Expert Opinion

Nanoparticulate drug carriers for delivery of HIV/AIDS therapy to viral reservoir sites

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Providing the optimum treatment of AIDS is a major challenge in the 21st Century. HIV is localised and harboured in certain inaccessible compartments of the body, such as the CNS, the cerebrospinal fluid, the lymphatic system and in the macrophages, where it cannot be reached by the majority of therapeutic agents in adequate concentrations or in which the therapeutic agents cannot reside for the necessary duration. Progression in HIV/AIDS treatment suggests that available therapy can lower the systemic viral load below the detection limit. However, on discontinuation of treatment, there is relapse of the infection from the reservoir sites and a potential for resistance development. This review discusses the aetiology and pathology of HIV, with emphasis on the viral reservoirs, current therapy of AIDS, and the opportunity for nanotechnology-based drug delivery systems to facilitate complete eradication of viral load from the reservoir sites. Literature-cited examples of drug delivery systems that are under investigation for the treatment of AIDS are discussed. The article also focuses on the future outlook and strategies for investigational drug formulations that use nanotherapeutic strategy for HIV/AIDS.

Keywords: AIDS, CNS, HIV, macrophages, nanocarrier technology, reservoir sites, targeted drug delivery

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1. Introduction

Development of AIDS from acquisition of HIV infection to disease progression represents a tremendous social, economical and political challenge in the 21st Century [1]. HIV infection results from the transfer of body fluids either through sexual contact, blood transfusion or through *in utero* maternal transfer to offspring. According to 2005 estimates from the WHO's AIDS Epidemic Update, 38.0 million adults and 2.3 million children have acquired HIV infection worldwide. There are > 3.0 million individuals who have died of HIV/AIDS in 2005, with > 2.4 million from sub-Saharan Africa [201-204].

Scientific understanding of HIV infection and the therapeutic progresses have been quite remarkable in the past 25 years, since the disease was first clinically identified [2]. An increasing number of prevention and therapeutic strategies have been developed to halt the progression of HIV and to combat AIDS in the world. During the early era of drug development, a number of antiretroviral drugs belonging to different classes, such as nucleoside reverse transcriptase inhibitors (NRTIs) [3,4] and non-nucleoside reverse transcriptase inhibitors (NNRTIs), were introduced that can efficiently lower the plasma viral RNA levels [5,6]. The introduction of protease inhibitors (PIs) followed by the use of combination highly active antiretroviral therapy (HAART) has certainly provided more options for treatment and better clinical outcomes. HAART therapy was a major step forward in the treatment of AIDS and has led to a significant reduction in the mortality rate of the disease [7-9]. As a result of HAART, the median survival of HIV-positive patients has been extended from

< 1 year to almost 10 years [205]. However, this therapeutic strategy does not offer a complete solution to the problem. Issues of viral reservoir sites, drug resistance development, administration of high doses and greater frequency of dosing, which results in increased toxicity, reduced patient compliance and the high cost of therapy have led to a significant crisis in the management of HIV/AIDS patients. HAART is also very expensive to implement and to maintain in developing nations, where there is the greatest need [10-12].

One of the predominant reasons for the lack of effectiveness of HIV/AIDS therapy is the poor drug transport, resulting in inefficient availability of the drugs to certain target sites in the body [13]. Lack of pharmacodynamic models to evaluate efficacy at different stages of infection is another problem. HIV infects and infiltrates intracellular sites, including $CD4^+$ T lymphocytes and macrophages. Furthermore, HIV is harboured in the CNS in the early stages of the infection [14,15]. Based on the dissemination of the virus, HIV reservoirs are classified into cellular and anatomical sites. The cellular reservoirs include $CD4^+$ T lymphocytes and macrophages, and the anatomical reservoirs are mainly in the CNS, lymphatic system, genital organs and lungs [16,17]. Direct infiltration of the HIV in these reservoir sites makes AIDS treatment extremely difficult, as many drugs cannot adequately reach or reside in these sites in sufficient concentrations and for the necesary duration to exert the therapeutic response. The advent of new drug compounds and the introduction of HAART for the treatment of HIV/AIDS has offered a variety of options to the clinical practitioners to combat this life-threatening infectious disease. However, because the penetration of these drugs into the viral reservoir sites is restricted, the results are often the administration of high drug doses, with consequent intolerance and, in turn, severe toxicity: all resulting in a vicious cyclic predicament.

The therapeutic strategy for the treatment of AIDS has undergone a paradigm shift in the past decade, wherein targeted or preferential delivery of the drugs is emerging as a new dimension, along with multiple drug therapy [18]. Preferential drug delivery may result in specific distribution at the target site with limited or poor distribution to the non-target sites. Improvement in bioavailability and higher systemic concentrations of the drugs can be achieved with the use of engineered drug delivery strategies that may help to reduce the viral load significantly, especially within the reservoir sites [19]. Engineered drug delivery systems can potentially increase the efficacy and reduce the toxicity of newer, as well as pre-existing, drugs by altering the pharmacokinetics and biodistribution, both of which restrict access of the drugs to the target and, in particular, these reservoir sites.

One of the recent trends in optimisation of drug delivery to target sites in the body is based on the use of nanocarrier delivery technology, where the drug payload is encapsulated within a delivery system of < 1000 nm in diameter, typically 100 – 500 nm [20,21]. In the last several years, nanocarriers are being actively investigated for preferential drug delivery to various disease sites, including cancer, cardiovascular diseases, and infectious diseases in the body, and to alter the drug pharmacokinetics in order to effectively treat a wide spectrum of conditions. Nanocarriers offer numerous advantages, such as a small particle size and narrow size distribution, which offers a large surface-area-to-volume ratio for efficient payload encapsulation and delivery. Depending on the physicochemical properties of the therapeutic agents, certain polymeric nanocarriers, for instance, can entrap > 20% (weight/weight) of the active agent. In addition, surface features for target-specific localisation, protective insulation of drug molecules and an opportunity for delivery of multiple therapeutic agents in a single formulation all are the advantages of using nanocarrier systems [22-24]. Regardless of the inherent properties of the drug candidates, the pharmacokinetics and the distribution pattern of the formulation will be dictated by the properties of the nanocarrier system. For instance, the particle size and surface charge of tailor-made nanocarriers can regulate biodistribution and target specific localisation of nanosystems in the circulatory system. Specific engineering of nanosystems can promote transport across a variety of biological barriers, including the gastrointestinal tract for oral absorption, the CNS and intracellular sites, where HIV typically is known to harbour [25-27]. Therefore, nanocarriers and therapeutic strategies that are associated with them offer very interesting opportunities and are starting to receive a great deal of attention, specifically for the delivery of antiviral drugs for HIV/AIDS.

This review addresses the use of nanoparticulate carrier systems for the treatment of HIV/AIDS, and especially for delivery to the viral reservoir sites. The significance and challenges of nanocarriers in the context of drug delivery systems, novel approaches that are used, and some of the reported examples of nanocarrier formulations for delivery of HIV/AIDS therapeutics are discussed. Nanocarriers may be used to enhance oral bioavailability of antiviral agents. However, in the context of viral reservoirs, the use of nanocarrier-based delivery system will predominantly focus on systemic administration through one or more parenteral route. Although broad analysis of HIV infection acquisition and AIDS development is beyond the scope of this review, and there are excellent references available, a brief introduction to HIV infection and AIDS pathogenesis, as well as development of viral reservoirs is described.

2. HIV/AIDS infection and therapy

Extensive research on the molecular virology continues to represent one of the most active areas for the treatment of complex disease, such as HIV/AIDS. The efforts to inhibit HIV/AIDS are continuously being made and some of the results have led to evolution of modern therapeutic strategies. However, specifically, the identification and characterisation of targets for antiviral agent drug design can be better understood from the basic virology study data [28]. HIV is known to proliferate in the cellular and anatomical reservoir sites and mostly remains protected due to the presence of biological

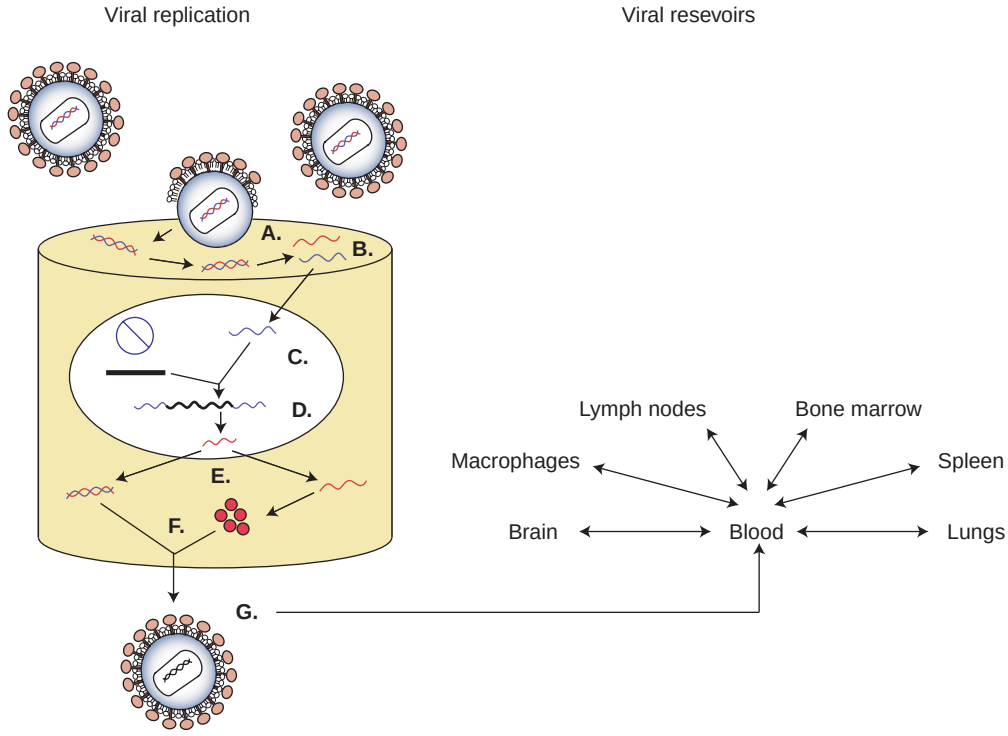

Figure 1. Schematic diagram illustrating the typical viral replication cycle of HIV and various reservoirs (sanctuaries) in the body. A. Attachment and viral fusion to the host cell. **B.** Reverse transcription. **C.** Integration. **D** and **E.** Protein synthesis and translation. **F.** Viral budding. **G.** Viral maturation, release and localisation at different reservoir sites. HIV penetrates into the reservoir sites, which become a potential viral reservoir that can be reseeded into the circulatory system when the drug concentration falls.

barriers and the higher resistance of the CNS to foreign substances [29]. A better understanding in terms of the life cycle of HIV, its major propagation sites and the associated detrimental effects on the human body would facilitate the development of modern therapeutic strategies and their effectiveness to combat AIDS [30-32]. Thus, it is imperative to comprehend the aetiology and pathology of HIV infection in order to enhance the effectiveness of AIDS therapy.

2.1 Aetiology and pathology of HIV infection

HIV infection in the human body is mainly caused by the integration of the viral genome into the host cell for the purpose of self replication. The infection process can be categorised into seven major steps that are illustrated in Figure 1. Primarily, $CD4^+$ receptors that are present on the cell membranes of T lymphocytes are recognised by the HIV, leading to gp120 glycoprotein-mediated interactions. Binding of HIV on these specific receptors infects the T cells, which causes cell membrane opening by the nucleoprotein present in the virus, followed by cell invasion. Virion-associated reverse transcriptase and tRNA synthesises proviral DNA and viral integrase. Subsequently, spliced and unspliced RNAs are formed following transcription of proviral DNA. Thus, translation takes place due to packaging of mRNA and the *gag*, *pol* and *env* genes at the cell membrane. Extracellular budding of the virions results in the acquisition of an envelope that contains the viral *env* proteins that are required for subsequent rounds of receptor recognition and fusion. Viral protease mediates the processing of *gag* and *gag–pol* polyproteins that are released, followed by the budding process. Hence, the propagation of the HIV virions occurs at the molecular level and is regulated by numerous enzymes and biochemical substrates. In general, anti-HIV drugs can be more effective if they get adequately distributed at the targeted sites and at the cellular level, and reside for the necessary duration to exert maximum pharmacological effect [33-36].

The CNS represents the most important anatomical sanctuary site of the virus after infection from the drug delivery standpoint. The disease progression is accompanied by devastating and major structural changes in the brain, such as cerebral atrophy, ventricular enlargement, chronic inflammation and astrocytosis [37,38]. HIV primarily infects the microglial cells in the brain and propagates within that site. HIV-infected brains usually undergo synaptic and dendritic damage, resulting in gross neuronal loss [39]. HIV can also damage neuronal subpopulations, particularly in the frontal cortex. Thus, HIV infection within the microglial cells of the brain causes substantial neuronal damage and loss that often results in HIV-associated

Table 1. Antiretroviral drugs approved by the FDA, and their classification based on mechanism of action.

Generic name	Brand name (manufacturer)	FDA approval (year)
Nucleoside reverse transcriptase inhibitors		
Zidovudine	Retrovir® (GlaxoSmithKline)	1987
Zalcitabine	Hivid® (Roche)	1992
Lamivudine	Epivir® (GlaxoSmithKline)	1995
Didanosine	Videx® (Bristol-Myers Squibb)	1991
Abacavir	Ziagen® ABC (GlaxoSmithKline)	1998
Stavudine	Zerit® (Bristol-Myers Squibb)	1994
Lamivudine and zidovudine	Combivir® (GlaxoSmithKline)	1997
Abacavir, lamivudine and zidovudine	Trizivir® (GlaxoSmithKline)	2000
Non-nucleoside reverse transcriptase inhibitors		
Nevirapine	Viramune® (Boehringer Ingelheim)	1996
Efavirenz	Sustiva® (Boehringer Ingelheim)	1998
Delavirdine	Rescriptor® (Pfizer)	1997
Protease inhibitors		
Indinavir	Crixivan® (Merck Laboratories)	1996
Saquinavir	Invirase® (Roche)	1995
Lopinavir	Aluviran® (Abbott Laboratories)	1997
Nelfinavir	Viracept® (Pfizer)	1997
Ritonavir	Norvir® (Abbott Laboratories)	1996
Atazanavir	Reyataz® (Bristol-Myers Squibb)	2003
Lopinavir and ritonavir	Kaletra® (Abbott Laboratories)	2000
Viral fusion inhibitors		
Enfuvirtide	Fuzeon® (Roche)	2003

Table adapted from [202,206].

dementia [40]. This dementia status is dependent on the viral load and is affected one way or the other by either increasing or decreasing the virus burden [41]. Penetration of HIV into reservoir sites further aggravates the problem, as the delivery and distribution of the drug are very poor due to high resistance and multiple barriers [42]. Therefore, the ability of antiviral drugs to enter into the CNS in therapeutic concentrations is pertinent for effective AIDS therapy. Anti-HIV drugs that can be preferentially delivered and distributed into and within the brain may be of great value in terms of enhancing the therapeutic effectiveness in AIDS patients.

2.2 Treatment of HIV/AIDS

In the past decade, when AIDS therapy was still in its infancy stage, the drugs for antiretroviral treatment were developed with the specific aim to reduce the viral burden by the inhibition of enzymes essential for viral replication. NRTIs were the first class of drugs that have been employed. In particular, NRTIs inhibit the viral reverse transcriptase enzyme that is vital for DNA chain elongation of the virus. At the same time, the second generation, NNRTIs, were introduced. The mechanism of action of NNRTIs was almost similar to NRTIs, and they were successfully deployed for reducing the viral burden. However, unlike NRTIs, these second-generation drugs were non-specific inhibitors of the enzyme reverse transcriptase. Following this, the third generation of antiretroviral drugs, PIs, have been introduced. PIs act by interfering in the process of the cleavage of proteins that are critical for viral assembly, and inhibit the growth of active retrovirus and viral burden. The examples of drugs categorised on the basis of their mechanism of action are shown in Table 1. The first-generation drugs require intracellular activation into their triphosphate active derivative, whereas NNRTIs and PIs do not require activation into the triphosphate derivative [43]. Studies reported in the literature have indicated that the effectiveness of NRTIs and NNRTIs for reducing viral burden is directly proportional to the presence of the activated component triphosphate, and not on the absolute concentration of these drugs at the site of action. Recently, another class of drugs, the integrase inhibitors, was introduced. These were found to avert catalysis of HIV DNA into host cell DNA.

The recent introduction of HAART has been a major revolution and has better acceptance due to the high success rate in suppressing the systemic viral burden. Regimens of multiple drugs from the class of NRTIs, NNRTIs, PIs and integrase inhibitors make it possible to suppress the viral burden as they inhibit retroviral growth through more than one synergistic mechanisms [44]. Some of the specific examples of antiretroviral drugs, their mechanisms of action, bioavailability and the CNS-to-plasma ratios are shown in Table 2 [45-54]. The mechanism of action of each class of antiretroviral drugs is illustrated in Figure 2. The HAART regimen has multiple drug combinations, and, depending on the inherent physicochemical characteristics of each individual drug, the drug distribution is expected to be more extensive in the body. In addition, HAART combines one or two NRTIs, an NNRTI, and a PI for synergistic therapeutic activity. These features make HAART unique and the most popular among the available options for the treatment of HIV infection. Since its introduction, HAART has been found to be more effective for suppression of the systemic viral load. However, the problems of additional toxicity from HAART therapy, lack of compliance with polypharmacy and significant potential for the development of drug resistance have led to severe shortcomings of HAART [55,56]. In addition, the efficacy of these drugs in the reservoir sites, such as the CNS, is unclear. As a matter of fact, studies have shown that macrophages and the CNS can in turn reseed the HIV back into the circulatory system when the systemic drug levels fall below subtherapeutic concentrations.

Table 2. Comparative chart of currently approved drugs on the market for HIV therapy and their oral bioavailability and CNS-to-plasma ratio.

Generic name	Brand name (manufacturer)	Dosage form (dose)	Oral bioavailability (%)	CNS-to-plasma ratio (%)
Saquinavir	Invirase® (Hoffmann-La Roche)	500-mg saquinavir capsules plus one 100-mg ritonavir capsule b.i.d. (a total of six capsules/day)	4 (following oral administration)	Negligible
Indinavir	Crixivan® (Merck & Co.)	Two 400-mg capsules, every 8 h (a total of six capsules/day)	> 77	7.0
Tipranavir	Aptivus® (Boehringer Ingelheim)	Two 250-mg capsules and two 100-mg retonavir capsules b.i.d. (a total of eight capsules/day)	Not reported	-
Nelfinavir	Viracept® (Pfizer)	Two 625-mg tablets, b.i.d. (a total of four tablets/day), or five 250-mg tablets b.i.d., or three 250-mg tablets t.i.d. (a total of 9 – 10 tablets/day).	~ 75	Negligible
Zidovudine	Retrovir® (GlaxoSmithKline)	One 300-mg tablet b.i.d.	65	50.0
Didanosine	Videx® EC (Bristol-Myers Squibb)	One delayed-release 400-mg capsule/day	36	21.0
Delavirdine	Rescriptor® (Pfizer)	Two 200-mg tablets t.i.d. (a total of six tablets/day)	85	0.40
Nevirapine	Viramune® (Boehringer Ingelheim)	One 200-mg tablet/day for 14 days, followed by one 200-mg tablet b.i.d. (a total of two tablets/day)	90	45.0
Efavirenz	Sustiva® (Bristol-Myers Squibb)	One 600-mg tablet/day (1 tablet/day)	80	1.0
Enfuvirtide	Fuzeon® (Hoffmann-La Roche)	Two 90-mg (in 1-ml solution) subcutaneous injections/day	84	
Abacavir plus zidovudine plus lamivudine	Trizivir® (GlaxoSmithKline)	One tablet (300-mg zidovudine plus 150-mg lamivudine plus 300-mg abacavir) b.i.d. (a total of two tablets/day)	-	-

Therefore, in addition to the selection of the right combination therapy, which may vary from patient to patient, depending on the severity of the infection and the type of HIV strain, an optimised delivery system is also quite critical. Considerable work has been done, and more is in progress, to address the issue of effective therapy to treat AIDS. Some of the critical factors that are important in deciding the best strategies for HIV/AIDS treatment are emphasised in the following section.

2.3 Critical factors for effective AIDS therapy

The introduction of various new drug compounds, and in particular the HAART, offers a variety of options to the clinical practitioners for effective management of HIV/AIDS. Nevertheless, as described in Section 2.2, it is increasingly clear that the physicochemical characteristics of drugs and drug resistance are the major challenges that need to be addressed for effective HIV therapy [57,58]. Poor absorption of certain anti-HIV compounds and low oral bioavailability may result in low therapeutic concentrations. For example, the anti-HIV PI, saquinavir, has a bioavailability of < 4% following oral administration [59]. Consistently low therapeutic concentrations of drugs may ease the HIV to penetrate remote areas, where they then multiply and reseed back into the systemic circulation when the drug levels fall below virustatic or virucidal concentrations. Persistent reseeding of HIV into the circulation may also result in the development of drug resistance by the generation of mutations, the development of sensitivity to the drug doses over time, and increased drug toxicity at other sites. The poor distribution of drugs at reservoir sites may not be effective to prevent or interfere with the viral multiplication process. Overall, not only are higher drug concentrations in systemic circulation required, but their distribution at the anatomical and cellular reservoir sites is also of utmost importance [13]. Strategical drug delivery systems could be one of the more effective alternatives from the perspective of enhanced drug absorption, higher bioavailability and distribution to the desired sites in the body.

The literature states that HIV infects macrophages in the early stages, and these cells can act as shuttles to the CNS and other sanctuary sites in the body. More importantly, the drug concentration and distribution in the potential reservoir sites, such as macrophages and the CNS, is very poor due to a high resistance, compared with other body tissues [60]. Macrophages

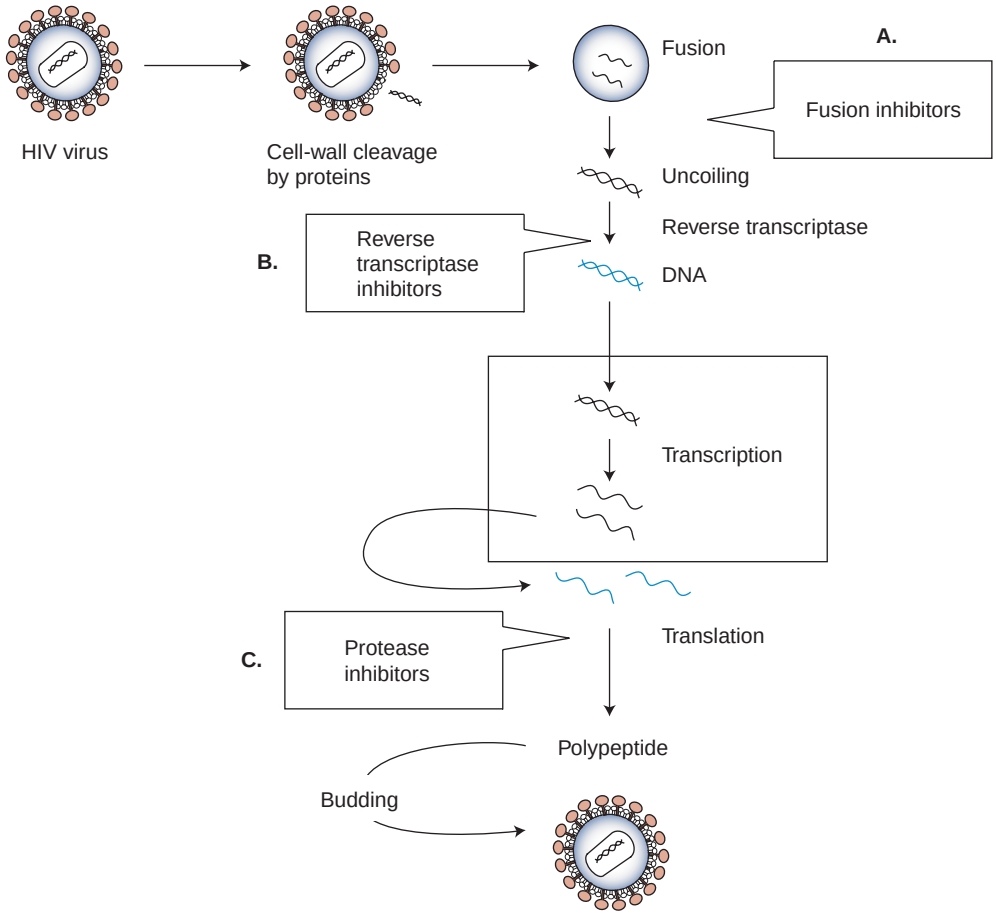

Figure 2. Schematic representation of the HIV replication cycle and the mechanism of anti-HIV agents. The major stages during the replication process, such as fusion, transcription, translation, budding and maturation, are illustrated. There are three different classes of anti-HIV drugs, which are shown. **A.** Fusion inhibitors interfere with the fusion process. **B.** Nucleoside and non-nucleoside reverse transcriptase inhibitors interfere at the transcription stage. **C.** Protease inhibitors inhibit the translation process.

may also absorb and rapidly degrade anti-HIV drugs. Furthermore, growth and dissemination of virus in the sanctuary sites aggravates the problem and increases the complexity of AIDS therapy. Therefore, prior to formulating drug delivery systems to treat AIDS/HIV, it is imperative to address the issue of low titre and subtherapeutic concentrations of the drug, in particular at the reservoir sites.

In addition, the efflux mechanisms of drugs at the reservoir sites is another very important issue that needs to be taken into account to understand the dynamics of drug transport. A number of efflux mechanisms take place within the brain and other tissues, whereby certain cells can influence and regulate drug concentrations within the brain. Some of these mechanisms are passive in nature, whereas others involve active efflux transport. A comprehensive understanding of the efflux mechanisms at the blood–brain barrier is imperative for targeting drugs to the brain, in order to achieve therapeutic concentrations within the brain, or for regulating the penetration of drugs across the blood–brain barrier, in order to minimise side effects in the CNS. Systemically delivered drugs must cross the blood–brain barrier for entry into the CNS. The net bioavailability of drugs in the brain is dependent on passive diffusion from the blood, on transport across the tight endothelial cell junctions of the blood–brain barrier and on the efflux of certain compounds that are recognised by specific transporters on the cell surface [60,61]. In addition to the physicochemical properties of the drug that can regulate the rate and extent of drug uptake within the brain, active efflux of the drugs from the reservoir sites via specific transporters can result in lower drug concentrations compared with theoretically derived values.

In the last decade, much attention has been paid to the multi-drug transporters such as the multi-drug resistance protein, P-glycoprotein (Pgp) and the multi-specific organic anion transporter. These multi-drug transporters belong to the members of the ATP-binding cassette (ABC) family of transport proteins [62,63]. In humans, multi-drug resistance proteins exist mainly as five different isoforms, and have different levels of expression in different tissues. On the other hand, the Pgp

efflux pump is encoded by the multi-drug resistance gene (*MDR-1*) in humans and accepts a wide range of structurally dissimilar lipid-soluble substrates that will be actively effluxed from the cells expressing the gene product. Multi-specific organic anion transporter is present in the choroid plexus and has some of the similarities in its substrate preference with multi-drug resistance protein. Brain exposure can be increased by enhancing influx in addition to restricting efflux through the blood–brain barrier. Therefore, therapeutic strategies that have the objective to increase brain uptake of drugs shall be primarily focused on reducing the interactions/reactivity with the Pgp transporter system, or by examining the pathways of inhibition of the activity of the efflux mechanism by co-administering a competitive or noncompetitive inhibitor of the efflux pump along with the desired drug. Pgp substrates and concomitant administration of a Pgp inhibitor can result in enhanced oral absorption and higher uptake within the brain [64,65]. Reports in the literature cite that co-administration of the Pgp inhibitor valspodar was found to enhance brain uptake of paclitaxel, a Pgp substrate, and also to improve its anticancer therapeutic effect in mice [66]. Co-administration of a Pgp inhibitor with the active therapeutic agent can decrease the efflux of the agent. However, this approach has generally shown higher toxicity *in vivo*, mostly from the high doses of the Pgp inhibitor that are needed, and the additional undesirable pharmacokinetic interactions between the Pgp substrate and the inhibitor. The other therapeutic strategy is based on a sequential metabolic approach using a prodrug concept, wherein influx is increased by passive diffusion through increased lipophilicity, followed by the decrease in efflux with the help of a lock-in mechanism when the prodrug is converted to the active moiety [67]. A better understanding of the Pgp-dependent transport mechanisms can result in the development of an appropriate therapeutic strategy for enhanced drug delivery to the intracellular reservoirs.

3. Drug delivery to intracellular reservoirs

In addition to the CNS, HIV infects other organs and cells of the body that can be potential reservoirs. In order to completely eradicate HIV, cure AIDS and to render the therapeutic treatment effective, it is essential to eradicate the viral burden from these compartments. It is well known that the virus infects intracellular compartments, such as $CD4^+$ cells and macrophages that eventually become an important reservoir for HIV.

3.1 Intracellular HIV reservoirs

Reports in the literature cite that HIV infects and infiltrates $CD4^+$ lymphocytes, peripheral blood mononuclear cells and macrophages during early stages of the infection, along with the other body organs/tissues/fluids [68]. Therapeutic treatment of the HIV/AIDS infection has recently shown that antiretroviral treatment suppresses the viral load in the systemic circulation below detectable levels. However, on discontinuation of the treatment, the virus usually reappears in the blood. This phenomenon is mainly attributed by the fact that the HIV virus resides in intracellular reservoir sites, such as macrophages and peripheral blood mononuclear cells. HIV replicates within the $CD4^+$ T lymphocytes and the systemic circulation on discontinuation of antiretroviral therapy. Moreover, being involved in the body's major defence mechanism, macrophages can engulf the foreign substances and inactivate them [69]. There is ~ 99% of the viral load that is in the $CD4^+$ T cells, and only 1% is internalised in macrophages. However, macrophages are long-lived cells (with a lifespan of > 14 days) and can be transported to different sites in the body. These factors make the HIV treatment dynamics more complex. These sanctuary sites not only reseed the HIV back into the circulatory system but also could result in the evolution of the mutation, followed by drug resistance with progression of the therapy. Therefore, delivering drugs to these intracellular compartments using engineered drug delivery approaches is pertinent to combat HIV/AIDS [70]. Various approaches for intracellular drug delivery are currently under exploration, and the advancement with regards to more effective therapeutic management of HIV/AIDS has certainly increased the pace. Some of these approaches are discussed in this section.

3.2 Strategies to enhance intracellular delivery

Some hydrophobic molecules can diffuse across the cell membrane by a simple diffusion process that is based on the concentration gradient between the extracellular and intracellular compartments. However, hydrophilic drugs require a facilitator, wherein membrane proteins form channels and the drug is transported across the cell membrane by facilitated transport. In general, the majority of drugs are pumped across the cell membrane against the concentration gradient, from a low concentration compartment outside (due to dilution in the extracellular fluid) to a much higher concentration in the intracellular compartment. Basic endocytosis and receptor-mediated endocytosis are the simplest examples for active transport, wherein ATP is used as the source of energy to push the drug substance against the concentration gradient. Endocytosis can also occur either as phagocytosis, where the cell engulfs the foreign substance by physical contact, or pinocytosis, which is often referred to as cell-drinking, where the substance is dissolved in water and then taken up within the cellular structure.

A considerable amount of work has been done in the area of intracellular drug delivery. Drug delivery at the intracellular level can be achieved by the most popular approaches, such as macromolecular drugs, liposomal drug delivery, micellar drug delivery and nanoparticle-based delivery [21]. The surface of these carriers can be fabricated with specific ligands, such as cell-penetrating peptides, for efficient transport into the cell. Liposomal drug delivery has been more focused, as it can be tailor-made for the targeting requirement. Cationic, anionic, neutral, PEG-modified or cell-penetrating peptide-modified

liposomes can be used for targeting different drugs to the specific intracellular sites [71-73]. Micelles are self-assembled nanosystems that are composed of molecules that have hydrophobic and hydrophilic functionalities. When placed in aqueous environment, the hydrophobic segments are preferentially restricted from aqueous environment. The result is a nanoparticulate self-assembled system where the hydrophilic groups are exposed to the surface and the hydrophobic groups are buried in the core. Hydrophobic drugs can be encapsulated in the core of the micelle. The system can then promote intracellular delivery either by non-specific or receptor-mediated endocytosis. Polymeric nanoparticles are also interesting candidates for intracellular delivery [74]. Various types of cell systems, including macrophages, are known to endocytose polymeric nanoparticles.

4. Drug delivery to anatomical reservoirs

An obvious route of delivery to the CNS and other reservoir sites would be via the cardiovascular system. The blood flow to the brain is high, ~ 750 – 1000 ml/min (~ 15% of total cardiac output). Therefore, it would be expected that such a high perfusion rate should be sufficient to deliver drugs into the brain. However, unlike the situation in most other organs, the cerebral blood compartment does not have free diffusion communication with the interstitium of the blood. Systemically administered drugs used against CNS diseases that need to reach the brain must pass through the blood–brain barrier. Thus, the blood–brain barrier is a predominant rate-limiting barrier and a major bottle neck in brain-targeted drug delivery systems. The function of the blood–brain barrier is dynamically regulated by various cells [42]. The transport mechanisms through this barrier and physicochemical properties of the drug molecules are major factors to be considered in designing a drug delivery system for the CNS. The capillaries in the brain are lined with special endothelial cells that lack fenestrations and are sealed with tight epithelium. This has a resistance that is similar to that of the blood–brain barrier. These layers are also found in other organs (the skin, bladder, colon and lungs). The tight junctures between endothelial cells results in a very high transendothelial electric resistance of 1500 – 2000 Ωcm^2, compared with only 3 – 33 Ωcm^2 in other tissues, which reduces the aqueous-based paracellular diffusion that is observed in other tissues [60,61].

Certain classes of CNS-acting drugs, such as the benzodiazepines (e.g., diazepam), have been used as sedative-hypnotic agents because these lipophilic drugs readily cross the blood–brain barrier. However, the blood–brain barrier transport of an immunosuppressive agent ciclosporin A, which is more lipophilic than diazepam, is highly restricted. Similarly, almost all of the lipophilic anticancer agents, such as paclitaxel, epipodophyllotoxin and vinca alkaloids (e.g., vincristine and vinblastine) hardly enter the brain, thereby causing difficulty in the treatment of brain tumours. Although levodopa, which is useful for the treatment of Parkinson's disease, is very hydrophilic, it can readily penetrate the blood–brain barrier. The mechanisms underlying these diverse drug transport characteristics, which are apparently structurally and pharmacologically unrelated, are not fully understood. The other problem that is encountered with the blood–brain barrier is enzymatic degradation of therapeutic agents. Solutes crossing the cell membrane are subsequently exposed to metabolising enzymes that are present in high concentrations inside the endothelial cells, which contain large densities of mitochondria (metabolically highly active organelles). Blood–brain barrier enzymes also recognise and rapidly degrade the majority of peptides, including naturally occurring neuropeptides.

Some of the strategies adopted to enhance transport across the blood–brain barrier for CNS delivery are discussed in the following subsections [61].

4.1 Hydrophobicity enhancement

The octanol/water partition coefficient (log $P_{o/w}$) is very commonly used and is a convenient approach to predict the lipophillicity of any system. However, log $P_{o/w}$ alone seems to have a very limited application in predicting brain-to-blood concentration ratios, so in order to be more successful, it is essential that combinations with other parameters, such as capillary membrane permeability, first-pass metabolism and volume of distribution, be used [75,76].

4.2 Prodrug strategy

A prodrug is defined as a drug derivative with enhanced transport properties to overcome biological barriers and which is able to be converted into the active therapeutic molecule at the site of interest. Many examples of prodrugs are in the clinic, including aspirin (acetylsalicylic acid). For CNS delivery, prodrugs can be designed to have properties that facilitate transport across the blood–brain barrier and be converted into the active form in the brain either by hydrolysis or enzymatic conversion [61,77]. Once converted to the active form, the drug is trapped (lock-in mechanism) and cannot diffuse back into the circulatory system. The prodrug strategy has been explored and has been found to be reasonably useful in the recent past in designing drugs for HIV/AIDS.

4.3 Temporary disruption of the blood–brain barrier

One of the approaches to circumvent the dense microvasculature of the brain was delivery using a transient osmotic opening. Hyperosmolar substances such as mannitol or arabinose are likely to cause disruption of the blood–brain barrier due to migration of water from endothelial cells to capillaries, which, in turn, cause shrinkage of the cells and result in intracellular gaps. The approach resulted in the breakdown of the self-defence mechanism of the brain, thereby leaving it vulnerable to infections. The other approaches are blood–brain barrier disruption using labradimil, which has selectivity for the bradykinin B_2-receptor. Ultrasound-induced mild hyperthermia can be controlled and localised to a small volume within the tissue

and may improve the permeability of drugs [78,79]. One of the most important considerations in blood–brain barrier disruption is the exact definition of the word temporary. As the disruption of the barrier is non-specific, it is possible that other toxic compounds can also enter the brain at the same time. Chronic use of this approach for HIV/AIDS therapy is probably not a strategic option.

4.4 Invasive administration by intracerebral delivery

The blood–brain barrier can be successfully traversed by using the most direct and invasive approach, such as intracerebral delivery of a broad class of drugs using traditional and novel drug delivery system-based dosage forms, including injectables, controlled-release polymers/microspheres or, in the future, microencapsulated recombinant cells. The basic impediment is very limited and has slow diffusion within the brain due to very compact, tightly packed brain cells, resulting in limited interstitial space and unusually tortuous pathways [80,81]. Long-term therapy may not be a practical option with intracerebral drug delivery to treat HIV/AIDS, as this is an invasive approach that is associated with significant risk and requires a trained professional for administration.

4.5 Invasive administration by intra-cerebroventricular delivery

The cerebrospinal fluid is in direct communication with the interstitial fluid of the brain. To a major extent, an alternative invasive strategy to bypass the blood–brain barrier is the delivery of drugs directly into the cerebral ventricles. The drug penetration from the cerebrospinal fluid is hindered by slow diffusion, especially in the human brain; therefore, this is a serious drawback. Moreover, as a result of rapid ventricular cerebrospinal fluid clearance, intra-cerebroventricular delivery is not beneficial over slow intravenous infusion [80,81]. Similar to intracerebral delivery, intra-cerebroventricular drug delivery requires advanced set-up and is associated with a high risk. This approach can only be administered by trained personnel in a clinical setting, which makes intra-cerebroventricular delivery impractical for the treatment of chronic diseases such as HIV/AIDS.

5. Nanocarrier delivery systems

In the last few years, there has been a tremendous amount of excitement over the use of nanotechnology for development of targeted drug delivery systems. Nano-based drug delivery systems, where the formulation is restricted to < 1000 nm in diameter (typically 100 – 500 nm), can be fabricated to protect drug molecules and to preferentially target the drugs to specific anatomical and cellular targets [82]. In addition, nanocarrier-based systems also offer a unique feature in terms of drug targeting, which makes this system the most versatile option, especially for HIV/AIDS. The role of nanocarrier systems can not be undermined, especially for delivering drugs to the sanctuary sites or reservoirs. Several applications pertaining to drug delivery using nanocarriers are emerging and some of them are outlined in this section.

5.1 Nanocarrier technology for HIV therapy

For HIV/AIDS therapeutics, nanocarriers have been reported to be used for transporting the drugs to reservoir compartments in the body, in particular to the macrophages, lymphatic system and/or CNS. Lipid and polymeric nanosystems are typically used for delivery to overcome cellular and anatomical barriers. Lipid nanosystems usually comprise a bilayer or multilayer system wherein one of the layers contains lipids (outer layer), whereas the core layer encapsulates the drug substance (inner layer). The lipid nanosystems not only protect the drug but also provide flexibility to encapsulate most hydrophobic pharmaceutical compounds. Enhanced lipophilicity and surface engineering of lipid nanocarriers can significantly influence the transport of the drugs across the mucosae and the physiological and anatomical barriers that are present in the body. These delivery systems can be designed in a tailor-made format, depending on the need to provide typical surface characteristics for targeting drug compounds. Polymeric nanocarriers can also provide many of the advantages of lipid systems and can be modified for target specificity. Liposomes, nanoemulsions, solid-lipid nanoparticles (SLNs) and polymeric nanocarriers are some of the examples of widely used nanoparticulate drug delivery systems that are reviewed in this section. Schematic representations of these nanocarriers are shown in Figure 3.

5.1.1 *Liposomes*

Liposomes are spherical, organised clusters of phospholipid molecules that form a lipid bilayer. Liposomes can be prepared using different lipids. Depending on the type of process and the constituting lipid, they vary in diameter ranging from 50 – 1000 nm. Liposomes can be broadly categorised as small unilamellar vesicles (20 – 200 nm) and large unilamellar vesicles (200 – 1000 nm). Due to the lipophilicity of the bilayer, liposomes have been successfully used as carriers for preferential drug delivery to macrophages and targeted brain delivery [83-85]. Liposomes are efficiently phagocytosed by macrophages and there have been investigations into liposomes for delivering drugs to macrophages both *in vitro* and *in vivo*. Moreover, liposomes may be an advantageous drug delivery system for highly hydrophobic drugs, such as many of the HIV PIs [83,84]. The only concern with liposomes is their long-term physical and biological stability, which can be compromised by aggregation and lead to drug leakage.

5.1.2 *Solid lipid nanoparticles*

SLNs have been widely employed for delivering drugs to the CNS by circumventing the blood–brain barrier. SLNs are 200 – 500 nm in diameter and can be prepared from solid or semisolid fatty acids (e.g., cetyl palmitate, salts of myristic acid), and stabilisation of dispersions with emulsifiers and co-emulsifiers, such as polysorbates, poloxamers, fatty acid

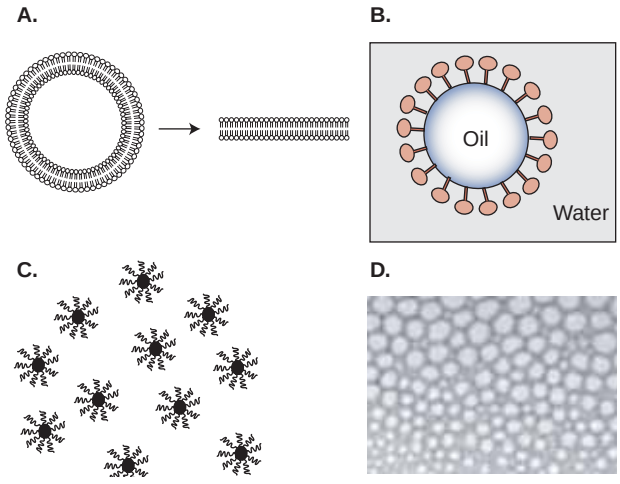

Figure 3. Schematic illustration of several relevant nanocarrier drug delivery systems. A. Liposome–cationic, PEG-modified and cell-penetrating peptide can be used to target various body tissues and cells. **B.** Micellar nanoparticles developed by self-assembly of molecules containing hydrophilic and hydrophobic segments. **C.** Nanoemulsions are the preparations wherein the oil droplet particle size is < 200 nm. As with microemulsions, nanoemulsions can be fabricated using dispersed phase, continuous phase and a surfactant/co-surfactant/charge-inducing agent. **D.** Polymeric nanoparticles: a very useful tool and drug delivery system that is commonly used to deliver the drugs at the intracellular level and for internalisation purpose. Nanocarriers are being increasingly considered as very promising drug delivery system for target-specific localisation and delivery into cellular and anatomical reservoir sites of HIV.

co-esters, lecithin and bile salts. SLNs are prepared by heating the components to cause them to liquefy and undergo emulsification in an aqueous media. On cooling, the solid nanocarriers separate out and can be easily filtered and dried. The majority of drugs can be incorporated into the SLNs in the liquid system during the preparation. SLNs can also be modified for size and surface charges in order to achieve site-specific drug delivery designed for immediate or prolonged release [86-89]. Finally, SLN can be engineered to release their payload in response to a specific external trigger, such as temperature or pH.

5.1.3 *Nanoemulsions*

Nanoemulsions are heterogeneous liquid dispersions where the droplet size of the internal phase is reduced to a nanometer scale. Nanoemulsions exist in a broad variety of forms that are designed using different types of oils and a variety of emulsifiers to render them specific for the given application. The oil droplets of nanoemulsions are generally considered to be in the size range of ≤ 400 nm in diameter. The emulsions can exist as water-in-oil and oil-in-water forms, wherein the core of the particle is usually either water or oil. The long-term properties of the internal phase are dependent on the composition of the adsorbed surface-active agent (surfactant) lying at the dispersed droplet interface with the dispersion medium. This has an impact on the partitioning and extraction of droplet contents. Nanoemulsions are thermodynamically stable particles and can be characterised by having a very low surface tension [21,90]. The small size of oil droplets leads to a very large surface-area-to-volume ratio for delivery and to a better physical stability of the formulation. The choice of oils with specific fatty acid composition can influence transport properties, as well as therapeutic activity. The surface properties and chemistry can strongly influence *in vivo* behaviour of nanoemulsions. Further developments in nanoemulsion-engineering technologies are likely to lead to a much greater use as carriers for targeted drug delivery for different disease conditions, as well as for newer generations of therapeutic agents [21,90].

5.1.4 *Polymeric nanoparticles*

Due to their versatility, polymers offer a unique opportunity for the development of nanocarrier systems. Nanoparticles are defined as solid, colloidal particles consisting of either non-degradable or biodegradable polymeric components. Nanoparticles have a particle size typically ranging from 200 – 800 nm. A large variety of synthetic and natural polymeric materials, such as poly(D,L-lactide-co-glycolide), poly(ε-caprolactone), chitosan, albumin and gelatin are used for the preparation of nanoparticles. The drug is either encapsulated or adsorbed on the nanoparticle surface. As with liposomes, polymeric nanoparticles also can be tailor-made with regard to the surface charge and particle size, based on the need. The particles can be coated by using surfactants for immediate-release preparations. However, the potential problem with nanoparticles is aggregation that can be decreased by surface modification with amphipathic copolymers, such as poloxamines or poloxamers [91]. Surface modification with PEG or poly(ethylene oxide), using a variety of poly(ethylene oxide)-containing copolymers, can prolong the circulation times in the plasma and allow for passive delivery [92]. The efficiency of particle uptake by peripheral blood mononuclear cells can be altered by varying the concentration of block polymers on the nanoparticle surface to regulate phagocytosis and preferential uptake by the reticuloendothelial system [93]. Reports in the literature cite that polymeric nanoparticles can be used for a wide spectrum of drug delivery applications, including inside macrophages and in the CNS [94]. Nanoparticle-based carrier systems can also be used to alter the drug release pattern and, in turn, to alter the biodistribution and pharmacokinetics of the drug.

5.2 Some examples of nanocarrier systems

A great deal of attention has been directed at the development of nanocarrier systems to target specific disease areas in the body and improve therapeutic outcomes. Specific examples of some of the nanocarrier drug delivery systems and their application for antiretroviral therapy in the management of HIV/AIDS are shown in Table 3 [95-102].

Table 3. Nanocarrier-based drug delivery systems for delivering antiretroviral drugs for HIV/AIDS therapy.

Drug	Dosage form	Reservoir site	Outcome	Ref.
Azidothymidine	Polyhexylcyanoacrylate nanoparticles	Macrophages	Enhanced drug delivery to macrophages and reduced toxicity.	[95]
Saquinavir	Polyhexylcyanoacrylate nanoparticles	Human monocytes/macrophages	Improved drug delivery to mononuclear phagocyte.	[96]
Azidothymidine	Nanoparticles colloidal carrier system	Macrophage targeting	Increased drug delivery to the sites containing abundant macrophages and reduced toxicity.	[97]
Indinavir	Lipid-associated delivery system	Lymph node mononuclear cells	Terminal half-life is extended by sixfold. Indinavir concentration at peripheral and visceral lymph nodes.	[98]
Indinavir	Immunoliposomes	Viral reservoirs	Novel therapeutic strategy for targeting the HIV reservoirs.	[99]
Dideoxy-cytidine-5'-triphosphate	Liposome	Mononuclear phagocytic system	Reduced proviral load in mononuclear phagocytic system in both the spleen and bone marrow.	[100]
2'-3'-Dideoxyinosine	Liposome	Reticuloendothelial system	Enhanced drug accumulation in the reticuloendothelial system.	[101]
Azidothymidine	Liposome	Monocytes	Reduced haematopoietic toxicity and enhanced delivery.	[102]

Salient features of some of the drug delivery systems, which can be used for delivery to the viral reservoir sites, are outlined in this section.

Lobenberg and Kreuter, have developed a nanoparticle colloidal drug carrier system for specific targeting of azidothymidine to the macrophage [97]. They found that the nanoparticle carrier containing azidothymidine resulted in an 18-fold higher *in vivo* concentration of the drug in the reticuloendothelial system. They inferred from their findings that significantly higher concentration in the reticuloendothelial system may result in reduction in the dose and perhaps toxicity of the drug. In another other study, indinavir-associated liposomes were developed and evaluated by Kinman *et al.* [98]. The formulations were administered subcutaneously to macaques that were infected with HIV-2287. The results from the liposomal indinavir formulation showed a 6-fold increase in the terminal half-life of the drug and an almost a 10-fold reduction in the viral burden in the plasma, compared with the aqueous solution formulation. Moreover, the indinavir concentration in the lymph nodes, a potential HIV reservoir site, was > 2.5-fold higher with the liposomal formulation relative to the aqueous solution formulation. Oussoren *et al.* formulated a dideoxycytidine-5′-triphosphate liposomal delivery system for preferential targeting to the mononuclear phagocytic system [100]. Following administration of the liposomal formulation into animals, they found a substantial reduction of the proviral HIV load in the mononuclear phagocytic system, and, in particular, in the spleen and bone marrow. Magnani *et al.* [103] have formulated dideoxycytidine-5′-triphosphate-containing erythrocytes for macrophage-targeted delivery and examined the efficacy *in vitro* and *in vivo* in a feline immunodeficiency virus infection model. The results of erythrocyte-targeted macrophage delivery of antiviral agents was quite promising and provides opportunity for other agents, as well as for combination HIV/AIDS therapy.

In addition to liposome and erythrocyte delivery systems, polymeric nanoparticles have also been used for delivery of antiretroviral therapy to cellular and anatomical reservoirs of HIV. For instance, Dembri *et al.* [104] have developed poly(isohexylcyanoacrylate) nanospheres for specific targeting of 3′-azido 3′-deoxythymidine to lymphoid tissue in the gastrointestinal tract, a potential viral sanctuary site. The drug concentration in the Peyer's patches was 4-times higher for the nanosphere formulation as compared with the control aqueous solution. The tissue concentration of 3′-azido 3′-deoxythymidine was 30 – 45 µM, which was much higher than the reported IC_{50} (0.06 – 1.36 µM) and was regularly distributed along the gastrointestinal tract.

6. Conclusions

Since the identification of HIV infection and AIDS from the early 1980s, therapeutic treatment has been successfully attempted with the help of potent drug substances, such as NRTIs, NNRTIs, PIs and integrase inhibitors. Even with ~ 20 different therapeutic agents that are available for the management of HIV/AIDS, the therapeutic outcomes of this devastating disease is far from optimal. The death toll from HIV/AIDS continues to increase, especially in developing nations.

Over the past decade, nanocarrier drug delivery systems have increasingly been used to enhance the bioavailability

of antiretroviral drugs to target sites in the body, and especially to enhance the eradication efficacy from HIV reservoirs. As discussed in this article, HIV/AIDS therapy represents a significant challenge at different anatomical and cellular levels. Although the introduction of newer drugs and combination therapy have improved the clinical outcomes to a great degree, there is still a need to develop more efficient delivery systems for enhancing the therapeutic efficacy with less toxicity. In this regard, nanotechnology offers tremendous potential for the appropriate management of HIV/AIDS. In addition to increasing the ability to target therapies, the nanocarrier formulations can be designed to reduce the effective dose, combine more than one agent in a single formulation, and provide rationale delivery mechanisms for attacking the virus at reservoir sites. Nanocarrier-based drug delivery systems, such as liposomes, nanoemulsions and polymeric nanotechnology-based products, have already been tried in various preclinical studies and have been shown to improve delivery efficacy to the reservoirs. The delivery of the drug at targeted sites and the maintenance of therapeutic drug concentrations for prolonged periods can help in an appreciable reduction of the viral load. Greater understanding of the mechanism of viral sanctuary formation, coupled with strategical engineering of the nanosystems (that can potentially reach the reservoir sites in high concentrations), would enable the development of more effective delivery strategies. As such, it is critical that research continue in this area so that we may be able to develop more efficient therapeutic strategies, combining potent therapies with drug delivery systems, to continue to further improve the clinical outcomes in HIV/AIDS.

7. Expert opinion

Although there has been tremendous effort in understanding the mechanism of HIV infection, which has led to the development of effective therapeutic strategies, the ultimate goal of complete eradication has not been achieved. In developed nations, where there is access to appropriate therapy, the lifespan and quality of life of HIV/AIDS patients has substantially improved. However, the high cost of therapy, lack of drug accessibility and poor compliance has created catastrophic consequences in developing nations. One of the most challenging aspects of HIV/AIDS therapy is the ability of the virus to harbour in cellular and anatomical reservoir sites, where systemically administered therapies do not reach in adequate concentrations or reside for the necessary length of time.

Nanotechnology offers a tremendous opportunity for targeted delivery of therapeutic agents against HIV/AIDS. Using different nanocarrier platforms, such as liposomes, micelles, nanoemulsions and polymeric nanoparticles, delivery systems could be designed that can be specifically targeted to, and will be internalised in, macrophages and other cellular reservoirs. Surface engineering of these nanosystems provides an opportunity to recognise their targets and deliver the payload specifically to the infected cell population. Surface modification with cell-penetrating peptide molecules allow for enhanced cell uptake and cytosolic availability of the nanocarriers. In addition, by judicious use of the materials in fabrication of the nanostructures, therapeutic systems could be developed that will either trigger the release of the drug content (such as a temperature- and pH-responsive nanocarrier system) or sustained release over a desired period of time for optimum pharmacological response. For increased accessibility to an anatomical reservoir, such as the CNS, lipid nanocarriers (e.g., liposomes and nanoemulsions), these systems are engineered to overcome the blood–brain barrier and deliver the therapeutic agent at the site of action. The biodistribution and pharmacokinetic properties are now dictated by the properties of the nanocarrier system instead of the drug molecule. This, in turn, results in encapsulation and delivery of a variety of different agents for maximum therapeutic effect.

One of the most interesting opportunities in nanocarrier-based delivery of HIV/AIDS therapy is multi-functionalisation of the nanocarrier system. With multi-functionalisation, one could incorporate several therapeutic agents (e.g., HAART) in one formulation for maximum clinical effect. Newer generation of anti-HIV therapies, such as peptides, small interfering RNA and oligonucleotides, will also require a delivery system in order to improve stability in the extracellular environment and provide effective delivery inside the cells where these agents are expected to work. When combining several therapies in one system, polymeric nanocarrier platforms allow for sustained release for the desired length of time, based on the diffusion and degradation kinetics of the biodegradable polymer matrix. As such, the polymeric material that is used for nanocarrier formulation can be engineered to release each of the therapeutic agents with its own desirable release profile. In addition, the multi-functional nanocarrier system could incorporate other agents that allow for macrophage ablation and other modes of antiretroviral therapy. For CNS delivery, multi-functional nanocarriers could combine antiretroviral therapy with Pgp and CYP450 inhibitors to enhance permeation across the blood–brain barrier. Overall, the design of nanocarrier delivery for HIV/AIDS therapy is highly versatile.

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