CPQ Microbiology (2022)
Commentary

Antiviral Drug Discovery Strategies

Shimon Shatzmiller

Department of Biological Chemistry, Ariel University, Ariel 40700, Israel

***Correspondence to:** Dr. Shimon Shatzmiller, Department of Biological Chemistry, Ariel University, Ariel 40700, Israel.

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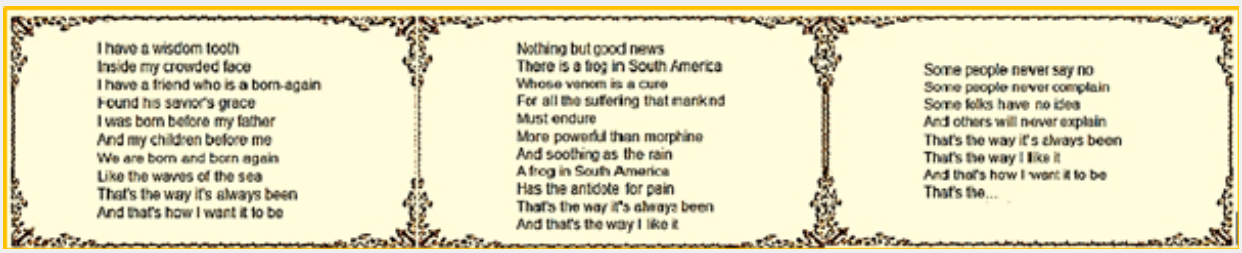
Received: 18 June 2022

Published: 27 June 2022

Keywords: *Antiviral Drug; Magic Bullet*

Foreword

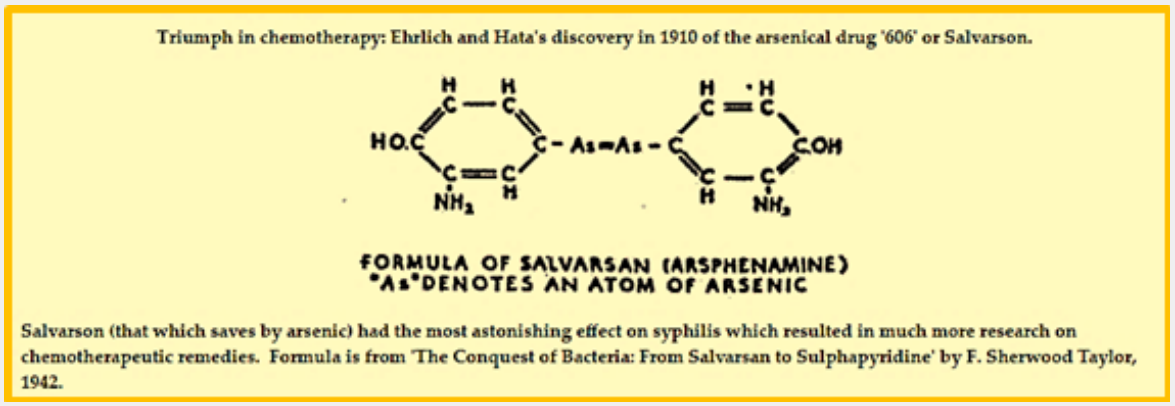
Here is a frog in South American jungles…. this is the beautiful song by Paul Simon Señorita with a Necklace of Tears, Paul Simon, the second verse [1]:



So we found the green little frog, *Phyllomedusa Savage* [2], from the Amazon/Orinoco jungles, whose skin contains many antimicrobial peptides, and focused on Dermaseptin S4 [3,4] as one of the most active one, and this in many ways.

Ehrlich and his co-workers [5] tried hundreds of chemicals on the microbes that caused syphilis. In 1909, Ehrlich's new colleague Sahachiro Hata (1873-1938) brought with him a method of producing syphilis

infections in laboratory rabbits, and discovered (1910) that drug no. 606 worked. The first 'magic bullet' had been found, and was marketed under the name Salvarsan. This was the first "magic bullet".



In the last period, of eight decades, with a peak at the period of the years 1960-1980, Humankind enjoyed on the basis of e4hrlich's findings, a period of triumph over the ancient dwellers. Our nemesis, the most ancient dwellers of this planet: the microbes (archaea, bacteria, fungi, viruses and more).

Since the days of Ehrlich, the progressive development of technology, in chemistry and Biotechnology, provided agents of different nature: those from chemical synthesis (Sulfa drugs, Domagk [6]) and others from bio-synthesis (penicillin, Fleming [7]). Materials that could eradicate the broad spectrum of microbes very efficiently and allowed in this short era the extension on human life longevity from 40 years on average to 80 years of today [8]. People took it for granted, these were days people thought they would never end, not knowing that the "sudden bullet bullets" did not completely eliminate the bacteria, the few organisms left on the margins spread, but this time to unknown new races that were resistant to "agents wonder". And here we are again today, in front of the world of germs without weapons and active at this stage of the campaign [9].

Discovery of Broad-spectrum Antiviral [10] Drug Against SARS-CoV-2

There are many sources to apply in the quest of pharmaceuticals.

Examples are:

1. Compounds extracted from creatures, like venoms, blood and tissues, plants, animal, sea flora, and earth bacteria.

2. Computer-aided drug design

3. 3 screening banks of chemicals in modern techniques like mass spectrometry,

4. Searching for unique compounds in a synthetic compound produced in many laboratories worldwide, screaming.

5. Modifying and mimicking bioactive natural products like polypeptides and carbohydrates or unique nucleosides isolated from living creatures and plants and modifying or mimicking to create novel bioactive compounds.

The highly pathogenic coronavirus is called acute respiratory syndrome coronavirus (SARS-CoV). Together with Middle East respiratory syndrome coronavirus (MERS-CoV) are lethal zoonotic viruses that have emerged into human populations these past 15 years. These coronaviruses are associated with novel respiratory syndromes that spread from person-to-person via close contact, resulting in high morbidity and mortality caused by the progression to acute respiratory distress syndrome (ARDS) [11].

The broad-spectrum antiviral drug is a kind of agent used to prevent and treat virus infection. By inhibiting virus replication/reproduction in infected cells or improving the cellular defense system, these broad-spectrum antiviral drugs are effective in the clinical treatment of viral infection and SARS-CoV-2 infection. Mechanisms drugs with broad-spectrum SARS-CoV-2 antiviral activities mainly involve: [12]

• Inhibiting or killing the virus directly.

• Interference with virus attachment/membrane fusion.

• Preventing the virus from penetrating into cells;

• Inhibiting the biosynthesis of the virus;

• Inhibiting the assembly and release of the virus;

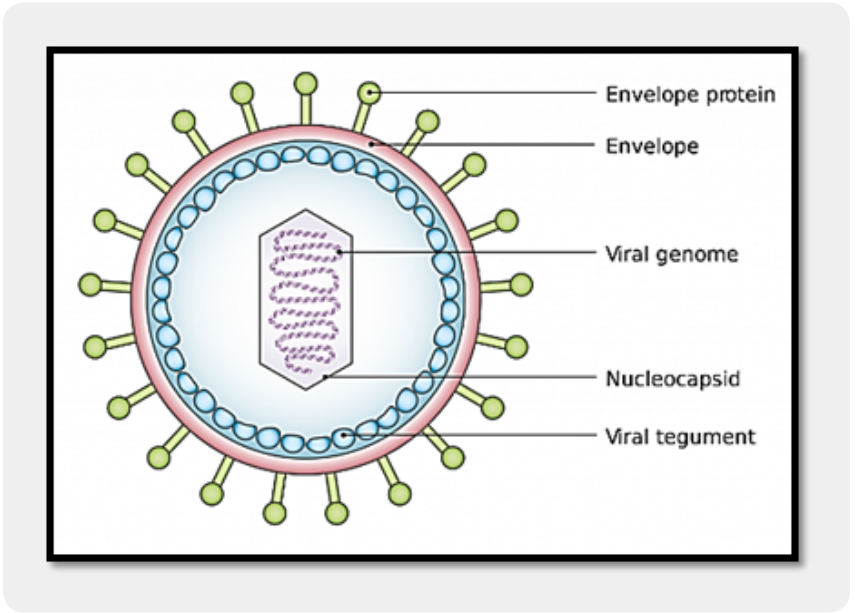
• Enhancing the antiviral ability of the host.

Clinically approved antiviral drugs are currently available for only 10 of the more than 220 viruses known to infect humans. The SARS-CoV-2 outbreak has exposed the critical need for compounds that can be rapidly mobilized for the treatment of re-emerging or emerging viral diseases, while vaccine development is underway. The current status of antiviral therapies focuses on RNA viruses, highlighting strategies for antiviral drug discovery, and discuss the challenges, solutions, and options to accelerate drug discovery efforts [13].

The fight between humans and viruses is rapidly improving the strategies of attacking and defending. In recent years, there has been tremendous progress in understanding diseases' genetic basis and molecular mechanisms [14].

Viruses [15]

Short Introduction



The components needed for host cell infection, is referred to as a virion.

Introduction

Viruses are commonly described as binding intracellular parasites, extracellular infectious agents that require the presence of a host Cell to reproduce. Viruses found infect all types of cells - humans, animals, plants, bacteria, yeast, archaea, protozoa... Some scientists even claim to have found a virus that infects other viruses! But this is it not going to happen without some cellular help Virus characteristics.

Viruses can be very simple in their design, consisting of nucleic acid surrounded by a protein shell known as a capsid. The capsid is composed of smaller protein components referred to as capsomeres. The capsid genome combination is called a nucleocapsid.

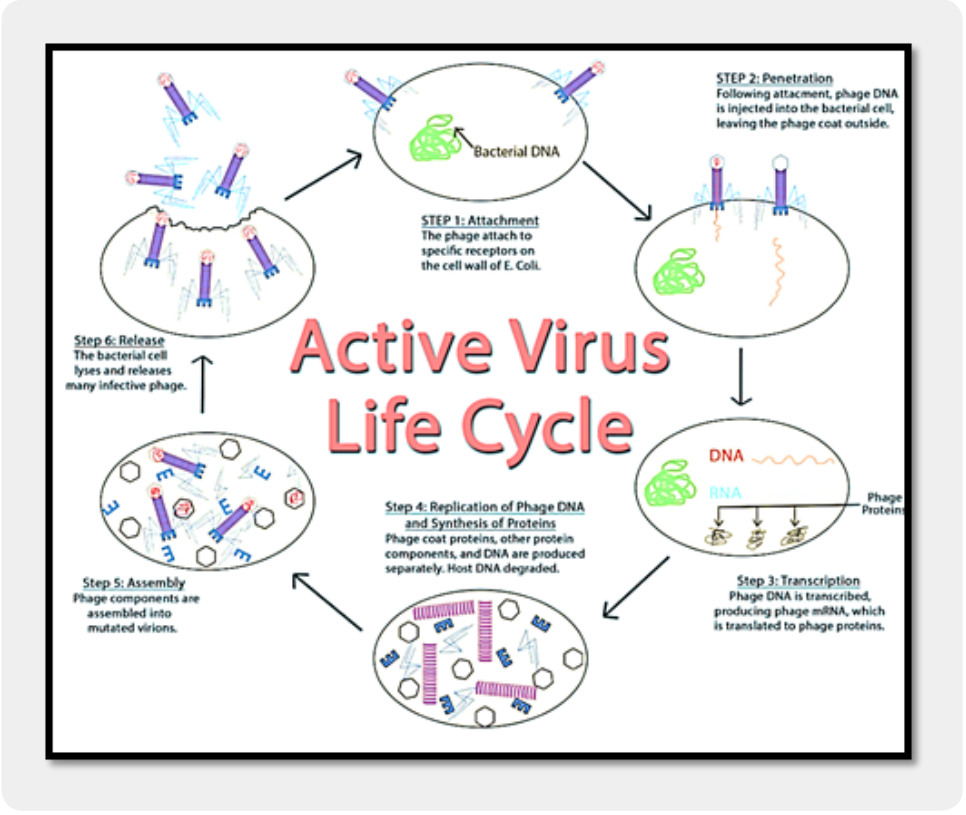
Viruses can also have additional components, with the most common Being another layer of membrane that surrounds the nucleocapsid, called the mantle. The envelope is actually purchased from the nucleus or plasma membrane of the infected host cell, and then modified with viral proteins called peplomers. Some viruses contain viral enzymes that are necessary for infection of a host cell and coded for within the viral genome. A complete virus, with all ssRNA can have a positive sense (+ ssRNA, meaning it can transcribe a message, like mRNA) or it can have a negative sense (-ssRNA, which indicates that it complements mRNA). There are viruses that even start with one form of the nucleic acid in a nucleocapsid and then convert it to another form during replication.

While in general, Cells contain double-stranded DNA for their genome, viruses are not limited to this form only. While there are dsDNA viruses, there are also viruses with single-stranded DNA (ssDNA), double-stranded RNA (dsRNA) and single-stranded RNA (ssRNA). plunder latter category, ssRNA can have a positive sense (+ ssRNA, meaning it can transcribe a message, like mRNA) or it can have a negative sense

(-ssRNA, indicating that it complements mRNA). Some viruses even begin with one form of nucleic acid in a nucleocapsid and then convert it to another format during replication. Or building blocks, so there is a third category known as complex viruses. This may include the smallpox virus with a white-shaped exterior appearance and a complex internal structure and a bacteriophage with tail fibers attached to the top of the icosahedral.

Virus replication cycle - the main point of virus replication by hijacking the biological mechanism of extracellular life [16].

While the proliferation cycle of viruses can change from virus to virus, there is a pattern that can be described, consisting of five.



a. Attachment - virion attaches to the proper host cell.

b. Penetration (Viral Entry) - the virus or corresponding nucleic acid gains entrance into the cell.

c. Transcription- Page DNA is transcribed. Producing a Phage mRNA which is translate to phage proteins

d. Synthesis - the nucleic acid copies and proteins are synthesized by the cells' machinery.

e. Assembly - The microbes are made from the components.

f. Release -the formed virions are released from the cell.

The six stages above can be set as targets of pharmaceuticals to halt and eradicate the virus. For instance, the stopping of transcription is a good target [17]. Or the interrupting of the penetration to the host cell by blocking the ACE2 receptor [18], is a proper target of research.

The Antiviral Activity of Short Peptides, Nucleosides, and Their Surrogates

Antibiotics are not effective against viruses, and many leading organizations now recommend against using antibiotics unless there is clear evidence of a bacterial infection. Vaccines have drastically reduced the number of viral diseases. In addition, vaccines can prevent infections such as the flu, hepatitis A, hepatitis B, human papillomavirus (HPV) infection, covid-19, and others. But curing viral infections has proved more challenging, primarily because viruses are relatively tiny and reproduce inside cells. Antiviral medications have become available for some viral diseases, such as herpes simplex virus and human immunodeficiency virus (HIV) infection. Specific antibodies and AMPs are urgently needed to resist viral infections [19].

Common Viruses that Plague Humans

Highly Pathogenic Avian Influenza, (HPAI)

Hepatitis Virus (A,B,C,D,E)

Dengue Virus

Enterovirus 71 (EV71)

SARS-CoV-2

Influenza Virus

HIV

SARS coronavirus

Ebola Virus

Zika Virus

MERS coronavirus

Rabies Virus

Multiple outbreaks of epidemic and pandemic viral diseases have occurred in the last 20 years, including those caused by Ebola virus, Zika virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The emergence or re-emergence of such diseases has revealed the deficiency in our pipeline for the discovery and development of antiviral drugs. One promising solution is the extensive library of antimicrobial peptides (AMPs) produced by all eukaryotic organisms.

AMPs are widely known for their activity against bacteria, but many possess additional antifungal, antiparasitic, insecticidal, anticancer, or antiviral activities. AMPs could therefore be suitable as leads for the development of new peptide-based antiviral drugs.

2 Dec 2021 -The FDA is considering authorizations for Pfizer's paxlovid and Merck & Co.'s molnupiravir, the first two oral COVID-19 antivirals.

Antimicrobial Peptides, Dermaseptins are a family of peptides isolated from skin of the from genus Phyllomedusa of the family of south American leaf frogs, Isolated from their skins [4,20,21]. The innate immunity of vertebrates to microbial invasion is arbitrated by a network of host-defense mechanisms involving both the long-lasting highly specific responses of the cell-mediated immune system and a nonspecific chemical defense system based on a series of broad-spectrum antimicrobial peptides that are analogous to those found in insects. Vertebrate antibiotic peptides secreted by non-lymphoid cells of the mucosal surfaces of the respiratory and gastrointestinal tracts as well as by the granular glands of the skin reportedly cause the lysis of numerous pathogenic microorganisms, including viruses, gram-positive and gram-negative bacteria, protozoa, yeasts, and fungi, as well as of cancer cells. The antiviral property of Dermaseptis and short fragments of these peptides was identified for the HIV and Herpes [22,23] viruses decades go. Amphibian skin glands have proven to be a rich source of antimicrobial peptides, with approximately 500 described [10,11,24]. These peptides include dermaseptins, a large family produced by the skin of tree frogs belonging to the genera Phyllomedusa [12,16]. Dermaseptins are linear polycationic peptides, 24 to 34 amino acids in length, adopting an amphipathic α-helical structure in a polar solvents [17] as well as in membrane environment.

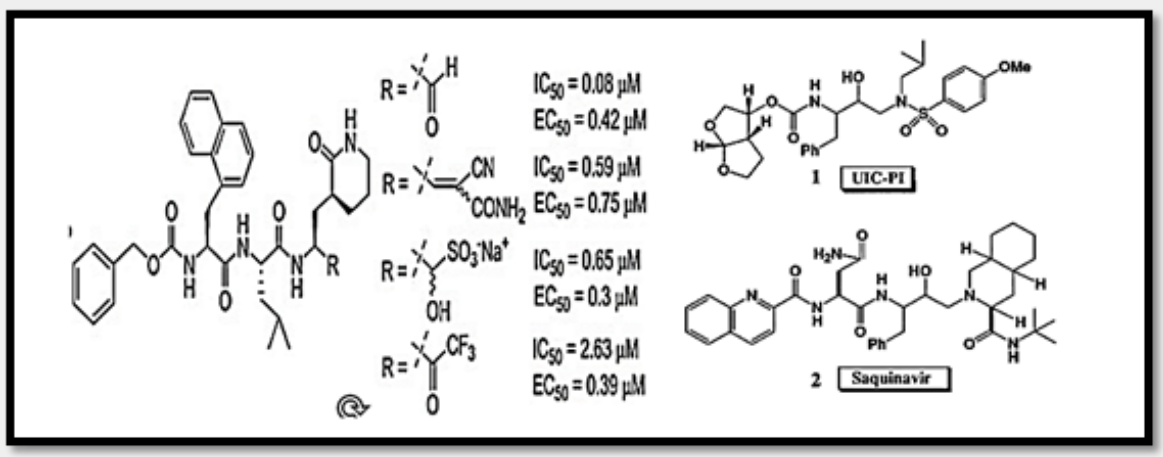
Recently, many outbreaks of virus-induced pandemics, Ebola, SARS and covid-19 have played our planet, millions died, the economy, the scientific and industrial societies are and lifestyles are busy to follow the quest for remedy. Although an effective vaccination is today available for the viral disease Known as COVID 19, only one effective medicine (Paxlovid [25]), Nirmatrelvir is a peptide surrogate, so is the pF-00835231 [26,27].

Mechanism of action is an inhibitor of a cysteine residue in the 3C-like protease (3CLPRO) of SARS-CoV-2. This cysteine is responsible to the activity of the 3CLPRO of SARS-CoV-2 and potentially other members of the coronavirus family. The 3CLPRO, also known as the main protease or non structural protein 5, is responsible for cleaving Nirmatrelvir polyproteins 1a and 1ab. These polyproteins contain the 3CLPRO itself, a papain-like (PL) cysteine protease, and 14 other nonstructural proteins. Without the activity of the 3CLPRO, nonstructural proteins (including proteases) cannot be released to perform their functions, inhibiting viral replication [26c].

The attempt to find in protease inhibitors remedy to viral infections was also attempted, The synthesis and antiviral evaluation of novel peptidomimetics; norovirus protease inhibitors [28] series of novel dioxin-containing triaryl-2-pyrazoline derivatives C1-C20 have been synthesized. Their BRaf inhibitory and anti-proliferation activities were evaluated. Compound C6 displayed the most potent biological activity against B-RafV600E and WM266.4 human melanoma cell line with corresponding IC50 value of 0.04 lM and GI50 value of 0.87 lM, being comparable with the positive controls and more potent than our previous best compounds. Moreover, C6 was selective for B-RafV600E from B-RafWT, C-Raf and EGFR and low toxic. The docking simulation suggested the potent bioactivity might be caused by breaking the limit of previous binding pattern. A new 3D QSAR model was built with the activity data and binding conformations to

conduct visualized SAR discussion as well as to introduce new directions. Stretching the backbone to outer space or totally reversing the backbone are both potential orientations for future research.

Also A series of tripeptidyl transition state inhibitors with new P1 and warhead moieties were synthesized and evaluated in a GI-1 norovirus replicon system and against GII-4 and GI-1 norovirus proteases.

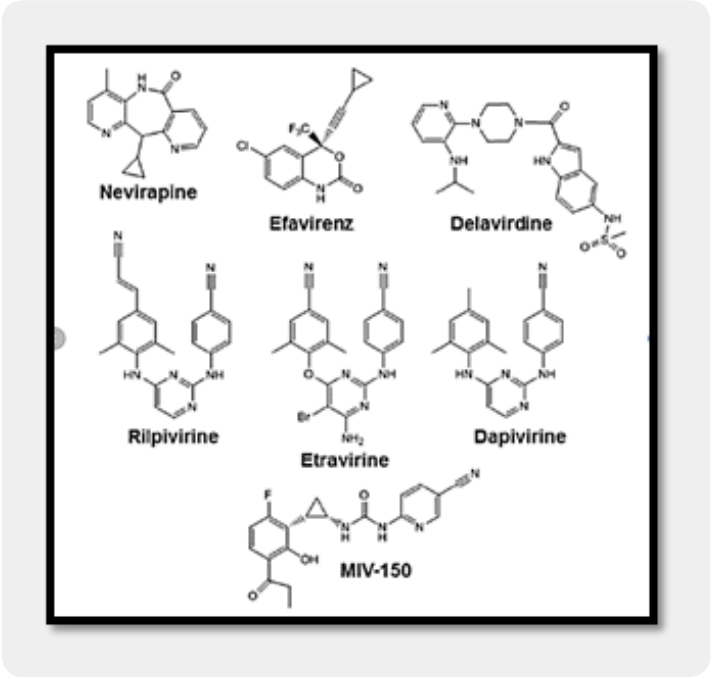


Protease inhibitors tested (credit ref [28])

Saquinavir was discovered and developed by the pharmaceutical company Roche. Saquinavir was the sixth antiretroviral and the first protease inhibitor approved by the US Food and Drug Administration (FDA), leading ritonavir and indinavir by a few months. At that time, considerable effort, both in design and syntheses of many envelope proteinase as a target toi block or inhibit, and bring thereby remedy to the AUIDS patients, This, as a separate branch in combat against the AIDS viris. other medications were aumd to interfere in the nucleic acids bio synthesis, like blocking of the reverse transcriptase mechanism. The reverse-transcriptase inhibitors (RTIs) are a class of antiretroviral drugs used to treat HIV infection or AIDS, and in some cases hepatitis B. RTIs inhibit activity of reverse transcriptase, a viral DNA polymerase that is required for replication of HIV and other retroviruses. Reverse-transcriptase inhibitors (RTIs) are a class of antiretroviral drugs used to treat HIV infection or AIDS, and in some cases hepatitis B. RTIs inhibit activity of reverse transcriptase, a viral DNA polymerase that is required for replication of HIV and other retroviruses.

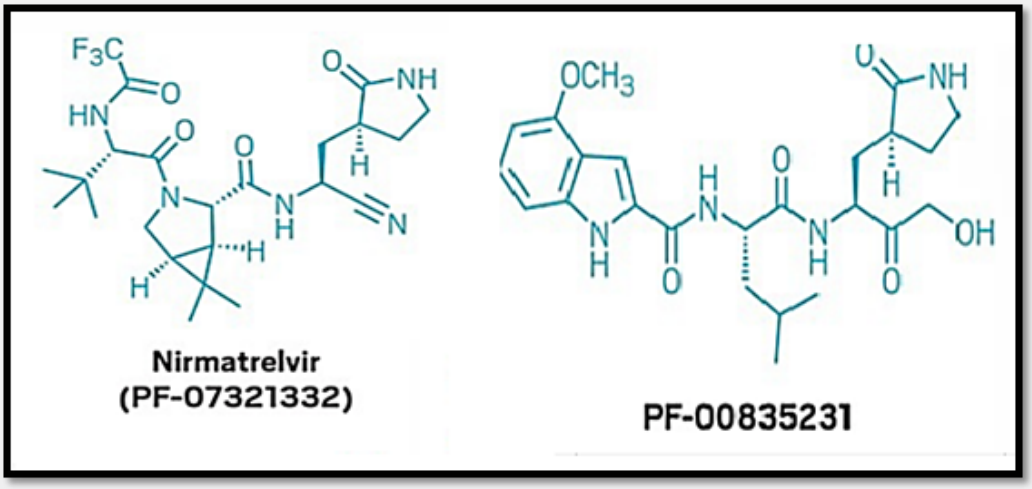
Mechanism:

When the HIV infects a cell, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation, to reproduce the virus. RTIs block reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA, thus preventing HIV from multiplying.



Reverse transcriptase inhibitors (Nevirapine) [29]

A similar process occurs with other types of viruses. The hepatitis B virus, for example, carries its genetic material in the form of DNA, and employs an RNA-dependent DNA polymerase to replicate. Some of the same compounds used as RTIs can also block HBV replication; when used in this way they are referred to as polymerase inhibitors.



PAXLOVID, PFIZER

Is approved for the early stages of the disease. And in 90% efficiency. It is still badly needed to uncover more efficient healing through an effective antiviral drug-compounds-based cure.

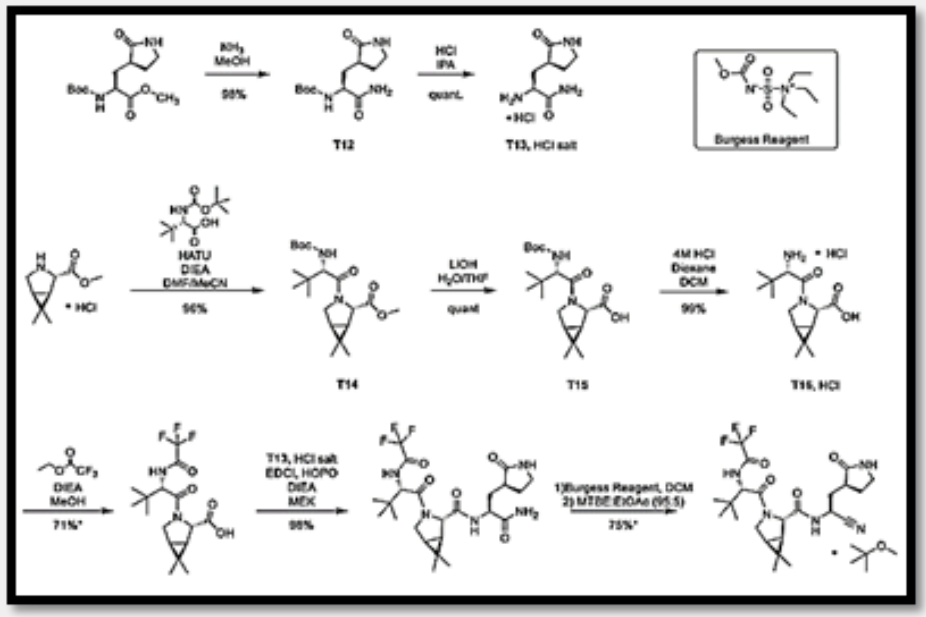
Antiviral drugs like Nirmatrelvir are synthesized in nost modern synthetic technology and are hard to come by.

How Does Paxlovid Work?

Nirmatrelvir (PF-07321332) is a very potent and orally active SARS-CoV 3C-like protease ($3CL^{PRO}$, cysteine proteinaze) inhibitor. Nirmatrelvir (PF-07321332) targets to the SARS-CoV-2 virus and can be used for COVID-19 research. Nirmatrelvir iworks as an inhibitor of a cysteine residue in the 3C-like protease ($3CL^{PRO}$) of SARS-CoV-2. This cysteine is a major participant in the cartalytic process of the activity of the $3CL^{PRO}$ of SARS-CoV-2 and potentially other members of the coronavirus family [1].

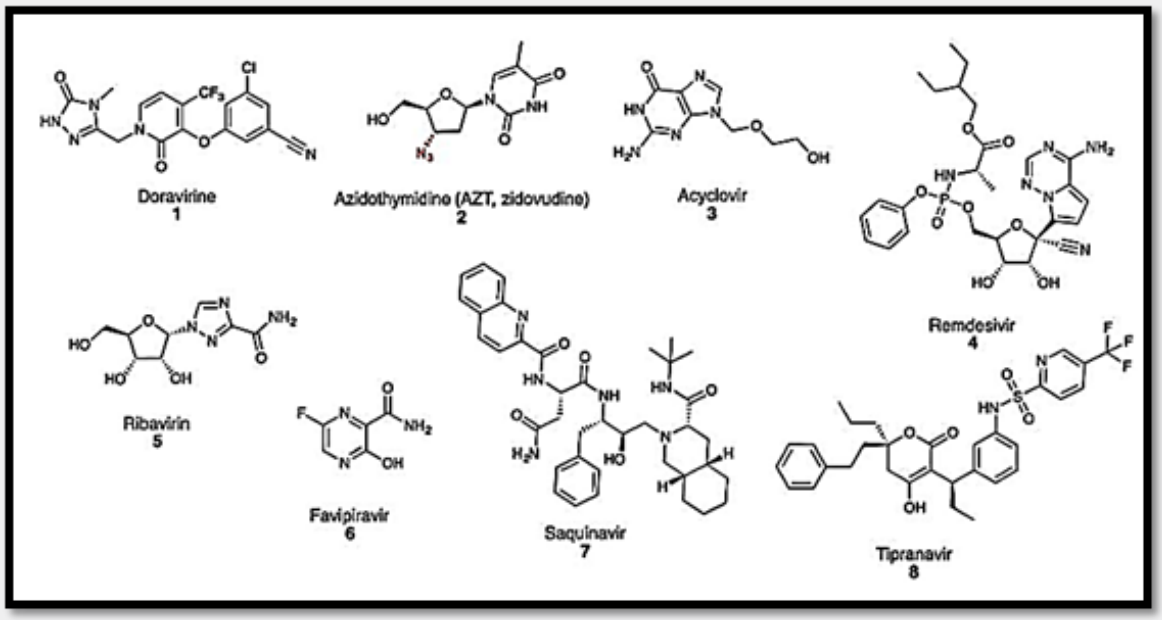
Ritonavir inhibits the HIV viral proteinase enzyme that normally cleaves the structural and replicative proteins that arise from major HIV genes, such as *gag* and pol. *Gag* encodes proteins involved in the core and the nucleocapsid, while pol encodes the the HIV reverse transcriptase.

Paxlovid is an antiviral therapy consisting of two separate drugs packaged together. When you take the dose of your three pills, two of these pills will be neuremetralvir, a key enzyme inhibitor that the COVID virus requires in order to create functional virus particles. After treatment with nirmatrelvir, the COVID virus released from the cells is no longer able to penetrate uninfected cells in the body, which in turn, stops the infection. The second is ritonavir, a drug that was once used to treat HIV / AIDS but is now being used to increase the levels of antiviral drugs. As a COVID-19 treatment, ritonavir essentially disables the metabolism of nirmaltavir in the liver so that it does not move from your body at the same rate, which means it can work longer - giving it a boost to help fight infection.



Here is synthetic scheme how the drug substance is prepared:

Here is an assembly of some modern antiviral molecules, some are depicted below:



It seems that a clue may exist in the natural product. These antimicrobial peptides may be instrumental, using most modern drug design and synthesis methods, like computer-aided drug research, to uncover the clue for remedy.

Viral diseases have contributed significantly to worldwide morbidity and mortality throughout history. Despite treatments for many viral infections, antiviral resistance and the threat posed by novel viruses highlight the need for an increased number of effective therapeutics. In addition to small molecule drugs and biologics, antimicrobial peptides (AMPs) represent an emerging class of potential antiviral therapeutics. While AMPs have traditionally been regarded for their antibacterial activities, many AMPs are now known to be antiviral. These antiviral peptides (AVPs) have been shown to target and perturb viral membrane envelopes and inhibit various stages of the viral life cycle, from pre-attachment inhibition to viral release from infected host cells [30].

The fight between human and viruses in on and both are rapidly improving the strategies of attacking and defense. In recent years, there has been tremendous progress in understanding diseases' genetic basis and molecular mechanism [14].

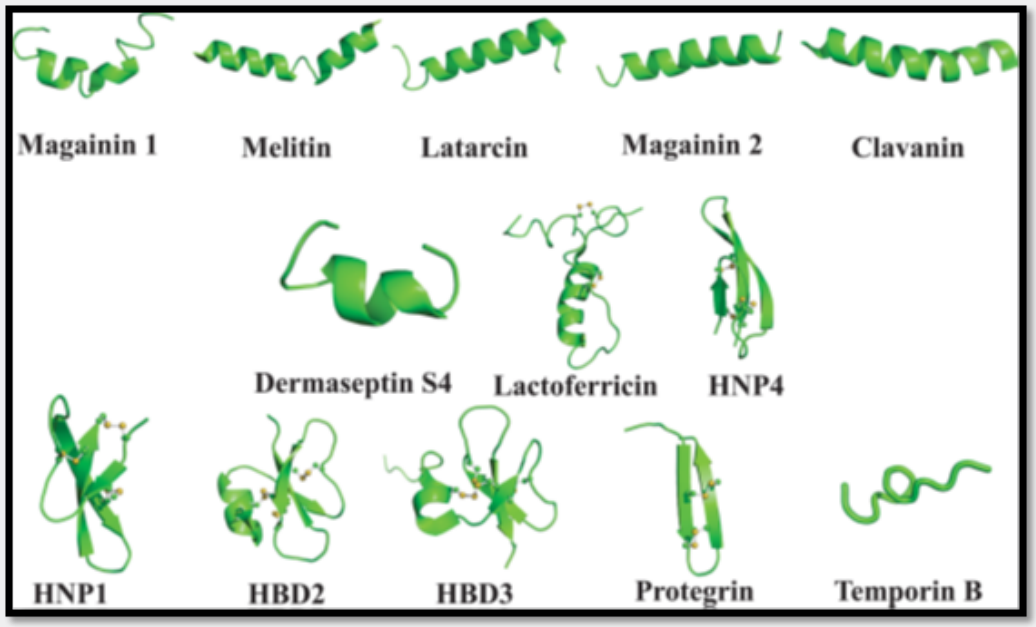
The 6 stages above can be set at targets of pharmaceuticals to halt and/or eradicate the virus. For instance the stopping of transcription is a good target [17]. Or the interrupting of the penetration to the host cell by blocking the ACE2 receptor [31], is a proper target of research.

In the case of the antiviral drug substance Nirmatrelvir the new active unit in the medicine PAXLOVID of Pfizer, the activity is focusing on the inhibition of synthesis of envelope proteins [32]. Nirmatrelvir is an inhibitor of cysteine residues in the 3C (3CLPRO) -protease of SARS-CoV-2. This cysteine is responsible for the activity of SARS-CoV-2 3 CLPRO and other potential members of the corona family. The 3 CLPRO, also known as the main protease or non-structural protein 5, is responsible for the cleavage of 1a and 1ab polypeptides. These polyproteins contain 3CLPRO itself, a papain-like cysteine (PL) -protein protease, and 14 other non-structural proteins. Without the activity of the 3 CLPRO, non-structural proteins (including proteases) cannot be released to perform their functions, inhibiting viral replication. Antiviral peptides as a strategy for antiviral drugs. Viral diseases have significantly contributed to morbidity and mortality worldwide throughout history. Despite the existence of therapeutic treatments for many viral infections, antiviral resistance and the threat posed by the new viruses emphasize the need for an increased number of effective treatments. In addition to small molecule drugs and biologics, antimicrobial peptides (AMPs) represent an evolving class of potential antiviral drugs.

While AMPs have traditionally been regarded in the context of their antibacterial activities, many AMPs are now known to be antiviral. These antiviral peptides (AVPs) have been shown to target and perturb viral membrane envelopes and inhibit various stages of the viral life cycle, from reattachment inhibition through viral release from infected host cells. The rational design of AMPs has also proven effective in identifying highly active and specific peptides and can aid in the discovery of lead peptides with high therapeutic selectivity. Here we highlight AVPs with strong antiviral activity largely curated from a publicly available AMP database. We then compile the sequences present in our AVP database to generate structural

predictions of generic AVP motifs. Finally, we cover the rational design approaches available for AVPs considering approaches currently used for the rational design of AMPs [33].

Antiviral Peptides as Promising Therapeutic Drugs [34]



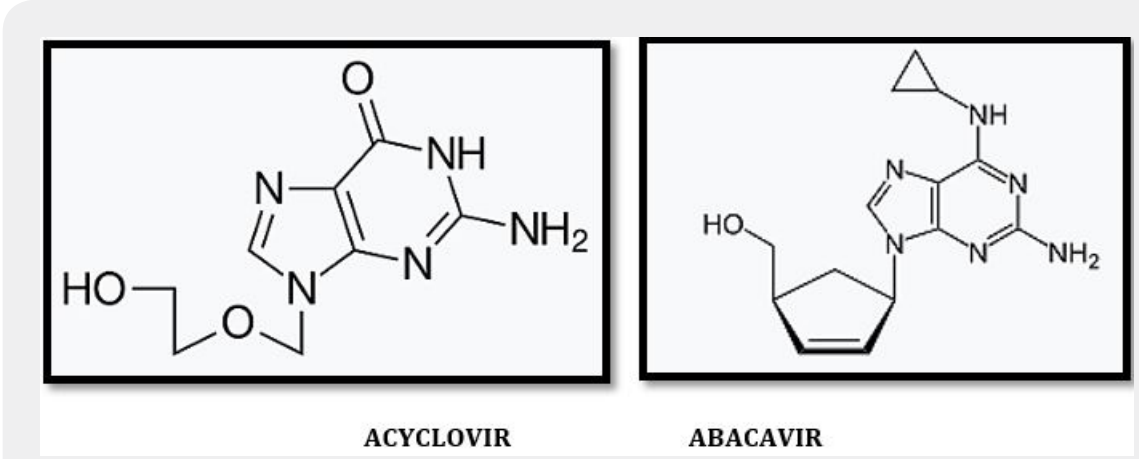
Structure of some AVPs already described. Magainin 1 and 2, melittin, lactarcin, clavanin, dermaseptin S4, lactoferricin, HNP1 and 4, HBD 2 and 3, protegrin, and temporin (credit ref, [17]).

While scientific advances have led to large-scale production and widespread distribution of vaccines and antiviral drugs, viruses remain a major cause of human diseases today. The ever-increasing reports of viral resistance and the emergence and re-emergence of viral epidemics pressure the health and scientific community to constantly find novel molecules with antiviral potential. This search involves numerous different approaches, and the use of antimicrobial peptides has presented itself as an interesting alternative. Even though the number of antimicrobial peptides with antiviral activity is still low, they already show immense potential to become pharmaceutically available antiviral drugs. Such peptides can originate from natural sources, such as those isolated from mammals and from animal venoms, or from artificial sources, when bioinformatics tools are used. This report aims to shed some light on antimicrobial peptides with antiviral activities against human viruses and update the data about the already well-known peptides that are still undergoing studies, emphasizing the most promising ones that may become medicines for clinical use.

With the development of techniques to produce and to improve both pharmacodynamics and pharmacokinetics of AVPs, such problems will be overcome one day, since interest in peptide-based drugs is rising. Large-scale production and screening are speeding up the drug discovery phase, and it is expected

that more antiviral peptides will enter the phase of clinical trials. Even so, for recently discovered viruses, there is little information, and the current methods for antiviral peptide design seem to work not only for drug description but also to help understand viral structure. In addition, some authors suggest the use of peptide-based drugs as adjuvants or in combination therapy with other antivirals with different mechanisms of action, thus diminishing drug resistance establishment and producing fewer side effects. Finally, the description of new antiviral drugs supplements the existing therapies and provides alternatives to treat viral diseases that cause serious pandemics, reducing the mortality/morbidity associated with them.

ACYCLOVIR, ABACAVIR



ACYCLOVIR ABACAVIR

Cumulative knowledge of viral and cellular replication events has made it possible to identify compounds that might interfere selectively with viral functions or malignant cells. Among these compounds, nucleoside analogues are of great importance [35,36].

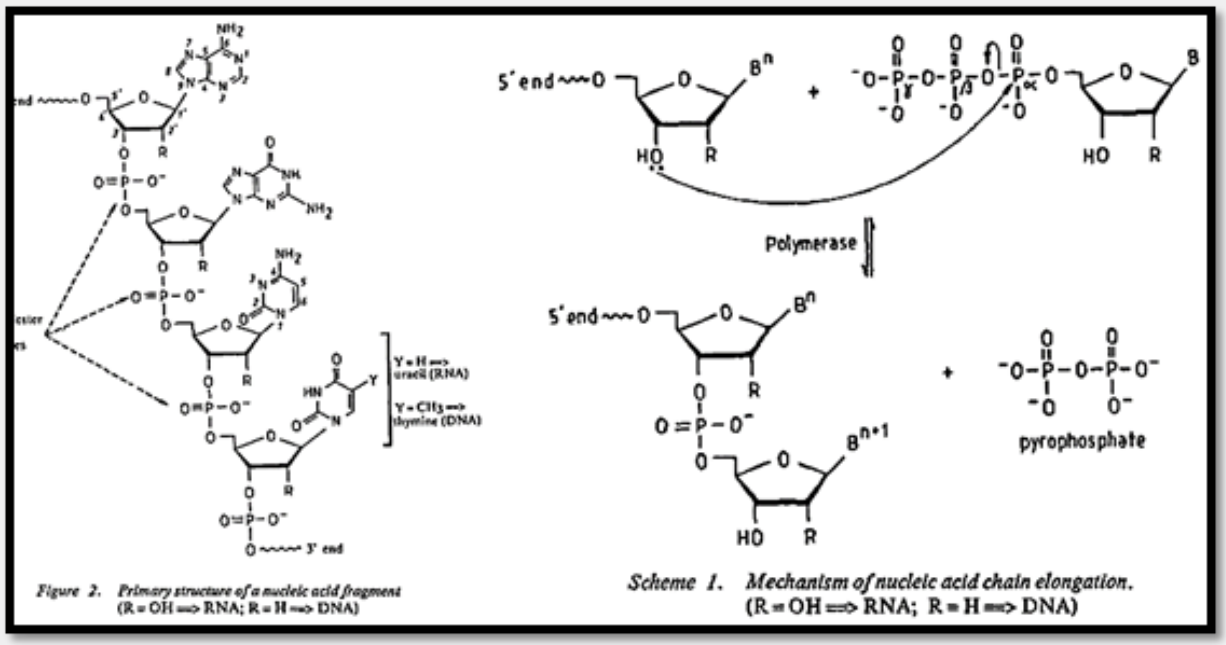


Figure 2. *Primary structure of a nucleic acid fragment* (R = OH ⟹ RNA; R = H ⟹ DNA)

Scheme 1. *Mechanism of nucleic acid chain elongation.* (R = OH ⟹ RNA; R = H ⟹ DNA)

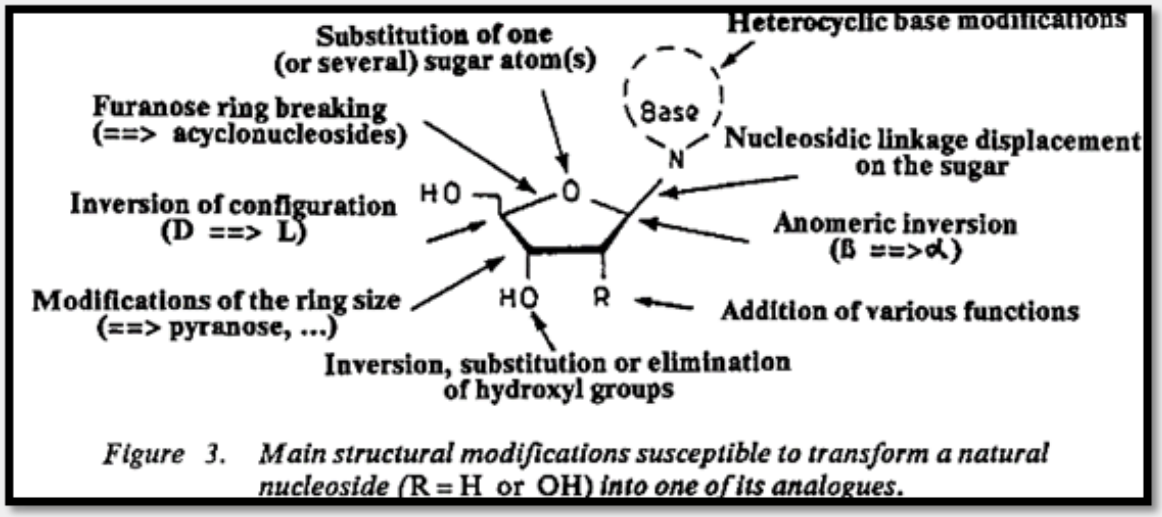


Figure 3. *Main structural modifications susceptible to transform a natural nucleoside (R = H or OH) into one of its analogues.*

Regular Nucleic Acid, Modifications Required for Antiviral and Anticancer Design

Aciclovir (ACV), also known as acycloviris an antiviral medication [37]. It is primarily used for the treatment of herpes simplex virus infections, chickenpox, and shingles. Other uses include prevention of cytomegalovirus infections following transplant and severe complications of Epstein-Barr virus infection. It can be taken by mouth, applied as a cream, or injected.

Cyclovir is converted to its triphosphate form, acyclovir triphosphate (ACV-TP), which competitively inhibits viral DNA polymerase, incorporates into and terminates the growing viral DNA chain, and inactivates the viral DNA polymerase.

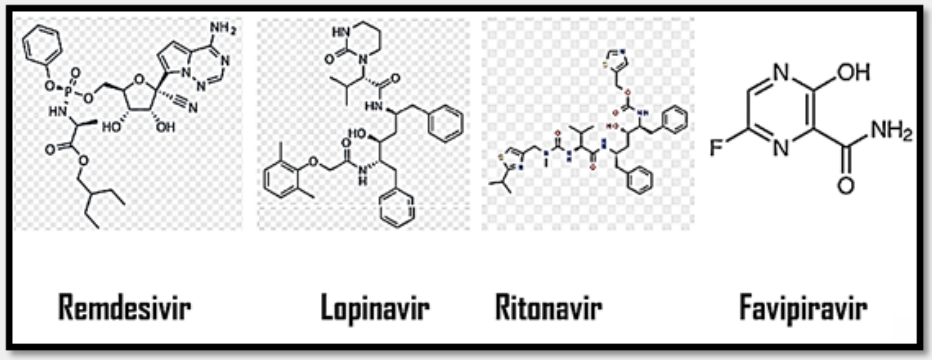
Nucleosides isolated from a Caribbean sponges, Cryptotethya crypta, were the basis for the synthesis of Acyclovir. It was discovered by Howard Schaeffer following his work with Robert Vince, S. Bittner and S. Gurwara on the adenosine analog acyclo-adenosine which showed promising antiviral activity. Later, Schaeffer joined Burroughs Welcomed and continued the development of acyclovir with pharmacologist Gertrude B. Elion. A U.S. patent on acyclovir listing Schaeffer as inventor was issued in 1979. Vince later invented abacavir, a Nucleoside analog reverse-transcriptase inhibitor (nRTI) drug for HIV patients. Elion was awarded the 1988 Nobel Prize in Medicine, partly for the development of aciclovir.

Abacavir, (sold under the brand name Ziagen,) is a drug used to prevent and treat HIV / AIDS. Similar to other analogous nucleoside inhibitors (NRTIs), Abequir is used in combination with other HIV drugs, and is not recommended on its own. It is taken orally as a tablet or solution and can be used in children over three months of age. Abacavir is generally well tolerated [4]. Common side effects include vomiting, sleep problems, fever and feeling tired. More serious side effects include hypersensitivity, liver damage and lactic acid. A genetic test can indicate whether a person is at higher risk of developing hypersensitivity. Abacavir is in the NRTI group of drugs, which act by blocking reverse transcriptase, an enzyme needed to replicate the HIV virus.

Within the NRTI class, abacavir is a carbocyclic nucleoside. Abacavir was granted a patent in 1988, and approved for use in the United States in 1998. It is on the World Health Organization's list of essential medicines. It is available as a generic drug. lamivudine / zidovudine, abacavir / dolutegravir / lamivudine, and abacavir / lamivudine. The combination of abacavir / lamivudine is also an essential drug.

Effectiveness of the Antiviral Drugs Remdesivir, Lopinavir/Ritonavir, and Favipiravir for COVID-19 Treatment

Although select antivirals have exhibited efficacy to improve clinical outcomes in COVID-19 patients, none demonstrated efficacy in reducing mortality. Larger RCTs are needed to conclusively establish efficacy [38].



Here are representatives of mimics, peptide mimics and nucleosides, None of them reduced mortality, Used as palliative treatment drugs.

This current review provides insights into the evidence- based role of remdesivir, lopinavir/ritonavir, and favipiravir in the treatment of COVID-19. The result on the effectiveness of currently used antiviral agents suggested that the use of these drugs in clinical trials showed conflicting results. Some studies stated that remdesivir is beneficial in improving recovery and the clinical improvement of hospitalized COVID-19 patients, although its impact in reducing mortality remains uncertain. Favipiravir has shown promising results in improving the clinical status of COVID-19 patients, although several studies suggested that there were no significant differences in some clinical parameters, eg, length of hospitalizations and clinical recovery. Combination of favipiravir with other supportive therapy such as tocilizumab for the treatment of COVID-19 showed more favorable results. Moreover, prior studies stated no significant clinical improvement between lopinavir/ritonavir compared to standard care with notable adverse effect reactions. Nevertheless, this current conclusion was based on limited clinical trials data. Also, there is currently very limited safety data for these antivirals, which need to be considered in further studies. A comprehensive assessment on both the benefit and risk of these antivirals is also urgently needed to allow a more comprehensive overview for a more informed decision of using these drugs in clinical settings. Due to limited studies on this topic, further high- quality evidence from well-designed clinical trials is needed.

Are we prepared for the next viral pandemic? The answer is still "no". The catastrophic impact of the SARS-CoV-2 pandemic has the potential to divert attention away from other viruses that cause human disease and have the potential to cause the next pandemic. To mitigate this risk, there needs to be continued surveillance and modelling to support the prediction of which deadly virus will be the next to emerge into the human population. Of critical importance is directing research effort and investment into the development of broadly acting antivirals that can be mobilized as the first line of defense upon emergence of new viral pathogens.

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