

A compilation of evidence on hydroxychloroquine and azithromycin in treatment of COVID-19

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By James M Todaro, MD

james@covidtrial.org

Twitter: @JamesTodaroMD

covidtrial.io

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I've been asked by multiple physicians to compile and summarize the available evidence in support and opposition of hydroxychloroquine (and azithromycin) in treatment and prophylaxis of COVID-19.

Given the nature of this rapidly spreading pandemic, some of this evidence is anecdotal or expert opinion.

This is not medical advice and is for informational purposes only. Any mention of dosages is for informational purposes only and not for medical use. Please consult a medical professional.

The list is organized such that the newest evidence is continually added to the top of the list.

Latest Evidence

- ❖ A [prospective pharmacokinetics study of 13 critical care patients](#) treated with hydroxychloroquine 200 mg three times daily (600 mg daily) showed that only 61% of patients achieved the supposed minimum HCQ therapeutic threshold of 1 mg/L with a mean time of 2.7 days. The authors propose a new regimen consisting of a loading dose of hydroxychloroquine 800 mg on day 1 followed by 200 mg twice daily for 7 days with the goal of rapidly achieving therapeutic level while not exceeding potentially toxic levels above 2 mg/L.
- ❖ [In a new research abstract published on April 9](#), Dr. Didier Raoult reports outcomes of a cohort of 1061 COVID-19 patients treated with hydroxychloroquine and azithromycin at IHU Méditerranée Infection in Marseille, France. Treatment with HCQ/AZ resulted in prolonged viral shedding in only 4.4% of patients, with 91.7% virologically cured within 10 days (prior studies report viral shedding duration over 20 days in 50% and 30% of patients, [F Zhou et al \(The Lancet\)](#) and [KKW To et al \(The Lancet\)](#)). Mortality rate in the total cohort was 0.47%. Of note, the study was without controls and required treatment with HCQ/AZ of at least 3 days.
- ❖ [Randomized controlled trial of 22 COVID-19 positive, symptomatic patients](#) treated with either chloroquine 500mg twice daily or Lopinavir/Rotinavir 400/100mg twice daily for 10 days. All chloroquine treated patients were PCR negative for SARS-CoV-2 by day 13 and 92% of Lopinavir/Rotinavir treated patients were PCR negative by day 14. All chloroquine treated patients were discharged from the hospital by day 14 compared to only 50% of Lopinavir/Rotinavir treated patients. Of note, the average time from symptom onset to treatment was 2.5 days and 6.5 days in the chloroquine and Lopinavir/Rotinavir groups, respectively ($P = < 0.001$).

- ❖ [Case report of symptomatic COVID-19 positive patient](#) admitted with irregular ECG, prolonged QT interval and diagnosis of acute myocarditis. The patient was then treated with hydroxychloroquine and lopinavir/ritonavir. Shortly thereafter, ECG normalized, prolonged QT resolved and the patient was discharged.
- ❖ In São Paulo, the Prevent Senior hospital had 96 deaths from coronavirus until March 22, 2020. [Since the hospital adopted a protocol of early treatment](#) with HCQ, AZ and zinc, **it has not registered any additional deaths from COVID-19 and had only one patient in the ICU.** April 4, 2020
- ❖ Of 3005 COVID-19 positive patients at the Méditerranée Infection hospitals (APHM/IHU) in France (as of April 4), **1818 patients have been treated with HCQ and AZ.** Below are the outcomes:

COVID-19 patients NOT treated with HCQ+AZ: 1187
Deaths: 28 (2.4%)

COVID-19 patients treated with HCQ+AZ: 1818
Deaths: 5 (0.3%)

Assuming randomization of these patients to treatment and control groups (unknown if this was actually the case), **the Chi-square test p-value would be <0.00001.** April 4, 2020
- ❖ The [COVID-19 Global Rheumatology Alliance](#) says no evidence of a protective effect from hydroxychloroquine against COVID-19 in a self-report survey of patients on the medication. April 4, 2020
- ❖ Dr. Vladimir Zelenko, a board-certified family practitioner in New York, [treated his 700th coronavirus patient](#) with combination therapy of HCQ, AZ and Zinc. Of these patients, **694 recovered with outpatient therapy** and, of the 6

requiring hospitalization, only one patient died after, per Dr. Zelenko, not following his treatment protocol. April 3, 2020

- ❖ A [global survey by Sermo of 6,227 verified physicians](#) found that hydroxychloroquine (HCQ) and azithromycin (AZ) were the most used treatments (outside of analgesics) in the treatment of COVID-19. **Out of 15 drug options, HCQ was also voted the most effective therapy.** April 2, 2020

- ❖ The [US FDA issued an Emergency Use Authorization](#) for **hydroxychloroquine and chloroquine** in treatment of novel-coronavirus. March 29, 2020

- ❖ In an [opinion piece in the Wall Street Journal](#) on "An Update on the Coronavirus Treatment", Dr. Jeff Colyer, former governor of Kansas, states:

*For my entire career, I have taken a conservative approach to medicine. I don't want to give false or premature hope. All of this is subject to further refinement as more information arrives. But likewise I can't ignore the available evidence. This [HCQ + AZ] appears to be the best widely available option for treating Covid-19 and not merely easing the suffering from the disease. **It would be irresponsible not to pursue this option aggressively.*** March 29, 2020

- ❖ In a [non-randomized trial of 11 COVID-19 positive patients](#) (10/11 with fever and on nasal oxygen) at the Saint Louis Hospital in France, treatment with hydroxychloroquine (600mg for 10 days) and azithromycin (500mg day 1 and 250mg days 2-5) showed no antiviral activity or clinical benefit. One patient experienced a prolonged QT interval from 405ms to 460/470ms on day 4 of treatment. March 28, 2020

- ❖ In a [trial by Dr. Didier Raoult](#) in South France of 80 patients treated with HCQ and AZ, 98% of patients had negative viral cultures on day 5 and 93% with negative PCR tests on day 8. When compared with prior studies by [F Zhou et al \(The Lancet\)](#) and [KKW To et al \(The Lancet\)](#) that demonstrated 50% and 30% of patients with viral shedding by day 20, respectively, Raoult et al shows that viral shedding times may substantially decrease with early HCQ and AZ treatment in COVID-19. **This suggests that early treatment may decrease the spread of novel-coronavirus infection.** *March 27, 2020*
- ❖ Unpublished data from an open-label, multicenter, non-randomized trial in China of 197 patients showed that COVID-19 positive **patients treated with chloroquine for 10 days had a higher rate of negative PCR testing** by day 10 compared to controls (91.4% vs 57.4%, $P < 0.001$) and **a shorter duration of fever** ($P = 0.003$). [Video and results slide here](#). *March 26, 2020*
- ❖ [Energetics based modeling](#) of hydroxychloroquine and azithromycin binding to the SARS-CoV-2 Spike (S)Protein-ACE2 Complex shows that hydroxychloroquine may increase the acidity of the ACE2 system in the interaction between the ACE2 and SARS-CoV-2 spike that results in degradation of the spike, and potentially the discontinuation of the virus' ability to spread further. Azithromycin on the other hand, may more directly block the binding interaction between SARS-CoV-2 spike and ACE2 complex. *March 23, 2020*
- ❖ In a [randomized clinical trial by Z Chen et al \(preprint\)](#) of 62 patients who received standard therapy vs standard therapy and HCQ, **the patients who received HCQ had a significantly shorter time to body temperature recovery and cough remission.** Also of note, 4 patients (13%) in the control group progressed to severe illness whereas no patients treated with HCQ progressed. *March 22, 2020*

- ❖ A [review of available clinical evidence on chloroquine and hydroxychloroquine in the treatment of COVID-19](#) in patients with or without diabetes **concluded that these therapies had minimal risk and should be carefully considered for clinical use as experimental drugs.** *March 22, 2020*
- ❖ The [National Task Force for COVID-19 in India](#) recommends **hydroxychloroquine for prophylaxis** in "Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19." *March 21, 2020*
- ❖ Dr, Hu Bijie, Shanghai Combined Task Force on COVID-19 on [treatment options for COVID-19](#) states:

In regard to the use of antiviral drugs, anti-HIV medication Lopinavir/Ritonavir, and a broad spectrum anti-viral drug, Abitor, the overall result compared to placebo group showed no significant difference...We truly felt hydroxychloroquine is the specific drug of choice for COVID-19. *March 20, 2020*
- ❖ A [Nature article in Cell Discovery](#) demonstrated that hydroxychloroquine is effective in inhibiting SARS-CoV-2 infection in vitro by blocking the transport of SARS-CoV-2 from EEs to ELs—a requirement to release viral genome. Authors conclude that "In combination with its anti-inflammatory function, we predict that the drug [hydroxychloroquine] has a good potential to combat the disease." *March 18, 2020*
- ❖ Dr. Didier Raoult publishes on [hydroxychloroquine and azithromycin as a treatment of COVID-19](#) in an open-label non-randomized clinical trial of 36 patients (14 treated with HCQ, 6 treated with HCQ+AZ, and 16 controls) that demonstrated significantly faster elimination of virus by PCR testing in the treatment group. **All 6 patients in the HCQ+AZ treatment arm were virologically cured by day 6 of treatment.** *March 17, 2020*

- ❖ In [a report](#) disseminated by Elon Musk on Twitter, **James Todaro, MD and Gregory Rigano, Esq explore the growing evidence of Chloroquine as a highly effective treatment and prophylaxis for COVID-19.** [Full report available here](#). *March 13, 2020*
- ❖ [In vitro study published by Oxford University Press](#) of the antiviral activity of hydroxychloroquine in treatment of SARS-CoV-2 showed **hydroxychloroquine to be about three times more potent than chloroquine** in inhibiting SARS-CoV-2. *March 9, 2020*
- ❖ An [expert consensus by the Guangdong Provincial Department of Science and Technology and Guangdong Provincial Health Commission](#) determined that **chloroquine may shorten hospital stay and improve patient outcomes.** Treatment of COVID-19 was standardized with 500mg chloroquine phosphate, twice a day for 10 days. *February 20, 2020*
- ❖ [South Korea guidelines](#) from the COVID-19 Central Clinical Task Force propose treatment with daily chloroquine or, alternatively, daily hydroxychloroquine if chloroquine is unavailable. *February 13, 2020*

Upcoming clinical trials on efficacy of HCQ in prevention of COVID-19

Active trials, no longer recruiting:

1. [Prevention of SARS-CoV-2 \(COVID-19\) Through Pre-Exposure Prophylaxis With Tenofovir Disoproxil Fumarate/Emtricitabine and Hydroxychloroquine in Healthcare Personnel: Randomized Clinical Trial Controlled With Placebo](#)

- a. Randomized, double-blind, placebo controlled trial comparing **prophylaxis** of daily single dose of tenofovir disoproxil fumarate (245 mg)/ Emtricitabine (200 mg), **a daily single dose of hydroxychloroquine (200 mg)**, a daily single dose of TDF (245 mg)/FTC (200 mg) plus HCQ (200 mg) versus placebo, during 12 weeks in hospital healthcare workers with primary outcome of incidence of symptomatic COVID-19.
- b. Estimated enrollment: **4000 participants**
- c. Research organization: **Plan Nacional sobre el Sida (Spain)**
- d. Estimated completion date: **July 31, 2020**

Trials recruiting:

- 2. [A Prospective Clinical Study of Hydroxychloroquine in the Prevention of SARS- CoV-2 \(COVID-19\) Infection in Healthcare Workers After High-risk Exposures](#)
 - a. Non-randomized open-label trial comparing **prophylaxis** of **hydroxychloroquine (400mg twice a day)** in healthcare workers versus those healthcare workers who opt out of receiving hydroxychloroquine that will serve as controls with primary outcome of rate of COVID-19 positive conversion on weekly NP sampling.
 - b. Estimated enrollment: **360 participants**
 - c. Research organization: **Baylor Research Institute (USA)**
 - d. Estimated completion date: **July 30, 2020**
- 3. [Pre-Exposure Prophylaxis With Hydroxychloroquine for High-Risk Healthcare Workers During the COVID-19 Pandemic: A Unicentric, Double-Blinded Randomized Controlled Trial](#)
 - a. Randomized, quadruple-blind, placebo controlled trial comparing **prophylaxis** of **weekly hydroxychloroquine (400mg)** versus placebo in healthcare works for 6 months with primary outcome confirmed positive testing for COVID-19.
 - b. Estimated enrollment: **440 participants**
 - c. Research organization: **Barcelona Institute for Global Health (Spain)**

d. Estimated completion date: **October 30, 2020**

4. [Pre-exposure Prophylaxis for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial](#)

- a. Randomized, quadruple-blind, placebo controlled trial comparing **prophylaxis** of **weekly hydroxychloroquine (400 mg) or twice weekly hydroxychloroquine (400 mg)** versus placebo in healthcare workers for 12 weeks with primary outcome negative testing for COVID-19.
- b. Estimated enrollment: **3500 participants**
- c. Research organization: **University of Minnesota (USA)**
- d. Estimated completion date: **August 2020**

Trials not yet recruiting:

5. [The PATCH Trial \(Prevention And Treatment of COVID-19 With Hydroxychloroquine\)](#)

- a. Randomized, double-blind, placebo controlled trial comparing **prophylaxis** of **daily hydroxychloroquine (600 mg)** versus placebo in healthcare workers for 2 months with primary outcome positive testing for COVID-19.
- b. Estimated enrollment: **400 participants**
- c. Research organization: **University of Pennsylvania (USA)**
- d. Estimated completion date: **December 1, 2021**

6. [Hydroxychloroquine Post Exposure Prophylaxis \(PEP\) for Household Contacts of COVID-19 Patients: A NYC Community-Based Randomized Clinical Trial](#)

- a. Randomized, quadruple-blind, placebo controlled trial comparing **prophylaxis** of **daily hydroxychloroquine (400 mg twice daily for day 1, followed by 200 mg twice daily for days 2-5)** versus placebo in household contacts of COVID-19 patients with primary outcome symptomatic, positive testing for COVID-19 within 14 days.
- b. Estimated enrollment: **1600 participants**
- c. Research organization: **Columbia University (USA)**
- d. Estimated completion date: **March 2021/2022**

7. [Chemoprophylaxis of SARS-CoV-2 Infection \(COVID-19\) in Exposed Healthcare Workers : A Randomized Double-blind Placebo-controlled Clinical Trial](#)
 - a. Randomized, triple-blind, placebo controlled trial comparing **prophylaxis of daily hydroxychloroquine (400 mg twice daily for day 1, followed by 200 mg daily)** versus placebo in healthcare workers for 2.5 months with primary outcome positive testing for COVID-19.
 - b. Estimated enrollment: **1200 participants**
 - c. Research organization: **Centre Hospitalier Universitaire de Saint Etienne (France)**
 - d. Estimated completion date: **November 30, 2020**
8. [Efficacy of Hydroxychloroquine for Post-exposure Prophylaxis \(PEP\) to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 \(SARS-CoV-2\) Infection Among Adults Exposed to Coronavirus Disease \(COVID-19\): a Blinded, Randomized Study](#)
 - a. Randomized, single-blind, placebo controlled trial comparing **prophylaxis of daily hydroxychloroquine (400 mg daily for days 1-3, followed by 200 mg daily for an additional 11 days)** versus placebo comparator ascorbic acid in household contacts of COVID-19 patients with primary outcome positive PCR testing for COVID-19 within 14 days.
 - b. Estimated enrollment: **2000 participants**
 - c. Research organization: **University of Washington in collaboration with NYU and Bill and Melinda Gates Foundation (USA)**
 - d. Estimated completion date: **October 31, 2020**

Antiviral properties of azithromycin

- ❖ [A Schögler, et al.](#) Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells.

European Respiratory Journal Feb 2015, 45 (2) 428-439; DOI: 10.1183/09031936.00102014.

- Summary: The **antibiotic azithromycin demonstrates antiviral properties in human bronchial epithelial cells** possibly by amplifying the response mediated by the IFN pathway.
- ❖ [Takeya H, Seki M, Izumikawa K, et al.](#) Efficacy of combination therapy with oseltamivir phosphate and azithromycin for influenza: a multicenter, open-label, randomized study. PLoS One. 2014;9(3):e91293. Published 2014 Mar 14. doi:10.1371/journal.pone.0091293.
 - Summary: A randomized trial of 107 patients with influenza A who received either combination therapy with oseltamivir and azithromycin or monotherapy with oseltamivir that **showed combination therapy with azithromycin resulted in early resolution of symptoms.**
- ❖ [V Gielen, SL Johnston, MR Edwards.](#) Azithromycin induces anti-viral responses in bronchial epithelial cells. European Respiratory Journal 2010 36: 646-654; DOI: 10.1183/09031936.00095809.
 - Summary: Azithromycin has anti-rhinoviral activity in bronchial epithelial cells and increases the production of interferon-stimulated genes upon infection. This benefit was not seen with erythromycin or telithromycin.
- ❖ [MT Labro.](#) Anti-inflammatory activity of macrolides: a new therapeutic potential?, Journal of Antimicrobial Chemotherapy, Volume 41, Issue suppl_2, 1 March 1998, Pages 37-46, https://doi.org/10.1093/jac/41.suppl_2.37.
 - Summary: A review of in vitro and ex vivo studies that **short-term administration of macrolide antibiotics may enhance the immune response** while long-term administration results in immunosuppression.
- ❖ [Menzel M, Akbarshahi H, Bjermer L, Uller L.](#) Azithromycin induces anti-viral effects in cultured bronchial epithelial

cells from COPD patients. Sci Rep. 2016;6:28698. Published 2016 Jun 28. doi:10.1038/srep28698.

- Summary: Azithromycin increased rhinovirus-induced expression of interferons in bronchial epithelial cells from COPD donors compared to cells from healthy donors. These effects could reduce bronchial viral load, and support azithromycin's role in prevention of exacerbations of COPD.

Cardiac injury and myocarditis in COVID-19

- ❖ [S Sala, et al.](#) Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection, European Heart Journal, ehaa286, <https://doi.org/10.1093/eurheartj/ehaa286>
 - Summary: Case report of a **symptomatic COVID-19 positive patient admitted with irregular ECG, prolonged QT interval and biopsy confirmed diagnosis of acute myocarditis**. The patient was then **treated with hydroxychloroquine** and lopinavir/ritonavir. Shortly thereafter, ECG normalized, **prolonged QT resolved** and the patient was discharged.
- ❖ [Arentz M, Yim E, Klaff L, et al.](#) Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. Published online March 19, 2020. doi:10.1001/jama.2020.4326.
 - Summary: In a case series of 21 critically ill novel-coronavirus patients in Washington State, **7 patients (33%) developed cardiomyopathy**.
- ❖ [Shi S, Qin M, Shen B, et al.](#) Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. Published online March 25, 2020. doi:10.1001/jamacardio.2020.0950.

- **Summary: In a cohort of 416 hospitalized patients in Wuhan, China, 82 patients (19.7%) had cardiac injury.** ECGs were performed on only 22 patients with cardiac injury (26.8%), with 14 patients undergoing ECG during periods of elevated cardiac biomarkers. All 14 ECGs were abnormal. The article does not specify if any patients received hydroxychloroquine or chloroquine.
- ❖ [Bansal M.](#) Cardiovascular disease and COVID-19 [published online ahead of print, 2020 Mar 25]. Diabetes Metab Syndr. 2020;14(3):247-250. doi:10.1016/j.dsx.2020.03.013.
 - **Summary: A literature search shows that approximately 8-12% of all COVID-19 patients experience cardiac abnormality/myocardial injury.**

Safety profile of hydroxychloroquine and azithromycin

- ❖ [N Costedoat-Chalumeau, et al.](#) Heart conduction disorders related to antimalarials toxicity: an analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases, Rheumatology, Volume 46, Issue 5, May 2007, Pages 808-810, <https://doi.org/10.1093/rheumatology/kel402>.
 - **Summary: Study of 85 patients with autoimmune disorders treated with hydroxychloroquine for at least one year showed no significant increase in PR interval, QTc interval, heart rate or conduction disorders,** demonstrating safety of hydroxychloroquine.
- ❖ [CI Wu, et al.](#) SARS-CoV-2, COVID-19 and inherited arrhythmia syndromes. Heart Rhythm. March 28, 2020. DOI: <https://doi.org/10.1016/j.hrthm.2020.03.024>
 - **Summary: The QT-prolonging effect of chloroquine is "very modest, and in general it does not result in clinically significant QT-prolongation in patients without LQTS." The combination of hydroxychloroquine**

with remdesivir or azithromycin may result in QT-prolongation, however, and ECG monitoring is recommended.

- ❖ [NJ White.](#) Cardiotoxicity of antimalarial drugs. Lancet Infect Dis. 2007 Aug;7(8):549-58. DOI: 10.1016/S1473-3099(07)70187-1.
 - Summary: Chloroquine can result in hypotension when injected rapidly and cardiovascular collapse with self-poisoning. Transiently hypotensive plasma concentrations of chloroquine can occur with intramuscular or subcutaneous injections of 5mg base/kg or more.
- ❖ [Kimani J, Phiri K, Kamiza S, et al.](#) Efficacy and Safety of Azithromycin-Chloroquine versus Sulfadoxine-Pyrimethamine for Intermittent Preventive Treatment of Plasmodium falciparum Malaria Infection in Pregnant Women in Africa: An Open-Label, Randomized Trial. PLoS One. 2016;11(6):e0157045. Published 2016 Jun 21. doi:10.1371/journal.pone.0157045.
 - Summary: Randomized, Phase 3 trial showing **no drug related deaths in 1446 pregnant women treated with 620mg chloroquine in combination with 1000mg azithromycin daily** for 3 days.
- ❖ [Cook JA, Randinitis EJ, Bramson CR, Wesche DL.](#) Lack of a pharmacokinetic interaction between azithromycin and chloroquine. Am J Trop Med Hyg 2006; 74:407-12.
 - Summary: Randomized, Phase 1 trial showing **no clinically relevant pharmacokinetic interaction in 24 subjects receiving 500-1000mg chloroquine & 1000mg azithromycin daily** for 3 days.
- ❖ [Chico RM, Chandramohan D.](#) Azithromycin plus chloroquine: combination therapy for protection against malaria and sexually transmitted infections in pregnancy. Expert Opin Drug Metab Toxicol. 2011;7(9):1153-1167. doi:10.1517/17425255.2011.598506.

- Summary: **Expert opinion finds chloroquine and azithromycin safely given any time in pregnancy.**
Pharmacokinetics in pregnancy suggest dose adjustments not necessary for azithromycin but chloroquine dosing needs to be 600 mg.

- ❖ [Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM.](#) Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012;366(20):1881-1890. doi:10.1056/NEJMoal003833.
 - Summary: Out of a cohort of 347,795 prescriptions of azithromycin, 1,348,672 prescriptions of amoxicillin and 1,391,180 control periods, **there was an additional 47 cardiovascular deaths per million prescription courses in the azithromycin cohort compared to amoxicillin cohort** (P = 0.002).

- ❖ [MW Dunne, et al.](#) A Multicenter Study of Azithromycin, Alone and in Combination with Chloroquine, for the Treatment of Acute Uncomplicated Plasmodium falciparum Malaria in India, The Journal of Infectious Diseases, Volume 191, Issue 10, 15 May 2005, Pages 1582-1588, <https://doi.org/10.1086/429343>.
 - Summary: Open-label study of combination therapy of hydroxychloroquine and azithromycin in treatment of falciparum malaria in 64 subjects demonstrated only **mild side effects of medication that did not require discontinuation of therapy.**

- ❖ [World Health Organization.](#) The cardiotoxicity of antimalarials. WHO Evidence Review Group Meeting, 13-14 October 2016. Varembe Conference Centre, Geneva, Switzerland.
 - Summary: "Apart from halofantrine, antimalarial medicines that prolong the QT/QTc interval, such as quinine, **chloroquine**, artesunate-amodiaquine and dihydroartemisinin-piperaquine, **have been associated with a low risk of cardiotoxicity.**"

- ❖ [Chun-Yu Chen, Feng-Lin Wang & Chih-Chuan Lin \(2006\).](#)
Chronic Hydroxychloroquine Use Associated with QT Prolongation and Refractory Ventricular Arrhythmia, *Clinical Toxicology*, 44:2, 173-175, DOI: 10.1080/15563650500514558.
➤ Summary: A case report of a 67-year-old female with SLE treated with daily hydroxychloroquine for one year who developed prolonged QT interval and, subsequently, Torsades de pointes that resolved after discontinuation of hydroxychloroquine.
- ❖ [JP O'Laughlin, PH Mehta, BC Wong.](#) Life Threatening Severe QTc Prolongation in Patient with Systemic Lupus Erythematosus due to Hydroxychloroquine. *Hindawi, Case Reports on Cardiology*, Volume 2016, Article ID 4626279, 4 pages, DOI: 10.1155/2016/4626279.
➤ Summary: A case report of a 50-year-old female with SLE and renal failure treated with daily hydroxychloroquine for two years who developed prolonged QT interval and, subsequently, syncope. The prolonged QT interval did not improve after discontinuation of hydroxychloroquine, and was possibly due to underlying SLE cardiomyopathy.
- ❖ [Mitra, Raman L. et al.](#) An algorithm for managing QT prolongation in Coronavirus Disease 2019 (COVID-19) patients treated with either chloroquine or hydroxychloroquine in conjunction with azithromycin: Possible benefits of intravenous lidocaine. *HeartRhythm Case Reports*. <https://doi.org/10.1016/j.hrcr.2020.03.016>.
➤ Summary: A case report of a 66-year-old female with RA, pulmonary fibrosis and asthma (not on hydroxychloroquine) presenting with COVID-19. Patient was treated with azithromycin for 3 days before adding hydroxychloroquine. After one dose of hydroxychloroquine, however, the QT interval prolonged to 620ms. Hydroxychloroquine was discontinued and IV lidocaine was started with improvement of QT interval. The patient was then able to complete the course of

hydroxychloroquine, but expired shortly thereafter from multi-organ system failure.

Antiviral effects of zinc supplements and synergy with chloroquine

- ❖ [Xue J, Moyer A, Peng B, Wu J, Hannafon BN, Ding WQ.](#) Chloroquine is a zinc ionophore. PLoS One. 2014;9(10):e109180. Published 2014 Oct 1. doi:10.1371/journal.pone.0109180.
 - Summary: **The combination of zinc with chloroquine enhanced chloroquine's cytotoxicity in human cancer cells.** Addition of copper or iron ions had no effect on chloroquine-induced zinc uptake.
- ❖ [A Velthuis, et al.](#) Zn Inhibits Coronavirus and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture. (2010). PLoS pathogens. 6. e1001176. 10.1371/journal.ppat.1001176.
 - Summary: In vitro study showing that **increased intracellular zinc concentration via zinc-ionophores can impair the replication of RNA viruses, including SARS-CoV-1, in cell cultures.**
- ❖ [The Zinc Against Plasmodium Study Group.](#) Effect of zinc on the treatment of Plasmodium falciparum malaria in children: a randomized controlled trial, The American Journal of Clinical Nutrition, Volume 76, Issue 4, October 2002, Pages 805-812, <https://doi.org/10.1093/ajcn/76.4.805>.
 - Summary: **Zinc in combination with chloroquine does not reduce fever, parasitemia or appear to have a beneficial effect in the treatment of acute, uncomplicated falciparum malaria in**

children compared to monotherapy with chloroquine.

- ❖ [Singh M, Das RR.](#) Zinc for the common cold. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD001364. DOI: 10.1002/14651858.CD001364.pub4.
 - Summary: Systematic review of randomized, double-blind, placebo-controlled trials shows **zinc administered within the first 24 hours of symptom onset and in doses \geq 75 mg/day significantly reduces the duration of symptoms caused by the common cold.** There was insufficient data to assess a prophylactic effect.
- ❖ [Singh M, Das RR.](#) Zinc for the common cold. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD001364. DOI: 10.1002/14651858.CD001364.pub3.
 - Summary: Systematic review of randomized, double-blind, placebo-controlled trials shows zinc administered within the first 24 hours of symptom onset significantly reduces the severity and duration of symptoms caused by viruses in the common cold.
- ❖ [Hemilä H.](#) Zinc lozenges may shorten the duration of colds: a systematic review. Open Respir Med J. 2011;5:51-58. doi:10.2174/1874306401105010051.
 - Summary: A meta-analysis of 13 placebo-controlled trials on the therapeutic effect of zinc lozenges on the common cold demonstrates that **zinc supplements over 75mg daily significantly reduced the duration of the common cold. There was no significant difference in zinc supplement doses under 75 mg daily.**

Efficacy of chloroquine against SARS-CoV-1

- ❖ [Vincent, M.J., Bergeron, E., Benjannet, S. et al.](#)
Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2, 69 (2005).
<https://doi.org/10.1186/1743-422X-2-69>.
 - Summary: Chloroquine is effective in preventing the spread of SARS-CoV in cell culture before and after exposure to the virus in primate cells, suggesting both prophylactic and therapeutic advantage.
- ❖ [E. Keyaerts, L. Vijgen, P. Maes, J. Neyts, M. Van Ranst.](#) In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun, 323 (2004), pp. 264-268, 10.1016/j.bbrc.2004.08.085.
 - Summary: Chloroquine is an effective inhibitor of the replication of SARS-CoV in vitro.

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