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Particular Aspects on Applying Nanocarbon Quantum Dots for HIV Inhibition and Theranostics: a Review

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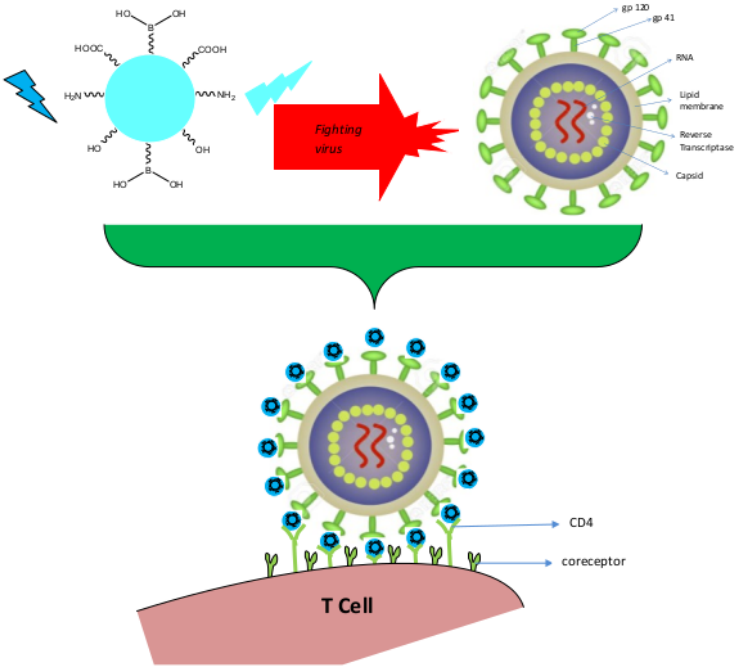
Summary: Viral infection is a globally leading health issue, causing significantly unfavourable mortality with an adversely decreasing socio-economic growth. To solve those infections of global pandemic HIV specifically, the current utilization of highly active antiretroviral therapy (HAART) in human deficiency virus (HIV) theranostics has remarkably improved the life's duration of HIV-infected patients; however, the unfortunate drawbacks in combination with prolonged HAART therapy need to be used continuously along patient's lifetime. Additionally, RNA virus of COVID-19 is also associated with viral pneumonia and acute respiratory distress syndrome causing significant morbidity and mortality. Meanwhile, many scientific researchers have explored the successive novelty of carbon quantum dots (CQDs) as alternative to HIV or other related viruses theranostics in the field of antiviral drugs research, but the attempt has been still challenging to introduce perfect antiviral CQDs with excellent biocompatibility, drug resistance, and safety at several areas in the virus's life cycle. On the contrary, CQDs-based nano-therapy is currently promising because those carbon quantum dots had multiple favourable properties, including significant antiviral response effects, water-soluble activity, color-tunable fluorescence, high yield, low cytotoxic behaviour, and promising biocompatibility. In this review, the recent progress of promising CQDs for viral inhibition and theranostics explored by many studies are systematically summarized.

Keywords: HIV, CQD-based therapy, Nanomedicine, HIV, Antiviral activity.



Scheme-1: A simple schematic diagram of carbon-based dots attacking RNA virus and inhibiting the viral attachment into the Host Cell.

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Introduction

Since the 1980s, the AIDS/ HIV pandemic has spread out all over the world; attacking 33 million people with more than 3 million people of new cases infection and 2 million people of the death rate have been increasing each year. Newly infected patients of approximately 7400 were increasing per day in 2008 and the pandemic has continued going on [1]. The common drug delivery systems together with highly active antiretroviral therapy (HAART) can increase the longevity of AIDS/HIV-infected patients. Nevertheless, there are still various challenges that remain including the fact that the virus cannot be eliminated completely due to some considerable restrictions. The main problem is that the treatment has failed because of poor patient compliance [2]. Hence, a nanotechnological approach has largely emerged as the opportunistic alternative.

Nanotechnology has been developing for using prominent small particles and their dimensions are as small as nanometer (10^{-9} or one billionth of a meter) [3]. Nanobiotechnology is connected to the definition and relation of nanoscience and biological knowledge, whereas another corresponding field is called 'nanomedicine' which interacts with using nanostructured materials to theranostics of many diseases [4]. This technology has been emerging as an integrative study along with promising progress to basically enhance the remedy and inhibition of HIV/AIDS [5]. Since the last decade, the extensive applications of nanotechnology in several biomedical fields have promised great efforts of research [6]. The crucially opportunistic strengths by using nanomedicine in contrast with traditional HIV treatment and prevention are being capable of incorporating, encapsulating, or conjugating with various drugs to definitely trace cell-populated areas and to specifically pass tuneable drug release site [6]. Moreover, there are some benefits to accelerate their antiviral mode of action by many mechanisms: small size of particles (which can help drug delivery go into bodily certain areas) [7], extended surface sites to volume ratios (which enables to accommodate large-scale loading drugs) [8], and charge-adjustable behaviour (to promote the entrance of cells over the negatively charged cellular membrane), and exert nanoparticles to become appealing for viral treatment [9]. Nanoparticles such as silver nanoparticles [10], and dendrimers include biomimetic properties [11, 12], which provide intrinsic antiviral properties. The encapsulation, surface functionalization, and structural modifications can lead to optimized drug dosing, which can enhance the delivery system of stability and specificity to anatomically privileged cellular sites, targeted tissues, or subcellular compartments [13].

Nanomedicine, using nanoscale materials aims to prevent and treat various viral diseases, and such a method is known as "theranostics" [14]. In addition, to treat HIV/AIDS by using nanomedicine of nanotechnology, some platforms of applications can be found such as gene therapy [15], immunotherapy [16], and vaccine delivery [17]. Moreover, nanotechnology platforms for HIV/AIDS theranostics involve polymer nanoparticles [18], liposomes [19], dendrimers [20], nano-emulsions [21] and nanosuspensions [22]. All of those nanomedicine-based therapies have considerable efforts and some advantages to fight the viral threat to a greater extent except they still need to improve solubility, good patient adherence, good biostability, and bioavailability. Moreover, nano-based particles have been synthesized for the use of HIV therapeutics like noble metals-attributed drug-delivering agents [23], polymers [24], composite materials [25], and lipids [26]. Nevertheless, these nanoparticles also have a limited use due to toxicity, their inert properties of starting material, colloidal stability, and complicated synthesized approaches. Consequently, many outstanding novel types of research have been stepped up to diminish the health problem of many virus-infected people around the world. The common lethal viruses infected by people are the acquired immune deficiency syndrome/the human immunodeficiency virus (AIDS/HIV) [27], dengue virus (DENV), Ebola virus (EBOV), and the terrible pulmonary syndrome coronavirus (SARS-CoV) [28]. The SARS-COVID-19 is now terribly spreading around the world.The novel strain (SARS-CoV-2) caused pneumonia that seriously caused lung injuries. To reduce infectious disease transmission, suitable methods are required based on the nature of the disease and mode of transmission [29].

As an added disadvantage, most of obtained research outcomes have failed to use in the real-life medical trials because of toxic problems and vaginal irritation, being more vulnerable to sexually transmitted infections rather than supplying prevention [30].Therefore, it is essential to find the development of method alternative to anti-HIV theranostics, which can profitably increase AIDS/

HIV remedy [31]. In this way, the use of carbon-based nanomaterials, in particular, carbon quantum dots (CQDs), have occupied considerable interest as promising nano-sized particles for the drug delivery tool in biomedical uses [32]. Carbon quantum dots (CQDs) are nano-crystals; their morphological studies have zero-dimensional materials and their sizes are smaller than 10 nm [33]. The well-known investigated carbon quantum dots showed spherical carbon nanomaterials with their unique properties, including favourable photoluminescence, good aqueous dispersibility, biocompatibility, chemical inertness, photostability against photo-bleaching, cost-effective synthetic method, good elasticity in modification and low toxicity as well [34]. Moreover, they are extensively used in the field of bio-imaging enhancement [35], bio-sensing [36], bio-labelling, which appeal to detect contaminants of chemical ions [37], photodynamic therapy technique [38], drug-delivering remedy [39], and viral treatment as well [40]. CQDs also have tuneable fluorescence and manageable their surface sites, which can improve the adsorption capability, corresponding to adhere multiple biological areas in order to inhibit various viruses [41].

CQDs which are in the form of graphene-like nanostructure have been shown to give promising good results due to potential properties which are aforementioned and their high affinity of multifunctional groups to various specific cellular sites [42]. There are some literature review articles concerning nanotechnology approaches for HIV treatment and prevention reported by [43-48], respectively.

However, as far as it can be known, studies of carbon-based nanomaterials (CQDs) for HIV theranostics have not been widely reviewed. Valizadeh, 2015 has reported that only optically diagnostic HIV with nanomaterials focused on the detection of serum biomarkers of the blood-borne contagious infections applying surface-upgraded Raman scattering (SERS) and Surface Plasmon Resonance (SPR) [49]. The current review differs from that approach because many studies of carbon-based nanomaterials and other nanoparticles have been widely demonstrated for both inhibition and theranostics for HIV to suppress the binding or the interaction between the gp120 and receptor CD4 and co-receptors (CCR5 or CXCR4) in the T cell, thereby blocking the viral entry and replication. The current review aims to largely outline the potential of the multidisciplinary field of carbon-based nanomaterials and other nanoparticles to enhance the field of HIV treatment and prevention.

Current Antiretroviral Therapy in HIV

Antiretroviral therapy, known as ART, is meant by the treatment method of HIV by combining medicines [50]. The combination with three or more antiretroviral drugs was used as "Highly active antiretroviral therapy (HAART)" so that the viral burden in a patient could be suppressed to effectively detectable levels (*i.e.*<50 copies of virus/mL of blood) and require to supply those drugs to patients simultaneously [51]. Moreover, the utilization of the highly active antiretroviral therapy (HAART) prepared from integrated three or more drugs focused on complex steps of the HIV biorhythm; it has paid the significant improvement to AIDS/ HIV-infected patients' life expectancy and lifestyle [31]. Although the conventional HAART treatment for HIV/AIDS has been used successfully, a few hurdles are still remaining. The main issue is the failure of giving treatment to patients, definitely due to poor patient adherence to those drugs. Also, this combination therapy is necessary for infected patients to always be taken so as to avoid there-occurrence of HIV from quiescently infected cells. As a consequence, it brings severe side effects and is profitless where the virus matures hostility, often thereby resulting in clinical unsuccessfulness. Besides, the effectiveness of their many potential therapeutic agents is restricted due to their poor solvent-soluble property, and that solvent is required for their medication delivery and cytotoxicity consideration of those ART drugs [52, 53].

The antiretroviral therapy is mainly aimed at two objectives, such as virologic control (the measurement of HIV RNA or p24 antigen quantity reduction) and immune rehabilitation (CD4 count re-establishment). HAARV therapeutics are generally classified by six categories: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 and CD4 antagonists, and integrase strand transfer inhibitors (INSTIs) [54]. The currently antiretroviral drugs are shown on Table-1.

Table-1: Current Antiretroviral Drugs Utilized in the Remedy of HIV.

Classes	Drug Agents FDA approved	Mechanistic Mode of Action
Nucleotide Reverse Transcriptase Inhibitors (NtRTI)	Abacavir(ABC), Didanosine (DDI), Emtricitabine (FTC). Lamivudine (3TC), Stavudine (d4T), Zalcitabine (ddC), Zidovudine (AZT),	•Block the reverse transcriptase enzyme which manages the viral transformation from RNA to DNA inside the harbor cell. •Necessitate intracellular metabolism to their triphosphate identity, before activated action [55].
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	Delavirdine (DLV) Efavirenz (EFV) Nevirapine (NVP)	•Non-competitive prevention of RT •Cohere immediately to RT and block DNA polymerase manner by impeding the synergistic plot of that enzyme. •Also prevent reverse transcriptase but intracellular activation is not required for activation [56].
Protease inhibitors	Atazanavir (ATV) Ritonavir (RTV) Lopinavir (LPV) Darunavir (DRV) Indinavir (IDV)	•Accountable for the cleavage of precursors of viral polypeptide complexity into useful proteins, required for the maturement and congregation of virions. •Impede the growth of new virions from incurably transmitted infection cells [57].
Integrase inhibitors	Raltegravir (RAL) Elvitegravir	•Impede the catalytic pursuit of HIV-1 integrase. •Inhibit the combination of linear HIV-1 DNA into the harbor cell genome by hindering stranded shifting [58].
CCR5 inhibitors	Maraviroc (MVC) Vicriviroc (VCV)	•Selectively adheres to the human chemokine, functioning receptor CCR5 • Prevent the inducement of CCR5 with the HIV-1 membrane glycoprotein gp120, which is essential for tropic HIV to enter T cells [59].
Fusion inhibitor	Enfuvirtide (ENF)	• Tie up the HIV-1 membrane glycoprotein gp41 and block the mingling of HIV with the harbor cell before the virus goes into the cell and initiates the replicating process [60].

Abbreviations: RNA, ribonucleic acid; **DNA**, Deoxynucleic acid; **CCR5**, chemokine coreceptor

Nano-Based Antiviral Therapy

Promising nanomaterials for antiviral agents are formulated for virus inhibition and theranostics because they have proven to exhibit antiviral activity against various viruses. Such nanoformulations are prepared from heavy metal nanoparticles, silver or gold nanoparticles, and other nanoparticles including carbon-based nanoparticles. However, the toxicity is the main concern for drug delivery systems into targeted cells. Regarding different toxicities derived from respective silver or gold-based nanoparticles, heavy metal-based quantum dots and carbon-based dots, the carbon-based dots are relatively non-toxic. And hence, carbon-based dots have attained significant attention to formulate nano-based antiviral agents [40, 61].

Inorganic Nanoparticle

Theoretically, what kinds of prepared nanoparticles (NPs) we used and how they formed are crucial for the adaptable model of viral inhibition. Therefore, it requires a general overview of the antiviral activity of NPs produced from various types/kinds and configuration/ composition of nanomaterials [62]. Antiviral agents derived from nanoparticles are extensively modified from easy inorganic NPs into complicated organic and hybrid nanosystems or nanostructures. The composition of nanospheres, nanocapsules, and nanocages derived from metallic nanoparticles (MNPs) and nanocomposites (NCs) could be divided by inorganic NPs (INPs), whereas organic NPs (ONPs) produce nanocapsules as in typical shapes of nanocomposites (NCs) with the modification of their chemical structure. Hybrid nanosystems or nanostructures are highly standardized by a mixture of either inorganic-organic or inorganic–inorganic (nanocomposites). Organic–organic nanoparticulated systems (lipid–polymer hybrid NPs) are standardized due to particular requirements of the delivery system to use at the targeted point [63, 64].

Inorganic nanoparticles have some significant properties such as photoluminescence, good solubility, tuneable size, shape, long-term stability, large surface-to-volume ratio, and attachment of multifunctional groups that have drawn the great attention for INPs in the biomedical field for numerous applications [65]. Of such applications, the widely investigated capability of INPs aims at displaying several surface binding sites and controlling their *in vivo* natural behaviour as well [66]. Recently, metal-based nanoparticles have been prepared for promising antiviral candidates in case of HIV-1 remedy, respiratory syncytial virus, hepatitis B virus, monkeypox virus, herpes simplex virus type 1, Tacaribe virus, and influenza virus [67].

The anti-HIV-1 responsive activities of these metal-based nanoparticles (gold/silver) are commonly studied (as shown on Table-2). Selecting the point to the reticuloendothelial system (RES)

tends to be opsonization (*i.e.*, agglomeration of effective nanoparticles in the RES), thereby activating the immunity via phagocytic functions. Those nanoparticles were delivered from intrinsic flowing movement, and thus assembling in the RES where the disease persistence of HIV remains [68]. However, there are some advantages of antiviral agents derived from inorganic nanoparticles to treat or prevent HIV. Gold and silver nanoparticles intrinsically exhibit antiviral effects to fight a large number of HIV-1 strains, behaving as viral inhibitory agents with the inhibition of post-entry phases of that HIV-1. Thus, the viral persistence could be weakened by these nanoparticles [69, 70]. Inorganic-attributed nanoparticles expose highly optical, electronic, catalytic, and magnetic properties. Moreover, they have distinctive characteristics, including small nanometer sizes, tuneable imaging behaviour, and multifunctionality. To improve cytotoxicity to be safe, it is significantly important for nanoparticles to effectively modify their surfaces. In other words, there are a few limitations for Au/Ag nanoparticles: highly toxic problems in DNA destruction and cellular apoptosis, and then the effects of AgNPs on such different toxicities may be a consequence of their ability to inflict cell damage [71-74].

Table-2: Various Nanoparticles Derived Multi-Viral Theranostics.

Nanoparticles	Typical Virus	Model of Cells	Mechanism of Antiviral Action	Purpose	References
Silver (Ag) AgNPs	HIV-1	HeLa-CD4-LTR-β-gal cells, MT-2 cells, Lymphoid human cell line	•Interconnection with gp120 to hinder CD4-based virion adhering, mingling, and pathogenesis	•To perform their antiviral property level in case of HIV-1 following a trial of individual *in vitro* assays	[75]
AgNPs	Avian influenza A virus, subtype H_7N_3	Vero cells	•Obstructing HA mode of action and deviating interrelation with viral propagation route	•To inhibit the viral entrance, thereby distorting viral propagation	[76]
AgNPs	Poliovirus type-1	Human Rhabdomyosarc-oma	•Interconnection with viral protein can weaken the interrelation with the T cell	•To inhibit viral penetration	[77]
AgNPs	Murine norovirus-1	RAW 264.7 cells	-	•To serve as virucidal agents	[78]
AgNPs	Infectious Bursal Disease (IBD) virus	Embryonated chicken eggs	•Interrelated with viral covering	•To inhibit viral entry and replication	[79]
AgNPs	S. cerevisiae dsRNA viruses	HeLa cells, NIH/3T3 cells	•Interact with viral genome and prohibit viral propagation	•To inactivate or destroy viruses	[80]
AgNPs	Hepatitis B virus	HepAD38 cell line	•Silver nanoparticles could prevent the *in vitro* growth of HBV RNA and extracellular virion	•For viral therapy	[81]
Graphene Oxide-Silver Nanocomposites (GO-AgNPs)	HIV-I RNA virus, PEDV (a member of the family *Coronaviridae*)	MARC-145 cells	•GO-AgNPs nanocomposites distinctively obstruct the virus entrance into harbor cells, consequently, restrain virus propagation.	•To boost viral inhibition	[82]
Titanium (Ti) Nanoparticles TiO2 NPs	H_3N_2	-	•Directly contacted with virus	•To use as virucidal agent	[83]
TiO2~DNA Loaded nanocomposites DNA	H_1N_1, H_5N_1, and H_3N_2	MDCK cells	•Selectively adhere to hidebound areas in the viral genetic makeup and prevention of viral replication	• To act as viral inhibition	[84]
TiO2 NPs	MS2, PRD1, ΦX174, Fr	-	•Interconnection with the viral shell of protein (glycine, alanine, and proline remnants)	• To exert photocatalytic deactivation of bacteriophage	[85]
Gold Nanoparticles Au NPs	HIV-1	HeLa-CD4-LTR-Bgal cell	•Attaching with viral glycoprotein (gp120) and inhibit CD4 binding	•To inhibit viral entry	[86]
Au NPs	Foot- and- mouth diseases virus (FMDV)	BHK-21	•Hinder viral reproduction in accompany with transcription	•To perform as a virucidal agent	[87]
Au NPs	Influenza virus A (H1N1, H3N2)	-	•Peroxidase-mimic enzymatic interaction	•To detect the viral pathway	[88]
Gold NPs (AuNPs) Loaded with synthetic peptide (FMDV protein)	FMDV	BALB/c mice	•Antibody interposed immune resistance	•To be size-dependent booster of immune system	[89]
AuNPs DNAzyme (DDZ)	Dengue virus (DENV)	Aedes albopictus C6/36 cells	•DDZ triggering interposed salt induced accumulation of AuNPs	•To use in viral detection	[90]
AuNPs conjugated	DENV	Vero cells	•Impeding viral propagation and	•To use as efficient	[91]

with SiRNA			releasing contagious virion	delivering agents for viral prevention	
AuNPs loaded Viral matrix 2 protein (M2e)	H_1N_1	BALB/c female mice	•Antibody interposed CpG (cytosineguanine rich oligonucleotide) immune activity	•As a influenza vaccine	[92]
AuNPs loaded recombinant trimetric A/Aichi/2/68 (H3N2), Hemagglutinin (HA) and TLR5 agonist flagellin (FliC)	H_3N_2	Female BALB/c mice, HEK 293 T cells, JAWS II cells	•Antigen-specific T cell- interposed immune capability	•To improve the booster of immune system	[93]
AuNPs loaded monoclonal anti-hemagglutinin antibody (mAb)	H_3N_2	-	•Viral surface removal with NPs-mAb	•To use as a colorimetric immunosensor viral detection	[94]
AuNPs load viral consensus matrix 2 peptide (M2e)	H_1N_1, H_3N_2, H_5N_1	BALB/c mice	•Highly humoral and cellular response	•To serve as the comprehensive influenza A vaccine	[95]
AuNPs loaded recombinant viral Hemagglutinin (HA)	H_3N_2	BALB/c mice	•Stronger degree of viral-specified IgA and IgG, advanced level of antigen certain interferon-γ (IFN-γ)-release, CD4+ cell growth and stimulating high effect or CD8+ T cell	•To enhance mucosal cellular immune capacity	[96]
Au nanoparticles capped with mercaptoethanes-ulfonate (Au-MES NPs)	Herpes simplex virus type 1	Vero cell	•Obstruct the viral attachment, entrance, and cell-to-cell distribution, suggesting that the Au-MESNPs can possibly be helpful for both a prophylactic and therapeutic candidate.	•To use an antiviral therapeutic agent	[97]

Abbreviations: CD4, cluster of differentiation 4; **HA**, hemagglutinin protein; **FMDV**, Foot-and-mouth disease virus; **IgG**, Immunoglobulin G; **IgA**, Immunoglobulin A

Organic Nanoparticles

Organic nanoparticles are very commonly useful for drug delivery, and become one of the most popular investigated platforms of nanoparticles. They also have promising properties to be used extensively in the biomedical field for a therapeutic system in humans [98]. The most widely used categories of organic nanoparticles are polymeric nanoparticles, nanocapsules, nanospheres, liposomes, micelles, and dendrimers [99].

First, polymeric nanoparticles seem to be colloidal solids and their dimensions range from 10 to 100 nm. The capillary penetration to tissue is helpful and uptake by cells due to their small size, resulting in enhanced concentrations at target cellular areas. Polymer-based nanoparticles with biologically active factors are water soluble, entrapped, and encapsulated into naturally synthesized polymer nanomaterials. Polymers such as polyglycolides, polylactides, poly (lactide-co-glycosides), polyorthoesters, polyanhydrides, polycyanoacrylates, and polycaprolactone are commonly used in medicine and pharmaceuticals with the approval of the World Health Organization (WHO) and the Food and Drug Administration (FDA). Polymeric nanoparticles have some agreeable advantages - chemically precise composition, remarkably promising physical properties (dissociated controlled rate, permeability, deterioration, eroding, and targeting efficacy), no toxicity, and lack of leachable or harmful impurities. Since they have their excellent biocompatibility and biodegradability signals, they are widely used for nanomedicine in clinical modes [100-102].

Second, nanocapsules are in the form of typically vacant domains, in which there is the drug's confinement to an internal gap, encapsulated by a polymeric covering. The average sizes range from 50 to 300 nm, and thus their tiny tenuity and fast-moving delivery rate could be identified [103]. De Oliveira *et al*. 2005 explored nanocapsules to be used to enhance drug distribution to confined antiviral brain tissue in accordance with the penetrability glycoprotein (P-gp) efflux carrier. They found that the HIV protease inhibitor, indinavir-loaded Solutol® HS15 nanocapsules exhibited highly enhanced cellular absorbing rate in the targeted brain site and testes of mice, in contrast with sample standard mice where alone indinavir solution was given in [104].

The third ones, nanospheres are in the typical form of a matrix where the drug is physically or correspondingly distributed, with the dimensional diameter ranging from100 to 200 nm [105]. There have been numerous research approaches of potential nanospheres to treat hepatitis B virus (HBV)

[106], herpes simplex virus (HSV) [97], influenza [107], and also other inclusive review articles concerning viral prevention and treatment by using these bioactive agents were also presented [108].

Fourth, liposomes are formed as spherical carriers with its dimensions, which generally ranged from 20 to 30 nm [109]. They functioned as the traditional vesicular transporters, which consist of phospholipid molecules in the form of a lipid bilayer encircling an aqueous nucleus [110]. They are helpful for the encapsulation of hydrophilic drugs, whereas amphiphilic and hydrophobic drugs enable them to solubilize the phospholipid bilayers. Additional advantages are that circulating by speedy clearance makes the delivery of antiretrovirals strong entrapment capacity and a longer half-life in circulation within macrophages. Moreover, they are relatively safe and biodegradable [111]. As a disadvantage, liposomes have a few considerable hurdles. Despite being the small core volume, deliquescent drug-delivery capacity of liposomes is restricted. And hence, their continuous usage and physical or biological stability of the antiretroviral is limited [6].

Fifth, micelles possess colloidal dispersions with their dimensions normally varying from 5 to 100 nm, based on the typical configuration of head categories and length of the alkyl series. Micelles can be self-assembled into a structural conformation in an aqueous solution by interacting with amphiphilic molecules themselves due to containing both hydrophobic and hydrophilic segments [112]. Polymeric micelles encapsulated by drugs have drawn great interest in nanotechnologies because these nanoformulations can increase both water solubility and stability. Micelles are beneficial in viral therapeutics, providing a slower and specific rate of dissociation or distribution. Thus, they promote a longer drug-withholding time. Finally, the drug would highly accumulate at the target site [6].

The sixth one of organic polymeric nanoparticles is dendrimers. Dendrimers are also well-known polymeric platforms for their designated types and shapes, adaptability in the drug delivery system, and highly functionalized compositions. Their properties are similar to biomolecules [113]. They are composed of a branched three-dimensional architecture, standardized by connecting numerous monomeric segments. Those large numbers of monomeric units possess minimal polydispersity and great functionality. Numerous chemical components, interior sheets, and the multivalent aspects can be encapsulated by a characterized polyfunctional core of dendrimers. The properties of dendrimers also rely on the multivalent site on the exterior composition. The characteristics of dendrimers can be maintained physically and chemically during the synthetic work by identifying the central categories, the intensity of the surface branch, and the naturally functional groups on the surface sites [114, 115].

At last, one of the promising organic polymers for use of the drug-loading system is solid lipid nanoparticles (SLNs). SLNs also function in the drug delivery system as novel lipid-based nanocarriers with the average size in the range of 10 - 1000nm. SLNs have interesting features for therapeutic goals [116]. They are noticeably advantageous because they are synthesized from pre-physiologically well-tolerated lipids. They are also effective for good biocompatibility and low toxicity. Interestingly, the delivery system of solid lipid nanoparticles is better enhanced by lipophilic drugs, and thus the system is physically stable. Solid lipid nanoparticles are one of the promising colloidal transporter systems as alternative agents to polymers which are generally similar to the oil in water-emulsified procedure for administering intravenous nutrition [117].

The nanoparticulate antiviral usages up to 2010 mainly comprised of nanoparticles (NPs), nanospheres, nanosuspensions, nano-emulsions, micelles, liposomes, dendrimers, solid lipid NPs (SLNs), nanogels, and cyclodextrin-based systems as well [43]. They are standardized as alternative supporting materials for antiviral therapy and part of their summary is listed on Table-3.

Table-3: Various Nano-Based Materials Come About for Antiviral Drugs Agents.

Organic Nanoparticles				
Nanoplatform Type	**Characteristic virtues (Size, Morphology, Toxicity, etc.)**	**Drug**	**Virus Type**	**References**
HPAC	•No toxicity in treating with different concentrations of HPAC in human epithelial cells (corneal, vaginal); • Average proliferation rate>75% following HeLa cells, foreskin fibroblasts; •Drug-loading capacity 99%;	ACV	HSV	[118]
PLGA	•Three GCV pro-drugs was individually inserted into PLGA NPs; • Uniform-sized NPs • Mean diameter 116 - 143 nm; •Zeta potential between -13.8 and -15 mv; • Non-toxic PLGA-NPs treated with three individual concentrations for 24 h and 48 h in HCEC cell;	GCV	HSV-1	[119]
PEG-PLGA	•Uniform sphere-shaped NPs; •Diphyllin-loaded NPs 178 nm, whereas bafilomycin-loaded ones 197 nm; •Biocompatible results and antiviral effects for the drugs-loaded NPs are significantly stronger than the free drugs;	Diphyllin and Bafilomycin	H1N1	[120]
Tf-Albumin-PEG	•Uniform-sized NPs with average size ranging from114 to 124 nm; •A negatively charged NPs surface	AZT	-	[121]
HAS +copolymes of maleic anhydride/ Alkyl vinyl ethers of oligo (ethylene-glycol)	•NPs sizes ranged from 100 to 300 nm; •Surface sites of functional components can provide affinities of liver cells receptors;	INFs-α	HIV	[122]
PLGA NPs	•LAM-loaded polydispersible NPs ranged from 221 to250 nm; •Zeta potential in the range of -4.64 and -3.65 mv; •The loading capacity of LAM and the polymer was provided by FTIR and DSC; •Slowly degradable NPs in affected intestinal fluid PBS;	LAM	-	[123]
Hybrid NPs (PLGA, MMA-SPM,PLA and PMMA)	•Particle size of PLGA ranged in 58–224 nm, whereas particle size of MMA-SPM ranged in 91–823 nm and nearly sphere-shaped NPs; • Non-cytotoxic NPs (male mice);	LAM+AZT	-	[124]
PLGA-PEG	•All possess sphere-shaped NPs; •SAHA and NFV-loaded NPs sizes are 125 nm, while only NFV-loaded NPs range118 nm and 119 nm for only SAHA-loaded NPs, respectively; •Non-toxic behavior of drugs-loaded NPs (tested on ACH-2 cells);	SAHA NFV	HIV	[125]
PLGA	•Uniform-sized and surface-smooth NPs NFV-loaded NPs ranged approximately185 nm; belonged to nearly narrow-spread NPs; •Zeta potential is 28 mV;	NFV	-	[126]
Lactoferrin	•Size of NPs 45–60 nm, hydrodynamic radius of 103 nm, zeta potential of-23 mV; •Polydispersible NPs; •Chemical stability of NPs confirmed by FTIR and DSC;	EFV	-	[127]
Folic acid-conjugated-P407	•NPs are promising following the conjugation of folic acid with P407, in particular, the number of HIV-replication in mice cells noticeably reduced due to the involvement of drugs of ATV and RTV;	ATV+RTV	-	[128]
PMA coated MNP	•Uniform-sized nanoparticles ranged 35.2 nm in accordance with their conjugation with ENF; zeta potential is -29 mV; •No toxicity was shown in *vitro* and *in vivo* treatment;	ENF	-	[129]
pMBA-Au NPs	•Average NPs size ranged 1.8 nm; •Non-cytotoxic in *vitro* assay;	RAL	-	[130]
PLGA	•Mean particle size of 138.3 nm and zeta potentialapproximately-13.7 mV; •NPs Drug-loaded NPs exhibited no toxicity in contrast with free NPs;	EFV+Lopinavir+RTV	-	[131]
PLGA+Pluronic F127	•Clearly expressed polydisperse NPs with mean size ranging to 220 nm; •-19.2 mV is of their zeta potential; •No serious toxicity within a 14 days pharmacokinetic treatment on mice;	TAF+EVG	HIV	[132]
Lactoferrin	Mean size of drug-loaded nanomaterials is around 67 nm; •No significant toxicity to red blood cells in *vitro*; •Developed bioavailability of the three drugs;	AZT+EFV+LAM	HIV	[133]
Nanospheres				
Cs	•Spherical NS with a fully smooth surface; •Mean size of approximately 200 nm, polydispersible NS formation, •Zeta potential approximately 40 mV; •ACV encapsulated capacity is 86% •Agreeable Vero cell viability after treated with NS;	ACV	HSV	[134]
Nanosuspensions				
Zirconium oxide beads	•Average particle size approximately ranged 320 nm;	EFV	HIV	[135]

stabilized with PVP, poloxamers, and SLS	•Zeta potential of -32.8 mV; •EFV bioavailability enhanced after associated with nanosuspensions (*in vivo*, rabbits);			
Nanoemulsions				
Mucoadhesive NEs	•Relied on triacetin-oil, tween 20-surfactant,transcutol P-cosurfactant; •Sphere-shaped NPs sizes of 23–200 nm; •Non-cytotoxic and nonirritant nanoplatforms (New Zealand albino rabbit);	GCV	HSV	[136]
Micelles				
Cs-g-oligo (NiPAam)	•Copolymers self-aggregation into multimicellar assembly with hydrodynamic diameter in the range of 330- 436 nm; •Zeta potential falls in the range of +7 to +22.8 mV; •Satisfactory mucoadhesion and cytocompatibility activities;	EFV	HIV	[137]
Liposomes				
Reverse phase evaporation	•GCV amalgamated with PC/CH/NaDC soluble in chloroform/diethyl; •Sphere-shaped liposomes; •Particle sizes range 210–17 nm; •Zeta potential ranged –52.4 mV; •Polydispersible Liposome NPs;	GCV	HSV	[138]
rHDL	•rDHL-ACV palmitate complicated size of 33.5 nm,appromately 10 times<ACV-liposomes;	ACV	HBV	[139]
Cationic	•Viral gene formulation decreased by 65–75% in liver cells after 48 hours of dosing at mice;	siRNA	HCV	[140]
Immunoliposomes	•Viral release decreased by 81% and free viral particles neutralized in vitro;	HIV gp 120 Folding inhibitor	HIV	[141]
Immunoliposomes	•In *vivo* the virus-infected resistance was improved;	anti-CCR5 siRNA	HIV	[130]
Immunoliposomes	•Immunoliposomes with mean size between 100 and 120 nm; significantly effective to deliver concentrated indinavir;	Indinavir	HIV	[142]
Dendrimers				
PG	•Non-cytotoxic peptide–PG conjugated in *vitro*; •Potential antiviral effect in *vitro*;	Peptides	IAV	[143]
Alginate-PEG	•Dendritic morphology provided by TEM; •Hydrodynamic diameter between 601 and782 nm; •Zeta potential ranges between-45.8 and -65 mv; •88% and 98% of cell viability confirmed satisfactory biocompatibility and non-cytotoxic behavior (neuro cells, Hela cells, glioma cells);	AZT	HIV	[144]
Solid Lipid Nanoparticles (SLNs)				
Bryostatin-2	•Lipid-loaded nanoparticles can trigger latent HIV and can prohibit virus's distribution in *vitro*;	NFV	HIV	[145]
PEG and phospholipids	•Drugs-loaded LNPs ranged between 33 and 68 nm and associated cell viability between is between 88% and 96%;	ATV+RTV or ATV+RTV+TFV	HIV	[146]
DSPC+MPEG+DSPE	•NPs diameters range between 52 and 68 nm; •In *vivo* anti-HIV LNPS did not show internal reactions and animal platelet counts are up to normal limits.	Liponavir+ RTV+TFV	HIV	[147]
Nanogels				
PVCLNGs	•TEM revealed that the size is between 40 and 50 nm. •At lower than 10 µg/mL, there is no cytotoxic response in the cervicovaginal epithelial cell line.	VCL	HIV-1	[30]

Abbreviations: **NRTIs**, nucleoside and nucleotide reverse transcriptase inhibitors; **NNRTIs**, non-nucleoside reverse transcriptase; **HPAC**, highly porous activated carbon; **ACV**, acyclovir; **HSV**, herpes simplex virus, **PLGA**, poly(lactic-co-glycolic acid); **GCV**, ganciclovir; **PEG**, polyethylene glycol; **AZT**, azidothymidine, **INFs-α**, intranasal fentanyl spray; **LAM**, levacetylmethadol; **MMA-SPM**, methylmethacrylate-Sulfopropylmethacrylate; **SAHA**, suberoylanilide hydroxamic acid; **NFV**, nelfinavir; **EFV**, efavirenz; **ATV**, atazanavir; **RTV**, ritonavir; **PMA**, paraformaldehyde; **MNP**, magnetic nanoparticles; **HAS**, human serum albumin; **ENF**, enfuvirtide; **pMBA**, p-mercaptobenzoic *acid;* **RAL**, raltegravir; **Cs**, chitosan; **ACV**, acyclovir; **PVA**, polyvinyl alcohol; **PVP**, polyvinylpyrrolidone; **NEs**, nanoemulsions; **GCV**, ganciclovir; **rHDL**, recombinant high density lipoproteins; **ssDNA**, single stranded DNA; **siRNA**, small interfering RNA; **HBV**, hepatitis Bvirus; **HCV**, hepatitis C virus; **PG**, poly(glutamic acid); **IAV**, influenza A *virus;* **TFV**, tenofovir; **DSPC**, distearoyl phosphatidylcholine; **MEPG**, methoxypoly(ethylene glycol); **DSPE**, distearoylphosphatidylethanolamine; **PVCLNGs**, poly(N-vinylcaprolactam) nanogels; **TEM**, transmission electron microscopy; **SEM**, scanning electron microscopy; FTIR: Fourier-transform infra-red; **DSC**, differential scanning calorimeter

Preparation and Properties of CQDs

Several carbon nanomaterials (CNMs) have been increasingly developed by advanced nanotechnology. The exploration of carbon-based materials has been widely improved since 1990. Namely, fullerene (C60), carbon nano-onions (CNOs), carbon nanotubes (CNTs), carbon nanohorns (CNHs), nanodiamonds, graphene derivatives, and carbon dots (CDs) which were characterized [148]. Of these nanomaterials, carbon quantum dots are the most widely used because they have drawn great interest for their unique properties in multiple applications. Carbon quantum dots were unexpectedly reclaimed when single-walled nanotubes (SWCNTs) luminescent carbon-based nanomaterials were purified by the electrophoretic method in 2004 [149]. In 2006, Sun *et al*. 2006 standardized CQDs from graphite fine particles and cement dust particles by a laser ablation method [150]. Generally, the chemical composition and physical characteristics of carbon dots (also called carbon quantum dots) or graphene-based dots are closely alike those of graphene oxide. However, their average sizes (below 10 nm) and typical form of being quasy-spherical nanoparticles are slightly different from those of graphene oxide [150].

The synthetic action of carbon quantum dots (carbon dots) is generally developed by using two methodological methods such as top-down and bottom-up approaches. The top-down approach covers acid dehydration, laser-ablated synthesis, electrochemical or chemical oxidation, and arc discharge from carbon-based raw materials. On the contrary, the bottom-up method includes pyrolysis, thermal carbonization, microwave or ultrasonic treatments, and solvothermal treatment from various starting materials [151].

Due to their multiple and outstanding merits such as photoluminescence, color-tunable behaviour, biocompatibility, water solubility, low toxicity, cost-effective synthesis and good photostability against photo-bleaching, those photoluminescent carbon dots have numerous biomedical applications *in vitro* and *in vivo* assays for example, as biosensing agents, bioimaging candidates, biolabeling techniques, drug delivery systems, photodynamic diagnosis, and viral treatment functions [152]. Moreover, nano-sized carbon quantum dots (CQDs) have received tremendous attention in accordance with their promising tiny size, high fluorescence emission, chemical stability, and easy functionalization. Concerning their optical properties, CQDs have become fluorescent due to two reasons: 1) the fluorescence emission from bandgap conversion of conjugated π-domains and 2) the fluorescence from the surface deformity. The optical emission in the near-infrared (NIR) spectral range of wavelength emitted by CQDs can be effective for biomedical applications [153]. Gaining strong fluorescence depends on the high percentage of quantum yield (QY) generated by prepared CQDs [154]. The color-tunable fluorescence can be made in favour of the excitation wavelength. The intrinsically photoluminescent CQDs can be helpful for photocatalysis, biomedicine, solar energy conversion, photosensors, and light-emitting diodes (LEDs) [154].

Some research investigated by many researchers and their co-workers to approve the non-toxic behaviour of prepared carbon-based nanomaterials on various cell lines, for example, HepG2 cells [155], HeLa [156], 293T [157], and *in vivo* biocompatibility on zebrafish (Danio rerio) [158, 159] have been developed. Moreover, CQDs strongly showed a virtual fluorescence depending on wavelength emission by controlling their size [160]. The fluorescent level would be turned with respect to the wavelength emission from the strong ultraviolet to visible or the near-infrared range of wavelength. Besides, the surface sites of CQDs were functionalized by miniature organic compounds, metals, and scale-down polymers so that water-dispersible and nano-fluorescence properties would be enhanced [161].

CQDs exhibit their stable photoluminescence with drug/gene-loaded treatment so that they could, therefore, be used for drug-delivering agents [162], and for delivering genetic matter via electrostatic interaction [163], and siRNA [164]. In particular, CQDs with several functional components were utilized for the multipurpose nano-system for intracellular photoluminescence and subcellular targeting drug delivery [152].

Lately, Ge *et al*. 2015 have prepared CQDs as photodynamic therapy (PDT) agents with uncommon singlet molecular oxygen (1O2) fabrication and used as superior photoacoustic and thermal treatment of cancer cells in living administrating mice [165]. Those CQDs exhibited photodynamic and photothermal results when irradiated by laser upon 635 nm following the excellent photothermal conversion capacity. Besides, Chen *et al*. explored a photosensitiser an alternative PDT system using the two-photon absorbance of CQDs. The action mode of those CQDs effectively

exhibited strong induction of apoptosis in cancer HeLa cells when excited by around 700 nm [164].

Fahmi and co-workers have explored the promising carbon dots (CQDs) as the viral entry inhibitory agents to block the attachment of gp120 from the viral envelope and CD4 receptor or coreceptor CCR5 from host cells, thereby preventing HIV infection [42]. Their project was prepared by using pyrolyzed-citric acid (CA) method to exhibit a graphene-like structure of CQDs with abundant functional groups (-OH, -COOH) on their surfaces. To crease the inhibitory efficiency, the prepared CQDs were conjugated with carboxyl phenylboronic acid (CBBA), thereby blocking the viral entry. Comparatively, the antiviral activity-evaluated assay of the modified CBBA carbon dots (CBBA-CQDs) behaved more synergistically to prohibit HIV infection than the prepared carbon dots alone. In regard to their cytotoxicity assessments, the average percentage of cell viability at different concentrations was higher than 80%, ascribing that both CQDs and modified CQDs are non-toxic in human cells. Thus, their findings highlighted that the intrinsically antiviral property of carbon dot-based applications would further be able to use in HIV prevention and treatment [42]. Therefore, it can be said that the preparation of carbon based-materials and their properties are worth to be used in multiple fields including antiviral blocking systems for human-effective surroundings.

Carbon Quantum Dots for Viral Theranostics

Carbon dots (CDs) or carbon-based quantum dots (CQDs) are the typical form of semiconductor nanocrystals with promising small dimensions as mentioned above. They intrinsically display optical properties, for example, photostability, high absorbance cross-section, comparatively long lifetime of stable fluorescence, and high quantum yield of around 70 to 80% [166].The tuneable colour of CQDs fluorescence with respect to the emission wavelength would be varied from 450 to 1800 nm by administering their size, structure, and framework of the nanocrystals. Their broad-excitation spectrum and narrow-emission spectrum can boost the tendency of numerous selected molecules *in vivo* or *in vitro* probes [167]. Since the carbon quantum dots have been increasingly researched in the field of antiviral applications, novel CQDs have been developed with good biocompatibility and antiviral activity. Currently, promising CQDs were prepared by the hydrothermal treatment and modified with functionalization to their surface sites in order to exhibit potent antiviral activity [168-170]. However, the detailed procedures of the antiviral activity of these CQDs still need to be further clarified, and also the cellular response to them is unrevealed [34].

Ju *et al*. 2020 have prepared the carbon quantum dots combining poly (ethylenimine) and citric acid using microwave-assisted pyrolysis and the as-prepared CQDs were conjugated with locked nucleic acid (LNA) as shown on Fig 1[171]. It was found that the inhibitory effects of viral miRNAs by green carbon quantum dots-interposed delivery of locked nucleic acid (CQDs-LNA)-base inhibitors suppress the reproduction of KSHV (Kaposi's sarcoma-associated herpesvirus)-related initial effusion lymphoma (PEL) cells [171].

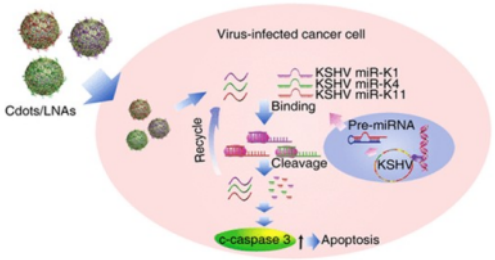

Fig. 1: The graphical abstract design of viral microRNAs inhibition by carbon quantum dots-interposed drug-loading of locked nucleic acids (CQDs-LNA) for viral therapy. Reproduced with the permission from reference [171].

Tong *et al*. 2020 [172], reported the glycyrrhizin acid-based carbon dots (Gly-CDs) prepared from Chinese herbal medicine by a hydrothermal treatment. The result showed that Gly-CDs can inhibit the porcine propagation and respiratory syndrome virus (PPRSV) invasion and reproduction, stimulating antiviral innate immune systems. The cell viability of both Vero cells and PK-cells makes them possible to use in biomedical fields because the mean percentage of their proliferation rate is above 80% (Fig 2a). They also inhibited the aggregation of intracellular reactive oxygen species (ROS) affected by PRRSV infection as indicated in Fig 2b, attributing a potential agent for alternative theranostics of PRRSV contagion [172].

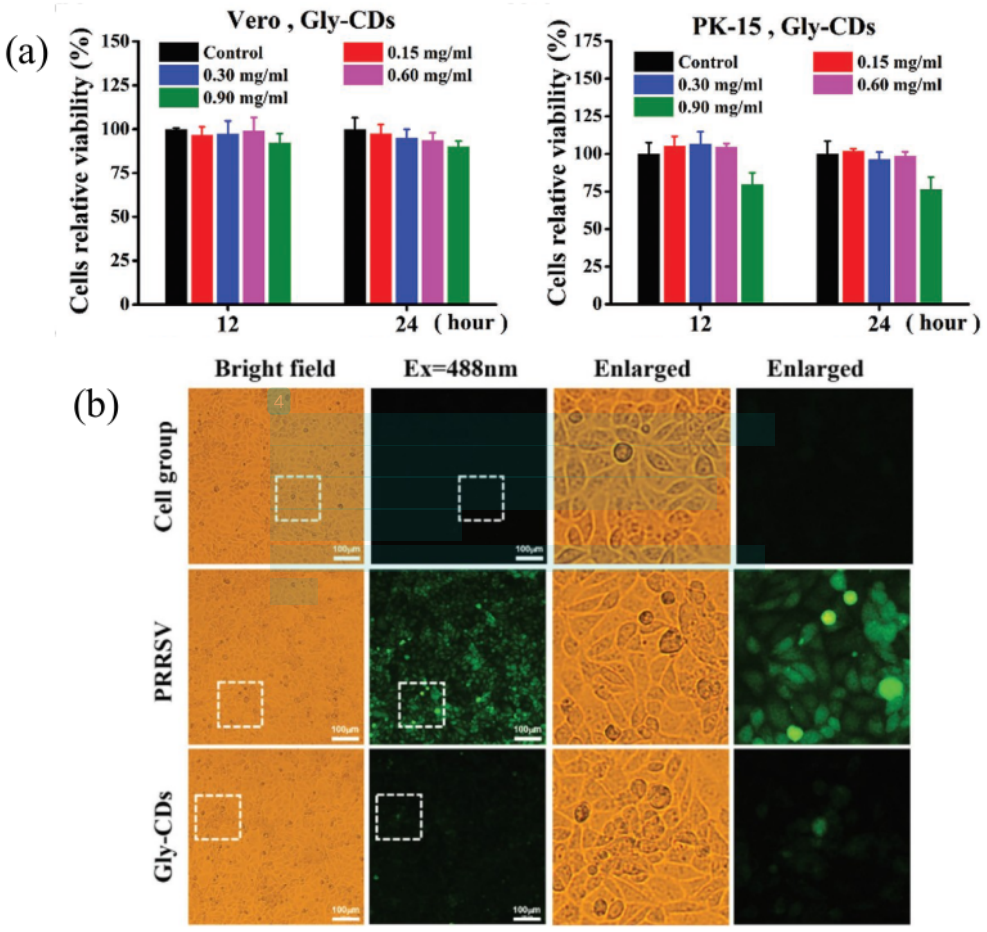

Fig. 2: (a) The broad-spectrum antiviral efficiency of Gly-CDs. The incubation of both Vero and PK-15 cells individually with Gly-CDs at different concentrations of 0.15, 0.30, 0.60, and 0.90 mg mL^{-1} for 12 and 24 h. (b) Cellular ROS levels in PPRSV (porcine propagation and respiratory syndrome virus)-infected MARC-145 cells post different treatments. The cell group showed normal cells with no contact by both Gly-CDs and PRRSV. The mock group exhibited the PRRSV-infected cells in the absence of Gly-CDs treatment. Gly-CDs group indicated the PRRSV-infected cells medicated with Gly-CDs. Scale bar = 100 μm. Reprinted with the permission from reference [172].

Another study reported by Huang *et al.* is the outstanding CQDs synthesized from a series of benzoxazine monomer (BZM-CQDs) and showed their virus-blocking activity in case of death-dealing flaviviruses (Japanese encephalitis, dengue viruses, and Zika) and a kind of non-enveloped viruses (porcine parvovirus and adenovirus-correlated virus) *in vitro* as shown on Fig 3 [168]. They found that BZM-CDs could immediately adhere to the virion surface, and finally, the initiative of virus-cell interconnection was destroyed and it was believed that the BZM-CDs could contribute to a fascinating broad-spectrum technique to suppress viral infections [168].

Hence, the CQDs or GQDs are one of the potential and efficient platforms for viral therapeutics and they would also be alternative antiviral prevention and treatment agents for HIV in the future, upgrading a new and upcoming development of nanomedicine with huge potential in the field of viral theranostics.

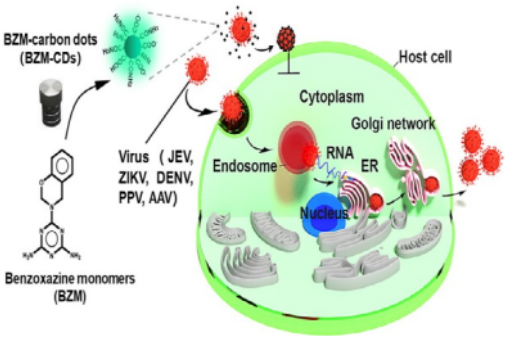

Fig. 3: The graphical abstract framework of prepared BZM-Carbon dots to block viral infectivity. Reproduced with the permission from reference [168].

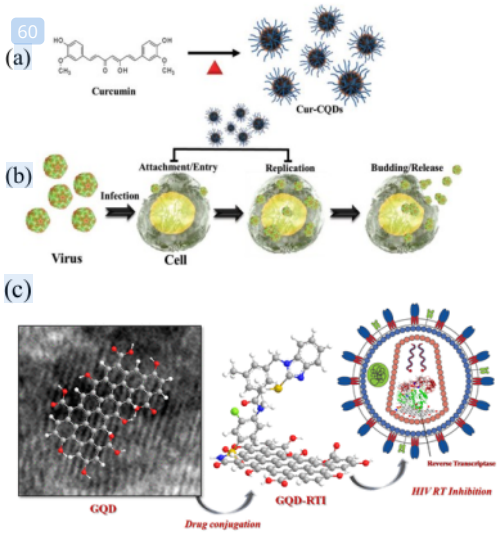

Fig. 4: (a) The schematic diagram of the one-step synthesis of Cur-CQDs [173], (b) their abstract framework of the antiviral application system, and (c) The RTIs (reverse transcriptase inhibitors)-conjugated compound GQDs as a promising candidate for HIV treatment [31]. Reprinted with the permission from represented references.

Carbon Quantum Dots' Antiviral Functions

The modified CQDs have been recently recognized as a cost-effective therapeutic strategy to exert a modifying or controlling influence on viral attachment and entry. The highly-concentrated and propagated ligands that exist on the surface of nanostructures can noticeably improve affinities toward multiple biological receptors [41, 174].

Virus-cell interactions primarily include the event that the viruses firstly attach and adsorb to biological receptors of the host cell, and then penetrated the cell and replicated. The viral envelope mediates the binding of HSV-1 to cells. Inhibiting this adsorption mechanism is thus regarded as an effective system to prevent the infection to the cell [175]. Some carbon sources of natural products (curcumin, flavonoids, polyphenol compounds) showed their intrinsic antiviral, antioxidant, anticancer, anti-inflammatory, and antibacterial functions [173]. Ali *et al*. claimed that curcumin prevents HIV-1 contagion from degrading Tat protein and decreasing the Tat-interposed transcription of the toll-like receptor (TLR) promoter [176]. Since they are poorly water-insoluble in physiological media and low bioavailability *in vivo* system, the direct usage of the pure natural products to cell lines is limited. Thus, it requires using the sustainable, safe, and effective alternative like natural products transformation into CQDs are required to enhance solubility, bioavailability, and antiviral and cancer staining mode of action as well [177, 178]. Like those sustainable nano-based antiviral agents, scientific researchers have investigated so far, as potential alternatives to treat viruses or diseases due to their unique biological properties, morphological characteristics (e.g. controllable size, structure), and physicochemical characteristics, which significantly differs from those of conventional small-molecule dyes or drugs. Among different nano-based materials, silver nanoparticles (AgNPs) have considerably received the commercial interest due to their higher intrinsic virtues and several investigations have approved that AgNPs have strong antiviral activities against multiple viruses, for example, human immunodeficiency virus (HIV), H_1N_1 influenza virus, herpes simplex virus (HSV) and so on [179].

However, silver/ gold nanoparticles are not guaranteed, regarding the cytotoxic safety to human cells. They are being evaluated before the use of those metal-based nanoparticles to theranostics enhancement, in case that the underlying long-term sequelae would be affected after post-treatment [70, 180]. Therefore, nano-antibiotics based on non-metallic nanoparticles or sustainable nanomaterials have widely drawn great interest owing to their solubility, safety, bioavailability, and synergistic antiviral effect. Both the promising investigations of semiconductor CQDs and sustainable or green carbon quantum dots for the antiviral activity were tabulated on Table-4.

Table-4: Carbon Quantum Dots Developed For Antiviral Activity.

Source or Name of CQDs	Bioconjucat-ed Agents/Method	Characteristics (Size, Morphology, Toxicity, and IC_{50})	Cells/Viru-s	Purpose	References
PBA-CQDs 3-APBA-CQDs 4-APBA-CQDs	•Hydrothermal carbonization	•Size diameters = 332±60 nm, 55 ±1nm, 96 ± 1nm, respectively •Zeta potential =−27.0 ± 6mV,−37±1mV,−41± 1mV, respectively •Cell viability = 67%, 95%, 97% •IC_{50} = 80 and 145 ng/mL^{-1}	•A549 Cells & Vero Cells/ •HSV-1	•To block viral attachment and entry.	[41]
CCM-CQDs	Citric acid/ A simple one-step pyrolysis method	•Particle sizes = 1.5 ± 0.3 nm, and zeta potential is 15.6 ± 2.05 mV. •Cell viability = 90%	•Vero cells/ •Coronavirus	•To inhibit the viral entry •To prevent budding of negative-strand RNA in virus.	[181]
Young barley leaves' powders B-CQDs	Citric acid/ Hydrothermal treatment	•Average diameter in size = 1.9 nm •Cell viability = over 85%	•Hela cells & PK-15 cells/ •Pseudorabies virus (PRV)	•To evaluate bioimaging and antiviral activities	[170]
Citric acid modified by boronic acid CQDS	Carboxyl phenylboronic acid (CBBA)/ Pyrolysis	•Diameter = 2.8 nm - 6.2 nm, zeta potential = 55.4 ±8.2 •Cell viability = < 80% •IC_{50} = 9506.3 and 26.7 µg/mL	•MT4 and MOLT-4 cells/ •HIV-1	•To inhibit HIV infection	[42]
BZM-CQDs	Hydrothermal method	•Mean size = 4.4 ± 0.6 nm •Cell viability = >80%	•BHK-21 Cells & Vero cells/ •Flaviviruses	•To block the viral infection	[168]
Curcumin	Apotransferrin NPs (Nano-curcumin) Sol-oil chemistry method	• Curcumin-loaded NPssize = 55– 70 nm •GI_{50} = 32.5 mM •IC_{50} =1.75 mM	•SUPT1 cells or stimulated PBMCs/ •HIV-1	•To inhibit HIV-1 propagation is targeted to viral cDNA synthesis.	[182]
Graphene oxide (GO)	-	•Particle size = 0.9 nm to 2.7 nm •Cell viability = <100%	•Neuroblasto-ma cells & T cells/ •HIV-1	•To reduce Virus protein R (Vpr)	[163]
AgNPs	Tannic acid	•Particle size = 33 nm •CC_{50} = 40.5 ± 6.5 •EC_{50} = 1.52 ± 0.18	•African green monkey kidney (GMK-AH1) cells / •HSV-1	•To suppress HSV-2 infectivity both *in vitro* and *in vivo*	[183]
Ethylenediam-ine + citric acid (CQDs)	Boronic acid/ Hydrothermal carbonization	•Particle size = 6.5 ± 0.2 •EC_{50} = 52 ± 8 µg mL^{-1}	•Huh-7 cells/ •HCoV	•To inhibit viral replication.	[174]
Citric acid and ethylene diamine (CQDs)	Streptavidin/Hy-drothermal thermal treatment	•Particle size = 4 – 5nm	•HIV-1	•To determine HIV-1 p24 antigen on developed Whatman filter paper and nitrocellulose paper	[184]
Cur-CQDs	Pyrolysis	•Mean diameters = 4.8 ± 0.8 •CC_{50} = 452.2 µg mL^{-1} •EC_{50} = 0.2 µg mL^{-1}	•RD cells/ •EV71	•To inhibit EV71 infection	[173]
Ritonavir-loaded NPs	Conjugated with TAT-peptide An emulsion-solvent evaporation technique	•Mean size=157 ± 8.9 •Zeta potential =+2.4 ± 0.3	•MDCK-MDR1 and MDCK-wt cells -	•To deliver the TAT-conjugated NPs in the CNS to inhibit replicating HIV-1 virus	[185]

Abbreviation: PBA, 4-phenylboronic acid; **3-APBA**, 3-aminophenylboronic acid; **4-APBA**, 4-aminophenylboronic acid hydrochloride; **PBMCs**, peripheral blood mononuclear cells; **CCM-CQDs**, cationic curcumin-based carbon quantum dots; **BZM-CQDs**, benzoxamine-based carbon quantum dots; **Cur-CQDs**, curcumin-based carbon quantum dots.

The collected articles have proven the satisfactory efficiency of carbon dots-based antiviral agents derived from molecules, compounds, combining complex nano-substances. Also, some of promising articles representing the antiviral activity of facile prepared-carbon dots with surface modification or conjugation are explained. The above-mentioned published research mostly explained the viral inhibition, and thus the cycle of virus affected by the antiviral activity from carbon-based dots nanomaterials. Therefore, there would be deduced from the above results, it is specifically clarified that carbon dots-based antiviral agents from curcumin-based carbon dots exhibited great ability against RNA viruses. Moreover, it is noticeable that surface modification or functionalization also

enhanced the efficiency of carbon dots antiviral agents.

Nano-Vaccines in HIV Prevention

To reduce infectious disease transmission, appropriate methods are required, depending on the nature of the disease and mode action of transmission. For example, vaccination is required for some diseases, which completely inhibits the illness such as polio and measles [29]. Hence, both prophylactic and therapeutic systems have been applied by nanovaccinology. They can make it possible to enhance the bodily immune response to antigen mode of action or used as an immunostimulatory adjuvant [186]. A prophylactic HIV vaccine is normally regarded as the anticipating one to suspend the movement of the AIDS pandemic; but the improvement of the simple, safe, and efficient HIV-1 vaccine is still in unknown condition [187]. Recently, there has been studied in Thailand to assess a prime-boost regimen of ALVAC HIV, and this canarypox virus vector can help HIV *env*, *gag*, and *pro* genes express, thereby stimulating with AIDSVAX, a recombinant envelope gp120 protein. Eventually, great efficacy was partially exhibited in inhibiting accretion of HIV. Despite good results of this investigation for vaccinology development in the future, new concepts remain to be further approved [188, 189].

The advantages of prophylactic HIV-1 vaccination preparation by using nanoparticles involve safety description provided by the usefulness of biocompatible biomaterials as well as vaccine dose titration; prohibition of HIV-1 antigens from being degradable enzyme dynamics, in this way, enhancing the *in vivo* stability of immunogens and their interactions with antigen-presenting cells (APCs) [190]. And hence, the targeting to APC-enriched lymphoid tissues, the phagocytosis, and the processing of HIV-1 antigens would be improved. Moreover, the smaller sizes of the nanoparticles are considered as one of the vaccine-delivery benefits because these used nanoparticles are as small as expressing viruses and bacteria which are easily identified by the immune system [191].

There are urgently two important issues to develop the HIV vaccine methodology, namely: innovating design and producing immunogens. The very effective immunogen design has hardly been confirmed because of various evasion pathways and the lifecycle of HIV. Within each HIV subtype, the amino acid series of the envelope glycoprotein (Env), which occupies the virion surface, change from 4 to 30%, while the amino acid sequences from the HIV subtype to subtype can vary from 20 to 36% [188].

The promising vaccine studies associating with nanotechnology are described as follows. The most suited and recent improvements in the vaccine delivery technologies for HIV vaccination including nanocarrier-based strategies are

(1) Live vaccine vectors for vaccination against HIV-1,
(2) Next-generation HIV-1 immunogens for eliciting bNAb responses,
(3) Self-assembling 'virus-like' nanoparticles for the presentation of HIV-1 antigens, and
(4) siRNA-based nanotherapeutics to inhibit HIV-1 infection [188, 192].

Despite the successful developments of many vaccines against polio, measles, mumps, rubella, and yellow fever worldwide, the performance of this innovative approach does not suit for HIV-1 because of its virulence and high mutation rate. As a first alternative strategy, live-vector-based vaccines use genetically weak pathogens to exert viral antigens, vitalizing the host immune system. Benlahrech *et al*. 2009 have reported that among vaccines with pre-existing immunity to Ad5, vaccination enhanced activation of Ad5-specific memory T cells and their consequent trafficking to mucosal tissues, thus accidentally facilitating a high frequency of target CD4+ T cells at the local site of HIV-1 entry [193].

An additional another point of the vaccine of HIV immunogens receives the optimal results from the RV144 Phase III trial. The trial proposed that the modest inhibition explored was from V1V2-specific antibodies, a region of HIV-1 gp120 involving unprotected surface areas regarded by bNAbs, such as PG9. While HIV-1 immunogens will need to be continuously improving and exploring, their vaccine delivery systems will make sure to enhance the immunity, inhibiting the immunogen in the absence of obstructing the key epitopes [194].

Moreover, self-assembling nature into nanoparticles imitates virus-like particles for the multivalent exhibition of Env-based immunogens, including germline targeting gp120 outer domains, Clade C ZM109-based V1V2 domain trimers, BG505 gp120 trimers, and BG505-SOSIP gp140 modelled trimers [195].

Contrary to self-assembling "virus-like" nanoparticles, synthetic polymer-based nanoparticles, and liposome-based nanovesicles provide adaptable acting technologies that can influence strong versatile immune responses while keeping away from antivectorial immunity and toxicity problems. For example, polymeric nanoparticles relied on biodegradable and biocompatible poly (lactic-co-glycolic) acid (PLGA) copolymer that has been widely investigated for vaccine delivery use. Kasturi *et al*. 2011 have smartly reported that PLGA nanoparticles co-loaded with TLR4 and TLR7/8 agonists can co-actively standardize the inauguration of antigen-specific antibody responses in nonhuman primates (NHPs) via activating germinal center and plasma cell responses in lymphoid tissues. These findings provided the adaptability of PLGA particle methods for the fast-loading mode of peptide antigens and adjuvants. The designing framework and synthetic method of polymeric particle vaccines have been elegantly advanced above; there remain a lot of challenges to obtain a suited multivalent presentation of complex immunogens, such as Env trimers, in their native composition from polymeric particles [196].

Another alternative HIV-1 vaccine strategy is siRNA-based nanotherapeutics, compressing CD4, and co-receptor CCR5 [197]. Kim *et al*. 2010 have prepared the development of liposomes decorated with antibodies against LFA-1, an integrin sit on leukocytes. Those LFA-1-targeted liposomes conveyed siRNA against CCR5, bringing abouta significant reduction in CCR5 mRNA levels among leukocytes for 10 days, which would label the transient effect of siRNA-based therapeutics and control long-term immunity against HIV-1 [1].

Conclusion

In summary, highly active antiretroviral theranostics, nano-theranostics, carbon quantum dots-based theranostics, and nano-vaccine therapy approaches for HIV or other viruses have been presented systemically in this review. Those approaches have had promising or advantageous effects on virus inhibition and treatment, whereas a few drawbacks have been challenging.

Due to the deadly multiple viruses, especially HIV/AIDS infection to human societies around the world especially to the developing countries at pandemic levels, scientific researchers have approached to explore new strategic prevention and treatments to eradicate those diseases. Various forms of nanocarriers (efficient drug-loading capability) have been needed to increase the potential delivery of antiretroviral drugs for HIV remedy so that the complicated issues of both the HIV infection cycle and the targets for delivery of drugs could be overcome. Meanwhile, scientific researchers have been looking for new ways to find the novelty of promising results. In regard to promising drug delivery systems, nano-based polymeric or inorganic materials play a significant role in numerous models ranging from *in vitro* to *in vivo* as nanocarriers.

Moreover, carbon-based nanomaterials, carbon quantum dots are also promising for HIV prevention and treatment. However, coating with different types of ligands is to better inhibit viruses [174]. Also, CQDs could significantly improve the merits of targeting and long-lasting mode of action only when their surface sites get modified with selected functional groups for better surface modification [198]. To be as low as toxic, green or sustainable carbon nanodots, intrinsic antiviral properties are also necessary for nano-delivery systems to increase the drug's capability and reduce the side effects.

As the nano-vaccine aspect, to further develop nanotechnology-based vaccines might require to keep targeting on the immunologic description of antigens preservation, immune cells of interest, and the system of administration optimization so as to fabricate a successful vaccine.

Taken all together, to have good patient adherence to treatment or excellent aqueous solubility, to achieve safe and better drug delivery nanocarriers, to obtain the high antiviral mode of action response, and to get a successful HIV-1 vaccine expanding immunogen arsenal are still demanded to pursue consistent clinical improvements for patients.

Conflict of interest

The authors declare no conflict of interest in the present study.

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