

**NANOTECHNOLOGY: A NEW TOOL FOR AIDS TREATMENT****Bhushan D.Tade^{1*}**,Viraj S. Saste¹, Anup M. Akarte¹, Dheeraj T. Baviskar¹, Dinesh K. Jain²¹Department of Pharmaceutics, Institute of Pharmaceutical Education, Boradi - 425428, Tal-Shirpur, Maharashtra, India²Department of Pharmaceutics, College of Pharmacy, IPS Academy, Indore 452 012 (M.P.), India**ABSTRACT**

A global challenge is progress of an effective drug delivery approach for the treatment of HIV/AIDS. The conventional drug delivery approaches including highly active anti retroviral Therapy (HAART) have increased the life span of the HIV/AIDS patient. For improving and prolonging the life of AIDS patient there is constant need of developing advanced anti-HIV drugs for better result. Recent advances in the field of drug delivery are providing evidence that engineered nanosystems may contribute importantly for the enhancement of current antiretroviral therapy. Additionally, groundwork is also being carried out in the field nanotechnology-based systems for developing preventative solutions for HIV transmission. The use of target oriented highly developed nanosystem is highly effective to avoid drug-drug interaction and adverse effect. The newly developed Liposomes, Ethosomes, nanoemulsion and nanosuspension, solid lipid nanoparticles, Silver nanoparticles, goldnanoparticle and lipid nanocapsule to improve the bioavailability, decreased drug resistance and improvement in patient compliance so increases in lifespan of patient.

Keywords: AIDS, HIV, HAART, Nanotechnology, Gold nanoparticles, Silver nanoparticles etc.

Correspondence to Author**Mr. Bhushan D.Tade**Institute of Pharmaceutical
Education, Boradi - 425428, Tal-
Shirpur, Maharashtra, India**Email:** bdtade@gmail.com**INTRODUCTION**

In the last quarter of a century human immunodeficiency virus infection and acquired

immune deficiency syndrome (HIV/AIDS) is rising global health, social, and economical worry. The first recorded sample of HIV was detected in 1959

in a blood specimen obtained at Leopoldville (Kinshasa) in the Belgian Congo. This was the first death caused by HIV. The term AIDS first appeared in Morbidity and Mortality death Weekly Report (MMWR) of the Center for Disease Control (CDC) in 1982 to describe a disease at slidingly reasonably analytical of a fault in cell mediate resistance, occurs with no known cause for diminished resistance to that disease”^[1,2]. The total amount of African people among which about 67 % people infected by HIV. The homosexuality is also major cause of death in advanced countries. In the absence of an effective cure, prevention and access to antiretroviral therapy are the best options to affect the HIV pandemic^[3]. However, current strategies for supply worldwide access to prevention and treatment, and their field used are not enough, urging the search for new and improved options. The importance, HIV therapy has been inadequate by many factors, such as its internal toxicity, insufficient effectiveness, and drug resistance. The growth and new approval improved drugs has manage to minimize some of this issues but the showing ability of HIV to resist the new therapeutic options has limited success. Inadequate physical–chemical properties of most of these HIV drugs (e.g. poor solubility, permeability, and stability) impair optimal absorption, biodistribution, and sustained antiretroviral effect, thus contributing to poor clinical outcome. To solve these problems, several new and improved delivery systems and dosage form have been proposed in the Review^[4,5]. Nanotechnology systems have been developed in improve HIV therapy, such polymeric nanoparticles, solid lipid nanoparticles (SLNs), liposomes, nanoemulsions, Gold Nanotechnology, Silver Nanotechnology^[6-10]. The wide range of systems share their submicron dimensions (from a few nanometers up to 1 micrometer), they differ in physical–chemical properties, biological behavior, preparation methods, or even characterization methodologies^[11-12]. The nanotechnology-basic Principle for the prevention of HIV/AIDS has been focused on the development of vaccines hence, the scope of this document is to review recent Available online on www.ijprd.com

developments in nanotechnology-based systems specifically designed and developed for the treatment and prevention of HIV/AIDS, with particular importance view on specific individual examples of significant Interest. Hence we discuss new prediction and future directions for advancing in the field of nanotechnology.

1.1) Structure Of HIV Virus:-

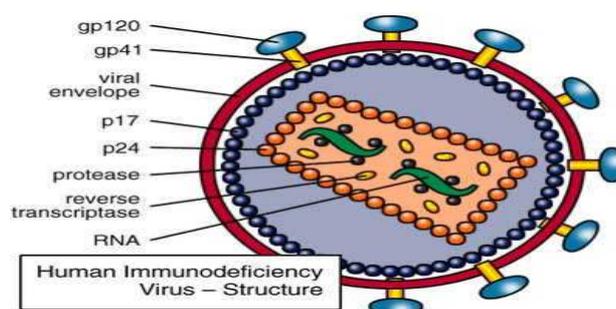


Fig-1. The structure of HIV Virus

1.2) The HIV Virus:

HIV is a lentivirus of the family Retroviridae, is known causative agent of AIDS^[13]. This virus can be seen nanostructure (around 100–150 nm), composed by a host derived membrane, a nucleocapsid and genetic material in the form of RNA containing three structural genes. These genes code for important group-specific antigens (gag gene), essential viral enzymes such as reverse transcriptase, integrase and protease (pol gene), and the two glycoproteins present in the outer viral membrane, gp120 and gp41, which are responsible for recognizing the CD4 receptor and the CCR5 or CXCR4 co-receptors of the host cell membrane, and for virus/ cell fusion, As a consequence of constant transcription errors, these viral structures present high polymorphism which leads to mutation, thus constituting a major source of antiretroviral-resistance development^[13].

Two types of HIV virus present is known as of HIV-1 and HIV-2, are known to cause infection and disease in humans^[14]. Among, these two viruses, HIV-2 is associated with slower development to immunodeficiency and is less efficiently transmitted^[15]. HIV-2 is also much less widespread than HIV-1, and HIV-2 mostly found in from West

Africa, India, rarely occurs Portugal and former Portuguese African colonies ^[16].

1.3) HIV lifecycle and drug targeting on HIV virus :-

Antiretroviral drugs principally act on in the HIV lifecycle, In these viral attachment to the host cell, fusion, reverse transcription, integration, protein processing and maturation ^[17]. Viral entry to the host cell begins with attachment of the HIV form glycoprotein (gp120) to the CD4 T-cell receptor . Gp 120 changes structurally , which enter the V3 region of HIV gp120 to bind to chemokine co-receptor, either CCR5 or CXCR4 ^[18]. These binding uncovers gp41, thus allowing fusion of viral envelope to the plasma membrane on CD4⁺ T lymphocyte cells and finally release of the HIV capsid contents into the cell cytoplasm ^[19]. Entry inhibitors target this early step in the HIV lifecycle. Three subclasses of entry inhibitor are currently marketed or in clinical phase trials: 1) fusion inhibitors (FIs), 2) CCR5 coreceptor antagonists (i.e., CCR5 inhibitors) and 3) monoclonal antibody against CD4 receptors (CD4 receptor antagonists). The HIV RNA is free into the cytoplasm of the CD4 cell, reverse transcriptase transcribes the single-stranded RNA into a double-stranded complementary viral DNA. The proviral DNA becomes part of the pre-integration complex, which transfer into the nucleus and is integrated into the cell genome via integrase ^[20]. NRTIs and NNRTIs target this reverse transcriptase enzyme. The enzyme integrase catalyses the insertion of the viral cDNA into the genome of infected cells. Two catalytic reactions are involved in the process of proviral integration, that is, 3' processing to prepare the proviral DNA nucleotide ends for attachment and strand transfer to covalently link the viral and cellular DNA components ^[21]. Integrase inhibitors competitively block the strand transfer reaction of proviral DNA integration. The viral enzyme protease cleaves these strands to make individual HIV proteins and enzymes, which then infected healthy human host cells. PIs interfere with the strand cleavage assembly step of the HIV life cycle. Maturation inhibitors block HIV

replication by disrupting virus maturation resulting in release of noninfectious viral particles ^[22].

1.4) HIV/host cell interaction:-

Human cells expressing the cell-surface protein CD4 may be productively infected by HIV. These include macrophages, T cells and dendritic cells (DCs) ^[23]. HIV-1 life cycle is complex and is dependent upon several viral and host factors. To infect target cells HIV requires the attachment of its envelope with the cell membrane interaction of gp120 (envelope glycoprotein) with the cell-surface receptor CD4 bond. it is established, gp120 undergoes a conformational change that facilitates its binding to one of two chemokine co-receptor molecules, CXCR4 or CCR5 and gp120 interacted with CD4 and co-receptors is vital for viral binding to human cells but interaction of gp41 with a cellular fusion receptor is responsible for the fusion of HIV cell. R5 viruses, i.e. virus presenting preferential CCR5-expressing cell tropism, which is responsible for most HIV new infections ^[24]. After HIV/ cell fusion, the viral core contains RNA, reverse transcriptase, and integrated are released inside the cell cytoplasm then the viral RNA is reverse transcribed into DNA by the viral reverse transcriptase and migrates into the cell nucleus, is inserted in the host chromosomal DNA by the viral integrase. Cell infection is irreversible, the cell of producing virions ^[25].

2] TREATMENT AVAILABLE AND PREVENTION OF HIV/AIDS:-

First antiretroviral drugs were introduced in late 1980s and early 1990s. and fast development of antiretroviral resistance in individuals treatment with single drug , the concept of highly active antiretroviral therapy (HAART) was introduced in the late 1990s, comprising the intense use of combination drug regimens ^[25]. The use of HAART increased life expectancy and its quality, shifting AIDS from a rapidly increase to a chronic disease ^[26-28]. antiretroviral treatment is newly the best option for prolonged and maximal viral suppression, and protection the immune system.

[29]. About 30 individual drugs and fixed-dose combinations available to treat HIV infection. Newly included drug is reverse transcriptase inhibitors (RTIs) ex-Zidovudine, protease inhibitors (PIs) ex-Indinavir, entry inhibitors (CCR5 antagonists ex-Maraviroc and fusion inhibitors ex-Enfuvirtide), and integrase inhibitors. The choice between this various drugs and drug regimens is not easy and it is depends upon multiple variables relating to its drug pharmacological and toxicological characterization, and therapy costs, disease performance and progression, drug resistance present and patient characteristics [29].

An important factor for the emergence of HIV/AIDS therapy resistance is the unable to attain effective and/or sustained drug levels with currently used formulations, thus contributing to ineffective viral suppression in reservoir sites. For example, PIs are substrate for the efflux cellular membrane transporter P-glycoprotein, which is able to mediate unidirectional transport of these drugs to the cell [30]. The presence of this membrane transporter in macrophages and endothelial cells of the BBB explains the less concentrations found by PIs in these reservoir sites. otherside, incomplete absorption of some PIs when administered by the oral route can be explained, alongside with their poor aqueous solubility, by the presence of this transporter in intestinal epithelial cells [30,31]. Poor placental penetration of PIs, which may have important for clinical implications in mother-to-child transmission, is also justified by the presence of high levels of P-glycoprotein in this tissue [32].

The use of multi-drug regimens, each drug possessing some toxicity, and problematic issues is that it may delay therapy initiation or determine its interruption [33]. The type, severity and frequency of clinical adverse effect are variable and dependent on individual drugs, drug regimens and patients. The drug toxicity is more if considering that for effective viral suppression it is essential a nearly perfect compliance of drug regimens for long time, if chronically, with interruption of drug treatment resulting in increased morbidity and mortality and interactions between antiretroviral drugs or with other drugs are frequent and greater Available online on www.ijprd.com

complex, this fact related for treatment course management. Antiretroviral drugs is an increasingly many burden for developed countries.

3] NANOTECHNOLOGY USED IN THE HIV/AIDS TREATMENT:-^[34-39]

The basic theory behind the use of nanotechnology systems for antiretroviral drug delivery is relating with the modulation of pharmacokinetics of incorporated molecules. The properties that govern drug absorption, distribution, and elimination in the human body are determined not only by the drug properties and the nanosystems physical–chemical properties, particularly surface showing molecules and electric charge, and its size. General properties of nanosystems that support the use in antiretroviral drug delivery are known and including flexibility the drugs may be encapsulated, good toxicity profile depends on used excipients, possibility of drug-release modulation, high drug payloads, relative low cost, easiness to produce and possible scale-up to mass production scale. Their ability to include protection and/or promote the absorption of non-orally administrable anti-HIV drugs, known as mono- or oligonucleotides, it is of importance to improving the bioavailability of molecule. Bioavailability protection of included drugs from metabolism is a favorably quality of nanosystems, allows prolonged drug residence in the human body, thus reducing needed doses and prolonging time between administrations. The use of nanoparticulate systems for antiretroviral drug delivery having advantageous for targeted delivery known to cells or organs that are directly implicated in HIV/AIDS. This can be applicable by passive or active targeting system. Passive targeting is based in the intrinsic properties of different nanosystems, it includes size, particle shape, and surface charge, which can be change its bioavailability, biodistribution and/or targeting; in the case of active targeting, nanotechnology-based systems are modified, most commonly by surface attachment to ligands that are able to identify target cells or sites, and/or escape bioelimination

processes . The limitation of many current antiretroviral drugs is their absence to circumvent efflux pumps such as P-glycoprotein that are present, in the membrane of several HIV-target cells and BBB endothelium. Nanoparticulate systems' able to get away these bioelimination processes is an added advantage in order to avoid this particular resistance mechanism to drug delivery, known to the CNS. The increasing the amount of availability antiretroviral drugs and its residence time at target area allow to thinking about dose reduction and simpler but improved regimens with few adverse effects and increased compliance.

The possibility of incorporating different antiretroviral drugs in the same delivery system and modulating their release individually has been shown. The fact may give to simplify drug administration is an important objective towards the reduction of antiretroviral drug administration. Nanosystems able to reduce antiretroviral drugs toxicity in the cellular level, providing the selection of materials and enough preparation techniques are assured . If the drug dose is increased when encapsulated in nanocarriers, cell toxicity seen to be diminished, probably due to the slow-release properties of these systems. This possibility is particularly interesting taking in consideration the well-known toxicity associated with anti-HIV therapy. The effects of the bioaccumulation of nanosystems components have not been addressed and may create a point for prolonged used. Nanosystems allow obtaining antiretroviral medicines with adequate shelf-life, even if the point has not been fully explored. Formulation should be carefully performed and long-term stability studied. Hence antiretroviral drug-loaded nanotechnology-based systems may undergo several physical–chemical changes that can potentially spoil efficacy and safety.

4] MODERN ADVANCED DRUG DELIVERY FOR AIDS TREATMENT:-

4.1) Liposomes:- ^[40]

Liposomes are the classical vesicular carriers comprised of phospholipid molecules that form a lipid bilayer surrounded an aqueous core. The single portion of the liposomes is that the hydrophilic drugs can be encapsulated in the aqueous layer while the lipophilic drugs is incorporated in the phospholipid bilayer in the same molecule. Liposomes are generally prepared from natural as well as synthetic phospholipids and cholesterol, and it include other lipids and proteins. And the Size of the liposomes ranges from 20 to 300 nm. This size range is depends upon the type of process and constituent lipid of the liposomes. Structurally these are classified as Small Unilamellar Vesicles 25-100 nm and Large Unilamellar Vesicles 200-1000 nm . The single and beneficial characteristic of the liposomes exists in their recognition as a foreign entity by the MPS of the body. HIV mainly resides in the macrophages and MPS of the body; and this forms a based of the antiretroviral drugs targeting to these reservoirs by the liposomes with reduced side effects of the drugs both in vitro and in vivo. liposomes is mostly used for the delivery of hydrophobic anti HIV/AIDS drugs; e.g. PIs. Liposomes can be surface-engineered for the tailor made functionality to achieve efficient targeting of encapsulated drugs to the desired affected areas in the body. These vesicular carriers having certain disadvantages like poor stability; both in the bloodstream, due to the presence of serum lipoproteins, and in storage; the problem of the low encapsulation effectiveness by this methods used to involved them, the presence of solvent residues in the final formulation, which is unacceptable to their possible toxicity, and the high costs of industrial production .

4.2) Solid lipid nanoparticles (SLN):- ^[41]

In the last years SLN have gaining interest as novel particulate drug delivery systems. SLN are solid, carriers with a size ranging from 1 to 1000 nm and consisting of materials such as physiological and biodegradable/biocompatible lipids, suitable for the incorporating of lipophilic and hydrophilic drugs within the lipid matrix in considerable amounts. SLNs can be prepared from

solid or semisolid fatty acids (e.g., cetyl palmitate, salts of myristic acid), and stabilization of dispersions with emulsifiers and co-emulsifiers, such as polysorbates, poloxamers, fatty acid co-esters, lecithin and bile salts. SLN are prepared by heating the components to cause converted them into liquefy and undergo emulsification in an aqueous medium. On cooling, the solid nanocarriers separate out and can be easily filtered and dried. SLN not only combine the advantages of traditional colloidal drug carrier systems like liposomes, polymeric nanoparticles and emulsions but also prevent the problems related with them. SLN have been working for efficient delivery of numerous therapeutic agents by various delivery routes. SLNs can also be modified for size and surface charges in order to achieve site-specific drug delivery designed for immediate or prolonged release. Additionally SLN can be engineered to release their payload in response to a specific external trigger, such as temperature or pH. Newly, SLN have been modified into a mixture of solid and liquid lipids (called as nano-structured lipid carriers or NLCs), high amounts of lecithins, amphiphilic cyclodextrins and para-acyl-calix-(4)-arenes. The possibility of any delivery system is governed by the cost of the material and the ease of manufacturing. Today, the commercial possibility of SLN is not a dream as they can be measured. SLN are composed of the easily available triglyceride lipids, and the cost of the components is not be an issue in most of the cases, unlike PLGA, PLA, PCL or phospholipids. SLN are mainly manufactured by using high-pressure homogenizers, which are commonly employed for the manufacturing of parenteral nutrition products. Muller and coworkers demonstrated the possibility of scaling up the SLN production with batch size varying from 2 to 150 kg. The production is performed in continuous as well as discontinuous manner. SLN can also be scaled up when microemulsions are used as the template for SLN production.

3. Ethosomes:-^[42]

Another vesicular carriers with capable resulted in the anti HIV/ AIDS drug delivery are ethosomes. Available online on www.ijprd.com

it is Discovered by Tuitou et al., ethosomes contain phospholipids, alcohol (ethanol/isopropyl alcohol) in comparatively high concentration and water. These vesicular carriers having the size range of few nanometers to microns are claimed to be most suitable for the transdermal drug delivery of bioactives. And the classical liposomes, ethosomes is shown to permeate through the stratum corneum barrier and is reported to possess higher transdermal flux in comparison to liposomes. The exact mechanism for better permeation into deeper skin layers from ethosomes is still not clear the synergistic effects of combination of phospholipids and high concentration of ethanol in vesicular formulations have been suggested to be responsible for deeper distribution and penetration in the skin lipid bi-layers. Ethosomal carriers having to be effective permeation enhancers.

4. Nanoemulsions and Nanosuspensions:-^[43]

Nanoemulsions or mini-emulsions are transparent or translucent oil-in-water (o/w) or water-in-oil (w/o) droplets with a droplet diameter between 100 and 500 nm. Nanoemulsions are known as submicron emulsions and the thermodynamically stable microemulsions, nanoemulsions are stable with great stability in suspension depend on the small droplet size. Advantages of nanoemulsions over macroemulsions or coarse emulsions include higher surface area and free energy without the intrinsic creaming, flocculation, coalescence and sedimentation related with macroemulsions. They can be formulated in a range of formulations such as liquids, sprays, foams, creams, ointments and gels. Currently nanoemulsions are of considerable interest in anti- HIV/AIDS drug targeting. Newly an o/w nanoemulsion stage was used to improve the oral bioavailability and brain localization of saquinavir. Nanoemulsions loaded with tritiated [3H]-saquinavir and administered to fasted Balb/c mice and compared to aqueous suspensions orally as well as parenterally. The orally administered drug-loaded nanoemulsions resulted in the highest plasma and brain concentrations. Pharmacokinetic

analysis suggested that this was attributed to higher rate and extent of absorption with orally administered zidovudine encapsulated in nanoemulsions. This formulation is claimed to be capable for targeting delivery of anti-HIV/AIDS therapeutics to viral reservoir sites such as the brain .

5. Lipid nanocapsules (LNC) [44]

Lipid nanocapsules are the core-shell structures made up of a liquid oily core and an amorphous surfactant shell. These are basically derived from nanoemulsions. LNC derived by Heurtault et al.. These are generally prepared by Phase Inversion Temperature (PIT) method. Biocompatible excipients like medium-chain triglycerides (caprylic triglycerides) as the oil phase, a polyoxyethylene-660-12-hydroxy stearate as the PEO nonionic surfactant and MilliQpsy® water plus NaCl as the aqueous phase are chosen for the development of LNC. These non-polymeric nanocarriers have currently reported in the anti- HIV/AIDS drug delivery. Pereira de Oliveira et al. evaluated indinavir-loaded nanocapsules (INV-LNC) including Solutol HS15, an excipient reported to possess in vitro P-gp inhibiting properties, as a means to improve indinavir distribution into brain and testes of mice. The LNC formulation was found to increase indinavir uptake in brain and testes by mechanisms, or additional to, Pgp inhibition.

6. Gold nanoparticles acting on HIV fusion inhibitor:-[45]

The anti-HIV potency of noble-metal nanoparticles has been described . Bowman and co-workers have acknowledged the first application of small-molecule coated gold nanoparticles as effective inhibitors of HIV fusion. Their concept arise from the basis of Mammen and co-workers that 'biological systems develop multivalency in the synthesis of high-affinity ligands because they allow an organism to take advantage of an existing set of monovalent ligands without the need for evolving completely new molecules for every required function'. The concept of 'multivalent therapeutics' is well conceived by the

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described system. The gold nanoparticles employed as a platform (2.0 nm diameter, mercaptobenzoic acid modified gold particles) transformed a weakly binding and biologically inactive small molecule into a multivalent conjugate that effectively inhibited HIV-1 fusion to human T-cells. the similarity of this class of gold particles to proteins and dendrimers in terms of their atomical accuracy and mono-disperse nano-size . A significant contribution is made by this study in representing the first application of small-molecule coated gold nanoparticles as effective inhibitors of HIV fusion. The demonstration that therapeutically inactive monovalent small organic molecules may be converted into highly active drugs by simply conjugating them to gold nanoparticles is considered to add impetus to the search of effective new drug formulations. Mintek (Pty) Ltd., (Randburg, South Africa), South Africa's national mineral research organization, aims to add value to mineral resources through technology, industrial growth and human development in a sustainable manner. The early 1990s saw the evaluation of some gold drugs for activity against HIV. Results generated indicated that there might be some inhibition of HIV exhibited by gold compounds, such as sodium aurothiomalate and aurothioglucose . Due to the biomedical group having a variety of gold-based drugs within their grouping, a range of these compounds has been submitted for HIV screening .

7.Silver nanoparticles used as microbicide delivery systems:-[46]

Silver nanoparticles shows the microbicide properties of silver with various materials to produce effective microbicide delivery systems for the prevention of HIV transmission Elechiguerra and co-workers study on the interaction of silver nanoparticles withHIV-1 The concept of surface chemistry predictability of interactions with external systems has been challenged in their investigation via the development and testing of silver nanoparticles with three different surface chemistries, namely, foamy carbon, poly (N-vinyl-2-pyrrolidone) (PVP), and bovine serum albumin (BSA). Contrary to

expectations, they established congruency amongst all the formulations in that only nanoparticles below 10 nm attached to the viral envelope and this occurred independently of the formulations' surface chemistry. Additionally, a regular spatial arrangement with equivalent center-to-center distances between the nanoparticles bind to the virus–cell was found. They ameliorated their findings with regard to both the spatial arrangement of nanoparticles and the size dependence of interaction in terms of the HIV-1 viral envelope. These investigations ultimately provided a deeper understanding into the mode of interaction between the virus and nanoparticles. Silver nanoparticles proposedly undergo specific interaction with HIV-1 via preferential binding with the gp120 subunit of the viral envelope glycoprotein, through interaction of the silver nanoparticle with the exposed disulfide bonds of the gp120.

This indicated the aforementioned probability that other noble-metal nanoparticles may also exhibit similar activity. However, the toxicity and inhibition results differed, despite the congruency among the surface modified nanoparticles with reference to their interaction with HIV-1. The differential behavior was attributed to the capping agents employed for each nanoparticles preparation. BSA- and PVP-protected nanoparticles displayed slightly lower inhibition because the nanoparticle surface was directly bind to and encapsulated by the capping agent.

CONCLUSION:

The modern aspects of anti HIV therapy improves the bioavailability of drugs and reduces the adverse effect. Challenge of successful implementation of long term control of HIV in patients resistant to ARVs has contributed to accelerated research in the field antiretroviral drug discovery. New classes of drug: namely, entry inhibitors, which include fusion inhibitors, chemokine co-receptor (CCR5) inhibitors and integrase inhibitors.

These newer drugs have either been approved or are at a very late stage of clinical development. The recent approvals of the CCR5 antagonists ex-
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maraviroc, the fusion inhibitor ex-Enfuvirtide, and protease inhibitors ex-Indinavir used in the treatment of HIV-infected patients, particularly for those with limited treatment options. There is tremendous research work doing on AIDS nanotechnology is beneficial for improving lifespan of AIDS patient and helpful for reducing the burden of AIDS worldwide.

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