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# Advances in Drug Delivery of Anti-HIV Drugs - An Overview

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## ABSTRACT

The advent of highly active antiretroviral (ARV) agents has led to striking reduction in plasma viral load, opportunistic infection and mortality from AIDS. Unfortunately most of these drugs have poor physiochemical, metabolism or transport properties that result in poor or variable absorption and side effects, which are often related to the accumulation of the drug at inappropriate sites. Various classes of antiretroviral agents are available, though monotherapy in HIV positive individuals can develop resistance more quickly as compared to combinational therapy or fixed dose combination or highly active antiretroviral therapy. The currently available ARV drugs mostly oral formulations, which are associated with several disadvantages and inconveniences to the HIV patients. The delivery of drugs via oral route suffers from significant first-pass effect, variation of absorption and degradation in the gastrointestinal, erratic bioavailability, limited duration of drug action, metabolism/elimination and transport barriers reducing the effect of anti-HIV drugs reaching the target site. Also half-life of several ARV drugs is short, which requires frequent administration of doses leads to poor patient compliance. Therefore, the usage of novel drug delivery systems is a logical approach to circumvent these problems and effectively treat the HIV infection. Various novel drug delivery techniques were tried or on trial for ARV drugs. Among the recent approaches of novel drug delivery system for anti-HIV drugs, controlled/sustained and targeted/intracellular drug delivery are the important ones. In this review the need for novel drug delivery, advantages, and recent development in drug delivery system of antiretroviral drugs were discussed, which may useful for further research in future.

**Keywords:** AIDS, HIV, Antiretroviral therapy, Novel drug delivery systems

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# INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus that infects cells of the human immune system, destroying or impairing their function.[1] Altered cellular functions in the macrophage population may contribute to the development and clinical progression of acquired immune deficiency syndrome (AIDS). HIV also affects the central nervous system **(**CNS) and furthermore, the infected brain may be continuously re-infecting the periphery by serving as a reservoir for the virus. Resistance is also a widespread problem.[2,3] The advent of highly active antiviral agents in late nineties has led to striking reduction in plasma viral load, opportunistic infection and mortality from AIDS. Unfortunately more of these drugs have poor physiochemical, metabolism or transport properties that result in poor or variable absorption and side effects;[4] which are often related to the accumulation of the drug at inappropriate sites.[5]

During the last decade promising evidence of immune system reconstitution and dramatic reduction in opportunistic infections, disease progression to AIDS, and death from the use of potent combinations of antiretroviral (ARV) agents have led to widespread enthusiasm that HIV might be eradicated. However, the discoveries of latent, resting reservoirs of HIV that are inaccessible to current ARV agents have dampened optimism for a "cure". Eradication of HIV is highly unlikely and chronic ARV therapy will likely be required to maintain viral suppression and reduce disease progression. During next decade, innovative therapies aimed at blocking HIV cell entry, continued suppression of HIV replication, and ARVs targeting resting HIV reservoirs will be critical to prolong survival and renew hopes for a cure. The complete lake of efficacy of the first two phase III AIDS vaccine trials clearly show that development of an effective AIDS vaccine is not forthcoming in the near future.[6,7]

Hence the aim of ARV therapy focused on reduction in the symptoms and disease progression to AIDS, reduction in the viral load to undetectable levels, elimination of resting reservoirs of HIV, minimizing the viral resistance and drug failure, minimizing the drug adherence problem, reducing the adverse effects of the drugs, optimizing drug therapy and improving the quality of life of the patients.[7]

**Therapy for HIV Infection**

Substantial advances have been made in antiretroviral therapy. There are five classes of antiretroviral agents are available for use: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion / entry inhibitors and integrase inhibitors. As new agents have become available, several

older ones have had diminished usage, because of either suboptimal safety profile or inferior antiviral potency.

**Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)**

The NRTIs act by competitive inhibition of HIV-1 reverse transcriptase and can also be incorporated into the growing viral DNA chain to cause termination. Each requires intracytoplasmic activation via phosphorylation by cellular enzymes to the triphosphate form. Most have activity against HIV-2 as well as HIV-1 infections. The currently available NRTIs includes; abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T), tenofovir disoproxil fumarate (TDF), zalcitabine (ddC) and zidovudine (AZT) **(Table 1)**. In addition few molecules from this class are under investigation such as alovudine**,** amdoxovir (DAPD), apricitabine**,** DPC817 (D-d4FC), elvucitabine**,** lobucavir, lodanosine, fosalvudine**,** and racivir,

**Table 1: US-FDA approved nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)**

| Generic Name | FDA Approval Date | Oral Adult Dose | Dose Frequency | $T_{max}$ (Hours) | Half-life (Hours) | Bioavailability (%) | Metabolism and Excretion |
|---|---|---|---|---|---|---|---|
| Abacavir (ABC) | 17-Dec.-1998 | 300 mg<br>600 mg | Twice daily<br>Once daily | 0.7 - 2 | 1 - 1.5 | 83 | Liver and Renal |
| Didanosine (ddI) | 09-Oct.-1991 | 200 mg<br>400 mg | Twice daily<br>Once daily | 0.6 - 1 | 1.3 - 1.5 | 21 - 43 | Renal Excretion |
| Emtricitabine (FTC) | 02-Jul.-2003 | 200 mg | Once daily | 1 - 2 | 10 | 93 | Renal Excretion |
| Lamivudine (3TC) | 17-Nov.-1995 | 150 mg<br>300 mg | Twice daily<br>Once daily | 1 - 1.5 | 3 - 7 | 82 - 87 | Renal Excretion |
| Stavudine (d4T) | 24-Jun.-1994 | 30 – 40 mg | Twice daily | 1 | 0.9 - 1.6 | 80 - 86 | Renal Excretion |
| Tenofovir disoproxil fumarate (TDF) | 26-Oct.-2001 | 300 mg | Once daily | 1 | 4 - 8 | 25 - 40 | Renal Excretion |
| Zalcitabine (ddC) | 19-Mar.-1992 | 0.75 mg | Every 8 hours | 1 - 2 | 1 - 3 | 80 - 88 | Renal Excretion |
| Zidovudine (AZT) | 19-Mar.-1987 | 200 mg<br>300 mg | 3 times a day<br>Twice daily | 0.5 - 1.5 | 0.5 - 3 | 64 | Liver and Renal |

Nucleoside analogs may be associated with mitochondrial toxicity, probably owing to inhibition of mitochondrial DNA polymerase gamma, and they can increase the risk of lactic acidosis with hepatic steatosis, which may be fatal, as well as disorders of lipid metabolism. NRTI treatment should be suspended in the setting of rapidly rising aminotransferase levels, progressive hepatomegaly, or metabolic acidosis of unknown cause.

**Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

NNRTIs inhibit the HIV-1 reverse transcriptase enzyme by binding directly to theHIV-1 active site. They do not require prior phosphorylation and can act on cell-free virions as well as infected cells. These are not effective against HIV-2. The NNRTIs available include; delavirdine (DLV), efavirenz (EFV), etravirine (TMC125), nevirapine (NVP) **(Table 2)**; and few newer molecules from this class are under investigation such as capravirine, DMC961, DMC963, DPC083, rilpivirine**,** and rilpivirine (TMC278).

**Table 2: US-FDA Approved Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

| Generic Name | FDA Approval Date | Oral Adult Dose | Dose Frequency | $T_{max}$ (Hours) | Half-life (Hours) | Bioavailability (%) | Metabolism and Excretion |
|---|---|---|---|---|---|---|---|
| Delavirdine (DLV) | 04-Apr.-1997 | 400 mg | 3 times a day | 1 | 2 - 11 | 60 – 100* | Liver and Renal/Feces |
| Efavirenz (EFV) | 17-Sep.-1998 | 600 mg | Once daily | 3 - 5 | 52 - 76 | 42* | Liver and Renal/Feces |
| Etravirine (TMC125) | 18-Jan.-2008 | 200 mg | Twice daily | 2.5 - 4 | 41 | Unknown | Liver and Feces |
| Nevirapine (NVP) | 21-Jun.-1996 | 200 mg | Once daily – First 14 days; then Twice daily | 2 - 4 | 45 | 90 | Liver and Renal |

(*Reported in animal studies)

NNRTI agents tend to be associated with varying levels of gastrointestinal intolerance and skin rash, the latter of which may infrequently be serious (eg, Stevens-Johnson syndrome). A further limitation to use of NNRTI agents as a component of HAART is their metabolism by the CYP450 system, leading to innumerable potential drug-drug interactions.

**Protease Inhibitors (PIs)**

PIs effect in the later stages of the HIV growth cycle, the Gag and Gag-Pol gene products are translated into polyproteins, and these become immature budding particles. Protease is responsible for cleaving these precursor molecules to produce the final structural proteins of the mature virion core. By preventing cleavage of the Gag-Pol polyprotein, protease inhibitors (PIs) result in the production of immature, noninfectious viral particles. The currently available PIs are; amprenavir (APV), atazanavir (ATV), Darunavir, fosamprenavir (FOS-APV), indinavir (IDV), lopinavir (LPV) (used in combination with ritonavir), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), tipranavir (TPV) **(Table 3)**; and few molecules from this class are under investigation such as Mozenavir (DMP-450), TMC 114, GW0385 and P-1946.

**Table 3: US-FDA Approved Protease Inhibitors (PIs)**

| Generic Name | FDA Approval Date | Oral Adult Dose | Dose Frequency | $T_{max}$ (Hours) | Half-life (Hours) | Bioavailability (%) | Metabolism and Excretion |
|---|---|---|---|---|---|---|---|
| Amprenavir (APV) | 15-Apr.-1999 | 1200 mg | Twice daily | 1 - 2 | 7 - 10 | Unknown | Liver and Renal/Feces |
| Atazanavir (ATV) | 20-Jun.-2003 | 400 mg | Once daily | 2 | 7 | Good oral bioavailability | Liver and Renal/Feces |
| Darunavir | 23-Jun.-2006 | 600 mg<br>800 mg | Twice daily<br>Once daily | 2.5 - 4 | 15 | 37 | Liver and Renal/Feces |
| Fosamprenavir (FOS-APV) | 20-Oct.-2003 | 1400 mg | Twice daily | 1.25 | 7.7 | Not established | Liver and Renal/Feces |
| Indinavir (IDV) | 13-Mar.-1996 | 800 mg | Every 8 hours | 0.8 | 1.4 - 2.2 | 30 | Liver and Renal/Feces |
| Lopinavir and Ritonavir (LPV/RTV) | 15-Sep.-2000 | 400/100 mg<br>Once daily<br>800/100 mg | Twice daily | 5/3.4 | 4.4/6.1 | No data available | Liver and Renal/Feces |
| Nelfinavir (NFV) | 14-Mar.-1997 | 1250 mg<br>750 mg | Twice daily<br>3 times a day | 2 - 4 | 3.5 - 5 | 20 - 80 | Liver and Renal/Feces |
| Ritonavir (RTV) | 01-Mar.-1996 | 600 mg | Twice daily | 2 - 4 | 3 - 5 | 80* | Liver and Renal/Feces |
| Saquinavir (SQV) | 06-Dec.-1995 | 1200 mg | 3 times a day | 3 | 13 | 4 | Liver and Renal/Feces |
| Tipranavir (TPV) | 22-Jun.-2005 | 500 mg | Twice daily | 2.9 - 3 | 5.5 - 6 | 30* | Liver and Renal/Feces |

(*Reported in animal studies)

Adverse effects associated with this class of agents includes a syndrome of redistribution and accumulation of body fat that results in central obesity, dorsocervical fat enlargement (buffalo hump), peripheral and facial wasting, breast enlargement, and a cushingoid appearance has been observed in patients with antiretroviral therapy, particularly associated with the use of PIs. Concurrent increases in triglyceride and LDL levels, along with glucose intolerance and insulin resistance, have also been noted. PIs have been associated with increased spontaneous bleeding in patients with hemophilia A or B.

**Fusion / Entry Inhibitors**

Fusion / entry inhibitors are the new class of antiretroviral agents that blocks entry into the cell. Enfuvirtide (T-20) (Table 4) is the first representative of this class. It is a synthetic 36-amino-acid peptide, binds to the gp41 subunit of the viral envelope glycoprotein, preventing the conformational changes required for the fusion of the viral and cellular membranes. Enfuvirtide must be administered by subcutaneous injection. Metabolism appears to be by proteolytic hydrolysis without involvement of the CYP450 system.

The most common adverse effects associated with enfuvirtide therapy are local injection site reactions. Hypersensitivity reactions may rarely occur, are of varying severity, and may recur on rechallenge. Eosinophilia has also been noted.

Maraviroc (Table 4) is an entry inhibitor drug which is chemokine receptor antagonist. It prevents HIV infection of CD4 T-cells by blocking the CCR5 receptor. Specifically, maraviroc prevents the membrane fusion events necessary for viral entry by blocking the binding of viral envelope, glycoprotein (gp) 120, to CCR5. Maraviroc is inactive against isolates that utilize CXCR4 as a co-receptor; therefore, the antiviral mechanism of action of maraviroc is exclusively CCR5 mediated. AMD070, PRO 140, TNX-355, and Vicriviroc (SCH-D) are the other fusion / entry inhibitors under investigation.

**New Classes of Antiretroviral Agents**

Various new classes of drugs are currently in both clinical and preclinical stages of development and are likely to increase the anti-HIV armamentarium over the next few years. These are include; integrase inhibitors, attachment blockers, maturation inhibitors. In addition, newer strategies for treating HIV are likely to be more widely studied, including; immunomodulatory therapies and adjunctive therapeutic vaccines.

**Integrase Inhibitors**

Integrase inhibitors work by blocking integrase, a protein that HIV needs to insert its viral genetic material into the genetic material of an infected cell. Raltegravir is a first drug in this class, also known as Isentress and MK-0518. Anemia, myocardial infarction, hepatitis are the serious drug-related adverse events reported. Pruritus, rash, Stevens-Johnson syndrome is also reported.[7-12]

**HIV Vaccines**

HIV vaccines are being developed to prevent and treat HIV infection. Preventive HIV vaccines are designed to protect HIV negative people from becoming infected or getting sick. Therapeutic HIV vaccines are designed to control HIV infection in people who are already HIV positive they are designed to boost the body's immune response to HIV. There are three main types of vaccines that are being studied for the prevention of HIV infection and AIDS. Subunit vaccines also known as "component" or "protein" vaccines, recombinant vector vaccines, and DNA vaccines. Currently no HIV vaccines are approved for use; however, many are in clinical trial studies.[13,14]

**Gene Therapy for HIV**

Gene therapy is becoming an increasingly important part in the future of HIV treatment. It offers

a new frontier for a cure, with great hope for promising new treatments. Gene transfer can be used to prolong the survival of CD4+ T cells and may, ultimately, help to sustain the immune systems of HIV-infected people. Stem cell research and new gene-editing technique may helpful for treating HIV. However, the gene therapy field is still in its infancy, but it holds promise for diseases such as HIV currently requiring lifelong treatment that is both costly and potentially toxic. Most experimental gene therapy methods, are complicated; therefore expensive and not without risks.[15,16]

**Combinational Therapy**

Monotherapy in HIV positive individuals can develop drug resistance more quickly as compared to those individuals taking combinational therapy or fixed dose combination (FDC) or highly active antiretroviral therapy (HAART). Fixed dose combination anti-HIV drugs contain two or more anti-HIV medications that can be from one or more drug classes, generally two NRTIs are combined with one or two PIs / NNRTIs. Combination therapy can lower the magnitude and durability of viral suspension and also reduces the total treatment cost, pill burden and optimize the patient compliance of HIV patients. Currently available FDC drugs are approved by the FDA as follows, abacavir and lamivudine; abacavir, zidovudine, and lamivudine; efavirenz, emtricitabine and tenofovir DF; emtricitabine and tenofovir DF; lamivudine and zidovudine.[17]

**Problems in Conventional Route of Anti-Retroviral Drugs**

The currently available ARV drugs associated with several disadvantages and inconveniences to the HIV patients. Most of the ARV drugs are formulated as solid dosage forms for oral route of administration. The oral dosage forms offer convenience; and the combined dose of compounds that make up a therapeutic regimen is usually high. High doses are preferred because the treatment objective is to completely inhibit viral proliferation, an effect which is proportional to drug concentrations.[18] The delivery of drugs via oral route suffers from significant first-pass effect, variation of absorption and degradation in the gastrointestinal tract due to enzymes and extreme pH conditions leading to low and erratic bioavailability. Same time the duration of drug action also limited. The metabolism / elimination and transport barriers will substantially reduce the effective amount of anti-HIV drug reaching the target action site. The half-life for several ARV drugs is short, which then requires frequent administration of doses leads to poor patient compliance. Therefore, the usage of novel drug delivery systems is a logical approach to circumvent these problems and effectively treat the HIV infection.[19]

**NOVEL DRUG DELIVERY SYSTEM FOR ANTI-HIV DRUGS**

Several approaches are currently being followed in the development of strategy for the treatment

of HIV infection. Evaluation of the effect of drug delivery systems on the efficacy and toxicity may improve the anti-HIV treatment.[20] To avoid hepatic first-pass effect and intestinal degradation, various researches have made efforts on the delivery of drug. Delivery of nucleoside analogues through percutaneous absorption, rectal adminis- tration, oral buccal permeation, nasal absorption, intratracheal administration, using enteric-coated dosage form and co-administration with antacid are being studied. Percutaneous absorption has been one of the most reported routes for non-oral administration of anti-HIV agents.[19]

Transdermal delivery of anti-HIV drugs is a suitable method to overcome the problems of conventional delivery, since it is very helpful in maintaining a suitable plasma concentration through zero-order delivery. Thus, it can enhance the anti-viral activity, and reduce the frequency and severity of side effects by optimizing blood concentration profiles within the therapeutic range for longer duration. Transdermal delivery can also bypass hepatic 'first-pass' elimination, which will improve the bioavailability of drugs.[21] Efforts have been made to design drug delivery systems for anti-HIV agents to reduce the dosing frequency, to enhance the bioavailability, to improve the CNS penetration and inhibit the CNS efflux and to deliver them to the target cells selectively with minimal side effects. Among the recent approaches of novel drug delivery system for anti-HIV drugs, controlled / sustained and targeted / intracellular drug delivery are the important ones.

**Controlled / Sustained Drug Delivery of Anti-HIV Drugs**

Controlled drug delivery system represents one of the frontier areas of drug delivery system; in order to fulfill the need of a long-term treatment with anti-HIV agents, where most of them suffer from the drawbacks of frequent administration, plasma concentration fluctuation, significant adjustment in the lifestyle, it is desirable to have controlled- or sustained-release drug delivery systems to improve the overall therapeutic benefit and to achieve an ideal therapy. By sustained or controlled delivery, it is possible to achieve effective plasma concentration without significant fluctuation, to avoid sub-therapeutic and toxic plasma concentrations, to facilitate release of the medication in a controlled manner to obtain a continuous delivery, to achieve an effective therapy with low dosage of the drug, to reduce the frequency of medication and thus to improve patient adherence, by preventing the interference of therapy with the day-to-day lifestyle.[22,23]

Bio-adhesive drug delivery systems are designed for prolonged retention on the mucosa to facilitate drug absorption over a prolonged period of time by interacting with mucin. Hence, the combination of both sustained release and bio-adhesive properties in a delivery system would

further enhance therapeutic efficacy.[24] Novel drug delivery carriers and dosage forms, such as nanoparticles, liposomes, microparticles and others, hold the promise of overcoming the pharmacokinetic obstacles of anti-HIV drugs, which are also under investigation.[25]

A study reveled the effect of the dose frequency of oral controlled release dosage forms on the drug level in the blood depend on the gastrointestinal time, which resulted the longer gastro-intestine tract time, lower the dose frequency.[26] A review discussed on the studies and progress on macromolecular pro-drugs in anti-HIV therapy by using as carriers either natural and synthetic polymers showed good release properties in a prolonged time.[27]

The research carried out on sustained release matrix tablet formulation of zidovudine shown prolonged constant plasma concentration through 12 hours, which is therapeutically better than conventional dosage forms and may reduce the frequency of administration.[28] A research involved on controlled release matrix tablets of zidovudine found; controlled release tablets with pH independent drug release characteristics and an initial release of 17 - 25% in first hour and extending the release up to 16 – 20 hours, can overcome the disadvantages of conventional tablets of zidovudine.[29] Another study of lamivudine oral controlled release tablets found the release of 20 - 30% drug in the first hour and extend the release up to 16 to 20 hours, can overcome the disadvantages associated with conventional tablet formulations of lamivudine.[30]

Applications of liposomes, microparticles and drug encapsulated erythrocytes have been utilized to extend the circulation time of anti-HIV agents. The liposomes used as carriers of the antiretroviral agents were studied to achieve a long-lasting plasma concentration, a dideoxycytidine (ddC) pro-drug dideoxycytidine-5'-triphosphate (ddCTP) has been encapsulated in erythrocytes, which serve as a bioreactor to convert the pro-drug to its parent drug, and slowly releases ddC to the blood circulation.[31,32] Result of a study on encapsulated ddCTP in liposomes can reduce pro-viral DNA in cells of the mononuclear phagocyte system (MPS) in both spleen and bone marrow.[33]

Lamivudine loaded ethyl cellulose microspheres for effective management of AIDS. One study demonstrated that, the efficiency of release of Lamivudine from ethyl cellulose matrix of prepared microspheres shown significantly slower release pattern in total drug load. The drug release rate was following zero order kinetic which complies with the controlled delivery of Lamivudine over 10 hours.[34]

**Targeted / Intracellular Drug Delivery of Anti-HIV Drugs**

Targeted drug delivery is the most important one in pharmaceutical research and development. The drug targeting is defined in the broadest sense, that is, to optimize a drug's therapeutic index

by strictly localizing its pharmacological activity to the site or organ of action. The result of the targeting would be a significant reduction in drug toxicity, reduction of the drug dose, and increased treatment efficacy.[35] Current approaches of drug delivery using polymeric or liposomal carriers, in which intracellular targeting is a crucial step in the enhanced delivery of macromolecular drugs (peptides, protein or DNA).[36] In HIV infection the viral load is found higher in cells like lymphocytes and macrophages than other cells, which prove that targeting delivery of anti-HIV drugs specifically to these cells would increase the efficacy of therapy.[19]

A review described the recent scientific breakthroughs in novel anti-HIV target discovery and validation denoted for the future antiretroviral drug development.[37] Another review discussed the recent developments in drug targets and delivery of anti-HIV drugs. The target of viral and cellular level that could interrupt viral replication, as well as novel and proven strategies to enhance the delivery of anti-HIV drugs to the lymphoid, CNS, and cells were low viral replication and limited drug levels exist.[38] Liposomes, nanoparticles and low-density lipoproteins (LDLs) are cell-specific transporters of drugs against macrophage-specific infections such as HIV 1; in the process of protein transduction, cell-permeable peptides of natural origin or designed artificially allow the delivery of drugs and genetic material inside the cell. Although important milestones have been reached in the development of carrier systems for the treatment of HIV, especially in the field of gene therapy, further clinical trials are required.[39]

Macrophages constitute important targets for HIV-1: they serve as virus reservoirs and represent the most important targets in the central nervous system (CNS). One report of research reveled erythrocytes (RBCs) can be used to enhance delivery of effective antiretroviral agents to the CNS, thus improving therapy for AIDS dementia and related encephalopathies.[40] A review summarized about the development of anti-HIV 1 ribozyme usage can effectively inhibit HIV 1 target cells.[41]

The research on novel anionic chemical delivery system (aCDS) used in zidovudine for braintargeted delivery which was shown controllable rate of metabolism, thus the approach is flexible enough.[42] A comprehensive review delivered on polymeric nanoparticles for ARV drug therapy, its applications for targeting to macrophages and the brain. Also it highlighted the significant potential that nanoparticles have for the future effective treatment of HIV/AIDS.[43]

Studies resulted the nanotechnology-based delivery systems can improve the therapeutic efficacy in HIV/AIDS by delivering drugs to cellular and anatomical viral reservoirs. Nanocarriers can facilitate lymphatic transport, delivery across the blood–brain barrier, and efficient internalization in cells by nonspecific or receptor-mediated endocytosis. The polymeric

nanoparticle micelles, liposomes and nanoemulsions can play important role in improving delivery efficiency.[44] A research with the delivery of zidovudine, saquinavir, and zalcitabine, using nanoparticles as a drug carrier system, could improve the delivery of antiviral agents to the mononuclear phagocyte system in-vivo, overcoming pharmacokinetic problems and increasing the activities of drugs for the treatment of HIV infection and AIDS. Nanoparticles hold the promise of improving the potency of anti-HIV agents by enhancing cellular uptake and by enrichment of these agents in HIV target cells and relevant tissues.[45]

## CONCLUSION

Over 25 drugs with six different classes of anti-HIV drugs are approved almost past two decades. Although effective therapies for HIV still a question; newer agents are still needed to confront the emergence of drug resistance and various adverse effects with long-term use of ARV therapy. Also the half-life for several ARV drugs is short, which then requires frequent administration of doses leads to poor patient compliance. Therefore, the usage of novel drug delivery systems is a logical approach to circumvent these problems and effectively treat the HIV infection. Among the recent approaches of novel drug delivery system for anti-HIV drugs, controlled / sustained and targeted / intracellular drug delivery are the important ones. In this review the need for novel drug delivery, advantages, and recent development in drug delivery system of antiretroviral drugs were discussed, which may useful for further research in future.

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