Review Article

# Recent advances in drug delivery systems in antiviral therapy

**Ekta Mishra, Amit K Goyal, Goutam Rath***

Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

**Correspondence:**
Dr. Goutam Rath, Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India.
E-mail: goutamrath123@gmail.com

**How to cite this article:**
Mishra E, Goyal AK, Rath G. Recent advances in drug delivery systems in antiviral therapy. Pharmaspire 2018;10(3):98-106.

**Source of Support:** Nil,
**Conflict of Interest:** None declared.

## ABSTRACT

Intracellular parasitic nature, quick adaptation to antiviral drugs, and rapid mutation pose a great challenge to create an effective therapeutic strategy to combat viral infection. Most of the antiviral drugs have low aqueous solubility, low permeability, and other associated physical properties which make them difficult for the antiviral therapy. Novel drug delivery systems due to their unique surface properties and physiochemical properties enable higher drug solubility, better targeting ability, and enhanced drug stability attracted a great deal of interest in the treatment of viral infections. Novel drug carriers such as liposomes, dendrimer, solid dispersion, microparticles, and nanoparticles are employed to improve therapeutic outcomes. The recent advancements made in the field of antiviral therapy have been discussed in this article.

**Keywords:** Viral infections, antiviral drugs, mechanism, novel drug delivery

## INTRODUCTION

Viral infections take place due to the growth of harmful viruses in the body. They act by making their copies and killing the host cells or by invading inactively inside the host cell for a period of time. They use the host cell to multiply and produce other viruses like themselves.[1] Viral infections can be treated with vaccines and antiviral medication. The vaccine reduces the chances of acquiring viral infections, but they require booster shots to maintain their effectiveness. The major challenge in vaccination is that it weakens the immunity and causes fast mutation. As the treatment of viral infections is a long race, there is a need of a way which can be used for a long period of time without getting any permanent change in the host cell. The antiviral drugs are class of medication which is used to treat viral infections. They are relatively harmless to the host cell if they are used as per the prescription. Hence, the treatment of viral infections is limited to the medications only.[2] When the virus enters a host cell, it follows a pathway to multiply itself inside the cell. The mechanism involved in the viral multiplication includes penetration, protein synthesis, and packaging and assembly. The antiviral medications are classified into different categories according to their site of action in the multiplication of the virus. The four categories of antiviral drugs are as folloews:

| Access this article online | |
|---|---|
| **Website:** www.isfcppharmaspire.com | **P-ISSN:** 2321-4732<br>**E-ISSN:** XXXX-XXXX |

1. Anti-herpes virus: Idoxuridine, acyclovir, valacyclovir, famciclovir, ganciclovir, foscarnet
2. Anti-retrovirus:
   a. Nucleoside reverse transcriptase inhibitors (NRTIs): Zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir
   b. Non-NRTIs (NNRTIs): Nevirapine, efavirenz
   c. Protease inhibitors: Ritonavir, indinavir, saquinavir.
3. Anti-influenza virus: Amantadine, rimantadine
4. Non-selective antiviral drugs: Ribavirin, Lamivudine, interferon alpha.

There are some drugs which act in cortisol during penetration and uncoating of viruses in the cell, while some others act in the nucleus during protein synthesis. Figure 1 depicts a pictorial representation of the mechanism of antiviral drugs.

Different viruses act on different sites of human body including the liver, brain, skin, reproductive parts, respiratory parts, and gastrointestinal parts. There is a wide range of viruses which have a specific site of action in the human body. Some of these viruses with their site of action are discussed in Figure 2.

Figure 2 clearly defines that there is a need of targeted drug delivery so that to minimize the toxicological effects and to enhance the pharmacological efficacy. Advancements have been done in antiviral

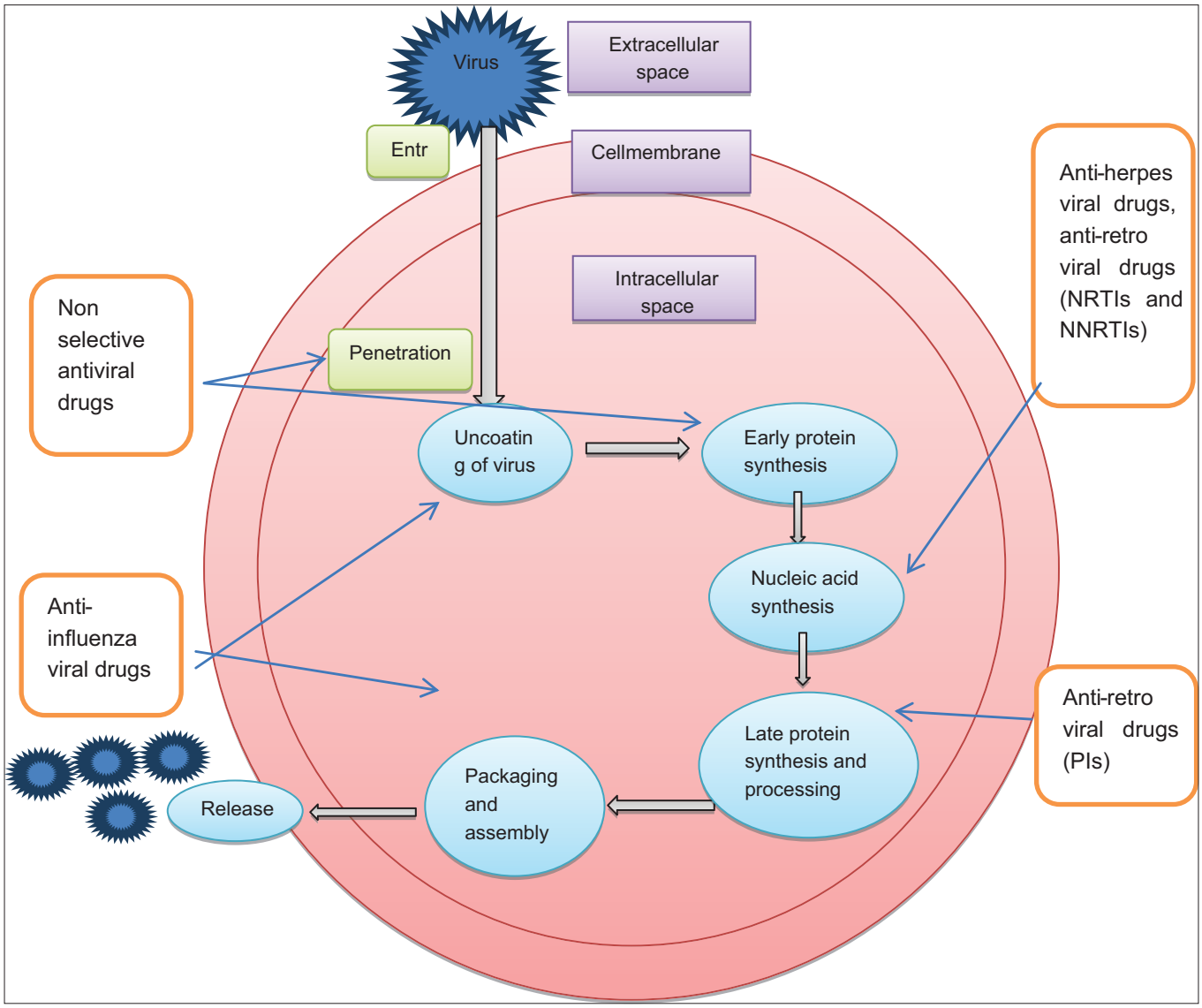


**Figure 1:** Mechanisms of antiviral drugs illustrating the therapeutic potential of nanocarriers

therapy keeping in mind the need to increase the efficiency of drug, improve its release, and to target at a specific site. Treatment of antiviral drug has proven challenging because they are very small and reproduce inside host cells and also because of the development of drug resistance which is associated with the multiple dosing.[3] Most of the available dosage systems have low aqueous solubility and low permeability across the biological membrane and gets metabolized by the cellular enzymes, leading to low absorption and require frequent dosing.[4]

It is a difficult task to develop a safe and effective drug in case of viral infections. There are many challenges in the development of antiviral therapy. The major challenge is that the drug treats only the exposed virus not the latent infections which can lead to a relapse of infection. The second key challenge involves modification of the physicochemical and biopharmaceutical properties of antiviral molecules to modify its bioavailability and pharmacokinetics. Another challenge is the emergence of new viruses and also the increasing resistance of viruses to current drugs which can be overcome by decreasing the frequency of drug and by targeting the drug to the infected site.[5] With the innovations in the drug delivery systems, antiviral researches are also more focused on novel therapies rather than on new diseases. The required characteristics of a good therapy are to ensure higher entrapment efficiency of drugs, controlled release, and degradation. They should have easily modifiable surface so that the release and *in vivo* fate can be controlled and they should be detectable by imaging techniques. The advancements are particularly necessary in those conditions where the doses are high, drugs are costly, and the success of a therapy depends on patient's adherence to the administration protocol.[6] There is a need of advancements in drug delivery systems, particularly in those cases of antiviral therapies which have problems such as multiple dosing and long-term therapy. The drug delivery system should maintain a steady release of the drug to the site of infection for prolonged periods. There is a need to optimize the therapeutic properties of drug products and render them in more safe, effective, and reliable manner.[7] The advancements

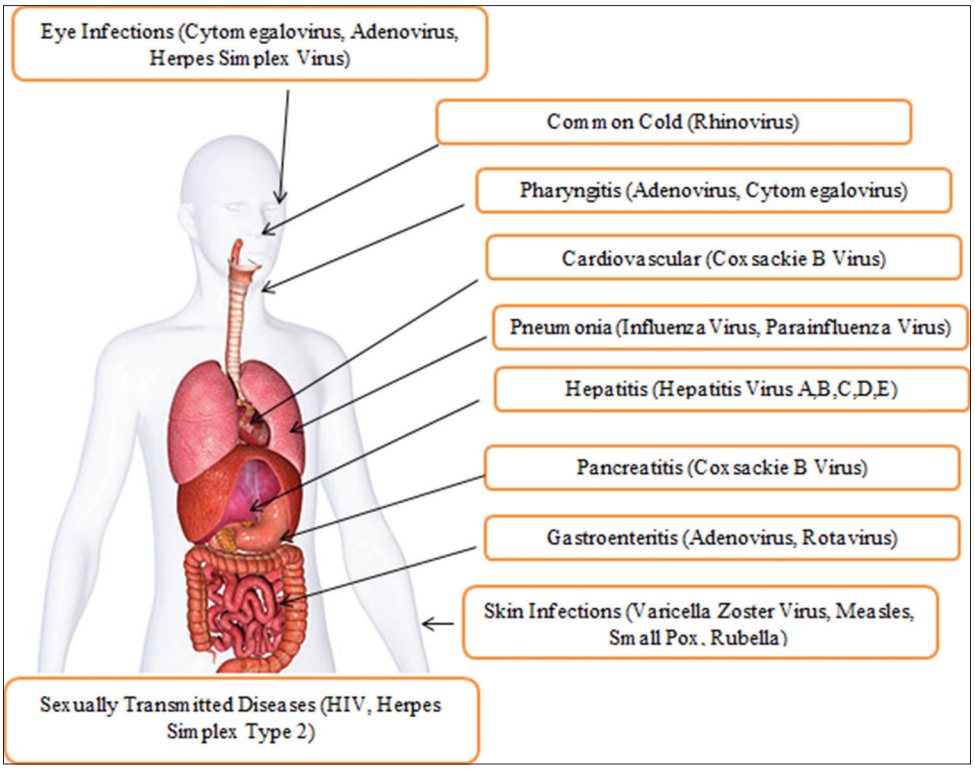


**Figure 2:** Site of action of viruses in the human body: Different viruses have different site of action, the viruses resides there and multiply using the host cell

in the antiviral dosage form are also important as the conventional dosage forms have several limitations which are matters of concern for the antiviral therapy. The virus acts inside the host cell, and thus, the treatment is mainly focused inside the cell or inside the nucleus. The limitations of conventional delivery can be overcomed by entrapping the drug in novel carriers, which have their advantages of enhancing the bioavailability, permeability, targeting, and sustained drug delivery. Table 1 depicts the difference between the conventional and novel drug delivery systems on the basis of their pharmacological and toxicological effects.

They also reduce the dose and dosing frequency, the associated side effects, and risk of drug resistance. The novel carriers such as nanoparticles, liposomes, dendrimers, and managers can be used for delivery of drug and site-specific targeting. In case of antiviral therapy, they have been explored by the researchers and seem to have a better scope in future.

## NOVEL CARRIER SYSTEMS

The manicures and other novel dosage forms are gaining interest in the field of drug delivery system due to the advantages like to target delivery and sustained drug release pattern. In case of antiviral therapy, most of the available dosage forms have multiple dosing frequencies which lead to patient in compliance and fluctuations in the required concentration for the activity.[8] The major problem associated with the antiviral therapies is that the viruses are invaded in the host cell and the activity of the drug is required inside the host cell.[9] The conventional dosage forms are unable to meet the requirements

**Table 1: Difference between conventional and novel drug deliveries**

| Conventional drug delivery | Novel drug delivery |
|---|---|
| Pharmacological efficacy is less | Pharmacological efficacy increased |
| Toxicological effect is more | Toxicological effectively decreased |
| No targeting | Targeting can be achieved by using specific carriers |

of antiviral therapy, and thus, there is a need of advancements. An ideal carrier system should be capable to overcome the limitations of conventional dosage form and should enhance the activity of the drug. The carrier system should be non-toxic, biocompatible, should target the site of infection, and should give prolonged activity to overcome the multiple dosing problems. The choice of the carrier system is important, and it depends on the need of therapy, the drug, and its physical properties.[10] The novel devices act as a reservoir-type devices which can deliver the drug in a sustained pattern and enhance the delivery of drugs to specific sites and viral deposits in the body. Nanotechnological approaches can be used to improve the design, formulation, and delivery of antiviral drugs. They can be used effectively in diseases such as cancer and viral infections to meet the current challenges in their delivery.[11] The drugs can be protected from degradation by delivering them in novel dosage form which is not identified by the immune system. The encapsulation of drug makes them potential candidate for antiviral drugs to selectively target them to infected cells. They can be used efficiently to entrap drug molecules in biodegradable polymeric aqueous-core nanocapsules and are considered as a promising candidate for antiviral nucleotide analogs.[12] Destache *et al*. patented a work on nanocarriers as a drug delivery system for hydrophilic antiretroviral drugs. They encapsulated the

hydrophilic antiretroviral drug in a biodegradable polymer to form a nanoparticle. The *in vivo* results showed that 0.5% tenofovir disoproxil fumarate nanoparticles when administered by intravaginal route were able to protect female mice from HIV-1 infection over a prolonged time period as compared to the controlled group.[13] Tuk *et al*. worked on different antiviral drugs to achieve a drug targeting to a specific site. The *in vitro* and *in vivo* studies showed that the drug targeting and the potency were increased when the drug was encapsulated in nanocarrier system.[14] Bergeron *et al*. worked on liposomes as a drug delivery for site-specific targeting in antiviral therapy. The results demonstrated that encapsulation of drug in liposome leads to high drug accumulation in tissues as compared to encapsulated drugs.[15] The advantages of the carrier systems have given immense scope for their use in antiviral therapy. The carrier system should be selected on the basis of the site of viral infections. The targeting and efficacy totally depend on the carrier system in which the drug is encapsulated. Table 2 describes some of the drug delivery systems, including particle size, advantages, and disadvantages.

## Solid dispersions

Solid dispersions are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state. Many antiviral drugs have low solubility due to which they cannot be administered orally. Solid dispersion is one of the methods to increase the solubility of drugs which have low solubility.[16] The incorporation of drugs into hydrophilic carriers has been reported to enhance the solubility of poorly soluble drugs. Improving oral bioavailability of solid dosage forms is a very challenging task due to their solubility problems.[17] The dissolution rate is a rate-limiting step in the absorption of poorly water-soluble drugs. Solid dispersion techniques improve the dissolution rate of highly lipophilic drugs by reducing drug particle size, improving usability and forming amorphous particles, and thus increasing the bioavailability.[18] Mogal *et al*. prepared solid dispersion by solvent evaporation method and using polyethylene glycol. They demonstrated that solid dispersions can increase the dissolution rate of drug and decrease the drug release time.[19] Nikghalb *et al*. discussed about methods of preparation and different carriers used for solid dispersions. They investigated dissolution characteristics and bioavailability of poorly aqueous soluble drugs and found that these parameters were increased by formulating solid dispersions.[20] Solid dispersions are used to reduce the particle size, to improve the dissolution of particles, and to prepare sustained release dosage form by using poorly soluble carriers. Solid dispersions have solved the problem of low solubility and permeability of drugs. The drug delivered in the form of solid dispersions has enhanced solubility, but these carrier systems are only limited to low aqueous solubility. Antiviral drugs have other problems which are to be taken into consideration like drug targeting.

## Nanoparticles

Nanoparticles (or nanopowder or nanocluster or nanocrystal) are microscopic particles with size in the range of nanometers. The drug release becomes highly targeted in case of miniaturized particles along with the increased solubility, and this fact can be used in support of nanoparticles.[21] They can penetrate across biological barriers through small capillaries to allow efficient drug accumulation at the targeted locations in the body. Encapsulation of drug in nanoparticles reduces the toxicity, decreases the side effects, and enhances the treatment efficacy.[22] Bender *et al*. worked on nanoparticles for targeting of antiviral drug for the inhibition of HIV. The *in vitro* results demonstrated that this drug targeting approach is effective as the nanoparticles can accumulate in the phagocytic cells of the mononuclear phagocyte system.[23] Lara *et al*. demonstrated that silver nanoparticles have effective virucidal activity and they inactivate HIV moiety quickly. They proposed that nanoparticles can be used against specific targets for viral infections.[24] Similarly, Galdiero *et al*. extensively reviewed that nanoparticles can be used as a better drug delivery system for antiviral therapy. They suggested that the use of metal nanoparticles can provide a better opportunity in the field of antiviral therapies as the metals have a broad range of targeting sites in viruses and thus have a lower possibility of developing resistance.[25] Singh *et al*. also reviewed on the role of nanoparticles in the antiviral drug delivery system. They suggested that nanoparticle-based delivery system has new opportunities which can deal with the problems associated with conventional antiviral therapies.[26] With the involvement of nanotechnology, nanoparticles are considered to be a potential candidate to target the therapeutic agents safely at the site of infection either in an organ, particular tissue, or cell. They provide new ways for attacking viruses, thus improving treatment success rates. They change the release kinetics of drugs, increase their bioavailability, improve their efficacy, restrict adverse drug side effects, and reduce treatment costs. Nanoparticles have increased

**Table 2: Summary of some delivery systems (including particle size, advantages, and disadvantages)**

| Delivery system | Size | Advantages | Disadvantages |
|---|---|---|---|
| Solid dispersion | <500 nm | Increased solubility and permeability | Crystal growth or conversion from the amorphous to the crystalline state |
| Nanoparticles | 1–1000 nm | Increased absorption and targeted delivery | Limited drug loading and toxic metabolites may formed |
| CNTs | 1–100 nm | High drug loading efficiency, targeted delivery | Toxic and can accumulate in tissues |
| Nanogels | 20–200 nm | Biocompatible and biodegradable, controlled delivery and surface can be modified | Costly and remaining surfactant may cause toxicity |
| Dendrimers | <10 nm | Can be carry both hydrophobic and hydrophilic drug and increased absorption | Interact with biological membranes leading to destabilization and cell lysis |
| Liposomes | 50–100 nm | Both hydrophilic and lipophilic drugs can be loaded and can stay longer in targeted tissue | Costly and leakage of loaded drug may occur |
| Implants | 2–4 cm long | Prolonged therapy and controlled drug delivery | Pain at the site of injection, termination is not possible |
| Inserts | 2–4 cm | No pain at the site of injection, termination is possible | Limited to some therapies only |

CNTs: Carbon nanotubes

the bioavailability and efficacy of the drug as well as the targeting of drug, but these carrier systems have disadvantages such as limited drug loading. The drug loading is an important factor for those cases where long-term therapy is required which make nanoparticles a not so selective carrier for antiviral therapy.

## Carbon nanotubes (CNTs)

CNTs are allotropes of carbon with a cylindrical nanostructure. They are extremely small tubes with either a single or multiwall carbon structure which make them an appealing candidate to encapsulate drugs inside their cavities. These are very helpful in drug delivery system as they are very strong in strength (approximately 100 times more than steel) and are still very light in weight (approximately 1/6 to that of steel).[27] They serve as a non-toxic carrier system for drugs and also increase the solubility efficacy and safety of the drug. CNTs have ability to deliver the drug inside the cell as well as nucleus as it can cross the cytoplasmic membrane and nuclear membrane without producing any toxic effect.[28] He *et al*. also reviewed the application of nanotubes in medical and pharmacy field. They suggested that drug can be delivered safely and effectively when they are delivered with CNTs.[29] Lamberti *et al*. reviewed the properties, applications, and risks associated with the nanotubes. He explained that, although the nanotubes have many advantages such a higher efficacy and less adverse effects, several unexpected toxicities have also been reported due to CNTs.[30] Hirlekar *et al*. reviewed the CNTs and their application in pharmaceutical filed. They suggested that CNTs have a promising future in the field of pharmaceuticals.[31] The advancements done to modify the CNTs have made it possible to solubilize and disperse them in water increasing the hydrophilicity so that they can pass through membranes. CNTs increase the drug loading which can make it efficient for those cases where long-term therapy is required. These carrier systems have increased the drug loading, but they have disadvantage of causing toxicity. The carrier system chosen should be such that it possesses high drug loading without causing toxicity.

## Nanogels

Nanogels are highly swollen and can incorporate 30% wt. or more of biological molecules and drugs and thus can decrease antiviral concentration by 30 folds, without increasing the toxicity of the drug. They have properties such as resistance against degradation an high drug loading and can carry molecules which are sensitive to external stimuli, such as pH, temperature, light, and redox reactions.[32] Sultana *et al*. summarized the biomedical application and current clinical trial studies of nanogel and suggested that nanogels can be suitable for drug delivery if they are intensively studied in future.[33] Feeney *et al*. designed thermosensitive hydrogels using a carboxymethyl derivative of scleroglucan for topical application of antivirals. They evaluated the release of acyclovir in phosphate buffer at different temperatures.[34] Kohli *et al*. formulated nanogel formulation which showed 30 times decrease in effective drug concentration ($EC_{90}$) and 10 times increase in selectivity index as compared to the drug when tested *in vitro*.[35] Vinogradov *et al*. reviewed that nanogels have ability to improve the central nervous system permeability of nucleoside analogs. They demonstrated that nanogels can efficiently deliver the drug inside the cell.[36] Nanogels are promising and innovative drug delivery system that can play a vital role by addressing the problems associated with old and modern therapeutics such as nonspecific effects and poor stability. Nanogels have made it possible to increase the drug loading as well as decreased chance of toxicity, but these carrier systems are more favorable for hydrophilic drugs. There is a need of such a carrier system which can incorporate a wide range of drug molecules.

## Dendrimers

They are nanoscale compounds with unique structure which are constructed by the successive addition of layers of branching groups called generations. They can incorporate both hydrophilic and lipophilic drugs as the presence of many chain-ends is responsible for high solubility, miscibility, and high reactivity.[37] The small sizes and the possibility of binding targeting ligands render dendrimers attractive for use in drug delivery. Due to the star-shaped architecture, they have attracted interest in loading drug molecules in either the interior or attaching to the surface groups.[38] The solubility and bioavailability of drug are increased when they are administered with dendrimers as they bypass the efflux transporters.[39] Noriega-Luna focused on their application in the field of pharmaceuticals such as in drug delivery, protein mimicking, and biomedical diagnosis. They suggested that dendrimers have better opportunities in antiviral therapeutics.[40] Vacas-Córdoba demonstrated that dendrimers are effective in cell targeting and it can inhibit cell-to-cell HIV transmission.[41] Luganini worked on peptide-derivatized dendrimers which have been found to inhibit human cytomegalovirus replication.[42] Researches proposed that dendrimers could provide a useful starting point for the development of novel molecules to inhibit the virus infections. These carrier systems are very effective for drug delivery system as they can incorporate a wide range of drug molecules. This drug delivery system has solved most of the problems associated with the drug such as solubility, permeability, and drug loading. The only major problem with this system is that it interacts with the cell membrane which makes it toxic as a carrier system. There is a need for a system which can increase the solubility, permeability, and drug loading as well as can decrease the toxicity.

## Liposomes

A liposome is a spherical vesicle having at least one lipid bilayer and can be used as a vehicle for the administration of drugs. It has an aqueous solution core surrounded by a lipophilic membrane forming a lipid bilayer so that both hydrophobic and hydrophilic molecules can be loaded. They improve the therapeutic index of drug by modifying the absorption, controlling the release, prolonging biological half-life, and reducing drug metabolism by enzymes. Liposomes create a layer over the drug to protect it from enzymes such as nucleases. It can be used to enhance the entry of drug inside the cell as it has similar bilayer membrane as the cell membrane.[43] Liposomes can be used for those types of infections in which viruses do not produce virions. They encapsulate a cytotoxic material which is targeted to the viral glycoproteins and decrease the reservoir of viral cells in the host.[44] Liposomes can efficiently deliver antiviral agents and can protect the drugs from environmental exposure. There can be several routes of administration of liposomes depending on the site of infection.[45] They can be administered parenterally for systemic infections, topically in

the form of creams and gels for superficial infections and orally for oral infections. They show the good capability to entrap the drug, good stability, and enhanced antiviral activity.[46] Valenti *et al*. worked on an essential oil which was incorporated in liposome to treat the antiviral infections. They demonstrated that (Santolina insularis) the essential oil has good efficacy against herpes simplex virus-1 and it also provided site-specific targeting which enhanced the activity of oil.[47] Lian *et al*. reviewed on trends and development in the field of liposomes as drug delivery system and elucidated that these developments have helped in designing liposomes which are small in size (~50 nm diameter) and are sterically stable. These liposomes will have prolonged therapy and increased systemic residence time which gives a better scope for their clinical applications.[48] Bulbake *et al*. reviewed on the clinical use of liposomal drug delivery system. According to them, the liposomes provide a better treatment as compared to the conventional dosage forms and the development of liposomes clinically will provide benefits to a large population of patient.[49] In recent years, liposomes have been used in antiviral therapy due to properties such as passive targeting, better pharmacokinetics, reduced toxicity, prolonged release, and targeted drug delivery. Drug which loaded in liposomes shows an improved pharmacokinetics, reduced dosing frequency, and better antiviral activity. Other vesicles such as museums, ethosomes, and examinations can also be used to deliver the drugs in antiviral therapy. They possess the advantages similar to the liposomes and can enhance the pharmacokinetic profile of the drug. The advantages of these carriers have attracted researchers and have made it successful to the clinical level. Horwitz *et al*. clinically evaluated acyclovir-loaded liposomal carrier system (ethosomes) in the topical treatment of herpes labialis. They studied the efficacy of ethosomes loaded with acyclovir as compared to the marketed formulation of acyclovir (i.e., cream) in a randomized clinical trial where data were collected based on 61 herpetic episodes in 40 subjects. The results have shown that no adverse effect was observed and increased efficacy of liposomal system as compared to cream for the treatment of recurrent herpes labialis.[50] Liposomes and the other vesicle systems have made it possible to decrease the toxicity of the carrier systems as well as give a wide range of drug entrapment efficiency. They can incorporate both hydrophilic in their hydrophilic core and lipophilic drugs at the lipophilic surface. It has emerged as a better carrier system for antiviral therapy as it increases the solubility, permeability, drug loading, and targeting. However, antiviral drugs suffer from a major problem of frequent dosing and this has to be taken into consideration too.

## Implants

Implants are single unit dosage form designed to deliver a drug moiety at a therapeutically desired rate over a prolonged period of time. It is suitable for those drugs which have low and variable bioavailability through oral route. Implants are mainly approached to overcome the problems associated with the drugs of low bioavailability and frequent dosing.[51] It provides long-term therapy, continuous drug administration, and sustained release. They allow site-specific drug administration and thus allow lower dosing of drug which minimizes the side effects.[52] This type of drug delivery system is effective for antiviral therapy as they can solve the problems associated with the drug molecule and dosing. Using a proper polymer, we can enhance the bioavailability, targeting, drug loading, and biocompatibility. It also decreases the toxicity and cell interaction as the drug in the system is very less in amount and thus cannot cause toxicity. The major advantage of this system is that it can be used in cases like antiviral therapy as they can provide long-term therapy and decreases the dosing frequency.[53] Johnson *et al*. developed and evaluated an implant of acyclovir to control herpes simplex virus type-1 infection. The results suggested that implant suppressed the virus successfully and the efficacy of drug was also enhanced.[54] Dash *et al*. extensively reviewed on therapeutic applications of implantable drug delivery systems. They explained the advantage of implants including targeted local delivery of drugs at a constant rate, less drug required to treat the disease state, minimization of possible side effects, and enhanced efficacy of treatment and suggested their superior effectiveness over conventional methods of treatment.[55] The only disadvantage with this therapy is that these implants are inserted by surgical procedures. This disadvantage can be overcome by formulating an injectable implant with a biodegradable polymer.[56] Injectable implants can be a better approach to solve all the problems which can lead to patient incompliance. The *in situ* gel and nanofibers have shown a better scope to be used as an injectable implant. These systems can enhance the therapeutic approach and can overcome the limitations associated with the therapy.[57] Implants release drugs to systemic circulation continuously making it comfortable for patient from being hospitalized and from taking frequent dosing. Implantable systems are at a crude stage of development in comparison to the other drug delivery systems particularly in the case of antiviral therapy. This field requires attention in drug delivery systems, and researchers are hopeful that the implants can be developed for long-term therapy. Implants are in early stage of development and require more clinical testing before using them in standard practice. The implants have overcome the problems of drug loading, multiple dosing frequencies, and other by providing high drug loading and controlled drug delivery. The only problem associated with the implants is that it causes pain at the site of injection associated with inflammation.

## Inserts

Inserts have shown immense scope in the field of drug delivery due to the possibility of termination of medication in case condition gets worsen. They are solid or semi-solid in nature which is placed in the body cavity and do not require any surgical procedure. They release the medicament, thereby providing localized and passive targeting. Vaginal rings are one of the inserts which have been used for delivery of drug in vaginal to protect HIV transmission. Dang *et al*. evaluated vaginal insert using polycaprolactone and tenofovir for the prevention of HIV transmission. They recommended that the antiviral-loaded inserts can be further exploited for controlling HIV transmission.[58] Asvadi *et al*. also evaluated and recommended the polycaprolactone inserts loading acyclovir for intravaginal delivery.[59] Nel *et al*. conducted a trial to evaluate the safety of a vaginal ring of silicone elastomer matrix containing antiviral drug. They designed a double-blind randomized trial in 16 HIV-negative women of age group between 18 and 40 years. The results have shown that these rings were safe and effective in the prevention of HIV.[60] Baeten *et al*. conducted a phase-3 randomized trial for a NNRTIs involving women of age group between 18 and 45.

The results have shown that the ring has reduced the risk of infection and increased efficacy of drug.[61] The clinical trials of vaginal ring have depicted that inserts are promising dosage form for the antiviral delivery of drug.

The novel dosage forms have solved most of the problems associated with the antiviral drugs, and the advances have suggested that these novel dosage forms have better futuristic scope in the field of drug delivery. Advancements in the area would not have been so interesting if the results in clinical trials have not shown a better scope. The commercialization and the advanced work on the different novel therapies have made the researchers interested in this area. The delivery of antiviral drugs in different carrier systems has solved the problems associated with the conventional therapy. The results from clinical trials clearly depict that there is a better futuristic scope for the delivery of antiviral drugs in novel dosage form. Some of the *in vitro* and *in vivo* outcomes including the clinical trials are summarized in Table 3.

## CONCLUSION

The administration of antivirals in proper carrier system may modify the therapeutic efficacy of drugs. In case of antiviral therapy, the most important point to be kept in mind is the multiple dosing which leads to drug resistance especially in case of long-term therapies. The novel dosage form has come in context to overcome the problems associated with the conventional dosage forms. There is a need of proper drug delivery systems that could maintain a steady release of drug to the specific site of action and to optimize the therapeutic properties of drug products and render them more safe, effective, and reliable. The implants and inserts have turned out to be a proper therapy for antiviral therapy as they have provided advantages over conventional dosage form. They have solved the problem of frequent dosing of antiviral drugs and also have provided sustained therapy. The advancements in antiviral drug delivery system are mainly objected on fulfilling the need of pharmaceutical industries and clinical importance. The toxicity of carriers is of concern when the toxic

**Table 3: Summary of *in vitro* and *in vivo* outcomes of novel dosage forms from recent research work**

| Delivery system | *In vitro* outcomes | *In vivo* outcomes | References |
|---|---|---|---|
| Solid dispersion | Results revealed that there was a distinct loss in crystallinity of rofecoxib in the formulation, leading to enhancement in dissolution rate | - | Ahuja *et al.*, 2007 |
| | Results suggest that the dissolution rate of ACV form I from solid dispersions is higher compared to that of anhydrous ACV form I | - | Karolewicz *et al.*, 2016 |
| Nanoparticles | The *in vitro* results showed that nanoparticles containing nucleoside analogs have dose-dependent activity. | - | Bender *et al.*, 1994 |
| | In multiple cell-lines and primary cells, TDF NPs were not more cytotoxic compared to TDF in solution *in vitro* | - | Distance *et al.*, 2015 |
| CNTs | The *in vitro* release suggests sustained release at lysosomal pH (5.3) ascribed to the greater hydrophilicity | Pharmacokinetics data clearly suggest the improved bioavailability of DOX as compared to free DOX | Mira *et al.*, 2013 |
| Nanogels | Ribavirin-Nanogel formulation demonstrated a 30-fold decrease in $EC_{90}$ and 10-fold increase in selectivity index compared to the drug alone in MDCK cells infected with influenza A virus | - | Kali *et al.*, 2007 |
| | The drug release rate of acyclovir is strictly related to the temperature: Increasing the temperature the release rate increases | - | Feeney *et al.*, 2009 |
| Dendrimers | Results demonstrate that dendrimers inhibit the *in vitro* replication of HCMV and MCMV | - | Luganini *et al.*, 2010 |
| | They demonstrated that dendrimers inhibited HIV-1 infection at the fusion and the entry step | - | Vacas-Córdoba *et al.*, 2016 |
| Liposomes | - | Trial was conducted in 40 subjects to compare the liposomal preparation of acyclovir and marketed formulation available in form of cream. The time to crusting of lesions was found to be less with the ethosomal acyclovir (1.8 days) than with the cream (3.5 days) | Horwitz *et al.*, 1999 |
| | Results showed that the entrapment of essential oil of *Artemisia arborescens* in liposomes improved the activity against HSV-1 | - | Sinico *et al.*, 2005 |
| Implants | ACV was continuously released from different-shaped implants over a 63-day trial period. A burst period of ACV lasting 5 days, after which the release levels of ACV were more consistent between replicates | There was a significant difference in reactivation levels between the untreated and ACV–implant-treated groups and there was no significant difference between the untreated and silicone-only implant groups | Johnson *et al.*, 2007 |
| Inserts | - | A randomized trial was held in 16 HIV-negative women for 28 days. The pharmacokinetic results have showed that the drug concentration in vaginal fluid was released in sustained manner from the vaginal ring | Nel *et al.*, 2014 |
| | - | A phase-3 randomized trial for a NNRTIs in women between18 and 45 years was conducted. The results showed that the inserts of dopivirine were lower by 27% than that in the placebo group | Baeten *et al.*, 2016 |

CNTs: Carbon nanotubes, HCMV: Human cytomegalovirus, MCMV: Murinecytomegalovirus, ACV: Apple cider vinegar, DOX: Doxorubicin, MDCK: Madin–Darby canine kidney, TDF: Tenofovir disoproxil fumarate, NNRTIs: Non-nucleoside reverse transcriptase inhibitor

metabolites circulate in the bloodstream and they get accumulated, and thus, it needs proper profiling before clinical application.

## REFERENCES


1. Akbarzadeh A, Kafshdooz L, Razban Z, Dastranj Tbrizi A, Rasoulpour S, Khalilov R, *et al.* An overview application of silver nanoparticles in inhibition of herpes simplex virus. Artif Cells Nanomed Biotechnol 2018;46:263-7.
2. Shiraki K, Daikoku T, Takemoto M, Himaki T, Kuramoto T. Mechanism of action of antiviral drugs. Nihon Rinsho 2012;70:545-51.
3. Zhang H, Zhang S, Liu N. Prevention and control of emergent infectious disease with high specific antigen sensor. Artif Cells Nanomed Biotechnol 2017; 45:1298-303.
4. Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, Collier AC, *et al.* Antiretroviral-drug resistance among patients recently infected with HIV. N Engl J Med 2002;347:385-94.
5. Littler E, Oberg B. Achievements and challenges in antiviral drug discovery. Antivir Chem Chemother 2005;16:155-68.
6. Calenbergh SV, Herdewijn P. A heterogeneous collection of novel antiviral pyrimidines. Exp Opin Ther Pat 2000;10:289-95.
7. Durai RD. Review article drug delivery approaches of an antiviral drug: A comprehensive review. Asian J Pharm 2015;9:1-2.
8. Hillaireau H, Couvreur P. Nanocarriers' entry into the cell: Relevance to drug delivery. Cell Mol Life Sci 2009;66:2873-96.
9. Szunerits S, Barras A, Khanal M, Pagneux Q, Boukherroub R. Nanostructures for the inhibition of viral infections. Molecules 2015;20:14051-81.
10. Horcajada P, Chalati T, Serre C, Gillet B, Sebrie C, Baati T, *et al.* Porous metal-organic-framework nanoscale carriers as a potential platform for drug delivery and imaging. Nat Mater 2010;9:172-8.
11. Mehendale R, Joshi M, Patravale VB. Nanomedicines for treatment of viral diseases. Crit Rev Ther Drug Carrier Syst 2013;30:1-49.
12. Lembo D, Cavalli R. Nanoparticulate delivery systems for antiviral drugs. Antivir Chem Chemother 2010;21:53-70.
13. Destache CJ, Date A, Inventors; Creighton University, Assignee. Encapsulation of Hydrophillic Antiretroviral Drugs in Nanocarriers. United States Patent Application US 14/792,288; 2015.
14. Tuk B, Jousma H, Gaillard PJ. Treatment with penicillin G and hydrocortisone reduces ALS-associated symptoms: A case series of three patients. F1000Res 2017; 6:410.
15. Bergeron MG, Desormeaux A, Inventors; Infectio Recherche Inc, Assignee. Liposomes Encapsulating Antiviral Drugs. United States Patent US 5,773,027; 1998.
16. Karolewicz B, Nartowski K, Pluta J, Górniak A. Physicochemical characterization and dissolution studies of acyclovir solid dispersions with pluronic F127 prepared by the kneading method. Acta Pharm 2016;66:119-28.
17. Ahuja N, Katare OP, Singh B. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. Eur J Pharm Biopharm 2007;65:26-38.
18. Balasaheb PA, Balaji TE, Avinash BI. Solid dispersions: An overview on solubility enhancement of poorly water soluble drugs. Int J Pharma Bio Sci 2014;5:7-25.
19. Mogal SA, Gurjar PN, Yamgar DS, Kamod AC. Solid dispersion technique for improving solubility of some poorly soluble drugs. Der Pharm Lett 2012; 4:1574-86.
20. Nikghalb LA, Singh G, Singh G, Kahkeshan KF. Solid dispersion: Methods and polymers to increase the solubility of poorly soluble drugs. J Appl Pharm Sci 2012; 2:170-5.
21. Christian P, Von der Kammer F, Baalousha M, Hofmann T. Nanoparticles: Structure, properties, preparation and behaviour in environmental media. Ecotoxicology 2008;17:326-43.
22. Yildiz I, Shukla S, Steinmetz NF. Applications of viral nanoparticles in medicine. Curr Opin Biotechnol 2011;22:901-8.
23. Bender A, Schfer V, Steffan AM, Royer C, Kreuter J, Rübsamen-Waigmann H, *et al.* Inhibition of HIV *in vitro* by antiviral drug-targeting using nanoparticles. Res Virol 1994;145:215-20.
24. Lara HH, Ayala-Nuñez NV, Ixtepan-Turrent L, Rodriguez-Padilla C. Mode of antiviral action of silver nanoparticles against HIV-1. J Nanobiotechnology 2010;8:1.
25. Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M, *et al.* Silver nanoparticles as potential antiviral agents. Molecules 2011;16:8894-918.
26. Singh L, Kruger HG, Maguire GE, Govender T, Parboosing R. The role of nanotechnology in the treatment of viral infections. Ther Adv Infect Dis 2017; 4:105-31.
27. Eatemadi A, Daraee H, Karimkhanloo H, Kouhi M, Zarghami N, Akbarzadeh A, *et al.* Carbon nanotubes: Properties, synthesis, purification, and medical applications. Nanoscale Res Lett 2014;9:393.
28. Mehra NK, Jain NK. Development, characterization and cancer targeting potential of surface engineered carbon nanotubes. J Drug Target 2013; 21:745-58.
29. He H, Pham-Huy LA, Dramou P, Xiao D, Zuo P, Pham-Huy C, *et al.* Carbon nanotubes: Applications in pharmacy and medicine. Biomed Res Int 2013; 2013:578290.
30. Lamberti M, Pedata P, Sannolo N, Porto S, De Rosa A, Caraglia M, *et al.* Carbon nanotubes: Properties, biomedical applications, advantages and risks in patients and occupationally-exposed workers. Int J Immunopathol Pharm 2015; 28:4-13.
31. Hirlekar R, Yamagar M, Garse H, Vij M, Kadam V. Carbon nanotubes and its applications: A review. Asian J Pharm Clin Res 2009;2:17-27.
32. Yadav HK, Al Halabi NA, Alsalloum GA. Nanogels as novel drug delivery systems - A review. J Pharm Pharm Res 2017;1:5.
33. Sultana F, Imran-Ul-Haque M, Arafat M, Sharmin S. An overview of nanogel drug delivery system. J Appl Pharm Sci 2013;3:S95-105.
34. Feeney M, Casadei MA, Matricardi P. Carboxymethyl derivative of scleroglucan: A novel thermosensitive hydrogel forming polysaccharide for drug delivery applications. J Mater Sci Mater Med 2009;20:1081-7.
35. Kohli E, Han HY, Zeman AD, Vinogradov SV. Formulations of biodegradable Nanogel carriers with 5′-triphosphates of nucleoside analogs that display a reduced cytotoxicity and enhanced drug activity. J Controll Release 2007; 121:19-27.
36. Vinogradov SV. Polymeric nanogel formulations of nucleoside analogs. Expert Opin Drug Deliv 2007;4:5-17.
37. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, *et al.* Dendrimers: Synthesis, applications, and properties. Nanoscale Res Lett 2014;9:247.
38. Madaan K, Kumar S, Poonia N, Lather V, Pandita D. Dendrimers in drug delivery and targeting: Drug-dendrimer interactions and toxicity issues. J Pharm Bioallied Sci 2014;6:139-50.
39. Swanson SD, Kukowska-Latallo JF, Patri AK, Chen C, Ge S, Cao Z, *et al.* Targeted gadolinium-loaded dendrimer nanoparticles for tumor-specific magnetic resonance contrast enhancement. Int J Nanomedicine 2008;3:201-10.
40. Noriega-Luna B, Godínez LA, Rodríguez FJ, Rodríguez A, Larrea G, Sosa-Ferreyra CF, *et al.* Applications of dendrimers in drug delivery agents, diagnosis, therapy, and detection. J Nanomater 2014;2014:39.
41. Vacas-Córdoba E, Maly M, De la Mata FJ, Gómez R, Pion M, Muñoz-Fernández MÁ, *et al.* Antiviral mechanism of polyanionic carbosilane dendrimers against HIV-1. Int J Nanomedicine 2016;11:1281-94.
42. Luganini A, Giuliani A, Pirri G, Pizzuto L, Landolfo S, Gribaudo G, *et al.* Peptide-derivatized dendrimers inhibit human cytomegalovirus infection by blocking virus binding to cell surface heparan sulfate. Antiviral Res 2010; 85:532-40.
43. Bayard B, Leserman LD, Bisbal C, Lebleu B. Antiviral activity in L1210 cells of liposome–encapsulated (2′–5′) oligo (adenylate) analogues. FEBS J

1985;151:319-25.

44. Düzgünes N, Pretzer E, Simões S, Slepushkin V, Konopka K, Flasher D, *et al.* Liposome-mediated delivery of antiviral agents to human immunodeficiency virus-infected cells. Mol Membr Biol 1999;16:111-8.
45. Düzgünes N, Simões S, Slepushkin V, Pretzer E, Flasher D, Salem II, *et al.* Delivery of antiviral agents in liposomes. Methods Enzymol 2005;391:351-73.
46. Sinico C, De Logu A, Lai F, Valenti D, Manconi M, Loy G, *et al.* Liposomal incorporation of *Artemisia arborescens* L. Essential oil and *in vitro* antiviral activity. Eur J Pharm Biopharm 2005;59:161-8.
47. Valenti D, De Logu A, Loy G, Sinico C, Bonsignore L, Cottiglia F, *et al.* Liposome-incorporated santolina insularis essential oil: Preparation, characterization and *in vitro* antiviral activity. J Liposome Res 2001;11:73-90.
48. Lian T, Ho RJ. Trends and developments in liposome drug delivery systems. J Pharm Sci 2001;90:667-80.
49. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: An updated review. Pharmaceutics 2017;9:12.
50. Horwitz E, Pisanty S, Czerninski R, Helser M, Eliav E, Touitou E, *et al.* A clinical evaluation of a novel liposomal carrier for acyclovir in the topical treatment of recurrent herpes labialis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87:700-5.
51. Ranade VV. Drug delivery systems 4. Implants in drug delivery. J Clin Pharmacol 1990;30:871-89.
52. Rajgor N, Patel M, Bhaskar V. Implantable drug delivery systems: An overview. Syst Rev Pharm 2011;2l:91.
53. Blackshear PJ. Implantable drug-delivery systems. Sci Am 1979;241:66-73.
54. Johnson TP, Frey R, Modugno M, Brennan TP, Margulies BJ. Development of an aciclovir implant for the effective long-term control of herpes simplex virus type-1 infection in vero cells and in experimentally infected SKH-1 mice. Int J Antimicrob Agents 2007;30:428-35.
55. Dash AK, Cudworth GC 2nd. Therapeutic applications of implantable drug delivery systems. J Pharmacol Toxicol Methods 1998;40:1-2.
56. Iqbal MM, Middha AK. Effect of polymers on progesterone implants for estrus synchronization in livestock. Int J Pharm Drug Anal 2016;1:6-14.
57. Morie A, Garg T, Goyal AK, Rath G. Nanofibers as novel drug carrier – An overview. Artif Cells Nanomed Biotechnol 2016;44:135-43.
58. Dang NT, Sivakumaran H, Harrich D, Coombes AG. An evaluation of polycaprolactone matrices for vaginal delivery of the antiviral, tenofovir, in preventing heterosexual transmission of HIV. J Pharm Sci 2013;102:3725-35.
59. Asvadi NH, Dang NT, Davis-Poynter N, Coombes AG. Evaluation of microporous polycaprolactone matrices for controlled delivery of antiviral microbicides to the female genital tract. J Mater Sci Mater Med 2013;24:2719-27.
60. Nel A, Haazen W, Nuttall J, Romano J, Rosenberg Z, van Niekerk N, *et al.* A safety and pharmacokinetic trial assessing delivery of dapivirine from a vaginal ring in healthy women. AIDS 2014;28:1479-87.
61. Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, *et al.* Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med 2016;375:2121-32.