Iranian Journal of Medical Microbiology | ISSN:2345-4342

Biological Aspects and Clinical Applications of Nanoparticles on Treatment and Prophylaxis of HIV

Mohammad Saeedi[1,2], Fatemeh Mehranfar[1,2], Shaghayegh Omidi[2], Fatemeh Zahra Ehsani[1,2], Omid Pajand[3*]

Department of Laboratory Science, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran
Student Research Committee, Semnan University of Medical Sciences, Semnan, Iran
Department of Microbiology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran

10.30699/ijmm.14.5.512

ABSTRACT

Acquired Immune Deficiency Syndrome (AIDS) is a descriptive type of immune system dysfunction disorder which is caused by HIV infection. Since its discovery, HIV has been responsible for the death of more than 25 million people worldwide, and many people are infected with HIV each year. Because of the structural complexity of the virus and the lack of a promising vaccine, several antiviral drugs, and nucleic acid therapies such as siRNA have been studied and evaluated for the HIV prevention. The antiviral treatments have considerably improved the quality and hope of life for the infected people, but along with the capacity to adapt to the virus, it has prevented further success. Nanotechnology approaches have had a positive impact on the prevention and treatment of different diseases. Various nanoparticles and substances have been evaluated for the antiviral drugs improvement for the prophylaxis and treatment of AIDS. Some nanoparticles which have been discussed in this article include liposomes, dendrimers, gold nanoparticles, polymeric nanoparticles, nanofibers, silver nanoparticles, and drug nanocrystals. In this review study, the nanotechnology approaches, the structure and properties of nanoparticles and their function in the prophylaxis and treatment of HIV were discussed.

Keywords: HIV, Nanoparticles, Gene therapy, Prophylaxis, Drug delivery

Received: 2020/06/08; **Accepted**: 2020/08/12; **Published Online:** 2020/09/26

Corresponding Information: **Omid Pajand,** Department of Microbiology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran
Email: om24pa@yahoo.com

Introduction

Acquired Immune Deficiency Syndrome (AIDS) is one of the basic public health issues in different societies. Unfortunately, the lack of awareness, equipment, and education has augmented the number of people suffering from this disease. Studies have shown that most individuals have this disease from adolescence. AIDS epidemics have significantly affected its side effects and mortality. It is estimated that 33.4 million people worldwide have HIV **(1)**, and 25 million people have died because of this disease **(2)**. It has been reported that more than 95% of individuals having HIV live in developing countries and more than 7 million are in Asia and the Pacific Ocean **(3)**. HIV is still an important problem for the public health, with about 1.8 million new cases of infection annually. It was reported that about 38 million people lived with HIV in 2018 **(4)**. New cases of HIV infection are decreasing annually; however, this decrease is not rapid enough to meet 90-90-90 target (90% diagnosis, 90% treatment, 90% virus surpass) until 2020 which

has been determined by the shared program of the United Nations on HIV and AIDS to end this disease **(5)**. To achieve the current target, which decreases the new cases of HIV infection to less than 500000 cases in 2020 throughout the world, producing durable, safe, effective, and acceptable products to decrease HIV sexual transmission is one of the most important priorities in preventing HIV **(6)**. The world program to remove AIDS infection among children until 2015 and keep their mothers alive include four items: 1) preventing AIDS transition to women of pregnancy age; 2) preventing unwanted pregnancies among women with AIDS; 3) inhibiting AIDS transmission using antiviral drugs during pregnancy and breastfeeding; and 4) providing care, therapy, and support for mothers, children, partners, and families that live with AIDS **(7)**. The service coverage for preventing HIV transmission from mother to child has been increased significantly since the beginning of world programs and reached 77% in 2015. As a result, new cases of HIV infection among children (0-14 years old) decreased by 51% from 2010. Moreover, the number of children receiving antiviral treatment has increased from 452000 in 2010 to 910000 in 2016, which decreased AIDS mortality among children by 44% **(8).** Remarkable development has been made in recognition of people with HIV: 21.7 million of the guesstimated 36.9 million people living with HIV worldwide are now on therapy **(9)**. The amount of AIDS-linked fatalities in 2017 was the lowest ever in the 21st century, and the occurrence of HIV infections has been lessening **(9)**. The limited access to treatment, especially for the people at risk, are barriers that need to be addressed **(10)**. The antiretroviral therapy is a treatment that does not cure the illness but is in high demand for the patients **(11)**. According to the World Health Organization (WHO), the instant action is required to control the disease **(12).** The HIV vaccine will presumably be needed to finish the HIV epidemics **(13)**. One of the most important features of HIV epidemics is the wonderful global genetic variety **(14)**. HIV variety influences the HIV diagnosis measurements, viral load evaluations **(15)**, expansion of drug resistance, and response to the antiretroviral therapy **(16, 17)**.

The goal of nanotechnology is to control substances at the atomic and molecular levels (18). The utilization of nanotechnology in medicine, referred to as nanomedicine, necessitates the application of nanoparticles for preventive, therapeutic, and diagnostic purposes **(19)**. Nanomedicine has made a considerable effect on the patients universally across different illness situations confining from hypercholesterolemia to macular degeneration and different cancers; present treatments Myocet for the breast cancer, Visudyne for macular degeneration and Tricor for cholesterol controlling **(20-22)**. The principal utilization of nanotechnology in the targeted drug delivery has been performed by nanoparticles that are particularly beneficial in the treatment of tumors **(23).** Nanoparticles play a significant role in the society via a diversity of applications ranging from electronics to medicine. Nano-compounds have been extensively exploited in biomedicine in various ways **(24-27)**. Nano-based delivery systems can be attuned to regulate medication release, lessen drug-related poisonousness, and protect medicines from metabolism **(28-31)**. Nanotechnology requires the synthesis and manipulation of the substances or systems where at least one dimension is in the nm size **(32-38)**. Particles in this size range have unrivaled physicochemical attributes, which are distinguished from those of bulk substances or single atoms or molecules **(33, 35, 36, 38, 39)**. The essential meaning of the application of nanotechnology-based systems for the antiretroviral medicine transfer is linked to the pharmacokinetics modulation of the synthetic molecules. The absorption, dissemination, and deletion in the human body are distinguished not by the medicine attributes, but the nanosystems physical and chemical attributes, especially surface-displayed molecules, electric charge, and the size **(40)**. The general attributes of nanosystems that are served in the antiretroviral medicine transfer contain adaptation, good toxicity characteristics, ability to modulate drug-dissemination, high drug payloads, and low expense **(41, 42)**. Some studies have demonstrated that nanomaterials can have a positive influence on the tissue repair **(43, 44, 45)**. Nanotechnology-based methods can be utilized to construct nanofibers and controlled-release nanoparticles to guide cell behavior. Nanoparticles have a high capability as carriers for the delivery of different molecules, including RNA, DNA, etc. The attributes and performance of nanomaterials have led to their application in the gene delivery programs **(46)**. Nanoparticles have been used as carriers for the drug delivery. Nanocarriers improve drug performance and reduce its side effects by altering the pharmacokinetic properties of the drug. In the manufacture of nanoparticles to transfer drugs, different materials such as polymers, metal particles, lipids, etc. are utilized, which can be produced depending on their production method, and disparate shapes and sizes. The future of research is on the development of multifunctional drug nanoparticles, such as particles with the targeted drug delivery capabilities.

1. HIV and Its Pathogenesis

HIV is a member of the Lentivirus genus and the *Retroviridae* family **(47)**. Lentiviruses share most of the morphological and biological characteristics. Most mammals are infected with Lentivirus, which is the cause of many long-term diseases with long latency **(48)**. Two types of HIV have been determined: HIV-1 and HIV-2. HIV-1 is the virus that was detected first. This has more viral load with more infectivity **(49)**, and is the main cause of HIV infections all over the world.

Milder infection of HIV-2 compared to the HIV-1 reveals that few people are exposed to HIV-2 infection. Due to low transmission capacity, HIV-2 is limited to some regions in the Western Africa **(50)**. HIV-2 is transmitted through sexual contact and blood and is rarely transmitted from mother to child **(51)**. Although HIV-2 causes AIDS, disease progress is slower than HIV-1 **(52-54)** and is generally less transmitted **(55)**. Molecular epidemiology studies have presented insights on the origin and patterns of wide geographical transmission of HIV-1 **(56)**. Young people between 15 and 24 years old are more exposed to this disease, and it is estimated that 6000 to 7000 individuals are infected daily **(57)** which 95% of them are in developing countries (58). Young men form one-fourth of the HIV patients and are exposed to HIV due to involving in high-risk behaviors **(59)**. After primary infection and local augmentation in the mucosa, the infected cells migrate to the local lymph nodes resulting in a slight primary viral reinforcement in the naïve T cells **(60)**. The viral infection is then rapidly disseminated by T cells to lymphoid organs, exclusively the lymphoid tissues related to the intestine, spleen, and bone marrow, being companioned by a burst in the viral load **(61)**. During the acute and early phases of the digestive system infection, it is exclusively affected by the virus, resulting in the considerable loss of CD4+ and CD8+ T cells, which is never fully ameliorated entirely and persist notwithstanding antiretroviral therapy (**62, 63**). People in the acute phase of infection are in the enhanced risk for the sexual transition as a consequence of high viral load in blood and reproductive tract **(64)**. In this case, the CD4+ T cell levels ameliorate soon after andCD8+ T cells ascend by a quick recovery of usual rates. The virus load is then decreased in the answer to the immune response, but is never entirely evacuated, eventuating in a latent, asymptomatic infection **(65)**. During latency, the virus insists on the extravascular tissues, dendritic cells, and resting CD4+ memory cells. This condition can be developed by diminished CD4+ T cell counts and escalating viral load **(66)**. By the development of infection, HIV genetic variety is enhanced dramatically owing to severe error-prone reverse transcription which helps to escape the immune system **(67)**.

2. Modalities for Prevention of HIV

2.1. Effects of Antiretroviral Drugs

2.1.1 Before Exposure

Initial treatment of individuals who are in contact with infected persons prevents AIDS transmission up to 96% **(68, 69)**. Prevention before exposure with certain doses of tenofovir with or without emtricitabine was effective in some groups which include gays or couples that one of them is infected **(70)**.

2.1.2 After Exposure

Prevention after exposure is the period of using antivirus, which is described as 48-72 hours after exposure to the infected blood or genital discharge **(71)**. Using zidovudine decreases HIV infection up to five times **(71)**. Current treatment programs generally use zidovudine or tenofovir/emtricitabine, and they can decrease the infection risk significantly **(71)**.

2.1.3 Mother to Child

If breastfeeding is only done by mother, long-term antivirus prevention period decreases the transmission risk **(72)**. This period includes using antivirus drugs during pregnancy, and after giving birth, and a special baby bottle should be used instead of breastfeeding **(73, 74)**.

2.2. Macromolecular Inhibitors

Various anionic macromolecules prevent HIV-1 from binding to CD4 via interactions with glycoproteins **(75)**. Therefore, their capability as a preventive method has been investigated in several clinical trials. However, macromolecular inhibitors demonstrated a supreme assurance in animal models; clinical trials in humans have shown no significant resistance to placebo **(75-77)**. Some inhibitors, for example, cellulose sulfate, have shown an augmented danger of HIV owing to the demolition of the vaginal epithelium **(77)**. Currently, nanotechnology-based macromolecular inhibitors are being evaluated in the clinical trials **(78-81)**. There is remarkable interest in expanding new vaginal ring designs for the continued release of large molecular weight, and particularly remedial peptides, and proteins. Much of the initiative in vaginal ring scheme has been driven by endeavors to extend microbicidal vaginal rings for the prophylaxis of sexual transmission of the HIV, and general-purpose prophylaxis technology rings for contemporary prophylaxis of HIV transferred infections **(82-84)**. Histone deacetylase inhibitors have been demonstrated to restrain HIV-1 infection in monocyte-isolated macrophages by activating SAMHD1 **(85)**. The HJ16 is a monoclonal antibody isolated from memory B cells from HIV-infected persons that can neutralize nearly 40% of HIV isolates **(86)**. The retrocyclins have been demonstrated to prevent the six-helix bundle formation of HIV, which is needed for the viral fusion **(87, 88)**. The M9 is an instance of single-chain antibody fragments efficacious against primary HIV in vitro **(89)**. The M36 molecule is an example of a heavy chain domain antibody that demonstrates higher neutralizing activity against primary HIV isolates in comparison with single-chain antibody fragments **(90)**.

2.3. Nucleic Acid Therapy (siRNA)

Detection of the RNA interference (RNAi) mechanism has revolutionized various bases, such as medicine. The RNAi uses an RNA structure to persuade

mRNA degradation in a particular sequence (91-94). In recent years, remarkable endeavors have been made to establish the RNAi structures for the HIV prevention with topical administration. It contains several HIV-1 encoded siRNAs such as tat, rev, pol, vif, env, vpr, and LTR that can prevent HIV-1 in the cells. The HIV transmission occurs through the use of different cellular recipients from the host (92-94). Thus, siRNAs targeting the expression of these recipients can prevent HIV. However, RNAi therapy can prevent HIV; although, there are different challenges with RNAi drug delivery. Severe hydrophilicity and an anionic load of siRNA substantially inhibit their cellular uptake (93-95). The advances in chemistry and drug delivery for remedial siRNAs have helped to prevail various obstacles to their clinical progress **(96)**. The transfection efficiency and cytotoxicity of the nanoparticles are the most significant parameters to be assumed for the siRNA delivery **(97)**. Among different nanocarriers utilized for in vitro and in vivo siRNA transfection, chitosan and its derivatives have attracted more attention for the treatment in the specific tissues such as lungs and colon **(98-100)**.

2.4. Nanotechnology for Prevention of HIV

According to the National Nanotechnology Improvisation, nanotechnology contains research of nm-sized substances in at least one dimension **(31, 101-104).** However, materials over 100 nm in size are also included under nanotechnology field. Currently, various nanotechnology-based products are being applied in the clinical trial. In recent years, various studies have focused basically on the use of nanotechnology to improve the therapeutic efficacy and target antiretroviral methods **(31, 101-107).** Their ability to combine, defend, and absorption of the non-orally prescriptible anti-HIV medicines, namely oligonucleotides **(108, 109),** significantly ameliorates the bioavailability of the various molecules **(110-112).** The application of nanoparticulate systems for the antiretroviral medication delivery can be especially beneficial for the targeted delivery, specifically to the cells that are straightly involved in Human Immunodeficiency Virus (HIV) **(41, 42).** The application of nanotechnology in medicine prepares innumerable facilities in the treatment of HIV **(113)**. Nanotechnology-based systems can influence drug delivery systems and ameliorate drug characteristics. They can also augment the effectiveness of treatment and lessen drug toxicity **(114)**. In HIV infection, CD4+ T cells are critical targets for the virus. This has stimulated a number of nanoparticle-based strategies to aim remedial factors like antiviral siRNA or antiretroviral drugs to CD4+ T cells to prevent HIV replication. Lipid nanoparticles enclosing the antiretroviral drug indinavir were aimed at CD4+ T cells using peptides that identify the CD4 co-receptor. Pre-treatment of CD4+ T cells with the targeted lipid nanoparticles resulted in a lessened number of the infected cells contrasted to the non-targeted lipid nanoparticles in vitro **(115)**. The NCT02549040 trial (phase 1) registered 16 patients and evaluated and compared the relative bioavailability of different MK-1439 experimental nano-formulations (NFs) with that of a MK-1439 film-coated tablet, in the patients with HIV-1 infection.

2.5. Nanotechnology and Gene Therapy

Nanotechnology-based gene therapy is a method of treating HIV by incorporating a gene into a cell that is associated with a viral infection or replication. Other compounds based on the nucleic acid can be used to interfere with viral replication **(116)**. Weber *et al.* have utilized carbosilane dendrimers to deliver siRNAs targeting HIV p24 **(117)**. The dendrimer siRNA collection demonstrated the best efficiency in HIV-infected peripheral blood mononuclear cells without any cytotoxicity, and maintained siRNA from degradation in the presentment of RNase. The dendrimer was examined in mice, and the efficient siRNA forwarding via blood-brain barrier was noticed **(118)**. The scientists in the University of California, Los Angeles have demonstrated that cell-derivative gene transmission is secure and active in people living with HIV. Delivery of particular CD4 siRNAs led to the RNA responses without side effects such as cell toxicity or immune stimulation. Antibody-based siRNA delivery displayed that the gag gene could suppress HIV proliferation in the initial T cells **(119)**. Another gene therapy method is to constantly inactivate CCR5 by the zinc finger nucleases. Zinc finger nucleases are genomic scissors containing DNA binding and cleaving domains **(120)**.

2.6. Nanotechnology and Vaccine

Nanoparticles not only prepare the ameliorated antigen delivery but also play a significant role in the starting immunity **(121-123)**. There are advantages in using nanoparticles in a vaccine structure. Nanoparticles can strengthen the absorbed antigens and act as an antigen **(121, 124)**. They can also imitate the characteristics of pathogens, such as viruses **(125)**. Nanoparticles can induce the adaptive and innate immune responses. They are applied as antigen carriers to augment the antigen processing and presenting, due to their high particular surface area and performance. These specifications of nanoparticles have led to the efficacious cell targeting and controlled release of the antigens **(126)**. Nanoparticles can enhance the half-life of most vaccines **(127)**. The first effort to obtain HIV antigens using liposomes was reported nearly two decades ago **(128).** Since then, the impact of various features including liposome components, ways of construction, HIV antigen, the path of prescription, and the sort of adjuvant for the expansion of liposomal HIV vaccines have been investigated, and research is still in progress.

Phillips *et al.* estimated the effect of liposome ingredients on the immune responses to HIV envelope glycoprotein gp120 after percutaneous prescription **(129)**. Polymeric nanoparticles are of immense interest in vaccine delivery because of having some attractive attributes, including biocompatibility, predictability, biodegradation, stability, easy surface modification, and the safety **(130)**. Polymer-based delivery systems demonstrated some advantages such as stable release, protection of the enclosed antigen against enzymatic degradation, targeted delivery, and adjuvant influences. Some polymer nanoparticles have been pursued for the development of mucosal vaccines to deliver antigens **(131-133)**. Carbon nanoparticles are utilized as another compound for the drug and vaccine delivery owing to their high biocompatibility. They can augment the level of IgG response by the protein antigen presentation **(134)**.

2.7. Nanomaterials for Prophylaxis and Treatment of HIV

2.7.1. Liposomes

Liposomes are vesicular carriers contained of two phospholipid layers and an aqueous nucleus. They are appropriate as drug carriers. It is worth noting that the aqueous nucleus is best to maintain hydrophilic drugs, while the two phospholipid layers maintain the hydrophobic and amphiphilic medicines. In addition, they are very useful for antiviral factors because of their native form that are taken up by the reticuloendothelial system and is rapidly removed from the bloodstream **(135)**. Liposomes were the first to be developed and also have the longest research history among all the commercial nanocarriers. The size of liposomes can be in the range of 80 nm-10 µm depend on the procurement way and combination. Many studies are providing detailed descriptions of liposome ingredients, ways of construction, types of liposomes, biophysical attributes, properties, and their usages **(136-138)**. The characteristic of liposomes to get quickly identified by the phagocytic cells of liver and spleen after intravenous prescription and get somewhat concentrated in lysosomes has been used for enhancing the prevention and treatment of different infectious illnesses **(137-141)**. The first liposomal formulation introduced to the world pharmaceutical market was the liposome containing doxorubicin called Doxil®. The presence of polyethylene glycol (PEG) on the surface of this liposome enhanced the half-life of doxorubicin **(142, 143)**. Malavia *et al.* formulated different liposomes, comprising cardiolipin and synthetic phospholipids by simple ethanol injection procedure. The combination of liposomes had a significant influence on the anti-HIV activity and the elective indicator of cardiolipin. Cardiolipin-tagged fluorescence liposomes were found to be maintained in the vaginal cavity of mice for almost 24hours after intrauterine prescription, and liposomal formulation had no side effects **(144, 145).** The MC-1220, a hydrophobic reverse transcriptase suppressor, was encapsulated in liposome and they were surrounded in Carbopol gel **(146)**. Liposomes have been utilized for the intravaginal transfer of siRNA targeting HIV-1 or HSV-2 **(147-149)**. Wu *et al.* expanded alginate-based scaffolds for the transfer of inert mucosal PEGylated cationic liposomes comprising fluorescently tagged siRNA **(148)**. It was perceived that liposomal siRNA could attain the vaginal epithelium and reticence gene expression **(148)**. The use of liposomes has also been presented in self-amplifying RNA vaccines transfer **(150)**. The liposomes used for this objective had significant countenances such as attendance of cationic lipid, ionizable lipid, and PEGylated lipids **(150)**. The liposomal AAR029b had the advantage of slower clearance rate, higher whole medicine exposure over time, and increasing serum half-life, resulting in the expansion of permanent proteolytic peptide triazoles for the HIV-1 treatment capability **(151)**. Surface-rectified liposomal nanocarriers have been used for the transfer of anti-HIV-1 drugs to provide access to lymphoid tissues **(152, 153)**. Liposomes are divided into cationic, anionic, and neutral types. Liposomes can retain the antigens from degradation, and increase their absorption by antigen-presenting cells. The cationic liposomes are usually applied in the adjuvant delivery system in DNA vaccines **(154)**. The following Tables highlight the clinical trials on the effects of nanoparticles, especially liposomes, in the treatment and prevention of HIV-related diseases (Tables 1 and 2) **(155)**. The hydrophobic and hydrophilic nature, biocompatibility, and ease of surface changes are among the factors that introduce liposomes as a suitable option for the drug delivery.

Table 1. Ongoing clinical studies exploring the contribution of liposomes

Conditions	Treatment Source	Enrollment	Phase	Sponsor	Clinical trial number
HIV-1-infection	ConM SOSIP.v7 gp140, adjuvanted with MPLA liposomes	24	Phase 1	Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	NCT03961438
People With Advanced or Refractory Kaposi Sarcoma	Pomalidomide in Combination With Liposomal Doxorubicin	99	Phase 1	National Cancer Institute (NCI)	NCT02659930

Table 2. Completed clinical studies exploring the contribution of liposomes

Conditions	Treatment Source	Enrollment	Phase	Sponsor	Clinical trial number
Severe AIDS-Related Kaposi's Sarcoma.	Doxorubicin hydrochloride (liposomal)	-	Phase 3	Sequus Pharmaceuticals	NCT00002147
Kaposi's Sarcoma in Patients With AIDS	Comparison of Liposomal Doxorubicin Used Alone or in Combination With Bleomycin Plus Vincristine	120	Phase 2	National Institute of Allergy and Infectious Diseases (NIAID)	NCT00001059
AIDS-Related Kaposi's Sarcoma	Randomized, Comparative Trial of DOX-SL (Stealth Liposomal Doxorubicin Hydrochloride) Versus Bleomycin and Vincristine	220	Phase 3	Sequus Pharmaceuticals	NCT00002105
AIDS-Related Kaposi's Sarcoma	Doxorubicin hydrochloride (liposomal) (DOX-SL)	-	Phase 3	Sequus Pharmaceuticals	NCT00002319
Patients With Newly Diagnosed Burkitt's Lymphoma or Burkitt-Like Lymphoma	Doxorubicin Hydrochloride Liposome and Rituximab With Combination Chemotherapy	25	Phase 2	Northwestern University	NCT00392990
Acquired Immunodeficiency Syndrome	Safety and Efficacy of Amphotericin B Lipid Complex in the Treatment of Cryptococcal Meningitis	-	NA	Liposome	NCT00002019
HIV-Associated Kaposi's Sarcoma	A Randomized Phase III Clinical Trial of Daunoxome Versus Combination Chemotherapy (Drug: Daunorubicin (liposomal) Drug: Bleomycin sulfate Drug: Vincristine sulfate Drug: Doxorubicin hydrochloride)	-	Phase 3	Nexstar Pharmaceuticals	NCT00002093
Adults With Advanced Kaposi s Sarcoma	Pilot Study of Liposomal Doxorubicin Combined With Bevacizumab Followed by Bevacizumab Monotherapy	16	Phase 2	National Cancer Institute (NCI)	NCT00923936

2.7.2. Dendrimers

Dendrimers are a type of polymeric nanostructures by special properties. Unlike normal linear polymers, dendrimers are composed of orderly monomeric branched macromolecules with unique structural specifications and have extremely branched three-dimensional tree-similar structures. They have the accurate number of terminal groups (102, 106, 156). They are usually less than 100 nm in size, with a narrow molecular weight, which are easily involved with the objective ligands. They are attracted to the ligands as suitable applicants for the drug delivery, particularly HIV because they can be applied separately from the virus for the target cell. Dendrimers have a low dispersion index and a high capability. Phosphorus dendrimers can transmit different siRNAs simultaneously. Three anticancer Bcl-2 family siRNAs could be transferred by phosphorus dendrimers **(157, 158)**. Dendrimers are determined by the attendance of three various topologic sites, multipurpose core, inner layers, and multi-agent surface **(102, 106, 156, 159)**. Dendrimers with the groups such as Ag NPs perform as anti-HIV activity as they incorporate with the gp120 of HIV, blocking the conjugation of HIV with CD4 of the host cell **(160)**. Dendrimers can be actively used as local microbicides. They are the only nanotechnology that has progressed to the human clinical trials for the HIV prevention **(102)**. The BRI2923 dendrimer not only blocks the virus entry but also restrains the reverse transcription of HIV replication

(161). Several researches on the linear multipolar suppressors offered a base for the convenient dendrimers design. The anionic moieties of the linear multipolar suppressors hinder the viral fusion to the cell membrane by attaching to the viral glycoproteins, including gp120 and gp41 (162). Sattin and co-worker, illustrated that tetravalent Boltron dendrimers terminated with linear trimannoside mimics (denominated as Dendron-12) could hinder infection of lymphocytes by CXCR4-(X4) and CCR5-utilizing HIV-1 strains (163). Dendron-12 considerably lessened HIV infection. Therefore, glycodendrimers could have the capability for the long-duration prevention (163). Dendrimers and liposomes have been characterized to augment antigen presentation in the human dendritic cells. It has been demonstrated that modification of liposome and dendrimers with the Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin binding glycans leads to the efficacious MHC presentation to CD cells (164). There are several methods based on the polyamidoamine dendrimers to struggle HIV-1. Polyamidoamine dendrimers can prevent HIV replication by binding to viral mRNA TAR and can be a significant member of the virus life cycle that frustrates TAR RNA (165-168). The capability of phosphorus dendrimers to transmit different types of biological molecules is well established. The phosphorus dendrimers affiliated with HIV-isolated peptides deliver HIV-1 peptides effectively and are applied instead of viral carriers (169). The phosphorus dendrimers augment peptide loading into the dendritic cells considerably and affect the capability for the cytokine secretion (169). Researches have demonstrated that a series of quinolone-3-carboxylic acids have remarkable anti-HIV activity (170). About 20 and 30%of the HIV-1 rate was inhibited by poly(propylenimine) decorated with sulfonate (PPI-S) and poly (propylenimine) decorated with carboxylate (PPI-C) dendrimers (171). The anti-HIV activity of G2 dendrimer illustrated that all concentrations of this dendrimer could inhibit HIV infection (172). The SPL7013 (VivaGel), a type of dendrimer, prevents viruses' attachment and entry (161). Different studies have mentioned a wide range of antiviral activities for the SPL7013 against HIV and HSV (Table 3) (173)..

Table. 3. Completed clinical studies exploring the contribution of dendrimer

Conditions	Treatment Source	Enrollment	Phase	Sponsor	Clinical trial number
HIV	3% w/w SPL7013 Gel (VivaGel™)	36	Phase 1	Starpharma Pty Ltd	NCT00370357
HIV Infections HSV-2 Genital Herpes	3% SPL7013 Gel (VivaGel)	12	Phase 1 Phase 2	Starpharma Pty Ltd	NCT00740584

2.7.3. Gold nanoparticles (Au NPs)

Gold is used in the biomedicine field. It has been used to treat inflammation since the early 20th century (174). The toxic effects of gold nanoparticles (Au NPs) was shown by research performed by Qiu *et al.* to disturb gene expression (175). Michael Faraday used colloidal Au NPs to design and prepare nano substances (176). The Au NPs are one of the most immensely studied nanoparticles in nanotechnology when evaluated for other metal-based nanomaterials. Their highly desirable attributes, including a large surface area-to-volume ratio, biocompatibility, exclusive optical and electronic attributes, and easy surface manipulation, have led to the severe focus on Au NPs for both academia and industry (177). The Au NPs can be extensively utilized to adsorb biomolecules like proteins and antibodies onto their surfaces (178). Different researches have demonstrated the capability of using Au NPs in some phases of clinical trials. The photothermal impact applied the unprecedented visible tunability of Au NPs that can transform the light into the heat to thermally kill prostate cancer (179). The Au NPs properties made them tremendous scaffolds for the extensive application in treatments, diagnosis, and drug transfer (180, 181). The Au NPs have been widely studied for a variety of medical applications (182). The synthesis of Au NPs can be accomplished using several ways, including the chemical reduction of salts, aerosol techniques, photochemical diminution of gold, and biological synthesis (183, 184). The Au NPs, in composition with chitosan, loaded with tetanus toxoids, substantially augmented the immune response in oral prescription (185). The Au NPs are extensively illustrated to be appropriate for many biosensing functions and applications. Their unprecedented photonic and catalytic attributes, coupled with the molecular interactions, particularly different biomolecules, demonstrated the design of an extensive range of the virus detection systems (182, 186, 187). Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin targeting methods have also been studied to design anticancer vaccines (188). In the context of HIV, the Au NPs presenting innumerable copies of the structural shapes of the N-connected high-mannose glycan are advantageous restrainers of Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin interceded infection of human T cells (189). The Au NPs could augment the innate immunity and cell uptake by a supplement associate mechanism that could propagate immune responses (190). The Au NPs enhanced IL-12 secretion (191). The Au NPs carrying TNF-α are presently used in clinical trials for the cancer treatment. Conversely, articles have concentrated on the

use of Au NPs for the HIV therapy or prevention. Melander and co-workers found out that Au NPs and SDC-1721 alone were not equal in inhibitory activity against HIV-1, but their conjugation demonstrated IC_{50} value against HIV-1 **(192)**. The Au NPs ameliorated the antiviral capability of CCR5 antagonist **(192)**.

2.7.4. Polymeric nanoparticles

Polymeric nanoparticles have different sizes from 10-1000 nm **(193)**. They contain synthetic homopolymers, intrinsic polymers, colloidal stabilizers, nanospheres, and nanocapsules. If the medications are surrounded inside the polymeric membrane, they are denominated nanocapsules. Furthermore, if medications are constantly physically interspersed in the polymeric matrix, they are named nanospheres. The most common and widely used polymeric nanoparticles are poly-lactic-co-glycolic acid, poly-alkylcyanoacrylates, polymethylmethacrylate, polyvinyl pyridine, polyacrylamides, polyethyleneimine, human serum albumin, chitosan, and gelatin **(194)**. The internalization of these nanoparticles is frequently via endocytosis, and the rate of uptake is assigned by their concentration and time. Furthermore, other systems comprise phagocytosis, fluid-phase pinocytosis, and recipient-mediated endocytosis **(195)**. The therapeutic factors can be solubilized, encapsulated, adsorbed, or combined with polymeric nanoparticles by variant procedures **(193)**. Several procedures have been extended to engineer polymeric nanoparticles that can transport a diversity of drugs also biomolecules resembling proteins and siRNA **(196)**. Ensign *et al.* have lately estimated the capability of acyclovir comprising poly-lactic-co-glycolic acid NPs to hinder HSV infection **(197).** The authors engineered normal poly-lactic-co-glycolic acid particles also poly-lactic-co-glycolic acid nanoparticles with rapid penetration into the vaginal mucus. The authors displayed that simple coating of poly-lactic-co-glycolic acid particles with Pluronic F127 represents the quick mucosal pervasive capability to poly-lactic-co-glycolic acid particles. A considerable amount of mucus penetrating poly-lactic-co-glycolic acid particles was maintained in the genital of mice compared to the normal poly-lactic-co-glycolic acid particles. Besides, normal poly-lactic-co-glycolic acid nanoparticles induced acute inflammatory responses similar to Nonxynol 9 after prescription, while mucosal pervasive NPs did not demonstrate such occurrences. Intravaginal prescription of acyclovir comprising mucus pervasive nanoparticles was established to keep a remarkably higher number of mice compared to the acyclovir solution. Moreover, the concentration of acyclovir dilution was 10 times higher than acyclovir NPs and presented 30% defense **(197)**. Zhang *et al.* and Meng *et al.* concentrated on extending polymeric NPs for transporting tenofovir. They expanded pH-sensitive poly-lactic-co-glycolic acid nanoparticles and also mucosal chitosan NPs for vaginal transfer of tenofovir **(198, 199)**. Polymer nanocapsules were utilized to directly transmit nucleoside reverse transcriptase inhibitors to the cytoplasm **(200)**. Poly Lactic-co-glycolic acid particles surrounding HIV-1 peptide antigens prescribed through the intranasal route evoked Th1/Th2-equilibrated cellular immune responses in mucosal surfaces **(201)**.

2.7.5. Nanofibers

Nanofibers are similar masses with diameters range from 1-1000 nm **(202-204)**. The extensive types of polymers have been electrospun to provide nanofibers. So far, more than 200 polymers have been used to manufacture the nanofiber structures. Generally, nanofibers are produced by applying the electrospinning method **(205)**. It is conceivable to alter the diameter, length, and the pore size of nanofibers by regulating specifications of the electrospinning procedure. The nano-scale dimensions of nanofibers are entirely close to that of extracellular matrix fibers **(202-204)**. Different factors affect the drug loading efficacy of electrospun nanofibers. Universally, drug solubility in the chosen solvent, polymer density, procedure of electrospinning, and medicine loading technique are among the significant factors that affect drug loading capacity of nanofibers. Lately, Xu and colleagues illustrated that 89% of drug loading capacity of paclitaxel in provided nanofibers could be linked to higher solubility of provided paclitaxel succinic acid complex in the chosen solvent system chremophor **(206)**. Paskiabi and colleagues demonstrated 100% drug loading efficacy of terbinafine in polycaprolactone nanofibers, which could be related to the high drug solubility in the chosen solvent system. The passive equilibration technique yields greater loading efficacy than the active loading technique **(207)**. The use of electrospun nanofibers in the pharmaceutical delivery application is very promising. The electrospun nanofibers have been applied in the drug delivery system for treating different illnesses which obtained popularity in the context of pharmaceutics **(208-211)**. Nanofibers have been studied and explored for transferring different microbicides for the HIV prevention **(212)**. Huang *et al.* constructed nanofibers of cellulose acetate phthalate (CAP), a macromolecular HIV-1 entry suppressor. The CAP nanofibers were well endured by vagina l epithelial cells and vaginal microflora. Owing to the pH-sensitive essence of CAP, nanofibers retained entirety in the acidic pH. Adding semen to the nanofibers resulted in an instant solution of CAP. The CAP nanofibers maintained the capability to hinder the HIV-1 entry. In addition, a combination of tenofovir with CAP nanofibers ameliorated its antiviral activity considerably **(212)**. Woodrow and co-workers synthesized nanofibers of different biodegradable polymers, including poly lactic acid and poly-caprolactone **(213)**. Nanofibers continued to be used as microbicides and displayed antiviral activities using in medicine. Intravaginal prescription of fluorescent

nanofibers demonstrated their maintenance in genital area **(213)**.

2.7.6 Silver Nanoparticles (Ag NPs)

Otiriou and Pratsinis (214) demonstrated that silver nanoparticles (Ag NPs) on nano-structured SiO2, gained by flame aerosol technology, authorized close control of silver content and size. The Ag NPs with comparatively narrow size dispensation were procured by flame spray pyrolysis **(215)**. The Ag NPs have demonstrated great bactericidal attributes against extensive range of microorganisms **(216-219)**. The biogenic synthesis of Ag NPs includes bacteria, fungi, and plant distillates **(218-223)**. In addition to antibacterial and antifungal activities, Ag NPs have antiviral activity and affect different types of viruses, including HIV and HBV **(224, 225)**. The Ag NPs can simplify the electron transfer from the reaction center to the electrode surface, which makes them able for higher severity electron transmission. The Ag NPs have few desirable attributes such as ease-of-functionalization, good biocompatibility, ease of immobilization of biomolecules, and the ability to increase the electrochemiluminescence severity of luminophores. These actualities have resulted in Ag NPs to be incorporated in electrochemiluminescence nanobiosensor fabrication **(226)**. The Ag NPs are extensively utilized to treat wounds and the control of different infectious diseases **(227, 228)**. The Articles have displayed that silver has both antibacterial and antiviral activities **(229, 230)**. There are several medical applications for the Ag NPs. They can be applied for drug transfer, and medical devices **(231-233).** The Ag NPs represented different modes of antiviral mechanisms against different viruses **(234)**. Elicheguerra *et al.* indicated the influence of Ag NPs on HIV-1 **(235)**. The Ag NPs covered with polyvinyl pyrrolidone were effective against a range of HIV-1 strains containing M tropic species, T tropic species, and medicine resistant breeds **(235, 236).** The Ag NPs showed considerably better electivity index than silver salts demonstrating the significance of the nanosize of the particles. Researches displayed that Ag NPs can bind to disulfide bonds in the CD4 binding domain of the envelope glycoprotein gp120 and exclude CD4-mediated viral fusion to the host cells **(236)**. The Ag NPs operated as antiviral factors against HIV-1, where Ag NPs prevent the replication of HIV-1 by interacting with the disulfide bond of CD4 of envelope glycoprotein gp120 receptor. The Ag NPs inhibited hepatitis B virus RNA by blocking the manufacture of extracellular virions in vitro **(234)**.

2.7.7 Drug Nanocrystals

Nanocrystals are stabilized by the aqueous surfactant dilutions. The subsequent high drug loading proportion restricts inconsistency and toxic responses related to the excipients **(237)**. The long-term drugs indicate improved treatment outcomes for HIV. The application of antiretroviral therapy can lessen the systemic toxicities, diminish viral mutations, and reduce HIV stigma, which can be affected by the long-term dose intervals and lower fluctuations in the drug concentrations **(238, 239)**. The pharmaceutical nanocrystals are solid drug particles that are sometimes referred to as solid micelles. Nanocrystals are unstable due to their small size, and a stabilizer is needed to prevent the accumulation of nanoparticles **(240-242)**. Nanocrystals have been reported to be in the crystalline condition, which is true in most cases, but has been expanded to characterize nanosized suspensions of crystalline **(243)** which alters from the crystalline to the amorphous form pending processing **(244, 245)**. Nanocrystals also augment adhesiveness to the digestive system mucosa and accordingly enhance the absorption through the digestive system **(246).** Jain *et al.* demonstrated that nanosuspensions of ciprofloxacin could treat typhoid fever **(247)**. The pharmaceutical nanocrystals are nanoparticles that disperse in an aqueous or non-aqueous environment. The pharmaceutical nanocrystals also comprise a convenient stabilizer to retain long-term colloidal consistency **(107, 248)**. Baert *et al*. expanded the nanocrystals of rilpivirine with the assistance of the media milling method **(249)**. Rilpivirine nanocrystals were perfused in mice and dogs and their pharmacokinetic behavior was investigated. The procedure demonstrated traceable rilpivirine levels in mice displaying their productivity in the long-term prevention of HIV **(249)**.

Conclusion

The presentation of nanotechnology in the context of drug delivery has opened up new approaches to the expansion of therapeutics for the treatment of various complex diseases, including cancer and infectious diseases. Nanotechnology has many benefits in providing anti-HIV remedies. Some nanomedicine approaches are used to treat patients with a wide range of conditions. Conforming to the published results of clinical and animal models, the effect of nanoparticles on the treatment and prophylaxis of HIV can be understood by the approaches such as drug delivery, gene therapy, and vaccine. The use of nanoparticles in the treatment and prophylaxis of HIV can be likened to a two-edged sword. In the future, nano particle-based clinical research should consider a variety of issues, including the development of pharmacodynamic and pharmacokinetic models in different situations, the sustainability of nanoparticles, and the interaction with tissues and cells.

The use of this technology in the treatment process has limitations and challenges that need to be addressed, and more research is needed. Nanoparticles can also be used to treat AIDS-related diseases such as Burkitt's syndrome. With the

development of nanotechnology and its effectiveness compared to the other sciences, different types of nanoparticles with different structures and ingredients were introduced, each of which has its own strengths and weaknesses and have been able to take an efficacious step in improving and preventing AIDS. One of the most widely used fields of nanoparticles is drug delivery, by which nanoparticles are able to play a major role in ameliorating drug delivery in several diseases in the form of polymer, lipid, metal, etc. carriers. In the studies reviewed in this article, by comparing the performance of each type of nanoparticles on the prophylaxis and treatment of AIDS, the considerable influences of liposomes and dendrimers compared to the other nanoparticles were noticed. In this article, we explored the capability of nanotechnology to provide an approach to HIV treatment and prophylaxis. New expansions in the antiviral drug systems are stabilizing this strategy as a therapeutic approach to HIV. Generally, the nanotechnology provides many interesting opportunities for the advanced HIV therapeutic and prophylaxis contexts.

Acknowledgment

The authors thank all those who helped them writing this article.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Funding and support

This research resulted from an independent research without receiving any financial support.

Conflict of Interest

Authors declared no conflict of interests.