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Advances in Antiviral Drug Development: Current Trends and Future Perspectives

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***Abstract*: Increased levels of morbidity and mortality, danger to the public's health, and a financial burden are all brought on by viral infections. Since being identified in December 2019, SARS-CoV-2 (Major Acute Thoracic Disease Coronavirus 2), the causal agent of COVID-19, has killed over 900, 000 people and infected over 29 million other people. Novel antiviral tactics are desperately needed, as demonstrated by the unrelenting advancement of infectious agents and the ongoing threat of newly developing infectious illnesses. This study offers a thorough analysis of current advances in the field of antiviral drug discovery, including breakthroughs in target identification, innovative methods for drug design, and encouraging therapeutic candidates. The substantial consequences of viral infections make the development of novel antivirals and control measures imperative. This document provides an overview of the 96 antivirals that the FDA (Food and Drug Administration) licensed between 1987 and 2019. Of these, 49 (51%) are used to treat HIV; four are used to treat human papillomavirus; six are used to treat cytomegalovirus; eight are used to treat hepatitis B virus; five are used to treat influenza; six are used to treat herpes simplex virus; 17 are used to treat hepatitis C virus; and one is used to treat respiratory syncytial virus. Future prospects for novel antiviral treatments, including CRISPR-Cas system, monoclonal antibodies, and nanotechnologies, are also covered in this review. The disquisition of different viral families, including RNA and DNA contagions, highlights the multifaceted challenges faced by experimenters in the field. The integration of slice-edge technologies, similar as structural biology, high-output webbing, and artificial intelligence, has revolutionized the medicine discovery process, enabling the identification of potent antiviral agents. In consideration of current global health issues, like as the COVID-19 pandemic, the changing field of antiviral research is also addressed, presenting insights on lessons acquired and possible directions for future research.**

***Keywords*: Monoclonal antibodies, CRISPR-Cas, Antivirals, Nanoparticles, COVID-19.**

1. Introduction

Viruses are ubiquitous all over the world and are the aetiological agents of many severe and chronic diseases. As seen throughout history, certain viruses can cause pandemics or epidemics. Examples include the influenza virus [1], the human immunodeficiency virus (HIV), which is the aetiological agent of the acquired immune deficiency syndrome (AIDS), and most recently COVID-19, a disease brought on by the novel coronavirus SARS-CoV-2. Viral infections have come a major global health concern in recent times, having a huge socioeconomic impact on communities each over the world. The rate at which contagious conditions spread between populations has increased due to a combination of reasons including accelerating population viscosity, worldwide trip, and climate change, as well as the unequaled pace of globalization. An overview of the prevailing global effect of viral infections is given in this part, along with a focus on important trends, obstacles, and public health implications [2]. The 2009 H1N1 influenza is an epidemic claimed the lives of basically 12,800 individual encyclopedically; South America had the topmost death rate, at 76.9 deaths per person [3]. South and Southeast Asia are the most suffering regions, comprising 1.8 million of the estimated 1.8 million people living with HIV nationwide [4]. High levels of mortality and morbidity are caused by respiratory virus infections because of their wide variation, ease of transmission, and propensity for serious consequences [5]. A population's quality of life is affected by viruses, which are also correlated with longevity and socioeconomic ratios. Recurrent Ebola infections in several African nations have been attributed to serious problems with public health and low rates of health development [6]. Researching novel antivirals has become crucial given the rising frequency of infections caused by virus, the scarcity of antivirals, the introduction of novel viruses, and the re-emergence of old viruses. Furthermore, the significant genetic diversity exhibited by many viruses demands ongoing surveillance for potential pandemics through the renewal of existing immunizations that have become inefficient due to the development of novel viral strains [7]. Though it can be hard to find and develop novel antiviral drugs, intriguing new treatments for viruses have been recommended. In this research, we examine newly indicated antiviral therapies as well as recently approved antiviral drugs. In the meanwhile, we're fighting diseases and don't yet have any effective antiviral treatments. The understanding of the inheritable, molecular, structural, and functional diversity of diseases, as well as their addition, immunological escape, and connection with host cell ministry for development and host vulnerable response, has all been supported by this [8].

2. Antiviral Therapies

The quantity and diversity of antibiotics for viruses are still rather restricted. Viruses are largely dependent on the mechanism and metabolic of a host cell because they are

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necessary intracellular pathogens. Thus, when developing novel antivirals, it is essential to prevent significant side effects and ensure selective toxicity to the host [9], [10]. Iododeoxyuridine (IDU), a 1959 nucleoside derivative that was first produced as a possible anticancer medication, was the first antiviral medication therapy [11]. The availability of biological models that replicate human illness in vivo and the constraints of vitro laboratory techniques, in addition to the potential for resistance posed by certain virus strains, further obstruct the search for a novel drug candidates for antivirals [12].

The identification of Acyclovir is (ACV) and succeeding preface of its prodrugs marked a significant advancement in the operation of viral infections in the late 1970s. since ACV operates on HSV- infected cells, it has low toxin and strong selectivity since its active form is efficiently attained through phosphorylation by a contagious enzyme (thymidine kinase) [13]. Antivirals are drugs that, by definition, prevent the growth of new viruses by obstructing crucial steps in the viral replication process. Therefore, recognizing these processes is crucial for creating novel antiviral medications [14]. The adhesion of the virus on the host's cell, permeation to the interior of the cell, removing and release of the viral nucleic acid, the replication of the genetic material, production of the viral substances, and the assembly of virion and release are all included in the generalized short of the viral genome replication steps shown in (Figure 1).

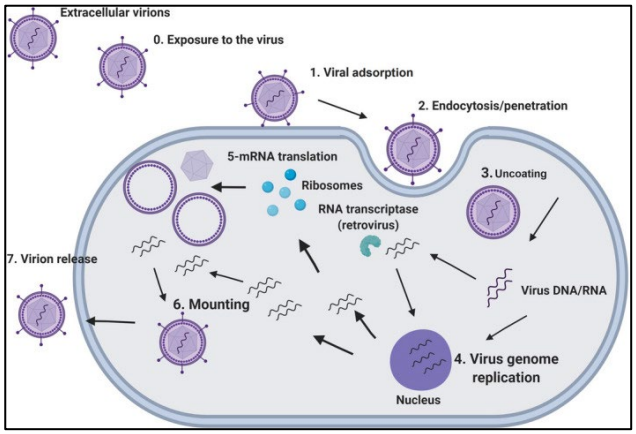

Fig. 1. Steps in viral replication [14]

Steps of viral replication: Exposure to the virus (0); viral adsorption onto the host cell surface (1); Penetration of the virus into the intracellular environment (2); uncoating and disassembly (3); viral genome replication and transcription (4); viral mRNA translation (5); mounting (6); and release of the viral progency (7).

Antiviral activity can effectively target adsorption and penetration. Enfuvirtide, an anti-HIV medication, for instance, binds to the glycoprotein (gp-41) of the viral envelope to prevent the envelope from fusing with the cell membrane [15]. Certain viruses require the utilization of microtubules to transfer their genetic material from the site of penetration to the nucleus of the host cell, indicating a possible target for medical treatment [16]. Antiviral therapies can entail the use of two or more medications in order to boost the efficiency of the treatment; this is known as antiviral multiple therapies or combination therapy. This is due to the intricacy of the viral development steps connected with the mutagenesis capacity of some viruses. When it comes to treating viruses like HIV, polytherapy appears to be a good substitute, especially when it comes to strains of the virus that are resistant [17].

Piecemeal from antivirals that serve by blocking the replication cycle, colorful composites that manage the viral infection by conforming the host immunological response are also being studied. starting the vulnerable system's natural defenses against viral infections, interferons are a family of cytokine that belongs to this group [18]. A type of immune response modifier is the antiviral agents imiquimod, which functions as an antagonist toll-like receptors [9]. The Food and Drug Administration's (FDA)-approved substances and drugs with other therapeutic signs have also been assessed as potential antivirals by broadening their pharmacological action. This approach is currently being used extensively in emergency efforts to contain the COVID-19 pandemic, using knowledge of pharmacokinetics and pharmacodynamics as well as understanding of the side effects of that was previously available drugs [19]. In another randomized experiment, 237 people suffering from severe COVID-19 were involved. The results showed no significant difference in either the rate of mortality (14%) or the time taken for the virus to be eliminated in the remdesivir-treated group as compared to the placebo-treated group. Yet, previous medical histories were present in every patient in our investigation [20]. It has been discovered that monoclonal antibodies are useful in neutralizing a variety of viruses and can elicit an immune response by functioning similarly to natural antibodies [21]. The CRISPR-Cas9 method relies on a gene-editing mechanism that employs naturally occurring prokaryotic CRISPR sequences, which are short palindromic repeats that are organized and regularly spaced [22].

3. Management of Chronic Viral Infections

Antiviral medications play a crucial role in the long-term therapy of chronic viral infections, including hepatitis B and C, herpes, and HIV. These drugs not only prevent the spread of viruses but also enhance the quality of life for those who suffer from these ailments, turning once-debilitating illnesses into chronic disorders that can be controlled [23].

4. Prevention of Viral Transmission

Antiviral medications are essential in preventing the spread of some viruses when used as preventative measures. This is especially true in the case of influenza, when those who are in close proximity to an infected person can receive antiviral treatment to reduce the spread of the infection.

5. Classification of Antivirals: Implications of Mode of Actions

The first smallpox cases were successfully medicated with antivirals (thiosemicarbazone) in the 1960s [24]. Since then,

Table 1
Mechanism of action

Antiviral drugs	Target	Mode of action	Example
Fusion inhibitors	Viral surface proteins or host cell receptors	Inhibit the virus's ability to attach, merge, and enter the host cell, preventing the infection of uninfected cells.	• Cyclosporine • Amantadine • Palivizumab • Docosanoi • Maraviroc
RT inhibitors	Viral propagation	Inhibits the activity of RT by attaching itself to the enzyme directly or by stopping the DNA chain from expanding.	NRTIs: • Didanosine • Zalcitabine • Stavudine • Zidovudine • Lamivudine ntRTIs • Tenofovir • Adefovir NNRTIs • Nevirapine • Etravirine
Integrase inhibitors	Viral DNA integration with host's genome	Blocks integrase's activity	• Raltegravir
Protease inhibitors	Viral proteases' activity	Inhibits the division of the virus's developing proteins, which are necessary for the assembly and creation of new virions.	• Amprenavir • Saquinavir • Indinavir • Nelfinavir
Signaling inhibitors	Signaling pathways	Stops signaling by inhibiting any crucial part of the signaling pathways, which are necessary for the spread of viruses.	• Diethyldithiocarbamate • Ribavirin • Resveratrol

NNRIT: Non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside analog reverse transcriptase inhibitor; ntRTI: Nucleotide analog reverse transcriptase inhibitor; RT: Reverse transcriptase.

over 100 antivirals have been developed [25]. The abundance of data acquired from these developments in our knowledge of viral lifespans and replicating mechanisms directly affects the development of antiviral drugs. By precisely focusing on the crucial phases of the viral life cycle, antiviral drugs that are highly targeted and potent can be developed, minimizing the effect of infections caused by viruses on the health of humanity.

Antivirals can be categorized into seven classes based on their targets: integrase inhibitors, portmanteau drugs, protease inhibitors, fusion inhibitors, DNA polymerase inhibitors (DPIs), reverse transcription inhibitors (RTIs), and signaling inhibitors. Examples of different antiviral medicine classes and the associated medications, along with their intended. Prospective Virol. (2009) 4(2)102 Prospective scientific community Mishra & Saxena, Editors Saxena, Fusion inhibitors stop the virus's adhesion to the host cell, preventing infection of uninfected cells. RTIs can be categorized into three groups.

- Analogues RTIs containing nucleosides (lamivudine, lamivudine, didanosine, zalcitabine, and stavudine);
- RTIs containing nucleotides (tenofovir and adefovir)
- RTIs without nucleosides: efavirenz, nevirapine, delavirdine, and etravirine.

Molecules known as integrase inhibitors, such as raltegravir, stop integrase from working and preventing viral DNA from being integrated into the host genome [26]. With the innovative technique known as portmanteau inhibitors, specialists are trying to create a medication that has both integrase and RTI properties [27]. Substantially influencing with essential elements of signaling pathways involved in viral replication, signaling inhibitors prevent signaling. For instance, ribavirin and viramidine were used as the inosine monophosphate (the IMP) de hydrogenase inhibitors [28]. By inhibiting viral proteases for being active, protease inhibitors prevent pathogens from replicating. They prevent the cleavage of emerging viral proteins, such as ritonavir, saquinavir, indinavir, amprenavir, and nelfinavir, which are necessary for the assembly and creation of new virions [29].

6. Applications in Antiviral Drug Discovery

Both FBDD and Ligand-Based Approaches have shown significant success in the field of antiviral medication discovery. Finding fragments that specifically target vital viral proteins, such proteases and polymerases, and obstruct important stages in the viral life cycle has been made possible due in substantial part to FBDD.

The use of antivirals in co-infections and accidental infections is concerning since treating one virus with an antiviral may result in antiviral resistance to other viruses. Many strategies, such as combination therapy and refraining from using antiviral medications for extended periods of time or discontinuing altogether, have been proposed to minimize resistance.

By utilizing the knowledge of available antiviral drugs, molecules with enhanced efficacy and decreased toxicity can be designed, aiding in the creation of next-generation antiviral therapeutics [30].

7. New Perspectives for the Treatment of Viral Diseases

A. Monoclonal antibodies against viral infections

In the 1970s, a process known as hybridoma was utilized for inducing antibody synthesis in animals using myeloma tumor cells, which led to the development and separation of monoclonal antibodies (mAbs). At the moment, camelid

chimeric monoclonal antibodies can be used to improve this production through "phage display," memory B cell isolation, and direct clone of the secreted plasmacytic or antibody itself through genetics and molecular coding [31].

The introduction of monoclonal antibodies has increased in the fight against newly developing viruses, such as SARS-CoV-2. For the treatment of COVID-19, certain antibodies, such as bamlanivima and etesevimab and casirivimab and imdevimab (REGN-COV2), have been approved Emergency Use Authorization. Viral infections can be effectively managed with immunotherapeutic techniques, as these antibodies specifically target certain viral proteins, thereby blocking viral entry into host cells [32]. mAbs have high particularity with direct and breathless viral suppression [33]. The first FDA - approved mAb was ibalizumab (TheratechnologiesInc.) and was used to treat HIV in adult cases refractory to conventional antiviral treatment [34]. It acts by blocking the entry of HIV-1 into host cells by non-competitive binding to TCD4+ lymphocytes [35].

Monoclonal antibodies (mAbs) have been found to be beneficial in the prevention of fetal development, particularly in the treatment of pregnant women against newly acquired viruses like ZIKV. In this regard, three antibodies, SMZAb1, SMZAb2, and SMZAb5, which stopped viral replication in monkeys, have already been developed and are being tested in labs [36]. Immune system cells can be genetically programmed to make modified antibodies by dmAb when it is released into the body. More protection for experimental models is offered by dmAbs' enhanced and more consistent treatment kinetics, which are a significant advance over current techniques [37].

The Ebola virus glycoprotein was encoded by the Venezuelan equine encephalitis virus. MIL77E is a cocktail made in Chinese hamster ovary cells that contains two mAbs, 13C6 and 2G4 from ZMapp. Though the issue with using mAbs to treat the Ebola virus is that large doses are needed to guarantee effectiveness. Furthermore, because new epitopes may evolve in epidemics, it is imperative to continuously design novel mAb mixes [38]. The immune system of a patient may create neutralizing antibodies, which could lead to resistance to the beneficial effects of mAbs, however this is uncommon. Thus, additional research is required to support this new technology that has recently been proposed.

B. Nanotechnology applied to antivirals

It was recently proposed that nanotechnology could be utilized for defense against SARS-CoV-2 infection. Using polymeric inorganic nanoparticles and self-assembling and peptide-based proteins, results of previous studies on respiratory viruses, such as SARS-CoV [39], could also be used to this novel coronavirus [40]. The increasing adaptation and numerous possibilities of applications of nanoparticles have generated scientific attention [41].

Nanotechnology has emerged as a potent research tool in the medical sciences, enabling the transformation of natural metals into nanoparticles that are employed for delivery of medications, illness diagnosis, and even a antibacterial and anticancer activity [42]-[44].

In addition to the many benefits of using nanostructured delivery systems for medication administration are their capacity to preserve active molecules from deterioration in physiological media and to release the active ingredient precisely where it is needed at the site of action. Therefore, by avoiding the issues with commercially accessible medications, biotechnology helps to conduct active molecules to their target sites with more specificity. Depending on the materials with which they are prepared, nanoparticles are classified as polymeric (usually prepared using biodegradable polymers to provide controlled release of encapsulated therapeutic substances), solid lipids, magnetics or metallics [45]. Novel antiviral medicines based on nanoparticles are also attracting interest. These nanoparticles can be made to resemble viral structures or to deliver antiviral medications direct to the cells that are infected. It is suggested that nanoparticles work direct on the infectious agent or that they cause structural alterations in the virus that stop it from entering the target cell, however this has not been verified or described.

Researchers want to usher in a new era of precise medicine in antiviral medicines by using nanotechnology to maximize beneficial effects, overcome resistance to drugs, and improve the effectiveness of antiviral treatments. Many advantages are associated with nanoparticles, particularly in the treatment and elimination of infectious diseases. They outperform other antivirals in terms of efficacy and overcome drawbacks such as low absorption, unfavorable side effects, frequent intake, and length of treatment. To target viral infection specifically while sparing healthy cells and tissues, this novel technology still requires complementary research on nanomaterial characterization and the creation of highly biodegradable, biocompatible, and non-cytotoxic nanocarrier systems and nano transporters.

C. CRISPR-Cas Against Viral Infections

The genomic mechanisms of defense of bacteria against bacteriophages led to the development of CRISPR. Naturally occurring genetic material in a wide range of clinically significant types of cells and in invertebrates that have historically proven difficult to genetically change have been modified fast, simply, and effectively using this technology [46]. Effective gene deletion and insertion of desired genetic material at certain gene locations in the widest variety of organisms was made possible by CRISPR's rapid adoption [47]. The development of CRISPR technology has allowed antiviral research to go to new heights. CRISPR-based strategies, such CRISPR-Cas9 and CRISPR-Cas13, have the ability to target viral genomes directly, offering a precise and adaptable way to treat viral infections. Although these techniques are still in the early phases of development, they have the potential to be highly precise antiviral therapies and could be a revolutionary step forward for antiviral therapeutics. Antiviral medications, which are part of traditional therapies, prevent the spread of viruses and lessen their symptoms, but they are unable to eradicate the invasive virus because of changes that allow the virus to evade treatment or create latent infections [48]. The principal mechanisms of action suggested for CRISPR-Cas are reported below:

1. Receptor modification for viral entrance: Viral proteins interact with cell membrane receptors to facilitate the virus's entry into the host cell. In addition to altering viral tropism, CRISPR-Cas-induced editing of receptor genes can block virus-receptor binding and limit the virus's ability to enter and disseminate.
2. Host transcriptional restriction factor induction: These factors are restricted by the interaction of inactive Cas9 (dCas9) with viral RNA, which either prevents replication or reduces both the transcription of viral RNA and the quantity of virions.
3. Viral factor segmentation in the host: The virus mostly relies on host proteins for reproduction and spread. Viral replication can be stopped and the virus becomes more vulnerable to the host immune response by using the CRISPR-Cas approach to silence certain genes that encode essential proteins.
4. The Integrated virus genome can be deleted and excised using CRISPR-Cass, which then causes the genes to be deleted and inactivated before the host genome is reintegrated. This process is commonly used for viruses that integrates their own DNA into the host genome.

All four of these strategies will lead to a reduction in viral replication (Figure 2).

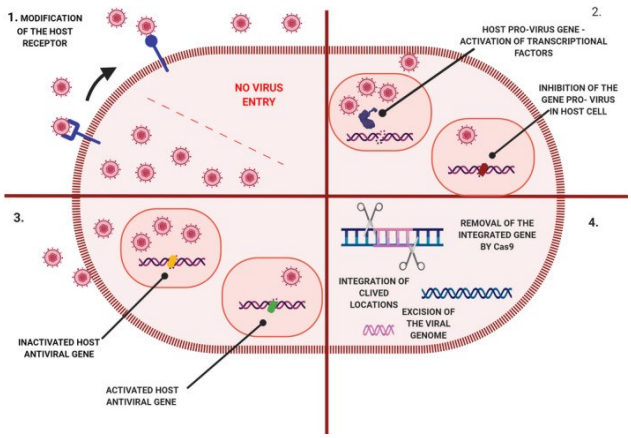

Fig. 2. Schematic representation of different CRISPR-Cas strategies [48]

Schematic representation of different CRISPR-Cas strategies with antiviral action aimed at host and viral genomes: 1. Modification of receptors for viral entry, preventing the entry of virions. 2. Segmentation of host viral factors by silencing provirus genes. 3. Induction of the expression of host transcriptional restriction factors – activation of the antiviral gene. 4. Excision and deletion of the integrated viral genome.

The antiviral efficacy of the CRISPR-Cas system has been proven in vivo and was validated in a leukaemia patient who did not exhibit a detectable HIV-1 viral load following bone marrow transplantation containing a homozygous for mutation of delta type 5 CC chemical receptor 32 (CCR5Δ32) [49]. This mutation is critical for immune cell infection. HBV replicates in infected hepatocytes by converting its circular DNA to covalent resolved circular DNA (cccDNA) at the onset of replication [50].

Additionally, the CRISPR-Cas technology is being used to develop several in vitro as well as in vivo treatments aimed at preventing infections [51]. Additional research is necessary to examine the immunological reactions to exogenously expressed CRISPR-Cas9 and develop methods to conceal this system, thereby lowering its immunogenicity. By decreasing off-target effects, high-fidelity Cas9 variations have demonstrated their effectiveness in practical applications of genome editing [52].

8. Approaches for Against Viral Resistance

Significant progress has been made in the field of antiviral drug discovery recently, but the efficiency of these therapies is seriously threatened by the rise of viral resistance. Antiviral medications may eventually lose their effectiveness or potency due to viruses' known propensity for fast mutation. Due to this phenomena, treating viral infections requires a proactive strategy that involves combination medicines due to their complicated nature.

A comprehensive evaluation of developments in the search for antiviral drugs highlights the vital need for creative thinking and interdisciplinary methods in order to keep up with the rapidly changing landscape of viral threats. In an environment where the landscape is always changing, it becomes crucial to emphasize the development of combination medicines in order to generate strong and long-lasting solutions for fighting viral infections. This approach not only extends the clinical usefulness of antiviral medications but also makes them more effective, which ultimately improves patient outcomes when dealing with viral infections.

9. Conclusion

In conclusion, investigating combination treatments in the field of antiviral medication development is a critical step in addressing the problems caused by viral resistance. A significant threat to public safety is the recurrent appearance and reemergence of viruses throughout the past few decades. Viral latency, incorrect diagnosis, viral resistance, toxicity, and immunosuppression brought on by antivirals could all be contributing factors. The curative treatment of potentially fatal viral infections has shown some promise thanks to a variety of alternative strategies, previous drug discovery initiatives, and current developments in biology and chemistry. The need for novel medications and antiviral treatment options is critical and urgent because of the epidemiological significance of viral illnesses and the challenges in managing them. An update on recently licensed antiviral medications is offered in this review, along with novel treatment prospects including the use of CRISPR-Cas system, monoclonal antibodies, and nanoparticles. In addition to improving therapeutic efficacy, the combination of various medicines that target different stages of the viral cycle reduces the likelihood of resistance developing.

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