



Nanotechnology in COVID-19 and SARS-CoV-2: Advances in Antiviral Therapies and Applications

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Innovative diagnostics, therapeutics, and preventive strategies must be developed to combat the emergence of new viral pathogens and the resurgence of known viruses. Using nanotechnology to enhance antiviral therapeutic efficacy through improved drug delivery, targeted viral inhibition, and immune modulation has emerged as a transformative approach to addressing these viral threats. SARS-CoV-2, hemorrhagic viruses, and zoonotic pathogens can be combated with nanotechnology-based platforms, including nanogels, dendrimers, and metal-based nanoparticles. As a result of recent advances in nanoparticle engineering, "smart" systems can respond to viral infection markers, deliver therapeutics to specific sites, and control drug release profiles. Using

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nanotechnology to develop vaccines, such as mRNA vaccines for COVID-19, can enhance immune responses and accelerate vaccine rollout. Additionally, multifunctional nanomaterials enable early and accurate detection of viral pathogens using antiviral diagnostics. As well as discussing advances in addressing viral resistance, this review examines theranostic applications, integrating diagnostic and therapeutic functionalities within single nanostructures. This study highlights the potential for nanomedicine to revolutionize antiviral therapies, improve treatment outcomes, and develop rapid-response solutions to future viral threats by examining the recent applications of nanotechnology in viral disease management.

Keywords: *Nanoparticles; antiviral agents; nanotechnology; drug delivery systems.*

1. INTRODUCTION

1.1 Epidemiology of Viral Infections

It is estimated that millions of individuals worldwide are affected by viral infections each year across a wide range of demographic and geographic groups. Viral diseases are associated with substantial morbidity and mortality rates worldwide, including acute infections and chronic conditions. Approximately 25-30% of all infectious disease cases worldwide are caused by viral infections, with particularly severe impacts in resource-limited settings. There are distinct patterns of transmission and prevalence of these infections across different regions, influenced by factors such as population density, healthcare infrastructure, and socioeconomic conditions (Shaik et al., 2021).

There are marked disparities in the incidence and severity of viral diseases worldwide. While seasonal respiratory viruses and chronic infections mostly plague high-income countries, low- and middle-income countries face an additional burden of endemic viral diseases and frequent outbreaks. According to epidemiological surveillance data, vector-borne viral infections have spread into previously unaffected areas and drug-resistant viral strains have emerged in clinical settings. Globally, viral infections are estimated to cost \$570 billion in healthcare expenses and lost productivity annually, primarily affecting working-age populations in developing economies (Baker et al., 2022).

The demographics of a population play a crucial role in the susceptibility and outcome of viral diseases, with certain populations more susceptible to certain virus pathogens than others. In addition to having higher morbidity rates and more severe clinical manifestations, children under five years of age, the elderly, and immunocompromised patients represent high-risk groups. International travel and urbanization

have also contributed to the spread of viral infections due to the interconnected nature of modern society. A recent mathematical modelling study suggests that the rate of viral disease emergence has increased by approximately 40% over the past two decades, which highlights the growing challenge of viral infections in contemporary public health (Bender et al., 2024).

Viral diseases are caused by viruses, which are microscopic infectious agents that can only replicate inside the living cells of hosts. Unlike bacterial infections, which can often be treated with antibiotics, viral diseases are usually managed through supportive care, antiviral medications, or vaccines. Viruses are classified based on their structure, genetic material, and mode of replication, leading to a wide array of diseases, some of which can be severe and even fatal.

SARS-CoV-2 (COVID-19):

- **Cause:** SARS-CoV-2 is a novel coronavirus that emerged in late 2019 and is responsible for the COVID-19 pandemic.
- **Transmission:** It spreads primarily through respiratory droplets when an infected person coughs, sneezes, talks, or breathes. It can also spread via contaminated surfaces.
- **Symptoms:** Common symptoms include fever, cough, fatigue, loss of taste or smell, and difficulty breathing. Severe cases can result in pneumonia and complications leading to death.
- **Prevention and Treatment:** Vaccines have been developed to reduce transmission and severity. Treatments include antiviral medications and supportive care for severe cases.

Zika Virus:

- **Cause:** The Zika virus is primarily transmitted to humans through the bite of

infected *Aedes* mosquitoes, especially *Aedes aegypti*.

- Symptoms: Many infected individuals are asymptomatic; however, the disease can cause mild symptoms such as fever, rash, joint pain, and conjunctivitis. A critical concern is its association with severe birth defects (microcephaly) when pregnant women are infected.
- Transmission: Besides mosquitoes, Zika can also be transmitted through sexual contact, and from mother to child during pregnancy or childbirth.
- Prevention and Treatment: There is no specific antiviral treatment; prevention focuses on avoiding mosquito bites and providing public health education.

Ebola Virus Disease (EVD):

- Cause: EVD is caused by several species of the Ebola virus, with the Zaire species being the most virulent.
- Transmission: Ebola spreads through direct contact with bodily fluids of infected individuals or with objects contaminated with these fluids. It can also be transmitted through infected animals (like fruit bats).
- Symptoms: Symptoms typically appear 2 to 21 days after exposure and include fever, severe headache, muscle pain, weakness, fatigue, diarrhea, vomiting, and unexplained hemorrhaging.
- Prevention and Treatment: There is no specific treatment for Ebola; however, supportive care is critical. Vaccines have been developed and are used to control outbreaks.

1.2 Emerging and Re-emerging Viruses

Viruses are dynamically evolving and adapting, resulting in the continuous emergence of new viral threats and the resurgence of previously controlled diseases. COVID-19, caused by SARS-CoV-2, illustrates the potential impact of emerging viruses on global health systems and economies. Also, Zika, Ebola, and various influenza strains have re-emerged, highlighting the need for improved therapeutic strategies. The emergence and spread of viral pathogens have been accelerated by climate change, global mobility, and environmental factors. In the face of these factors, viral disease management faces unprecedented challenges, necessitating innovative approaches to prevention and treatment (Hakim et al., 2024).

Viral emergence and re-emergence are complex and multifaceted processes, involving both viral evolution and environmental factors. Through high mutation rates and genetic recombination events, RNA viruses, in particular, exhibit remarkable adaptability. Several molecular mechanisms have been implicated in cross-species transmission, including adaptive mutations in viral surface proteins and enhanced receptor binding abilities. With approximately 60% of emerging infectious diseases originating from animal reservoirs, the spillover of zoonotic viruses into human populations continues to pose significant challenges. There has been an increase in the number of novel coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2), highly pathogenic avian influenza strains, and hemorrhagic fever viruses in the past few decades (Choi, 2021).

Recent years have seen an increase in the impact of anthropogenic factors on viral emergence. Deforestation, urbanization, and changes in land use patterns have intensified human-animal contact, creating new opportunities for viral transmission. As a result of global warming, previously tropical viruses have established themselves in temperate regions. *Aedes* mosquito habitat expansion has facilitated the spread of dengue, chikungunya, and Zika viruses into new areas. As evidenced by the rapid spread of SARS-CoV-2 variants worldwide, the interconnectedness of modern society has shortened the time between local outbreaks and global spread. In addition to these challenges, antiviral resistance is emerging, especially in chronic viral infections such as HIV, hepatitis B, and herpes viruses, which necessitates the development of novel therapeutic approaches for addressing both current and future viral threats (Theijeswini et al., 2024; Anikeeva et al., 2024).

Antiviral therapies are designed to inhibit the replication and spread of viruses. They function through various mechanisms, depending on the type of virus and the specific antiviral agent. Here's an overview of both traditional antiviral therapies and newer nanoparticle-based solutions:

1.3 Traditional Antiviral Mechanisms

1. Inhibition of Viral Entry

- Mechanism: Some antivirals block the virus from entering host cells. For instance, certain fusion inhibitors prevent the viral envelope from merging with the host cell membrane.

- Examples: Enfuvirtide for HIV operates by blocking the fusion of the virus with the host cell membrane.

2. Reverse Transcriptase Inhibitors

- Mechanism: These agents inhibit reverse transcriptase, an enzyme crucial for converting viral RNA into DNA, which allows viruses (like HIV) to integrate into host cell DNA.

- Examples: Zidovudine (AZT) is a well-known reverse transcriptase inhibitor used in HIV treatment.

3. Protease Inhibitors

- Mechanism: These antivirals inhibit viral proteases, enzymes that are essential for viral protein processing and maturation after the virus replicates within the host cell.

- Examples: Drugs like lopinavir and ritonavir are used to treat HIV by blocking protease activity.

4. Nucleotide and Nucleoside Analogues

- Mechanism: These compounds mimic the building blocks of viral nucleic acids (DNA or RNA). When incorporated into the viral genome, they disrupt replication.

- Examples: Acyclovir is a nucleoside analogue used to treat herpes virus infections by inhibiting viral DNA synthesis.

5. Interferons

- Mechanism: Interferons are proteins produced by host cells in response to viral infections. They boost the immune response and inhibit viral replication.

- Examples: Interferon-alpha is used for treating chronic hepatitis B and C infections.

1.4 Nanoparticle-Based Solutions

Nanoparticle-based antiviral therapies represent a cutting-edge approach in treating viral infections:

1. Targeted Delivery

- Mechanism: Nanoparticles can be engineered to deliver antiviral agents specifically to infected cells, increasing therapeutic efficacy while minimizing side effects.

- Examples: Lipid nanoparticles are used in mRNA vaccine delivery, like the Pfizer-BioNTech and Moderna COVID-19 vaccines, which help prompt an immune response against the virus.

2. Direct Viral Inhibition:

- Mechanism: Some nanoparticles can directly interact with viral particles to neutralize them. This can be achieved through physical mechanisms (e.g., altering the viral structure) or

chemical interactions that impede the virus's ability to infect cells.

- Examples: Gold nanoparticles have shown promise in lab settings by binding to viral proteins, rendering them inactive.

3. Modulation of Immune Response:

- Mechanism: Nanoparticles can be designed to stimulate the immune system, enhancing the body's natural antiviral defenses. They can act as adjuvants, boosting the effectiveness of vaccines or other therapies.

- Examples: Virus-like particle (VLP) vaccines mimic the structure of viruses but are non-infectious; they provoke an immune response without the associated disease.

2. LIMITATIONS OF CURRENT ANTIVIRAL THERAPIES

2.1 Antiviral Drug Resistance

Viral infections are difficult to treat effectively because of the development of antiviral drug resistance. Virus mutations and adaptive mechanisms often reduce the efficacy of conventional antiviral medications. HIV, influenza viruses, and herpes viruses frequently develop resistance to first-line therapeutics, necessitating the development of alternative treatment strategies (Amponsah and Tagoe, 2023). In particular, maintaining therapeutic effectiveness is challenging due to the rapid mutation rates of RNA viruses. Multiple mechanisms of resistance development have been revealed by molecular studies, including mutations in viral enzymes that alter drug binding sites, changes in viral surface proteins that affect drug entry, and escape mutants that evade immune responses enhanced by antiviral treatment (Kumari et al., 2022).

2.2 Pharmacokinetic and Bioavailability Challenges

The pharmacokinetic properties and bioavailability profiles of traditional antiviral drugs are severely limited, which adversely affect their therapeutic efficacy. Several antiviral compounds exhibit poor solubility, limited cellular uptake, and suboptimal tissue distribution patterns, resulting in lower concentrations at viral target sites (Amponsah and Tagoe, 2023; Gerhart et al., 2024). In the treatment of viral infections of the central nervous system, the blood-brain barrier presents a particular challenge, as most conventional antivirals have limited penetration

into neural tissue. A short half-life of many antiviral drugs necessitates frequent dosing regimens, which can result in decreased patient compliance and resistance. It has been reported that up to 40% of antiviral candidates fail in clinical trials because of unfavorable pharmacokinetic profiles (Kumawat et al., 2024).

2.3 Adverse Effects and Therapeutic Index

Current antiviral therapies are limited by their narrow therapeutic window and significant adverse effects. The liver, kidneys, and bone marrow are among the organs affected by antiviral drugs that exhibit dose-dependent toxicity. Chronic viral infections are particularly vulnerable to long-term antiviral therapy. Managing therapeutic drug levels while minimizing adverse effects is particularly challenging for vulnerable populations, such as pediatric patients, the elderly, and those with compromised immune systems. According to clinical data, about 15-20% of patients receiving long-term antiviral therapy discontinue treatment due to adverse effects, underscoring the need for more targeted and better-tolerated therapeutic approaches. As a result of drug-drug interactions, patients requiring multiple medications face significant challenges, particularly in the context of HIV treatment and organ transplant recipients, where complex drug regimens are common (Garg et al., 2024; Lieber et al., 2024).

2.4 Limited Spectrum of Activity

Most antiviral drugs have a narrow spectrum of antiviral activity due to their highly specific nature. Since these drugs are specific, they cannot be used in emerging viral infections or situations where rapid therapeutic intervention is essential. It has proven challenging to develop broad-spectrum antivirals due to the diversity of viral replication mechanisms and the need to maintain specificity for viral over host processes. When novel or emerging pathogens are responsible for viral outbreaks, existing antiviral therapies may prove ineffective or require significant modification for therapeutic use (Karim et al., 2023).

2.5 Challenges with Conventional Therapeutics

Traditional antiviral therapeutics face multiple limitations that impact their clinical efficacy. These include:

- Poor bioavailability and limited tissue penetration

- Unfavorable pharmacokinetic profiles
- Significant adverse effects and toxicity
- Limited spectrum of activity
- High production costs and accessibility issues

These challenges have prompted researchers to explore novel therapeutic approaches that can overcome these limitations (Baker et al., 2022).

3. THE ROLE OF NANOTECHNOLOGY IN ANTIVIRAL STRATEGIES

3.1 Definition and Scope of Nanotechnology

In nanotechnology, matter is manipulated at the nanoscale (1-100 nm) to create new materials and devices. Nanotechnology presents unprecedented opportunities for developing more effective antiviral treatment strategies. In this field, principles from materials science, engineering, and biomedicine are integrated to create innovative therapeutic platforms (Yasamineh et al., 2022).

3.2 Importance in Drug Development and Delivery

To address the limitations of conventional antiviral therapies, nanotechnology-based approaches have emerged as promising solutions. There are several advantages to these systems:

- Improved solubility and bioavailability of drugs
- Delivered to specific tissues or compartments within the body
- Controlled release profiles for optimal therapeutic effects
- Reduced side effects through precise targeting
- Potential for multiple drug loading and combination therapy

Advances in nanocarrier design have significantly improved antiviral drug delivery efficiency and therapeutic outcomes. As a result of their versatility and unique physicochemical properties, nanomaterials can be developed into multifunctional platforms that can address multiple antiviral challenges at the same time. Nanotechnology provides potential solutions to overcome the limitations of conventional treatments while offering new opportunities to

combat emerging viral threats through the integration of antiviral strategies. Nanotechnology-based antiviral therapies are explored in this review, highlighting their potential impact on the future of viral disease management (Chakravarty and Vora, 2021; Sharifi et al., 2023).

4. NANOTECHNOLOGY-BASED ANTIVIRAL PLATFORMS

4.1 Nanoparticles (NPs)

Metal-Based Nanoparticles: Metal-based nanoparticles are proving to be powerful antiviral agents, exhibiting unique physicochemical properties and diverse mechanisms of action. Several mechanisms, including disruption of viral membranes and interference with viral attachment processes, are responsible for the remarkable antiviral activity of silver nanoparticles (AgNPs). A variety of viral pathogens are effectively inhibited by AgNPs, including influenza, herpes simplex virus, and several respiratory viruses (Chakravarty and Vora, 2021).

Due to their exceptional biocompatibility and versatility in surface functionalization, gold nanoparticles (AuNPs) have attracted significant attention. Their plasmonic properties make them suitable for both therapeutic and diagnostic applications, particularly in photothermal antiviral therapy. By directly interacting with viral proteins, zinc oxide nanoparticles (ZnO-NPs) exhibit promising antiviral activity (Nasrollahzadeh et al., 2020).

Carbon-Based Nanomaterials: Antiviral therapeutic approaches have been revolutionized by carbon-based nanomaterials, including graphene and its derivatives. The inherent antiviral properties of graphene oxide (GO) can be explained as follows:

- Physical viral inactivation via sharp edges
- Chemical interactions with viral proteins
- Enhanced drug delivery capabilities

Due to their high aspect ratio and surface area, carbon nanotubes (CNTs) are capable of delivering drugs and targeting viruses efficiently (Innocenzi and Stagi, 2020).

Polymeric Nanoparticles: Polymeric nanoparticles represent a versatile class of delivery systems, offering controlled release

properties and enhanced stability. Natural and synthetic polymers, including:

- Poly(lactic-co-glycolic acid) (PLGA)
- Chitosan
- Polyethylenimine (PEI)
- Poly(ϵ -caprolactone) (PCL)

have been extensively studied for antiviral applications. These systems demonstrate superior drug encapsulation efficiency and controlled release profiles, significantly improving therapeutic outcomes (Spirescu et al., 2021).

4.2 Lipid-Based Nanocarriers

Liposomes: Liposomes have emerged as prominent drug delivery vehicles due to their biomimetic nature and versatile structure. These phospholipid-based vesicles offer:

Enhanced drug solubility and bioavailability
Reduced toxicity through targeted delivery
Protection of therapeutic cargo from degradation
Cellular uptake enhancement

Recent advances in liposomal technology have led to the development of pH-sensitive and stimuli-responsive systems, enabling controlled drug release at specific cellular locations (Spirescu et al., 2021).

Solid Lipid Nanoparticles (SLNs): SLNs represent an innovative class of lipid-based carriers composed of physiological lipids that remain solid at body temperature. Their advantages include:

- Enhanced stability compared to liposomes
- Controlled drug release properties
- Cost-effective scalable production
- Improved drug protection

Studies have demonstrated successful incorporation of various antiviral agents into SLNs, resulting in enhanced therapeutic efficacy and reduced side effects (Scioli Montoto et al., 2020).

Nanostructured Lipid Carriers (NLCs): NLCs, the second generation of lipid nanocarriers, address several limitations of SLNs through their unique structure combining solid and liquid lipids. This hybrid system offers:

- Increased drug loading capacity
- Enhanced stability during storage

- Improved drug release profiles
- Better biocompatibility

Recent studies have shown promising results in delivering antiviral drugs using NLCs, particularly for treating respiratory viral infections (Ghasemiyeh and Mohammadi-Samani, 2018).

5. NANOGELS AND DENDRIMERS

Structure and Properties: Among the many applications of nanogels and dendrimers, antiviral applications are particularly suited to their unique structural features. In addition to their high-water content, nanogels possess a flexible structure that allows them to adapt to physiological conditions, stimuli-responsive behavior enabling targeted drug release, as well as enhanced drug loading capacity through multiple binding mechanisms. Nanogels, derived from cross-linked polymer networks, possess several properties that enhance their therapeutic potential. By using various polymerization and cross-linking techniques, nanogels can be precisely engineered with tailored properties like mesh size, degradation rate, and surface chemistry. Technological advances have enabled the creation of "smart" nanogels that respond to physiological triggers like pH, temperature, or enzyme activity, allowing unprecedented control over drug delivery profiles (Mastella et al., 2024).

In antiviral therapy, dendrimers offer several advantages due to their highly branched, tree-like architecture. Through generational synthesis, they are capable of precisely controlling molecular weight, conjugating and targeting drugs, encapsulating drugs within internal void spaces, and controlling their biodegradability. With each generation, dendrimers have double the number of terminal groups, allowing precise control over size, branching density, and surface chemistry. Several advanced characterization techniques have revealed that higher-generation dendrimers (G4-G7) possess optimal size ranges (4-12 nm) for cellular internalization and structural integrity. In combination with therapy and theragnostic applications, dendrimer surfaces enable simultaneous attachment of multiple therapeutic agents, targeting ligands, and imaging probes, providing versatile platforms (Mauri et al., 2021).

Physicochemical Characteristics and Drug Loading Mechanisms: Nanogels and dendrimers are highly effective in antiviral applications due to their physicochemical

properties and drug-loading mechanisms. Swelling ratios of nanogels in aqueous environments typically range from 10-50 times their dry weight, depending on cross-linking density and polymer composition. In addition to physical entrapment, electrostatic interactions, and chemical conjugation, this property facilitates high drug loading capacity. By modulating nanogel internal structure, lipophilic antiviral drugs can be loaded better while hydrophilic surface properties ensure colloidal stability. By improving circulation time and cellular specificity, surface modification strategies, such as PEGylation, can further enhance their biological performance (Kumar et al., 2024).

Due to their hierarchical structure, dendrimers exhibit unique drug-loading characteristics. In addition to internal cavities (dendroids), the high density of surface groups enables efficient drug conjugation through a variety of chemical bonds. Small molecule antivirals have demonstrated loading capacities of 10-30% w/w, with higher efficiencies achieved by optimizing surface chemistry and generation number. In response to specific biological triggers, such as reduced pH levels in endosomes or increased glutathione levels in cancer cells, dendrimers can be synthesized with stimuli-responsive linkages, enabling targeted drug release. As a result of recent developments in dendrimer chemistry, biodegradable variants have been developed that maintain structural integrity during drug delivery but undergo controlled degradation for safe elimination, addressing concerns about long-term accumulation (Zhang et al., 2018; Zhang et al., 2021).

Therapeutic Potential Against Viruses: Nanogels and dendrimers have been extensively investigated for their antiviral potential, revealing multiple mechanisms of action that enhance their efficacy. The researchers found that multivalent interactions enhanced viral inhibition, improved cellular uptake of antiviral drugs, and reduced viral resistance development. In recent studies, these platforms are effective against a variety of viral pathogens, including HIV, influenza, and hepatitis viruses. These systems have the potential to develop targeted antiviral therapies due to their ability to precisely control their surface chemistry and architecture. These nanostructures can interfere with multiple stages of the viral life cycle, from initial attachment to production of viral progeny (Tang et al., 2019).

Mechanism of Action and Antiviral Efficacy: Multiple mechanisms contribute to the antiviral

activity of nanogels and dendrimers. Multivalent interactions between surface-modified dendrimers and viral envelope proteins have been demonstrated to effectively prevent virus attachment to host cells. Dendrimers functionalized with sialic acid moieties can achieve IC₅₀ values as low as 10 nM against influenza viruses compared with conventional entry inhibitors. The ability of nanogels, especially those incorporating stimuli-responsive elements, to deliver antiviral drugs to specific cellular compartments has been demonstrated to be exceptional. The intracellular concentration of antiviral drugs can be enhanced 10-fold when delivered via nanogel systems. Some studies have reported restoration of drug sensitivity in previously resistant viral populations after physical viral blockade and enhanced drug delivery were combined (Tyssen et al., 2010).

Clinical Applications and Therapeutic Outcomes: Nanogel and dendrimer-based antiviral treatments have shown promising therapeutic potential in recent clinical trials. In phase I and II clinical trials, dendrimer-based topical microbicides have shown significant protection against HIV and HSV infections, with excellent safety profiles and user acceptance. Patients' compliance and treatment outcomes have improved with nanogel formulations containing approved antiviral drugs due to enhanced bioavailability and reduced dosing frequency. Nanogel-delivered entecavir maintained therapeutic drug levels for 72 hours versus 24 hours with conventional formulations in patients with hepatitis B. Furthermore, these systems have shown promise in addressing challenging viral infections, such as those affecting the central nervous system, where conventional drug delivery has significant challenges (Cena-Diez et al., 2016; Maciel et al., 2019).

Emerging Applications and Future Directions: Antiviral therapy development continues to be driven by the versatility of nanogels and dendrimers. In recent years, "smart" systems have been developed that release targeted drugs specifically in infected tissues in response to viral infection markers (Anderson et al., 2042). Theranostic platforms can monitor both viral load and treatment efficacy simultaneously thanks to diagnostic and therapeutic integration. Emerging applications include:

- Dual-targeting systems that simultaneously block viral entry and inhibit replication

- Combination therapy platforms incorporate multiple antiviral agents with different mechanisms of action
- Stimuli-responsive systems that release drugs in response to specific viral proteins or enzymes
- Novel prophylactic formulations for high-risk populations
- Targeted delivery systems for tissue-specific viral infections

Researchers have also begun exploring the potential of these nanostructures in developing broad-spectrum antiviral agents that target multiple viral families using common structural targets (Roberts et al., 2024). These advanced delivery systems are becoming safer and more effective as biodegradable variants and surface chemistry are optimized (Cena-Diez et al., 2016, Rehan et al., 2024).

6. MECHANISMS OF NANOTECHNOLOGY-BASED ANTIVIRAL ACTION

6.1 Inhibition of Viral Entry and Replication

Interference with Viral Surface Proteins: Viral surface proteins are disrupted by nanotechnology-based platforms, a critical mechanism for preventing viral infection. Multiple pathways are involved in this interference:

- Direct Physical Interaction
- Nanoparticles can bind to viral surface glycoproteins
- Conformational changes in viral proteins impair their function
- Physical damage to viral envelope structures

The interaction of metal nanoparticles with viral surface proteins, particularly silver and gold, has been demonstrated in recent studies to render viruses non-infectious. Enhanced binding affinity of surface-modified nanoparticles with specific ligands has been demonstrated to enhance their antiviral efficacy (Galdiero et al., 2011; Luceri et al., 2023).

Blockage of Virus-Host Cell Interactions: In nanotechnology-based antiviral strategies, preventing virus-host cell interactions is critical. Key aspects include:

- Competitive binding to cellular receptors
- Steric hindrance of viral attachment
- Modification of cell membrane properties

It has been demonstrated that functionalized nanoparticles can effectively block ACE2 receptor binding sites, preventing viral entry of SARS-CoV-2 and related viruses. In addition, dendrimers modified with sialic acid have been shown to prevent influenza virus attachment to host cells (Ren et al., 2021; Erkoc and Ulucan-Karnak, 2021).

6.2 Enhancement of Immune Responses

Immunomodulatory Effects: Nanotechnology-based platforms enhance both innate and adaptive immune responses against viral infections. These effects include:

- Activation of Pattern Recognition Receptors (PRRs)
- Stimulation of Toll-like receptors (TLRs)
- Enhancement of cytokine production
- Activation of natural killer (NK) cells
- Modulation of Inflammatory Responses
- Balanced pro- and anti-inflammatory cytokine production
- Prevention of cytokine storm
- Enhanced antigen-presenting cell function

Metal nanoparticles and carbon-based nanomaterials increase type I interferon production. Additionally, polymer-based nanocarriers have been shown to enhance viral clearance by modulating T-cell responses (Khatun et al., 2023).

Use in Vaccination Platforms: Nanotechnology has revolutionized vaccine development and delivery through:

- Advanced Antigen Presentation
- Enhanced stability of vaccine antigens
- Improved cellular uptake
- Controlled release properties
- Adjuvant Properties
- Built-in immunostimulatory effects
- Synergistic enhancement of immune responses
- Reduced need for traditional adjuvants

Recent developments in mRNA vaccine delivery using lipid nanoparticles have demonstrated unprecedented success in generating protective immunity against viral infections. Additionally, virus-like particles (VLPs) engineered at the

nanoscale have shown promise as self-adjuvanting vaccine platforms (Look et al., 2010; Pardi et al., 2018).

6.3 Targeted Drug Delivery Systems

Nanocarriers for Antiviral Drugs: Nanocarrier systems have significantly improved the delivery of antiviral therapeutics through:

- Enhanced Drug Properties
- Improved solubility and bioavailability
- Protected drug stability
- Controlled release kinetics
- Cellular Targeting Mechanisms
- Active targeting through surface modification
- Passive targeting via enhanced permeability
- Stimuli-responsive drug release

Recent studies have demonstrated that lipid-based nanocarriers can enhance the therapeutic efficacy of antiviral drugs by up to 10-fold while reducing systemic side effects. Polymer-based nanocarriers have shown particular success in delivering nucleoside analogs to viral reservoir sites (Mallipeddi and Rohan, 2010; Pradhan et al., 2021).

Advantages in Precision Targeting: Precision targeting capabilities of nanotechnology-based systems offer several key advantages:

- Site-Specific Delivery
- Enhanced accumulation in target tissues
- Reduced systemic exposure
- Improved therapeutic index
- Cellular-Level Targeting
- Specific cell type recognition
- Intracellular compartment targeting
- Reduced off-target effects
- Advanced targeting strategies have been developed using:
 - Receptor-specific ligands
 - Cell-penetrating peptides
 - Antibody-conjugated nanoparticles
 - Stimuli-responsive systems

Researchers have demonstrated successful targeting of viral reservoirs using pH-responsive nanocarriers that selectively release antiviral drugs into acidic endosomal compartments. Furthermore, magnetic nanoparticles guided by external magnetic fields have shown promise in delivering antivirals to specific anatomical sites.

Nanotechnology-based antiviral platforms exhibit multiple mechanisms of action, providing significant advantages over conventional therapeutics. They often work synergistically, enhancing overall therapeutic efficacy and minimizing viral resistance development. Nanotherapeutics for the treatment of viral diseases must be designed and applied by understanding these mechanisms (Shukla et al., 2019; Majumder and Minko, 2021).

6.4 Current Applications in Emerging Viral Diseases

New viral pathogens and re-emergences of known viruses continuously threaten global public health. These challenges can be addressed through innovative diagnostic, therapeutic, and preventive strategies based on nanotechnology. Nanomaterial design and engineering have made significant breakthroughs in treating viral infections, such as mRNA vaccines for SARS-CoV-2 and novel therapeutic approaches for hemorrhagic fevers and zoonotic diseases. Using nanomaterials, viral pathogens can be directly inhibited, drugs are delivered more efficiently, and immune responses are improved. In this section, we discuss recent advances in SARS-CoV-2 therapeutics, respiratory virus treatments, hemorrhagic fever management, and zoonotic virus control. As a result of integrating nanotechnology into these fields, therapeutic outcomes have been improved and new tools have been developed to respond to emerging viral threats rapidly (Sharifi et al., 2023).

7. NANOTECHNOLOGY IN SARS-COV-2 THERAPIES

Diagnostics and Drug Delivery Systems: During the COVID-19 pandemic, nanotechnology-based diagnostics and therapeutics have seen unprecedented advances, revolutionizing both diagnosis and treatment. In the diagnostic field, gold nanoparticle-based lateral flow assays have revolutionized rapid testing. In addition, advanced quantum dot fluorescence detection platforms improve virus detection sensitivity and specificity. CRISPR-nanoparticle diagnostic platforms have provided unprecedented precision in viral detection, similar to plasmonic biosensors. A gold nanoparticle-based biosensor has demonstrated remarkable sensitivity in detecting SARS-CoV-2, with results within 15 minutes (Wilson et al., 2024). Using nanoplasmonic platforms with multiplexed

sensing systems, multiple viral variants can be detected simultaneously. In various healthcare settings, nanotechnology-based diagnostics have improved viral detection speed and accuracy and established new paradigms in point-of-care testing, making rapid and reliable diagnosis more accessible. These platforms have been adapted to detect other emerging viral pathogens because of their success and scalability. Studies have shown that lipid nanocarriers conjugated with ACE2-binding peptides enhance antiviral drug delivery to infected cells (Zhang et al., 2022). SARS-CoV-2 drugs have been repurposed with novel inhalable nanoformulations that have improved their therapeutic efficacy (Moabelo et al., 2021; Bhutta et al., 2021).

Nanoparticle-Based Vaccines: Modern vaccine development relies heavily on nanotechnology, particularly through innovative delivery platforms, as demonstrated by the unprecedented success of mRNA vaccines. Due to their multiple advantages, lipid nanoparticle platforms have emerged as a cornerstone technology for vaccine delivery. The systems improve mRNA stability, a historically challenging aspect of RNA degradation. Due to their optimized structure and composition, LNPs enable efficient cellular uptake while ensuring sustained and effective immune responses. These platforms are less inflammatory than traditional vaccine adjuvants. Aside from LNPs, alternative nanoplatforms have expanded the vaccine landscape, including polymer-based delivery systems that can be customized. Protein nanoparticles that self-assemble provide precise control over antigen presentation, while virus-like particles (VLPs) mimic viral structures while maintaining safety. Hybrid nanocarriers, which combine multiple platform technologies, have shown promise in solving complex vaccination challenges. Several recent developments have shown improved thermal stability at higher temperatures for modified LNP formulations, eliminating the cold-chain requirements that have historically restricted vaccine distribution in resource-limited settings. By using nanoparticle-based vaccine technology, it will make effective vaccination more accessible worldwide (Sharma et al., 2015; Muramatsu et al., 2022).

8. APPLICATIONS IN INFLUENZA AND RESPIRATORY VIRUSES

Nanoparticle-Mediated Treatment Approaches: By combining direct antiviral effects with immunomodulatory benefits,

nanotechnology has revolutionized the treatment of respiratory viral infections. The use of metal nanoparticles as direct antiviral agents has emerged as a powerful antiviral strategy, offering broad-spectrum activity against a variety of respiratory pathogens. In addition to mucoadhesive nanoformulations that ensure prolonged contact with respiratory surfaces, targeted delivery systems designed specifically for respiratory epithelium improve therapeutic efficiency. Nanotherapeutics have also demonstrated immunomodulatory properties, with advanced formulations enhancing mucosal immunity, the first line of defence against respiratory infections. They are excellent at maintaining controlled inflammatory responses, and preventing excessive inflammation while ensuring adequate immune activation. Furthermore, they have been used as improved vaccine adjuvants to enhance the effectiveness of respiratory viral vaccines. In recent studies, zinc oxide nanoparticles have demonstrated remarkable synergistic effects against influenza viruses when combined with conventional antiviral medications. Through multiple mechanisms of action, this synergistic approach represents a significant advancement in respiratory viral treatment strategies (Ghaffari et al., 2019; Jha et al., 2023).

Enhanced Efficacy of Existing Antivirals: The nanoformulation of established antivirals has resulted in remarkable improvements in therapeutic outcomes through enhanced bioavailability and reduced side effects. Nanotechnology has enabled previously challenging compounds to achieve optimal therapeutic concentrations by significantly improving their solubility, overcoming longstanding challenges in antiviral therapy. Nanoformulations demonstrate prolonged circulation times in the bloodstream, allowing for sustained therapeutic effects with less frequent dosing. In addition, antiviral agents reach their intended sites of action more efficiently thanks to sophisticated targeted tissue distribution mechanisms. As a result of improved bioavailability, lower required doses have been achieved, systemic exposure has been minimized through targeted delivery, and tolerability profiles have improved that support better patient compliance. This has been achieved through multiple mechanisms. Researchers have demonstrated that nanoencapsulated neuraminidase inhibitors achieve up to a 5-fold increase in therapeutic efficacy compared to conventional inhibitors.

With such significant improvements in efficacy and reduced side effects, antiviral therapy represents a significant advancement, potentially revolutionizing how viral infections are treated (Kushawaha et al., n.d.; Chatterjee et al., 2021; Colino et al., 2018).

8.1 Role in Treating Hemorrhagic Viruses

Virus Inactivation via Nanoparticles : Through sophisticated virus inactivation mechanisms and enhanced barrier protection strategies, nanotechnology can provide novel and promising approaches for managing hemorrhagic viral infections. Direct viral inactivation using metal nanoparticles has emerged as a powerful tool capable of physically disrupting viral structures and functions. Surface-modified viral binding inhibitors, which target specific viral entry mechanisms, and combination therapeutic approaches that leverage multiple mechanisms of action simultaneously complement these approaches. In addition to barrier protection systems, advanced nanocoating technologies provide a robust defense against viral transmission. By using innovative anti-adhesive surfaces and specialized blood-contact materials designed for optimal compatibility with blood components, these protective systems are enhanced. Recently, silver nanoparticles functionalized with specific peptides have demonstrated remarkable capability in neutralizing Ebola virus particles while maintaining crucial blood compatibility, demonstrating the effectiveness of these approaches. This breakthrough represents a significant advancement in hemorrhagic virus treatment, as it offers a promising balance between potent antiviral activity and biological safety, which is particularly important in the context of blood-borne viruses (Sharifi et al., 2023; Maduray and Parboosing, 2021).

8.2 Protection Through Nanoparticle Coatings

Advanced Preventive Barrier Systems: Hemorrhagic virus prevention has been revolutionized by nanoparticle coating technologies. By incorporating sophisticated surface decontamination properties, these advanced systems actively neutralize viral particles. With nanocoating technologies, healthcare workers' protective equipment has been enhanced, providing an additional layer of protection against viral transmission. These coatings have also created a new paradigm in

protection, ensuring that critical medical equipment stays sterile and virus-resistant for extended periods (Rai et al., 2016; Singh et al., 2024).

Innovation in Active Protection Technologies:

Nanoparticle coating technology has advanced significantly with the development of active protection systems. Sustained-release antimicrobial coatings provide continuous protection by releasing antiviral agents gradually. The development of smart reactive materials has emerged as an especially promising innovation, capable of adapting their protective properties in response to environmental triggers or viral presence. Self-cleaning surfaces have further enhanced these systems, enabling autonomous decontamination and long-term protection. Graphene oxide-based coatings have demonstrated exceptional long-term protection against hemorrhagic viruses in recent years. Creating more effective and sustainable protective barriers against viral threats has never been easier thanks to this breakthrough in coating technology (Amirtharaj Mosas et al., 2022; Ebrahimi et al., 2021).

8.3 Nanotechnology in Combatting Zoonotic Viruses

Innovative Environmental Control Strategies: In the fight against zoonotic viruses, nanotechnology has revolutionized environmental control measures through multifaceted approaches. By removing viral particles from enclosed spaces and reducing transmission risks, advanced nano filters have transformed air purification systems. A cutting-edge surface decontamination system provides persistent protection against viral contamination in addition to these innovations. Furthermore, nanotechnology has enhanced the removal of viral pathogens from water sources, addressing a critical pathway of zoonotic virus transmission (Leifels et al., 2022; Campos et al., 2020).

Advanced Vaccination Platforms: Nanotechnology-based approaches have significantly enhanced vaccination strategies against zoonotic viruses. Multiple viral antigens can be targeted simultaneously with multi-epitope vaccine platforms. These systems are enhanced by cross-protective immunization strategies that provide broader protection against various viral strains. The development of thermostable vaccine formulations has addressed crucial challenges in vaccine

distribution and storage, especially in resource-limited settings. It has recently been demonstrated that nanoparticle-based vaccines can provide comprehensive protection against multiple strains of Hantavirus (Zhang et al., 2024; Afzal et al., 2023).

Specialized Antiviral Nanomaterials: With the application of specialized nanomaterials, new paradigms have been introduced in the control of zoonotic viruses through direct antiviral effects and enhanced protection systems. Multiple layers of defence against viral infection can be provided by broad-spectrum viral inhibitors and host-targeted therapeutics. Often, these approaches are combined to maximize therapeutic efficacy. In addition to enhanced barrier materials and smart systems, sustained-release platforms ensure protection systems' long-term effectiveness. In recent studies, polymer-based nanomaterials have shown effective inhibition of Nipah virus entry into cells while maintaining sustained protection (Ali et al., 2023).

Future Perspectives and Implications: In emerging viral diseases, nanotechnology has the potential to significantly improve therapeutic outcomes. Nanomaterial platforms enable rapid response to new viral threats while providing enhanced efficacy over conventional approaches. Future outbreaks and pandemics will require continued research and development in this area. As a result of the integration of multiple technological approaches, from environmental control to therapeutic intervention, a comprehensive framework for managing zoonotic viral threats is created, demonstrating the transformative potential of nanotechnology in global health (Bennett-Woods, 2018).

Challenges and Limitations of Nanotechnology in Antiviral Therapy: Despite its promise, nanotechnology in antiviral therapy faces several challenges that merit careful consideration in both research and implementation. Nanomedicine-based approaches face unique challenges across safety, regulatory, and economic dimensions (Chakravarty and Vora, 2021).

Safety and Toxicity Concerns: In their therapeutic applications, nanoparticles' safety profile remains a top priority. Due to their unique physicochemical properties and potential interactions with biological systems, nanoparticle toxicity presents complex challenges in humans.

Nanoparticles can cross biological barriers and accumulate in various organs, potentially causing unexpected toxic effects. Some nanoparticles have been shown to trigger inflammatory reactions, oxidative stress, and cellular damage, especially in vital organs such as the liver, kidneys, and central nervous system (Kumah et al., 2023).

The long-term environmental effects of nanoparticles pose significant ecological concerns beyond immediate health effects. Since these materials enter the environment through a variety of pathways, such as pharmaceutical waste and human excretion, their persistence and potential bioaccumulation in food chains remain uncertain. Nanoparticles have the potential to interact with environmental microorganisms and disrupt ecosystem balance, which requires thorough investigation and monitoring (Asmatulu et al., 2022).

9. REGULATORY AND ETHICAL ISSUES

Existing regulatory frameworks present unique challenges to the approval process for nanomedicine products. A current set of guidelines and testing protocols designed for conventional pharmaceuticals may not adequately address the unique properties and behaviors of nanoscale materials. Globally, regulatory agencies are struggling to establish appropriate safety assessment methods and standardization protocols for nanomedicine products. As a result of the complexity of characterization, nanoparticle-based therapeutics often take longer to approve and cost more to develop. In the context of global access to nanomedicine-based antivirals, ethical considerations raise important questions about healthcare equity. Developing nanomedicine often requires sophisticated technology and expertise, potentially exacerbating existing health disparities. In addition, intellectual property rights and patent protection may restrict access to these innovative therapies in resource-limited settings, raising ethical concerns about how medical advances should be shared (Foulkes et al., 2020; Đorđević et al., 2022; Wasti et al., 2023).

10. COST AND SCALABILITY

Nanotech-based antiviral therapies face significant manufacturing challenges. Producing nanoparticles requires sophisticated equipment,

precise control over synthesis conditions, and rigorous quality control. It is challenging to maintain consistency in particle size, shape, and surface properties across large-scale production batches, which directly affects manufacturing costs and product reliability. In addition to these challenges, specialized facilities and trained personnel are required (Farjadian et al., 2019).

Global health initiatives face the challenge of affordability in low-income regions. Nanomedicine-based antivirals are often prohibitively expensive for developing nations due to their high production costs and complex storage and transportation requirements. In regions where antiviral treatments are most needed, this economic barrier significantly limits the potential impact of nanotechnology-based solutions. A cost-effective manufacturing process and alternative funding mechanisms are crucial to ensuring broader access to these innovative therapeutic approaches (Pradhan et al., 2021).

The multifaceted challenges underscore the need for continued research, regulatory adaptation, and innovative solutions to realize nanotechnology's potential in antiviral therapy. Collaboration across scientific, regulatory, and economic domains, as well as a commitment to ethical and equitable healthcare delivery, are necessary to address these limitations (Rangayasami et al., 2021).

11. FUTURE PERSPECTIVES AND EMERGING TRENDS

Antiviral nanotechnology is rapidly evolving, offering promising avenues for advancement in therapeutic approaches and disease management. The development of these sophisticated and targeted methods for addressing viral infections marks a transformative era in medical science (Dawre and Maru, 2021).

Personalized Nanomedicine for Viral Infections: Personalized medicine has been revolutionized by the integration of genomic technologies with nanotechnology-based treatments. Genomic-guided nanotechnology therapies are proving to be powerful tools for tailoring antiviral treatments to individual genetic profiles. Using this approach, nanocarriers can be designed that optimize drug delivery based on patient-specific genetic markers, which influence drug metabolism, immune response, and viral susceptibility. Targeted therapeutic delivery

allows for more precise dosing strategies and fewer adverse effects (Dawre and Maru, 2021).

Precision medicine has further enhanced the potential of nanomedicine in the treatment of viral diseases. Combining high-throughput screening technologies and artificial intelligence has enabled the development of sophisticated nanoplateforms that respond to individual patient characteristics. By adjusting the release of therapeutic payloads based on biological markers, these platforms can provide more effective and personalized treatment protocols for various viral infections (Yasamineh et al., 2022).

Nanotechnology in Future Pandemic Preparedness: Global pandemic preparedness strategies increasingly rely on nanoparticle-based rapid response platforms. Modular design approaches allow these platforms to adapt quickly to new viral threats. Nanoparticle properties can be modified in response to emerging viral variants by using advanced manufacturing techniques. With the integration of smart materials and biosensors into these platforms, real-time monitoring capabilities and treatment efficacy are enhanced (Xu et al., 2022).

Nanotechnology-based detection systems have significantly enhanced global virus surveillance strategies. Nanosensor networks provide early warning systems for viral outbreaks, which enables more rapid and coordinated responses to emerging threats. Combined with advanced data analytics, these surveillance systems enable more effective pandemic management strategies by tracking viral evolution and spread (Araste et al., 2023).

Novel Nanomaterials and Drug Development: Nanomaterials for antiviral drug design are evolving beyond traditional nanocarrier systems. Researchers are developing smart materials with programmable properties that can respond dynamically to viral infections. A few examples include self-assembling nanostructures that adapt their configuration based on the presence of specific viral markers and hybrid materials that combine organic and inorganic components to enhance therapeutic efficacy. Antiviral treatments are becoming more biocompatible and effective as biomimetic approaches are incorporated into material design (Araste et al., 2023).

Nanotechnology-driven vaccine development offers particularly promising prospects. A next-generation vaccine platform based on nanoengineered particles offers improved stability, enhanced immune responses, and potentially a broader range of protection against viral variants. Among these advances are self-amplifying RNA vaccines delivered with specialized nanocarriers, and synthetic nanoparticles mimicking viral structures for more effective immune system training. Vaccine distribution and accessibility could be revolutionized by needle-free delivery systems and thermostable formulations (Pereira, 2022).

The convergence of these trends suggests that antiviral treatments will become increasingly precise, accessible, and effective in the future. Together with advances in personalized medicine and global surveillance capabilities, nanotechnology is positioned as a critical tool for addressing current and future viral challenges. To ensure responsible development and equitable access to these innovative technologies, sustained investment in research, international collaboration, and careful consideration of ethical and regulatory frameworks will be required (Pradhan et al., 2021).

In the years to come, the integration of these technologies into mainstream medical practice will likely reshape our approach to viral infections and pandemic responses, potentially leading to more resilient and adaptable healthcare systems worldwide.

12. CONCLUSION

A significant advance in modern medicine has been the integration of nanotechnology into antiviral therapeutics, fundamentally transforming our approach to viral disease management. There has been remarkable progress in antiviral therapy in recent years, addressing previously intractable challenges. Novel nanomaterials have enabled more effective viral inhibition strategies through nanoparticle-based delivery systems. A robust foundation for future innovations in viral disease treatment has been established by these developments, as well as improvements in diagnostic capabilities and vaccine delivery systems.

Summary of Current Advances:

- Enhanced drug delivery systems with improved bioavailability and targeting

- Development of smart nanomaterials for viral inhibition
- Advanced diagnostic platforms with increased sensitivity
- Novel vaccine delivery mechanisms
- Integration of AI and machine learning in nanotech design
- Improved understanding of nano-bio interactions

This technology could have a significant impact on the management of viral diseases in the future. Nanotechnology-enabled solutions can revolutionize both therapeutic and preventive approaches to viral infections. In the future, personalized nanomedicine and advanced diagnostic platforms will allow treatment strategies to be precisely tailored to individual patients and viral strains. Global healthcare can better respond to emerging viral threats and potential pandemics with rapid-response platforms and improved surveillance systems powered by nanotechnology. Due to scalable manufacturing processes and cost-effective production methods, these cutting-edge treatments may also be more accessible.

Key Impact Areas for Future Management:

- Personalized medicine approaches using nano-based platforms
- Rapid response capabilities for emerging viral threats
- Enhanced global surveillance systems
- Improved vaccine effectiveness and distribution
- Cost-effective treatment options for developing nations
- Reduced side effects through targeted delivery
- Better patient compliance through simplified administration

The potential of nanotechnology in antiviral therapies surpasses conventional therapeutic approaches. Its ability to address multiple aspects of viral disease management - from prevention and diagnosis to treatment and monitoring - highlights its comprehensive impact on healthcare delivery. With nanotechnology and other advancing fields, such as artificial intelligence and genomics, antiviral strategies may be even more effective and innovative. Safety, regulatory compliance, and ethical implications, particularly regarding global access

and environmental impact, must be carefully considered in light of this potential.

Critical Considerations Moving Forward:

Research and Development

- Continued innovation in nanomaterial design
- Integration with emerging technologies
- Focus on scalable manufacturing processes

Implementation Challenges

- Safety and toxicity assessments
- Regulatory compliance
- Environmental impact studies
- Cost optimization

Global Health Impact

- Equitable access to nanomedicine
- Technology transfer to developing nations
- International collaboration frameworks
- Standardization of protocols

With nanotechnology continuing to develop in antiviral applications, viral diseases will be understood and managed in a whole new way. The demonstrated benefits and ongoing innovations in this field suggest that viral infections can be addressed with unprecedented precision and effectiveness in the future, despite challenges in areas such as scalability, cost-effectiveness, and regulatory approval. For these developments to succeed, sustained research efforts, international collaboration, and equitable access will be essential.

From concept to clinical application, nanotechnology in antiviral therapy illustrates the power of innovative scientific approaches in addressing global health challenges. The role of nanotechnology as a cornerstone of modern antiviral strategies will become increasingly important as viral threats evolve, offering hope for more effective, accessible, and personalized treatment options.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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