Antivirals for COVID-19 (An Update)

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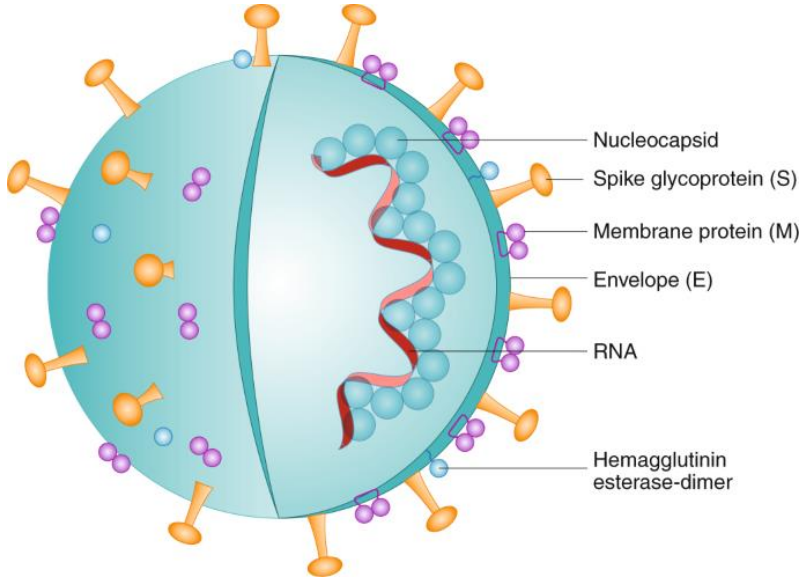
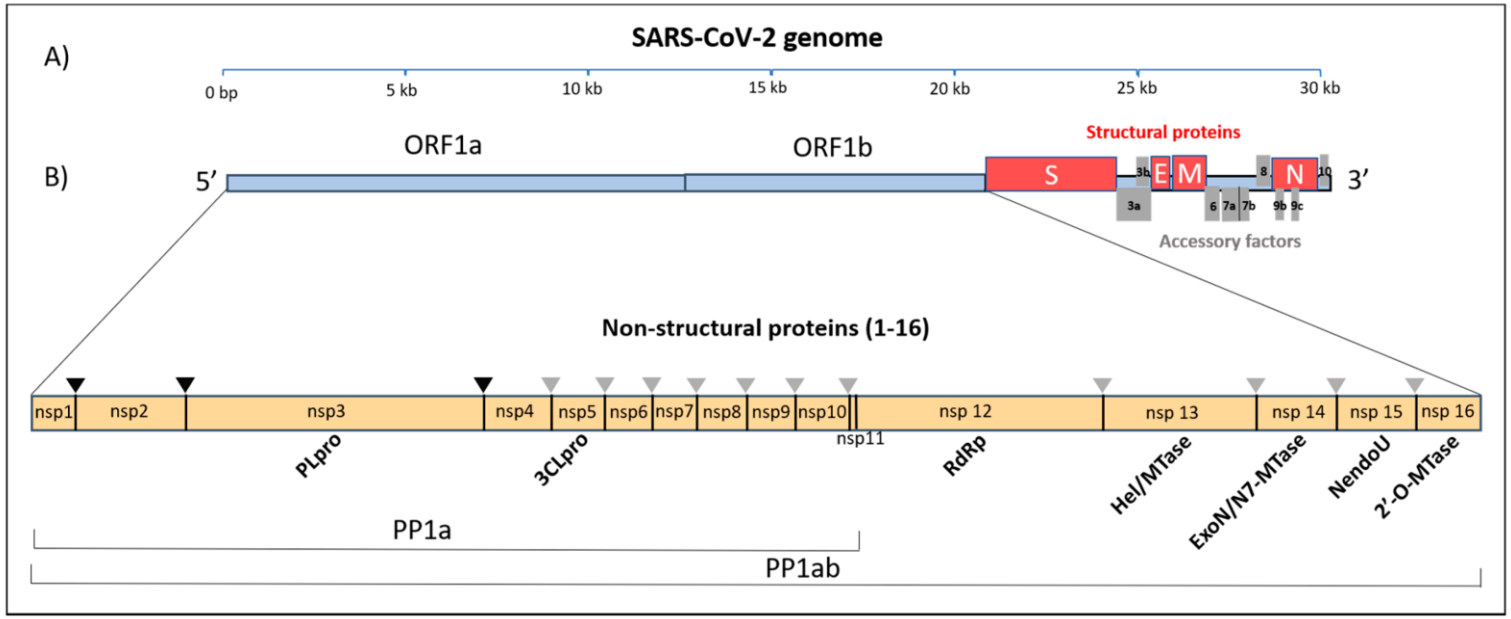
https://www.freepik.com/premium-vector/people-fight-corona-virus-illustration-corona-mascot-cartoon-character-people-concept-isolated_7294452.htm

COVID-19 and SARS-CoV-2

- COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2).
- SARS-CoV-2 is the seventh human coronavirus after 229E, NL63, OC43, HKU1, MERS-CoV, and SARS-CoV.
- SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus of approximately 30 kb in length.
- Based on the genome organization of SARS-CoV-2, **four enzymes are recognized as attractive drug targets**:
  - **3CLpro (nsp5)**
  - **PLpro (nsp3)**
  - **RNA helicase (nsp13)**
  - **RNA-dependent RNA polymerase (RdRp, nsp12). The RdRp catalyzes the synthesis of viral RNA and thus plays a central role in the replication and transcription cycle of CoV-2.**

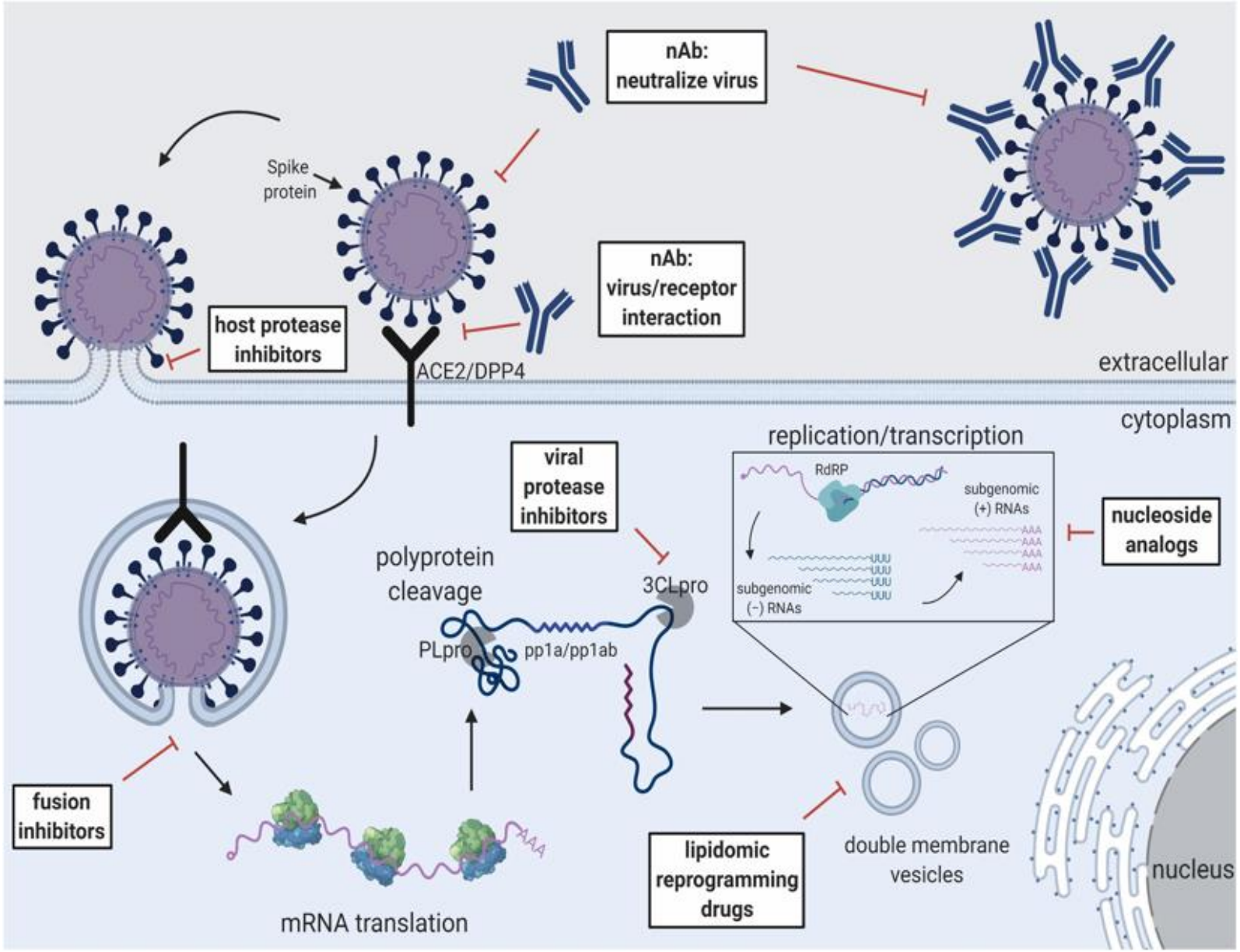


https://www.nature.com/articles/s41565-020-0732-3



Romano et al, Cells,2020, 9, 1267.

SARS-CoV-2 Replication Cycle and Potential Antiviral Targets for SARS-CoV-2

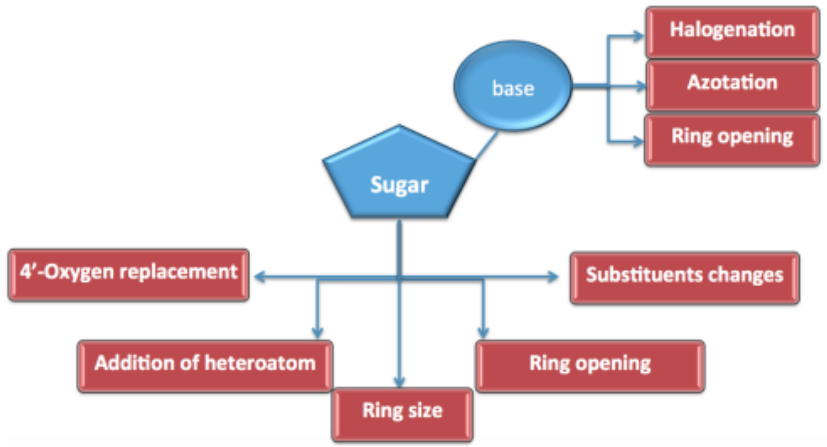


Li & De Clerq. Nature Reviews Drug Discovery, 2020

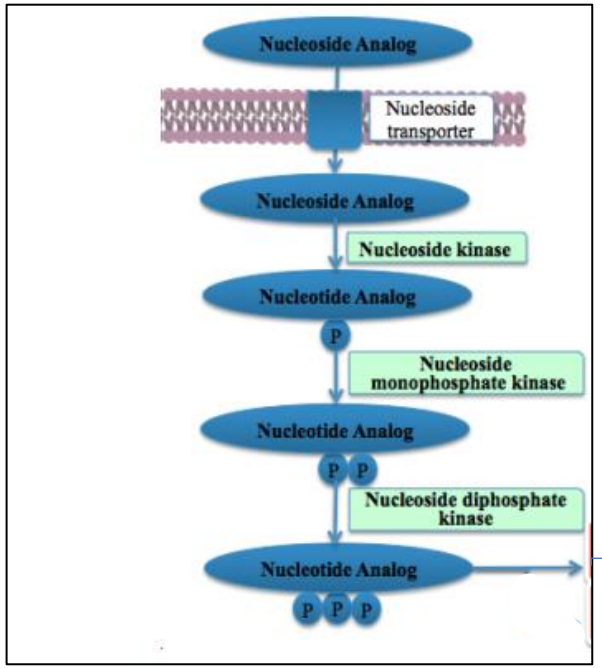
Nucleoside Analogs as Antivirals

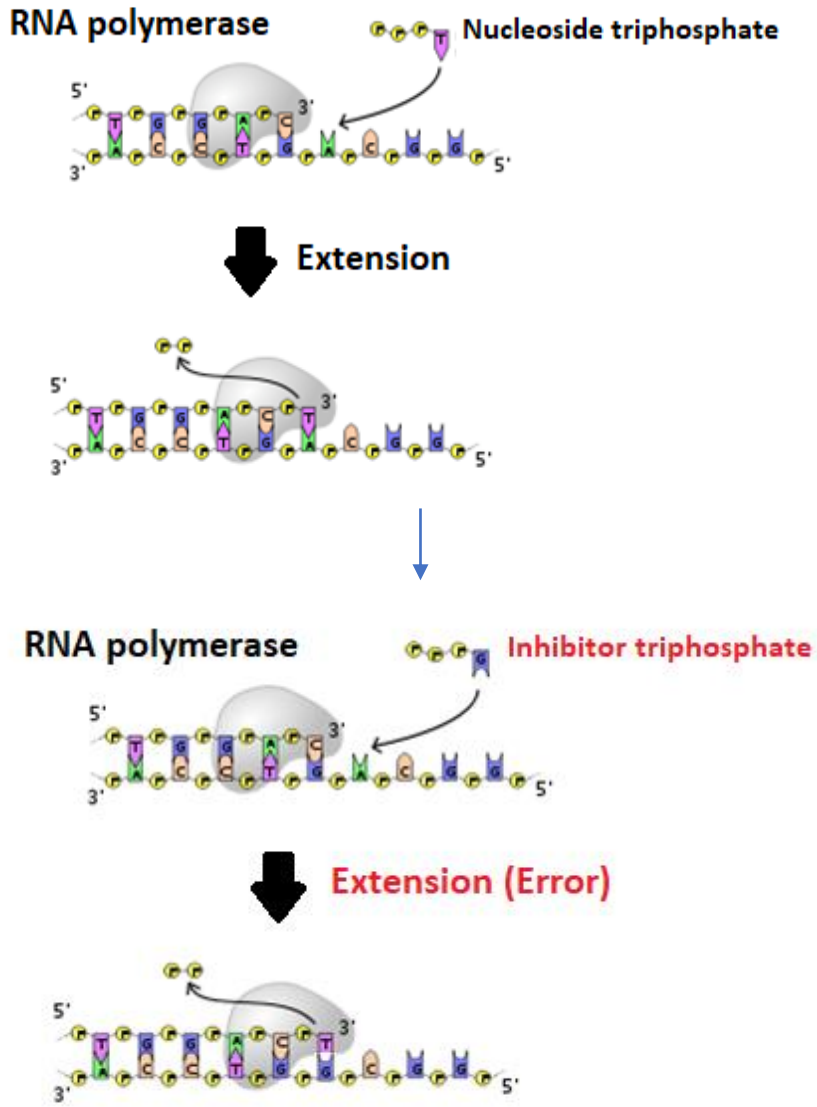
- Nucleoside analogs represent a well-established class of antiviral agents that inhibit viral replication.
- Notable drugs in this class are emtricitabine and tenofovir disoproxil fumarate for HIV-1 infections and sofosbuvir as the curative agent for hepatitis C virus (HCV) infections.

General chemical modifications of nucleoside analogs.



Mechanism of action of nucleoside analogs





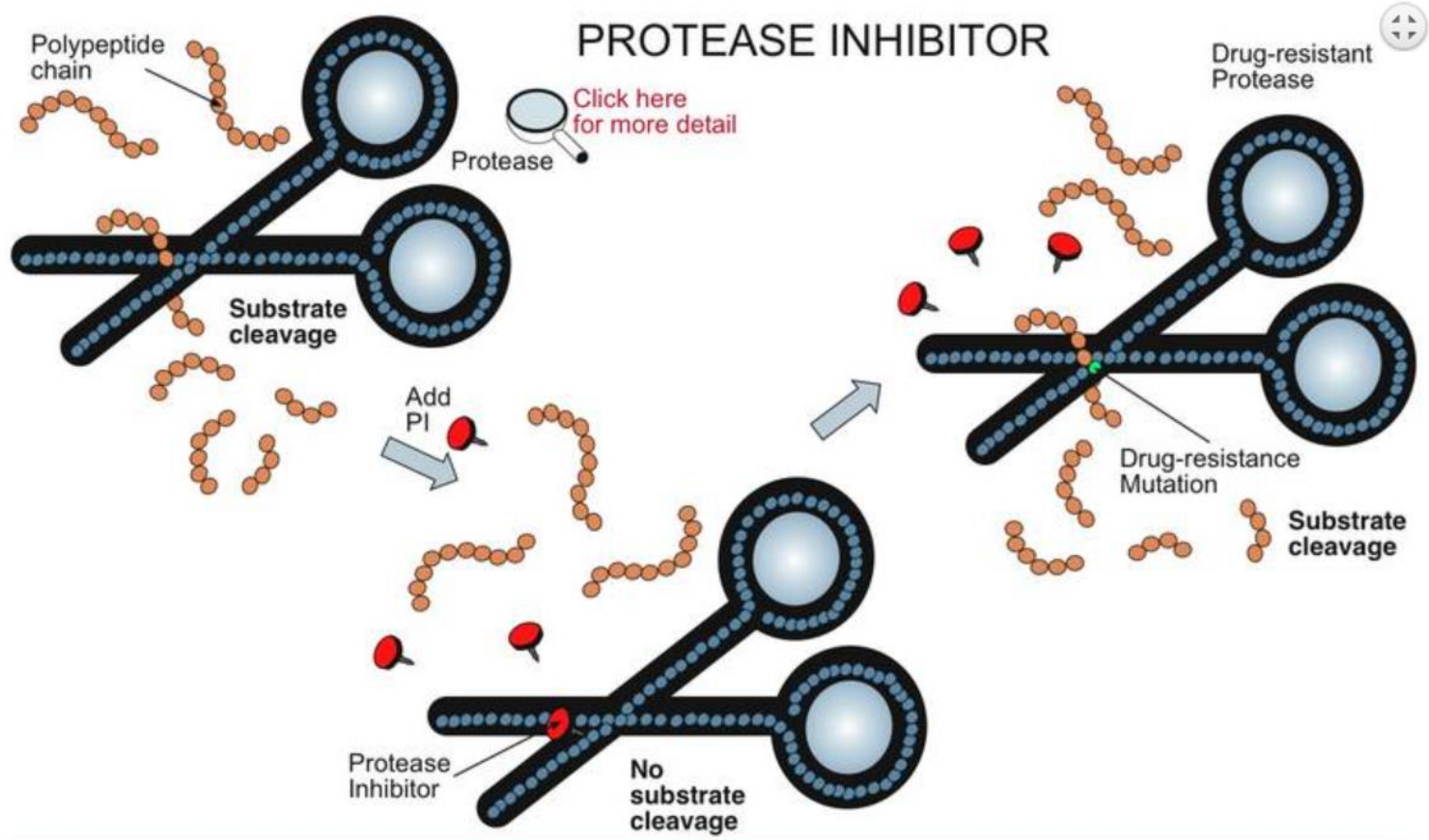
Mahmoud et al, J Adv Pharm res, 2018, 2:73-88

Protease inhibitors (**PIs**) are medications that act by interfering with enzymes that cleave proteins. Some of the most well known are antiviral drugs widely used to treat HIV/AIDS and hepatitis C. These protease inhibitors prevent viral replication by selectively binding to viral proteases and blocking proteolytic cleavage of protein precursors that are necessary for the production of infectious viral particles.

Antiretroviral HIV-1 protease inhibitors — class stem –**navir**
Amprenavir, Darunavir, Fosamprenavir, Lopinavir, Ritonavir, etc.

HCV protease inhibitors — class stem –**previr**
Asunaprevir, Boceprevir, Grazoprevir,Glecaprevir, etc.

SARS-CoV-2 chymotrypsin-like protease inhibitors
Nirmatrelvir



A protease inhibitor binds directly to the active site of protease enzyme causing the enzyme to lock and prevents cleavage of natural substrate. A drug resistance mutation against a protease inhibitor is an amino-acid change that reduces the binding affinity of the drug to the enzyme so that enzyme activity resumes.

immunopaedia.org

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ANTIVIRAL AGENTS

Repurposing Nucleoside Analogs for Human Coronaviruses

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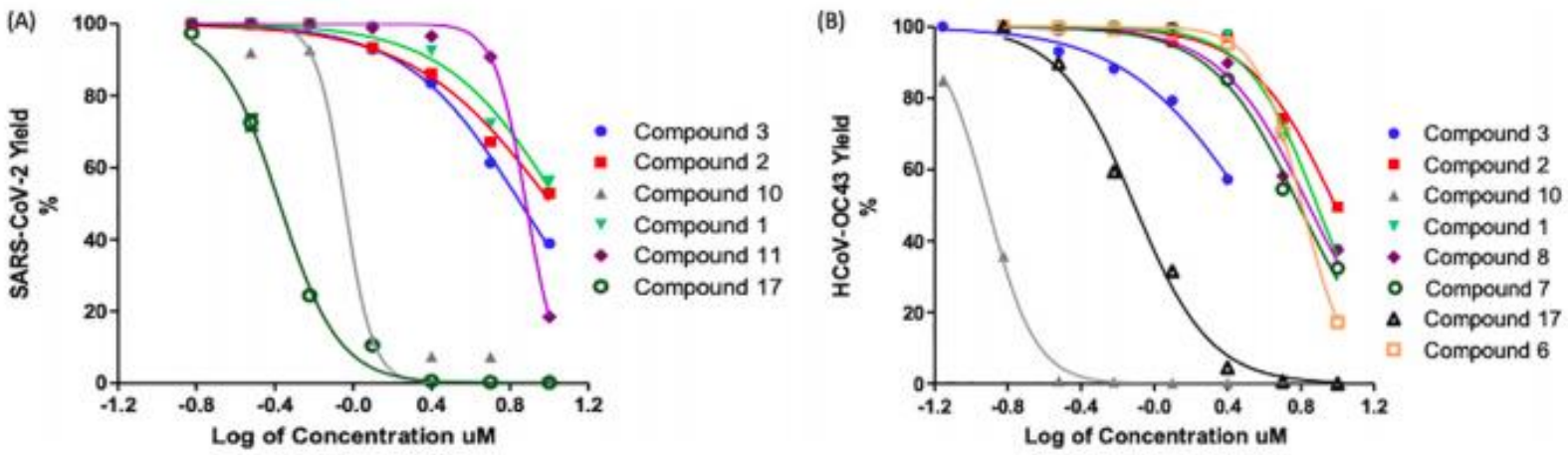


FIG 3 Dose-response antiviral activity. Dose response study of selected nucleoside analogs against SARS-CoV-2 in Vero cells (A) and HCoV-OC43 in Huh-7 cells (B). All experiments were done in triplicate.

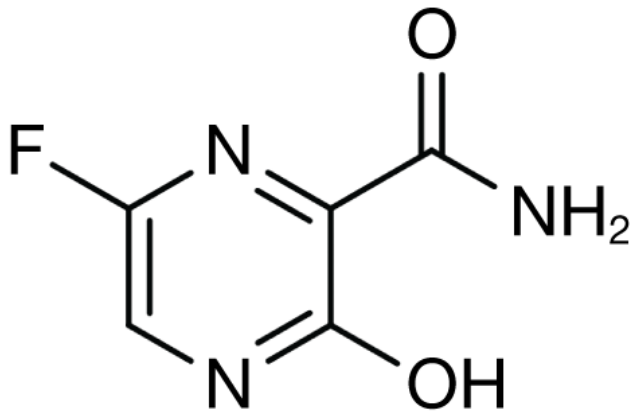
TABLE 2 Antiviral activity and cytotoxicity of compounds against SARS-CoV-2 and HCoV-OC43 in different cell lines

	Antiviral activity against (μM):							
	SARS-CoV-2		HCoV-OC43					
	Vero cells		Huh7 cells		Cytotoxicity (CC_{50} [μM])			
Compound	EC_{50}	EC_{90}	EC_{50}	EC_{90}	PBM	CEM	Vero	Huh7
1 (2′-MeC)	9.2 ± 0.1	29.6 ± 0.4	10 ± 0.7	15.1 ± 0.1	65.4	84.3	>100	>100
2	7.6 ± 0.4	28.8 ± 0.8	6.7 ± 1.1	13.8 ± 0.2	72.4	63.9	>100	38
3 (sofosbuvir cyclic phosphate prodrug)	6.3 ± 0.1	18.9 ± 0.2	>2[a]	ND[b]	58.4	31.6	16.4	2.9
4 (sofosbuvir)	>20	>20	>20	>20	>100	>100	>100	>100
5 (ALS-8112, lumicitabine)	>20	>20	>20	>20	4.2	2.8	>100	4.2
6	>20	>20	6.8 ± 0.2	12.8 ± 0.4	>100	>100	>100	72.4
7	>20	>20	5.9 ± 0.6	18.6 ± 0.3	>100	>100	>100	>100
8 (favipiravir)	>20	>20	6.8	>10	>100	>100	>100	>100
9 (entecavir)	>20	>20	>20	>20	21.5	>100	>100	>100
10 (remdesivir)	1.0 ± 0.1	3.5 ± 0.3	0.04 ± 0.1	0.09 ± 0.09	4.5	11.6	>100	2.1
11 (parent nucleoside of remdesivir, GS-441524)	8.2 ± 0.4	13.2 ± 0.8	>10	>20	>100	>100	>100	>100
12 (ribavirin)	>20	>20	20.6	>20	>100	7.5	>100	22.1
13 (3TC)	>20	>20	>20	>20	>100	>100	>100	>100
14 (FTC)	>20	>20	>20	>20	>100	>100	>100	>100
15 (TAF)	>20	>20	>20	>20	50.8	13.67	36.4	>100
16 (TDF)	>20	>20	>20	>20	44.4	33.9	>100	>100
17 (NHC)	0.3 ± 0.2	0.8 ± 0.1	0.8 ± 0.03	1.8 ± 0.1	44.3	3.5	12.6	80.3

[a]To avoid the cytotoxicity, 2 μM was chosen as the highest concentration for antiviral assays for compound 3 for HCoV-OC43 in Huh-7 cells.

[b]ND, not determined.

Favipiravir, sold under the brand name Avigan among others, is an antiviral medication used to treat influenza in Japan.



Japan approval for Avigan to treat COVID-19 delayed

27-05-2020

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

LETTER TO THE EDITOR
May 2021 Volume 65 Issue 5 e00020-21
https://doi.org/10.1128/AAC.00020-21

The Anti-Influenza Virus Drug Favipiravir Has Little Effect on Replication of SARS-CoV-2 in Cultured Cells

Yuriko Tomita, Makoto Takeda, Shutoku Matsuyama

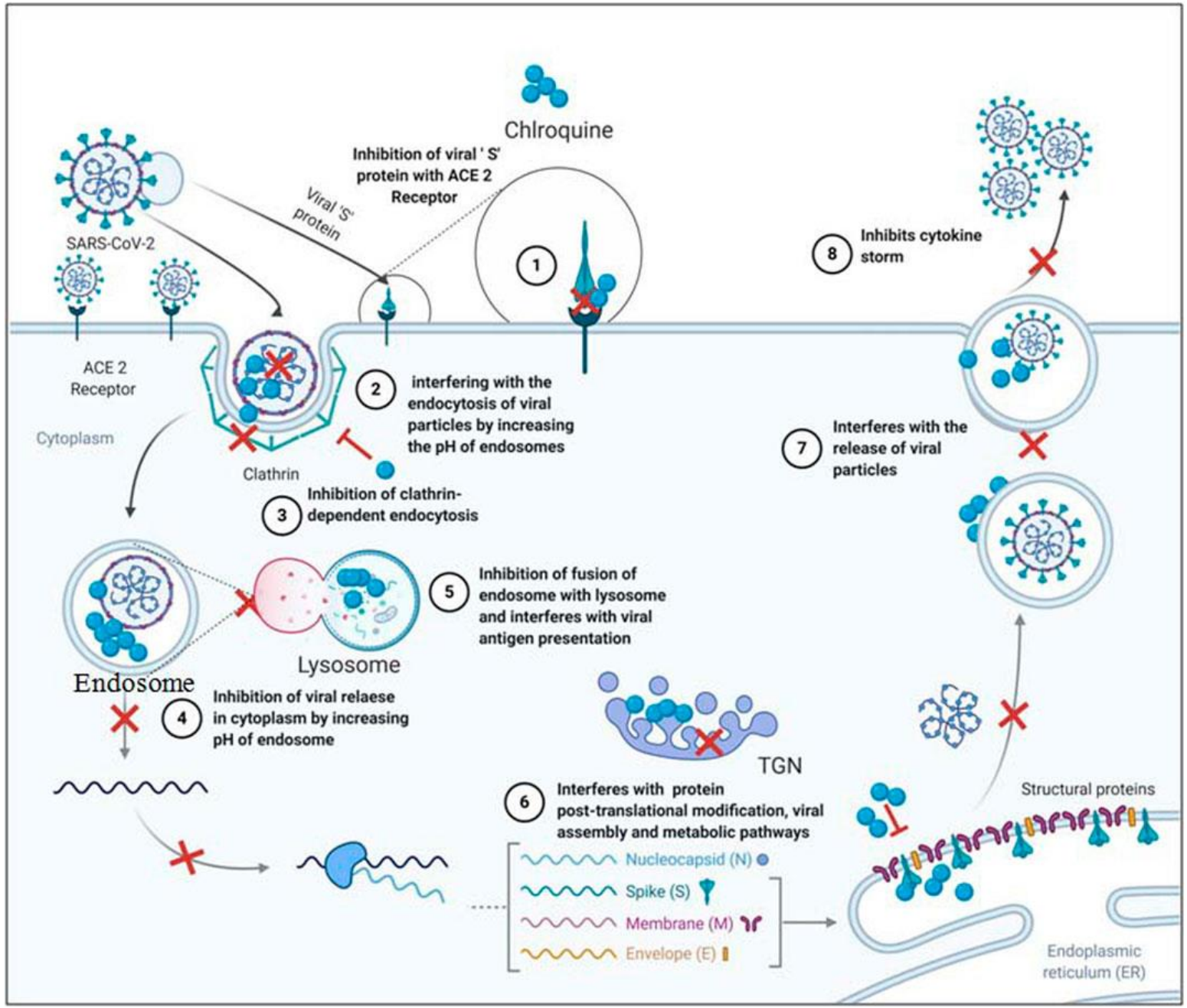
Department of Virology III, National Institute of Infectious Diseases, Tokyo, Japan

KEYWORDS COVID-19, SARS-CoV-2, T-705, Avigan, drug, favipiravir, influenza

Doubt cast over Avigan (favipiravir) and DAS181 potential to fight COVID-19

A new report has highlighted that the early successes of Avigan (favipiravir) and DAS181 do not guarantee their efficacy against COVID-19.

Chloroquine and Hydroxychloroquine vs SARS-CoV-2



- CQ and HCQ are known to **interfere with endosomal acidification** necessary to the proteolytic activity of **cathepsins**.
- Following receptor binding and endocytosis, cathepsin L can cleave the SARS-CoV-1 and SARS-CoV-2 spike (S) proteins, thereby activating membrane fusion for cell entry.
- The plasma membrane-associated protease **TMPRSS2** can similarly cleave these S proteins and activate viral entry at the cell surface.

PLOS PATHOGENS

RESEARCH ARTICLE

Hydroxychloroquine-mediated inhibition of SARS-CoV-2 entry is attenuated by TMPRSS2

Tianling Ou*, Huihui Mou, Lizhou Zhang, Amrita Ojha, Hyeryun Choe, Michael Farzan*

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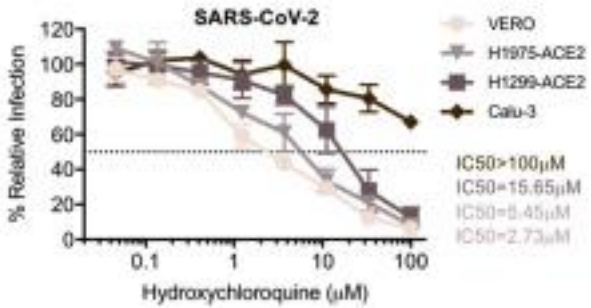
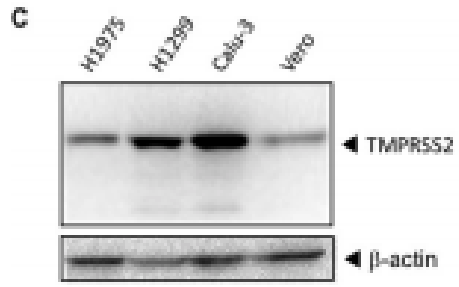
Hypothesis → TMPRSS2 expression on physiologically relevant SARS-CoV-2 target cells may bypass the antiviral activities of hydroxychloroquine, and explain its lack of in vivo efficacy



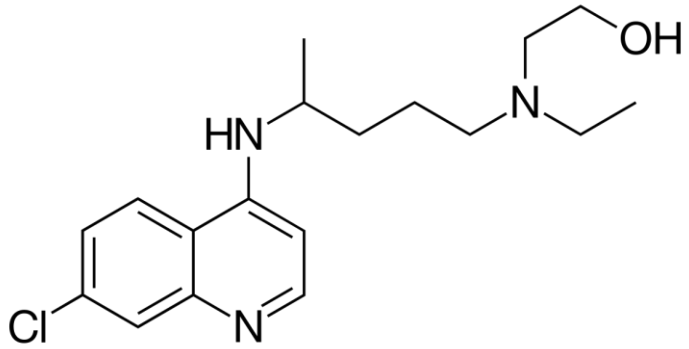


TMPRSS2 expression significantly attenuates the antiviral effect of hydroxychloroquine against SARS-CoV-2-S

↓

Suppression of TMPRSS2 restores the antiviral efficiency of hydroxychloroquine

Hydroxychloroquine is used to treat malaria. It is also used to prevent malaria infection in areas or regions where it is known that other medicines (eg, chloroquine) may not work.



Monday, November 9, 2020

Hydroxychloroquine does not benefit adults hospitalized with COVID-19

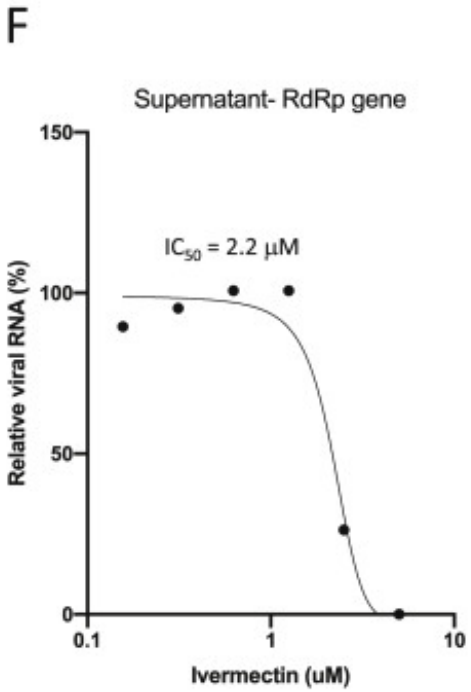
THE LANCET

COMMENT | ONLINE FIRST

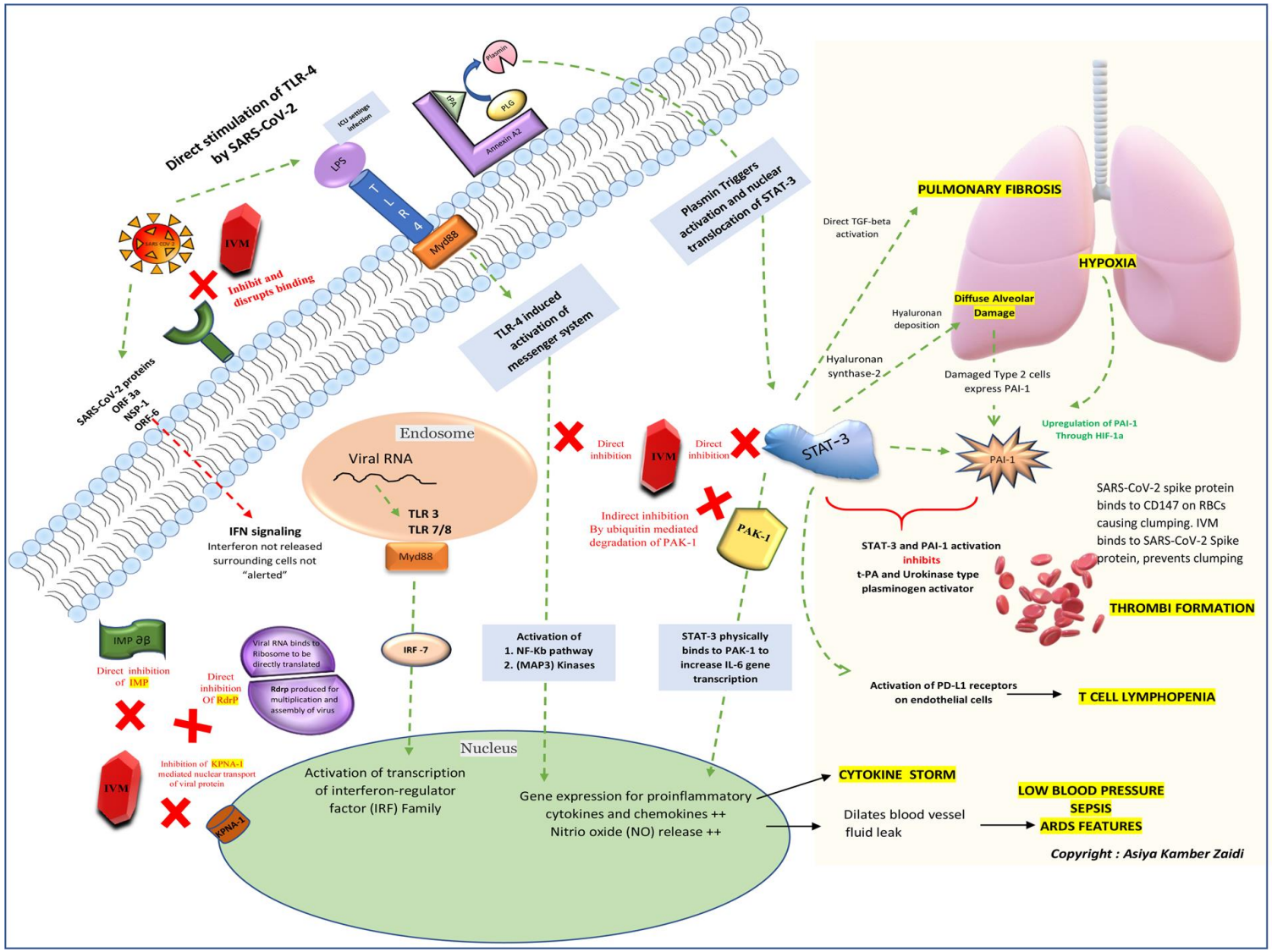
Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Ivermectin vs SARS-CoV-2

Ivermectin belongs to a group of avermectins (AVM), which is a group of 16 membered macrocyclic lactone compounds discovered at the Japanese Kitasato institute in 1967 during actinomycetes cultures with the fungus *Streptomyces avermitilis*. This drug radically lowered the incidence of **river blindness and lymphatic filariasis** and was discovered and developed by William C. Campbell and Satoshi Ōmura for which they received the Nobel Prize in Physiology or Medicine in 2015.



Wehbe, Z., et al. Front Immunol (2021)



Zaidi, A.K., Dehgani-Mobaraki, P. *J Antibiot* (2021).

WHO advises that ivermectin only be used to treat COVID-19 within clinical trials

31 March 2021

Randomized Controlled Trial > BMC Infect Dis. 2021 Jul 2;21(1):635.

doi: 10.1186/s12879-021-06348-5.

Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial

Ivermectin had **no significant effect** on preventing hospitalization of patients with COVID-19.

Randomized Controlled Trial > JAMA. 2021 Apr 13;325(14):1426-1435.

doi: 10.1001/jama.2021.3071.

Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial

Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, **did not significantly improve the time to resolution of symptoms**. The findings do not support the use of ivermectin for treatment of mild COVID-19

Latest Update By NIH April 29, 2022

Results from 2 recently published, large randomized controlled trials showed that the use of ivermectin did not provide a clinical benefit for patients with mild to moderate COVID-19. Based on these results, the Panel now **recommends against** the use of ivermectin for the treatment of COVID-19, except in clinical trials

FDA NEWS RELEASE

FDA Takes Actions to Expand Use of Treatment for Outpatients with Mild-to-Moderate COVID-19

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For Immediate Release: January 21, 2022

The U.S. Food and Drug Administration took two actions to expand the use of the antiviral drug remdesivir to certain non-hospitalized adults and pediatric patients for the treatment of mild-to-moderate COVID-19 disease.

Remdesivir

- Remdesivir has been studied in non-hospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease.
- The PINETREE trial showed that 3 consecutive days of IV remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death compared to placebo.
- Remdesivir is expected to be active against the Omicron variant.
- Because remdesivir requires IV infusion for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings, but it is an option if ritonavir-boosted nirmatrelvir (Paxlovid) and sotrovimab are not available.
- **Remdesivir 200 mg** IV on Day 1, followed by **remdesivir 100 mg** IV daily on Days 2 and 3, initiated as soon as possible and **within 7 days of symptom onset** in those aged ≥12 years and weighing ≥40 kg.
- Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion.

ACCEPTED MANUSCRIPT

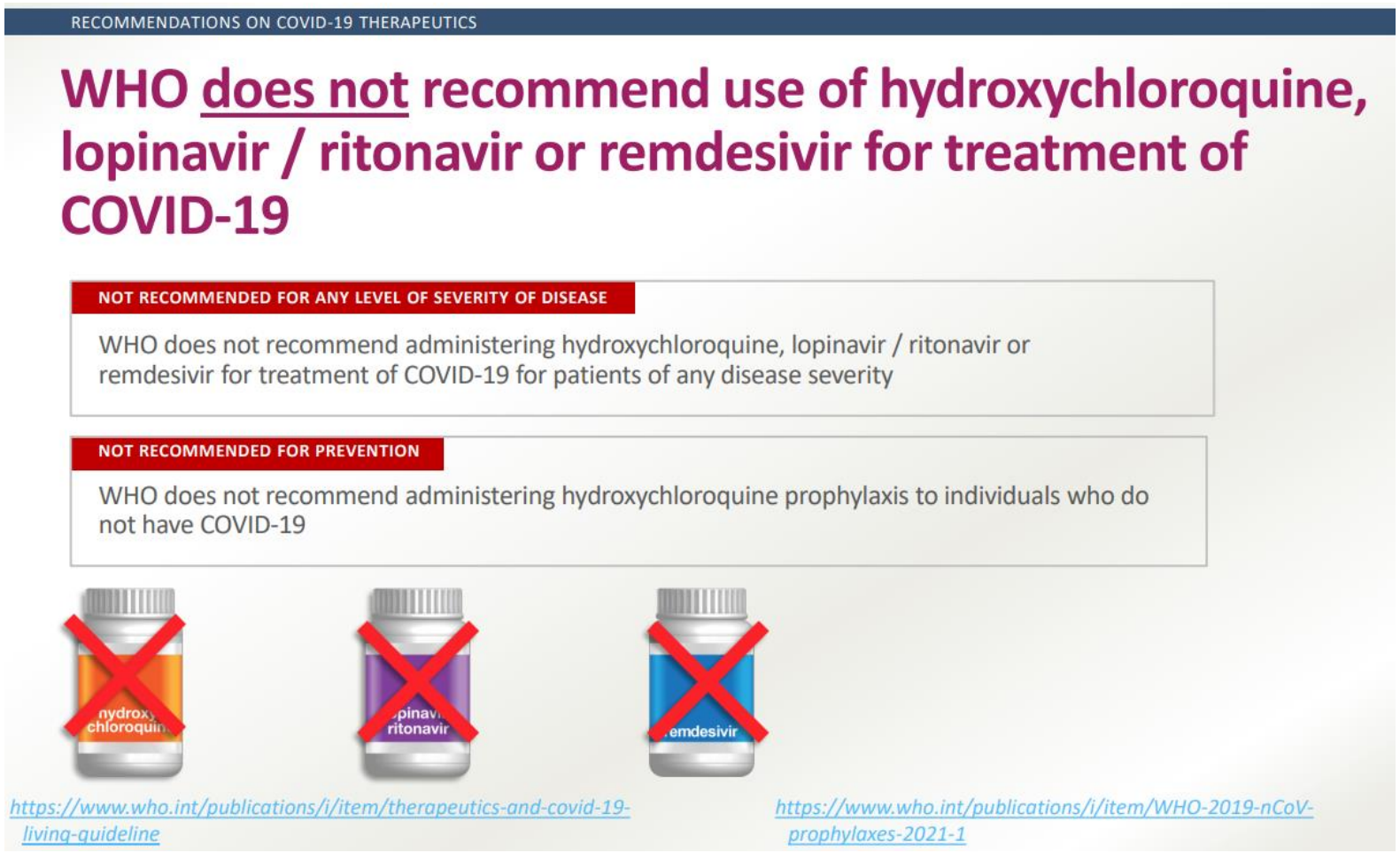
Real-World Effectiveness Of Remdesivir In Adults Hospitalized With Covid-19: A Retrospective, Multicenter Comparative Effectiveness Study FREE

Brian T Garibaldi, MD MEHP ✉, Kunbo Wang, MS, Matthew L Robinson, MD, Joshua Betz, MS, G Caleb Alexander, MD MS, Kathleen M Andersen, MSc, Corey S Joseph, MPH, Hemalkumar B Mehta, PhD, Kimberly Korwek, PhD, Kenneth E Sands, MD ... Show more

Clinical Infectious Diseases, ciab1035, https://doi.org/10.1093/cid/ciab1035

Published: 15 December 2021 **Article history** ▾

- These results from 96,859 COVID-19 patients support the use of remdesivir for hospitalized COVID-19 patients on no or low-flow oxygen.
- Routine initiation of remdesivir in more severely ill patients is unlikely to be beneficial.

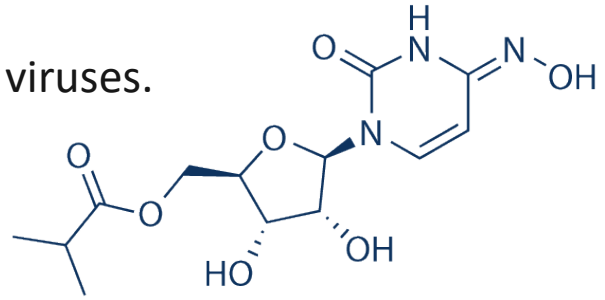


Conditional recommendation for the use of remdesivir issued on 22 April 2022 by WHO in patients with non-severe COVID-19 at the highest risk of hospitalization

- Remdesivir should be administered as soon as possible after onset of symptoms, ideally within 7 days.

Molnupiravir

- An oral prodrug of beta-D-N4-hydroxycytidine (NHC), has broad antiviral activity against RNA viruses.



- NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.

- As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations.
- Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays.
- **The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity.**

- **Molnupiravir** 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years **ONLY** when none of the above options can be used.

- The NIH panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir (Paxlovid), sotrovimab, and remdesivir are not available or cannot be given, because **molnupiravir has lower efficacy than the other options.**

- Molnupiravir is active against the Omicron variant.

https://www.covid19treatmentguidelines.nih.gov/

Molnupiravir Contradictions

- Patients of childbearing potential should be counseled about abstaining from sex or **using reliable contraception** for the duration of therapy and for up to 4 days after receiving molnupiravir.
- Men of reproductive potential who are sexually active with individuals of childbearing potential should abstain from sex or use a reliable method of contraception for the duration of treatment **and for at least 3 months after the last dose of molnupiravir**.
- The FDA EUA states that molnupiravir is not recommended for use in **pregnant patients**.
- However, when preferred therapies are not available**,** pregnant people who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly those who are beyond the time of embryogenesis (i.e., >10 weeks' gestation).
- Based on the **lack of data** on the use of molnupiravir in lactating **avoid breasfeeding** for 4 days after the final dose is recommended.
- Molnupiravir is **not authorized for use in children aged <18** years due to potential effects on bone and cartilage growth.
- No drug-drug interactions have been identified for molnupiravir.

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

- Nirmatrelvir (PF-07321332) is an orally bioavailable protease inhibitor that is active against M^{PRO}, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.
- It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.
- Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor **and pharmacokinetic boosting agent.**
- Ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic ranges.
- **Nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg.

- Ritonavir-boosted nirmatrelvir (Paxlovid) is active against the **Omicron variant**.

Pfizer Shares In Vitro Efficacy of Novel COVID-19 Oral Treatment Against Omicron Variant

- Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients

https://www.covid19treatmentguidelines.nih.gov/

Paxlovid Contradictions

- ❑ PAXLOVID is contraindicated in patients with a history of clinically **significant hypersensitivity** reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.
- ❑ PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions:

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

PAXLOVID **cannot be started immediately** after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:

- **Anticancer drugs**: apalutamide • Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- **Antimycobacterials**: rifampin
- **Some herbal products**

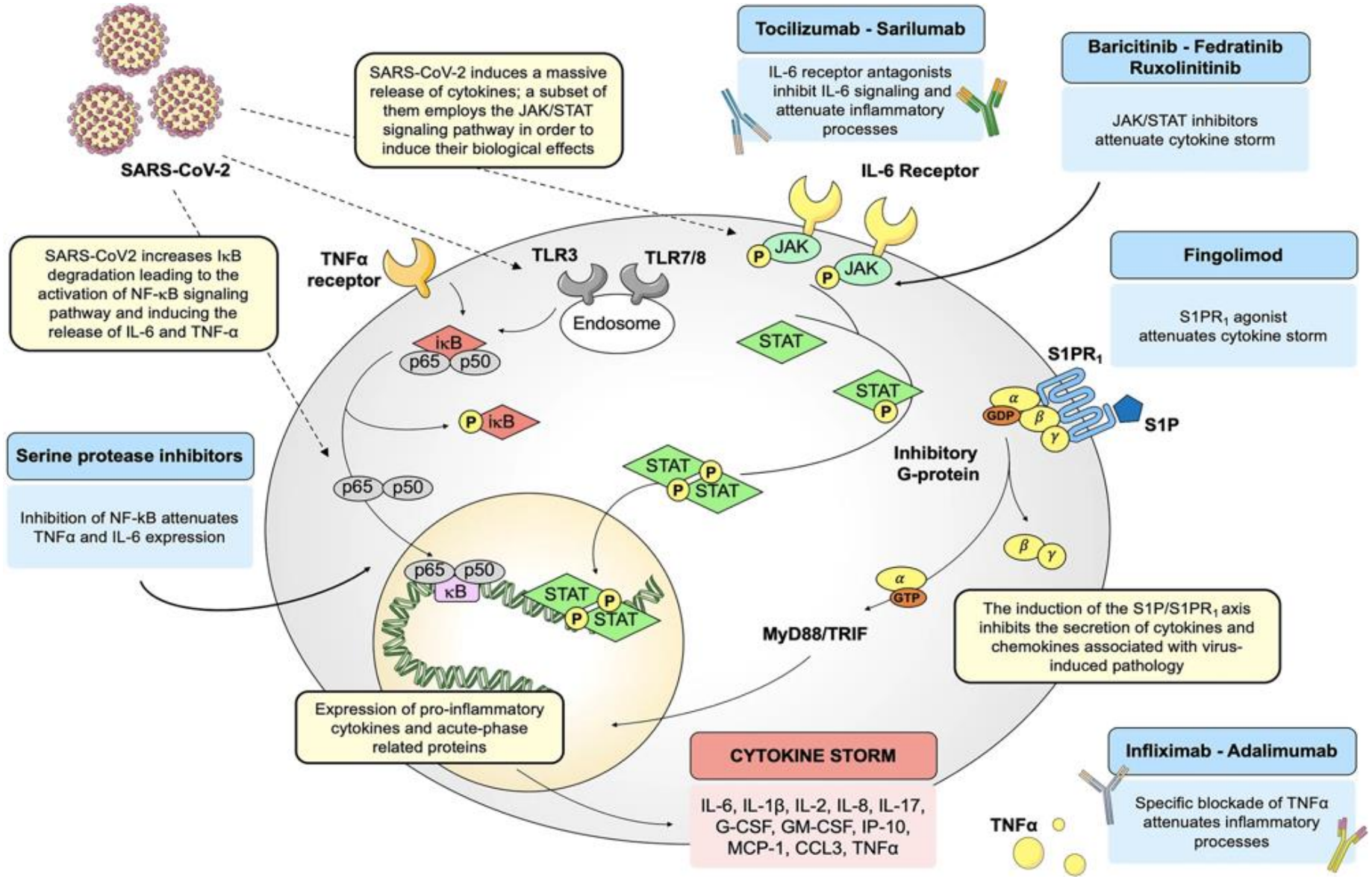
https://www.covid19treatmentguidelines.nih.gov/

WHO recommends highly successful COVID-19 therapy and calls for wide geographical distribution and transparency from originator

22 April 2022 | Statement | Geneva | Reading time: 2 min (592 words)

- WHO made a strong recommendation for Paxlovid, for mild and moderate COVID-19 patients at highest risk of hospital admission, calling it the best therapeutic choice for high-risk patients to date.
- WHO suggests against its use in patients at lower risk, as the benefits were found to be negligible.

Anti-Inflammatory Agents and COVID-19



https://www.nature.com/articles/s41392-020-0191-1

Cell

Available online 10 November 2020

In Press, Journal Pre-proof

Article

Baricitinib treatment resolves lower airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques

Timothy N. Hoang [1, 13], Maria Pino [1, 13], Arun K. Boddapati [2, 13], Elise G. Viox [1], Carly E. Starke [3], Amit A. Upadhyay [2], Sanjeev Gumber [4, 5], Michael Nekorchuk [3], Kathleen Busman-Sahay [3], Zachary Strongin [1], Justin L. Harper [1], Gregory K. Tharp [2], Kathryn L. Pellegrini [2], Shannon Kirejczyk [5], Keivan Zandi [6], Sijia Tao [6], Tristan R. Horton [2], Elizabeth N. Beagle [2] ... Mirko Paiardini [1, 4, 14, 15]

EMORY | news center

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Emory, Lilly, NIAID join academic centers in clinical trial to demonstrate efficacy of remdesivir and baricitinib against COVID-19

Woodruff Health Sciences Center | May 8, 2020

World Health Organization recommends JAK inhibitor for treatment of severe or critical COVID-19

- The first drug, baricitinib, is strongly recommended for patients with severe or critical COVID-19. It is part of a class of drugs called Janus kinase (JAK) inhibitors that suppress the overstimulation of the immune system. WHO recommends that it is **given with corticosteroids**.

Monoclonal Antibodies

- Several anti-SARS-CoV-2 mAb products (i.e., bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab) have received EUAs from the FDA for the treatment of **non-hospitalized patients with mild to moderate** COVID-19 who are at high risk of progressing to severe disease.

- The Omicron variant of concern has become the dominant SARS-CoV-2 variant in the world. This variant, which includes numerous mutations in the spike protein, has markedly reduced in vitro susceptibility to several anti-SARS-CoV-2 mAbs.


News > Medscape Medical News

FDA Halts Use of Some COVID Monoclonal Antibodies Due to Omicron

Megan Brooks

January 25, 2022

- **Bebtelovimab**

- The NIH Panel recommends using **bebtelovimab** 175 mg intravenous (IV) injection in patients aged ≥12 years as an alternative therapy **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate.
- Treatment should be initiated as soon as possible and within 7 days of symptom onset.

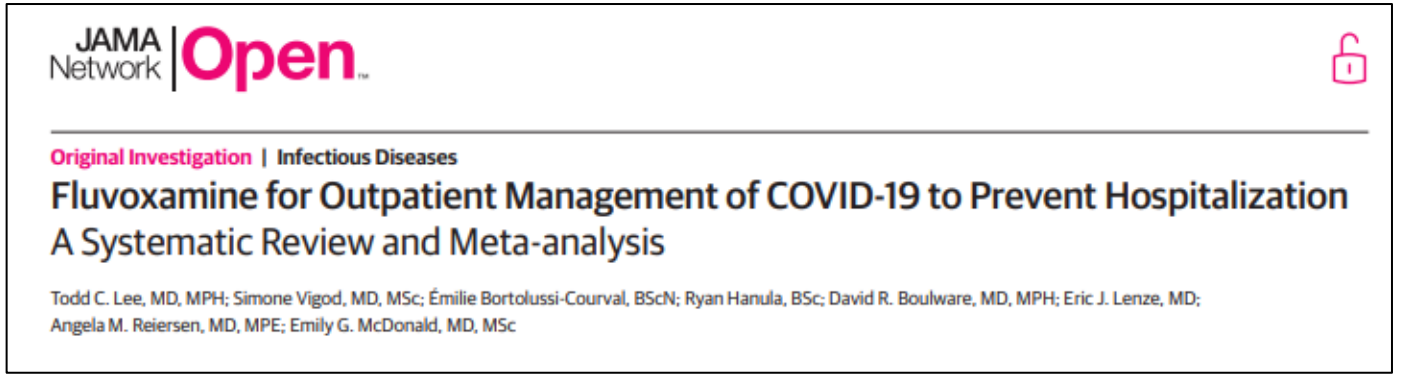
- **Sotrovimab** is no longer recommended as a treatment option for patients with COVID-19 because it has substantially reduced in vitro activity against the Omicron BA.2 subvariant.

Fluvoxamine

- Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is approved by the Food and Drug Administration (FDA) for the treatment of obsessive-compulsive disorder and is used for other conditions, including depression.
- Fluvoxamine is not FDA-approved for the treatment of any infection.

Anti-Inflammatory Effect of Fluvoxamine and Rationale for Use in COVID-19

- In an in vitro study of human endothelial cells and macrophages, fluvoxamine reduced the expression of inflammatory genes.
- In a murine sepsis model, fluvoxamine was found to bind to the sigma-1 receptor on immune cells, resulting in reduced production of inflammatory cytokines.
- Ongoing studies are establishing whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans and are clinically relevant in the setting of COVID-19.



- In this systematic review and meta-analysis of data from 3 trials, under a variety of assumptions, fluvoxamine showed a high probability of being associated with reduced hospitalization in outpatients with COVID-19.
- Ongoing randomized trials are important to evaluate alternative doses, explore the effectiveness in vaccinated patients, and provide further refinement to these estimates.
- Meanwhile, fluvoxamine could be recommended as a management option, particularly in resource-limited settings or for individuals without access to SARS-CoV-2 monoclonal antibody therapy or direct antivirals

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Thank You For Your Attention