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Nano-Technological Approach towards Anti-Viral Therapy

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Abstract

With time viral infections are increasing day by day due to various reasons like new viruses, the resistance of viruses to antiviral therapy, and mutation of one form of the virus to another form; these types of problems create many challenges in the field of research. Furthermore, a lot of challenges are encountered in the treatment of antiviral therapy, like interaction with other medication and use of increased frequency and a high dose of antiviral due to infection in CNS or synovial fluid where drug permeation is less. Consequently, toxicity and other side effect chances will be more. Nano-technological approaches are used to overcome these challenges. The beneficial properties come from such engineering, including stimuli sensitivity, targetability, and longevity; these are all combined to give multifunctional nano-carriers that concurrently execute different beneficial tasks.

Key Words: Antiviral Therapy, Nano-Technology, Nano-Carriers, Nanoparticulate, and Nanomedicines.

Introduction

Viral infections' worldwide impact, the rise of new viruses, and the resistance development to current medications all these factors are the continuous scientific challenges of formulation development and drug discovery. Over the last three decades, a lot of scientists have concentrated on synthesizing such antivirals having the ability to target therapeutic processes that are considered important. In 1990, only five antiviral drugs had got the license (Milroy & Featherstone, 2002), whereas the numbers increased with time, approx. Twenty years later, there were more than forty drugs in the market. The majority of these drugs were active against HIV infection, while the others were developed to treat various infections like influenza viruses (A & B) and hepatitis viruses (B & C), and many herpes viruses like (varicella-zoster virus, human cytomegalovirus, and herpes simplex virus). By 2009, the worldwide sales for the antiviral agents moved to approx—28 billion USD. From 2004 to 2006, the sales increased by approximately 20% in antiviral agents, and until 2011 a proceeding with development pattern has been assessed. Furthermore, the market is probably going to observe much more future development due to the presence of expanding populations, new therapeutics, innovative drugs, unmet needs, and better diagnostics; however, the development of safety and efficacy of an antiviral agent is a very difficult task, and the antiviral therapies are still generally short that are available in the viral diseases list. Several factors are responsible for hindrance in the growth of the antiviral agents. Viruses are parasites that are obligate and intracellular as they mainly depend on the biosynthetic machinery of the host cell for replication because they cannot reproduce outside the host cell; therefore, the antiviral drugs can target only metabolic functions of a limited number that are virus-specific without any harm to the host cell. Ideally, viral proteins are these targets that are important for viral pathogenesis and

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replication that are adequately unique to permit selectivity to any host protein. Moreover, these functions are mostly virus-specific, so making antivirals drugs that have broad-spectrum is very difficult, which have activity against different viruses causing almost similar symptoms. Some of the viruses like HIV and HSV against which the antivirals agents that are developed only treat the acute diseases, but they do not have any role in the hidden infection cure. This open on to chronic or recurrent diseases that need longer timeframes therapy. In the development and research of antivirals, these issues and some others represent the main challenge. The development of the formulations of new drugs for therapeutics antivirals is the 2nd most important challenge. This includes modifying the biopharmaceutical and physicochemical properties of the antiviral agents in the formulation of their dosage forms by using technological approaches. For example, for the modification of pharmacokinetics and bioavailability of an antiviral agent that is already available in the market, its reformulation might be performed. The administration of antivirals by the use of an Innovative Drug-Delivery System can provide improvements to the therapy; for example, carriers of nano-particulate have been developed by nano-technology use. The approaches of nano-technology can be utilized to enhance the delivery, formulation, and design of antiviral agents. Of therapeutic nanomaterials, nano-pharmaceuticals is a new class; due to their small sizes, they show distinctive properties, modifiable surfaces, and high ratios of surface-to-volume. Molecules of small size, as well as nucleic acids and proteins, can be incorporated in carriers of nano-particulate, hence giving nanomaterials with applications of broad-spectrum prospective therapeutic and where antiviral agents are required it also providing the potential for site-specific targets. This review describes nano-particulate delivery systems of the current and future generations and the use as transporters for antiviral agent's transport.

Viral Infection's Pathogenesis

The immune system of the body counterattacks the virus before its symptoms appear on the body. Viral infections are spreading through populations; that's why these infections are very important to tackle. There are various stages of this attack

1. The virus attaches itself to the point Which helps in virus entry into the body
2. The virus uses the host machinery when it penetrates the host,
3. The virus removes the coating in this step.
4. They are preparing the virus-specific proteins by countering the transcription and translation process of the host cells,
5. The virus is assembling the visible capsid using nucleocapsid, and
6. They are releasing special factors called virions for further attack (Mao, Wang, Chinchar & Chinchar, 1999).

Factors that affect the mechanisms of pathogenesis consist of the virus's resistance towards the human immune system, the susceptibility of the cell to viral replication, and accessibility of tissue to the causative virus. The virus attacks only those cells of the host where the specific sight of attachment is available to them; various cell transcriptions factors are present which recognizes the promoters and enhancers sequence, local pH, temperature, and presence of enzymes, and also these factors can recognize the pH, temperature and the enzymes that are using to inactive the virus (Baron, Baron & Baron, 2015). Viruses are using the host biosynthetic machinery to destroy the host cells. They are integrating their genome with the host genome and destroy the host cell. The process of infection is studied based on virulence, the extent to which the viral infections are spreading, speed of replication, amount of inoculum, virus dependent factors, and virulence genes (Ocadiz-Delgado et al., 2013). The major problem is that it is very hard to know how the host immunity is interacting with the coming guest. It is not sure whether cell immunity is inhibiting or promoting the growth of the virus (Rouse & Sehrawat, 2010)

Certain FDA approved vaccines graph are showing that the viral structure, specific proteins of virus and also the host cells machinery is responsible for spreading the infection. This behavior is also noted down in different viral species like influenza, Ebola, and Zosters, etc.

Challenges During Anti-Viral Therapy

The passage of time and advancement in studies and research are making the health of patients infected

with the disease caused by the virus better. The upcoming new viral strains all over the world and the resistance to certain viral therapies are making the job tougher for researchers and clinicians.

(i) The antiviral drugs are also interacting with the daily prescribing medicine's which are producing hazardous side effects (Oshikoya, Ogunleye, Lawal, Senbanjo & Oreagba, 2013). The patients are not able to take their daily viral therapies because they are expecting noxious side effects.

(ii) Patient compliance is lowering day by day due to shorter half-life and increased frequency of antiviral drugs or medicines (Gerber, 2000).

(iii) The prolonged exposure of the patients to viral drugs is responsible for the resistance development (Strasfeld & Chou, 2010).

(iv) These drugs are poorly soluble as well as poorly bioavailable; the patient is emphasized to take the higher dose, which in turn leads to toxic side effects. (Singh & Lillard, 2009).

(v) Viruses like Ebola, HIV, and Zoka are attacking the sensitive parts of the body, including the CNS and synovial fluids, so the antiviral drugs prescribing, in this case, may show lower therapeutic effects. (Vyas, Subhedar & Jain, 2006).

(vi) The diagnosis and treatment of some antiviral infections are very tough because they are maintaining their latent stage for a long period. (Chaudhuri, 2002).

(vii) Another prominent challenge for antiviral therapy is the identification of the target and selecting antiviral drugs to the virus over the host cell (Fujii & Rohan, 2019).

(viii) The complex and distinctive structure of the virus is making it difficult to develop newer broad-spectrum antiviral drugs (Adalja & Inglesby, 2019).

Current Antiviral Therapies

The approved drugs that are used nowadays for antiviral therapy are protein or small molecular weight drugs that basic function is to stimulate interferon (innate immune response). Furthermore, for the treatment of retinitis, which is caused by the strain of Human cytomegalovirus resistant to usual drugs (Henahan, 1998). A lot of antiviral drugs are available on the marketplace that is utilized for antiviral therapy. The majority of antiviral agents are approved for HIV infection. Most antiviral drugs that are approved for use are administered orally, while some antivirals are administered by other routes like parenteral, subcutaneous, intravenous, and intravitreal or topical. Most of the antiviral agents have some drawbacks that affect the efficacy, half-life, solubility, and incomplete absorption. As a result, increased frequency and dose are required, so it can cause severe side effects, as well as compliance of a patient is compromised. Most of the antivirals, when administered orally, show low bioavailability, e.g. ganciclovir and anti-retroviral acyclovir. For an antiviral to show its complete effect, enough bioavailability is required so that good permeability and solubility are the basic need for it. Orally administered drugs are categorized on the bases of solubility and permeability into four classes 1, 2, 3, and 4 using the Biopharmaceutics Classification System in a decreasing manner (Amidon, Lennernäs, Shah & Crison, 1995). When the highest dose of the drug is solubilized in ≤250ml of water when the pH range is 1-7.5, and the temp is 37°C, a molecule is observed as extremely soluble according to Biopharmaceutics Classification System. On the other hand, it is considered highly permeable when it gives more than 90% of intestinal absorption in contrast to an intravenous reference dose. Moreover, some other aspects are also there to disturb the bioavailability of oral antiviral, including efflux transporter, food and enzymes' intestinal metabolizing action. As a result, the absorption of orally administered drugs depends on many conditions. So orally administered antiviral require a higher dose and higher frequency and an increased duration of treatment to completely eradicate the virus from the human body. For instance, many protease inhibitors of the Human Immunodeficiency Virus are of higher molecular weight, that is,>500 Da and having solubility dependent on pH (less soluble at high pH) and high lipophilicity; these are the factors that each of them could adversely disturb bioavailability orally (Williams & Sinko, 1999). According to the Biopharmaceutics Classification System, these are classified as both 3 and 4. Most of the nucleoside reverse transcriptase inhibitors have satisfactory systemic absorption, while zidovudine and didanosine (Biopharmaceutics Classification System class 3) have variable bioavailability. Sharma and Greg (Sharma & Garg, 2010) summarized the anti-retroviral drugs that are commercially available

dosage form, which states that most of them have limited absorption. For instance, acyclovir requires a higher dose (1200mg/day) and increased frequency because of incomplete absorption in GIT, consequently decreased bioavailability when administered orally. However, it is utilized in different dosage forms for therapy of Herpes simplex virus and Varicella-zoster virus infections. When acyclovir is administered orally, up to 80% is not absorbed in GIT; for this purpose, some derivatives and prodrugs are synthesized to tackle the problem of absorption. For example, famciclovir, the -valine ester of acyclovir, and valaciclovir, a prodrug of penciclovir, which gives increased absorption as compared to the parent drug. The topical dosage form of the antiviral drug needs to apply 5 to 6 times a day, as acyclovir shows less efficacy when used topically because of low penetration of the drug over the basal epidermis. Here we have the example of ganciclovir which is anti-HCMV has very poor bioavailability, approximately 6-9% that need to be administered in very high doses (>1g) and increased frequency. Furthermore, the oral administration of antivirals is impossible. For instance, some antiviral must be administered intravenously because of very low absorption orally and GIT toxicity, e.g. cidofovir and foscarnet. But in some case for ocular complications, the intravitreal administration of fomivirsen and ganciclovir is more effective than intravenous administration, but a higher dose and increased frequency is required for treatment. While the intraocular injections are risky and cannot be tolerated. One more drawback of antiviral is with the increased frequency, and higher dose can lead to toxicity and serious complications in the patient. Furthermore, with the increased duration of therapy, there are more chances that drug-resistant strains will produce (Liaw, 2005). To change the dosage form of antiviral drugs, therapeutic activity may be improved. Modification of dosage form is nowadays an easy task like improved topical delivery system, depot like injectable and modified-release tablets, so many pharmaceutical industries are currently investigating on developing a dosage form for antiviral that meet the best possible requirement for adequate bioavailability. Hence will increase the Biopharmaceutics Classification System score of antiviral agents, especially if the formulations are made so that their solubility, dissolution, and permeability are increased. Such formulation that can alter residence time and decrease the administered dose will also eliminate the problem of noncompliance. One example of this type of development is long-acting interferon conjugated with PEG molecule so that it is one dose per week as compared to 3 doses per week. Furthermore, advanced technological approaches are being used to improve the formulation, and other strategies are being used to treat viral infection in different ways.

Application of Nanotechnology in Antiviral Therapeutics

Technology is advancing day by day, so as the nano-technology as well; with the help of nano-technology, it is quite easy nowadays to understand the actual cellular mechanism of a cell and develop such technological method that will help in diagnosing and treatment of different viral infections (Villanueva-Flores, Castro-Lugo, Ramírez & Palomares, 2020). While some of the nano-technological application comprises of gene and drug delivery; detection of proteins, use of fluorescent biological labels, tumors and pathogens; purification and segregation of biological cells and molecules; tissue engineering; pharmacokinetics studies and MRI contrast heightening (Cojocaru et al., 2020). Therefore nano-technology has a vital part in dealing with the disease; it clears the way for new researchers to find a method of diagnosing and advanced treatment of viral diseases (Blecher, Nasir & Friedman, 2011). With the help of nano-technology, nano-formulations are prepared that has far better solubility permeability, stability, and bioavailability

Improving the Devilry of Antiviral Drugs by use of Nanotechnology

For 20 years, active molecular delivery has been enhanced due to improvements in the solutions of nano-technology. Nano-technology is developing and using systems and materials on a very small scale that is one billion of a meter. Nano-medicines are the nano construct and nano-particles that are used for diagnosing and therapeutic purposes (Jain, 2006). The use of nano-particle technology for the delivery of antiviral drugs to the human body minimize the risk factors and increase efficacy, safety, stability, higher potencies, and decrease toxicity in the patient. Recent research states that now day's industry for drug delivery worth 80 billion US dollars,

and the most portion of this amount is specified to the target drug delivery and controlled release design. So to develop novel techniques for a controlled release system will clear the way not only for healthcare systems but also for some pharmaceutical companies to patent a product and earn revenue. Cientifica Ltd reported (Sosnik & Amiji, 2010) that the market for nano-based drug delivery will be worth 3.4 billion US dollars in 2007, and it would rise further to 26 billion dollars approximately in 2012.

Different nano carrier's types

- Emulsion
- Cyclodextrin-based systems
- Vesicles
- Dendrimers
- Liposomes
- NLC
- SLN
- Polymeric nano-particle
- Microspheres
- Micelles

Nano-delivery system generally comprises nano-particles consisting of dendrimers, micelles, nano-capsules, inorganic nanomaterials, and vesicles that are formulated to deliver micro molecule of low weight drugs. However, it can be utilized for the delivery of large molecules such as oligonucleotides (Mishra, Patel & Tiwari, 2010). The small size of materials has some new physicochemical properties. As the size of the particle decreases, the greater number of atoms are present over the surface as compared to its central part, so the surface area to volume ratio will be increased; consequently, the particle will be more reactive. Carriers that are used for nano-particle delivery are prepared by different techniques such as vapor, electrostatic deposition and self-assembly, solvent evaporation and solvent diffusion methods, nano-manipulation, and coacervation. By using this type of nano-carriers, it is quite probable to tackle most of the problems of antivirals in standard dosage forms; use of nano-carriers may aid in controlling dissolution and solubility rates, enhancing Biopharmaceutics Classification System score, enhancing the bioavailability of the drug, shielding drugs from degradation, improve drug tissue tolerance and minimizing side effect. Furthermore, the advanced technological approach towards nano-particles clears the way to target specific biological sites either actively or passively by nano-carriers. Their size and lipophilicity impart uniqueness to the nano-carriers due to which it can be utilized to target the antiviral agents to specific tissues or organs, for instance, brain or liver while altering its surfaces makes them reach specific target sites and carry the drugs to cellular targets. Nano-particulate delivery systems may be used for local or systemic antiviral drug administration. In the case of administration of drug intravenously, the drug must be in the range of nanometer so that it can circulate in blood without retaining drug in pulmonary capillaries. To minimize the reuptake by RES (Reticolo-endothelial System), some strategies have been planned. The most common method to increase the durability of nano-carriers escaping Reticolo-endothelial System uptake is to alter the surface of it with hydrophilic polymers, e.g., polyethene glycol (PEG).

Advantages of nano-carriers

- Specific targeting
- The overcoming of anatomical/ cellular barriers
- Minimize the development of drug resistance
- Shielding of drugs
- Controlled release
- Improved bioavailability

The nano-particulate systems also have some properties that are appropriate for pulmonary, nasal, and ocular administration routes. For respiratory tract infections, e.g., rhinovirus, respiratory syncytial virus, and influenza viruses, nano-carrier can be used for targeted drug delivery of antiviral agent or siRNA (small interfering RNA) to the lungs and nasal epithelia to tackle the virus that is responsible for the infection. A lot of compounds are found to have antiviral properties outside the body (in-vitro) however, are not compatible for administering inside the body (in-vivo) because of solubility, stability, and bioavailability issues, but it can be administered to the body via nano-carriers, this comprises of peptide and nucleic acid delivery (Ketzinel-Gilad, Shaul & Galun, 2006). Some of the nano-particulate delivery systems may be appropriate for the delivery of proteins and peptides, shielding them from degradation due to incompatibility and the outer environment. Over previous years, RNAi (RNA interference) arise as a hopeful antiviral technique that works by quieting the expression of the gene responsible for causing severe acute respiratory

syndrome virus, influenza viruses, HBV, HCV, and HIV (Zhou & Rossi, 2014). DeVincenzo et al. (DeVincenzo et al., 2014) explain in recent times in his study that gave matchless evidence of theory for an RNAi based treatment in human aim against RSV (DeVincenzo et al., 2014). Yet most of the problems are there that inhibit the translation of RNA interference into the possible therapeutic stand, and the major problem is the transport of siRNA in-vivo. The efficacy could be improved, and toxic effects could be reduced by targeting the siRNA to specific cells and tissues. Nevertheless, if siRNA manages to reach the specific cell, the negative charge and size of siRNA are problematic for them to pass through the membrane and several other cells are also intractable to uptake small interfering RNA. As a result, many techniques are in the stage of development to cope up with such problems (Tiemann & Rossi, 2009). Instead of all the advantages, the size of the nano-particulate delivery system matters a lot which is in the submicron range that can provide transport of active compounds and intracellular uptake. Particularly the macromolecule (having high weight) transportation is restricted by the permeability of the membrane, which is low for macromolecule and degradation in the endosomal environment after endocytosis. So by incorporating it in a nano-particulate delivery system will protect them from degradation and enhance cell internalization. This is a very vital property because mostly antivirals like nucleoside analogues work by targeting viral functions that are inside the cell. Different mechanisms control the incoming of nano-particulates into the cells, consisting of macropinocytosis, phagocytosis, clathrin-mediated endocytosis, and caveolae-mediated endocytosis (Hillaireau & Couvreur, 2009). To check whether the particle is uptake by cells or not, a technique is used in which nano-particles are labeled with florescent, and cell trafficking is also checked with this method. Additionally, carriers for nano-particles are capable of overcoming barriers. Medicines that are delivered through nano-carriers technology can reach the CNS. Different studies on carriers used for nano-delivery suggest that it increases the in vitro and in vivo permeability and accumulation of the drug in the brain (Wong, Chattopadhyay, Wu & Bendayan, 2010). The transport of drugs to the brain by nano-technology is increased in three ways: blocking the transporter at the BBB so that the drug may not efflux only the efflux transport is blocked, allowing drug trafficking by some non-specific endocytosis, and increasing the concentration gradient of a local drug at BBB by targeting it passively. Looking at the parameters of formulation and component, it is quite easy to synthesize such carriers based on nano-technology to have such physicochemical characteristics that will easily pass to the brain. Three types of groups have been discussed and examined for the transportation of anti-retroviral to the CNS; dendrimer based / polymer, micelle based, and lipid-based system (Wong, Chattopadhyay, Wu & Bendayan, 2010). Similarly, the blood-retinal barrier, the anatomical barrier that is for the purpose to shield the eye, will also be minimize using nano-medicine technology. Furthermore, with the help of nano-carrier technology, it is now an easy task for a drug to reach viral reservoirs of a cell or anatomical compartments that is not possible to reach with the current conventional dosage form. For example, CNS, the lymphatic system, the CSF, the semen, and macrophages are nearly unreachable to drugs, so that's why some compartments where HIV is protected grow independently instead of very active anti-retroviral therapy (Alexaki, Liu & Wigdahl, 2008). Penetration of sub-optimal drugs in these compartments makes the treatment of the Human Immunodeficiency Virus and the complete removal of these viral reservoirs very complicated. The same is the case with herpes-viruses, that unapparent infect tissues and cells. The delivery of antiviral in nano-carriers may affect the efficacy of the drug by inhibiting the transporters of efflux. Transporters of efflux, for example, p-gp (p glycoprotein), have a vital role in restraining xenobiotic transport over different barriers present in our body. Most of the oral drugs essentially cross the basolateral membrane in the epithelium of the intestine to reach the blood. P-glycoprotein could move compounds back to the lumen of the intestine from the cells to prevent their absorption. While in cancer, p-glycoprotein makes the way clear to develop resistance to the anti-cancer agent (Chan, Lowes & Hirst, 2004). Sub-therapeutic drug concentration is the result of efflux transporters that move the drugs out of the cells. Certainly, the hindrance of p-glycoprotein is one of the possible approaches to enhance antiviral absorption n the intestine. It is already suggested that antiviral drug, such as acyclovir absorption is increased with the inhibition of p-glycoprotein in-vitro, but this inhibition has some potential side-effects (Li et al., 2016). One more approach is to use

the nano-carriers system, which is also called nano-medicines, that deliver the drug to the cell that favor the absorption. Furthermore, nano-technology may be used to modify the surfaces of nano-particle, which may be advantageous to perform multifunctional tasks. The beneficial properties come from such engineering, including stimuli sensitivity, targetability, and longevity; these are all combined to give multifunctional nano-carriers that concurrently execute different beneficial tasks (Torchilin, 2009) Nano-carriers of such multifunctionality could considerably enhance the efficacy of numerous therapeutic practices. Developing nanosystems of integrated multifunctionality is an additional emerging area of research for therapy and diagnosis. These novel systems are known as theranostics, which are made particularly for the diagnosis of cancer and treatment simultaneously. Nanosystems should be capable of bio-marking the cells of cancer to attain targeted imaging and treatment simultaneously (Riehemann et al., 2009). These nanosystems of integrated medicine in the future could be proved helpful in diagnosing and treatment and as well as monitoring at the cellular level of viral infections. In the dimensions of the nanometre, the nano-particles are similar to viruses. Many researchers are led by this feature to examine the nano-particles physical interaction with the viruses and, for the discovery of this interaction, whether it could be utilized as an approach of antiviral. In Fact, for inhibition of infection caused by several viruses like monkeypox virus, HBV, HIV, and syncytial respiratory virus, the range of particle mean diameters of the silver nano-particles has been proven to be from 10 to 50 nm. (Lara, Garza-Treviño, Ixtepan-Turrent & Singh, 2011). It can be concluded from all these studies that the observed activity of antiviral agents was due to interaction between the virus and the nano-particles. The antiviral activity of nano-particles is seemed to be due to replication of viruses at an early stage, probably as an inhibitor agent or as a virucidal of viral entry and attachment. (Baram-Pinto, Shukla, Perkas, Gedanken & Sarid, 2009) this strategy can be developed further by designing the nano-particles of silver capped with mercaptoethanol sulphonate so that to target the Herpes simplex virus and to heparan sulfates cell-surface for binding competing. This approach led to efficient inhibition of Herpes simplex virus type 1 infection in the cell culture and for viral infections prevention guided the authors to suggest topical microbicides capped as active ingredients for the entry that depends on heparan sulfates.

Conclusion

With the increasing rate of infections, technology is also combating infections in new and modern ways to cope with them. Every passing year new scientific methods and tools are developed to face new problems. Nano-technology removes the hurdles in the way of antiviral treatment by different means like targeting the delivery of a drug, minimizing the dose and frequency of drug for treatment, utilizing different strategies like nano-carries, increasing permeability, and enhancing the efficacy of drugs. As the conventional dosage forms of drugs are less permeable, low efficacy, and require a higher dose and increased frequency, so it is more prone to develop resistance against drugs. Antiviral drugs are administered as a nano-particle to reach the specific site and show its action; nano-particle reaches the site easily because of their very small size that can cross almost all biological barriers, and gives maximum bioavailability. RNAi arises as a hopeful antiviral technique that works by quieting the expression of a gene responsible for causing viral infections. In the same way, different technological strategies are improving day by day, upgrading the previous techniques by removing drawbacks with the help of research. As well as some of the nano-particulate delivery systems may be appropriate for the delivery of proteins and peptides, shielding them from degradation due to incompatibility and the outer environment. Nano-technology brought a revolutionary change in the field of science by minimizing the efforts and time taken on a single therapy. Further research will achieve a great milestone not only in antiviral therapy but also in the overall healthcare system.

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