WWW.IJRPR.COM

International Journal of Research Publication and Reviews

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

EMERGING NANOTECHNOLOGY APPROACHES FOR HIV/AIDS TREATMENT AND PREVENTION: A REVIEW

Subhashish Mahakur[1], Ms. Sarita Sharma[2], Dr. Gaurav Kumar Sharma[3], Dr.Kaushal Kiashore Chandrul[4]

[1]STUDENT OF B. PHARMA (4TH YEAR), [2]PROFESSOR, [3]H.O.D, [4]PRINCIPLE
DEPAETMENT OF PHARMACY MEWAR UNIVERSITY CHITTORGRH (RJ), INDIA

ABSTRACT

There is currently no treatment for HIV/AIDS and no vaccine to prevent it. Combination antiretroviral medication has significantly improved treatment, but it must be used for the rest of one's life, has serious side effects, and is useless in people whose viruses become resistant to it. In the twenty-first century, the multidisciplinary science of nanotechnology is changing medicine. It has the potential to significantly advance HIV/AIDS therapy and prevention. In this evaluation, we go over the problems with the disease's present therapy and highlight the amazing potential of nanotechnology to give more efficient antiretroviral therapy, gene therapy, and immunotherapy for HIV/AIDS treatment and prevention, microbicides and vaccination.

The main routes for the particle to reach the body include inhalation, direct injection, and oral ingestion. It has been demonstrated to have the potential to improve viral agent prevention and therapy. In vitro testing of several NPs revealed self-therapeutic efficacy against the virus.

Keywords: AIDS, antiretroviral therapy, gene therapy, HIV, immunotherapy, microbicides, nanomedicine, nanoparticles, nanotechnology, vaccines

1. INTRODUCTION

There is now no effective treatment for the HIV virus, which affects over 37 million people globally. The virus comes in two primary varieties: HIV-1 and HIV-2. The focus of the treatment options presented in this study is HIV-1, which is more common and harmful and preferentially infects CD4+ T cells. Assistive cells. Dendritic cells, macrophages, and other cell types are also susceptible to HIV-1.Despite the fact that the mechanisms of infection for microglia and astrocytes have not yet been identified fully comprehended HAART(highly active antiretroviral therapy) is a successful HIV-1 treatment plan, yet it allows the virus to continue to exist and does not offer patients a functional or sterilising cure. Additionally, HAART (highly active antiretroviral therapy) results in a number of harmful comorbidities. Since HAART (highly active antiretroviral therapy) targets the HIV-1 replication cycle, HIV-1 evades targeting by undergoing latency. The onset of AIDS was initially noted in 1981, and HIV was then recognised as the disease's aetiology in 1983. As the world's most common infectious killer of adults, HIV/AIDS has now spread globally. Globally, 25 million people had died from AIDS by 2006, and more than 65 million individuals had contracted the HIV virus. About 33 million individuals were infected with the virus as of the end of 2007, and 2 million people died from it annually. Globally, this has had a significant negative social and economic impact, notably on emerging nations in Sub-Saharan Africa.

Numerous fields of medicine are being advanced by the emerging science and engineering discipline of nanotechnology. It entails a grasp of how materials operate at the atomic and molecular level as well as its design, engineering, and manufacture. The National Nanotechnology Initiative defines nanotechnology as the study of structures having a size of around 1-100 nm in at least one dimension, however applications using structures as small as several hundred nm are also taken into consideration. Nanomedicine, or the application of nanotechnology to medicine, involves the use of tiny materials for therapeutic, diagnostic, and preventive reasons. Over the past few decades, nanomedicine has made significant strides, particularly in the detection and treatment of cancer. Applications of nanotechnology for HIV/AIDS prevention and therapy, however still in its early stages. Additionally, certain nanomaterials work as medicines on their own. Additionally, nanotechnology has a significant impact on the development of vaccinations and microbicides, two preventive measures. In this examination, we go through the likelihood that Nanotechnology advances novel therapeutic approaches, enhances current treatments, and offers alternatives to the search for a vaccine and advancements in microbicides for HIV/AIDS.

2. NANOTECHNOLOGY FOR HIV/AIDS TREATMENT

Platforms based on nanotechnology that transport antiretroviral medications throughout the body may offer comparable benefits. Their half-lives can be lengthened by controlled-release delivery systems, which keeps them in the bloodstream at therapeutic concentrations for prolonged periods of time. This could have a significant impact on enhancing medication adherence. Due to their small size, nanoscale delivery methods also improve and regulate the distribution of hydrophobic and hydrophilic medicines into and throughout various tissues. The most promising aspect of nanoscale delivery systems for the therapeutic treatment and prevention of HIV appears to be this particular characteristic.

Nanosuspensions (200 nm) of the medication rilpivirine (TMC278) stabilised by polyethylene-polypropylene glycol (poloxamer 338) and PEGylated tocopheryl succinate ester (TPGS 1000) were examined in dogs and mice in a recent study based on polymeric systems [35]. Compared to a half-life of 38 hours for free medication, a single dose of the drug administered in nanosuspensions caused sustained release over 3 months in dogs and 3 weeks in mice. These findings show that nanoscale medication delivery has the potential to reduce dosage frequency and boost adherence.

Types of Nanoparticles and Nano pharmaceuticals:

1. Organic Nanoparticles
    - Polymeric Nanoparticles
    - Nano capsules
    - Nanospheres
    - Liposomes
    - Micelles
    - Dendrimers
2. Solid Lipid Nanoparticles
3. Inorganic Nanoparticles
    - Gold Nanoparticles (GNPs)
    - Silver Nanoparticles (SNPs)

1. **Organic Nanoparticles**: - In the delivery of pharmaceuticals and for therapeutic use in human systems, organic nanoparticles are the most extensively investigated and widely accepted type of nanoparticle. The prevalent types of organic nanoparticles include:

    - **Polymeric Nanoparticles**: - Solid colloids called polymeric nanoparticles range in size from 10 to 1000 nm. Smaller size improves capillary entrance and cell absorption, resulting in higher concentrations at the target sites. NPs produced from biodegradable and Biocompatible polymers have undergone substantial research in order to therapy providers. Those in use in medicine and pharmacology Polyglycolides are approved by the WHO and FDA. Polylactides (PLA), poly (PGA), and poly (lactide-coglycolides) Poly (D,L-lactide-co-glycolide, or PLGA) (PLG)PLGA-based nanoparticles are widely utilised because to their excellent capacity for biocompatibility and biodegradation. They frequently have the ability to increase the effectiveness and the security of the pharmaceuticals they contain. It can be classified as nanospheres or nano capsules.
    - Nano Capsules: - With a size range of 50 to 300 nm, high loading capacity, and low density, nano capsules are spherical hollow spheres with coats of polymers inside.

    - **Nanospheres**: - They have a matrix system with a size range of 100 to 200 nm in which the medicine is evenly distributed. Numerous studies on the therapeutic potential of nanospheres for viruses other than HIV/AIDS have been conducted.

    - **Liposomes**: - The first NP platform for the transfer of genes and medications is liposomes. They are 20 to 30 nm-sized sphere-like vesicles. It is composed of a bilayer phospholipid structure with an aqueous structure at its core. Drugs that are hydrophilic or lipophilic can be added to the inner aqueous cavity or bilayer phospholipid, respectively. Liposomes are distinguished by their diverse compositional range, capacity to contain and safeguard a variety of biomolecule types, and biodegradable and biocompatible properties. Due to their potential as immunological adjuvants, liposomal formulations are heavily studied in vaccination. We have roughly twelve liposome-based medications with clinical registration.

    - **Micelles**: - Micelles have a diameter that ranges from 10 to 100 nm. They are composed of an exterior water-loving polymer and an interior water-phobic core. They consist of polymeric micelles, which have drawn interest as vehicles for drug delivery with significant therapeutic potential. One intriguing application of nanotechnologies that can increase the water solubility and stability of unstable medications is the encapsulation of pharmaceuticals in polymeric micelles. Micelles' lower dissociation rate, which increases medication retention duration and accumulation at the target site, is a major benefit of using them in treatment.

    - **Dendrimers**: - Having a structure of hyper-branches that emerge from a central stick through connectors and units of branches, dendrimers are symmetrical macromolecules where interaction occurs. The terminal groups are in charge of managing the target domain. These feature three distinct domains and are spherical in shape. groups functioning. The outside face could be changed to create chemical functional groupings for groups you want to target molecularly, detecting, imaging, and therapeutic agent's website attachments.

2. **Solid Lipid Nanoparticles (SLNs)**: - As an alternative to the generic colloidal nanoparticles stated above, SLNs are a method of medication delivery. The use of SLNs also benefits from the coupled traditional nanocarriers while staying away from their drawbacks for instance, mass production of polymeric nanoparticles is a major obstacle that lowers the use of medicine delivery, whereas Financial support can be provided for the synthesis of SLNs, and otherwise.

3. **Inorganic Nanoparticles**: - Compared to organic nanoparticles, inorganic nanoparticles are substantially smaller in size. Its 1-100 nm size ranges have improved loading efficiency. Inorganic nanoparticles can be produced in two main ways: "top-down" methods that use physical and/or chemical methods to reduce the inorganic nanoparticles to their usual nanosized size, and "bottom-up" methods that develop the nanoparticle step by step. In particular, the shape and size of the nanoparticles can be modified by the reaction conditions, whilst the choice of reducing agent can change other aspects of the nanoparticles, such as their loading capacity and aggregation and release profiles.

    - **Gold Nanoparticles (GNPs)**: - Due to their excellent conductivity, flexibility in surface modification, biocompatibility, and simple production methods, GNPs are being extensively explored as nanoparticle carriers. Their distinctive physical and chemical characteristics, photophysical characteristics, and adaptability of functionalization through thiol linkages are among their other advantages.

    - **Silver Nanoparticles (SNPs):** - Due to the intrinsic inhibitory and antibacterial properties of silver as well as their improved conductivity, catalytic properties, and chemical durability, SNPs are the important inorganic nanoparticles with effectiveness and efficacy. The primary mechanism of action of SNPs is the release of silver ions, which boosts the activity of antimicrobials and causes cell membrane deformation and denaturation of nucleic acids.

3. FEATURES OF NANOPARTICLES AND NANOPHARMACEUTICALS IN THE SYSTEM

The three main ways that nanoparticles reach the body are through oral ingestion, direct injection, and inhalation. The first thing that happens after circulation and before distribution to the appropriate organs once the particle and protein have entered the system is their contact. The lymphatic system receives the particles once they are taken up from the blood capillaries and gives and destroys them further. The system primarily plays three roles. The lymphatic system filters fluids from blood capillaries during fluid recovery, which comes in at number one. In the second, which deals with immunity, the body absorbs foreign particles from the tissues and gains back more fluids. The lymphatic nodes detect any odd particles leaving the body as the liquids are filtered into the blood stream. If it is recognised as weird and unfamiliar, macrophages promptly ingest it and remove it from the body.

The following are the features of nanoparticles in the system:

Shape and Size of Particles The interactions, target, and toxicity capacity of nanoparticles are determined by their size and shape, which also affects how cells perceive them. It is important to note that nanoparticles can cross the BBB, providing a reliable drug delivery system for illnesses that may be difficult to treat. This approach can be changed to stop the spread of medications and the ability to reach new target locations. According to reports, 100 nm nanoparticles exhibited an absorption that was 2.5 times greater than that of 1 m diameter particles and 6 times greater than that of 10 m diameter particles. The surface area to volume ratio of particles increases as their size decreases. In contrast to a larger molecule, this indicates that the medicine is located closer to the particle surface. Greater proximity to the surface might cause rapid drug release. A system of nanoparticles with a higher surface area to volume ratio for monitoring toxicity would be useful.

Surface Properties:

The adjustment of surface properties offers yet another opportunity to develop a strong system. The correct targeting ligands, reactivity, and surface curvature must be included in the creation of an effective nanoparticle drug delivery systemin order to assess the regimen's stability, pharmacological effects, control of complexes, and receptor binding. Due to the increased adsorption of blood components, the more water-fearing a nanopharmaceutical is, the more likely it is to be removed. It seems technical to speculate that creating a water-loving surface will lengthen the duration that water-fearing nanoparticles circulate because they are destroyed quickly. Polyethylene glycol, polyethylene oxide, poloxamine, polyoxamer, and polysorbate 80 have all demonstrated their effectiveness in reducing opsonization when applied to nanoparticles. When attached to the surface of nanoparticles, PEG, a water-loving inert polymer, prevents opsonization and hence controls the significant loss of the precise dose. Due to their ability to opsonize, these nanoparticles are frequently referred to as "stealth" particles. Particularly more likely to agglomerate are dendrimers and micelles nanoparticles. It has been suggested that covering particles with agents of capping and changing surface charges are effective approaches to prevent aggregation.

Load and Release of Drug:

Nanoparticles have been researched for their high stability, decreased clearance, and optimised bioavailability. If the medicine is not then loaded and released from the nanoparticle's matrix, the procedure will not be complete. Temperature, pH, drug solubility, surface-bound drug desorption, drug diffusion via the nanoparticle matrix, swelling and erosion of the nanoparticle matrix, and the synergy of the diffusion and erosion processes are just a few of the crucial factors that affect the release of drugs from nanoparticle-based formulations. The medicine is physically and evenly distributed within the matrix system of nanospheres, where it is released through matrix erosion. If the drug is in nano capsules, the release is tracked by drug diffusion through the polymeric layer. A fast burst of the drug releases weakly bound drug to the greater surface area of the nanoparticle and then an advanced release.

4. NANOTECHNOLOGY FOR HIV/AIDS TREATMENT

Nanotechnology for antiretroviral drug delivery:

Numerous aspects of illness therapy are being revolutionised by the use of nanotechnology platforms for medication delivery. Since there have been considerable advancements in the last few decades, cancer patients have so far benefited the most from this revolution. Numerous FDA-approved or currently undergoing clinical trials nanoscale technologies for systemic cancer therapy. This tremendous success has been due to the unique features that nanotechnology imparts on drug delivery systems. Improved drug delivery of poorly water-soluble medications, targeted drug administration to particular cells or tissues, and intracellular distribution of macromolecules are all now possible thanks to nanotechnology.

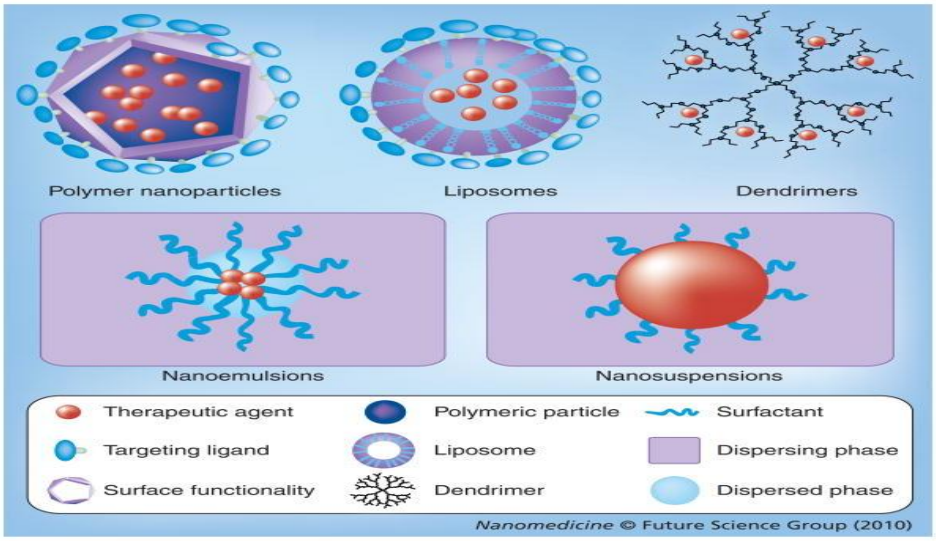
Platforms based on nanotechnology that transport antiretroviral medications throughout the body may offer comparable benefits. Their half-lives can be lengthened by controlled-release delivery systems, which keeps them in the bloodstream at therapeutic concentrations for prolonged periods of time. This could have a significant impact on enhancing medication adherence. Due to their small size, nanoscale delivery methods also improve and regulate the distribution of hydrophobic and hydrophilic medicines into and throughout various tissues. The most promising aspect of nanoscale delivery systems for the therapeutic treatment and prevention of HIV appears to be this particular characteristic. Antiretroviral medications could be delivered specifically to CD4+ T cells, macrophages, the brain, and other organ systems to ensure that they reach latent reservoirs. Additionally, medications could be released over a longer period of time and at greater effective doses to the designated targets by regulating the release profiles of the delivery systems. For these goals, several nanoscale drug delivery systems like those in Figure 1 could be investigated. Nowacek et al. and Amiji et al. have evaluated the application of nanotechnology systems for the administration of antiretroviral medications in great detail. Only a handful of the most recent and noteworthy instances of drug delivery based on nanotechnology are highlighted in this section.

Nanosuspensions (200 nm) of the medication rilpivirine (TMC278) stabilised by polyethylene-polypropylene glycol (poloxamer 338) and PEGylated tocopheryl succinate ester (TPGS 1000) were examined in dogs and mice in a recent study based on polymeric systems. Compared to a half-life of 38 hours for free medication, a single dose of the drug administered in nanosuspensions caused sustained release over 3 months in dogs and 3 weeks in mice. These findings show that nanoscale medication delivery has the potential to reduce dosage frequency and boost adherence.

A series of studies by Dou et al. demonstrated that the drug indinavir's nanosuspension can be stabilised by a surfactant system made up of Lipoid E80 for efficient distribution to different tissues. The absorption of the indinavir nanosuspensions was examined after they were injected into macrophages. Mice were then intravenously injected with macrophages that had been loaded with indinavir nanosuspensions, causing a significant distribution in the lungs, liver, and spleen. More notably, intravenous delivery of a single dosage of the nanoparticle-loaded macrophages produced detectable drug levels in the blood up to 14 days after treatment in a rodent mouse model of HIV brain infection, leading to considerable antiviral activity in the brain.
Given that indinavir's half-life in its typical dosage form is 2 hours, these investigations demonstrate the feasibility of delivering indinavir to the brain and maintaining drug levels there for up to 14 days. Future in vivo nanoparticle-targeted medication delivery to the brain may benefit from the discovery that macrophages can be employed to target pharmaceuticals to the brain.

Antiretroviral drug delivery has also used active targeting techniques. A variety of receptors, including formyl peptide, mannose, galactose, and Fc receptors, are present on the surface of macrophages, which are the main HIV reservoir cells. These receptors may be used for receptor-mediated internalisation. In order to boost cellular uptake in comparison to free drug or plain liposomes, the medication stavudine was encapsulated using different liposomes (120-200 nm) coupled with mannose and galactose, leading to considerable levels of the drug in the liver, spleen, and lungs. A water-soluble medication with an extremely short serum half-life is stavudine (1 h). As a result, targeted liposomes provide greater cellular absorption and prolonged release in the tissues, which is a significant improvement over free medication. Zidovudine, a medication with a 1-hour half-life and limited solubility, was similarly encapsulated in a stearylamine-derived mannose-targeted liposome, which led to greater localisation in the lymph node and spleen. Although the majority of nucleoside medications, like zidovudine and stavudine, have brief serum half-lives, the therapeutically significant half-life of the medication is that of the intracellular triphosphate form. For example, despite zidovudine's 1 h half-life in plasma, it is dosed twice daily based on intracellular pharmacokinetic and clinical efficacy data. Therefore, future nanotechnology-based delivery systems will have to focus in showing significant increase of the half-lives of the encapsulated drugs to achieve a less frequent dosing such as once weekly, once-monthly or even less.

To deliver the medication efavirenz to human monocytes/macrophages in vitro, a mannose-targeted poly (propyleneimine) dendrimer nanocarrier was employed in a different study. When compared to free medication, cellular absorption was increased by 12 times with the targeted nanocarrier. The drug lamivudine was administered in vitro using a similar approach, and both the targeted and nontargeted dendrimer systems shown much higher anti-HIV activity when compared to free medicines. In a more recent investigation, the same dendrimer was conjugated to the tetrapeptide tuftsin (Thr-Lys-Pro-Arg) to target the medication efavirenz to macrophages in vitro. In comparison to free medication, the tailored dendrimer approach produced a sevenfold increase in anti-HIV activity, a sixfold extended release, and a 34-fold enhanced cellular absorption.
In a novel strategy to target macrophage HIV reservoirs, N-formyl-methionyl-leucyl-phenylalanine (fMLF), a bacterial peptide sequence for which macrophages express a receptor, is linked to the PEG for targeting. This peptide is conjugated to the backbone of peptide-PEG. According to the study, fMLF-targeted peptide-PEG nanocarriers exhibit more cellular uptake and accumulation in liver, kidney, and spleen macrophages than nontargeted ones do.



All of the aforementioned initiatives serve as illustrations of the possibilities that nanotechnology platforms offer for enhancing the targeted delivery of antiretroviral medicines to the cellular and anatomical reservoirs of HIV. These early initiatives assist ongoing attempts to begin clinical studies and offer proof of the potential of nanotechnology to enhance antiretroviral therapy administration. A portion of these preclinical technologies may eventually enter clinical examination, despite the fact that the early attempts have not yet reached clinical trials.

Nanomaterials as therapeutic agents:

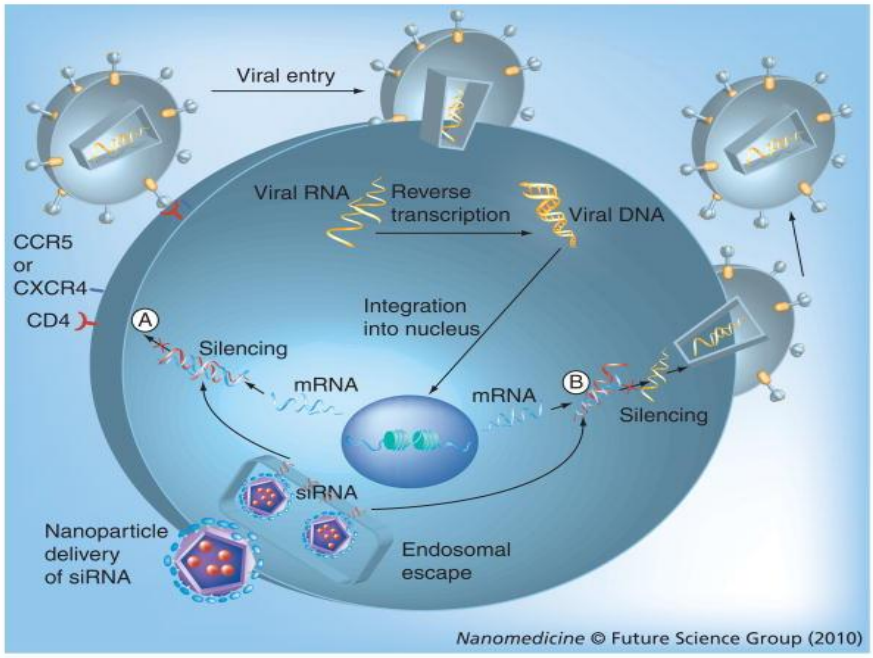
Nanomaterials are employed as delivery systems but have also been found to have therapeutic properties on their own. According to studies, structure-based medication development could target the HIV capsid to prevent viral replication. As a result, substances that might prevent the HIV capsid from being assembled have been found in computational and experimental research. In vitro viral replication has been observed to be inhibited by a variety of nanomaterials, and it is hypothesised that these effects are due to structural interference with viral assembly.

It has been demonstrated that a variety of fullerene (C-60)-based structures, dendrimers, and inorganic nanoparticles, including gold and silver, exhibit anti-HIV activity in vitro. These initiatives show the promise of therapeutic nanomaterials to prevent HIV replication, even though they are still limited to in vitro investigations.

Gene therapy for HIV/AIDS:

Existing antiretroviral medicine is being improved, and attempts are also being made to find new HIV/AIDS treatment options. Gene therapy is a promising alternative strategy that involves inserting a gene into a cell to prevent viral infection or multiplication. To prevent viral reproduction, other nucleic acid-based substances can be utilised, such as DNA, siRNA, RNA decoys, ribozymes, and aptamers, or protein-based substances, such as fusion inhibitors and zinc-finger nucleases.
Viral vectors were the primary delivery mechanism employed in the early stages of gene therapy for HIV/AIDS, and some clinical trials are still ongoing. In one of these studies, Benitec Ltd. and City of Hope are working together in a current clinical trial to investigate the viability and safety of a gene therapy approach based on the combination of three distinct inhibitory genes in a single lentiviral vector that uses stem cells for the delivery process. A Phase II gene therapy clinical experiment conducted by UCLA researchers recently demonstrated that cell-derived gene transfer is both safe and biologically effective in HIV-infected individuals. The excitement surrounding gene therapy for the treatment of HIV/AIDS is growing, and these initiatives are encouraging and supportive of that. The use of viral vectors for gene delivery, however, is thought to present basic issues such as toxicity, immunogenicity, insertion mutagenesis, and restrictions with scale-up methods, according to lessons acquired over the previous two decades. These issues have prompted research towards nonviral vectors for gene delivery, an area where nanotechnology platforms seem particularly promising.

RNA interference (RNAi), which was discovered in 1998 by Fire, Mello, and colleagues and won them the Nobel Prize, has recently received a lot of attention in the clinical treatments arena and is driving billion-dollar investments in therapeutic applications. Clinical trials that are now being conducted to treat age-related macular degeneration and respiratory syncytial virus have produced results that have sparked a great deal of interest in the sector. Also thought to have therapeutic potential for HIV/AIDS is RNAi. Double-stranded siRNA, which targets the mRNA of the target gene for destruction, causes gene silencing. For HIV/AIDS, RNAi can either target different viral replication cycle stages or different cellular targets, like CD4, CCR5, and/or CXCR4, which are the main cell surface co-receptors implicated in viral entry. HIV copies itself using reverse transcription to create DNA, which it then utilises to make copies of its mRNA for protein synthesis. HIV's mRNA can be silenced with siRNA therapy. In figure, these two mechanisms are depicted.



Mechanism for siRNA-based gene therapy of HIV/AIDS:

The siRNA works by degrading mRNA in at least two ways: (A) by blocking the formation of receptors or co-receptors, which inhibits entry and fusion; and (B) by preventing the translation and transcription of viral genes, which prevents the generation of proteins and genomic RNA. (The antiretroviral medications mentioned above target the viral entry and replication stages indicated below.)

Realizing the potential of RNAi has been largely hampered by the difficulty of delivering siRNA to certain cells and tissues, as has been the case with previous gene therapy methods. This issue is being addressed by new nanotechnology platforms that offer nonviral substitutes for efficient and secure distribution. Phase I clinical studies for the first nontargeted delivery of siRNA using self-assembling, cyclodextrin polymer-based nanoparticles in humans have just started.

Although still in its infancy, nonviral siRNA delivery for the treatment of HIV infection is making progress. To encapsulate and transport siRNA to T cells in vivo, a fusion protein featuring a peptide transduction domain and a double stranded RNA-binding domain was employed. Delivery of siRNAs targeting CD4 and CD8 led to RNAi responses without cytotoxicity or immunological activation as side effects. Similar to this, it was shown that siRNA reduction of the gag gene can prevent HIV multiplication in primary T cells via a protamine-antibody fusion protein-based siRNA delivery.
It has been demonstrated that human T cells and peripheral blood mononuclear cells may receive siRNA targeted to CXCR4 and CD4 from single-walled nanotubes. On T cells, CXCR4 receptors were knocked down by up to 90%, while CD4 expression was reduced by up to 60%, and CXCR4 receptors were knocked down by up to 60% on peripheral blood mononuclear cells. In a different study, siRNA was delivered to HIV-infected cells using amino-terminated carbosilane dendrimers, which had interior carbon-silicon linkages.

A peptide linked to an antibody was utilised in a recent study to target the delivery of siRNA to T cells and to prevent humanised mice from becoming infected with HIV. The delivery method known as scFvCD7-oligo-9-arginine was created by conjugating the antibody (scFvCD7) that is specific to the CD7 receptor on T cells with the oligo-9-arginine peptide. Most human T lymphocytes express the CD7 antigen, which is quickly internalised upon antibody interaction. It has been demonstrated that the short, positively charged oligo-9-arginine peptide is very effective at promoting cellular uptake of nucleic acids. The siRNA and the peptide's interaction improve delivery to the target cells. In this study, viral replication was reduced and CD4 T

cell loss was avoided using anti-CCR5 and antiviral siRNA given with scFvCD7-oligo-9-arginine. Additionally, the therapy effectively reduced viremia in humanised mice with HIV infection while restoring CD4 T cell numbers and lowering viral titers. This research opens up new possibilities for the delivery of siRNA to HIV-specific cells using antibody-targeted nanoparticles in the future.
These groundbreaking research show that nonviral siRNA delivery for HIV/AIDS treatment is feasible. However, additional work needs to be done to improve delivery methods and use strategies for effective intracellular delivery and targeting. The most recent advancements in siRNA delivery systems based on polymers and liposomes may be tailored to specifically target HIV-infected cells like T cells and macrophages. Moreover, combined siRNA therapy targeting several genes should be pursued because HIV mutates and has numerous strains with various genetic sequences. Nanotechnology platforms with co-delivery and targeting capabilities must be created specifically for cells that are sensitive to HIV for these applications. Combination gene therapy that targets macrophages and T cells and is based on nanotechnology may be a potential approach to effective HIV/AIDS treatment.

5. IMMUNOTHERAPY FOR HIV/AIDS

In order to effectively treat HIV/AIDS, the various therapy modalities discussed above either directly target HIV at the level of the host cell or the virus itself. Immunotherapy is an alternate strategy that modifies the immune system's response to HIV. While the generation of neutralising antibodies by B cells is delayed or nonexistent, CD8+ cytotoxic T-cell responses to acute HIV infection seem to be reasonably normal. The cytotoxic capability of CD8+ T cells is lost over time as a result of viral mutation. However, the depletion of CD4+ T cells is the main consequence of an HIV infection. These "helper" T cells provide a variety of supportive roles for other immune populations, and their loss causes severe immunosuppression, which is exhibited in chronic HIV-infected patients by the presence of abnormal B-cells, natural killer cells, and macrophages. The therapeutic use of immune responses to reinstate the immune system's normal functioning as a successful HIV/AIDS treatment has garnered more attention in recent years. There is growing evidence that, in certain people, the immune system can keep HIV under control. Therefore, one of the best methods for effective treatment could be techniques to rebuild or allow the reconstitution of immune function.

The use of immunomodulatory drugs to alter the immune system's response to a disease is known as immunotherapy. It works similarly to vaccinations by immunising people with different immunologic formulations; however, the goal is to treat HIV-infected patients rather than to protect healthy people (preventive vaccines will be discussed in an upcoming section). Delivering cytokines (such IL-2, IL-7, and IL-15) or antigens could be the basis for the many immunotherapy strategies for HIV/AIDS. Antigen-presenting cells (APCs), which process and present antigens to CD4+ and CD8+ T cells, are necessary for the establishment of both cellular immunity and, to a considerable extent, humoral immunity. The formation of cellular and humoral (antibody) immunity is initiated and orchestrated by dendritic cells (DCs), the prototypical professional APCs. Then, viral vectors could be used to transport protein/peptide antigens or DNA immunogens to endogenous or ex vivo-produced DCs, resulting in the production of endogenous proteins.
The first immunotherapeutic clinical trial for HIV/AIDS was conducted in 1983, and numerous trials have been conducted and are still being conducted today. Unfortunately, the majority of clinical research have continuously failed to offer therapeutic advantages for patients, despite the preclinical studies showing improved immune responses. The majority of these clinical trials have relied on ex vivo DCs or viruses to deliver the immunogenic components. As was mentioned above in the section on gene therapy, there are a number of dangers associated with delivery via viral vectors. Ex vivo production of autologous DCs is moreover a therapeutic approach that is challenging to apply widely due of the labor-intensive, expensive, and numerous processes required for product control at various sites. Therefore, novel strategies utilising tailored nanotechnology platforms for immunomodulatory factor delivery and antigen targeting to DC surface receptors in vivo offer enormous prospects. In the part that follows, the rationale for vaccine delivery and DC targeting based on nanotechnology will be covered in more detail. Here, the most significant developments in immunotherapy based on nanotechnology will be discussed.

Different polymeric systems have been investigated for the in vivo targeting of DCs and delivery of chemicals, proteins, or DNAs with immunotherapeutic potential. Poly(propylene sulphide) polymer nanoparticles stabilised by poly(ethylene glycol) (PEG) accumulated in lymph node DCs. After being injected with nanoparticles, DCs harbouring the particles gathered in lymph nodes, reaching a peak at 4 days with 40–50% of DCs and other APCs internalising the particles. In a different work, proteins and small compounds were delivered to DCs using cross-linked polymer nanoparticles with a pH-responsive core and hydrophilic charged shell. The 3-part PEG dimethacrylate, 2-aminoethyl methacrylate, and 2-diethylamino ethyl methacrylate cross-linked polymers. Fluorescence microscopy revealed that bone marrow-derived DCs were able to carry the model protein antigen ovalbumin to their cytosol, where it may be processed for cross-presentation to CD8+ T cells in addition to the more traditional exogenous antigen presentation to CD4+ T cells.

In a different study, poly(D,L-lacticide-co-glycolide) (PLGA) copolymer nanoparticles demonstrated effective antigen delivery to murine bone marrow-derived DCs in vitro, indicating their potential use in immunotherapy. In a highly intriguing study published more recently, it was demonstrated that mouse DCs successfully absorbed anionic poly(D,L-lactide) (PLA) nanoparticles that had the HIV p24 protein adsorbed on their surfaces, resulting in the maturation of DCs. Mice with the p24-nanoparticles had improved cellular and mucosal immune responses. The effective delivery of the antigen to DCs by the nanoparticles is a crucial demonstration that may potentially be applied to in vivo DC targeting, even if this targeting is shown in ex vivo-generated DCs rather than in vivo DCs.

The DermaVir patch, which has gone to Phase II clinical trials, is the most technologically sophisticated application of nanotechnology for HIV/AIDS immunotherapy. DermaVir is a targeted nanoparticle approach based on polyethyleimine mannose (PEIm), glucose, and HIV antigen coding DNA plasmid that is delivered as a patch following skin preparation. The particles are about 100 nm in size. The epidermal Langerhans cells that trap the nanoparticles and develop to become highly immunogenic on their trip to the lymph nodes receive the nanoparticles. The nanoparticle-containing mature DCs expose T cells to antigens, triggering cellular immunity. The DermaVir patch's safety and tolerability were demonstrated in preclinical research and Phase I clinical trials, which paved the way for Phase II trials. Since this is the first nanotechnology-based immunotherapy for HIV/AIDS to enter a clinic, more research in this field is encouraged. Table lists many nanotechnology delivery systems for antiretroviral drugs, gene therapy, and immunotherapy.

6. NANOTECHNOLOGY FOR HIV/AIDS PREVENTION

In the nearly three decades after the disease was discovered, the search for a safe and effective HIV/AIDS vaccine has been difficult. Recent high-profile clinical trial failures have sparked a lot of discussion about vaccine research, with some arguing that there should be more emphasis on fundamental research and less on clinical trials.

The wide viral strain and sequence diversity, viral evasion of humoral and cellular immune responses, combined with the lack of techniques to elicit broadly reactive neutralising antibodies and cytotoxic T cells, have been the main obstacles in the development of a preventive HIV/AIDS vaccine.

Protein antigens need to enter APCs (like DCs) where peptides are digested and loaded into MHC molecules for presentation to CD4+ T cells (extracellular antigen in MHC class II) and CD8+ T cells in order to trigger T cell responses (intracellular antigen in MHC class I). Exogenous antigens need particular "cross-presentation" in order to be presented by MHC class I and activate CD8+ cytotoxic T cells, which makes their distribution to APCs difficult (ex. nanoparticles). Another obstacle for the HIV intracellular antigen vaccine and perhaps a benefit of nanodelivery is the requirement for cytosolic delivery of antigens and cross-presentation. The challenge is not to achieve a single cellular or humoral response, but rather to achieve both. Humoral responses (neutralising antibodies produced by B cells) are generated to intact antigen presented on the surface for the virus, or nanoparticles. However, these humoral responses typically require "help" from CD4+ T cells.

Nanoparticles have the potential to be used as vaccination adjuvants and delivery methods. For the sustained release of various agents during the past few decades, controlled-release devices have been employed. This has significant benefits for vaccine delivery since the regulated release of antigens may result in a prolonged and stronger beginning of the immune response. The half-life of an immunising antigen can be extended via nanoparticle antigen encapsulation by shielding the given antigen from bodily fluids (such as lymph, serum, and mucus). APCs can also be successfully targeted with nanoparticles. Using surface-functionalized nanoparticles to direct antigen delivery to DCs offers a significant possibility for antigen delivery and the start of immune responses. The ability to tailor nanoparticle vaccines for different administration methods is another significant advantage. The majority of conventional vaccines are given intramuscularly, however nanoparticles provide up new possibilities for immunizations given orally and nasally, where mucosal immunity may be established.

Nanoparticles can be utilised to either absorb antigens on their surfaces or encapsulate them in their cores to convey antigens. Depending on whether a humoral or cellular immune response is intended, both approaches have advantages. Encapsulating antigens can result in the efficient delivery of an extracellular antigen (nanoparticle) into the cytoplasm for effective antigen presentation employing DCs. The subject of designing nanoparticles for effective intracellular delivery of different medicines has made significant development recently. On the other hand, the capacity to functionalize nanoparticle surfaces offers the capacity to directly expose antigens to B cells for antibody-specific immune responses. Rationally constructed nanoparticles will be able to present antigens to both DCs (encapsulated) and B cells in order to establish the coordinated humoral and cellular responses that are necessary for the prevention of HIV/AIDS (surface absorbed).

Although the creation of HIV/AIDS vaccines based on nanoparticles is still in its early stages, recent developments have been made. Here, we go over the early advancements of polymer- and liposome-based nanoparticles for HIV/AIDS vaccines.

The delivery of an HIV/AIDS vaccine has been researched using a variety of lipid-based technologies. In a previous work, mice were nasally immunised with a liposomal form of the HIV gp160 protein to produce high titers of gp160-specific neutralising antibody responses. Cholesterol, sphingomyelin, phosphatidylethanolamine, phosphatidylcholine, and phosphatidylserine were used to make the liposomes. Various liposomes (110–400 nm) were used to transport the HIV gp 41 protein, which produced potent antibody responses in mice and rabbits. It seems unlikely that an antibody response to a monovalent encapsulated antigen alone will be sufficient for a sterilising HIV vaccine because, to date, there have been no vaccinations that can induce a broadly neutralising antibody response to HIV. Therefore, it is necessary to expand these nanodelivery systems to incorporate a variety of HIV epitopes, and perhaps even epitopes tailored to provide access to the formation of antibody responses to regions of the HIV glycoproteins not evoked by acute HIV infection.

A number of microbial pattern recognition receptors, including Toll-like receptors, are expressed by dendritic cells, one of which, TLR9, binds CpG oligonucleotides (CpG ODN). A lot of research is being done on CpG ODNs for DC-targeted vaccines since CpG stimulation causes DCs to become activated and mature into powerful immune response-initiating cells. In comparison to a control immunisation, rhesus macaques that received CpG ODN via liposomes composed of 1-(2-[oleoyloxy] ethyl)-2-oleyl-3-(2-hydroxy-ethyl) imidazolinium chloride (DOTIM) and cholesterol exhibited greater anti-simian immunodeficiency virus (SIV) T and B cell responses. Even though cationic lipids like DOTIM are not chosen for drug administration, their immunogenic qualities can be used to boost adjuvanticity in vaccination applications.

A nanosized (250 nm) oil-in-water emulsion called MF59 is made of squalene, polysorbate 80, and sorbitan trioleate as surfactants. Its use as an adjuvant for an influenza vaccine has been authorised in more than 20 countries after human trials demonstrated its safety. Baboons immunised with HIV env and gag DNA and then received booster immunizations with oligomeric Env protein in MF59 produced more potent antibodies and cellular responses than when immunised with DNA alone. In a different investigation, it was discovered that priming rabbits with altered HIV env DNA and then boosting them with the oligomeric protein in MF59 resulted in larger titers of env-binding and autologous neutralising antibodies than DNA priming alone. In a more recent experiment, mice were immunised with DNA plasmids that encoded the proteins gp140, Complete protection against a challenge with HIV-infected murine cells was achieved by the Gag and Tat formulation in MF59. Furthermore, compared to immunisation with MF59 alone, immunisation with env proteins in MF59 containing CpG ODN also evoked larger titers of binding and neutralising antibodies.

The gp120 protein was delivered via the nasal route using an additional oil-in-water nanoemulsion (350 nm) made from cetylpyridinium chloride, a nonionic surfactant, and soybean oil. This method induced antibody and cellular immunological responses in mice and guinea pigs. In terms of the development of mucosal immunity, nasal vaccination offers an alternative to the traditional intramuscular route of administration.

HIV/AIDS vaccines based on proteins and DNA could potentially be delivered using nanoparticles made from the polymers PLA and PLGA. Mice, rabbits, and macaques had high antibody titers in response to surfactant-free PLA nanoparticles (300-600 nm) coated with HIV p24 protein. Mice also developed potent cytotoxic T cell responses. The possibility for using PLA nanoparticles as multivalent vaccines was also demonstrated by the co-adsorption of the proteins p24 and gp120 onto PLA nanoparticles (185-250 nm). Additionally, equivalent levels of antibody titers were induced after immunising rabbits with any of the three HIV antigens (p24, WT Tat, and mutant, detoxified Tat) combined with either PLA nanoparticles or the emulsion MF59. The continuous use of PLA in nanoparticle vaccines seems to be aided by its capacity to surface adsorb antigens and trigger cellular and antibody responses.

When mice were nasally immunised with polystyrene nanospheres (350 nm) coated with inactivated HIV particles, mucosal antibody responses that were specific to HIV were successfully induced. Concanavalin A is immobilised on the surface of the poly(methacrylic acid) branches found in the nanospheres. In a more encouraging trial, administration of the polystyrene nanospheres to mice resulted in DC-mediated immune responses, as evidenced by the development of effective anti-HIV antibodies that could be detected in the genital tract and of targeted cytotoxic T cells in the spleen. This study is distinctive because it provides a brand-new strategy that combines both the traditional method of delivering vaccinations via inactivated viral particles and the more recent strategies using polymeric nanoparticles.

When delivered to DCs in Balb/c mice, nanoparticles (200 nm) made of hydrophobically modified poly (gamma-glutamic acid) (gamma-hPGA) encapsulating gp120 protein substantially activated antigen-specific cellular immunity. Additionally, it was discovered that these nanoparticles significantly increased CD8+ T cell responses in mice when compared to gp120 alone. In a different study, gamma-hPGA nanoparticle vaccination of

mice with the p24 protein stimulated antigen-specific CD8+ T cells in the spleen and produced p24-specific serum antibodies in comparison to p24 vaccination alone. Comparable amounts of p24-specific serum antibodies were produced by the nanoparticles compared to the complete Freund's adjuvant, an effective immunomodulator.

7. IMPLICATION OF NANOPARTICLES IN HIV/AIDS THERAPY

When this disease was first being treated, patients were had to take up to 40 medications a day. In the last few decades, improvements and innovations have been made in the treatment, which now only requires a few pills every day. The development of nanoparticles with polymers that can transport ART treatments to the systems and brain cells has been shown to be an improved method for making treatment effective and long-lasting. ART medications are essentially categorised according to the stages of the viral agent's life-supporting replication cycle. HAART is the name of a combination treatment regimen that is used to prevent drug resistance and actively stop the spread of HIV. Nanotechnology has been crucial in the administration of antiretroviral medications and in increasing compliance rates. Typically, lymphatic tissues are HIV-loving and infection locations. According to research, in vitro macrophages and monocytes were the target of ART drug-loaded nanoparticles. A classic case of a breakthrough in the targeted and long-term delivery of pharmaceuticals using nanoparticle technology has been studied. The researchers created three ART drug-encapsulated nanoparticles using PLGA (efavirenz, ritonavir, and lopinavir). While free medicines were eliminated in 48 hours, the nanoparticle method delivered a steady release of medication for 4 weeks and beyond. A severe HIV-associated neurocognitive impairment occurs from HIV infection and dwelling in the CNS, another place (HAND). It is also known that nanoparticles can phagocytose their way across the BBB. Anti-HIV drugs are successfully delivered, according to studies.

The best method of preventing infections, and the ones for which vaccinations are the best medicines, is prevention rather than treatment. A lot of effort has been put into creating vaccinations that are efficient and effective at stopping the viral agent. New approaches, such genetic therapy and immunotherapy, are emerging that can be utilised to advance nanotechnology. Some nanoparticles themselves have medicinal qualities.

8. CONCLUSION

A problem for global public health continues to be HIV/AIDS.

Through this review, it is clear that the use of nanoparticles in HIV prevention and treatment has gained more traction recently. However, there are still barriers that need to be removed in order for NPs to reach their intended target sites, particularly in macrophages and brain tissues where antiretroviral drug penetration is less than ideal, leading to a slow and ongoing intracellular replication of the viral agent. Different NPs are utilised to deliver ART medications both within and outside of cells, and some NPs, including fullerenes, inorganic nanoparticles, and dendrimers, have demonstrated anti-HIV efficacy outside of cells.

With a number of cutting-edge strategies, nanotechnology has the potential to influence HIV/AIDS prevention and therapy. Using nanotechnology platforms for antiretroviral drug delivery may enhance treatment choices. The effectiveness of the treatment may rise as a result of better patient adherence to medication regimens brought on by controlled and prolonged drug release. Targeted nanoparticles have been utilised to attack macrophages, a significant HIV viral reservoir, using ligands such mannose, galactose, tuftsin, and fMLF peptides. Targeted co-delivery of two or more antiviral medications in a nanoparticle technology may significantly enhance treatment of viral reservoirs in the future. Our team, together with other researchers, has created nanoparticles that may co-deliver hydrophobic and hydrophilic pharmaceuticals or genes, offering adaptability for the co-delivery of antiviral medications. Nanomaterials have demonstrated their capacity to prevent viral multiplication on their own, in addition to delivering antiviral medications. Dendrimers, gold nanoparticles, fullerenes, and inorganic nanoparticles like silver have antiviral properties or enhance the antiviral properties of other compounds.

Nanotechnology can improve more recent therapeutic modalities like gene therapy and immunotherapy. One of the most active fields of nanotechnology research is siRNA delivery nonvirally. Delivery of siRNA to HIV-specific cells has been established, but more research is needed in this field since safe and efficient RNAi nanotechnology for HIV/AIDS applications has not yet been created. Another important field where nanotechnology might have a big impact is immunotherapy. The DermaVir Patch's entry into Phase II trials is a sign that nanoimmunotherapy might be the first type of nanotechnology-based HIV/AIDS treatment to be made available.

HIV/AIDS vaccines based on nanotechnology are also showing promise in preliminary research. Nanoparticles are a wonderful alternative to viral vectors because of their capacity to target particular cells and release antigens in a regulated and sustained manner. In animal experiments, lipid- and polymer-based nanoparticles were found to stimulate cellular immunological responses and HIV-specific antibody production. Preclinical research is still crucial to establish a comprehensive knowledge of the mechanisms involved in the induction of robust humoral and cellular immunity by nanoparticles, notwithstanding the advances made so far. In addition to ongoing efforts to develop vaccines, research into the creation of microbicides is still crucial. By offering cutting-edge methods for therapeutic chemical or RNAi administration via nanoparticles, nanotechnology can significantly contribute to the development of microbicides.

Since the most affected and susceptible populations live in underprivileged and economically underdeveloped nations, the economic component is another crucial factor to take into account while researching nanotechnology-based systems for HIV/AIDS. Nanotherapeutics may raise the overall cost of treatment in the case of antiretroviral therapy, lowering the overall value. However, if the nanotherapeutics could increase patient adherence by lowering dosing frequency as anticipated and if they could also eliminate viral reservoirs, creating a sterile immunity, these benefits might more than make up for the higher price. When compared to the other potential alternatives, the utilisation of nanotherapeutics may even result in cost savings for novel therapeutic modalities like gene therapy and immunotherapy. Although there isn't any information to support these comparisons, it can be anticipated that nanotherapeutics might be more advantageous for mass production than viral or ex vivo DC-based gene or immunotherapy. In the same way, nanotherapeutics shouldn't be more expensive than current systems when used as preventative measures. One of the most economical ways to combat the global HIV/AIDS epidemic is to produce vaccinations enabled by nanotechnology because bulk vaccine supplies are widely disseminated by government organisations. For efficient dissemination to economically underdeveloped nations, nanotechnology-enabled microbicides may also require assistance from governmental or nongovernmental organisations.

Overall, the field of nanotechnology research is experiencing exciting times, and scientific progress is quickening. It is commonly acknowledged that, with ongoing funding, nanotechnology will continue to have a significant positive impact on medicine and the fight against HIV/AIDS.

REFERENCES

[1] Blattner W, Gallo RC, Temin HM. HIV causes AIDS. Science. 1988;241(4865):515–516. [PubMed] [Google Scholar]

[2] Gallo RC. Historical essay. The early years of HIV/AIDS. Science. 2002;298(5599):1728–1730. [PubMed] [Google Scholar]

[3] Gallo RC, Montagnier L. The discovery of HIV as the cause of AIDS. N Engl J Med. 2003;349(24):2283–2285. [PubMed] [Google Scholar]

[4] Montagnier L. Historical essay. A history of HIV discovery. Science. 2002;298(5599):1727–1728. [PubMed] [Google Scholar]

[5] Furin JJ, Behforouz HL, Shin SS, et al. Expanding global HIV treatment: Case studies from the field. Ann NY Acad Sci. 2008;1136:12–20. [PubMed] [Google Scholar]

[6] Merson MH. The HIV-AIDS pandemic at 25 – the global response. N Engl J Med. 2006;354(23):2414–2417. [PubMed] [Google Scholar]

[7] Joint United Nations Programme on HIV/AIDS. Joint United Nations Programme on HIV/AIDS. Geneva, Switzerland: 2008. Report on the global HIV/AIDS epidemic. [Google Scholar]

[8] Rodriguez-Monguio R, Seoane-Vazquez E. Patent life of antiretroviral drugs approved in the US from 1987 to 2007. AIDS Care. 2009:1–9. [PubMed] [Google Scholar]

[9] Lang L. FDA grants tentative approval for 75th generic antiretroviral drug. Gastroenterology. 2009;136(1):5. [PubMed] [Google Scholar]

[10] Walensky RP, Paltiel AD, Losina E, et al. The survival benefits of AIDS treatment in the United States. J Infect Dis. 2006;194(1):11–19. [PubMed] [Google Scholar]

[11] Richman DD, Margolis DM, Delaney M, Greene WC, Hazuda D, Pomerantz RJ. The challenge of finding a cure for HIV infection. Science. 2009;323(5919):1304–1307. [PubMed] [Google Scholar]

[12] Richman DD. HIV chemotherapy. Nature. 2001;410(6831):995–1001. [PubMed] [Google Scholar]

[13] Ledford H. Merck's HIV vaccine flop brings vectors under closer scrutiny. Nat Biotechnol. 2008;26(1):3–4. [PubMed] [Google Scholar]

[14] Ledford H. HIV vaccine developers battle on, despite high-profile failures. Nat Biotechnol. 2008;26(6):591–592. [PubMed] [Google Scholar]

[15] Uberla K. HIV vaccine development in the aftermath of the step study: Re-focus on occult HIV infection? PLoS Pathog. 2008;4(8):e1000114. [PMC free article] [PubMed] [Google Scholar]

[16] Cohen J. Aids research. Microbicide fails to protect against HIV. Science. 2008;319(5866):1026–1027. [PubMed] [Google Scholar]

[17] Grant RM, Hamer D, Hope T, et al. Whither or wither microbicides? Science. 2008;321(5888):532–534. [PMC free article] [PubMed] [Google Scholar]

[18] Farokhzad OC. Nanotechnology for drug delivery: The perfect partnership. Expert Opin Drug Deliv. 2008;5(9):927–929. [PubMed] [Google Scholar]

[19] Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles in medicine: Therapeutic applications and developments. Clin Pharmacol Ther. 2008;83(5):761–769. [PubMed] [Google Scholar]

[20] Ferrari M. Cancer nanotechnology: Opportunities and challenges. Nat Rev Cancer. 2005;5(3):161–171. [PubMed] [Google Scholar]

[21] Nie S, Xing Y, Kim GJ, Simons JW. Nanotechnology applications in cancer. Annu Rev Biomed Eng. 2007;9:257–288. [PubMed] [Google Scholar]

[22] Heath JR, Davis ME. Nanotechnology and cancer. Ann Rev Med. 2008;59:251–265. [PMC free article] [PubMed] [Google Scholar]

[23] Harrigan PR, Hogg RS, Dong WW, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. J Infect Dis. 2005;191(3):339–347. [PubMed] [Google Scholar]

[24] Chun TW, Davey RT, Jr, Engel D, Lane HC, Fauci AS. Re-emergence of HIV after stopping therapy. Nature. 1999;401(6756):874–875. [PubMed] [Google Scholar]

[25] Marsden MD, Zack JA. Eradication of HIV: Current challenges and new directions. J Antimicrob Chemother. 2009;63(1):7–10. [PMC free article] [PubMed] [Google Scholar]

[26] Sax PE, Cohen CJ, Kuritzkes DR. HIV Essentials. Physicians' Press; Royal Oak, MI, USA: 2007. [Google Scholar]

[27] Lamers SL, Salemi M, Galligan DC, et al. Extensive HIV-1 intra-host recombination is common in tissues with abnormal histopathology. PLoS One. 2009;4(3):E5065. [PMC free article] [PubMed] [Google Scholar]

[28] McGee B, Smith N, Aweeka F. HIV pharmacology: Barriers to the eradication of HIV from the CNS. HIV Clin Trials. 2006;7(3):142–153. [PubMed] [Google Scholar]

[29] Vyas TK, Shah L, Amiji MM. Nanoparticulate drug carriers for delivery of HIV/AIDS therapy to viral reservoir sites. Expert Opin Drug Deliv. 2006;3(5):613–628. [PubMed] [Google Scholar]

[30] Wan L, Pooyan S, Hu P, Leibowitz MJ, Stein S, Sinko PJ. Peritoneal macrophage uptake, pharmacokinetics and biodistribution of macrophage-targeted peg-fmlf (n-formyl-methionyl-leucyl-phenylalanine) nanocarriers for improving HIV drug delivery. Pharm Res. 2007;24(11):2110–2119. [PMC free article] [PubMed] [Google Scholar]

[31] Nowacek A, Gendelman HE. Nanoart, neuroAIDS and CNS drug delivery. Nanomed. 2009;4(5):557–574. [PMC free article] [PubMed] [Google Scholar]

[32] Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. ACS Nano. 2009;3(1):16–20. [PubMed] [Google Scholar]

[33] Davis ME, Chen ZG, Shin DM. Nanoparticle therapeutics: An emerging treatment modality for cancer. Nat Rev Drug Discov. 2008;7(9):771–782. [PubMed] [Google Scholar]

[34] Amiji MM, Vyas TK, Shah LK. Role of nanotechnology in HIV/AIDS treatment: Potential to overcome the viral reservoir challenge. Discov Med. 2006;6(34):157–162. [PubMed] [Google Scholar]

[35] Baert L, van't Klooster G, Dries W, et al. Development of a long-acting injectable formulation with nanoparticles of rilpivirine (tmc278) for HIV treatment. Eur J Pharm Biopharm. 2009;72(3):502–508. [PubMed] [Google Scholar]

[36] Dou H, Destache CJ, Morehead JR, et al. Development of a macrophage-based nanoparticle platform for antiretroviral drug delivery. Blood. 2006;108(8):2827–2835. [PMC free article] [PubMed] [Google Scholar]

[37] Dou H, Morehead J, Destache CJ, et al. Laboratory investigations for the morphologic, pharmacokinetic, and anti-retroviral properties of indinavir nanoparticles in human monocyte-derived macrophages. Virology. 2007;358(1):148–158. [PubMed] [Google Scholar]

[38] Dou H, Grotepas CB, McMillan JM, et al. Macrophage delivery of nanoformulated antiretroviral drug to the brain in a murine model of neuroAIDS. J Immunol. 2009;183(1):661–669. [PMC free article] [PubMed] [Google Scholar]

[39] Garg M, Asthana A, Agashe HB, Agrawal GP, Jain NK. Stavudine-loaded mannosylated liposomes: In-vitro anti-HIV-i activity, tissue distribution and pharmacokinetics. J Pharm Pharmacol. 2006;58(5):605–616. [PubMed] [Google Scholar]

[40] Garg M, Dutta T, Jain NK. Reduced hepatic toxicity, enhanced cellular uptake and altered pharmacokinetics of stavudine loaded galactosylated liposomes. Eur J Pharm Biopharm. 2007;67(1):76–85. [PubMed] [Google Scholar]

[41] Garg M, Garg BR, Jain S, et al. Radiolabeling, pharmacoscintigraphic evaluation and antiretroviral efficacy of stavudine loaded 99mtc labeled galactosylated liposomes. Eur J Pharm Sci. 2008;33(3):271–281. [PubMed] [Google Scholar]

[42] Kaur CD, Nahar M, Jain NK. Lymphatic targeting of zidovudine using surface-engineered liposomes. J Drug Target. 2008;16(10):798–805. [PubMed] [Google Scholar]

[43] Dutta T, Agashe HB, Garg M, Balakrishnan P, Kabra M, Jain NK. Poly (propyleneimine) dendrimer based nanocontainers for targeting of efavirenz to human monocytes/macrophages in vitro. J Drug Target. 2007;15(1):89–98. [PubMed] [Google Scholar]

[44] Dutta T, Jain NK. Targeting potential and anti-HIV activity of lamivudine loaded mannosylated poly (propyleneimine) dendrimer. Biochim Biophys Acta. 2007;1770(4):681–686. [PubMed] [Google Scholar]

[45] Dutta T, Garg M, Jain NK. Targeting of efavirenz loaded tuftsin conjugated poly(propyleneimine) dendrimers to HIV infected macrophages in vitro. Eur J Pharm Sci. 2008;34(2–3):181–189. [PubMed] [Google Scholar]

[46] Dutta T, Agashe HB, Garg M, Balakrishnan P, Kabra M, Jain NK. Poly (propyleneimine) dendrimer based nanocontainers for targeting of efavirenz to human monocytes/macrophages in vitro. J Drug Target. 2007;15(1):89–98. [PubMed] [Google Scholar]

[47] Dutta T, Jain NK. Targeting potential and anti-HIV activity of lamivudine loaded mannosylated poly (propyleneimine) dendrimer. Biochim Biophys Acta. 2007;1770(4):681–686. [PubMed] [Google Scholar]

[48] Dutta T, Garg M, Jain NK. Targeting of efavirenz loaded tuftsin conjugated poly(propyleneimine) dendrimers to HIV infected macrophages in vitro. Eur J Pharm Sci. 2008;34(2–3):181–189. [PubMed] [Google Scholar]

[49] Wan L, Zhang X, Pooyan S, et al. Optimizing size and copy number for PEG-FMLF (n-formyl-methionyl-leucyl-phenylalanine) nanocarrier uptake by macrophages. Bioconjug Chem. 2008;19(1):28–38. [PMC free article] [PubMed] [Google Scholar]

[50] Ganser-Pornillos BK, Yeager M, Sundquist WI. The structural biology of HIV assembly. Curr Opin Struct Biol. 2008;18(2):203–217. [PMC free article] [PubMed] [Google Scholar]

[51] Pornillos O, Ganser-Pornillos BK, Kelly BN, et al. X-ray structures of the hexameric building block of the HIV capsid. Cell. 2009;137(7):1282–1292. [PMC free article] [PubMed] [Google Scholar]

[52] Friedman SH, Decamp DL, Sijbesma RP, Srdanov G, Wudl F, Kenyon GL. Inhibition of the HIV-1 protease by fullerene derivatives – model-building studies and experimental-verification. J Am Chem Soc. 1993;115(15):6506–6509. [Google Scholar]

[53] Bosi S, Da Ros T, Spalluto G, Balzarini J, Prato M. Synthesis and anti-HIV properties of new water-soluble bis-functionalized[60] fullerene derivatives. Bioorg Med Chem Lett. 2003;13(24):4437–4440. [PubMed] [Google Scholar]

[54] Kotelnikova RA, Bogdanov GN, Frog EC, et al. Nanobionics of pharmacologically active derivatives of fullerene c-60. J Nanopart Res. 2003;5(5–6):561–566. [Google Scholar]

[55] Marchesan S, Da Ros T, Spalluto G, Balzarini J, Prato M. Anti-HIV properties of cationic fullerene derivatives. Bioorg Med Chem Lett. 2005;15(15):3615–3618. [PubMed] [Google Scholar]

[56] Troshina OA, Troshin PA, Peregudov AS, Kozlovskiy VI, Balzarini J, Lyubovskaya RN. Chlorofullerene c60cl6: A precursor for straightforward preparation of highly water-soluble polycarboxylic fullerene derivatives active against HIV. Org Biomol Chem. 2007;5(17):2783–2791. [PubMed] [Google Scholar]

[57] Durdagi S, Supuran CT, Strom TA, et al. In silico drug screening approach for the design of magic bullets: A successful example with anti-HIV fullerene derivatized amino acids. J Chem Inf Model. 2009;49(5):1139–1143. [PubMed] [Google Scholar]

[58] Tanimoto S, Sakai S, Matsumura S, Takahashi D, Toshima K. Chem Commun. 44. 2008. Target-selective photo-degradation of HIV-1 protease by a fullerene–sugar hybrid; pp. 5767–5769. [PubMed] [Google Scholar]

[59] Blanzat M, Turrin CO, Aubertin AM, et al. Dendritic catanionic assemblies: In vitro anti-HIV activity of phosphorus-containing dendrimers bearing gal beta(1)cer analogues. Chembiochem. 2005;6(12):2207–2213. [PubMed] [Google Scholar]