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An Overview on: Nanotechnology and its Therapeutic Interventions on HIV

Samiksha Aher [1*], Vinayak Gaware [2], Rajshree Kadam [1], Varsha Pangale [1]

[1]Department of Quality Assurance, College of Pharmacy (For Women), Chincholi, Nashik.
[2]Department of Pharmaceutics, College of Pharmacy (For Women), Chincholi, Nashik.
Email id: ahersamiksha1999@gmail.com

ABSTRACT

Many antiretroviral drugs have been developed in treating HIV/AIDS which has increase the life span of the patients but it also have many serious side-effects. The HIV virus still has many challenges worldwide with no cure and vaccine not developed till date. The development of nanotechnology for the treatment and prevention of HIV is the most emerging field of 21st century. The different types of nano particles such as liposomes, micelles, dendrimers and nano capsules have different therapeutic applications which are given to the patients via oral route, direct injection and inhalation. The study has shown that these nanoparticles have potentials of advancing the prevention and treatment of the viral agent and have self therapeutic activity for the virus *in vitro*. This review article provided a general overview of nanoparticles, their types and characteristics, and their implications for HIV/AIDS treatment and prevention.

KEYWORDS: Antiviral, HIV, Nanotechnology, Nanoparticles

INTRODUCTION

Nanotechnology is science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers. Nanoscience and nanotechnology are the study and application of extremely small things and can be used across all the other science fields, such as chemistry, biology, physics, materials science, and engineering. Nanotechnology is considered a new and rapidly emerging area in the pharmaceutical and medicinal field. Nanoparticles, as drug delivery systems, impart several advantages concerning improved efficacy as well as reduced adverse drug reactions [1]. Nanomedicine is one of the most well-known nanotechnology research fields. It uses nanotechnology to develop highly targeted medicinal interventions for disease detection, prevention, and treatment. Over the last few decades, there has been a spike in nanomedicine research, which is currently being turned into commercialization activities around the world, culminating in the marketing of numerous products [2]. Drug delivery systems now dominate nanomedicine, with revenues accounting for over 75% of total sales. Size reduction is a fundamental unit operation having important application in pharmacy. Major advantages of nano sizing include :

- Increase surface
- Enhanced solubility
- Increase rate of dissolution and oral bio availability
- Rapid onset of action
- Less amount of dose required in the field of pharmacy [3].

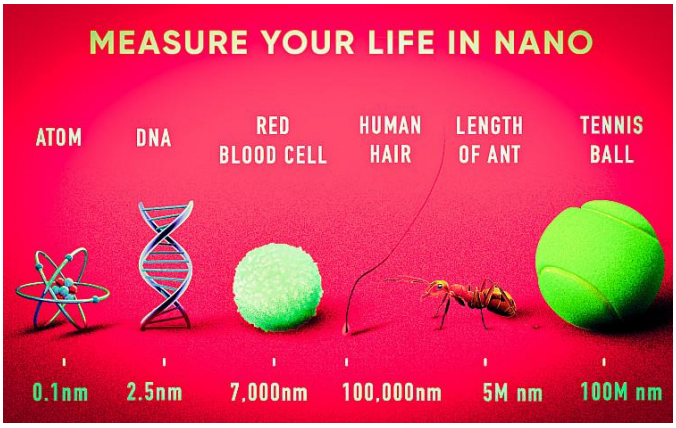


Figure 1: Measure Your Life in Nano

The human immunodeficiency virus (HIV) targets the immune system and weakens people's defense against many infections and some types of cancer that people with healthy immune systems can more easily fight off. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immune deficient. Immune function is typically measured by CD4 cell count. The most advanced stage of HIV infection is acquired immunodeficiency syndrome (AIDS), which can take many years to develop if not treated, depending on the individual. AIDS is defined by the development of certain cancers, infections or other severe long-term clinical manifestations. A potent cure for this viral agent has been challenging and mind bugling in decades of studies [4]. Early therapy was sign-posted at antiretroviral treatments (ARTs) which were efficacious to some limit. The first ART drug (zidovudine) was registered and approved in the US by the US FDA in 1987, after which 25 more drugs were approved till date which are available and in usage as fixed-dose combinations and generic formulations for consumption in developing countries [5]. It was the development of a drug class called protease inhibitors as well as the advent of the triple-drug treatment in the mid-1990s that changed HIV/AIDS therapy perspective. This resulted in dawn of a new era of Highly Active Antiretroviral Therapy (HAART), in which three or more drug classes are given in synergy [6]. Serious studies have been put forward to develop a free and efficacious HIV/AIDS vaccine which will succeed in times to come. There is a need for further and continuous research and clinical trials in the development of technologies and design better systems for HIV/AIDS therapy [7].

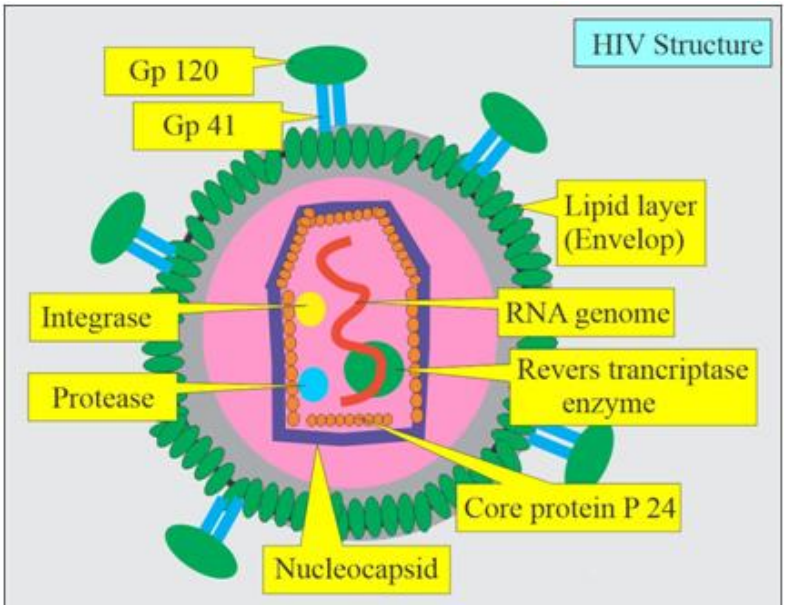


Figure 2: HIV Virus Structure

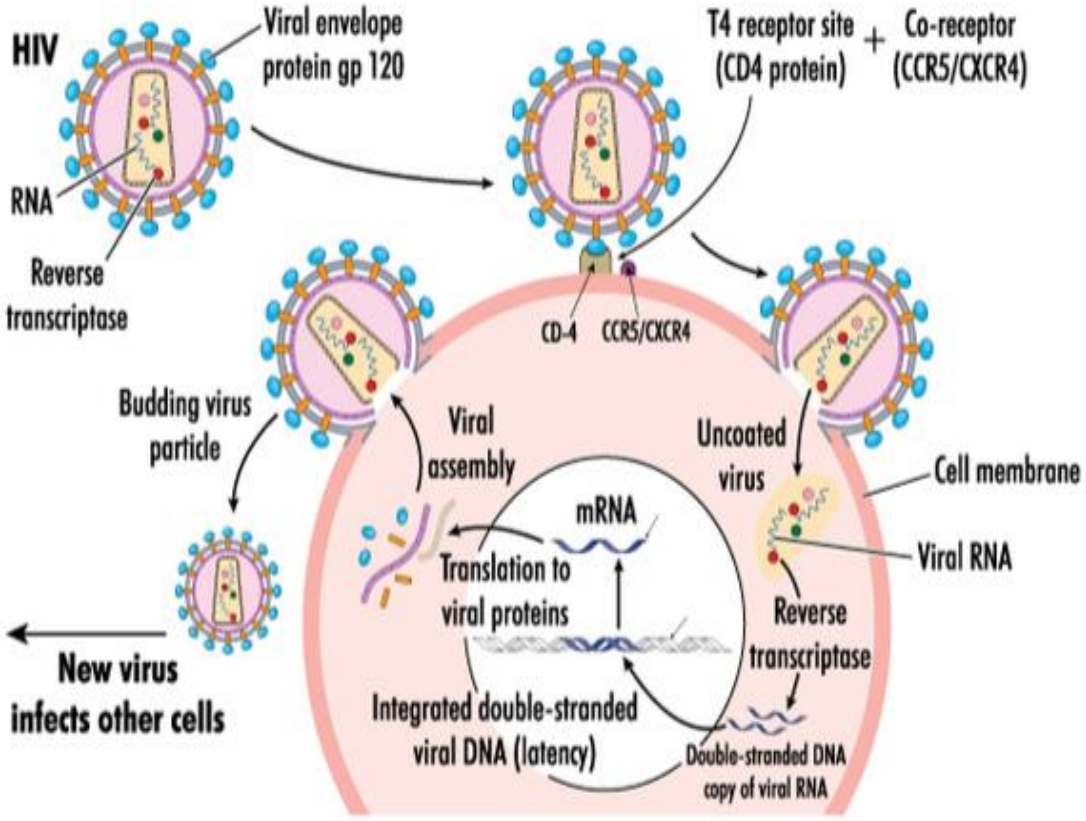


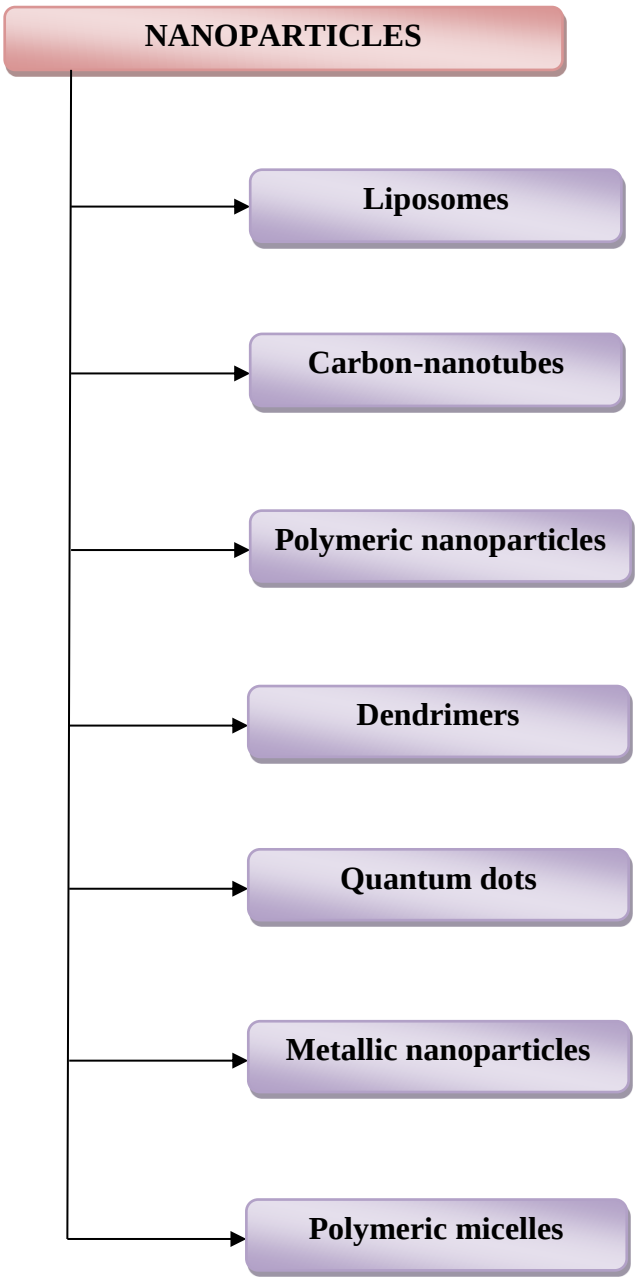
Figure 3: Life Cycle of HIV Virus

HISTORY OF NANOTECHOLOGY [8]

Year	Details
2000 years ago	Sulfide nano crystals used by Greeks and Romans to dye hairs.
1000 years ago	Gold nano particles of different sizes used to produce different colours in stained glass windows.
1959	There is plenty of room at the bottom by R.FEYNMAN where the term nanotechnology was used.
1974	Taniguchi was the first person to use the term Nanotechnology.
1981	IBM developed Scanning Tunneling Microscope to see nanoparticles.
1985	Buckyball scientists at Rice university and university of Sussex discovered C_{60}
1986	First book on nanotechnology "Engines of Creation" published by K.Eric Drexler. Atomic force microscope invented by Binnig, Quate and Gerbe.
1989	IBM logo where made with individual atoms.
1991	First carbon nano tubes discovered by S.Lijima
1999	Nanomedicine first nanomedicine book published by R.Freitas
2000	National Nanotechnology Initiative was launched

Table 1: History of Nanotechnology

TYPES OF NANOPARTICLES



- **Liposomes:**

Lipid vesicles, or liposomes, were the first form of nanomaterial used in medication delivery and were initially identified in 1976. Liposomes are sphere vesicles made of cholesterol and amphiphilic phospholipids that self-assemble into bilayers to enclose an aqueous core. In an effort to protect their hydrophobic core from the aquatic media while still keeping touch with it through the hydrophilic head group, the amphiphilic phospholipid molecules create a closed bilayer sphere [9]. A liposome can contain an aqueous solution inside of a membrane that is hydrophobic, preventing hydrophilic solutes from passing through the lipids. Thus, the outer membrane of lipsomes can contain both hydrophobic and hydrophilic molecules (the inner aqueous core). Depending on the amount and quantity of their bilayers, Multilamellar vesicles, large unilamellar vesicles, and small unilamellar vesicles are the three types of liposomes that can be categorised. The potential for using liposomes in the treatment of cancer has been thoroughly examined. The tiny size, lower drug toxicity, time-controlled drug release, altered pharmacokinetics, and altered biological dispersion of the medication all contribute to the efficiency of drug-delivery systems [10].

- **Carbon-nanotubes:**

These are hexagonal networks of carbon atoms. Length and diameter of these tubes are 1nm and 1-100nm in length. Nanotubes are of two type's single walled nanotubes (SWNTS) and multi walled nanotubes (MWNTS). These are small macro molecules have unique size, shape and remarkable physical properties [11].

- **Polymeric nanoparticles**

According to their passive tumor-targeting capabilities, polymeric nanoparticles are being developed as efficient delivery systems, which enable them to increase the efficacy and decrease the negative effects of chemotherapeutic medicines. Additionally, the ability of nanoparticles to selectively collect in and around the tumour mass provides a platform for enhanced tumour detection, providing the groundwork for the creation of multifunctional nanoparticle systems for such treatment of cancer [12, 13]. Due to their intrinsic qualities including biocompatibility, non-immunogenicity, non-toxicity, and biodegradability, those nanoparticles serve as an alternative to the nanosystems listed above. Natural macromolecules can also be employed to generate nanospheres, including silica, metal oxides, nonpolar lipids, proteins, and polysaccharides [14].

- **Dendrimers:**

These are hyper branched, tree-like structures and have compartmentalized chemical polymer. It contains three different regions core, branches and surface. The core forms the central part and the branches radiates from it forming an internal cavity and a sphere of groups. The branches can be altered or modified according to requirements. The dendrimers can be made more biocompatible compounds with low cytotoxicity and high biopermeability according to the requirements. These can deliver bioactive s like drug, vaccines, materials and genes to desired sites. The space between the core and branches accommodates drugs or bioactive products [15].

- **Quantum dots:**

These are semi conducting materials consisting of a semi conductor core coated by a shell to improve optical properties. Their properties originate from their physical size which ranges from 10-100A^{O} in radius. These have a large impact on imaging, in-vitro and in-vivo detection and analysis of biomolecules, immunoassay, and DNA hybridization and in non-viral vectors for gene therapy. It has main function in labeling of cells and therapeutic tools for cancer treatment [16].

- **Metallic nanoparticles:**

Although several metals have been used to create nanoparticles, silver and gold nanoparticles are of particular significance for biological applications. Numerous ligands, including sugar, peptides, proteins, and DNA, have been coupled to nanoparticles. Due to their potential to have surfaces functionalized, they have been employed as an alternate to quantum dots for active administration of bioactive, drug discovery, bioassays, detection, imaging, and numerous other purposes [17].

- **Polymeric micelles:**

A polymer micelle is a nanoparticle with a core that is hydrophobic and a shell that is hydrophilic. It can be classified into two primary groups: polyion-complex micelles and hydrophobically constructed micelles. The past ones often include hydrophobic and hydrophilic blocks in amphiphilic copolymers. In an aqueous phase, a balance in between these two building blocks causes the spontaneous production of nano-sized particles. Poly (ethylene glycol, or PEG), is employed as a hydrophilic block in the majority of block copolymers [18]. Diverse micelle features result from the hydrophobic nature of the polymers that comprise their cores, which includes biodegradable polyesters like poly (lactic acid), poly(e-caprolactone), and poly(glycolic acid) (PGA). Micelles are aggregation of the constituent molecules that accumulate in liquids and have a hydrophobic core that is protected from the water by a shell of hydrophilic groups. These are employed for the systemic administration of water-insoluble medications [19, 20].

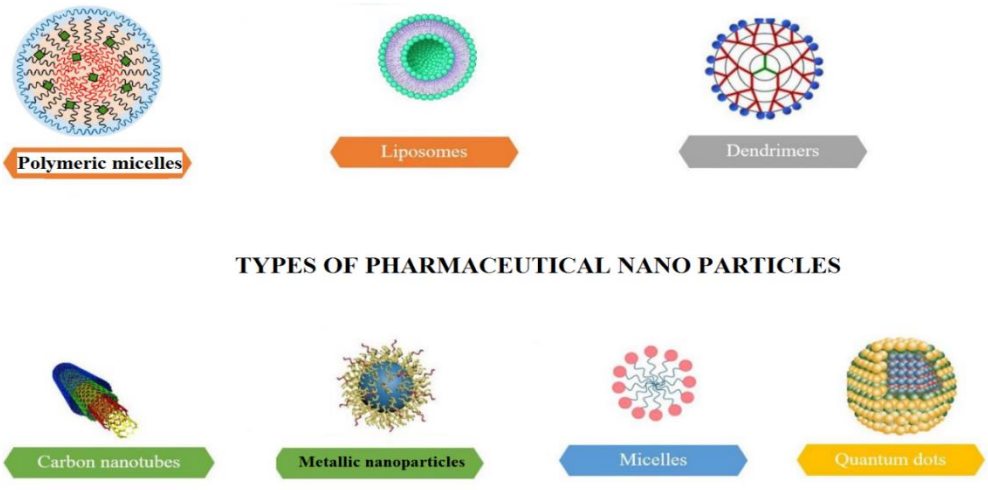


Figure 4: Types of Pharmaceutical Nano Particles

APPLICATION OF PHARMACEUTICAL NANOTECHNOLOGY

A dose adequate to be efficient against by the diseased part of the body is probable to have markedly harmful effects on the body as a whole if weak adhesion and uptake are added over the whole remainder of the body. The pharmaceuticals currently used rely on slight difference specificity of adhesion or absorption. The following uses have also been the focus of pharmaceutical nanotechnology [21].

- **Engineering Tissue:** The use of nanotechnology can aid in tissue regeneration or repair. "Tissue engineering" uses growth hormones and scaffolding based on appropriate nanomaterials to artificially increase cell proliferation. Modern conventional therapies like organ transplants and implanted devices might be replaced by tissue engineering. Biomaterials can be combined with nano- and micro-technologies to create scaffolding for tissue - engineered that can sustain and control cell behaviour [22].

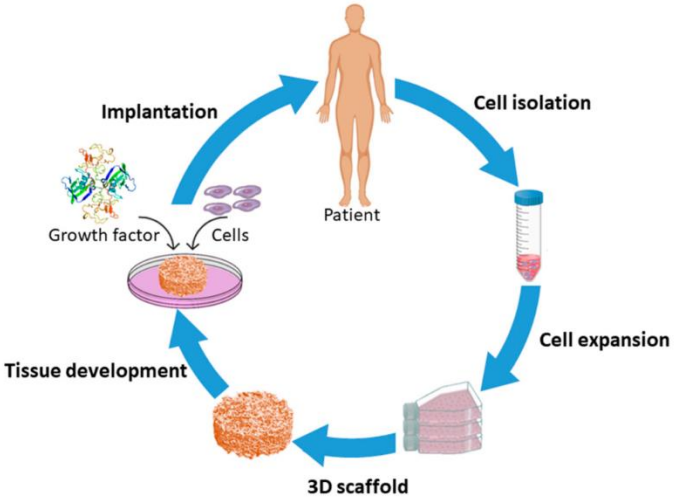


Figure 5: Engineering Tissue Illustration

- **Chemical diagnostics:** This new problem could be solved and technologies that allow diagnosis at the level of individual molecules and cells could be created by combining nanoparticles with the other nanotechnology-based substances. In bioimaging, QD particles act as contrast agents and offer far higher resolution than current fluorescent dyes. The most commonly used QDs include cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide (InAs) [22, 23].

- **Efficient delivery of drugs**: Medicine delivery using nanoparticles offers various benefits, including improving the therapeutic effectiveness and pharmacological properties of the drug. Even though nanoparticles enhance the solubility of poorly water-soluble drugs, alter pharmacokinetics, lengthen the half-life of drugs by lowering immunogenicity, increase drug precision for the target cell or tissue (thus lowering side effects), improve bioavailability, reduce drug metabolism, allow for a more controlled release of therapeutic compounds, and facilitate the concurrent delivery of two or more medications for combination treatment [24, 25].

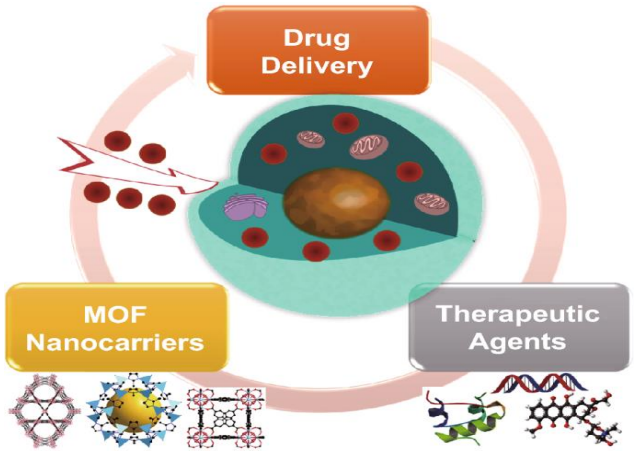


Figure 6: Efficient Delivery of Drugs

- **In curing cancer:** For application in cancer treatment, colloidal drug delivery systems like liposomes, micelles, and nanoparticles have undergone extensive research. The tiny size, lower drug toxicity, time-controlled drug release, altered pharmacokinetics, and altered biological dispersion of the medication all contribute to the efficiency of drug-delivery systems [26].

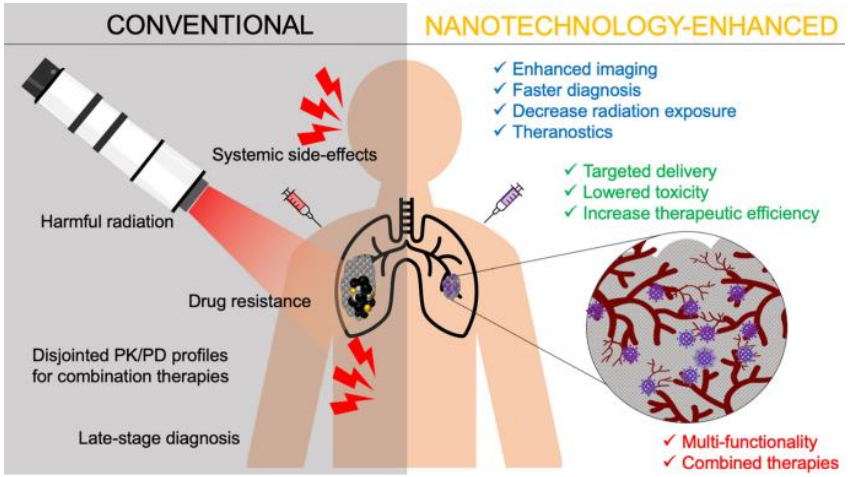


Figure 7: Nanotechnology in Treating Cancer

- **Implants and artificial organs:** The development of artificial cells, tissues, and organs is another area in which the advancements of nanotechnology could be effectively utilised. Artificial cells, especially those that perform metabolic activities, are being intensively researched for application in the replacement of damaged or improperly functioning cells and organs [26].
- **Pharmaceutical drug discovery:** By recognizing the protein on the interface or one was, nanotechnology aids in target identification and validation. Nanotechnology will improve medicine delivery by miniaturization, mechanization, imitated, and test reliability. Single - walled carbon nanotubes are effective at identifying pathogen surface proteins. For durations spanning from milliseconds to hours, quantum dots are used to track individual glycine receptors and evaluate their movements in the neuronal membrane of living cells. Some frequently utilized nanomaterials in diagnosis include gold nanoparticles and nano-bodies (smallest, accessible, entire antigen-antibody fragments) made by ablynx [27, 28].

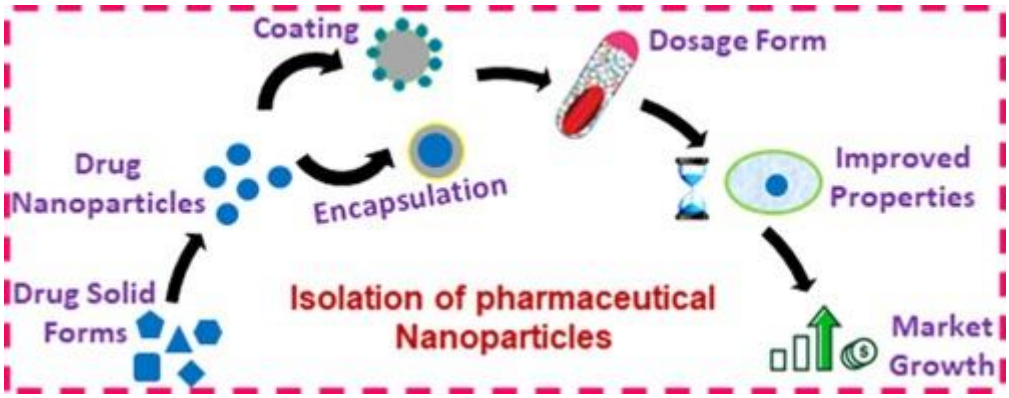


Figure 8: Pharmaceutical Drug Discovery

CURRENT TREATMENT OF HIV/AIDS (ANTIRETROVIRAL THERAPY)

In a standard antiretroviral therapy commonly called as ART is combination of at least 3 antiretroviral (ARV) drugs which is intended for maximal suppression of HIV virus in the body. It is also used to stop progression of HIV infection. This therapy has proven to be beneficial in reduction of large amount of death rates and sufferings when used effectively in early stages stage of infection.

Besides, risk of HIV transmission at population level is also reduced which preserve families. According to survey by WHO and UNAIDS, 34 million people were living with HIV in 2011 and about 15 million people were in need pf ART. By the end of 2012, ART was accessible to 9.7 million people in developing and under developed countries. Guidance, tools and support is provided by WHO which supports delivery and increased assay of ART within public. Treatment 2.0 strategy was launched by WHO and UNAIDS in the year 2010 that promoted radical simplification of ART. Along with this, acceleration of treatment scale-up and integrity of prevention was done to make it universally accessible. Furthermore, WHO launched new guidelines with recommendations of ART in July 2013 for adults and adolescents.

Drugs Used In Art Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

HIV virus is forced to use faulty versions of building blocks by NRTIs so that more HIV are not made by infected cells.

- Abacavir
- Zidovudine
- Stavudine
- Didanosine
- Emtricitabine
- Lamivudine
- Tenofovir alafenamide
- Tenofovir disoproxil fumarate

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs function by binding to specific protein, making HIV unable to make more copies of it and are also called as “non-nukes”

- Delavirdine
- Rilpivirine
- Etravirine
- Doravirine
- Efavirinz
- Nevirapine

Protease Inhibitors (PIs)

Infected cells need to put together a protein to form a new HIV virus particle. These drugs function by blocking those proteins.

- Atazanavir
- Darunavir
- Tipranavir
- Ritonavir
- Lopinavir + ritonavir
- Fosamprenavir
- Indinavir
- Nelfinavir
- Saquinavir

Integrase strand transfer inhibitors (INSTIs)

Integrase inhibitors act by blocking a key protein and inhibit HIV from making copies of itself. Key protein allows the virus to put its DNA into healthy cell’s DNA.

- Bictegravir or combined with other drugs
- Dolutegravir
- Elvitegravir
- Raltegravir

Fusion Inhibitors

At the very first place, HIV is blocked from getting into healthy cells. The function of FIs is totally different from NRTIs, NNRTIs, PIs, and INSTIs- as these work on infected cells.

- Enfuvirtide

CCR5 Antagonist [29]

It also stops HIV from getting into healthy cells but by blocking a specific kind of "hook" on certain cells. Ultimately, virus is not able to plug on cell.

- Maraviroc

MARKETED ANTI- HIV DRUGS

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	• Ziagen • Emtriva • Epivir • Viread • Retrovir
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	• Pifetro • Sustiva • Intelence • Viramune • Viramune XR (extended release) • Edurant
Protease Inhibitors (PIs)	• Reyataz • Prezista • Lexiva • Norvir • Aptivus
Fusion Inhibitors	• Fuzeon
CCR5 Antagonists	• Selzentry
Integrase Strand Transfer Inhibitor (INSTIs)	• Vocabria • Tivicay Tivicay PD • Isentress • Isentress HD
Attachment Inhibitors	• Rukobia
Post-Attachment Inhibitors	• Trogarzo
Capsid Inhibitors	• Sunlenca
Pharmacokinetic Enhancers	• Tybost

ombination HIV Medicines	• Epzicom • Triumeq • Triumeq PD • Trizivir • Evotaz • Biktarvy • Cabenuva • Prezcobix • Symtuza • Dovato • Juluca • Delstrigo • Atripla • Symfi • Symfi Lo • Genvoya • Stribild • Odefsey • Complera • Descovy • Truvada • Cimduo • Combivir • Kaletra

Table 2: Marketed Drug for Treating HIV

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR HIV-AIDS TREATMENT

Nanotechnology represents technological revolution in the field of pharmaceutical drug delivery. The basic concept behind nanotechnology is to modulate pharmacokinetics of incorporated molecule so that it can become worthy for effective removal of the HIV. When anti-HIV drug gets enclosed in a nano-system then its absorption, distribution, metabolism, and excretion is not governed by drug the properties, rather by the nano systems physical chemical properties, particularly surface-exposed molecules and electric charge, and its size [30, 31]. Application of nanotechnology to ARV drug delivery holds promise in the cure of HIV, because it could modify tissue distribution by targeting drugs to HIV reservoirs and by increasing the half-lives of drugs. A brief overview of nanotechnology-based system is given in Figure 9 [32].

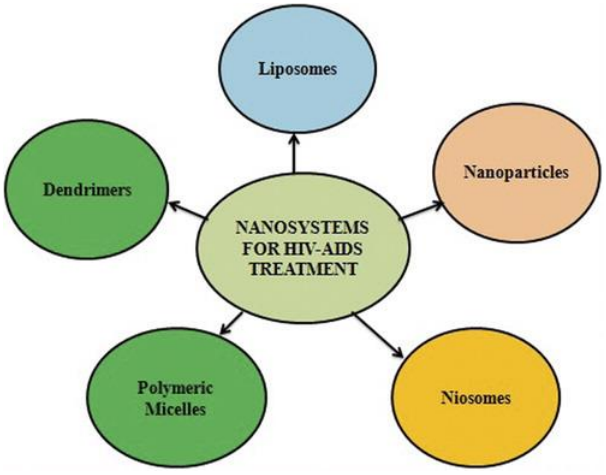


Figure 9: Nanotechnology-Based Systems for HIV-AIDS Treatment

NANOPARTICLES FOR IMPROVING HAART

HAART can successfully inactivate HIV-1; however the virus is able to persist within latent lymphoid, gut, and CNS reservoirs [33, 34]. This requires patients to remain adherent to the HAART regimen for the duration of their lifetime to prevent viral rebound. Since nanoparticles facilitate the sustained release of drugs, a group of researchers have developed a long-acting slow effective release antiretroviral therapy (termed "LASER ART"), which utilizes nanoparticles for controlled release of HAART agents, thereby improving regimen adherence [35, 36]. In a recent study, the same group of researchers demonstrated that a nanocrystallized product of lamivudine, a nucleoside reverse transcriptase inhibitor (NM23TC), maintained antiretroviral activity in HIV-1-infected monocyte-derived macrophages after viral challenge for up to 30 days. NM23TC was taken up by HIV-1-infected monocyte-derived

macrophages and remained in high prodrug concentration in whole blood for 30 days after a single dose. In addition, at day 28, M23TC, a metabolized version of lamivudine, was detected at high levels in the liver, lymph nodes, and spleen, suggesting that this nanoplatform may improve delivery of the drug to HIV-1 niches. Other groups have also developed nanoparticles for improving HAART [37].

NANOPARTICLES FOR IMPROVING LATENCY REVERSAL

Latency-reversing agents (LRAs) are able to reactivate viral replication. LRAs are used in "shock and kill" treatment approaches, wherein the LRA-elicited viral replication is coupled to the actions of HIV-1 cell-specific cytotoxic agents or immune mediated clearance [38]. Several classes of molecules and macromolecules have been used as LRAs including protein kinase C (PKC) agonists, histone deacetylase inhibitors, and cytokines, and their mechanisms of latency reversal are well-described. For example, PKC agonists function via the NF-KB pathway. Activated PKC isoforms down regulate the inhibitor IKB, thereby releasing the transcription factor NF-KB, which translocates into the nucleus, and binds to the HIV-1 proviral long terminal repeats, thereby mediating viral transcription [39]. Their nanoplatform targeted CD4+ cells in a peripheral blood mononuclear cells (PBMC) culture, activated latent virus, and inhibited viral spread. In a more recent study, Cao et al. synthesized hybrid lipidcoated PLGA nanocarriers that incorporated diverse LRAs. These lipid-coated nanoparticles could selectively activate CD4+ T cells in nonhuman primate PBMCs as well as in murine lymph nodes with substantially reduced toxicity [40]. Despite the fact that it is currently impossible to identify and target every HIV-1-infected cell in the latent reservoir, the ability of nanoparticles and nanocarriers to traffic and deliver LRAs to sites of latent HIV reservoirs can maximize their therapeutic benefit, and serve as an important component of successful shock and kill cure regimens.

NANOVACCINES

Traditional vaccines for HIV-1 have been difficult to develop, and clinical trials using HIV-1 vaccines have demonstrated poor efficacy [41, 42]. Vaccines fail for several reasons including poor delivery to dendritic cells, reversion of a live attenuated virus to its virulent form, or if the vaccine is too weak to facilitate an immune response. Consequently, an ideal vaccine should be clinically safe, stable, and capable of inducing a potent immune response. Nanoparticles have been shown to overcome these limitations by protecting antigens from proteolytic enzymes, promoting antigen uptake and processing by antigenpresenting cells (APCs), in addition to being biocompatible and biodegradable. One effective strategy is utilizing nanovaccines to activate dendritic cells (DCs), which in turn cause T cell activation. To this end, Rostami et al. decorated antigens onto the surface of nanoparticles to facilitate greater interaction with the APCs due to the high surface area to volume ratio of the nanoparticles [43]. Specifically, a flagellin molecule sequence derived from Pseudomonas aeruginosa (FLiC), a toll-like receptor 5 agonist, was conjugated to an HIV-1 p24-NeF peptide, and encapsulated within PLGA nanoparticles. The FLiC-p24-NeF-encapsulated nanoparticle elicited higher levels of lymphocyte proliferation and cytotoxic T cell activity compared to controls, suggesting its potential use in an HIV-1 vaccination strategy. DermaVir is currently undergoing a phase 3 clinical trial evaluation based on excellent responses observed in Phase I/II clinical trials [44].

NANOPARTICLES TARGETING HIV VIRAL FUSION TO IMMUNE CELLS

Fusion or entry inhibition leads to inhibition of viral activity and viral cytotoxicity. In one approach, Lara et al. showed that silver nanoparticles are antiviral and prophylactic against HIV-1 fusion to target cells [45]. Silver nanoparticles exert anti-HIV activity at an early stage of viral replication, likely as a virucidal agent or as an inhibitor of viral entry. Silver nanoparticles bind to gp120 in a manner that prevents CD4-dependent virion binding, fusion, and infectivity, acting as an effective virucidal agent against cell-free and cellassociated virus. Further, silver nanoparticles inhibit post-entry stages of the HIV-1 life cycle. Another approach utilized semen-derived enhancer of viral infection (SEVI), which is a type of amyloid fibril present in human semen that enhances HIV-1 infection of target cells by capturing HIV-1 virions, resulting in increased viral fusion. SEVI serves as a mediator for HIV-1 viral attachment due to its highly cationic nature. In their study, synthesized a hydrophobic polymeric nanoparticle to reduce SEVI fibril-mediated infection. The hydrophobicity of the nanoparticle interferes with Aβ amyloid structure, forming amorphous aggregates, thereby disrupting the amyloid HIV-1 trafficking protein to target cells. Thus, the hydrophobic nanoparticles were able to reduce HIV-1 virion binding affinity toward their target cells. Biomimicry approaches, such as plasma membrane-coated nanoparticles, represent a unique strategy to target a variety of human pathologies. A pivotal study showed the efficacy of coating a nanoparticle with a cell membrane to imitate and model endogenous cell activity. HIV-1 infection begins when an exposed HIV-1 surface protein, gp120, interacts with CD4 receptor and chemokine receptor type 5 (CCR5) co-receptor on target cells. Wei et al. coated polymeric nanoparticles with a CD4+ T cell membrane, causing the modified membranecoated nanoparticle to preferentially interact with HIV-1. This preferential binding ultimately neutralized HIV-1 viral activity in PBMCs in vitro, illustrating the potential of biomimicking nanoparticle approaches to reduce HIV-1 viral spread by blocking viral fusion to T cells. Unlike synthetic nanoparticles, extracellular vesicles (EVs) are naturally occurring nanoscale structures that carry cargo (e.g., proteins, lipids, nucleic acids) and can be released from both healthy and apoptotic cells. Recently, Palomino et al. discovered that EVs released by Lactobacillus in the healthy vaginal microbiota prevented HIV-1 attachment to target cells and thereby inhibited HIV-1 infection. In a recent study by Welch et al., EVs extracted from semen inhibited HIV-1 in vitro regardless of HIV infection status of the donor, while EVs extracted from the blood and semen of ART-treated subjected inhibited HIV-1 in vivo. These studies suggest a potential avenue for bacterial and/or EV-based treatment strategies in preventing HIV-1 viral spread [46].

NANOPARTICLES TO ENHANCE GENE EDITING APPROACHES

Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (CRISPRCas9) is a gene editing platform wherein genes can be added, removed, or altered at given genetic loci [47]. CRISPR-Cas9 is a faster and more efficient technique than other genetic editing platforms using other viral vectors or the Cre-Lox system, although current CRISPR-Cas9 delivery techniques use electroporation to facilitate DNA entry into living cells, which is difficult to control and can generate cytotoxicity. Previously, gene-editing tools have knocked out CCR5 in CD4+ T cells to block HIV-1 viral entry. However, gold nanoparticles (AuNPs) have a unique ability to safely deliver CRISPR-Cas9 components to their targets. AuNPs have large

surface area to volume ratios and are biocompatible with low toxicity. AuNP/CRISPR was able to penetrate into CD34+ hematopoietic cell line, which is difficult to transfect. At micromolar concentrations, AuNP/CRISPR exhibited an overall low amount of gene editing and homologous directed repair (HDR) at the CCR5 and the gamma-globin promoter locus. This demonstrates that AuNP/CRISPR functioned with low efficacy. However, genetic editing and HDR via AuNP/CRISPR was higher than the electroporation-driven process. This suggests that AuNP/CRISPR could be effective in delivering gene editing for HIV-1 therapy. With the promising innovations of LASER ART and CRISPR-Cas9, Dash et al. combined the two methodologies to evaluate a potentially synergistic functionality. Two of seven HIV-1-infected mice that received LASER ART followed by subsequent AAV9-CRISPR-Cas9 treatment targeting a fragment of the HIV-1 genome were cured of viral rebound and experienced a restoration of their CD4+ T cells, suggesting HIV1 regression/elimination . Additionally, HIV-1 RNA levels diminished to undetectable levels in the plasma, spleen, liver, gut, and brain in the cured mice. Further, naïve humanized mice that were challenged with adoptively transferred cells isolated from the cured mice showed no detectable HIV-1 viral loads. This study demonstrates the possibility of eliminating HIV-1 in plasma and infectious tissues through this novel combination approach [48].

NANOPARTICLES TO ENHANCE CLEARANCE BY ADOPTIVELY TRANSFERRED IMMUNE CELLS

Recent studies show promising effects of cell therapies for treating HIV-1. Here, autologous or allogenic immune cells are transferred to the patient after ex vivo expansion and/or modification to clear HIV-1 infected cells. Nanoparticles may offer the ability to enhance the ability of immune cells to target and kill target cells in the context of HIV-1. In their study, Sweeney et al. generated a PLGA nanoplatform that co-encapsulated an LRA and a target cell-specific antibody to improve NK cell effector function in an in vitro cell model of latent HIV-1 [49]. The nanoplatform was able to increase NK cell cytotoxicity of the target cells, thereby illustrating an example of nanoparticles enhancing immune cell function in the context of latent HIV-1. In another studies, Jones et al. demonstrated that cytotoxic T lymphocytes (CTLs) were made more potent by conjugating drug-loaded lipid nanoparticles to their surface. HIV-1-specific CTLs were able to specifically target HIV-1-infected cells and deliver the nanoparticle-encapsulated payload.

OTHER FOCUS AREAS

- **Nanoparticles to Boost Innate Immunity:** HIV-1, like many other viruses, has evolved mechanisms to evade or disrupt immune surveillance. Therefore, one strategy to eliminate HIV-1 viral load is to reverse immune evasion. HIV-1 typically inhibits the cGAS-STING pathway that normally functions via cGAMP binding to STING on the endoplasmic reticulum resulting in an IFN-1-mediated antiviral response [50]. P^H-sensitive polymeric nanoparticles were engineered to deliver a STING agonist to counteract HIV-1 immune evasion via the cGAS-STING pathway. These STING agonist nanoparticles demonstrated potent antiretroviral activity for up to 12 days.

- **Nanoparticles to Inhibit HIV-1 Reverse Transcriptase Activity:** Quantum dots are biocompatible semiconductor crystal nanoparticles with low toxicity that have been used for biosensing, image contrast, and drug delivery. These nanomaterials are attractive due to their intrinsic antiviral activity and thus, their potential as inhibitors of HIV-1. In a proof-of-concept study by Iannazzo et al., a reverse transcriptase inhibitor (RTI; CHI499) was readily conjugated onto the surface of the graphene quantum dots (GQDs) via intrinsic functional groups. The conjugated GQD product (GQD-CHI499) achieved remarkable anti-reverse transcriptase and cellular anti-HIV-1 activities compared to the free drug alone. This additive improvement may be the result of the GQDs' intrinsic structure, where the polycarboxylation group could mediate the inhibition of HIV-1 reverse transcriptase through viral fusion, suggesting the potential of GQDs in treatment for HIV-1 **[51].**

- **Nanoparticles to Enhance Blood Brain Barrier Penetration:** Aside from persistent HIV-1 in CD4+ helper T cells, HIV1 may also persist in microglial cells, which are the resident macrophages of the CNS. These cells may confer HAART resistance, perpetuate HIV-1 infection in peripheral tissues, and are critical in the development of HIV-1 associated neurocognitive diseases. The brain poses an anatomical barrier, where there is low drug penetration by virtue of the blood brain barrier (BBB). Therefore, there is a need to develop ways to penetrate the BBB to target persistent HIV-1 in microglial cells . Nanodiamonds are ∼10 nm diamonds which are known for their inexpensive production, surface modifications, and low cytotoxic profile. ND-EFV allowed for sustained release of EFV in a BBB model in vitro. In addition, ND-EFV was effective in controlling HIV-1 replication for 7 days, where the EFV alone drug was able to inhibit HIV-1 for 5 days. Similarly, gold nanoparticles have also been used entry through the BBB [52].

- **Nanoparticles for Prophylactic HIV-1 Prevention:** Another application of nanoparticles is in improving preexposure prophylaxis (PrEP), which provides a >90% effective approach to prevent HIV-1 infection but requires daily oral administration. PrEP comprises tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), two nucleoside RTIs that have low half-lives and require high dosing, thereby increasing the risk of adverse effects . Alternatively, loaded TDF into PLGA nanoparticles (TDF-NPs), and subsequently incorporated them within a thermosensitive vaginal gel. Mice challenged with two strains of HIV-1 and treated with the TDF-NP gel were 100% protected against the virus with no detectable viral plasma load, suggesting the efficacy of sustained release of TDF by nanoparticles via vaginal administration to prevent HIV-1 infection. In another study, encapsulated dolutegravir (DTG), an integrase strand transfer inhibitor, within nanoparticles made from cellulose acetate phthalate, a pH sensitive polymer that intrinsically inhibits HIV-1 entry into its target cells (DTG-CAP-NPs). Similarly to above, DTG-CAPNPs were incorporated into a thermosensitive vaginal gel. Vaginal epithelial cells were able to take up DTG-CAP-NPs, where they persisted for up to 7 days with low cytotoxicity [53]. These studies demonstrate the potential of nanoparticles for use in HIV-1 preventative strategies, including enhancing PrEP.

FUTURE DEVELOPMENTS

Researchers have observed that combination antiretroviral therapy (cART) limits HIV replication significantly. However, lifelong and daily treatment is needed to manage the illness of the patient since cART does not remove the infected cells neither does it reconstitute HIV-specific immunity that can destroy infected cells.

Several nanomedicine classes have been developed with the following characteristics to combat HIV:

- Eradicating the virus by activating latently infected CD4+ T cells and flushing reservoirs
- Preventing infection using microbicides with drug half-life and enhanced epithelial penetration

CONCLUSION

The present scenario about HIV/AIDS is still facing challenges to achieve global public health. To reduce the spread of HIV and eradicate it from remote reservoirs, a number of drug delivery strategies have been developed and proposed. However, there are still obstacles, such as dose-related toxicities and non targeting effect and low efficacy. By increasing the drug's potency and efficacy, decreasing dose-related toxicities, and providing active targeting options to the extreme HIV reservoirs, nano pharmaceuticals enable the virus to be nearly eradicated, making them excellent treatment options for HIV infections. Nanomedicines are both economically viable and have the potential to significantly improve HIV-infected individuals' health. In the near future, it is hoped that this promising technology will aid in the search for a cure for HIV/AIDS.

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