



Potential Anti-COVID-19 Drug Options

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ABSTRACT

COVID-19, the infection caused by the recently identified coronavirus, is currently a disease with no pharmaceutical weapons against it. Researchers across the world are racing to find the investigation of existing drugs for new therapeutic purposes (Drug repositioning, also called drug repurposing) to develop safe and effective COVID-19 treatments. Other research directions include the development of a COVID-19 vaccine. Developing new vaccines takes time, and they must be rigorously tested and confirmed safe via clinical trials before they can be routinely used in humans. WHO launched the multinational trial to jumpstart the search for coronavirus drugs. The drugs to be tested are the antiviral drug remdesivir; a combination of two HIV drugs, lopinavir and ritonavir, lopinavir, and ritonavir plus interferon beta and the antimalarial drug chloroquine and Hydroxy Chloroquine. All show some evidence of effectiveness against the SARS-CoV 2 virus, which causes COVID-19, either in vitro and animal studies. The four drugs or combinations will be compared to what is called a standard of care the regular support hospitals treating these patients use at present, such as supplementary oxygen when desired. Clinical trials in China and several other countries have been conducting on drugs such as Remdesivir, Lopinavir + Ritonavir, Tenofovir, Oseltamivir, Baloxivir marboxil, Umifenovir, Novaferon, IFNs, Chloroquine, Traditional Chinese Medicines: Lianhua Qingwen.

Keywords: COVID-19, SARS-CoV-2, Novel coronavirus, Hydroxy Chloroquine, Remdesivir, Lopinavir, Ritonavir, Chloroquine.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally, resulting in the ongoing 2019-2020 coronavirus pandemic¹⁻³ (occurring over a wide geographic area and affecting an exceptionally high proportion of the population). The name "coronavirus" is derived from Latin *corona*, meaning "crown." Coronaviruses contain a positive-sense, single-stranded RNA genome. The genome size for Coronaviruses ranges from approximately 27 to 34 kilobases. The genome size is one of the largest among RNA viruses. The genome has a 5' methylated cap and a 3' polyadenylated tail. Common symptoms include fever, cough, and shortness of breath. Other symptoms may include muscle pain, sputum production, diarrhea, sore throat, loss of smell, and abdominal pain. The virus is mainly transmission⁴ during close contact and by small droplets produced when people cough, sneeze or talk. Respiratory droplets may be produced during breathing, but the virus is not generally airborne. People may also contract COVID-19 by touching a contaminated surface and then their face. It is most contagious when people are symptomatic, although spread may be possible before symptoms appear.

The standard method of diagnosis is by reverse transcription-polymerase chain reaction (rRT-PCR)⁵ from a nasopharyngeal swab. The infection can also be

diagnosed from a combination of symptoms, risk factors, and a chest CT scan showing features of pneumonia. Recommended measures to prevent disease include frequent hand washing, social distancing (maintaining physical distance from others, especially from those with symptoms), covering coughs and sneezes with a tissue or inner elbow, and keeping unwashed hands away from the face. The use of masks is recommended for those who suspect they have the virus and their caregivers. Currently, there is no vaccine or specific antiviral treatment for COVID-19. Management involves the treatment of symptoms, supportive care, isolation, and experimental measures. The incubation period for COVID-19 is typically five to six days but may range from two to 14 days. Electron microscope image of SARS-CoV-2 (orange). (National institute of allergy and infectious diseases) is shown in Figure 1.

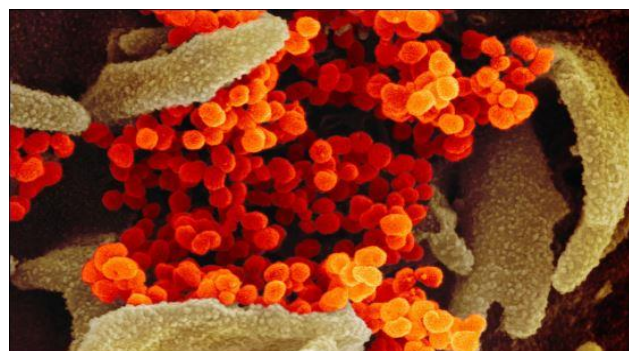


Figure 1: Electron microscope image of SARS-CoV-2 (orange). (National institute of allergy and infectious diseases)

Three strains (two species) produce potentially severe symptoms; all three of these are β -CoV strains:

1. The Middle East respiratory syndrome-related coronavirus (MERS-CoV)⁶, previously known as novel coronavirus 2012 and HCoV-EMC (It was transmitted from dromedary camels to humans).
2. Severe acute respiratory syndrome coronavirus (SARS-CoV or "SARS-classic")⁷ (It was transmitted from civet cats to humans).
3. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously known as 2019-nCoV or "novel coronavirus 2019." A novel coronavirus -19 is a new strain that has not been already identified in humans. Coronavirus is zoonotic, which means they are transmitted between animals and people.

Basic protective measures against the new coronavirus.

Wash your hands frequently (alcohol-based hand rub or wash them with soap and water), Maintain social distancing 1 meter (3 feet), Avoid touching eyes, nose, and mouth, Practice respiratory hygiene, If you have a fever, cough and difficulty breathing, seek medical care early, Stay informed and follow the advice given by your healthcare provider.

Coronavirus disease (COVID-19)⁸ advice for the public: Myth busters

To date, there is no specific medicine recommended to prevent or treat the new coronavirus (2019-nCoV). However, those infected with the virus should receive appropriate care to relieve and treat symptoms, and those with severe illness should receive optimized supportive care. It is most essential to be educated with the correct information about nCOVID-19 disease to protect the self and the significant others from contacting the disease.

Antibiotics do not work against 2019-nCoV. Antibiotics only work against bacteria. But sometimes antibiotics are used because of bacterial co-infection.

People of all ages can be infected by the new coronavirus (2019-nCoV). Older people and people with pre-existing medical conditions (such as asthma, diabetes, heart disease) appear to be more vulnerable to becoming severely ill with the virus.

Garlic is a healthy food that may have some antimicrobial properties. However, no evidence from the current outbreak eating garlic has protected people from the new coronavirus.

No evidence regularly rinsing the nose with saline can help people recover more quickly from the coronavirus.

Vaccines against pneumonia, such as pneumococcal vaccine and Haemophilus influenza type B (Hib) vaccine, do not protect against the 2019-nCoV.

No. Spraying alcohol or chlorine all over your body will not kill viruses that have already entered your body. Spraying

such substances can be harmful to clothes or mucous membranes (i.e., eyes, mouth).

Thermal scanners cannot detect people who are infected but are not yet sick with a fever. This is because it takes between 2 and 10 days before people who are affected become ill and develop a fever.

UV lamps should not be used to sterilize hands, or other areas of skin as UV radiation can cause skin irritation. UV disinfection lamp won't kill the new coronavirus.

Hand dryers are not effective in killing the 2019-nCoV. To protect yourself against the new coronavirus, you should frequently clean your hands with an alcohol-based hand rub or wash them with soap and water.

To date, there has been no information nor evidence to suggest that mosquitoes could transmit the new coronavirus.

The hot bath will not prevent you from catching COVID-19. Your normal body temperature remains around 36.5°C to 37°C, regardless of the temperature of your bath or shower.

There is no reason to believe that cold weather can kill new coronavirus or other diseases. The normal human body temperature remains around 36.5°C to 37°C, regardless of the external temperature or weather

From the evidence so far, the COVID-19 virus can be transmitted in ALL AREAS, including areas with hot and humid weather. Regardless of climate, adopt protective measures if you live in, or travel to an area reporting COVID-19. The best way to protect yourself against COVID-19 is by frequently cleaning your hands. Frequent or excessive alcohol consumption can increase your risk of health problems.

The most common symptoms of COVID-19 are dry cough, tiredness, and fever. Some people may develop more severe forms of the disease, such as pneumonia. The best way to confirm if you have the virus-producing COVID-19 disease is with a laboratory test. You cannot prove it with this breathing exercise, which can even be dangerous.

You can catch COVID-19, no matter how sunny or hot the weather is. Countries with hot weather have reported cases of COVID-19. To protect yourself, make sure you clean your hands frequently and thoroughly and avoid touching your eyes, mouth, and nose.

Table 1 shows the solidarity clinical trial for covid-19 and four treatment options. Figure 2 shows the Mechanisms of the four most promising coronavirus drugs interfering with different steps in the coronavirus replication cycle. (possible treatment). Table 2 represents the World Health Organization (WHO) for information purposes only concerning 2019-2020 global of the novel coronavirus. The following drugs are currently being trialled and the status of clinical development for COVID-19. The drugs mentioned in the below table represents a list of selected clinical trials for the amelioration of COVID-19.



Table 1: Solidarity clinical trial for Coid-19 and four treatment effective drug options⁸

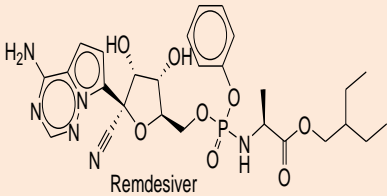
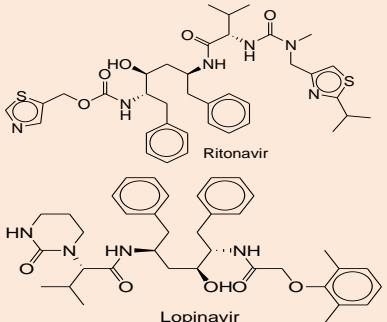
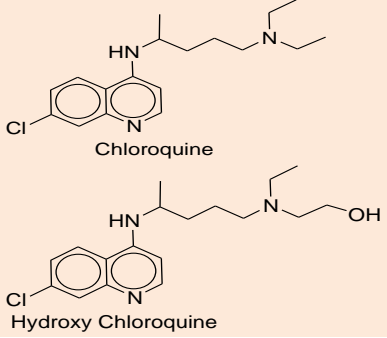
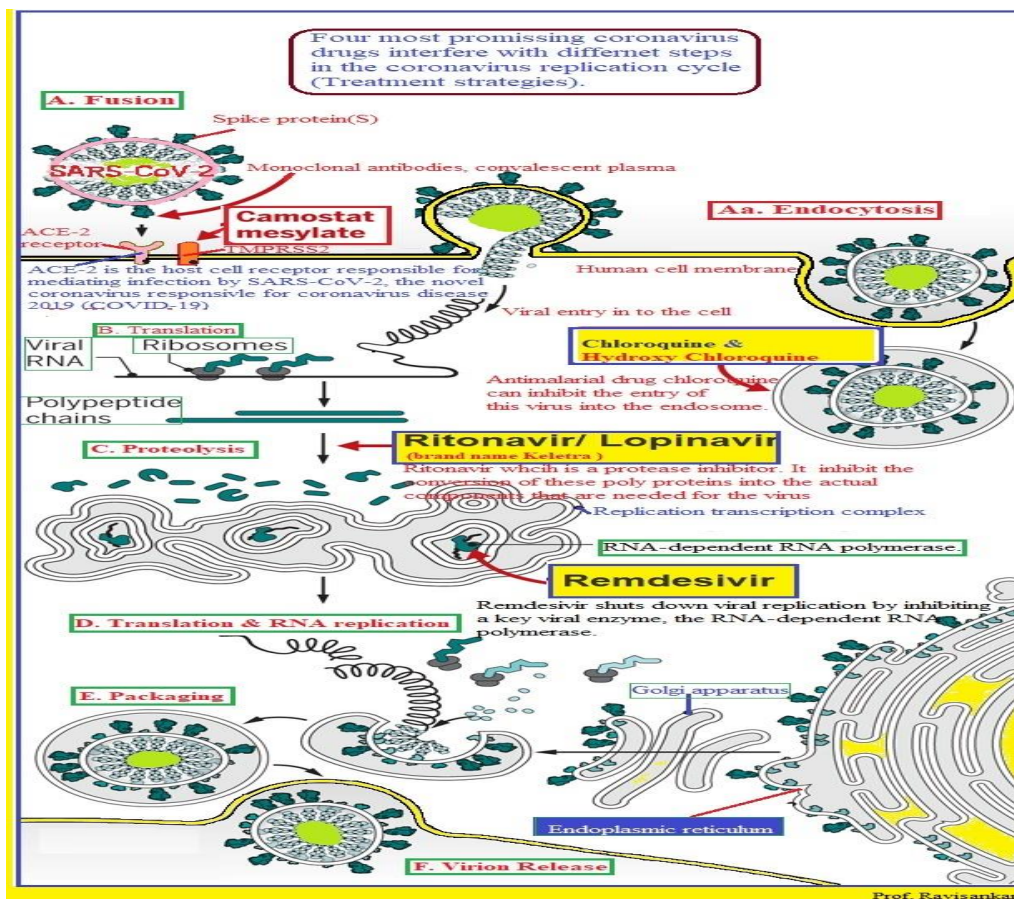
Drug candidate	Description	Proposed dose for COVID-19
 <p>Remdesivir</p>	Remdesivir ⁹⁻¹³ (GS-5734) is a Nucleoside inhibitor and was originally investigated as a treatment for Ebola virus. Remdesivir is a prodrug that metabolizes into its active form an adenosine nucleotide analog. GS-441524 interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production.	CT NCT04252664: 200 mg loading dose on day one is given, followed by 100 mg iv once-daily maintenance doses for nine days.
 <p>Ritonavir Lopinavir</p>	Lopinavir/Ritonavir ¹⁴ (Kaletra) is used for the treatment of HIV inhibition. Evidence for COVID-19, MERS and SARS. These are Protease inhibitors.	500 mg once, twice a day, two weeks.
 <p>Chloroquine Hydroxy Chloroquine</p>	Chloroquine and Hydroxychloroquine (HCQ) ¹⁵⁻¹⁸ are used to treat malaria and rheumatology conditions. Chinese medical res and certain inflammatory conditions. Hydroxy Chloroquine (HCQ) (Plaquenil) seemed to have "fairly good inhibitory effects" on the 2019 novel coronavirus. These are heme polymerase inhibitors ¹⁹ . Chloroquine is also used against some autoimmune diseases.	COVID-19 clinical trial: Hydroxychloroquine 400mg per day for five days
Lopinavir + Ritonavir + IFN β 1b	Interferon beta-1b is used to treat multiple sclerosis. Lopinavir and Ritonavir ²⁰ are antiretroviral protease inhibitors combination protease inhibitor and host. IFN- β a drug that was originally developed to treat COPD.	For MERS: Lopinavir /Ritonavir 400mg +100 mg /ml twice daily for 14 days and Interferon beta-1b 0.25 mg subcutaneous every alternate day for 14 days

Table 2: World Health Organization (WHO) for information purposes only concerning 2019-2020 global of the novel coronavirus. The following drugs are currently being trialled and the status of clinical development for COVID-19.

Drug candidate	Description	Proposed dose for COVID-19
Methylprednisolone 40 mg	It is a glucocorticoid and Clinical trial COVID-19, clinical studies SARS, clinical studies MERS	COVID-19 clinical trial: Methylprednisolone 40 mg q12h for 5 days.
Ribavirin + Ritonavir + Lopinavir	Nucleoside Inhibitor + protease inhibitor	Clinical trial: (1) lopinavir 400 mg/ritonavir 100 mg orally twice daily, plus (2) ribavirin 2.4 g orally as a loading dose followed by 1.2 g orally every 12 hours. Duration of treatment for up to 10 days. Case study: ribavirin 600mg 2x day and lopinavir + ritonavir 1000mg 1x day
Darunavir (with cobicistat) (Prezista® / Prezcobix® and Generic)	Antiretroviral, protease inhibitor. Used with low doses of cobicistat to increase bioavailability and half-life	Darunavir 800 mg/Cobicistat 150 mg QD
Emtricitabine + tenofovir (Truvada)	Non-nucleoside reverse transcriptase inhibitor + nucleotide reverse transcriptase inhibitor for HIV	Dosage clinical trial not available
Sirolimus(Rapamycin, Rapamune®)	mTor inhibitor IL2, immunosuppressant	Influenza: 1 mg 1xday. Severe H1N1 pneumonia: 2mg 1xday
IFN- α 2a (Pegasys® and others PEGylated IFN α 2a)	type I interferon made by leukocytes during viral infection	MERS: Pegylated interferon alfa-2a (Pegasys): 180 μ g subcutaneously per week for 2 weeks
IFN- α 2b (PegIntron®, Sylatron®, IntronA®)	type I interferon made by leukocytes during viral infection	MERS: Pegylated interferon alfa 2b (PEG-Intron): 1.5mcg/kg subcutaneously once per week x 2

IFN-β1a (Avonex®, Plegridy® (peginterferon β1a), Rebif®, CinnoVex®)	type I interferon made by leukocytes during viral infection	MERS: rIFN-β1a (Rebif): 44 mg subcutaneously three times weekly
Lopinavir + Ritonavir + IFN + Ribavirin	combination of protease inhibitor + proteins made and released by host cells + antiviral	oral (p.o.) lopinavir/ritonavir (400/100 mg twice daily), pegylated interferon (180 µg subcutaneously once per week for 12 days) and ribavirin (2000 mg p.o. loading dose, followed by 1200 mg p.o. every eight hours for eight days)
Lopinavir + Ritonavir + IFNβ1b	Lopinavir and ritonavir are antiretroviral protease inhibitors combination protease inhibitor and host	For MERS use was: Lopinavir /Ritonavir 400 mg +100 mg/ml twice daily for 14 days and Interferon beta-1b 0.25 mg subcutaneous every alternate day for 14 days
Baloxavir marboxil (Xofluza)	Antiviral (endonuclease inhibitor)	clinical trial: 80 mg on day1, 80mg on day 4, and 80mg on day seven as necessary. No more than three times administration in total.
Favipiravir (or T-705 or Avigan)	Experimental antiviral drug. Pyrazinocarbox amide derivative viral RNA polymerase inhibitor.	600 mg tid with 1600mg first loading dosage for no more than 14 days
Arbidol (Umifenovir)	Antiviral. Russian-made small indole derivative molecule	CT NCT04252885: ordinary treatment plus a regimen of arbidol (100mg) (oral, tid, 200 mg each time, taking for 7-14 days).
Novaferon, Nova	The recombinant protein produced by DNA-shuffling of IFN-α	20g/ time, atomized inhalation (in one trial, in combination with Arbidol tid.Arbidol Tablets 200 mg/ time, p.o.tid)
Alferon® (IFNα-n3)	Natural, human interferon-alpha protein	In Phase II CT NCT00215826 SARS 650 IU vs. 1300 IU trialed
Sab-301	Polyclonal anti MERS-CoV (likely MERSspecific, but possible to crossreact) (clinical trial phase 1)	1 to 2 doses at 50 mg/kg.
Ivermectin	Usually prescribed for pinworm and nematode infections, and sometimes headlice, ivermectin (Stromectol) was shown to reduce viral colonies of COVID-19.	



PREVENTION

Preventive measures to reduce the chances of infection include staying at home, avoiding crowded places, washing hands with soap and water often and for at least 20 seconds, practicing good respiratory hygiene, and avoiding touching the eyes, nose, or mouth with unwashed hands. The CDC recommends covering the mouth and nose with a tissue when coughing or sneezing and recommends using the inside of the elbow if no tissue is available. They also recommend proper hand hygiene after any cough or sneeze. Social distancing strategies aim to reduce contact of infected persons with large groups by closing schools and workplaces, restricting travel, and canceling mass gatherings. Social distancing also includes that people stay at least six feet apart (1.83 meters).

Because a vaccine against SARS-CoV-2 is not expected to become available until 2021 at the earliest, a crucial part of managing the COVID-19 pandemic is trying to decrease the epidemic peak, known as "flattening the curve," through various measures seeking to reduce the rate of new infections. Slowing the infection rate helps decrease the risk of health services being overwhelmed, allowing for better treatment of current cases, and delaying additional cases until therapeutics or a vaccine becomes available.

According to the WHO, the use of masks is recommended only if a person is coughing or sneezing or when one is taking care of someone with a suspected infection.

The CDC also recommends that individuals wash hands often with soap and water for at least 20 seconds, especially after going to the toilet or when hands are visibly dirty, before eating and after blowing one's nose, coughing, or sneezing. It further recommends using an alcohol-based hand sanitizer with at least 60 % alcohol, but only when soap and water are not readily available.

For areas where commercial hand sanitizers are not readily available, WHO provides two formulations for local production. In these formulations, the antimicrobial activity arises from ethanol or Isopropanol. Hydrogen peroxide is used to help eliminate bacterial spores in the alcohol; it is "not an active substance for hand antiseptics." Glycerol is added as a humectant.

CONCLUSION

No pharmaceutical products have yet been shown to be safe and effective for the treatment of COVID-19. However, several medicines have been suggested as potential investigational therapies, many of which are now being or will soon be studied in clinical trials, including the SOLIDARITY trial co-sponsored by WHO and participating countries. WHO continues to call on all countries to implement a comprehensive approach to slow down transmission and flatten the curve. This approach is saving lives and buying time for the development of vaccines and treatments. Two candidate vaccines in clinical evaluation. Fifty-two candidate vaccines are in preclinical evaluation. This is an incredible achievement. We commend the

researchers around the world who have come together to evaluate experimental therapeutics systemically. This large, international study is designed to generate the robust data we need to show which treatments are the most effective. We have called this study the solidarity trial. The solidarity trial provides simplified procedures to enable even hospitals that have been overloaded to participate. We need about which treatments help to save lives. WHO continues to recommend that isolating, testing and treating every suspected case, and tracing every contact, must be the backbone of the response in every country. This is the best hope of preventing widespread community transmission. Most countries with sporadic cases or clusters of cases are still in the position to do this. No therapeutics have yet been licensed against 2019-nCoV. In order to reduce mortality and improve clinical disease outcome, there is an urgent need to prioritize investigational candidates most suitable for efficacy trials. Clinical trials conducted under a Master Protocol will aim to evaluate the efficacy and safety of these therapeutics across multiple locations. Several other drugs such as investigational antivirals²¹, immunotherapeutic, host-directed therapies are under investigation in clinical trials or are being considered for clinical trials of pre-exposure prophylaxis, post-exposure prophylaxis, or treatment of COVID-19 in the United States and worldwide also. In India The union health Ministry has allowed the use of hydroxychloroquine in combination with Azithromycin²² under close monitoring for patients with severe disease and requiring ICU management as per the revised Guidelines on Clinical Management of COVID-19.

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