Global HCQ studies. PrEP, PEP, and early treatment studies show efficacy, while late treatment shows mixed results.

Pre-Exposure Prophylaxis study

Gentry et al., Lancet Rheumatology, doi:10.1016/S2665-9913(20)30305-2 (Peer Reviewed)

Long-term hydroxychloroquine use in patients with rheumatic conditions and development of SARS-CoV-2 infection: a retrospective cohort study

Retrospective patients with rheumatologic conditions showing zero mortality with HCQ, odds ratio OR 0.0, \(p = 0.10\). 0 of 10,703 COVID-19 deaths for HCQ patients versus 7 of 21,406 for control patients.

COVID-19 cases OR 0.79, \(p = 0.27\). There are several significant differences in the propensity matched patients that could affect results, e.g., 20.9% SLE versus 24.7%.

Pre-Exposure Prophylaxis study


Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial

PrEP RCT showing HR 0.73, \(p = 0.12\) (~209,084 potential lives saved with global HCQ).
Trial halted after 47% enrollment, \( p < 0.05 \) will be reached at \( \sim 75\% \) enrollment if similar results continue. Trial halted due to low enrollment. US prescriptions only stopped briefly, resuming in June, so the authors can complete the study [1].

HR 0.66/0.68 for full medication adherence, 0.72/0.74, \( p = 0.18/0.22 \) overall (1x/2x dosing).

Efficacy for first responders was higher, OR 0.32, \( p = 0.01 \). First responders had a much higher incidence, allowing greater power, and reducing the effect of confounders such as misdiagnosis of other conditions or survey issues.

Performance is similar to placebo for the first 3 weeks. The effect may be greater with a dosage regimen that achieves therapeutic levels faster [2]. \( \sim 40\% \) of participants suspected they might have had COVID-19 before the trial, the effect in people without prior COVID-19 may be higher.

Authors note:
- the trial was underpowered
- investigation into more frequent dosing may be warranted
- insufficient dosing with no participants achieving more than the \( \text{in vitro} \) EC\textsubscript{50}

Internet survey RCT subject to survey bias. There was no death or ICU admission. Low risk healthcare workers, median age \( \sim 40 \). 494 1x/week dosing, 495 2x/week dosing, 494 control participants (1x and 2x participants received the same overall dosage).

Small PrEP RCT showing that PrEP with HCQ is safe at the dosage used. No deaths, hospitalizations, or serious adverse events. With only one case (in the placebo arm), efficacy was not evaluated.

Late treatment study

Axfors et al., medRxiv, doi:10.1101/2020.09.16.20194571 (Preprint) (meta analysis - not included in study count)

Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials

Meta analysis assigning 87% weight to the RECOVERY trial, producing the same result. The RECOVERY trial used excessively high non-patient-customized dosage in very sick late stage patients and the result is not generalizable to typical dosage or earlier treatment.

N/A

Karatza et al., Xenobiotica (Peer Reviewed) (not included in the study count)

Optimization of hydroxychloroquine dosing scheme based on COVID-19 patients’ characteristics: a review of the literature and simulations

Analysis of HCQ dosing, suggesting that high initial doses followed by low and sparse doses may offer significant benefits to patients by decreasing the viral load without reaching levels considered to produce adverse effects.

For instance, the dosing scheme proposed for a 70kg adult with moderate COVID-19 symptoms would be 600mg upon diagnosis, 400mg after 12h, 300mg after 24h, 200mg after 36h, followed by 200mg BID for 4 days, followed by 200mg OD for 5 days.

Suboptimal dosing regimens that do not fully account for the long half-life of HCQ or the patient characteristics are likely contribute to either limited efficacy where therapeutic levels take too long to reach, or significant adverse effects due to excessive dosage.

Late treatment study

Lauriola et al., Clinical and Translational Science, doi:10.1111/cts.12860 (Peer Reviewed)

Effect of combination therapy of hydroxychloroquine and azithromycin on mortality in
COVID-19 patients

Retrospective 377 patients, 73% reduction in mortality with HCQ+AZ, adjusted hazard ratio HR 0.27 [0.17-0.41]. Mean age 71.8. No serious adverse events. Subject to incomplete adjustment for confounders.

Source  Study Page  Submit Corrections or Comments

Early treatment study


The Effect of Early Hydroxychloroquine-based Therapy in COVID-19 Patients in Ambulatory Care Settings: A Nationwide Prospective Cohort Study

Observational prospective 5,541 patients, adjusted HCQ mortality odds ratio OR 0.36, p = 0.012 (~495,608 potential lives saved with global HCQ). Adjusted hospitalization OR 0.57, p < 0.001. Zinc supplementation was used in all cases. Early treatment in ambulatory fever clinics in Saudi Arabia.

Late treatment study

Heberto et al., IJC Heart & Vasculature, doi:10.1016/j.ijcha.2020.100638 (Peer Reviewed)

Implications of myocardial injury in Mexican hospitalized patients with coronavirus disease 2019 (COVID-19)

Observational prospective 254 hospitalized patients, HCQ+AZ mortality odds ratio OR 0.36, p = 0.04.

Ventilation OR 0.20, p = 0.008.

Source  Study Page  Submit Corrections or Comments
Mortality Risk Factors among Hospitalized COVID-19 Patients in a Major Referral Center in Iran

Retrospective 396 patients in Iran 93% using HCQ, showing HCQ mortality RR 0.45, \( p = 0.028 \). HCQ was the only antiviral that showed a significant difference. Small number of control patients and subject to confounding by indication. Average admission delay 5.72 days.

Source Study Page Submit Corrections or Comments

Characteristics and outcomes of admitted patients infected with SARS-CoV-2 in Uganda

Retrospective 56 patients in Uganda, 29 HCQ and 27 control, showing 25.6% faster recovery with HCQ, 6.4 vs. 8.6 days (\( p = 0.20 \)). There was no ICU admission, mechanical ventilation, or death.

Treatment delay is not specified but at least a portion of patients appear to have been treated early.

Source Study Page Submit Corrections or Comments

Hydroxychloroquine for prevention of COVID-19 mortality: a population-based cohort study

Observational database study of RA/SLE patients in the UK, 194,637 RA/SLE patients with 30,569 having >= 2 HCQ prescriptions in the prior 6 months, HCQ HR 1.03 [0.80-1.33] (HR 0.78 before adjustments).

70 patients with HCQ prescriptions died. One major problem is that there is no knowledge of medication adherence for these 70 - for example, it is possible that they were part of the expected percentage of patients that did not take the medication as prescribed, invalidating the result.

Both confirmed and suspected deaths were included. It is not clear why the authors did not report the result for only confirmed cases. It has been reported that several thousand deaths were incorrectly declared as COVID-19 in the UK.
Other limitations: confounding by use of bDMARDs, confounding by severity of rheumatological disease.

Source  Study Page  Submit Corrections or Comments

Pre-Exposure Prophylaxis study

Laplan et al., medRxiv, doi:10.1101/2020.09.03.20158121 (Preprint)

Lack of protective effect of chloroquine derivatives on COVID-19 disease in a Spanish sample of chronically treated patients

Survey of 319 autoimmune disease patients taking CQ/HCQ with 5.3% COVID-19 incidence, compared to a control group from the general population (matched on age, sex, and region, but not adjusted for autoimmune disease), with 3.4% incidence.

It not clear why authors did not compare with autoimmune patients not on CQ/HCQ. Other research shows that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall, Ferri et al. show OR 4.42, p<0.001 [1], which is the observed real-world risk, taking into account factors such as these patients potentially being more careful to avoid exposure. If we adjust for the different baseline risk, the result becomes RR 0.36, p<0.001, suggesting a substantial benefit for HCQ/CQ treatment (as shown in other studies).

There may also be significant survey bias - those experiencing COVID-19 may be more likely to respond to the survey.

Authors note that they "could not eliminate completely the possibility of some bias due to the intrinsic condition of the individuals within the treatment group that are undergoing chloroquine or derivative drug treatment due to other diseases that alter their health status and may have different comorbidities", however they could account for one significant bias by comparing with matched autoimmune disease patients.

[1] c19study.com/ferri.html

Source  Study Page  Submit Corrections or Comments

Meta

Early, Late

Prodromos et al., Preprint, doi:10.13140/RG.2.2.29781.65765 (Preprint) (meta analysis - not included in study count)

Hydroxychloroquine is Effective and Safe for the Treatment of COVID-19, and May be Universally Effective When Used Early Before Hospitalization: A Systematic Review

Meta analysis of 41 studies concluding: "HCQ has been shown to have consistent clinical efficacy for COVID-19 when it is used early in the outpatient setting, and in general would appear to work better the earlier it is used. Overall HCQ is effective against COVID-19. There
is no credible evidence that HCQ results in worsening of COVID-19. HCQ has been shown to be safe for the treatment of COVID-19 when responsibly used.

**Review**

*IHU, Expert Review of Clinical Immunology (Peer Reviewed) (Review) (not included in the study count)*

Natural history and therapeutic options for COVID-19

Review of the current state of knowledge regarding the natural history of and therapeutic options for COVID-19.

Treatment with an oral combination of hydroxychloroquine, azithromycin and zinc may represent the best current therapeutic option in relation to its antiviral and immunomodulatory effects.

**Late treatment study**

*Synolaki et al., medRxiv, doi:10.1101/2020.09.05.20184655 (Preprint)*

Activin/Follistatin-axis deregulation is independently associated with COVID-19 in-hospital mortality

Retrospective 117 patients, 58 HCQ. HCQ, AZ, and other treatments were found to be independently associated with survival when treatment commenced early.
Late treatment study

Furtado et al., The Lancet, doi:10.1016/S0140-6736(20)31862-6 (Peer Reviewed)

Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial

Small RCT comparing the addition of AZ for very late stage patients on ventilation or oxygen. No significant difference was found, OR 1.36, p=0.11. One notable result is that even within this extremely late stage population, results suggest increased efficacy with the addition of AZ for patients with earlier use of AZ/HCQ, OR 0.71, p=0.28.

Since all patients were on HCQ, this study does not provide information on the efficacy of HCQ.

Source  Study Page  Submit Corrections or Comments

In Vitro

Wang et al., Phytomedicine, doi:10.1016/j.phymed.2020.153333 (Peer Reviewed) (In Vitro) (not included in the study count)

Chloroquine and hydroxychloroquine as ACE2 blockers to inhibit viropexis of 2019-nCoV Spike pseudotyped virus

In Vitro study providing novel insights into the molecular mechanism of CQ/HCQ treatment, showing that CQ and HCQ both inhibit the entrance of 2019-nCoV into cells by blocking the binding of the virus with ACE2.

Source  Study Page  Submit Corrections or Comments

Positive

Early treatment study

Heras et al., Research Square, doi:10.21203/rs.3.rs-70219/v1 (Preprint)

COVID-19 mortality risk factors in older people in a long-term care center

Retrospective 100 elderly nursing home patients, HCQ+AZ mortality 11.4% vs. control 61.9%, RR 0.18, p<0.001 (~634,997 potential lives saved with global HCQ). Median age 85.

COVID-19 confirmed. 70% treated with HCQ+AZ. Details of differences between groups are not provided, and no adjustments are made. It is not clear how the groups were selected. Authors indicate treatment was early but do not specify the treatment delay.
Pre-Exposure Prophylaxis study

de la Iglesia et al., medRxiv, doi:10.1101/2020.08.31.20185314 (Preprint)

Hydroxichloroquine for pre-exposure prophylaxis for SARS-CoV-2

Analysis of autoimmune disease patients on HCQ, compared to a control group from the general population (matched on age and sex, but not adjusted for autoimmune disease), showing non-significant differences between groups.

Other research shows that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall, Ferri et al. show OR 4.42, p<0.001 [1], which is the observed real-world risk, taking into account factors such as these patients potentially being more careful to avoid exposure.

If we adjust for the different baseline risk, the mortality result becomes RR 0.35, p=0.23, suggesting a substantial benefit for HCQ treatment (as shown in other studies).

[1] c19study.com/ferri.html
Zinc(II)—The Overlooked Éminence Grise of Chloroquine’s Fight against COVID-19?

Review of zinc as an inhibitor of SARS-CoV-2’s RNA-dependent RNA polymerase, and zinc ionophores including CQ/HCQ, showing the latest evidence for zinc and CQ/HCQ having antiviral, and in particular anticoronaviral action.

Early treatment study

Elbazidi et al., New Microbes and New Infections, doi:10.1016/j nmni.2020.100749 (Peer Reviewed)

Pandemic and social changes, political fate

Analysis of US states and countries. Country analysis shows a significant correlation between the dates of decisions to adopt/decline HCQ, and corresponding trend changes in CFR. US state analysis shows a significant correlation between CFR and the level of acceptance of HCQ.

Late treatment study


Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study

RCT on calcifediol (25-hydroxyvitamin D) treatment for hospitalized COVID-19 patients showing significantly reduced intensive care unit admissions. All patients received standard care including HCQ+AZ. Significantly lower ICU admission with the addition of Calcifediol - odds ratio OR 0.02 [0.002-0.17].
Late treatment study

*Fried et al., Clinical Infectious Disease, doi:10.1093/cid/ciaa1268 (Peer Reviewed)*

Patient Characteristics and Outcomes of 11,721 Patients with COVID19 Hospitalized Across the United States

Database analysis of 11,721 hospitalized patients, 4,232 on HCQ. Strong evidence for confounding by indication and compassionate use of HCQ. 24.9% of HCQ patients were on mechanical ventilation versus 12.2% control. Ventilation mortality was 70.5% versus 11.6%.

This study does not adjust for the differences in comorbid conditions and disease severity, and therefore does not make a conclusion. Unadjusted HCQ mortality was 24.8% versus control 19.6%. Adjusting for ventilation only gives us 17.7% HCQ versus 19.6% control (adjusting the HCQ group to have the same proportion of ventilation patients), RR 0.90. Hopefully authors can do a full adjustment analysis. Comorbidities may favor control, while patients remaining in the hospital (5.3%) may favor HCQ (other studies show faster resolution for HCQ patients).

Source  Study Page  Submit Corrections or Comments

Pre-Exposure Prophylaxis study

*Ferri et al., Clinical Rheumatology, doi:0.1007/s10067-020-05334-7 (Peer Reviewed)*

COVID-19 and rheumatic autoimmune systemic diseases: report of a large Italian patients series

Analysis of 1641 systemic autoimmune disease patients showing csDMARD (HCQ etc.) RR 0.37, p=0.015.

csDMARDs include HCQ, CQ, and several other drugs, so the effect of HCQ/CQ alone could be higher.

This study also confirms that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall, OR 4.42, p<0.001 (this is the observed real-world risk which takes into account factors such as these patients potentially being more careful to avoid exposure).

(results are for “definite + highly suspected” cases and the main result is presented in the paper as the OR for not taking csDMARDs, we have converted this to RR for taking csDMARDs).

Source  Study Page  Submit Corrections or Comments

Early, Late

*IHU Marseille* (Preprint) *(meta analysis - not included in study count)*
Meta-analysis on chloroquine derivatives and COVID-19 mortality

Updated meta-analysis of 26 studies showing CQ/HCQ OR 0.60 [0.50 - 0.73], p<0.0001 from clinical studies.

For big data studies authors find inconsistent results and OR 0.84 [0.75 - 0.94], p=0.003.

Horby et al. excluded due to toxic doses, Skipper et al. excluded due to low PCR testing, Peters et al. excluded due to treatment being delayed until deterioration. Only a summary is provided. Different treatment delays (except Peters), risk level of patients, differences in dosage (except Horby), and usage of Zinc are not considered.

Source  Study Page  Submit Corrections or Comments

Late treatment study

Fiolet et al., Clinical Microbiology and Infection (Peer Reviewed) (meta analysis - not included in study count)

Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis

Meta analysis of late stage studies (and one early treatment study with only 2 deaths), showing HCQ RR 0.83 [0.65-1.06], before exclusions RR 0.80 [0.65-1.0].

Authors claim "HCQ alone is not effective", but the result directly contradicts this, RR 0.83 [0.65-1.06], i.e., inconclusive but much more likely to be effective than not.

There are many errors in this meta analysis which introduce critical bias, for example:

- Very biased sample of studies, including <4% of early treatment studies (only 1), and <30% of late treatment studies, focused on negative studies.

- Arshad et al. (propensity matched HR 0.49, p=0.009) was excluded because the authors claim a "critical" risk of confounding bias due to steroid use, however steroids were controlled for in the multivariate and propensity analyses [1].

- For Skipper et al., authors use an RR of 1.01, however the study had one hospitalized control death and one non-hospitalized HCQ death. Since the HCQ death was non-hospitalized, it may not be caused by COVID-19, or the patient did not receive standard care, therefore this should not be treated as equal to the control death. Further, medication adherence was only 77%, the HCQ patient may not have taken the medication (Skipper et al. neglects to answer this question). In any case, including a trial with only 1-2 deaths is likely to increase bias.

- Cavalcanti et al. received the lowest bias rating, despite having treatment delayed up to 14 days after symptoms, randomizing 14% of patients in the ICU, having significant protocol deviations, unusually low medication adherence, randomization that resulted in 64.3% male patients (HCQ) vs. 54.2% (control), and excluding patients already receiving longer and potentially therapeutic doses of the study treatments.
- Sbidian el al. received the lowest bias rating, however many more control patients are still in hospital at 28 days suggesting there will be a significant improvement when extending past 28 days.

- The RECOVERY trial received the lowest bias rating, despite using a very high dose likely responsible for the increased mortality. Results of this trial are not relevant to use at normal dosages.

- Inclusion criteria required RT-PCR confirmed cases, but this was disregarded when including Horby et al. (very negative, excessive dose) and Skipper et al.

- Authors do not consider different treatment delays, risk level of patients, differences in dosage, or usage of Zinc.

Also see [2] indicating that this study is fatally flawed. For other problems, see. [3, 4]. This analysis is also missing several recent studies, for a more up-to-date analysis see [5].

[3] francesoir.fr/societe-sante/covid-19-les-anti-hydroxychloroquine-et-une-certaine-science...

Source Study Page Submit Corrections or Comments

8/25 Positive

Early treatment study

Ip et al., medRxiv, doi:10.1101/2020.08.20.20178772 (Preprint)

Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: A multi-center observational study

Retrospective 1,274 outpatients, 47% reduction in hospitalization with HCQ with propensity matching, HCQ OR 0.53 [0.29-0.95]. Sensitivity analyses revealed similar associations.
Adverse events were not increased (2% QTc prolongation events, 0% arrhythmias).

Late treatment study

**Di Castelnuovo et al.,** *European J. Internal Medicine,* doi:10.1016/j.ejim.2020.08.019 (Peer Reviewed)

Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study

Retrospective 3,451 hospitalized patients, 30% reduction in mortality with HCQ after propensity adjustment, HR 0.70 [0.59 - 0.84].

8/25 Positive

Late treatment study


Low-dose Hydroxychloroquine Therapy and Mortality in Hospitalized Patients with COVID-19: A Nationwide Observational Study of 8075 Participants

Retrospective 8,075 hospitalized patients, 4,542 low-dose HCQ, 3,533 control. 35% lower mortality for HCQ (17.7% vs. 27.1%), adjusted HR 0.68 [0.62–0.76]. Low-dose HCQ monotherapy was independently associated with lower mortality in hospitalized patients.

Patients exposed to others therapies (TCZ, AZ, LPV/RTV) were excluded.

8/24 Positive
Statistical analysis was performed by an independent group. Calendar time of prescription and immortal time bias was taken into account. Corticosteroids prescriptions was low in both groups.

Early treatment study

*Ly et al., Preprint, 2020 (Preprint)*

Pattern of SARS-CoV-2 infection among dependant elderly residents living in retirement homes in Marseille, France, March-June 2020

8/21  Positive

Retrospective analysis of retirement homes, HCQ+AZ >= 3 days mortality OR 0.39, p=0.026. 1690 elderly residents (mean age 83), 226 infected residents, 116 treated with HCQ+AZ >= 3 days.

Detection via mass screening also showed significant improvements (16.9% vs. 40.6%, OR 0.20, p=0.001), suggesting that earlier detection and treatment is more successful.

Source  Study Page  Submit Corrections or Comments

8/21  Safety

N/A

*Lane et al., The Lancet Rheumatology, doi:10.1016/S2665-9913(20)30276-9 (Peer Reviewed) (not included in the study count)*

Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Retrospective study of RA patients using HCQ vs. sulfasalazine (another DMARD). HCQ treatment showed no increased risk in the short term (up to 30 days) among patients with RA. Long term use was associated with excess cardiovascular mortality.
Addition of AZ increased the risk of cardiovascular mortality with combined use up to 30 days. This is several times longer than typical COVID-19 use. This result also comes from just 2 of the 14 databases, with the negative result from just one database (VA) and much lower statistically insignificant difference in mortality from the other database (Clinformatics).

Confounding by indication. Patients conditions vary, the severity of a patient's RA or other conditions was not taken into account. Results varied widely across different databases, and different subsets of databases were used in different analyses. Baseline risk of serious adverse events unknown. Health care database analysis subject to misclassification errors.

Source  Study Page  Submit Corrections or Comments

Late treatment study

**Gonzalez et al., medRxiv, doi:10.1101/2020.08.18.20172874 (Preprint)**


Retrospective study focused on eosinophil recovery with 9,644 hospitalized patients in Spain, showing lower mortality for HCQ (14.7% vs 29.2%, \( p < 0.001 \)), and AZ (15.3% vs. 18.4%, \( p < 0.001 \)). With a multivariate model including potential confounding factors, HCQ and AZ are associated with lower mortality, HCQ OR 0.662, \( p = 0.057 \).

Source  Study Page  Submit Corrections or Comments

Late treatment study

**Dubernet et al., J. Global Antimicrobial Resistance, doi:10.1016/j.jgar.2020.08.001 (Peer Reviewed)**

A comprehensive strategy for the early treatment of COVID-19 with azithromycin/hydroxychloroquine and/or corticosteroids: results of a retrospective observational study in the French overseas department of Reunion Island

Retrospective analysis of 36 hospitalized patients showing HCQ/AZ associated with lower ICU admission, \( p = 0.008 \). Median age 66, no mortality. Confounding by indication, however it was patients with hypoxemic pneumonia that were treated with HCQ/AZ, patients were not treated with HCQ/AZ if they didn't need oxygen therapy.

Source  Study Page  Submit Corrections or Comments

8/20  **Safety**

Early treatment study

**Prodromos, C., New Microbes and New Infections, doi:10.1016/j.nmni.2020.100747 (Peer Reviewed) (not included in the study count)**
Hydroxychloroquine is protective to the heart, not harmful: A systematic review

Review concluding that HCQ/AZ does not cause Torsade de Pointes or related deaths, HCQ decreases cardiac events, and HCQ should not be restricted in use for COVID-19 patients because of fear of cardiac mortality.

Source  Study Page  Submit Corrections or Comments

Late treatment study

Pinato et al., Cancer Discovery, doi:10.1158/2159-8290.CD-20-0773 (Peer Reviewed)

Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients

8/18  Positive

Restrospective 890 cancer patients with COVID-19, adjusted mortality HR for HCQ/CQ 0.41, $p<0.0001$.

Confirmed SARS-CoV-2 infection was required, which may help focus on more severe cases. Analysis with Cox proportional hazard model. Potential unmeasured confounders.

Source  Study Page  Submit Corrections or Comments

Early treatment study

Mohana et al., medRxiv, doi:10.1101/2020.08.16.20175752 (Preprint) (not included in the study count)

Hydroxychloroquine Safety Outcome within Approved Therapeutic Protocol for COVID-19 Outpatients in Saudi Arabia

8/17  Safety

Safety study of 2,733 patients in Saudi Arabia showing HCQ in mild to moderate cases in an outpatient setting, within the protocol recommendation and inclusion/exclusion criteria, is safe, highly tolerable, and has minimal side effects. No ICU admission or deaths were reported.

Source  Study Page  Submit Corrections or Comments

Late treatment study


Outcomes of Persons With COVID-19 in Hospitals With and Without Standard Treatment With (Hydroxy)chloroquine

8/15  Negative

Retrospective study of HCQ use in 9 hospitals in the Netherlands, showing no significant difference in mortality with HCQ/CQ or dexamethasone. Late stage (admitted to hospital
with positive test or CT scan abnormalities). 4 of 7 hospitals started treatment only after further deterioration. Short cutoff (21 days) - other studies have shown treated patient cases resolved faster and more control patients remaining in hospital at this time.

Significant differences between hospitals - HCQ hospitals had significantly older patients with significantly more comorbidities. Non-HCQ hospitals were "tertiary academic centres" whereas HCQ hospitals were "secondary care hospitals". Residual confounding likely. This study compares overcrowded regular hospitals with undercrowded academic hospitals.

A subset of patients were excluded due to transfer to other hospitals. This introduces bias because patients in critical condition are not transferred. For examples, patients benefiting from HCQ treatment may have been transferred to the tertiary centres and excluded from analysis, increasing the percentage of critical cases in the secondary hospitals.

Most patients received CQ instead of the safer HCQ, receiving late treatment with CQ. Patients were given an initial dose of 600mg CQ then every 12 hours, for 5 days a dose of 300 mg, for a total of 3600mg CQ. This dose is likely to be toxic, see for example [1].

Authors mention a subset of hospitals started treatment relatively earlier, which seems like the most important area to analyze, but no results are provided.


Late treatment study

*Abd-Elsalam* et al., *American Journal of Tropical Medicine and Hygiene*, 10.4269/ajtmh.20-0873 (Peer Reviewed)

Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study

Small RCT in Egypt with 97/97 HCQ/control patients, showing 58% more recovery @28days for HCQ (53.6% HCQ, 34% control), $p=0.009$ (0.06 in the paper refers to the 5 combined recovery/death/ICU values).

No significant difference in ventilation and mortality ($<=6$ examples in each case). Authors note the "sample size was not adequately powered for [the] survival endpoint".

Other studies have also shown treated patient cases resolved faster. Continuing analysis past 28 days would be useful. Group characteristics are given, with for example 36% vs. 26% smokers, but they do not identify which group is which. Group 1 and 2 have 97 patients but the total given is 175.
**Roomi et al., J. Medical Internet Research, doi:10.2196/21758 (Peer Reviewed)**

Efficacy of hydroxychloroquine and tocilizumab in patients with COVID-19: A single-center retrospective chart review

Retrospective 176 hospitalized patients (144 HCQ, 32 control) showing no significant differences with HCQ or TCZ. Confounding by indication.

**Early treatment study**

**Bakhshaliyev et al., J. Electrocardiology, doi:10.1016/j.jelectrocard.2020.08.008 (Peer Reviewed) (not included in the study count)**

The effect of 5-day course of hydroxychloroquine and azithromycin combination on QT interval in non-ICU COVID19(+) patient

Safety study of 109 patients showing 5 days of HCQ+AZ did not lead to clinically significant QT prolongation or other conduction delays compared to baseline ECG in non-ICU patients.

**Late treatment study**

**Saleemi et al., medRxiv, doi:10.1101/2020.08.05.20151027 (Preprint)**

Time to negative PCR from symptom onset in COVID-19 patients on Hydroxychloroquine and Azithromycin - A real world experience

Retrospective 65 HCQ+AZ, 20 control patients, showing median time to negative PCR of 23 days for HCQ+AZ vs. 19 days for control. Confounding by indication. 100% of non-HCQ group had mild disease vs. 63% of the HCQ+AZ group. More comorbidities and symptoms in the HCQ+AZ group.

**Review**

**McCullough et al., The American Journal of Medicine, doi:10.1016/j.amjmed.2020.07.003 (Peer Reviewed) (Review) (not included in the study count)**

Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection

Review of pathophysiological principles related to early outpatient treatment and therapeutic
approaches including reduction of reinoculation, combination antiviral therapy, immunomodulation, antiplatelet/antithrombotic therapy, and administration of oxygen, monitoring, and telemedicine.

Proposes an algorithm based on age and comorbidities that allows for a large proportion to be monitored and treated at home during self-isolation with the aim of reducing the risks of hospitalization and death.

Concerns regarding the misinterpretation of statistical hypothesis testing in clinical trials for COVID-19

Open letter signed by 38 professors and doctors regarding misinterpretation of statistics in HCQ RCTs.

Authors note [1] that data from RCTs for early treatment in outpatients to date actually show favorable effects, especially in high-risk patients such as the elderly, where efficacy was up to three times higher than in young people. Because most samples were made up of young people without comorbidities, the studies were statistically inconclusive with the entire samples. Author's note that instead of the papers reporting this, they incorrectly claim that the treatment had no effect compared to the placebo. “This misinterpretation in statistical tests is well known and explained in most undergraduate books in the field,” says Watanabe. “An article published in Nature last year states that about 51% of the work on clinical trials with this type of result has incorrect conclusions.”


Clearing the fog: Is HCQ effective in reducing COVID-19 progression: A randomized controlled trial

Study of 349 low-risk hospitalized patients with 151 non-consenting or ineligible patients used as controls. SOC included zinc, vitamin C and vitamin D. A statistically significant improvement in PCR negativity is shown at day 7 with HCQ treatment, 52.1% (HCQ) versus 35.7% (control), \( p = 0.001 \), but no statistically significant difference at day 14, or in progression. Patients were relatively young and there was no mortality. Only 3% of patients had any disease progression and all patients recovered, so there is little if any room for treatment benefit. Progression among higher-risk patients with comorbidities was lower with treatment (12.9% versus 28.6%, \( p = 0.3 \), very few cases).

Despite the title, this is not an RCT since patients self-selected the arm, or were chosen based on allergies/contraindications. The treatment group had about twice the number of patients with comorbidities. Treatment delay is unknown - it was recorded but not reported in the paper.

Viral load was not measured. As with other studies, PCR may detect non-replicable viral nucleic acid, this is more likely at day 14. Details on the test accuracy are not provided, authors note that RT-PCR sensitivity ranges from 34-80%.

Source Study Page Submit Corrections or Comments

8/3 Positive

Late treatment study


Beneficial effects exerted by hydroxychloroquine in treating COVID-19 patients via protecting multiple organs

Retrospective 2,882 patients in China, median age 62, 278 receiving HCQ, median 10 days post hospitalization, showing that HCQ treatment can reduce systemic inflammation and inhibit the cytokine storm, thus protecting multiple organs from inflammatory injuries, such as detoxification in the liver and attenuation of cardiac injury. IL-6 levels significantly reduced after HCQ treatment, \( p < 0.05 \), and elevated after HCQ withdrawal. The significantly lower dose used here is potentially related to the different observations from the RECOVERY trial results.
Authors suggest that treatment should be started as soon as possible.

![Graph showing IL-6 levels over time for COVID-19 patients treated with HCQ, Withdrawal of HCQ, and NHQ treated.](image)

Late treatment study


Impact of medical care including anti-infective agents use on the prognosis of COVID-19 hospitalized patients over time

Retrospective of 132 hospitalized patients. HCQ+AZ significantly reduces death/ICU, HR=0.45, p=0.04. Adjusted for Charlson Comorbidity Index (including age), obesity, O2, lymphocyte count, and treatments. Mean delay from admission to treatment 0.7 days.

*In Vitro*

*Sheaff, R.,* bioRxiv, doi:10.1101/2020.08.02.232892 (Preprint) (In Vitro) (not included in the study count)

A New Model of SARS-CoV-2 Infection Based on (Hydroxy)Chloroquine Activity

*In vitro* study presenting a new theory on SARS-CoV-2 infection and why HCQ/CQ provides benefits, which potentially explains the observed relationships with smoking, diabetes, obesity, age, and treatment delay, and confirms the importance of accurate dosing. Metabolic analysis revealed HCQ/CQ inhibit oxidative phosphorylation in mitochondria (likely by sequestering protons needed to drive ATP synthase), inhibiting infection and/or slowing replication.
**Positive**

Late treatment study


Effectiveness of Hydroxychloroquine in COVID-19 disease: A done and dusted situation?

HCQ+AZ adjusted death HR 0.44, *p*=0.009. Propensity scores include baseline COVID-19 disease severity, age, gender, number of comorbidities, cardio-vascular disease, duration of symptoms, date of admission, baseline plasma CRP. IPW censoring. Retrospective study of 539 COVID-19 hospitalized patients in Milan, with treatment a median of 1 day after admission. HCQ 197 patients, HCQ+AZ 94, control 92. Control group received various other treatments. Authors excluded people receiving other drugs which could have biased the effect of HCQ when used in combination. Residual confounding is possible (e.g., people with CVD were more frequent in control), however people in the control group were more likely to require mechanical ventilation.

**Inconc.**

Late treatment study


Outcome of Non-Critical COVID-19 Patients with Early Hospitalization and Early Antiviral Treatment Outside the ICU

Observational study of 174 hospitalized patients in Turkey, median age 45.4, 23 treated with HCQ, 113 with HCQ+AZ, and 32 with regimens including favipiravir. 75% reduction in the median time to clinical improvement for HCQ+AZ vs. FAV, RR 0.25, *p*<0.001. 83% reduction for HCQ. However, there was significant confounding by indication.

There were no significant adverse events.

**Inconc.**

Post Exposure Prophylaxis study


A Cluster-Randomized Trial of Hydroxychloroquine as Prevention of Covid-19 Transmission and Disease

Death rate reduced from 0.6% to 0.4%, RR 0.68, not statistically significant due to low incidence (8 control cases, 5 treatment cases).

For positive symptomatic cases, a greater effect is seen for nursing home residents, RR=0.49 [0.21 - 1.17], vs. overall 0.89, possibly because the exposure events are identified faster in this context, versus home exposure where testing of the source may be more delayed. The trial is
too small for significance here. If the trend continued this result would be significant at 
$p<0.05$ after about 25% more patients were added.

There are 2 groups in this study: PCR+ at baseline (n=314) and PCR- at baseline (n=2000),
which should be separated as they are different populations (primary outcome rates 18.6%
and 22.2% compared to 3.0% and 4.3%). PCR+ already have COVID-19, so PEP analysis
should be for the 2,000 PCR-, showing symptomatic COVID-19 of 4.3% (control) and 3.0%
treatment), RR 0.7, $p=0.154$.

The paper has different RR values here, stating that they are adjusted for contact-level
variables. It is not clear how they are computed - the adjusted RR for the overall sample is 4%
lower, for PCR+ it is 20% lower, but for PCR- it is 107% higher, even though PCR- represents
86% of the sample.

Hopefully, supplementary data will provide a breakdown on cases in this PCR- @baseline
sample by number of days since exposure, and also provide relevant hospitalisation and
death results.

Enrollment was up to 7 days after exposure, median 4 days. Treatment delay is unclear. The
exposure event timing is not detailed. It appears to be based on the date of a positive test for
a contact, which is likely to be much later than the actual exposure time. 13.1% were already
positive at baseline, which is consistent with the actual exposure time being significantly
earlier. PCR testing has a very high false-negative rate in early stages (e.g., 100% on day 1,
67% on day 4, and 20% on day 8 [1]), hence it is likely that a much higher percentage were
infected at an unknown time before enrollment. Medication administration is not detailed.
Sensitivity and specificity of the tests is not provided.

Given the delay identifying index cases, PCR test delay, and PCR false negative rate at early
stages, the treatment delay in general was very long and could be over 2 weeks.

The RR for non-PCR positive at baseline is 0.74. Including the PCR-positive at baseline
patients reduced this to 0.89. This is also consistent with earlier treatment being more
effective.

The paper does not mention zinc. Zinc deficiency in Spain has been reported at 83% [2], this
may significantly reduce effectiveness. HCQ is a zinc ionophore which increases cellular
uptake, facilitating significant intracellular concentrations of zinc, and zinc is known to inhibit
SARS-CoV RNA-dependent RNA polymerase activity, and is widely thought to be important
for effectiveness with SARS-CoV-2 [3].

This study focuses on the existence of symptoms or PCR-positive results, however severity
of symptoms is more important. Research has shown HCQ concentrations can be much
higher in the lung compared to plasma [4], which may help minimize the occurrence of
severe cases and death.

There is a treatment-delay response relationship consistent with an effective treatment,
however the authors only provide 3 ranges and do not break down the earliest treatment
delay times.

The definition of COVID-19 symptoms is very broad - just existence of a headache alone or
muscle pain alone was considered COVID-19. There was an overall very low incidence of
confirmed COVID-19 (138 cases across both arms). There were no serious adverse events
that were adjudicated as being treatment related. Authors exclude those with symptoms in the previous two weeks, however, those with symptoms up to several months before may still test PCR-positive even though there may be no viable virus.

There appears to be incorrect data. Table 2, secondary outcomes, control, hospital/vital records shows that 8 of 1042 is 9.7% (we get 0.8%).

Nasopharyngeal viral load analysis issues include test unreliability and temporo-spatial differences in viral shedding [5].

In summary, this study appears positive in the context of very delayed treatment and very small sample sizes, however we have classified it as inconclusive for now pending further analysis and feedback. Preliminary analysis. Supplementary Appendix is not currently available. Please submit any corrections or comments.

[2] mdpi.com/2072-6643/9/7/697
[4] ncbi.nlm.nih.gov/pmc/articles/PMC7122276/

Source Study Page Submit Corrections or Comments

Pre-Exposure Prophylaxis study


Prevalence and clinical correlates of COVID-19 outbreak among healthcare workers in a tertiary level hospital

**7/24 Positive**

Study of hospital health care workers showing HCQ prophylaxis reduces COVID-19 significantly, OR 0.30, *p*=0.02. 94 positive health care workers with a matched sample of 87 testing negative. Full course prophylaxis was important in this study which used a low dose of 400mg/week HCQ (800mg for week 1), so it may take longer to reach therapeutic levels. Actual benefit of HCQ may be larger because severity of symptoms are not considered here but HCQ may also reduce severity.

Source Study Page Submit Corrections or Comments

Late treatment study

*Cavalcanti et al., NEJM, July 23, 2020, doi:10.1056/NEJMoa201901 (Peer Reviewed)*

Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19

**7/23 Negative**

Late stage RCT of 667 hospitalized patients with up to 14 days of symptoms at enrollment and receiving up to 4 liters per minute supplemental oxygen, not finding a significant effect after 15 days.
Authors note: "the trial cannot definitively rule out either a substantial benefit of the trial drugs or a substantial harm", sample sizes are too small.

The paper uses the terms mild and moderate, however all patients had serious enough disease to be hospitalized, and 14% were actually randomized in the ICU.

The trial had significant protocol deviations and unusually low medication adherence. Randomization resulted in 64.3% male patients (HCQ) vs. 54.2% (control) which may significantly affect results due to the much higher risk for male patients.

Authors note: "our aim was to exclude patients already receiving longer and potentially therapeutic doses of the study treatments" in explanation for why the study protocol was changed to exclude patients with previous use of the medications >24hrs. Analyzing these patients rather than excluding them may have revealed effectiveness with early use as shown in other studies.

The trial initially required enrollment within 48 hours of admission and was changed to remove this requirement, this change is likely to reduce effectiveness because enrollment was moved later, compared to the time the disease became serious enough for hospitalization.

A correction for 17 errors has been published: [1]


Source Study Page Submit Corrections or Comments

In Vitro


(not included in the study count)

Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2

The title of this paper does not appear to match the results. Fig. 1b @100uM shows CQ results in a ~4.5 fold decrease (on a linear scale) in extracellular virus, \( p=0.05 \), after 24 hours (we do not see the supplementary data at this time so this is estimated from the graph). This decrease may continue if examined over longer time periods. Fig. 1a shows a ~45-50% entry inhibition @100uM for HCQ/CQ (\( p=0.0005/0.0045 \)), ~10-30% @10uM (\( p=0.13/0.99 \)). Inhibition is significantly better with Vero cells.

*In vitro* study of CQ and HCQ inhibition of SARS-CoV-2 into Vero (kidney), Vero-TMPRSS2, and Calu-3 (derived from human lung carcinoma) cells.

Authors reportedly used sodium pyruvate which may inhibit CQ from entering cells [1].

Although there are several theories on how HCQ may help with COVID-19, authors do not consider the most common theory where HCQ functions as a zinc ionophore, facilitating significant intracellular concentrations of zinc. Zinc is known to inhibit SARS-CoV RNA-dependent RNA polymerase activity, and is widely thought to be important for effectiveness with SARS-CoV-2 [2].
Calu-3 is one of many cell lines derived from human lung carcinomas [3]. Calu-3 cells resemble serous gland cells. They do not express 15-lipoxygenase, an enzyme specifically localized to the surface epithelium, but they do express secretory component, secretory leukocyte protease inhibitor, lysozyme, and lactoferrin, all markers of serous gland cells. [4] note that the absence of systemic inflammation, circulatory factors, and other paracrine systemic influences is a potential limitation of the isolated cell system.

RT-PCR is used, we note that nucleic acid may persist even after the virus is no longer viable [5].

It is unclear how the authors conclude “CQ does not block SARS-CoV-2 infection of Calu-3” cells, when the results show statistically significant inhibition at higher concentrations.

Further, it is unclear how the authors go from these results in one specific type of pulmonary adenocarcinoma cells that resemble serous gland cells, in vitro, into the title of the paper which claims no inhibition in lung cells.

Further, it is unclear how another leap is made to "will not be effective against COVID-19" given the multiple theories of HCQ/CQ effectiveness.

[1] twitter.com/JaclynHord/status/1302680394244947969
[5] fda.gov/media/136472/download

### 7/22 Negative

**Late treatment study**


Clinical outcomes and adverse events in patients hospitalised with COVID-19, treated with off-label hydroxychloroquine and azithromycin

Retrospective 82 hospitalized patients HCQ/AZ, 52 SOC, not finding statistically significant differences. Confounding by indication. No attempt to adjust for confounders. HCQ/AZ patients were more severely ill with higher C-reactive protein and fraction of inspired oxygen requirements at baseline.

### 7/21 Positive

**Late treatment study**


Observational Study of the Efficiency of Treatments in Patients Hospitalized with Covid-19 in Madrid
HCQ HR 0.83 [0.77-0.89] based on propensity score matched retrospective analysis of 1,645 hospitalized patients. Prednisone HR 0.85 [0.82-0.88], 14 other medications showed either no significant benefit or a negative effect.

Source Study Page Submit Corrections or Comments

Early treatment study


Response to: “Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients” and “Re: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis”

Updated meta analysis including 7 new studies of high-risk outpatients, for a total of 12 studies, all showing significant benefit.

Post Exposure Prophylaxis study

Watanabe, M., arXiv.org, arXiv.2007.09477 (Preprint) (meta analysis - not included in study count)

Efficacy of Hydroxychloroquine as Prophylaxis for Covid-19
Secondary analysis of Boulware et al.'s PEP trial and treatment delay-response data, confirming that HCQ is effective when used early, $p<0.01$.

The effectiveness found is especially notable considering the limitations of the study. Treatment was relatively late, with enrollment up to 4 days after exposure, and an unspecified shipping delay. While the paper does not provide shipping details, the study protocol gives some detail allowing us to estimate the treatment delay as ~70 to 140 hours after exposure on average for the 1-4 days since enrollment specified in the paper (we will update this when authors respond to our request for details). There was only 75% medication adherence, including 16% who did not take the medication at all. The study relies on Internet surveys.

Some issues have been raised with this analysis. 1-tailed vs. 2-tailed tests - this is debatable, an argument can be made for both cases. However, it doesn't affect the conclusion in terms of the delay-response relationship showing statistically significant efficacy. Secondly, the paper projects the "1-4" day results to a day "0" result (in reality about 46 hours later in all cases), while the trend may well continue, we do not know this. However it doesn't change the outcome that the 1-4 day results show a statistically significant delay-response relationship.

Source: Study Page | Submit Corrections or Comments

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Late treatment study


COVID-19 Case Series at UnityPoint Health St. Luke's Hospital in Cedar Rapids, IA

HCQ+AZ early in the epidemic had a fairly good success rate with few complications, 86% of HCQ patients survived and 92% of HCQ+AZ patients. Patients not receiving either had 93% survival but were not considered comparable because the treated groups were significantly more ill (100% hypoxic at admission vs. 59%) and this study does not adjust for the differences.

Transition from an early intubation strategy to aggressive utilization of high flow nasal cannula and noninvasive ventilation (i.e, BiPAP) was successful in freeing up ICU resources.

Source: Study Page | Submit Corrections or Comments

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Late treatment study

*Lyngbakken et al., Research Square, doi:10.21203/rs.3.rs-44055/v1 (Preprint)*

A pragmatic randomized controlled trial reports the efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics

Small RCT of nasopharyngeal viral load not showing significant differences. The rate of reduction for HCQ was 0.24 [0.03-0.46] RNA copies/mL/24h, and 0.14 [-0.10-0.37] for the
control group (71% faster with HCQ but not statistically significant with the small sample size of 27 HCQ and 26 control patients). Analysis only over 96 hours.

Source Study Page Submit Corrections or Comments

Early treatment study

Hong et al., Infect. Chemother., 2020, doi:10.3947/ic.2020.52.e43 (Peer Reviewed)

Early Hydroxychloroquine Administration for Rapid Severe Acute Respiratory Syndrome Coronavirus 2 Eradication

HCQ 1-4 days from diagnosis was the only protective factor against prolonged viral shedding found, OR 0.111, p=0.001. 57.1% viral clearance with 1-4 days delay vs. 22.9% for 5+ days delayed treatment. Authors report that early administration of HCQ significantly ameliorates inflammatory cytokine secretion and that COVID-19 patients should be administrated HCQ as soon as possible. 42 patients with HCQ 1-4 days from diagnosis, 48 with HCQ 5+ days from diagnosis.

Source Study Page Submit Corrections or Comments

Early treatment study

Skipper et al., Annals of Internal Medicine, doi:10.7326/M20-4207 (Peer Reviewed)

Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial

~70 to 140 hour (inc. shipping) delayed outpatient treatment with HCQ reduced combined hospitalization/death by 50%, p=0.29 (5 HCQ cases, 10 control cases), and reduced hospitalization by 60%, p=0.17. There was one hospitalized control death and one non-hospitalized HCQ death. It is unclear why there was a non-hospitalized death, external factors such as lack of standard care may be involved. Excluding that case results in one control death and zero HCQ deaths (not statistically significant but noted as reducing mortality is the most important outcome). Details for the hospitalizations and deaths such as medication adherence and treatment delay may be informative but are not provided.
The paper states the end point was changed from hospitalization/death to symptom severity because they would have required 6,000 participants. However, if the observed trend continued, they would hit 95% significance on the reduction in hospitalization at ~725 patients, and 95% on the reduction in combined hospitalization/death at ~1,145 patients, which is a lot less than 6,000, and also less than the original plan of 1,242 patients. We hope the trial can be continued for statistical significance.

Treatment is relatively late, ~70 to 140 hours after symptoms, including the shipping delay. The paper does not mention the shipping delay but partial details are provided in the study protocol. They are not clear but indicate no shipping on the weekends and a possible 12pm cutoff for same day dispensing and mailing. Assuming that enrollments were evenly distributed between 6am and 12am each day, we get an average of ~46 hours shipping delay. We have asked for shipping details and will update with more accurate values when available. In any case the treatment delay is quite long and there is no overlap with the more typical delays used such as 0 - 36 hours for oseltamivir.

The paper compares 0 - 36 hour delayed treatment with oseltamivir (influenza) and ~70 to 140 hour delayed treatment with HCQ (COVID-19), noting that oseltamivir seemed more effective. However, a more comparable study is McLean (2015) who showed that 48 - 119 hour delayed treatment with oseltamivir has no effect. This suggests that HCQ is more effective than oseltamivir, and that HCQ may still have significant effect for some amount of delay beyond the delay where oseltamivir is effective.

6 people were included that enrolled with >4d symptoms, although they do not match the study inclusion criteria. This reduces observed effectiveness. The paper says 56% (236) were enrolled within 1 day of symptoms, but results show only 40% for "<1d'', 56% is possibly for <48hrs, we have asked for clarification.

Patients in this study are relatively young and most of them recover without assistance. This reduces the room for a treatment to make improvements. The maximum improvement of an effective treatment would be expected before all patients approach recovery, as shown in the figure below. Authors focus on the end result where most have recovered, but it is more informative to examine the curve and the point of maximum effectiveness. Authors did not collect data for every day but they do have interim results for days 3, 5, 10. The results are consistent with an effective treatment and show a statistically significant improvement, $p = 0.05$, at day 10 (other unreported days might show increased effectiveness).

Results also show a larger treatment effect for those >50, not statistically significant due to the small sample, but noted as COVID-19 risk dramatically increases with age. The effect may be more visible here because younger patients may on average have more mild cases with less room for improvement. In general patients in this study have relatively mild symptoms on average, limiting the chance to observe improvement.

The study relies on Internet surveys. Known fake surveys were submitted to the similar PEP trial and there could be an unknown number of undetected fake surveys in both trials. The study shows a high incidence of side effects in the placebo arm, which could be in part due to fake entries [1].

The granularity change in the histograms of Figure S4 raise concerns [2]. Data on increasing severity, less affected by the lower bound where everyone has recovered, also supports effectiveness [3].
Research shows the placebo used in the US may be protective for COVID-19 [4] so the true effectiveness of HCQ could be higher than observed.

Treatment delay reporting has changed from the companion PEP trial which reported results for enrollment delays 1, 2, 3, and 4 separately (and from which we can confirm a statistically significant delay-response relationship), while this trial combines 1-2 and 3-4, and adds <1. Since the two trials share reporting (some patients were moved between trials) it’s not clear how the new category was added.

RCT of 423 patients with Internet surveys. Medication adherence was only 77% so the true effect of treatment is likely higher. Analysis of primarily low risk patients, authors note the results are not generalizable to the COVID high-risk population. We will update when hearing back on questions asked.

In summary, we believe the results of this study are positive for HCQ being an effective treatment, however we have classified this study as inconclusive for now pending feedback and further analysis.

Also see: [5] and [6] regarding flaws in this study.

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[1] twitter.com/Covid19Crusher/status/1284515906375356416
[5] drive.google.com/file/d/1NZOJ57fM0RTaHD1t_9w2iu7JUJh0gWT/view
[6] twitter.com/cnpaiva/status/1303324404630388738

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Early treatment study

Mitjà et al., Clinical Infectious Diseases, ciaa1009, doi:10.1093/cid/ciaa1009 (Peer Reviewed)

Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial

This paper has inconsistent data - some of the values reported in Table 2 and the abstract correspond to 12 control hospitalizations, while others correspond to 11 control
hospitalizations.

There was a 25% reduction in hospitalization and 16% reduction in the median time to symptom resolution for HCQ, without statistical significance due to small samples.

Treatment delay is unknown at this time. They report a delay of up to 120 hours after symptoms plus an additional unspecified delay where medication was provided to patients at the first home visit. We have asked for details of the treatment delay and will update when hearing back. They do not break down results by treatment delay.

The paper does not mention zinc. Zinc deficiency in Spain has been reported at 83% [1], this may significantly reduce effectiveness. HCQ is a zinc ionophore which increases cellular uptake, facilitating significant intracellular concentrations of zinc, and zinc is known to inhibit SARS-CoV RNA-dependent RNA polymerase activity, and is widely thought to be important for effectiveness with SARS-CoV-2 [2].

Undetectable viral load was changed to 3 log10 copies/mL potentially masking effectiveness. For viral load authors use nasopharyngeal swabs, we note that viral activity in the lung may be especially important for COVID-19, and that research has shown HCQ concentrations can be much higher in the lung compared to plasma [3]. We also note that viral detection by PCR does not equate to viable virus [4]. Accuracy of the tests is not provided.

Nasopharyngeal viral load analysis issues include test unreliability and temporo-spatial differences in viral shedding [5].

293 low-risk patients with no deaths. No serious adverse events. We have asked for more details on the treatment delay and viral load change and will update when hearing back.

Also see this open letter: [6]

[1] mdpi.com/2072-6643/9/7/697
[3] ncbi.nlm.nih.gov/pmc/articles/PMC7122276/HQC
[6] drive.google.com/file/d/1NZOJ57fM0RTaHD1t_9w2iuag7UJhOgWT/view

Source: Study Page: Submit Corrections or Comments

7/14 Inconc.

Early treatment study

Chowdhury et al., Research Square, doi:10.21203/rs.3.rs-38896/v1 (Preprint)

A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients

Small 116 patient RCT comparing Ivermectin-Doxycycline and HCQ+AZ, not showing a significant difference in time to PCR negative or symptom resolution. Time to symptomatic recovery was 5.93 days for Ivermectin-Doxycycline vs. 6.99 days for HCQ+AZ. Given the long
half-life of HCQ and the lack of a loading dose, it may take several days for HCQ to reach therapeutic levels. 10% of HCQ+AZ patients were lost to followup (2x Ivermectin-Doxycline). There is no comparison with a control group.

Source Study Page Submit Corrections or Comments

Late treatment study

Lecronier et al., Critical Care, 24:418, 2020, doi:10.1186/s13054-020-03117-9 (Peer Reviewed)

Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis

Retrospective 80 ICU patients, 22 SOC, 20 lopinavir/ritonavir, 38 HCQ. 28 day mortality 24% (HCQ) versus 41% (SOC), a 41% decrease, but not statistically significant due to very small sample sizes. No statistically significant differences found for treatment escalation, ventilator-free days, viral load, or mortality. Authors consider treatment escalation more important than mortality, for unknown reasons.

Source Study Page Submit Corrections or Comments

Early, Late

Raoult et al., Preprint (Preprint) (meta analysis - not included in study count)

Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial: Response to David Spencer (Elsevier)

Updated meta analysis showing significant reductions in mortality and viral shedding. Mortality OR 0.53 [0.4-0.71] for clinical studies, 0.92 big data studies, 18,211 patients. Persistent viral shedding OR 0.47 [0.28-0.79], 4,540 patients.

Source Study Page Submit Corrections or Comments

Review

Goldstein, L., Preprint, July 7, 2020 (Preprint) (Review) (not included in the study count)

Hydroxychloroquine-based COVID-19 Treatment, A Systematic Review of Clinical Evidence and Expert Opinion from Physicians’ Surveys

85% of globally surveyed physicians recognized HCQ as at least partially effective in treating COVID-19, according to Sermo W3. More than half of the surveyed US physicians would take the drug or give it to family members early or even before onset of symptoms, according to JC.
Aside from the rarely used plasma, HCQ / HCQ+AZ based treatments are preferred by physicians by wide margin over other drugs. HCQ / HCQ+AZ based treatments are the most used, most recommended, and most highly rated by physicians treating COVID-19 at an early stage.

Source  Study Page  Submit Corrections or Comments

## Late treatment study


Treatment Response to Hydroxychloroquine and Antibiotics for mild to moderate COVID-19: a retrospective cohort study from South Korea

Retrospective of hospitalized patients with 31 HCQ patients and 195 standard treatment patients, not showing a significant difference in terms of viral clearance or recovery. There was no mortality in either group.

"It is notable that HQ plus antibiotics group had worse baseline clinical profiles (i.e. higher percentage of moderate severity patients, more patients with fever >=37.5C, higher average body temperature) and prognostic indicators such as age, LDH, lymphocyte count, and CRP".

We note that propensity score matching removed almost all of the male patients in the control group (40% -> 5%) but increased the percentage of male patients in the treatment group. This provides a large advantage to the control group because there is a very large difference in severity and mortality based on gender [1].

In terms of viral RNA clearance we note that other research has found that "active viral replication drops quickly after the first week, and viable virus was not found after the second week of illness despite the persistence of PCR detection of RNA" [2].

[1] ncbi.nlm.nih.gov/pmc/articles/PMC7247289/

Source  Study Page  Submit Corrections or Comments

## Positive

Pre-Exposure Prophylaxis study

**Zhong et al., Lancent Rheumatology, 10.1016/S2665-9913(20)30227-7 (Peer Reviewed)**

COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study

Rheumatic disease patients on HCQ had a lower risk of COVID-19 than those on other disease-modifying anti-rheumatic drugs, OR 0.09 (0.01–0.94), p=0.044 after adjusting for age, sex, smoking, systemic lupus erythematosus, infection in other family members, and comorbidities. 43 patients with rheumatic disease and COVID-19 exposure.

Source  Study Page  Submit Corrections or Comments
Early treatment study

Scholz et al., Preprints 2020, 2020070025, doi:10.20944/preprints202007.0025.v1 (Preprint)

COVID-19 Outpatients – Early Risk-Stratified Treatment with Zinc Plus Low Dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study

Early treatment with HCQ+AZ+Z results in 84% lower hospitalization and 80% lower death - hospitalization OR 0.16 (p<0.001), death OR 0.2 (p=0.16). No cardiac side effects.

Retrospective 518 patients (141 treated, 377 control).

Late treatment study

Arshad et al., Int. J. Infect. Dis., July 1 2020, doi:10.1016/j.ijid.2020.06.099 (Peer Reviewed)

Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19

HCQ decreases mortality from 26.4% to 13.5% (HCQ) or 20.1% (HCQ+AZ). Propensity matched HCQ HR 0.487, p=0.009. Michigan 2,541 patients retrospective. Before propensity matching the HCQ group average age is 5 years younger and the percentage of male patients is 4% higher which is likely to favor the treatment and the control respectively in the before-propensity matching results.

Some reported limitations of this study are inaccurate [1]. Corticosteroids were controlled for in the multivariate and propensity analyses as were age and comorbidities including cardiac disease and severity of illness. Age was an independent risk factor associated with mortality. HCQ was independently associated with decreased mortality, distinct from the steroid effect. 91% of all patients began treatment within two days of admission. HCQ was used throughout the study period, limiting time bias. Patients assigned to HCQ group had moderate and
severe illness at presentation, which would favor worse outcome with HCQ.


In pediatric patients with PCR positive active COVID-19 infection, significant arrhythmias are infrequent, but occur at an incidence higher than expected in a general pediatric population. Comorbidities are not more common in patients with arrhythmias than in patients without arrhythmias. However, providers still need to be vigilant for comorbidities that may independently place patients at risk for arrhythmias. COVID-19 treatment using HCQ leads to significant QTc prolongation, but was not associated with arrhythmias in pediatric patients. The long term sequelae of arrhythmia development in this population and their impact on outcome needs to be studied.


Risk Factors for Mortality in Patients with COVID-19 in New York City

HCQ decreases mortality, HR 0.53 (CI 0.41–0.67). IPTW adjustment does not significantly
change HR 0.53 (0.41-0.68). Retrospective 6,000 patients in New York City.

Pre-Exposure Prophylaxis study


Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection

Chronic treatment with HCQ provides protection against COVID, odds ratio 0.51 (0.37-0.70).

The actual benefit is likely to be larger because research shows that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall. Ferri et al. show OR 4.42, \( p<0.001 \) [1], which is the observed real-world risk, taking into account factors such as these patients potentially being more careful to avoid exposure.

[1] c19study.com/ferri.html

Early treatment study


Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis

Early treatment leads to significantly better clinical outcome and faster viral load reduction. Matched sample mortality HR 0.41 \( p \)-value 0.048. Retrospective 3,737 patients.

Electrocardiographic safety of daily Hydroxychloroquine 400mg plus Azithromycin 250mg as an ambulatory treatment for COVID-19 patients in Cameroon

No life-threatening modifications of the QT interval was observed in non-severe COVID-19 patients treated ambulatory with HCQ+AZ. 51 relatively young patients 39 +/- 11.
Early treatment study

Chen et al., medRxiv, doi:10.1101/2020.06.19.20136093 (Preprint)

Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study

Significantly faster clinical recovery and shorter time to RNA negative (from 7.0 days to 2.0 days (HCQ), p=0.01. 67 patients with mild/moderate cases.

Pre-Exposure Prophylaxis study

SMSH Sawai Man Singh Hospital, India (News) (not included in the study count)
HCQ beneficial as preventive drug: SMS doctors told ICMR

PrEP with 4,300 very high risk healthcare workers in a hospital with up to 500+ COVID patients at a time, only 1% cases, all recovered. Currently no formal study is available so this is not included in the study count.

Source  Study Page  Submit Corrections or Comments

Late treatment study

NIH, study not available yet (News) (not included in the study count)

NIH halts clinical trial of hydroxychloroquine

NIH halts late stage trial reporting no harm and no benefit. 470 patients. Currently no formal study is available so this is not included in the study count.

Source  Study Page  Submit Corrections or Comments

Positive

Sbidian et al., medRxiv, doi:10.1101/2020.06.16.20132597 (Preprint)

Hydroxychloroquine with or without azithromycin and in-hospital mortality or discharge in patients hospitalized for COVID-19 infection: a cohort study of 4,642 in-patients in France

Retrospective of 4,642 hospitalized patients in France showing significantly faster discharge with HCQ and HCQ+AZ. No significant effect is seen on 28-day mortality, however many more control patients are still in hospital at 28 days. Other studies show faster resolution for HCQ, suggesting there will be a significant improvement when extending past 28 days. Hopefully authors will extend the analysis. Note that the median age is higher in the group not treated with HCQ or AZ.
For other issues with the adjustments see [1]. Also see the analysis here [2].

[1] medrxiv.org/content/10.1101/2020.06.16.20132597v1#disqus_thread

Late treatment study

Paccoud et al., Clinical Infectious Diseases, doi:10.1093/cid/ciaa791 (Peer Reviewed)

Compassionate use of hydroxychloroquine in clinical practice for patients with mild to severe Covid-19 in a French university hospital

Retrospective of 89 hospitalized patients, survival HR 0.89 [0.23-3.47], not statistically significant. Authors note that unmeasured confounders may have persisted and the study may be underpowered.

Source  Study Page  Submit Corrections or Comments

Late treatment study

6/18  Inconc.

6/17  Positive

Hydroxychloroquine treatment in COVID-19: a descriptive observational analysis of 30 cases from a single center in Wuhan, China

30 hospitalized patients. Early use of HCQ is more effective, 43% reduction in progression from moderate to severe. 'Early' is relative here, within 7 days of hospitalization.

Source  Study Page  Submit Corrections or Comments

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**6/17 Negative (news)**

Late treatment study

*World Health Organization*, study not available yet (News) (not included in the study count)

"Solidarity" clinical trial for COVID-19 treatments

WHO stopped the Solidarity late stage trial of HCQ reporting no benefit. Later news reported "little or no reduction in mortality" [1]. The study has not been released yet and few details are available. This trial used an extremely high dose which may be related to the relatively poor results [2]. Currently no formal study is available so this is not included in the study count.

[1] who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopina...
[2] francesoir.fr/politique-monde/oxford-recovery-et-solidarity-overdosage-two-clinical-trials...

Source  Study Page  Submit Corrections or Comments

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**6/16 Positive (news)**

Pre-Exposure Prophylaxis study

*WHIP COVID-19 (News) (not included in the study count)*

Henry Ford Health System still moving forward with hydroxychloroquine study

Ongoing WHIP COVID-19 HCQ PrEP study reports analyzing their data and seeing a significantly improved outcome in a group of COVID-19 patients who received HCQ. For more details on the study see [1]. Currently no formal study is available so this is not included in

Source  Study Page  Submit Corrections or Comments
the study count.

6/16  Positive

Pre-Exposure Prophylaxis study


Clinical characteristics of 17 patients with COVID-19 and systemic autoimmune diseases: a retrospective study

Analysis of 1255 COVID-19 patients in Wuhan Tongji Hospital finding 0.61% with systemic autoimmune diseases, much lower than authors expected (3%–10%). Authors hypothesise that protective factors, such as CQ/HCQ use, reduce hospitalization.

Source  Study Page  Submit Corrections or Comments

6/12  Theory

Theory

**Scherrmann, AAPS J 22, 86 (2020), doi:10.1208/s12248-020-00465-w (Peer Reviewed) (Theory) (not included in the study count)**

Intracellular ABCB1 as a Possible Mechanism to Explain the Synergistic Effect of Hydroxychloroquine-Azithromycin Combination in COVID-19 Therapy

Theory paper, not included in the study count or percentages. Proposes a new mechanism supporting the synergistic interaction between HCQ+AZ.
Late treatment study

Giacomelli et al., Journal of Medical Virology, doi:10.1002/jmv.26407 (preprint 6/12) (Peer Reviewed)

Early administration of lopinavir/ritonavir plus hydroxychloroquine does not alter the clinical course of SARS-CoV-2 infection: a retrospective cohort study

Late stage study of hospitalized patients comparing treatment starting within 5 days versus later. Note that 'early' here is only relative - all patients are hospitalized so this is 'late' and 'very late'. The 'early' treatment group is significantly older. Severe adverse events attributed by authors to concurrent administration of LPV, making it difficult to make conclusions about HCQ.

6/12  Negativo

Early treatment study

Otea et al., medRxiv, doi:10.1101/2020.06.10.201101105 (Preprint)


80 moderate cases, HCQ+AZ appears to reduce serious complications and death. Moderate treated cases resulted in hospitalization at the same rate as mild untreated cases suggesting efficacy.

6/10  Positivo
Positive

Early treatment study

Pirnay et al., Hosp. Pharm. and Clinician, doi:10.1016/j.phclin.2020.06.001 (Peer Reviewed)

Beneficial effect of Hydroxychloroquine-Azithromycin combination in the treatment of elderly patients with Covid-19: results of an observational study

68 very high risk nursing home residents, median age 86, HCQ+AZ early treatment within 2.5 days onset, 2 stopped due to QTc. Only 7 died, significantly less than other nursing homes in France and the same as the median death for the same period in 2019/2018.

Pre-Exposure Prophylaxis study

Bhattacharya et al., medRxiv, doi:10.1101/2020.06.09.20116806 (Preprint)

Pre exposure Hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers

HCQ reduced cases from 38% to 7%. 106 people. No serious adverse effects.
Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative metaanalysis between the Big data and the real world


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Source  Study Page  Submit Corrections or Comments

Late treatment study


Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial

RECOVERY trial reports no significant benefit seen for very late stage very sick patients. Results may be due to the unusually high dosage used [1, 2]. Patients were extremely sick (average of 9 days post symptoms, 60% requiring oxygen and an additional 17% requiring ventilation/ECMO), and unusually high death rate was seen in both arms. 1,561 HCQ patients, 3,155 SOC.

A secondary analysis has found several inconsistencies in the data [3], and found evidence of excess mortality within the first few days that could be due to overdose.

Hypoxia may inhibit HCQ entering cells [4], making it less effective for late stage use.

[1] twitter.com/JamesTodaroMD/status/1272661099985481733
[2] twitter.com/JamesTodaroMD/status/12762456693727323200
[3] francesoir.fr/politique-monde/oxford-etu-de-recovery-ou-sont-les-morts

Source  Study Page  Submit Corrections or Comments

Hypoxia may inhibit HCQ entering cells [4], making it less effective for late stage use.
Post Exposure Prophylaxis study

*Boulware* et al., *NEJM*, June 3 2020, doi:10.1056/NEJMoa2016638 (Peer Reviewed)

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

COVID-19 cases are reduced by [49%, 29%, 16%] respectively when taken within ~[70, 94, 118] hours of exposure (including shipping delay). The treatment delay-response relationship is significant at *p*=0.002. PEP delayed treatment RCT.

Currently this is the only study where we have evaluated the result as positive while the authors indicate it is negative. We provide a detailed explanation of why the results presented here are positive [1]. Note that author comments also differ from the published conclusion.

Also see: [2, 3, 4].

![Reduction in cases with HCQ](image)

[1] c19study.com/boulware.html
[2] drive.google.com/file/d/1NZOJ57fMORTaHD1t_9w2iuia7lUJh0gWT/view
[4] medrxiv.org/content/10.1101/2020.08.19.20178376v1

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### Dosing

N/A

*Al-Kofahi* et al., *Clin. Pharmacol. Ther.*, Jun 1, 2020, doi:10.1002/cpt.1874 (Peer Reviewed) (not included in the study count)

Finding the Dose for Hydroxycholoroquine Prophylaxis for COVID-19: The Desperate Search for Effectiveness

Analysis of HCQ dosing regimens, recommending:

**PrEP:** 800mg loading dose followed by 400mg 2 or 3 times weekly to maintain weekly troughs above EC$_{50}$ in >50% of patients at steady-state.

**PEP:** 800mg loading dose followed in 6 hours by 600mg, then 600mg daily for 4 more days to achieve daily troughs above EC$_{50}$ in >50% subjects.
Early treatment study


Azithromycin and Hydroxychloroquine Accelerate Recovery of Outpatients with Mild/Moderate COVID-19

Mean clinical recovery time reduced from 26 days (SOC) to 9 days, \( p<0.0001 \) (HCQ+AZ) or 13 days, \( p<0.0001 \) (AZ). No cardiac toxicity. Small retrospective study of 88 patients with case control analysis with matched patients.

5/29    Positive

Late treatment study

Ayerbe et al., Journal of Thrombosis and Thrombolysis, doi: 10.1007/s11239-020-02162-z (Peer Reviewed)

The association between treatment with heparin and survival in patients with Covid-19

2075 hospital patients in Spain. HCQ reduces mortality from 30% to 13%. Not adjusted for age and gender. HCQ group 10% more males and 6 years younger. Study primarily interested in Heparin.
**Late treatment study**

**Chamieh et al., medRxiv 2020.05.28.20114835, doi:10.1101/2020.05.28.20114835 (Preprint)**

Viral Dynamics Matter in COVID-19 Pneumonia: the success of early treatment with hydroxychloroquine and azithromycin in Lebanon

HCQ+AZ potentially explains 94.7% success in treating a fairly complex cohort.

Source  Study Page  Submit Corrections or Comments

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**Pre-Exposure Prophylaxis study**


Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19

4+ doses of HCQ associated with a significant decline in the odds of getting infected, dose-response relationship exists.

Source  Study Page  Submit Corrections or Comments

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**Late treatment study**

**Huang et al., National Science Review, nwaar113, doi:10.1093/nsr/nwaar113 (Peer Reviewed)**

197 CQ patients, 176 control. Mean time to undetectable viral RNA and duration of fever significantly reduced. No serious adverse events.

Late treatment study

Goldman et al., NEJM, doi:10.1056/NEJMoa2015301 (Peer Reviewed)

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Study focused on Remdesivir but with results for HCQ in the supplementary appendix, showing 9% death with HCQ versus 12% control, RR 0.78, \( p = 0.46 \).

Early treatment study


Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis

Five studies, including two controlled clinical trials, have demonstrated significant outpatient treatment efficacy.

Late treatment study

Ip et al., medRxiv, doi:10.1101/2020.05.21.20109207 (Preprint)
Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients - An Observational Study

Retrospective study of late stage use on 2,512 hospitalized patients showing no significant differences in associated mortality for patients receiving any HCQ during the hospitalization (HR, 0.99 [95% CI, 0.80-1.22]), HCQ alone (HR, 1.02 [95% CI, 0.83-1.27]), or HCQ+AZ (HR, 0.98 [95% CI, 0.75-1.28]). Misclassification is possible due to manual abstraction of EHR data. They observed a change in the prescribing patterns of HCQ during the study timeframe. Confounding by indication.

PEP, PrEP

ICMR, Indian Council of Medical Research (Advisory) (not included in the study count)

Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for SARS-CoV-2 infection

Healthcare workers on HCQ prophylaxis less likely to get COVID. Significant dose-response relationship. Extends recommended HCQ prophylaxis to asymptomatic household contacts of cases and frontline workers. Degree of benefit not quantified. Currently no formal study is available so this is not included in the study count.

1.3 Studies on prophylaxis of SARS-CoV-2 infection

- A retrospective case-control analysis at ICMR has found that there is a significant dose-response relationship between the number of prophylactic doses taken and frequency of occurrence of SARS-CoV-2 infection in symptomatic healthcare workers who were tested for SARS-CoV-2 infection.
- Another investigation from 3 central government hospitals in New Delhi indicates that amongst healthcare workers involved in COVID-19 care, those on HCQ prophylaxis were less likely to develop SARS-CoV-2 infection, compared to those who were not on it. The benefit was less pronounced in healthcare workers caring for a general patient population.
- An observational prospective study of 334 healthcare workers at AIIMS, out of which 248 took HCQ prophylaxis (median 6 weeks of follow up) in New Delhi also showed that those taking HCQ prophylaxis had lower incidence of SARS-CoV-2 infection than those not taking it.

Late treatment study

Mehra et al., The Lancet, May 22, 2020, doi: 10.1016/S0140-6736(20)31180-6 (Peer Reviewed) (not included in the study count)

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

Incorrect at first read (implausible death, ventilation, and population numbers). This paper was retracted.
Meta analysis not seeing a significant effect other than time to resolution of chest CT. Limited by heterogeneous nature of studies, baseline severity varied, most studies have a small sample size, endpoints reported at varying times, dosage varied, and AZ, Zinc are not considered.

Chacko et al., medRxiv, doi:10.1101/2020.05.14.20101774 (Preprint) (meta analysis - not included in study count)

Hydroxychloroquine in COVID-19: A systematic review and meta-analysis

Late treatment study

Singh et al., medRxiv, doi:10.1101/2020.05.12.20099028 (Preprint)

Outcomes of Hydroxychloroquine Treatment Among Hospitalized COVID-19 Patients in the United States- Real-World Evidence From a Federated Electronic Medical Record Network

EHR analysis of 3,372 hospitalized COVID-19 patients not showing a significant difference for mortality or the risk of mechanical ventilation. Subject to the limitations of EHR analysis. Misclassification is possible. Confounding by indication.

Kim et al., medRxiv, doi:10.1101/2020.05.13.20094193 (Preprint)

Treatment Response to Hydroxychloroquine, Lopinavir/Ritonavir, and Antibiotics for Moderate COVID 19: A First Report on the Pharmacological Outcomes from South Korea

Retrospective of 97 moderate cases. Time to viral clearance significantly shorter for HC Q+antibiotic. Preprint withdrawn pending peer review.

Ahmad et al., doi:10.1101/2020.05.18.20066902 (Preprint)

Doxycycline and Hydroxychloroquine as Treatment for High-Risk COVID-19 Patients:
Experience from Case Series of 54 Patients in Long-Term Care Facilities

54 patients in long term care facilities. 6% death with HCQ+AZ compared to 22% using a naive indirect comparison.

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Pre-Exposure Prophylaxis study

*Macias et al.,* medRxiv, 10.1101/2020.05.16.20104141 (Preprint)

Similar incidence of Coronavirus Disease 2019 (COVID-19) in patients with rheumatic diseases with and without hydroxychloroquine therapy

Very small retrospective study of rheumatic disease patients, sample size is too small for statistical significance (HCQ 0.5-4.0%, no-HCQ 0.4-2.7%). Confirmed cases were 1 HCQ and 2 no-HCQ, confirmed+likely cases were 1 HCQ and 3 no-HCQ. 1 HCQ and 2 no-HCQ patients were admitted to hospital. We do not think a conclusion can be drawn based on these sample sizes. Further, there are very significant differences between the groups, for example 30% of the HCQ group have SLE vs. 2.5% of the no-HCQ group. SLE patients have a 5.7 times relative risk of pneumonia according to [1], whereas the relative risk with glucocorticoids and TNF-α inhibitors is significantly lower [2]. Two more recent studies with rheumatic disease/autoimmune condition patients provide higher confidence.

[1] ncbi.nlm.nih.gov/pmc/articles/PMC4516647/

Source  Study Page  Submit Corrections or Comments

Late treatment study


Low Dose of Hydroxychloroquine Reduces Fatality of Critically Ill Patients With COVID-19

Retrospective, 550 critically ill patients. 19% fatality for HCQ versus 47% for non-HCQ, RR 0.395, p=0.002.

The levels of inflammatory cytokine IL-6 were significantly reduced from 22.2 pg/mL to 5.2 pg/mL (p<0.05) at the end of the treatment in the HCQ group but there was no change in the control group.
Late treatment study

Mahévas et al., BMJ 2020, 369, doi: https://doi.org/10.1136/bmj.m1844 (Peer Reviewed)

Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data

Observational study of 181 patients with advanced disease requiring oxygen showing no benefit for HCQ. Power of study appears too low to support conclusions [1]. None of the 15 patients receiving HCQ+AZ were transferred to intensive care or died compared to 23% overall.

[1] bmj.com/content/369/bmj.m1844/rapid-responses

Late treatment study

Hydroxychloroquine and azithromycin as potential treatments for COVID-19; clinical status impacts the outcome

Odds of PCR-positive decrease by 53% for each unit increase in HCQ log-concentration. Similarly, the odds decrease by 61%, and by 12% for each day increase, and for azithromycin co-treatment, respectively. Computes the minimum HCQ concentration needed based on severity, and corresponding dosage regimens. A loading dose is found to be important. For LRTI and URTI patients the addition of AZ is needed. Extended analysis of Gautret et al. using the observed HCQ concentrations and pharmacokinetic analysis to compute concentrations for all days.

Source

Study Page

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Late treatment study


Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State

Restrospective observational late stage study showing no significant differences but calling for clinical trials.

Zervos et al. [1] point out serious limitations that they say should be corrected on the record: patients receiving HCQ with or without AZ were overall sicker on presentation and had multiple other risk factors including much higher risk based on ethnicity; patients receiving HCQ were more likely to be obese, diabetic, have chronic lung disease, and cardiovascular conditions; yet these sicker patients had approximately the same mortality rates compared to patients with a milder course of the disease and less risk factors. However, the authors
conclude that "there are no significant benefits." It is noteworthy that HCQ was associated with a significant survival benefit in a larger cohort of patients from New York City as reported by Mikami et al [2].


Late treatment study


A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection

Analysis of 94 hemodialysis COVID-19 positive patients. Reduction in death seen with HCQ but $p=0.12$, OR 0.44 [0.16–1.24].

Ex Vivo

Grassin-Delye et al., Clinical Infectious Diseases, doi:10.1093/cid/ciaa546 (Peer Reviewed) (Ex Vivo) (not included in the study count)

Chloroquine Inhibits the Release of Inflammatory Cytokines by Human Lung Explants

On human lung parenchymal explants, CQ concentration clinically achievable in the lung (100 µM) inhibited the lipopolysaccharide-induced release of TNF-α (by 76%), IL-6 (by 68%), CCL2 (by 72%), and CCL3 (by 67%). In addition to antiviral activity, CQ may also mitigate the cytokine storm associated with severe pneumonia caused by coronaviruses.

Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients

Retrospective 932 patients. Addition of Zinc to HCQ+AZ reduces mortality / transfer to hospice, ICU admission, and the need for ventilation.
Reduction in mortality or transfer to hospice adjusted odds ratio OR 0.56, \( p = 0.002 \); increase in being discharged home, adjusted OR 1.53, \( p = 0.008 \).

Source  Study Page  Submit Corrections or Comments

Theory


Excessive lysosomal ion-trapping of hydroxychloroquine and azithromycin

Discusses pharmacokinetic properties of HCQ+AZ as a potential underlying mechanism of the observed antiviral effects.

Source  Study Page  Submit Corrections or Comments

Inconc.

Late treatment study


Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

There appears to be a major error in this paper. Before propensity matching, 38 control patients had hypertension. After propensity matching, 146 patients had hypertension (Table 1). This is not possible. Even if all propensity matched control patients had hypertension, the control prevalence would only be 14% compared to 49% for treatment. Since patients with hypertension are at much greater risk of mortality (HR 2.12, see [1]), this appears to invalidate the results.

Observational study of 1,446 hospitalized patients showing no significant effect on a combined intubation/death outcome for late treatment.

However, secondary analysis shows the success of HCQ was hidden by combining intubation and death - death / (combined death/intubation) for HCQ was 60% vs. control 89%, for details see: [2].

RCT recommended. No AZ or Zinc. HCQ group much sicker - patients already in mild/moderate ARDS, most of the control group not in ARDS. Control cases received other therapeutics.
Sermo (News) (not included in the study count)

Sermo reports: COVID-19 treatment trends over 6 weeks and 33,700 interviews: Usage, efficacy and safety perceptions of most-used therapies

HCQ used by 55% of physicians worldwide for COVID. Survey of 6,150 physicians. Currently no formal study is available so this is not included in the study count.

Source  Study Page  Submit Corrections or Comments

Maisonnasse et al., Nature, 2020, doi:10.1038/s41586-020-2558-4 (preprint 5/6) (Peer Reviewed) (not included in the study count)

Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates

Monkey study which reports no effect of HCQ or HCQ+AZ. However, there are several signs of effectiveness despite the very small sample sizes and 100% recovery of all treated and control monkeys.

58% reduction in lung lesions: the final day lung lesion data shows 63% of control monkeys have lesions, while 26% of treated monkeys do, p=0.095 (the final day data is missing for 7 monkeys, these are predicted based on the day 5 results and the trend of comparable monkeys).

97% increase in viral load recovery after one week: 3 of 8 control monkeys (38%) have recovered with <= 4 log10 copies/mL viral load, compared to 17 of 23 treated monkeys (74%), p=0.095. 3 of 8 (38%) control monkeys also have a higher peak viral load than 100% of the 23 treated monkeys post-treatment. The group with the lowest peak viral load is the PrEP group.
All animals were infected with the same initial viral load, whereas real-world infections vary in the initial viral load, and lower initial viral loads allow greater time to mount an immune response.

Severity of disease is not analyzed as compared to humans. The steep viral drops observed could also be related to immune system response.

Source Study Page Submit Corrections or Comments

Late treatment study

Membrillo de Novales et al., Preprints 2020, 2020050057, doi:10.20944/preprints202005.0057.v1 (Preprint)

Early Hydroxychloroquine Is Associated with an Increase of Survival in COVID-19 Patients: An Observational Study

166 patients hospitalised with COVID-19, HCQ increased survival 1.4 - 1.8 times when patients admitted in early stages. Early is relative to hospital admission here - all patients relatively serious condition.

Source Study Page Submit Corrections or Comments

Early, Late

Million et al., Travel Med Infect Dis., 2020 May 5, doi:10.1016/j.tmaid.2020.101738 (Peer Reviewed)

Early Treatment of COVID-19 Patients With Hydroxychloroquine and Azithromycin: A Retrospective Analysis of 1061 Cases in Marseille, France

Retrospective 1061 patients. HCQ+AZ safe and results in a low fatality rate.

Source Study Page Submit Corrections or Comments

5/5 Inconc.

Pre-Exposure Prophylaxis study


Continuous Hydroxychloroquine or Colchicine Therapy Does Not Prevent Infection With SARS-CoV-2: Insights From a Large Healthcare Database Analysis

Very small study of rheumatic disease/autoimmune disorder patients showing no significant difference but with only 3 chronic HCQ patient cases. Only considers people tested at a time when primarily symptomatic cases were tested.
Other research shows that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall, Ferri et al. show OR 4.42, p<0.001 [1], which is the observed real-world risk, taking into account factors such as these patients potentially being more careful to avoid exposure.

Adjusting for the difference in baseline risk using the result in Ferri et al. shows substantial benefit for HCQ, RR 0.211, but with only 3 HCQ cases the result is inconclusive. More recent studies with rheumatic disease/autoimmune condition patients provide higher confidence.

[1] c19study.com/ferri.html

Source  Study Page  Submit Corrections or Comments

Pre-Exposure Prophylaxis study

*Mitchell* et al., SSRN, doi:10.2139/ssrn.3586954 (Preprint)

Markedly Lower Rates of Coronavirus Infection and Fatality in Malaria-Endemic Regions – A Clue As to Treatment?

Analysis of COVID-19 amongst 2.4B people shows a wide counterintuitive disparity between well-developed and less-developed countries, with more affluent countries about one hundred times more likely to be infected and die due to COVID-19. They find the effect is most apparent when comparing to countries with the highest rates of endemic malaria. Since travelers to malaria-endemic countries are likely to be taking antimalarial prophylaxis and there is evidence of efficacy with COVID-19, authors find the data highly probative for the hypothesis that prophylactic antimalarial use by incoming visitors markedly attenuates a country's COVID-19 fatality rate. While authors do not adjust for age differences, those adjustments can only account for a small fraction of the observed difference.

Source  Study Page  Submit Corrections or Comments

Pre-Exposure Prophylaxis study

*Huh* et al., medRxiv, doi:10.1101/2020.05.04.20089904 (Preprint)

Association of previous medications with the risk of COVID-19: a nationwide claims-based study from South Korea

Database analysis of many drugs and COVID-19 cases, with 23 cases taking HCQ, and 251 control patients not taking HCQ, showing OR 1.07, p=0.77, and in multivariable analysis OR 1.48, p=0.086. Patients taking HCQ are most likely taking it for systemic autoimmune diseases where the risk of COVID-19 is much higher, for example OR 4.42, p<0.001 according to [1] (which includes factors such as systemic autoimmune disease patients potentially being more careful to avoid exposure). The result therefore suggests a substantial benefit for HCQ, as is also shown in Ferri et al. Adjusting for the difference in baseline risk of systemic autoimmune patients results in RR 0.24. Details of the multivariable analysis in the paper are not provided for assessment, but the analysis may be significantly affected by overfitting.
and/or multicollinearity. We note that many results in this study differ significantly from other research, for example proton pump inhibitors show OR 0.62, \( p < 0.001 \) whereas PPIs are classified as “no expected benefit” and other research suggests they increase risk.

[1] c19study.com/ferri.html

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Mercuro et al., JAMA Cardiol., May 1, 2020, doi:10.1001/jamacardio.2020.1834 (Peer Reviewed) (not included in the study count)

Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19)

Study of 90 hospitalized patients given HCQ, 53 also receiving AZ, 53% hypertension, 29% diabetes mellitus, baseline median QTc 473ms for HCQ, and 442ms for HCQ+AZ. Median change for HCQ+AZ \( \Delta \text{QTc} \) of 23ms vs. 5.5ms for HCQ. Other factors such as stress cardiomyopathy or myocarditis could not be ruled out. Without a control arm, they could not conclude that HCQ and AZ conferred increased cardiotoxic risk; however, compared with HCQ alone, \( \Delta \text{QTc} \) differences were likely associated with the addition of AZ. The likelihood of prolonged QTc was greater in those who received concomitant loop diuretics or had a baseline QTc of 450 milliseconds or more. HCQ was discontinued in 10 patients due to adverse events including nausea, hypoglycemia, and 1 case of torsades de pointes. There were no deaths reported.

Appropriate use and careful analysis of contraindications, risks, and benefits are important. More recent and much larger studies have not shown significant safety concerns, including outpatient RCTs showing no serious adverse events, and even the RECOVERY trial which used an unusually high dose of HCQ (including 237 patients also receiving AZ) reports they “did not show any excess in ventricular tachycardia (including torsade de pointes) or ventricular fibrillation in the hydroxychloroquine arm”, and “serious cardiovascular toxicity has been reported very rarely despite the high prevalence of cardiovascular disease in hospitalized patients, the common occurrence of myocarditis in COVID-19, and the extensive use of hydroxychloroquine and azithromycin together.”

Bessière et al., JAMA Cardiol., May 1, 2020, doi:10.1001/jamacardio.2020.1787 (Peer Reviewed) (not included in the study count)

Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With
Azithromycin in an Intensive Care Unit

Study of 40 very serious condition ICU patients, 75% required invasive mechanical ventilation, 63% received vasoactive drugs, 50% received other treatments favoring QT prolongation. HCQ with or w/o AZ was given to 45% and 55% respectively. They showed an increase in QTc, more significant with the combination of HCQ+AZ where prolonged QTc was observed in 36% (10 with ΔQTc >60 milliseconds and 7 with QTc ≥500 milliseconds). No ventricular arrhythmia, including torsades de pointes, was recorded. While these results may not be generalizable outside the ICU, caution is recommended in use, especially with the combination.

Appropriate use and careful analysis of contraindications, risks, and benefits are important. More recent and much larger studies have not shown significant safety concerns, including outpatient RCTs showing no serious adverse events, and even the RECOVERY trial which used an unusually high dose of HCQ (including 237 patients also receiving AZ) reports they "did not show any excess in ventricular tachycardia (including torsade de pointes) or ventricular fibrillation in the hydroxychloroquine arm", and "serious cardiovascular toxicity has been reported very rarely despite the high prevalence of cardiovascular disease in hospitalized patients, the common occurrence of myocarditis in COVID-19, and the extensive use of hydroxychloroquine and azithromycin together."

Source  Study Page  Submit Corrections or Comments

Late treatment study

Seydi (News) (not included in the study count)

Coronavirus: a study in Senegal confirms the effectiveness of hydroxychloroquine

Preliminary results of Senegal trial with 181 patients showing faster recovery with HCQ, and even faster recovery with HCQ+AZ. Currently no formal study is available so this is not included in the study count.

Source  Study Page  Submit Corrections or Comments

Early treatment study


Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19

Analysis of COVID-19 and malaria, finding that COVID-19 is highly pandemic in countries where malaria is least pandemic, and vice versa, suggesting that CQ/HCQ (widely used for malaria) are protective for COVID-19. This paper also includes a review of 9 articles supporting the efficacy of HCQ and CQ.

Source  Study Page  Submit Corrections or Comments
Late treatment study


4/27  Positive

Analysis of 868 patients on renal replacement therapy. Statistically significant reduction in mortality with HCQ for patients on dialysis (OR 0.47, \( p = 0.005 \)).

No statistically significant change was found for transplant patients (the result is not given but likely the sample size is too small - the number of transplant patients was half the number of dialysis patients).

Source  Study Page  Submit Corrections or Comments

N/A

*Saleh et al.,* Circulation: Arrhythmia and Electrophysiology, doi:10.1161/CIRCEP.120.008662 (Peer Reviewed)

The Effect of Chloroquine, Hydroxychloroquine and Azithromycin on the Corrected QT Interval in Patients with SARS-CoV-2 Infection

4/29  Safety

201 hospitalized patients. No serious side effects of HCQ. No instances of Torsade de pointes, or arrhythmogenic death were reported. They report that although use of these medications resulted in QT prolongation, clinicians seldom need to discontinue therapy.

Source  Study Page  Submit Corrections or Comments

In Vitro

*Andreani et al.,* Microbial Pathogenesis, doi:/10.1016/j.micpath.2020.104228 (Peer Reviewed) (In Vitro) (not included in the study count)

4/25  In Vitro

In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect

HCQ and AZ has a synergistic effect *in vitro* on SARS-CoV-2 at concentrations compatible with that obtained in human lung.

Source  Study Page  Submit Corrections or Comments

4/24  Inconc.
Early treatment study

Ashraf et al., medRxiv doi:10.1101/2020.04.20.20072421.t (Preprint)

COVID-19 in Iran, a comprehensive investigation from exposure to treatment outcomes

Small limited trial with 100 patients concluding that HCQ improved clinical outcome, OR 0.016 [0.002-0.11] in regression analysis.

Source  Study Page  Submit Corrections or Comments

Early treatment study

Izoulet M., SSRN, doi:10.2139/ssrn.3575899 (Preprint)

Countries which Primarily Use Antimalarial Drugs As COVID-19 Treatment See Slower Dynamic of Daily Deaths

Compares the dynamics of daily deaths in the 10 days following the 3rd death in countries using and not using [H]CQ, showing dramatically lower death in [H]CQ countries. This paper does not attempt to account for population age and other differences between the countries and recommends further study.

Source  Study Page  Submit Corrections or Comments

Late treatment study


Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19

Retrospective 368 hospitalized patients, no statistically significant reduction in mortality or the need for mechanical ventilation with HCQ or HCQ+AZ, or for death with HCQ+AZ, HR 1.83, p=0.009 for HCQ mortality. Study notes that HCQ was more likely to be prescribed to patients with more severe disease.

Source  Study Page  Submit Corrections or Comments

Post Exposure Prophylaxis study


Can Post-Exposure Prophylaxis for COVID-19 Be Considered as an Outbreak Response Strategy in Long-Term Care Hospitals?
Post exposure prophylaxis of 211 high-risk people after major exposure event in a long term care hospital, showing no positive cases after 14 days.

Late treatment study

*Borba et al., JAMA Network Open, doi:10.1001/jamanetworkopen.2020.8857 (Peer Reviewed)*

Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection. Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study)

Comparison of typical CQ dosage with high dosage CQ (600mg CQ twice daily for 10 days), showing higher mortality with high dosage, OR 2.8 [0.9 - 8.5] when controlled by age in multivariate analysis.

Increased incidence of prolonged QT and death in high dose treatment arm. Patients >75 only enrolled in high dose arm, age of high dose arm significantly higher than low dose arm (p=0.02). Very sick at baseline, 43% in ICU, 88.9% on respiratory therapy prior to treatment.

Early, Late

*Esper et al., Prevent Senior Institute, São Paulo, Brazil (Preprint)*

Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine

636 patients. HCQ+AZ reduced hospitalization 79% when used within 7 days (65% overall). Non-randomized.

Theory

*Brufsky, A., J. Medical Virology, doi:10.1002/jmv.25887 (Peer Reviewed) (Theory) (not included in the study count)*

Hyperglycemia, hydroxychloroquine, and the COVID-19 pandemic

Theory on the effectiveness of HCQ. HCQ has been shown to block the polarization of macrophages to an M1 inflammatory subtype and is predicted to interfere with glycosylation of a number of proteins involved in the humoral immune response, possibly including the
macrophage FcR gamma IgG receptor and other immunomodulatory proteins, potentially through inhibition of UDP-N-acetylglucosamine 2-epimerase. In combination with potential other immunomodulatory effects, this could possibly blunt the progression of COVID-19 pneumonia all the way up to ARDS.

**Late treatment study**

Tang et al., BMJ 2020, 369, doi:10.1136/bmj.m1849 (Peer Reviewed)

Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial

150 patients very late stage RCT. No significant difference. More symptomatic relief with HCQ. Treatment very late, average 16.6 days after symptom onset.

Data favorable to HCQ was deleted in the second version, see analysis [1]. Original conclusions included greater alleviation of clinical symptoms with HCQ in patients not receiving antiviral treatment.

[1] mediterranee-infection.com/tang-et-al-bmj-donnees-favorables-a-lhydroxychloroquine-s...

**Update on Use of Chloroquine/Hydroxychloroquine to Treat Coronavirus Disease 2019 (COVID-19)**

Increasing evidence from completed clinical studies shows CQ and HCQ effective (HCQ more effective).

**Late treatment study**

Gao et al., Biosci Trends, May 21, 2020, 14:2, 156-158, doi:10.5582/bst.2020.03072, Epub Apr 13, 2020 (Peer Reviewed) (not included in the study count)

**Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: a quasi-randomized comparative study**

Small retrospective study with 63 patients (32 treated with HCQ), showing no effectiveness, however the baseline state of each arm significantly differs. This preprint was submitted to
NEJM but has not been published several months later.

Early treatment study

**Gautret et al., Travel Medicine and Infectious Disease, doi:10.1016/j.tmaid.2020.101663 (Peer Reviewed)**

Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study

Pilot study suggesting improvement with HCQ+AZ and recommending further study. 80 patients with relatively mild cases, no control group, and no attempt to analyze confounding factors.

Late treatment study

**Lover, medRxiv, doi:10.1101/2020.03.22.20040949 (Preprint) (meta analysis - not included in study count)**

Quantifying treatment effects of hydroxychloroquine and azithromycin for COVID-19: a secondary analysis of an open label non-randomized clinical trial (Gautret et al, 2020)

Secondary analysis of Gautret et al. showing "modest to no impact of HCQ treatment, with more significant effects from [HCQ+AZ].”

Theory


Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection

In-silico analysis confirming the antiviral properties of CQ, showing a new mechanism of action of CQ, and showing that HCQ is more potent than CQ.
Early treatment study


Treating COVID-19 with Chloroquine

22 patients. All CQ patients discharged by day 14 versus 50% of Lopinavir/Rotinavir patients. Symptom onset to treatment 2.5 days for CQ vs. 6.5 days for Lopinavir/Rotinavir.

Late treatment study

Chen et al., medRxiv doi:10.1101/2020.03.22.20040758 (Preprint)

Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial

62 patients. RCT showing significantly faster recovery with HCQ. 13% progressed to severe cases in the control group, versus 0% for the treatment group. Significant improvement seen in pneumonia on chest CT for 61% of treated patients and 16% of control patients.

In Vitro study


Combined Prophylactic and Therapeutic Use Maximizes Hydroxychloroquine Anti-SARS-CoV-2 Effects in vitro

In vitro study, not included in the study count or percentages, showing greater inhibition for combined pre and post-exposure treatment for Vero E6 and Caco-2 cells.

Late treatment study


No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection.
11 patients with severe cases. No evidence of benefit for HCQ.

Source  Study Page  Submit Corrections or Comments

Late treatment study

Zhong Nanshan (钟南山) (News) (not included in the study count)

Efficacy and safety of chloroquine for treatment of COVID-19. An open-label, multi-center, non-randomized trial

197 patients. CQ effective. Day 10 viral RNA negative 91.4% HCQ versus 57.4% control.
Median time to negative test 3 days versus 9 days for control. Currently no formal study is available so this is not included in the study count.

Source  Study Page  Submit Corrections or Comments

Theory

(Theory) (not included in the study count)

Is Hydroxychloroquine a Possible Post-Exposure Prophylaxis Drug to Limit the Transmission to Health Care Workers Exposed to COVID-19?

CQ and HCQ inhibit replication at early stages of infection, no similar effect reported for other drugs which are only able to interfere after cell infection. Large volume of existing data on safety. (8/23: we corrected the classification of this study)

Source  Study Page  Submit Corrections or Comments

Theory

Hu et al., Nature Nanotechnology, 15, 247–249, 2020, doi:10.1038/s41565-020-0674-9 (Peer Reviewed) (Theory) (not included in the study count)

Insights from nanomedicine into chloroquine efficacy against COVID-19

CQ is known in nanomedicine research for the investigation of nanoparticle uptake in cells, and may have potential for the treatment of COVID-19.

Source  Study Page  Submit Corrections or Comments

Positive (advisory)

Pre-Exposure Prophylaxis study
ICMR, Indian Council of Medical Research (Advisory) (not included in the study count)

Advisory on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection

Recommends HCQ for prophylaxis in asymptomatic healthcare workers as found effective in-vitro and in-vivo. Currently no formal study is available so this is not included in the study count.

Source  Study Page  Submit Corrections or Comments

Late treatment study

Hu et al., Shanghai Combined Task Force on COVID-19 (News) (not included in the study count)

Shanghai Experience of COVID-19 Management

Clinical studies of HCQ with 184 cases and 21 hospitals show HCQ is effective. Currently no formal study is available so this is not included in the study count.

Source  Study Page  Submit Corrections or Comments

In Vitro

Liu et al., Cell Discovery 6, 16 (2020), doi:10.1038/s41421-020-0156-0 (Peer Reviewed) (In Vitro) (not included in the study count)

Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro

HCQ effective in vitro and less toxic than CQ. In addition to direct antiviral activity, HCQ is a safe and successful anti-inflammatory agent that has been used extensively in autoimmune diseases and can significantly decrease the production of cytokines and, in particular, pro-inflammatory factors. Therefore, in COVID-19 patients, HCQ may also contribute to attenuating the inflammatory response. Careful design of clinical trials is important to achieve efficient and safe control of the infection.

Source  Study Page  Submit Corrections or Comments

Inconc.

Early treatment study


Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an openlabel non-randomized clinical trial
HCQ was significantly associated with reduction / elimination of viral load, which was enhanced with AZ. Updated 8/13: responses to this paper have raised methodological issues [1, 2, 3].

Despite the limitations, this early observational study was a milestone in the discovery process, including detailed daily evolution of PCR positivity. This study should be viewed in the context of the series of studies from this group.


Source | Study Page | Submit Corrections or Comments


3/17 | Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine
Discussion of mechanisms of action, CQ vs. HCQ, early studies, safety.

Source | Study Page | Submit Corrections or Comments

3/13 | Review | Todaro and Rigano (Preprint) (not included in the study count)
An Effective Treatment for Coronavirus (COVID-19)
Discussion of existing research, treatment guidelines, and mechanisms of action for CQ and HCQ, recommending use.

Source | Study Page | Submit Corrections or Comments
<table>
<thead>
<tr>
<th>Date</th>
<th>Category</th>
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<tr>
<td>3/6</td>
<td>Negative</td>
<td><strong>Chen et al., J. Zhejiang University (Med Sci), doi:10.3785/j.issn.1008-9292.2020.03.03 (Peer Reviewed)</strong>&lt;br&gt;Later treatment study</td>
</tr>
</tbody>
</table>
A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)

30 moderate hospitalized cases, all recovered. Time to RNA negative comparable. Less frequent radiological progression with HCQ but not statistically significant. One HCQ patient developed to a severe case. Treatment group 4 years older and with higher incidence of hypertension.

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Source  Study Page  Submit Corrections or Comments

Late treatment study


Chloroquine and Hydroxychloroquine as Available Weapons to Fight COVID-19

Recommending CQ and HCQ for COVID-19 based on 20 clinical studies in China and a strong rationale for use.

Source  Study Page  Submit Corrections or Comments

Early trials in China show CQ results in shorter hospital stays and improved patient outcomes.

Source  Study Page  Submit Corrections or Comments
<table>
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<tr>
<th>Date</th>
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<th>Study Details</th>
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<tbody>
<tr>
<td>2/19</td>
<td>Positive</td>
<td>Late treatment study</td>
<td><strong>Gao et al., BioScience Trends, 2020, doi:10.5582/bst.2020.01047 (Peer Reviewed)</strong>&lt;br&gt;Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies&lt;br&gt;Results from 15 clinical trials in China showing CQ is effective.</td>
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<tr>
<td>2/17</td>
<td>Positive (news)</td>
<td>Late treatment study</td>
<td><strong>Sun Yanrong, deputy head of the China National Center for Biotechnology Development</strong> (News)&lt;br&gt;(not included in the study count)&lt;br&gt;Antimalarial drug confirmed effective on COVID-19&lt;br&gt;HQQ under clinical trials in &gt;10 hospitals in China and has shown fairly good efficacy. Currently no formal study is available so this is not included in the study count.</td>
</tr>
<tr>
<td>2/11</td>
<td>Positive</td>
<td>Late treatment study</td>
<td><strong>Xia et al., ChiCTR2000029741 (Preprint)</strong>&lt;br&gt;Efficacy of Chloroquine and Lopinavir/ Ritonavir in mild/general novel coronavirus (CoVID-19) infections: a prospective, open-label, multicenter randomized controlled clinical study&lt;br&gt;Early results from a very small trial, reported within the application for a later trial. Very minimal details are provided, but we include this as the earliest published results. For COVID-19 patients with pneumonia the viral negative conversion rate was 50% (5/10) with CQ versus 20% (3/15) with lopinavir/ritonavir.</td>
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<tr>
<td>2/4</td>
<td>In Vitro</td>
<td>In Vitro</td>
<td><strong>Wang et al., Cell Res. 30, 269–271, doi:10.1038/s41422-020-0282-0 (Peer Reviewed) (In Vitro)</strong>&lt;br&gt;(not included in the study count)&lt;br&gt;Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro</td>
</tr>
</tbody>
</table>
In vitro study, not included in the study count or percentages. Remdesivir and CQ potently blocked virus infection in vitro.

Source   Study Page   Submit Corrections or Comments

N/A


Simultaneous quantitation of hydroxychloroquine and its metabolites in mouse blood and tissues using LC-ESI-MS/MS: An application for pharmacokinetic studies

Presents a method for quantification of HCQ in mouse blood and tissues. They show a lung concentration significantly higher than other organs, and about 30 times the blood concentration.

Source   Study Page   Submit Corrections or Comments

In Vitro

de Wilde et al., Antimicrobial Agents and Chemotherapy, Jul 2014, 58:8, 4875-4884, doi:10.1128/AAC.03011-14 (Peer Reviewed) (In Vitro) (not included in the study count)

Screening of an FDA-Approved Compound Library Identifies Four Small-Molecule Inhibitors of Middle East Respiratory Syndrome Coronavirus Replication in Cell Culture

CQ inhibits SARS-CoV, MERS-CoV, and HCoV-229E-GFP replication in the low-micromolar range.

Source   Study Page   Submit Corrections or Comments

2012   Animal

Animal study

Yan et al., Cell Research, 23, 300–302, doi:10.1038/cr.2012.165 (Peer Reviewed) (not included in the study count)

Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model

CQ, a known autophagy inhibitor that is in clinical use, can efficiently ameliorate acute lung injury and dramatically improve the survival rate in mice infected with live avian influenza A H5N1 virus.

Source   Study Page   Submit Corrections or Comments
Antiviral Activity of Chloroquine against Human Coronavirus OC43 Infection in Newborn Mice

CQ inhibits HCoV-OC43 replication in HRT-18 cells. A lethal HCoV-OC43 infection in newborn C57BL/6 mice can be treated with CQ acquired transplacentally or via maternal milk. The highest survival rate (98.6%) was found when mother mice were treated daily with a concentration of 15 mg of CQ per kg of body weight. Survival rates declined in a dose-dependent manner, with 88% survival when treated with 5 mg/kg CQ and 13% survival when treated with 1 mg/kg CQ. CQ can be highly effective against HCoV-OC43 infection in newborn mice and may be considered as a future drug against HCoVs.

Inhibition of human coronavirus 229E infection in human epithelial lung cells (L132) by chloroquine: Involvement of p38 MAPK and ERK

CQ significantly decreased viral replication of HCoV-229E at concentrations lower than in clinical usage. CQ affects the activation of p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK). p38 MAPK inhibitor, SB203580, inhibits CPE induced by HCoV-229E infection and viral replication.

New insights into the antiviral effects of chloroquine

Update to 2003 paper, not included in the study count or percentages. Hypothesis of CQ inhibiting SARS replication has been confirmed in two in-vitro studies. CQ affected an early stage of SARS replication.
Chloroquine is a potent inhibitor of SARS coronavirus infection and spread

In vitro study, SARS-CoV-1, not included in the study count or percentages. CQ has strong antiviral effects on SARS CoV infection when cells treated either before or after exposure, suggesting prophylactic and treatment use. Describes three mechanisms by which the drug might work and suggests it may have both a prophylactic and therapeutic role in coronavirus infections.

In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine

In vitro study, SARS-CoV-1, not included in the study count or percentages. IC50 of CQ for antiviral activity (8.8) is significantly lower than cytostatic activity CC50 (261.3), selectivity index of 30. IC50 for inhibition of SARS-CoV in vitro approximates the plasma concentrations of CQ reached during treatment of acute malaria. CQ may be considered for immediate use in the prevention and treatment of SARS-CoV infections.
Effects of chloroquine on viral infections: an old drug against today's diseases

Not included in the study count or percentages. Discussion/review noting that CQ exerts antiviral effects, inhibiting the replication of several viruses including members of the flaviviruses, retroviruses, and coronaviruses. Notes that CQ has immunomodulatory effects, suppressing the production/release of tumour necrosis factor α and interleukin 6, which mediate the inflammatory complications of several viral diseases.

Source
Study Page
Submit Corrections or Comments

1918
Inconc.

N/A

Burrows, E., Medical Record, 97:6, 235, Feb 7, 1920 (Peer Reviewed) (not included in the study count)

A confirmatory report upon the abortive action of quinine dihydrochloride

Quinine was found to be effective for the Spanish Flu in 1918.
Quinine use for the Russian influenza pandemic if 1889-1890

Quinine and antipyrine, a bitherapy for defying death during the Russian influenza pandemic of 1889-1890 (around 40,000 deaths in France at the beginning of 1890). Currently no formal study is available so this is not included in the study count.
Quinine has been used for respiratory infections since 1889. Not included in the study count or percentages, just as an interesting observation.
Why fear colds, grip or influenza when Laxative Bromo Quinine Tablets are handy

It is easy to get rid of a cold if you don’t neglect it. People who know the beneficial effects of Laxative Bromo Quinine keep well during the winter months by taking these tablets when they feel a cold coming on.

The tonic and laxative effect of Laxative Bromo Quinine Tablets fortifies the system against colds, grip, influenza and other serious ills which often begin with a slight cold... Since 1887 the signature of C.P. Brown on every box of Laxative Bromo Quinine has identified it as the first and original cold and grip tablet. Price 30c.

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