Chapter

Role of Anti-Viral Drugs in Combating SARS-CoV-2

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Abstract

Viruses are the eventual assertion of parasitism, they not only take nutriments from the host cell, apart from that they direct its metabolic machinery to amalgamate novel virus particle and to diminish the ability of flu viruses to reproduce in an individual antiviral drugs are used. When used as directed, antiviral drugs may help to lessen the duration of flu symptoms and may reduce the severity of common flu symptoms. Antiviral drugs are the class of drugs which comes under the antimicrobials, and that also accommodates the larger group i.e. of antibiotics. They are broad-spectrum in nature and can be effective against a wide range of viruses. They can be used as a single drug as well as in combination of drugs. Antiviral drugs are dissimilar from the antibiotics, they do not demolish their target pathogen ideally they obstruct development of pathogen. To the greatest extent antiviral drugs currently accessible are delineate to deal with herpes viruses, covid-19, HIV, the hepatitis b and c viruses herpes simplex, small pox, picornavirus and influenza a and b viruses etc. Scientists are searching to drag out the range of antiviral to the other families of pathogens. They mainly act by inhibiting the attachment of viruses on cells, prevent genetic reproduction of virus, prevent viral protein production and vital for production of virus. The emanation of antiviral is generally the outcome about an appreciably expanded skills or proficiency of the generative, microscopic and atomic activity of organisms, allowing biomedical analyst to acknowledge the structure, mechanism of action and activity of viruses, significant progress within the procedure for come across the current drugs**.** Coronavirus 2019 (COVID 19) is highly infectious disease triggered by SARS-CoV-2 (severe acute respiratory syndrome) coronavirus 2 causing nearly 2.9 million deaths worldwide. With the emergence of SARS-CoV-2, the repurposing of antiviral drugs has come into picture.

Keywords: Parasitism, Broad spectrum, Genetic development of virus, Target pathogen, Viral protein production

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus also known as SARS- CoV, a medical condition arises due to viral infection of SARS-CoV. It was proved to be major threat to human civilization in 21st century was declared as pandemic by World Health Organization in March 2020 as the exposure of this syndrome affected the human life cycle poorly causing deaths at an average of 10 percent

of the affected population globally. This was first emerges in the Wuhan (a state of China) in December 2019 and later on feast globally by the transmission from affected person to the other person through physical contact [1, 2] and later on when it was established and discovered, the first preventive measure was social distancing which came into force February 2020 according to WHO guidelines and other coronavirus like MERS (Middle east respiratory syndrome) in 2017 and Covid-19 which emerges before 2020.

1.1 Symptoms of SARS

Symptoms of COVID-19 are homogenous to influenza to some extent, and it also causes a pneumonia type symptom, which has been seen in many patients throughout the world. The patients who have fallen ill are reported to suffered cough mainly with sputum, high temperature of the body, difficulties while breathing, headache and sore throat, shaking chills, and diarrhea.

1.2 Structure of coronavirus

SARS-CoV belongs to Coronaviridae family having spherical enveloped particle containing positive stranded RNA that binds to nucleocapsid present inside the membrane protein having glycoprotein spike in the envelop [3, 4] further explained in **Figure 1**.

1.3 Phases of development of SARS

As a virus, it also confiscates the host body system and then multiplies via viral attachment, fusion, penetration; uncoating, transcription, translation, and virion release [5].

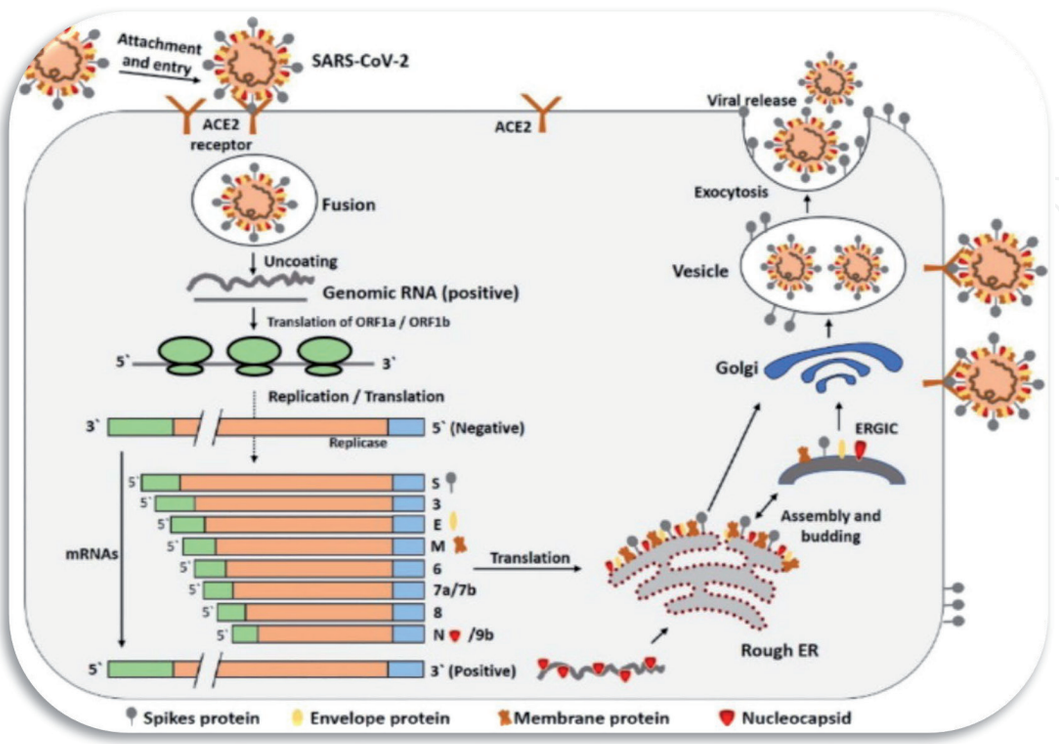

Figure 1.
Mechanism action of coronavirus.

Pathway used to combat SARS through direct inhibition of coronavirus either by inhibiting the vital viral protein corresponds to genome reproduction or else by impeding viral entry into eukaryotic cells. In second place, by modulating immune system either by boosting the immediate response or by inhibiting the inflammatory response [6].

2. Antiviral drugs

Although viral infections have been disclosed since earliest times, it was only during the nineteenth century that scientists were able to isolate "the filterable particles", later called viruses. Viruses are the infectious agent that reproduces only inside the living cell and they can infect all types of living cells and direct the cell to produce more viruses. They are smaller than the bacteria's. The entire infectious virus particle, called a virion, consists of the nucleic acid and an outer shell of protein. Antiviral drugs are classified as the medicines which are mainly used to treat viral infection. Many of the antiviral drugs target the specific viruses and they are considered as the broad spectrum drugs. Most viral infections rectify spontaneously in immunocompetent individuals. The objective of antiviral therapy is to diminish the symptoms and infectivity additionally to shorten the duration of illness [7]. These drugs react by arresting the viral replication cycle at numerous stages. Most of the antiviral drugs currently available are used to treat infections caused by HIV, herpes viruses, hepatitis Band C viruses, and influenza A and B viruses, and C viruses, and influenza A and B viruses etc. Designing effective and safe antiviral drugs is difficult as viruses use host cells to replicate. It is back-breaking to find targets for drugs that would affect only viruses leaving host cells. Viral variation is also one of the reasons posing difficulty in the development aof antiviral drugs and vaccines. Furthermore, antiviral drugs are classified as non-retroviral and retroviral drugs which act on the different types of viruses and stop their further growth or their replication and these results in the cure of viral disease [8]. Coronavirus 2019 (COVID 19) is highly infectious disease triggered by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2 causing nearly 2.9 million deaths worldwide Currently, a variety of antiviral drugs are in clinical trails to treat SARS-CoV-2 which inhibit viral replication.

3. Classification of viruses

3.1 ICTV classification

The ICTV evolves the current classification system and wrote guidelines that put a bigger weight on certain virus properties to maintain family consistency. A unified taxonomy has been accepted. Solitary a little part of the entire variety of viruses has been studied. Till 2019 ICTV explained 9 kingdoms, 4 realms, 2 subphyla, 16 phyla, 36 classes, 55 orders, 9 suborders, 168 families, 10 sub-families, 1421 genera, 68 subgenera and 6589 species of viruses [9].

The general taxonomic structure of ranges of taxon and the suffixes used in taxonomic names are mentioned under. Till 2019, the ranks of sub realm, subkingdom and subclass are unemployed whereas all ranks are in usage.

Realm (*-viria*), Subrealm (*vira*), Kingdom (*-virae*), Subkingdom (*-virites*), Phylum (*-viricota*), Subphylum (*-viricotina*), Class (*-viricetes*), Subclass (*-viriceti-dae*), Order (*-virales*), Suborder (*-virineae*), Family (*-viridae*), Subfamily (*-virinae*), Genus (*-virus*), Subgenus (*-virus*) [10].

3.2 Baltimore classification

This is based on the mechanism of mRNA production. Viruses produce proteins from their genomes and replicate themselves. Viral genome can be single-stranded (ss) and or double stranded (ds). ssRNA viruses may be either antisense (−) or sense (+) [11]. Viruses are classified in seven groups:

i. ssDNA viruses (+strand or sense) DNA (e.g., Parvovirus)

ii. dsDNA viruses (e.g., Adenovirus, Poxvirus)

iii. dsRNA viruses (Reovirus)

iv. (+) ssRNA viruses (+ strand or sense) RNA (e.g. Coronavirus,Picornavirus)

v. (−) ssRNA viruses (+ strand or antisense) RNA (e.g.Orthomyxovirus, Rhabdovirus)

vi. dsDNA-RT viruses DNA with RNA intermediate in life cycle (e.g., Hepadnavirus)

vii. ssRNS-RT viruses (+strand or sense) RNA with DNA intermediate in life cycle (eg. Retroviruses)

3.3 Based on their shape

Viruses are present in various sizes and shapes (**Figure 2**), but are composed of two vital components i.e., a core of genetic material, either RNA or DNA and a protein coat, capsid. A virion comes in four different shapes i.e. spherical, helical,

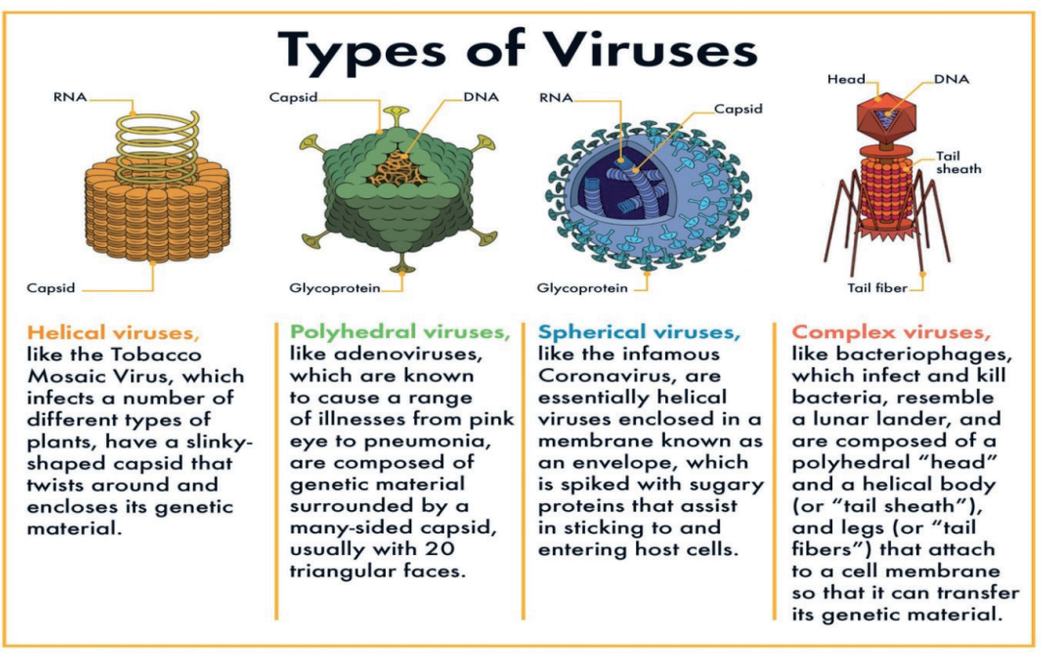

Figure 2.
Types of viruses.

polyhedral and complex Coronaviruses have positive stranded RNA (+ssRNA) with crown like structure possessing spike glycoproteins on the envelop [12].

4. Evolution

A virus is a tiny parasite, infectious substance of small size and basically structure that can multiply only in living cells of plants, animals or bacteria etc. The name is derived from a Latin word meaning "poison." Highly viruses have either RNA or DNA as their genetic material. The nucleic acid of viruses may be single or double stranded. The complete infectious virus element, called a virion, comprises of the nucleic acid and an outer shell is made up of protein [13]. Identifying evolving viruses are those that are freshly appeared or have recently expanded in predominance and/or geographical range uncovers several vital vague patterns. Primary virtually all emerging viruses have RNA more readily than DNA genomes. RNA viruses are more customarily familiar than DNA viruses. Additionally, almost all emergent viruses have an animal reservoir, such that the process of viral emergence can frequently be categorized as cross-species transmission. The extremely substantial exception for the rule is that cross-species transmission is central to viral emergence is HCV, which was first identified in 1989 but which is expected to have a considerably extended history in human populations [14]. In numerous cases, the specific cause of emergence, why the virus has traversed from animals and obsessed by humans can be assigned to ecological factors, involving to alterations in land use and deforestation. Although a multitude of such factors exist, either variations in the proximity of the donor and recipient populations, so that humans have an amplified coincidental of exposure to animal pathogens and variations in the size and density of the donor and recipient populations result in increase in both the exposure and the probability that continued networks of transmission will be established once a virus has inserted into a new species. Although biologists have assembled huge amount of knowledge how present day viruses evolve. When investigating the evolutionary history of most organisms, scientists can look at fossil record and homogenous historic evidence. While many of the viruses do not have the single ancestors. Generally recognizing the significance of ecology, it is also possible that genetic factors, whether in the host or further probably the virus, contribute to the process of disease emergence. As observed with other RNA viruses, SARS-CoV-2 is undergoing genetic mutations while adapting to new individual hosts. Several variants are reported, however only few are affecting public health. In United Kingdom, VOC 202012 (B.1.1.7 lineage) was described in December 2020 followed by B.1.351 lineage (501Y.V2) in South Africa. B.1.1.248/B.1.1.28/P1 (or 501Y.V3) was reported in Brazil in January 2021 and recently in California B.1.427/B.1.429 is discovered. As per WHO, 7 variants are of interest viz. B.1.525, B.1.526, B.1.427/B.1.429, B.1.1.28.2 alias P2, B.1.1.28.3, alias P.3 and B.1.616 [15].

5. How virus replicate

As viruses are obligate pathogen they cannot replicate on their own but they need the host to replicate and produce multiple copies of them. This typically occurs by the virus inserting its genetic material in host cells, co-opting the proteins to create viral replicates, until the cell bursts from the high volume of new viral particles.

There are six fundamental stages that are essential for viral replication (**Figure 3**).

1. Attachment
2. Penetration
3. Uncoating
4. Replication
5. Assembly
6. Virion Release

1. Attachment: This stage involves the interaction between the virus and host cell surface, there they interact with receptors peculiar to them and their host cells. This is also known as the tropism of a virus.

2. Penetration: The attachment to the specific receptor can produce conformational changes in the viral capsid protein that lead the way to the viral and cellular membranes fusing. Some DNA viruses can also undertake into the host cell through receptor-mediated endocytosis.

3. Uncoating: Once inside the cell, the first step is uncoating. This process requires the viral capsid degrading, either by the action of viral or host enzymes and release of genomic information takes place. This enables the start of replication through transcription or translation for RNA or DNA viral genomic information, respectively. The result of the replication step is the synthesis of the viral genome and proteins.

4. Replication: this process is different both in RNA and DNA viruses and also in viruses with dissimilar nucleic acid polarity. This procedure terminates in de novo synthesis of genome and viral proteins.

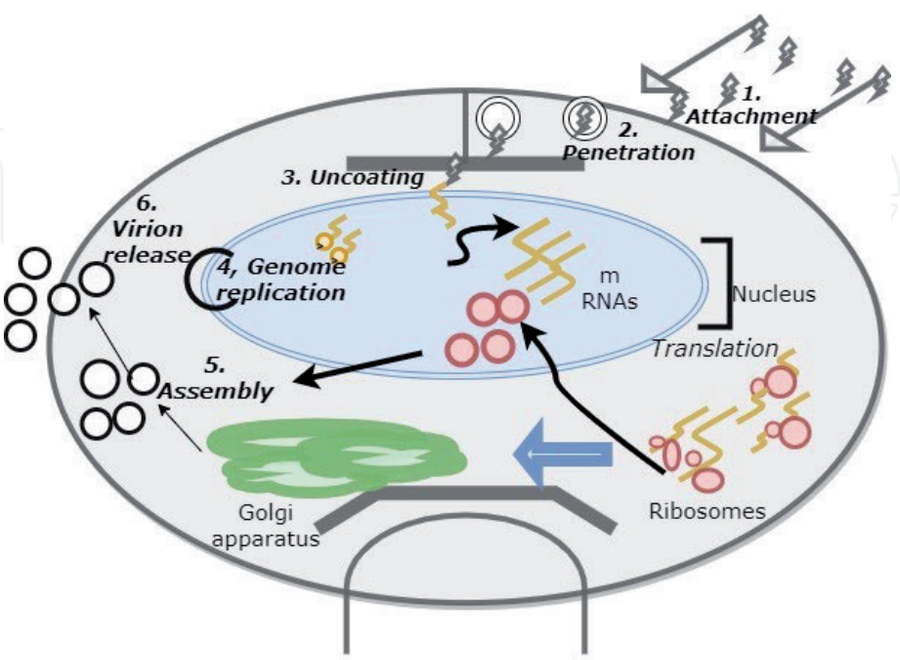

Figure 3.
Stages of viral replication.

5. Assembly: After de novo synthesis of viral proteins and genome, which can be altered post-transcriptionally, viral proteins are wrapped with newly replicated viral genome into new virions that are unconfined from host cells. This process is called maturation.

6. Virion Release: There are two mechanisms of viral freeing: lysis or budding. After virion release some viral proteins remain within the host's cell membrane, which acts as potential targets for circulating antibodies [16].

CoVs are positive stranded RNA enveloped viruses. Upon entry into the host, viral RNA replication begins with synthesis of polyprotein 1a/1ab(pp1a/pp1ab). By the synthesis of subgenomic RNAs sequences and replication-transcription complex, transcription occurs. Termination of transcription occurs at transcription regulatory sequences. Six open reading frames (ORF) are present on CoV genome. Frameshift between ORF 1a and ORF1b helps in production of both pp1a and pp1ab polypeptides which are further processed by chymotrypsin like protease (3CLpro) or main protease or may include papain like proteases which produces non-structural proteins (NSPs 1–16). Besides ORF1a and ORF1b, other ORFs encode structural proteins including nuclecapsid proteins, membrane, envelope, spike and accessory proteic chains [17]. Dedicated sgRNAs translate accessory and structural proteins. Researchers have also reported NSPs in stalling hosts immunity [18]. The envelop plays crucial role in viral pathogenesis as it encourages viral release and assembly [19].

5.1 Classification of antiviral drugs

Anti-viral drugs and their activity mention in **Table 1**.

A. Antiviral Drugs (Non-Retroviral).

1. Anti-herpes drugs

   - Acyclovir
   - Idoxuridine
   - Valacylovir
   - Famcicylovir
   - Cidofovir
   - Penciclovir

2. Anti-influenza virus drugs

   - Amantadine
   - Rimantadine
   - Oseltamivir
   - Zanamivir

Sr. No.	Name of Drugs	Description	Absorption	Metabolism	Protein Binding	Clearance	Dose	Toxicity
1.	Acyclovir	Acyclovir is a nucleotide analog antiviral drug	oral bioavailability of acyclovir is 10–20%	<15% oxidized to 9-carboxymethoxymethylguanine, 1% 8-hydroxylated to 8-hydroxy-acyclovir	9–33% protein bound in plasma	Renal clearance is 248 mL/min/1.73 m	200 mg 5 times a day oral (15 mg/kg/day) 5–10 mg/kg 8 hourly by slow i.v. infusion 5% topical application 6 times a day;	agitation, coma, seizures, lethargy, reduced kidney function
2.	Penciclovir	Penciclovir is a synthetic acyclic guanine derivative	Following single or repeat application of the 1% cream at a dose of 180 mg penciclovir daily.	Hepatic	Less than 20%.	Total plasma clearance of 39.3 L. $hr.^{-1}$	1% cream at a dose of 180 mg	Headache, abdominal pain, increased serum lipase, nausea, dyspepsia, dizziness, and hyperbilirubinemia
3.	Amantadine	An antiviral that is used in the prophylactic or symptomatic treatment of influenza A	well absorbed orally from the gastrointestinal tract	It is metabolized to a small extent (5–15%) by acetylation.	67% bound to plasma proteins	0.2–0.3 L/hr./kg	100 mg BD, elderly—half dose children 5 mg/kg/day	cardiac, respiratory, renal or central nervous system toxicity, arrhythmia, tachycardia and hypertension
4.	Rimantadine	An RNA synthesis inhibitor that is used as an antiviral agent	Well absorbed, with the tablet and syrup formulations being equally absorbed after oral administration	Glucuronidation and hydroxylation are the major metabolic pathways.	40%	Less than 25% of the dose excreted in the urine as unchanged drug	100 mg BD elderly 100 mg OD 5 mg/kg/day	agitation, hallucinations, cardiac arrhythmia and death

Sr. No.	Name of Drugs	Description	Absorption	Metabolism	Protein Binding	Clearance	Dose	Toxicity
5.	Lamivudine	A reverse transcriptase inhibitor and zalcitabine analog in which a sulfur atom replaces the 3′ carbon of the pentose ring	Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution	The only known metabolite of lamivudine is the trans-sulfoxide metabolite. This biotransformation is catalyzed by sulfotransferases.	<36% bound to plasma protein	Total clearance is 398.5 ± 69.1 mL/min	For chronic hepatitis B—100 mg OD For HIV infection—150 mg BD	headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough
6.	Ribavirin	Ribavirin is a synthetic guanosine nucleoside and antiviral agent that interferes with the synthesis of viral mRNA	The oral bioavailability is 64% following a single oral dose administration of 600 mg ribavirin	It is phosphorylated by adenosine kinase to ribavirin mono-, di-, triphosphate metabolites. After activation and function, it undergoes metabolic pathways where it is reversibly phosphorlyated or degraded via deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite	No protein binding	total apparent clearance rate of 1200 mg is 26 L/h	200 mg QID (children 10 mg/kg/day);	flu-like symptoms, depression, suicide, insomnia, irritability
7.	Zidovudine	A dideoxynucleoside compound in which the 3′-hydroxy group on the sugar moiety has been replaced by an azido group	Rapid and nearly complete absorption from the gastrointestinal tract. Systemic bioavailability of zidovudine capsules and solution is approximately 65% (range, 52 to 75%)	Hepatic. Metabolized by glucuronide conjugation to major, inactive metabolite, 3′-azido-3′-deoxy-5′- O-beta-D-glucopyranuronosylthymidine (GZDV)	30–38%	1.85 +/− 0.47 L/hr./kg	Adults 300 mg BD Children 180 mg/m2 (max 200 mg) BD.	fatigue, headache, nausea, and vomiting

Sr. No.	Name of Drugs	Description	Absorption	Metabolism	Protein Binding	Clearance	Dose	Toxicity
8.	Didanosine	Didanosine is a potent inhibitor of HIV replication, acting as a chain-terminator of viral DNA by binding to reverse transcriptase	Rapidly absorbed (bioavailability 30–40%) with peak plasma concentrations appearing within 0.5 and 1.5 hrs	Rapidly metabolized intracellularly to its active moiety, 2,3-dideoxyadenosine-5-triphosphate (ddA-TP). It is then further metabolized hepatically to yield hypoxanthine, xanthine, and uric acid	Low (<5%)	Renal clearance	400 mg/day 250 mg/day 1 hour before or 2 hours after meals	pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia and hepatic dysfunction
9.	Nevirapine	A potent, non-nucleoside reverse transcriptase inhibitor (NNRTI	The absolute bioavailability in healthy adults following a single dose administration is 93 ± 9% for a 50 mg tablet and 91 ± 8% for an oral solution	nevirapine is extensively biotransformed via cytochrome P450 3A4 metabolism to several hydroxylated metabolites.	60% bound to plasma protein	Renal clearance	200 mg/day oral to be increased after 2 weeks to 200 mg BD	edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonaryinfiltrates, rash, vertigo, vomiting, and weight decrease
10.	Ritonavir	Ritonavir is an HIV protease inhibitor that interferes with the reproductive cycle of HIV. Although it was initially developed as an independent antiviral agent	Following oral administration, peak concentrations are reached after approximately 2 hours and 4 hours	Ritonavir circulates in the plasma predominantly as unchanged drug. Five metabolites have been identified. The cytochrome P450 enzymes CYP3A and CYP2D6 are the enzymes primarily involved in the metabolism of ritonavir.	~98–99%	The apparent oral clearance at steady-state is 8.8 ± 3.2 L/h	600 mg BD to be taken with meal	hepatotoxicity, pancreatitis, and allergic reactions/ hypersensitivity
11.	Indinavir	A potent and specific HIV protease inhibitor that appears to have good oral bioavailability	Rapidly absorbed	Hepatic. Seven metabolites have been identified, one glucuronide conjugate and six oxidative metabolites	60%	Less than 20% of indinavir is excreted unchanged in the urine	800 mg TDS	Symptoms of overdose include myocardial infarction and angina pectoris.

Sr. No.	Name of Drugs	Description	Absorption	Metabolism	Protein Binding	Clearance	Dose	Toxicity
12.	Efavirenz	It is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used as part of highly active antiretroviral therapy (HAART)	EFV is readily *absorbed* and achieves peak serum concentration (Cmax) of 4.07 mcg/ml 3–5 hours following 600 mg standard adult oral dose.	Efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation	99.5–99.75%	Nearly all of the urinary excretion of the radiolabeled drug was in the form of metabolites	600 mg OD on empty stomach	The most common adverse effects with efavirenz therapy are central nervous system symptoms, rash and hepatitis
13.	Raltegravir	Raltegravir is an antiretroviral drug	Absorbed from the gastrointestinal tract	Hepatic (UGT1A1)	83%	9% of total dose	600 mg BD to be taken with meal	CNS toxicitySS

Table 1.
Anti-viral drugs and their activity [17–21].

3. Anti-hepatitis virus drugs

A. For hepatitis B

- Lamivudine
- Tenofovir

b. For hepatitis C

- Ribavirin
- Interferon alpha

B. Anti-Retrovirus Drugs.

1. Nucleoside reverse transcriptase Inhibtors (Nrtis)

- Zidovudine
- Didanosine
- Stavudine
- Lamivudine

2. Non-Nucleoside Reverse Transcriptase Inhibitor (Nnrtis).

- Nevirapine
- Efavirenz
- Delavirdine

3. Protease inhbitor (PIs)

- Ritonavir
- Atazanavir
- Indinavir
- Nelfinavir

4. Entry inhibitor

- Enfuviritide

5. Ccr-5 receptor inhibitor

- Maraviroc

6. Integrase inhibtor

   - Raltegravir

6. Mechanism of action of non- retroviral drugs

6.1 Anti-Herpes drugs

The recognition of acyclovir and penciclovir has leaded the way evolution of a fortunate systemic therapy for medicating herpes simplex virus infection. Acyclovir is a nucleotide analogue antiviral which is used to treat against herpes simplex. It is generally used as the first line drug in the treatment viruses. Acyclovir is converted into acyclovir monophosphate due to the action of viral thymidine kinase. Acyclovir monophosphate is further converted to the diphosphate form by guanylate kinase. Acyclovir diphosphate is become acyclovir triphosphate by help of nucleoside diphosphate kinase. Acyclovir triphosphate effectively binds to viral DNA polymerase than cellular DNA polymerase and enters into DNA where 2′ and 3′ carbon leads to DNA chain termination. Acyclovir stronger affinity for viral DNA polymerase did not allow other bases to bind it, making them inactive [20].

Dose and Preparation: 200 mg 5 times a day oral (15 mg/kg/day), 5–10 mg/kg 8 hourly by slow i.v. infusion, 5% topical application 6 times a day; ZOVIRAX 200 mg tab, 250 mg/vial for i.v. injection; CYCLOVIR 200 mg tab, 5% skin cream; HERPEX 200 mg tab, 3% eye ointment, 5% skin cream; OCUVIR 200, 400, 800 mg tab, 3% eye ointment, ACIVIR-DT 200, 400, 800 mg tab.

Toxicity: Symptoms of overdose include agitation, coma, seizures, lethargy, and precipitation in renal tubules. These symptoms are more unsophisticated in patients given high doses without monitoring of fluid and electrolyte balance or reduced kidney function.

6.2 Anti-influenza virus drugs

- As per CDC four antiviral drigs are approved by FDA against influenza virus.
- Relenza (zanamivir)
- Tamiflu (oseltamivir phosphate)
- Rapivab (peramivir)
- Xofluza (baloxavir marboxil)
- Amantadine and rimantadine were approved long back ago to cure influenza A virus infection. But new strains of influenza like 2009 H1N1 are resistant to these drugs. Zanamivir acts by inhibition of influenza virus neuraminidase thereby altering particle release and aggregation. It renders the virus inactive by making it unable to break into host cells and infect others [21].

Dose and Preparation: Therapeutic Dose 10 Mg Bd By Inhalation; Prophylactic Dose 10 Mg Od; Relenza 5 Mg Per Actuation Powder Inhaler.

Toxicity: The toxicology studies illustrated that zanamivir has very little toxicity and no drug-specific toxicities were observed in animal toxicity studies.

Arbidol which is popularly used to cure influenza is reported to inhibit SARS-CoV-2 [22]. Similarly, Favipiravir, an anti-influenza drug, also is undergoing clinical trials against COVID19 [23].

6.3 Anti-hepatitis virus drugs

To date, two classes of antiviral drugs have been accepted by the Food and Drug Administration for the treatment of hepatitis B, and nucleos(t)ide analogs (lamivudine, telbivudine, adefovir, tenofovir [TDF] and for hepatitis C, immunomodulators (interferon [IFN]-α and pegylated-interferon [PEG-IFN]-α). Lamivudine, a synthetic nucleoside analogue, is phosphorylated intracellularly to lamivudine triphosphate, 5′-triphosphate metabolite. The nucleoside analogue is inserted into viral DNA by HBV polymerase and HIV reverse transcriptase leading to DNA chain termination. Interferons are glycoproteins synthesized by host cells in response to viral infection and some other inducers. These are effective against DNA and RNA virus and have a no-specific inhibitory effect on the viral replication against a wide variety of unrelated viruses [24].

Dose and Preparation: For Chronic Hepatitis B 100 Mg Od; For Hiv Infection 150 Mg Bd (Along With Other Antiretroviral Drugs); Lamivir 150 Mg Tab, 150 Mg/5 Ml Solution; Lamivir-Hbv 100 Mg Tab; Heptavir, Lamidac, Lamuvid 100, 150 Mg Tabs.

Toxicity: The most common reported adverse reactions in adults were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough etc.

Remdesivir which was developed to treat Hepatitis C has also demonstrated antiviral activity against SARS-CoV-2 [25]. As per results of controlled, randomized clinical trials, remdesivir has shortened the time of recovery in adults employed to treat hospitilized COVID-19 patients [26–30]. However, remdesivir potential against new SARS-CoV-2 variants is under trail and should be monitored.

Ribavirin used to cure COVID-19 [31] approved to cure respiratory syncytial virus and HCV leads to anemia at higher dose [32]. Ribavirin is administered intravenously at a dose of 500 mg, 2–3 times a day [33].

Some Antiretroviral Combinations:

1. Lamivudine 150 Mg + Zidovudine 300 Mg Table (1 Tab Bd); Combivir, Cytocom, Duovir, Lamuzid, Zidolam Table.

2. Lamivudine 150 Mg + Stavudine 30 Mg Or 40 Mg Table (1 Tab Bd); Lamivir-S, Lamostad, Virolis Table.

3. Lamivudine 150 Mg + Zidovudine 300 Mg + Nevirapine 200 Mg Table (1 Tab Bd); Duovir-N, Cytocom-N, Nexivir-Z.

7. Mechanism of action of retroviral drugs.

7.1 Nucleoside reverse transcriptase inhibitors (NRTIS)

The nucleotide/nucleoside reverse transcriptase inhibitors are the first class of antiretroviral drugs approved by FDA. NRTIS are taken up by host cells and phosphorylated and activated by cellular kinases. NRTIS lack 3′-hydroxyl group at the 2'deoxyribosyl moiety and have nucleotide/nucleoside as base. They prevent the

formation of 3′-5′-phosphodiester bond in DNA chains thus preventing the replication of virus. An important aspect these drugs is that they inhibit the production of either negative or positive strands of DNA if incorporated during DNA- dependent DNA synthesis or RNA-dependent DNA synthesis [34].

Dose and Preparation: Didanosine: 400 Mg/Day (For >60 Kg Bw), 250 Mg/Day (< 50 Kg Bw); 1 Hour Before or 2 Hours After Meals; Dinex Ec, Dd Retro, Virosine Dr. 250, 400 Mg Tabs. Zidovudine (Azidothymidine, AZT): Adults 300 mg BD; Children 180 mg/m2 (max 200 mg) BD. Retrovir, Zidovir 100 Mg Cap 300 Mg Tab, 50 Mg/5 Ml Syr, Zidomax, Zydowin 100 Mg Cap, 300 Mg Tab (To Be Taken With Plenty Of Water).

Toxicity: Symptoms of overdose include fatigue, headache, nausea, and vomiting. LD_{50} is 3084 mg/kg (orally in mice).

7.2 Non-nucleoside reverse transcriptase inhibitor (NNRTIS)

These are second class of reverse transcriptase inhibitors. They act by binding to reverse transcriptase and create hydrophobic pocket proximal to active site. This pocket generates novel spatial configuration of substrate binding site to decrease the overall activity of polymerase. By producing different configuration, synthesis of DNA slows down. NNRTIS are not effective against HIV-2 reverse transcriptase, because of non-competitive inhibitor action.

Dose and Preparation: Nevirapine: 200 mg/day oral to be increased after 2 weeks to 200 mg BD; Nevimune, Nevivir, Nevipan, Neviretro 200 Mg.

Toxicity: Symptoms of overdose include edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, and weight decrease. The most common adverse reaction is rash.

8. Protease inhbitor (PIs)

The HIV viral proteinase enzyme which always fragment the replicative and structural proteins which evolve from major HIV genes mormally as gag and pol, is restrain by Ritonavir. Ritonavir inhibits the cleavage of gag-pol polyprotein leading in non-infectious immature viral particles. Ritonavir is also potent inhibitor of cytochrome P450 CYP3A4 isoenzyme which is present in both liver and small intestine. It is type II ligand which binds into CYP3A4 and further irreversibly to heme iron via thiazole nitrogen linkage which reduces proteins redox potential and impedes its reduction with cytochrome P450 reductase, redox partner. Ritonavir may edge cellular transport and efflux of other protease inhibitor via MRP efflux channel and P-glycoprotein.

Ritonavir/ Lopinavir is FDA approved therapy to treat HIV and is also reported to treat COVID19. However in patients with severe COVID-19, this combination showed no benefit [35].

PREPARATIONS: RITOVIR 250 mg tab, RITOMUNE, RITOMAX 100 mg cap.

Entry inhibitors obstruct HIV entry into CD4 cells in organism cells. They act in a different way other than nucleoside reverse transcriptase inhibitors, protease inhibitors and non-nucleoside reverse transcriptase inhibitors which function after they it has infected CD4 cells. They work by taking themselves to proteins which is composed of amino acids on superficial side of CD4 cells, the proteins present on surface of CD4 cells or on the surface of HIV. The proteins on HIV outer coat must bind to proteins present on the surface of CD4. Entry proteins inhibit the above process.

PREPARATION: - Efavirenz: is available as 600 mg tab, also FFERVEN, VIRANZ, and EVIRENZ, 200 mg cap, 600 mg tab.

9. Conclusion

In this review we have concluded that the treatment of the viral infection and current covid 19 includes the combination therapy of antiviral drugs and the immune modeling drugs. Use of the antiviral drugs for the treatment of viral infection prevents from illness and as well as mortality rate. Lot of clinical trails are going on to prove their efficacy against SARS-CoV-2 and will definitely prove to be fruitful and help to save the human community.

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