

COVID-19

Potential Treatments Part 2

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April 2, 2020

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Overview

- Situation update
- Pharmaceutical Research 101
- Antiviral medications
- Losartan
- Convalescent serum

New Mexico

4/1/2020

- <https://cv.nmhealth.org/>
- 315 cases, 5 deaths, 24 hospitalized, 26 recovered
- Expanded testing criteria – asymptomatic people
 - Close contacts from confirmed COVID-19 patient
 - Nursing homes
 - “Congregant settings” – shelters, group homes, detention centers

Nationally

4/1/2020

<https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>

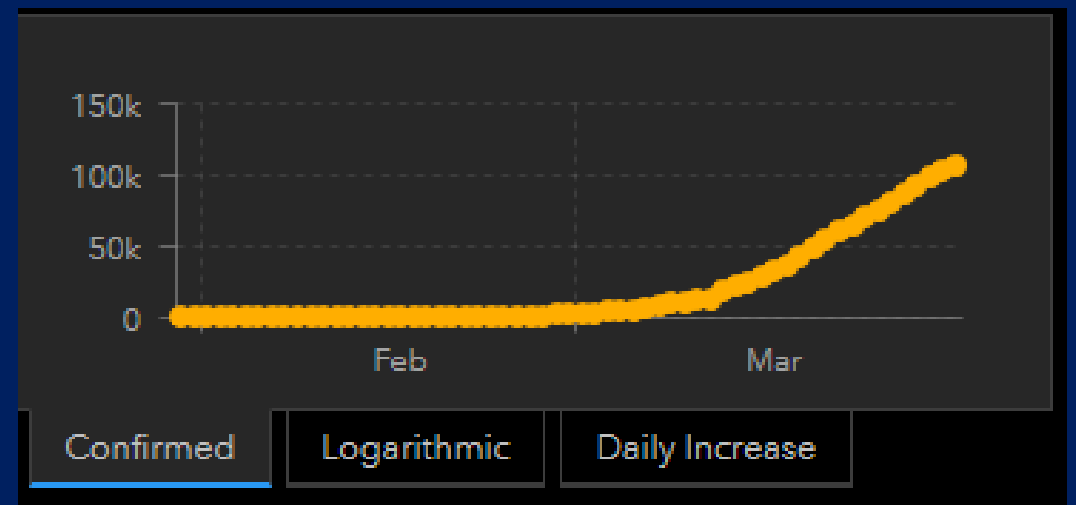
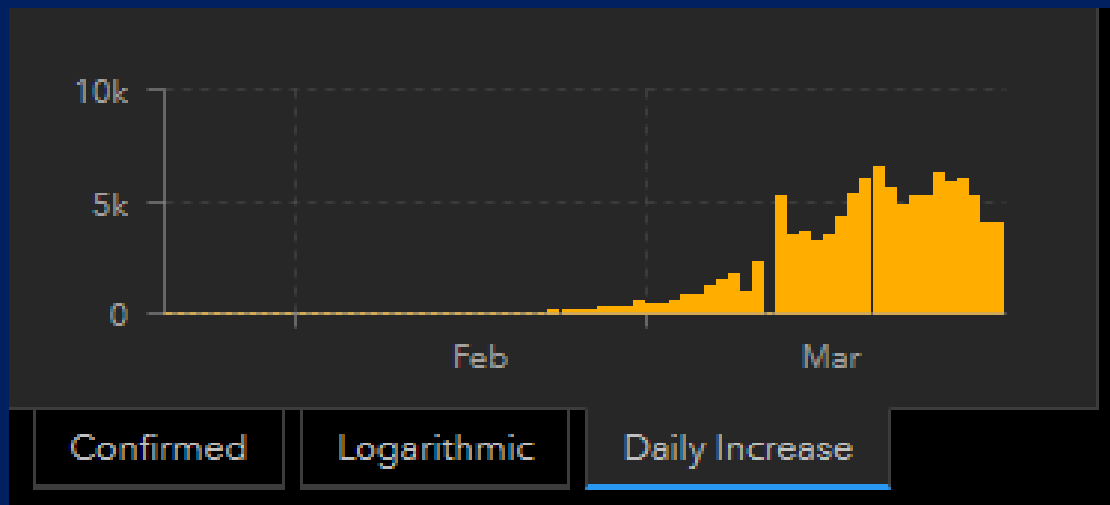
- 186,101 cases, 3603 deaths (CFR 1.9%)
- NY 74,427; NJ 18,696
- Extended social distancing guidelines through end of April
- Project 100,000 to 240,000 deaths

Globally

4/1/2020

<https://coronavirus.jhu.edu/map.html>

- 905,279 cases 45,497 deaths (CFR 5%)



Italy

Pharmaceutical Research 101

- Does drug x work for disease y ?
- Randomized controlled clinical trial
 - *Clinical* = People
 - *Randomized* = 2 groups of patients who are equivalent at the beginning - “apples to apples”, so at the end, the only difference is the drug
 - *Controlled* = 1 group gets the drug, one group doesn't
- Statistical significance
 - The results of a study are not merely due to chance
- Clinical significance
 - Translates to direct patient care

Pharmaceutical Research 101

- Clinical significance
 - Translates to direct patient care

Numbers we can measure → Affect on a person's life

Blood pressure → Prevent stroke?

Cholesterol → Prevent heart attack?

Negative nasal swab → Go home from hospital sooner?

Need less oxygen? Prevent transmission?

Registered Clinical Trials on COVID-19 3/31

- <https://clinicaltrials.gov/ct2/results?cond=COVID-19>
 - Study type = interventional
 - 155
- <https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19>
 - 20
- <http://www.chictr.org.cn/searchprojen.aspx>
 - Target disease = COVID-19
 - Study type = interventional
 - 266

Registered Clinical Trials on COVID-19

The screenshot shows the ClinicalTrials.gov website with search results for COVID-19. The browser address bar shows the URL: https://clinicaltrials.gov/ct2/results?cond=COVID-19&age_v=&gndr=&type=Intr&rslt=&Search=Apply. The page header includes the NIH logo and navigation links: Find Studies, About Studies, Submit Studies, Resources, and About Site. The search results section indicates 155 studies found for 'Interventional Studies | COVID-19'. Below this, there are buttons for 'List', 'By Topic', 'On Map', and 'Search Details'. A table of results is displayed, showing the first study: 'The Efficacy and Safety of Huaier in the Adjuvant Treatment of COVID-19'. The table has columns for Row, Saved, Status, Study Title, Conditions, Interventions, and Locations. The status of the first study is 'Not yet recruiting' with a 'NEW' tag. The browser's taskbar at the bottom shows the time as 1:49 PM on 3/31/2020.

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: <https://www.coronavirus.gov>.
Get the latest research information from NIH: <https://www.nih.gov/coronavirus>.

NIH U.S. National Library of Medicine
ClinicalTrials.gov
Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾

Home > Search Results

[Modify Search](#) [Start Over](#) +

155 Studies found for: **Interventional Studies | COVID-19**
Also searched for **SARS-CoV-2, 2019 novel coronavirus, and 2019-nCoV**. [See Search Details](#)

Applied Filters: **Interventional**

[List](#) [By Topic](#) [On Map](#) [Search Details](#)

[Hide Filters](#) [Download](#) [Subscribe to RSS](#) [Show/Hide Columns](#)

Showing: 1-10 of 155 studies studies per page

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Not yet recruiting NEW	The Efficacy and Safety of Huaier in the Adjuvant Treatment of COVID-19	• COVID-19	• Drug: Huaier Granule	

Type here to search

1:49 PM 3/31/2020

Registered Clinical Trials on COVID-19

- Antiviral medications
- Convalescent plasma
- Immune system modulators
- Antibodies
- Cancer drugs
- Blood pressure medications – ACE inhibitors, ARBs
- Traditional Chinese medications
- Chloroquine, hydroxychloroquine
- Steroids
- NSAIDs
- Vitamin supplements, antioxidants
- Stem cells
- Amniotic fluid
- Nitric oxide gas

Published Clinical Trials for COVID-19

- Cao, B. et. al. *A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19.* New England Journal of Medicine. 2020 Mar 18. [doi: 10.1056/NEJMoa2001282](https://doi.org/10.1056/NEJMoa2001282)
- Shen, C. et.al. *Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma* JAMA. 2020 March 27. [doi:10.1001/jama.2020.4783](https://doi.org/10.1001/jama.2020.4783)

Lopinavir-ritonavir

- HIV medication
- Prevents creation of virus proteins – virus can't reproduce
- Works *In vitro* (cells in a petri dish) against SARS and SARS-CoV-2

Lopinavir-ritonavir

- Side effects – most common (> 10% of patients)
 - Abdominal pain, nausea, diarrhea
 - Liver dysfunction
 - Rash
- Drug interactions – 100s!
 - Statins – cholesterol medicines
 - Calcium channel blockers – blood pressure medications
 - Blood thinner medications
 - Diabetes medications
- Possibility of creating resistance in patients with HIV

Cao et. Al.

[doi: 10.1056/NEJMoa2001282](https://doi.org/10.1056/NEJMoa2001282)

- Randomized-controlled trial – 199 patients
 - 99 Treatment
 - 100 control group
 - Overall, median time to improvement was 1 day earlier with treatment
 - Treatment group
 - Decreased mortality
 - Shorter ICU stay
 - Shorter hospitalization
 - *14 people dropped out because of side effects*
- Not statistically significant – could be due to chance

Lopinavir-ritonavir – the bottom line

- Trends towards better outcomes, but no proof
- Might work better if given earlier in the illness
- Merits more studies
 - 14 registered on clinicaltrials.gov
- Side effects were bad enough that 1 in 7 people quit taking the medication

Remdesivir

- Investigational anti-viral medication
- Not currently used to treat any diseases
- Side effects and drug interactions - unknown
- Stops viral reproduction by terminating RNA transcription
- Works *in vitro* (cells in petri dish) SARS-CoV-2, SARS, MERS, Ebola, +
- Works in mice against MERS
 - Prevents infection when given 1 day before virus exposure
 - Improves lung function when infected

Remdesivir – the bottom line

- We need large randomized controlled trials
 - 9 registered on clinicaltrials.gov

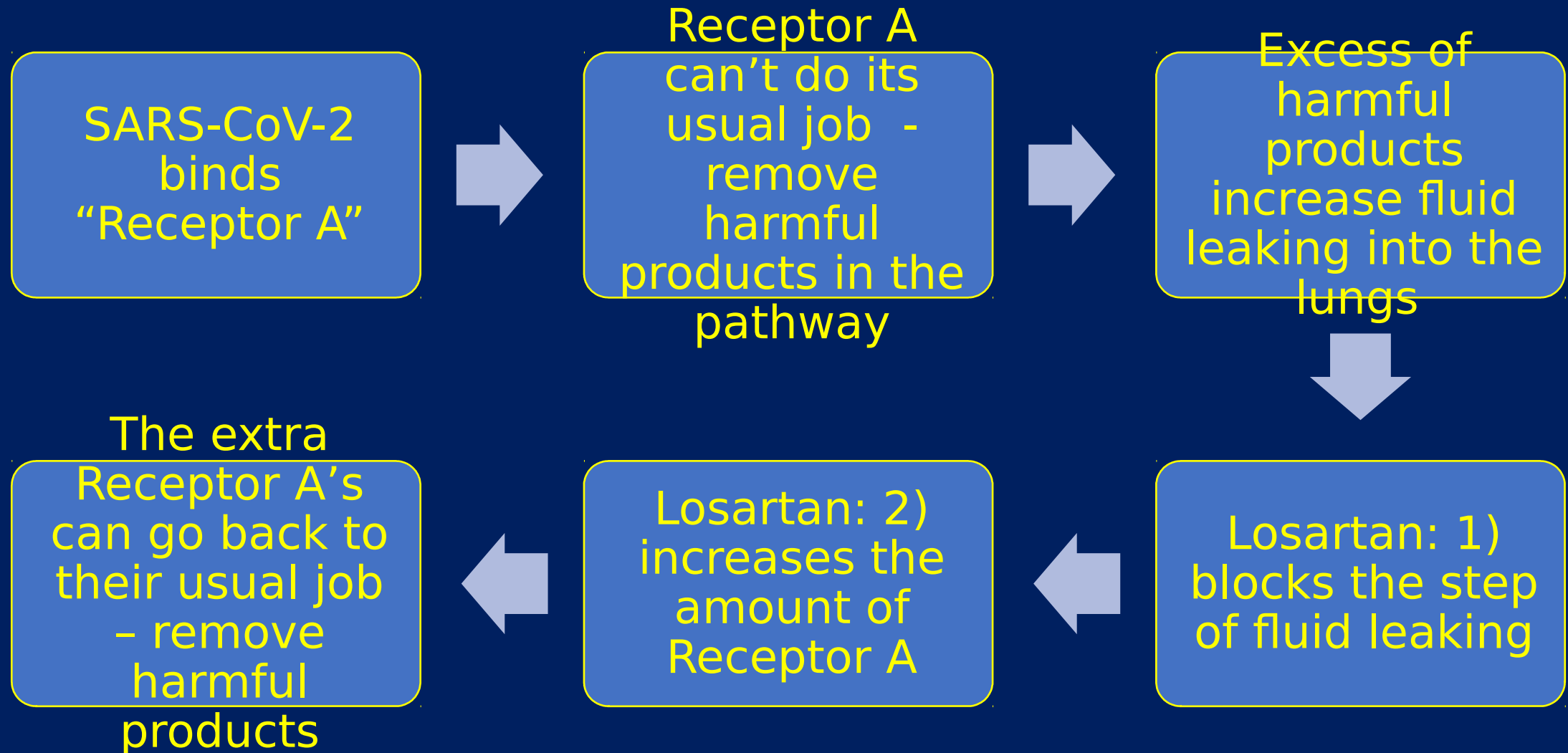
Losartan and family

- Blood pressure
- Protects kidneys in patients with diabetes
- Side effects – overall rare
 - Dizziness
 - Upper respiratory infection
 - Back pain
- Drug interactions – rare
 - NSAIDs – kidney damage

Losartan and family

- Blocks last step in a pathway of enzymes that ultimately regulate blood pressure
- What does this have to do with SARS-CoV-2?
- The receptor that the virus attaches to is upstream in this same pathway

Losartan and family -- THEORY



Losartan and family

- Interesting theory
- Could also be harmful -- receptors = viral attachment/invasion

ARBs (“-sartans”) and ACE-Is (“-prils”)

- I am already taking one of these medications for my blood pressure/heart failure/ kidneys, should I stop?
- **NO**
- *These medications are helping you for your chronic condition!*
- We don't know yet if they are helpful/harmful/neutral in COVID-19

The American Heart Association, the Heart Failure Society of America, and the American College of Cardiology put out a joint statement advocating for patients to continue ACEIs and ARBs as prescribed

Losartan and family – the bottom line

- We need large randomized controlled trials
 - 3 Registered on clinicaltrials.gov
- We can use information from previous patients to see if there is any association between taking these medications and COVID-19 mortality

Convalescent Plasma

- Immune system creates antibodies to an infection in 10-14 days
- Give antibodies from people who have *recovered* from the infection to people who are sick with the infection

Shen et. al.

[doi:10.1001/jama.2020.4783](https://doi.org/10.1001/jama.2020.4783)

- 5 critically ill patients
 - Mechanical ventilation
 - Not improving with antiviral treatments
- Received convalescent plasma from recovered donors
 - Donors consent to give blood
 - Screened for infections
 - Plasma with antibodies extracted
 - Match blood type to recipient
 - Infused on same day

Shen et. al.

[doi:10.1001/jama.2020.4783](https://doi.org/10.1001/jama.2020.4783)

- Improvements after treatment – all 5 patients
 - Oxygen requirements
 - Organ dysfunction
 - Pneumonia on CT scan
 - Fever
 - Blood tests for inflammation
- 3 patients off of ventilator, discharged home
- 2 patients remain on ventilator

Shen et. al.

[doi:10.1001/jama.2020.4783](https://doi.org/10.1001/jama.2020.4783)

- Takeaways – not much
- Small group
- Not randomized or controlled
- “last resort treatment”

Convalescent Plasma

- 1918 Influenza Pandemic
 - Ebola and other hemorrhagic fever viruses
 - SARS
 - Influenza H5N1 (Bird flu)
 - Influenza H1N1 (Swine flu)
 - West Nile Virus
-
- In all of these papers, it was given as a “last resort”

Convalescent plasma

- All of the papers reported benefits
 - Increased survival
 - Shorter hospital stays
 - Decreased symptoms
- No complications from the plasma treatment
- All of the papers had flaws
- Only 1 randomized, controlled study - Influenza H1N1
 - Increased survival
 - 35 patients total

Convalescent Plasma – the bottom line

- Might improve mortality and shorten illness
- Probably more effective if given earlier in the illness
- We need large randomized controlled studies
 - 3 registered on clinicaltrials.gov
- We need widespread antibody testing in the population
 - Determine who has already recovered
 - With permission, use antibodies for treatment.

Conclusion

- First, do no harm
- There are no proven effective treatments for COVID-19
- There are many potential avenues of treatment being studied
- Results will start to be published in the next couple of months
- Social distancing, hand hygiene, and respiratory hygiene remain the best actions

Thank you!

- Amanda Lewis
- Janet Phillips
- Greg Shores
- Brittney VanDerWerff

These presentations don't get out to you without their help!

jsplibrary.org

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References

- 1) Cao B, et. al. *A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19*. New England Journal of Medicine. 2020 Mar 18. [doi: 10.1056/NEJMoa2001282](https://doi.org/10.1056/NEJMoa2001282)
- 2) Wang M, et. al. *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro*. Cell Research. 2020 Mar;30(3):269-271 [doi: 10.1038/s41422-020-0282-0](https://doi.org/10.1038/s41422-020-0282-0)
- 3) Sheahan TP, et. al. *Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV*. Nature Communications. 2020 Jan 10;11(1):222 [doi: 10.1038/s41467-019-13940-6](https://doi.org/10.1038/s41467-019-13940-6)

References

4) Gurwitz D. *Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics* Drug Development Research 2020, 1-4 [doi: 10.1002/ddr.21656](https://doi.org/10.1002/ddr.21656)

5) Chen L, et.al. *Convalescent plasma as a potential therapy for COVID-19* Lancet Infectious Disease. 2020 [doi: 10.1016/S1473-3099\(20\)30141-9](https://doi.org/10.1016/S1473-3099(20)30141-9)

6) Soo Y, et. al. *Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients.* Clinical Microbiology and Infection. 2004; 10: 676-678 [doi:10.1111/j.1469-0691.2004.00956.x](https://doi.org/10.1111/j.1469-0691.2004.00956.x)

References

7) Cheng Y, et. al. *Use of convalescent plasma therapy in SARS patients in Hong Kong.* Eur J Clin Microbiol Infect Dis. 2005; 24: 44-46 [doi: 10.1007/s10096-004-1271-9](https://doi.org/10.1007/s10096-004-1271-9)

8) WHO *Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks.* 2014 <http://apps.who.int/iris/rest/bitstreams/604045/retrieve>

9) Hung IF, et. al. *Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection.* Clin Infect Dis. 2011; 52: 447-456 [doi:10.1093/cid/ciq106](https://doi.org/10.1093/cid/ciq106)

References

10) Hung IF, et. al. *Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection*. Chest. 2013; 144: 464-473 [doi: 10.1378/chest.12-2907](https://doi.org/10.1378/chest.12-2907)

11) Mair-Jenkins J, et. al. *The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis*. J Infect Dis. 2015; 211: 80-90 [doi: 10.1093/infdis/jiu396](https://doi.org/10.1093/infdis/jiu396)

References

12) Wu J, et.al. *Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19)* Journal of Internal Medicine 2020 [doi: 10.1111/joim.13063](https://doi.org/10.1111/joim.13063)

13) Vaduganathan, M et.al. *Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19* NEJM March 30, 2020 [doi: 10.1056/NEJMsr2005760](https://doi.org/10.1056/NEJMsr2005760)

14) Hanff, T et.al. *Is There an Association Between COVID-19 Mortality and the Renin-Angiotensin System—a Call for Epidemiologic Investigations* Clinical Infectious Diseases March 26, 2020 [doi:10.1093/cid/ciaa329](https://doi.org/10.1093/cid/ciaa329)

References

15) Patel, AB and Verma A *COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers What Is the Evidence?* JAMA March 24, 2020

[doi:10.1001/jama.2020.4812](https://doi.org/10.1001/jama.2020.4812)

16) https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp

17) www.drugs.com – side effects and drug interactions