R; Nef, negative regulatory factor; CCR5, C-C chemokine receptor type 5; CXCR4, C-X-C chemokine receptor type 4; HAART, Highly Active Antiretroviral Therapy; CNrS, central nervous system; siRNA, small interfering RNA; NIMS, nanobased immunomodulatory system.

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Disclosure

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