Should antimalarials be used for COVID-19?

This clinical evidence summary outlines existing evidence on the use of antimalarials, chloroquine or hydroxychloroquine, for prophylaxis or treatment of patients with COVID-19 infection. The information may be revised as new evidence emerges. The summary is not exhaustive of the subject matter and does not replace clinical judgement. The responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.

Background

An article by Gao et al. titled "Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies" announced preliminary findings of 15 clinical trials from 10 hospitals in China on 19 February 2020.[1] The authors reported that results from more than 100 patients have shown chloroquine, an antimalarial treatment, is efficacious in preventing exacerbation of pneumonia, improving lung imaging findings, promoting virus free conversion, and shortening the disease course. This led them to recommend chloroquine as a treatment option for COVID-19 in the 7th edition of Chinese Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia.[2] Preliminary results of a clinical study by Gautret et al. published on 17 March 2020 reported that hydroxychloroquine is effective in treating COVID-19.[3]

In view of early study findings, U.S. President Trump publically advocated the use of hydroxychloroquine and azithromycin in COVID-19.[4] Following this event, news of chloroquine poisoning from inappropriate over the counter use of the medication, including a report of a fatality, have surfaced in the U.S. and Nigeria.[5,6]

Clinical evidence

There is insufficient high-quality evidence to demonstrate the efficacy of chloroquine or hydroxychloroquine for post-exposure prophylaxis or treatment of COVID-19 currently. Instead, evidence to date suggests the use of these agents is associated with more harms than standard of care.

A pilot randomised controlled trial (RCT) conducted by Chen et al. investigated the effect of hydroxychloroquine versus conventional treatment on negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swabs of 30 patients, seven days after randomisation.[7] On day seven, 13 (86.7%) cases in the hydroxychloroquine group were negative compared to 14 (93.3%) cases in the control group ($p>0.05$). There was no significant difference in median duration from hospitalisation to virus nucleic acid negative conversion and time for body temperature normalisation between the two groups.

In a small RCT by Huang et al., 22 patients with moderate to severe COVID-19 infections were randomised to either chloroquine or lopinavir/ritonavir treatment arms.[8] The authors reported that 6 (60%) patients achieved lung clearance based on CT imaging in the chloroquine group compared to 3 (25%) in the lopinavir/ritonavir group at day 9. By day 14, the incidence rate of lung improvement was not significantly higher in the chloroquine group compared to the lopinavir/ritonavir group (rate ratio 2.21, 95% CI 0.81–6.62).

An open-label RCT was conducted by Tang et al. in 150 hospitalised patients with mild to moderate COVID-19.[9] The results showed that administration of hydroxychloroquine + standard of care did not significantly increase the probability of virus elimination (measured as negative conversion of SARS-CoV-2 by 28 days) compared with standard of care alone. Adverse events, mostly gastrointestinal, were more frequent in patients who received hydroxychloroquine + standard of care (30%) compared with standard of care alone (9%).

A double-blind RCT by Boulware et al. investigated the use of hydroxychloroquine as post-exposure prophylaxis for COVID-19.[10] A total of 821 asymptomatic adults received a 5-day course of hydroxychloroquine or placebo within 4 days after household or occupational exposure to a confirmed COVID-19 contact. The results showed that hydroxychloroquine did not significantly reduce the incidence of laboratory-confirmed COVID-19 or symptomatic illness compatible with COVID-19 within 14 days compared with placebo. Side effects, mostly gastrointestinal, were more common with hydroxychloroquine than placebo (40.1% vs. 16.8%). No serious adverse reactions or cardiac arrhythmias were reported. The authors acknowledged the limitations of this pragmatic trial. There was no consistent laboratory confirmation of symptomatic illness, and almost all data were reported by participants.[11] The long delay between COVID-19 exposure and hydroxychloroquine initiation (mostly ≥3 days) suggested that what was being assessed was prevention of symptoms or progression, rather than prevention of COVID-19 infection.

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The RECOVERY Trial is an open-label, adaptive design RCT conducted in the UK to test a range of drugs, including hydroxychloroquine, for treating patients hospitalised with COVID-19.[12] On 5 June 2020, the chief investigators of the trial announced closure of the hydroxychloroquine arm due to lack of benefit. When 1,542 patients who received hydroxychloroquine were compared with 3,132 patients who received usual care alone, the preliminary results showed no significant difference in 28-day mortality (25.7% vs. 23.5%, hazard ratio 1.11, 95% CI 0.98–1.26). There was also no evidence of benefit of hydroxychloroquine treatment on hospital stay duration or other outcomes. Publication of the full results in a peer-reviewed journal is currently pending.

In an observational study by Mahévas et al. involving 181 hospitalised patients who required oxygen for COVID-19 pneumonia, hydroxychloroquine treatment did not reduce admissions to the intensive care unit or deaths at day 21 after hospital admission, when compared to no hydroxychloroquine treatment.[13]

A single centre, observational study by Geleris et al. involving 1,376 patients hospitalised with COVID-19 found that hydroxychloroquine treatment was not associated with a significantly higher or lower risk of intubation or death, when compared to no hydroxychloroquine treatment.[14]

A retrospective cohort study was conducted by Rosenberg et al. in 1,438 patients with COVID-19.[15] After adjusting for confounding variables, the results showed no significant differences in in-hospital mortality for patients who received hydroxychloroquine + azithromycin, hydroxychloroquine alone, or azithromycin alone, compared with patients who received neither drug. However, cardiac arrest was reported more frequently in patients who received hydroxychloroquine + azithromycin (adjusted odds ratio 2.13, 95% CI 1.12–4.05), but not hydroxychloroquine or azithromycin alone, compared with patients who received neither drug. There were no significant differences in the relative likelihood of abnormal ECG findings between the groups.

A multinational, observational study by Mehra et al. that was published in The Lancet on 22 May 2020 reported outcomes from 14,888 patients with COVID-19 who received treatment with hydroxychloroquine or chloroquine with or without a macrolide compared with 81,144 control group patients who received none of these treatments.[16] The authors reported that each of the four drug regimens was independently associated with an increased risk of in-hospital mortality and an increased frequency of ventricular arrhythmias compared with the control group. However, the validity of this study was subsequently called into question due to serious methodological and data integrity concerns, which led to the retraction of the study by its authors on 4 June 2020.[17,18]

In a retrospective cohort study by Kuderer et al. involving 928 patients with COVID-19 who have cancer, a strong association with increased 30-day all-cause mortality was observed in the subgroup treated with azithromycin plus hydroxychloroquine (versus treatment with neither drug: odds ratio 2.93, 95% CI 1.79–4.79), but not in the subgroups treated with either drug alone.[19] The authors acknowledged that the findings could not be considered conclusive, given the non-randomised study design and the possibility of other potential clinical imbalances.

In a retrospective cohort study by Mercuro et al. involving 90 patients with COVID-19, 7 of the 37 patients (19%) who received hydroxychloroquine monotherapy and 11 of the 53 patients (21%) who received hydroxychloroquine with azithromycin developed prolonged QTc of 500 ms or more.[20]

In a case series conducted by Bessière et al. in 40 ICU patients with COVID-19, 33% of patients treated with hydroxychloroquine and azithromycin developed an increase in QTc of 500 ms or more versus 5% of those treated with hydroxychloroquine alone ($p = 0.03$).[21]

Amid safety concerns with the use of hydroxychloroquine reported in the observational study by Mehra et al., the World Health Organization (WHO) announced on 25 May 2020 that the hydroxychloroquine testing arm within their global SOLIDARITY trial had been temporarily suspended.[22] In addition, WHO planned to make a final decision on the harm, benefit or lack of benefit of hydroxychloroquine after safety evidence from the SOLIDARITY trial and other ongoing trials had been reviewed by the Data Safety Monitoring Board.[23] On 3 June 2020, WHO decided to resume the hydroxychloroquine arm within their SOLIDARITY trial, after the integrity of the study by Mehra et al. was called into question and a review of available data by the WHO Data Safety Monitoring Board did not find any reason to discontinue this arm from the trial.[24] On 17 June 2020, WHO decided to stop the hydroxychloroquine arm on the basis of new data from the SOLIDARITY and RECOVERY trials and other evidence which showed no benefit for patients with COVID-19.[25,26]

Several ongoing RCTs for hydroxychloroquine and chloroquine are likely to report results in the months ahead and determine the role of these agents in the treatment and post-exposure prophylaxis of COVID-19 (Appendix 1).

Recommendations from professional bodies

Several international professional bodies, acknowledging the lack of robust scientific evidence, have provided advice on the use of antimalarials for patients with COVID-19:

- The Pan American Health Organization (PAHO), in collaboration with WHO, has published a rapid review, stating that there is a lack of quality evidence to demonstrate that chloroquine and/or hydroxychloroquine are effective in the treatment of COVID-19.[27]
- The Centers for Disease Control and Prevention (CDC) in the US has communicated there are no drugs or other therapeutics presently approved by the US FDA to prevent or treat COVID-19.[28]
- The US FDA issued an emergency use authorisation (EUA) on 28 March 2020 to allow hydroxychloroquine and chloroquine to be used in hospitalised patients with COVID-19 for whom a clinical trial is not available or participation is not feasible.[29] On 24 April 2020, the US FDA released a safety communication that it has received case reports in its Adverse Event Reporting System database of serious heart-related adverse events and death in patients with COVID-19 receiving hydroxychloroquine and chloroquine, either alone or in combination with azithromycin or other QT prolonging medications.[30] Close supervision was strongly recommended in patients receiving these drugs. On 15 June 2020, the EUA was revoked after a review of emerging scientific data by the FDA showed that hydroxychloroquine and chloroquine are unlikely to be effective in treating COVID-19. Additionally, in light of serious cardiac adverse events and other serious side effects, the FDA determined that the known and potential benefits of hydroxychloroquine and chloroquine no longer outweigh the known and potential risks for the authorised use.[30]
- The American College of Cardiology (ACC) has highlighted concerns of QT interval prolongation with the individual or concurrent use of hydroxychloroquine and azithromycin which increases the risk of arrhythmic death.[31]
- The National Institutes of Health (NIH) in the US has recommended against the use of chloroquine or hydroxychloroquine with or without azithromycin for treating COVID-19 except in the context of a clinical trial.[32] It also recommends monitoring the patient for adverse effects, particularly prolonged QTc interval, if these drugs are used.
- The American College of Physicians (ACP) has recommended against the use of hydroxychloroquine or chloroquine, alone or in combination with azithromycin, as prophylaxis or treatment for COVID-19 except in the context of a clinical trial for treating COVID-19 due to known harms and uncertain evidence of benefit.[33]
- Locally, the National Centre for Infectious Diseases (NCID) does not recommend the use of hydroxychloroquine or chloroquine for treating COVID-19 outside of a clinical trial due to possible toxicity and a lack of clear clinical benefit from available data.[34]

Conclusion

There is insufficient high-quality evidence to show chloroquine or hydroxychloroquine are effective for post-exposure prophylaxis or treatment of COVID-19. Instead, evidence to date suggests the use of these agents is associated with more harms than standard of care. Several clinical trials are ongoing and are likely to report results in the months ahead which will determine the role of these agents for COVID-19.

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Appendix 1: Table of RCTs registered internationally for chloroquine or hydroxychloroquine in patients with COVID-19

Study identifier	Study Design	Intervention	Comparator	Date of primary completion
ChiCTR2000030054[1] ChiCTR2000029992[2]	SC*, OL, RCT, ph0-IV	Hydroxychloroquine and chloroquine	Standard treatment	Unknown
ChiCTR2000029899[3] ChiCTR2000029898[4]	OL, MC*, RCT, phIV	Hydroxychloroquine	Chloroquine	Unknown
ChiCTR2000029868[5]	OL, MC*, RCT, phIV	Hydroxychloroquine	Standard treatment	Unknown
ChiCTR2000029803[6]	OL, SC, RCT, ph0	Hydroxychloroquine	Arbidol	Unknown
ChiCTR2000029559[7]	SC*, DB, RCT, phIV	Hydroxychloroquine	Placebo	Unknown
ChiCTR2000029740[8]	OL, SC*, RCT, phIV	Hydroxychloroquine	Standard treatment	Unknown
ChiCTR2000031204[9]	MC*, SB, RCT, phII	Chloroquine	Placebo	Unknown

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ChiCTR2000030987[10]	SC, RCT, phII-III	Favipiravir and chloroquine	Favipiravir or placebo	Unknown
ChiCTR2000030718[11]	SC, RCT, phIV	Chloroquine	No intervention	Unknown
ChiCTR2000029988[12]	OL, SC*, RCT, phIV	Chloroquine	Standard treatment	Unknown
ChiCTR2000029939[13]	SC*, RCT	Chloroquine	Standard treatment	Unknown
ChiCTR2000029741[14]	OL, SC*, RCT, phIV	Chloroquine	Lopinavir/Ritonavir	Unknown
NCT04286503[15]	OL, MC*, phII, RCT	Carrimycin	Lopinavir/ritonavir or arbidol or chloroquine	February 2021
NCT04261517[16]	SC*, OL, phIII, RCT	Hydroxychloroquine	Standard treatment	August 2020
NCT04315896[17]	DB[#], RCT, phIII	Hydroxychloroquine	Placebo	October 2020
NCT04318444^[18] NCT04318015[#19]	QB, RCT, phII-III	Hydroxychloroquine	Placebo	March 2021
NCT04322123[20]	OL[ν], RCT, phIII	Hydroxychloroquine	Hydroxychloroquine + azithromycin	August 2020
NCT04316377[21]	OL[§], RCT, phIV	Hydroxychloroquine	Standard care	April 2021
NCT04308668[22]	QB, MC^[¶], RCT, phIII	Hydroxychloroquine	Placebo	April 2021
NCT04328272[23]	SB, SC[▽], RCT, phIII	Hydroxychloroquine	Hydroxychloroquine + azithromycin or placebo	May 2020
NCT04328285[24]	DB, MC[□], RCT, phIII	Hydroxychloroquine or lopinavir/ritonavir	Placebo	November 2020
NCT04328012[25]	DB, SC^, RCT, phII-III	Hydroxychloroquine or lopinavir/ritonavir or losartan	Placebo	January 2021
NCT04325893[26]	DB, MC[□], RCT, phIII	Hydroxychloroquine	Placebo	September 2020
NCT04307693[27]	OL, MC[∅], RCT phII	Hydroxychloroquine or lopinavir/ritonavir	Placebo	May 2020
NCT04323631[28]	OL, MC[Σ], RCT, phI	Hydroxychloroquine	Standard care	December 2020
SOLIDARITY[29]	OL, Multicountry, RCT	Remdesivir or lopinavir/ritonavir or lopinavir/ritonavir and interferon β or hydroxychloroquine	Standard care	March 2021
NCT04333914[30]	MC[□], RCT, phII	Chloroquine analog (GNS651) or nivolumab or tocilizumab	Standard care	June 2020
NCT04304053[31]	MC[Ƴ], Cluster RCT, phIII	Chloroquine and darunavir/cobicistat or hydroxychloroquine and darunavir/cobicistat	Standard care	June 2020
NCT04303299[32]	OL[Π], RCT, phIII	Chloroquine in combination with various other antiviral regimens	Standard care	October 2020
NCT04303507[33]	DB, RCT[Ω]	Chloroquine or hydroxychloroquine	Placebo	April 2021
NCT04321278[34]	OL, MC[ν], RCT, phIII	Hydroxychloroquine and azithromycin	Hydroxychloroquine	August 2020
NCT04322396[35]	QB, SC[Ψ], RCT, phII	Hydroxychloroquine or azithromycin	Placebo	October 2020
NCT04323527[36]	QB, SC[ν], RCT, phII	Low dose chloroquine	High dose chloroquine	August 2020
NCT04324463[37]	OL[¶], RCT, phIII	Chloroquine and azithromycin	Standard care	September 2020
NCT04331600[38]	OL[¤], MC, RCT, phIV	Chloroquine	Standard care	September 2020
NCT04333732[39]	DB, MC^[ω¶θγΩ], RCT, phII	Low or mid or high dose chloroquine	Placebo	February 2021
NCT04333628[40]	OL, SC[Σ], RCT, phII–III	Chloroquine	Placebo	April 2021

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[33] ClinicalTrials.gov. Accessed: 13 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04303507?term=NCT04303507&draw=2&rank=1
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NCT04328493[41]	OL, MC[β], RCT, phII	Chloroquine	Standard care	April 2021
NCT04329611[42]	SC[¶], DB, RCT, phIII	Hydroxychloroquine	Placebo	July 2020
NCT04329832[43]	MC^, OL, RCT, phII	Hydroxychloroquine	Azithromycin	December 2020
NCT04329923[44]	OL, SC^, DB, RCT, phII	Low, mid or high dose hydroxychloroquine	Placebo	April 2021
NCT04331834[45]	SC[Y], QB, RCT, phIII	Hydroxychloroquine	Placebo	October 2020
NCT04328961[46]	SB, MC^, RCT, phI	Hydroxychloroquine	Placebo	September 2020
NCT04330495[47]	DB, RCT[Y], phIV	Hydroxychloroquine	Placebo	November 2020
NCT04332094[48]	OL, MC[Y], RCT, phII	Tocilizumab, hydroxychloroquine and azithromycin	Hydroxychloroquine and azithromycin	September 2020
NCT04332991[49]	QB, SC^, RCT, phIII	Hydroxychloroquine	Placebo	April 2021
NCT04333654[50]	DB, MC^□, RCT, phI	Hydroxychloroquine	Placebo	May 2020
NCT04335552[51]	OL, MC^, RCT, phII	Hydroxychloroquine or azithromycin alone or in combination	Standard care	August 2020
NCT04334967[52]	SB, SC^, RCT, phIV	Hydroxychloroquine	Placebo	September 2021
NCT04334148[53]	DB, SC^, RCT, phIII	Hydroxychloroquine	Placebo	July 2020
NCT04334928[54]	DB, SC[Y], RCT, phIII	Emtiricitabine with tenofovir or hydroxychloroquine alone or in combination	Placebo	June 2020
NCT04336748[55]	DB, RCT[ς], phIII	Hydroxychloroquine	Placebo	July 2020
NCT04338906[56]	QB, RCT, phIV	Camostat and hydroxychloroquine	Hydroxychloroquine and placebo	June 2021
NCT04330586[57]	OL, MC[∅], RCT, phII	Ciclesonide metered dose inhaler alone or in combination with hydroxychloroquine	Standard care	June 2020
NCT04315948[58]	OL, MC, RCT, phIII	Hydroxychloroquine or remdesivir or lopinavir/ritonavir alone or in combination with interferon ß-1a	Standard care	March 2023
NCT04328467[59]	QB, RCT^, phIII	Hydroxychloroquine	Placebo	August 2020
NCT04340544[60] NCT04342221[61]	QB, RCT[Ж], phIII	Hydroxychloroquine	Placebo	March 2021
NCT04343092[62]	DB, RCT[Д], phI	Hydroxychloroquine and ivermectin	Hydroxychloroquine and standard care	August 2020
NCT04341870[63]	OL, RCT□, phII–III	Sarilumab and azithromycin and hydroxychloroquine	Sarilumab	April 2020
NCT04341441[64]	DB, MC^, RCT, phIII	Hydroxychloroqine	Placebo	June 2020
NCT04342650[65]	DB, RCT[v], phII	Chloroquine	Placebo	September 2020
NCT04340349[66]	DB, RCT[#], phI	Hydroxychloroquine and bromhexine	Bromhexine	June 2020
NCT04342156[67]	OL, MC[†▼], RCT, phIII	Hydroxychloroquine	Standard care	August 2020
NCT04342169[68]	OL, RCT^, phII	Hydroxychloroquine	Placebo	April 2022
NCT04339816[69]	DB, MC[♦], RCT, phIII	Hydroxychloroquine or hydroxychloroquine and azithromycin	Placebo	December 2021
NCT04341727[70]	OL, MC^, RCT, phIII	Hydroxychloroquine or chloroquine in combinations with azithromycin	Hydroxychloroquine or chloroquine	April 2021
NCT04343768[71]	OL, RCT■, phIV	Hydroxychloroquine + lopinavir/ritonavir + interferon-β 1a	Hydroxychloroquine and lopinavir with ritonavir	April 2020

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[65] ClinicalTrials.gov. Accessed: 14 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04342650?term=NCT04342650&draw=2&rank=1
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[70] ClinicalTrials.gov. Accessed: 14 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04341727?term=NCT04341727&draw=2&rank=1
[71] ClinicalTrials.gov. Accessed: 14 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04343768?term=NCT04343768&draw=2&rank=1

		or hydroxychloroquine + lopinavir / ritonavir + interferon-β 1b		
ISRCTN14326006[72]	DB, MC¶, RCT, phIII	Hydroxychloroquine	Placebo	January 2022
NCT04347915[73]	OL, RCT⌀, phII	Clevudine	Hydroxychloroquine	September 2020
NCT04343677[74]	DB, RCT^, phII	Hydroxychloroquine	Placebo	June 2020
NCT04344444[75]	OL, RCT^, phIII	Hydroxychloroquine alone or in combination with azithromycin	Placebo	April 2021
NCT04345692[76]	OL, RCT^, phIII	Hydroxychloroquine	Standard care	December 2021
NCT04349228[77]	OL, RCT☼, phIII	Hydroxychloqoruine	Placebo	July 2020
NCT04346147[78]	OL, RCTʏ, phII	Hydroxychloroquine	Lopinavir/ritonavir, imatinib, baricitinib	August 2020
NCT04344379[79]	DB, MC□, RCT, phIII	Hydroxychloroquine	Azithromycin	July 2020
NCT04346667[80]	DB, RCTᵛ, phIV	Hydroxychloroquine	Chloroquine	April 2020
NCT04347512[81]	OL, RCT□, phIII	Hydroxychloroquine	Standard care	August 2021
NCT04347889[82]	OL, RCT^, phII	Hydroxychloroquine	Vitamin C	December 2020
NCT04349592[83]	DB, RCT╫	Hydroxychloroquine alone or in combination with azithromycin	Placebo	May 2020
NCT04345861[84]	DB, RCT□, phII–III	Hydroxychloroquine	Hydroxychloroquine and azithromycin	September 2020
NCT04347031[85]	OL, RCT♣, phII	Mefloquine, hydroxychloroquine, mefloquine and azithromycin ± tocilizumab or hydroxychloroquine and azithromycin ± tocilizumab	None	August 2020
NCT04345289[86]	QB, MCᵠ, RCT, phIII	Convalescent plasma, sarilumab, hydroxychloroquine, baricitinib	Placebo	June 2021
NCT04346329[87]	DB, MCᵡ, RCT, phIII	Hydroxychloroquine	Placebo	June 2020
NCT04349371[88]	QB, RCT^, phII	Chloroquine	Placebo	April 2021
ISRCTN50189673[89]	OL, MCΩ, RCT, phII–III	Lopinavir/ritonavir or dexamethasone, or hydroxychloroquine or azithromycin or tocilizumab or convalescent plasma	Standard care	June 2021
NCT04351191[90]	QB, RCTᵛ, phIV	Hydroxychloroquine regular or loading dose, chloroquine	Placebo	April 2020
NCT04351516[91]	QB, RCTᵡ, phII–III	Hydroxychloroquine	Placebo	December 2020
NCT04350281[92]	OL, RCT❁, phII	Interferon β-1b and hydroxychloroquine	Hydroxychloroquine	March 2022
NCT04351724[93]	OL, RCTς, phII–III	Chloroquine or hydroxychloroquine or lopinavir/ritonavir and multiple other interventions	Standard care	December 2020
NCT04352933[94]	QB, RCTΩ, phIII	Hydroxychloroquine	Placebo	October 2020
NCT04353271[95]	QB, RCT^, phII–III	Hydroxychloroquine	Placebo	July 2020
NCT04353037[96]	OL, RCT^, phII	Hydroxychloroquine	Placebo	April 2021
NCT04354597[97]	OL, MC╪, RCT	Hydroxychloroquine and azithromycin	None	August 2020
NCT04354428[98]	DB, MC^, RCT, phII–III	Hydroxychloroquine and azithromycin or folic acid	Placebo	July 2020
NCT04354441[99]	QB, RCT¶, phII	Hydroxychloroquine	Placebo	November 2020

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[74] ClinicalTrials.gov. Accessed: 17 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04343677?term=NCT04343677&draw=2&rank=1
[75] ClinicalTrials.gov. Accessed: 17 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04344444?term=NCT04344444&draw=2&rank=1
[76] ClinicalTrials.gov. Accessed: 17 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04345692?term=NCT04345692&draw=2&rank=1
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[78] ClinicalTrials.gov. Accessed: 17 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04346147?term=NCT04346147&draw=2&rank=1
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[80] ClinicalTrials.gov. Accessed: 17 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04346667?term=NCT04346667&draw=2&rank=1
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[82] ClinicalTrials.gov. Accessed: 21 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04347889?term=NCT04347889&draw=2&rank=1
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[84] ClinicalTrials.gov. Accessed: 21 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04345861?term=NCT04345861&draw=2&rank=1
[85] ClinicalTrials.gov. Accessed: 21 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04347031?term=NCT04347031&draw=2&rank=1
[86] ClinicalTrials.gov. Accessed: 21 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04345289?term=NCT04345289&draw=2&rank=1
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ACTRN12620000445976[100]	OL, MCω♭, RCT, phIII	Hydroxychloroquine and lopinavir/ritonavir alone or combination	Standard care	Not stated
NCT04358068[101]	DB, RCT^, phII	Hydroxychloroquine and azithromycin	Placebo	October 2020
NCT04356495[102]	OL, MC□, RCT, phIII	Hydroxychloroquine, imatinib, favipiravir, telmisartan	Vitamins	July 2020
NCT04358081[103]	DB, MC, RCT, phIII	Hydroxychloroquine alone or with azithromycin	Placebo	July 2020
ACTRN12620000417987[104]	OL, MCω, RCT, phIV	Chloroquine	Placebo	Not stated
NCT04361318[105]	DB, RCTφ, phII–III	Hydroxychloroquine and nitazoxanide	Placebo	October 2020
NCT04359537[106]	SB, RCT▽, phII	Hydroxychloroquine at various doses	Placebo	August 2020
NCT04362332[107]	OL, RCT▼, phIV	Hydroxychloroquine or chloroquine	Placebo	April 2021
NCT04359953[108]	OL, MC□, RCT, phIII	Hydroxychloroquine or azithromycin or telmisartan	Standard care	June 2021
NCT04359316[109]	DB, RCT■, phIV	Hydroxychloroquine	Azithromycin	May 2020
NCT04360759[110]	OL, MCγ, RCT, phIII	Chloroquine or hydroxychloroquine	Standard care	May 2021
NCT04359615[111]	DB, RCT■, phIV	Favipiravir and hydroxychloroquine	Hydroxychloroquine	May 2020
NCT04362189[112]	DB, SC^, RCT, phII	Allogeneic adipose-derived mesenchymal stem cells and hydroxychloroquine and azithromycin	Hydroxychloroquine and azithromycin and placebo	October 2020
NCT04359095[113]	OL, RCTϟ, phII–III	Hydroxychloroquine alone or with lopinavir or azithromycin	Standard treatment	October 2020
NCT04361422[114]	OL, RCTφ, phIII	Isotretinoin	Hydroxychloroquine and oseltamivir and azithromycin/clarithromycin	June 2020
NCT04364815[115]	DB, RCT𝕃, phIII	Hydroxychloroquine	Placebo	May 2021
NCT04365231[116]	OL, RCT□, phIII	Hydroxychloroquine	Standard treatment	June 2020
NCT04363866[117]	DB, RCT^, phIV	Hydroxychloroquine	Placebo	December 2020
NCT04371406[118]	OL, RCT□, phIII	Hydroxychloroquine and azithromycin	Dietary supplement	August 2020
NCT04372017[119]	DB, RCT^, phIII	Hydroxychloroquine	Vitamin D	April 2020
NCT04369742[120]	DB, MC^, RCT, phII	Hydroxychloroquine	Calcium citrate	June 2020
NCT04370782[121]	OL, RCT^, phIV	Hydroxychloroquine, azithromycin, and zinc	Hydroxychloroquine, doxycycline, and zine	September 2020
NCT04371926[122]	RCT^	Hydroxychloroquine	Standard treatment	June 2021
NCT04372082[123]	OL, MC□, RCT, phIII	Hydroxychloroquine or diltiazem and niclosamide	Standard treatment	May 2023
NCT04370015[124]	QB, RCT▽	Hydroxychloroquine	Placebo	July 2020
NCT04363827[125]	OL, RCT𝕀, phII	Hydroxychloroquine	None	September 2020
NCT04363450[126]	DB, MC^, RCT, phIII	Hydroxychloroquine	Placebo	July 2020
NCT04363203[127]	QB, RCT^, phIV	Hydroxychloroquine	Placebo	March 2021
NCT04370262[128]	DB, MC^, RCT, phIII	Hydroxychloroquine and famotidine or placebo	Historical control	September 2020
NCT04371523[129]	QB, MC¶, RCT, phIII	Hydroxychloroquine	Placebo	July 2020
NCT04364022[130]	OL, MC≡, RCT, phIII	Hydroxychloroquine	Lopinavir/ritonavir	October 2020

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NCT04366245[131]	OL, MC^{Y}, RCT, phI–II	Convalescent plasma	Hydroxychloroquine and azithromycin and lopinavir/ritonavir and interferon β-1b	December 2021
NCT04366089[132]	RCT‖, phII	Hydroxychloroquine and azithromycin (standard care)	Oxygen-ozone therapy, probiotic supplementation plus standard care	October 2020
NCT04365582[133]	OL, MC, RCT□, phIII	Azithromycin or hydroxychloroquine or lopinavir/ritonavir	Standard care	July 2020
NCT04374903[134]	OL, MC, RCT‡	Hydroxychloroquine and azithromycin	Hydroxychloroquine and sirolimus	August 2020
NCT04377646[135]	DB, RCT*, phIII	Hydroxychloroquine and zinc	Hydroxychloroquine or placebo	May 2020
NCT04374552[136]	DB, RCT^, phII	Hydroxychloroquine and azithromycin	Placebo	November 2020
NCT04372628[137]	DB, MC, RCT^, phII	Hydroxychloroquine	Lopinavir/ritonavir or placebo	December 2020
NCT04374019[138]	OL, RCT^, phII	Hydroxychloroquine	Hydroxychloroquine and azithromycin, or hydroxychloroquine and ivermectin, or camostat mesilate	May 2021
NCT04379492[139]	DB, RCT^, phII	Hydroxychloroquine	Placebo	May 2021
NCT04374942[140]	DB, RCT¶, phIII	Hydroxychloroquine	Placebo	August 2020
NCT04373733[141]	OL, RCTΩ, phIII	Favipiravir	Hydroxychloroquine and azithromycin and zinc, or standard care	March 2021
NCT04387760[142]	OL, RCTα, phII/III	Hydroxychloroquine	Favipiravir or standard care	July 2020
NCT04382625[143]	OL, RCT^, phIV	Hydroxychloroquine	Usual care	January 2022
NCT04392973[144]	OL, RCTλ	Hydroxychloroquine and favipiravir	Standard of care	November 2021
NCT04392128[145]	DB, RCT□, phII	Hydroxychloroquine and azithromycin	Placebo	December 2020
NCT04385264[146]	DB, RCT$^{\equiv}$, phII/III	Hydroxychloroquine	Placebo	August 2020
NCT04391127[147]	DB, RCT$^{\#}$, phIII	Hydroxychloroquine	Ivermectin or placebo	August 2020
NCT04394442[148]	OL, RCTλ, phII	Hydroxychloroquine	No intervention	August 2020
NCT04397328[149]	DB, RCT¶, phIII	Hydroxychloroquine	Placebo	April 2021
NCT04389359[150]	OL, RCTΩ, phII/III	Hydroxychloroquine	Usual care	August 2021
NCT04381988[151]	DB, RCT^, phII	Hydroxychloroquine and radiation therapy	Placebo and radiation therapy	May 2021
NCT04390594[152]	OL, RCTμ, phIII	Hydroxychloroquine	Hydroxychloroquine and azithromycin	December 2020
NCT04400019[153]	DB, RCT^{Y}, phII/III	Hydroxychloroquine	No intervention	December 2020
NCT04395768[154]	RCTω, phII	Vitamin C and active comparator treatment (hydroxychloroquine and azithromycin and zinc and vitamins D3 and B12)	Active comparator treatment	May 2021
NCT04384380[155]	OL, RCTτ, phIV	Hydroxychloroquine	Standard of care	June 2020
NCT04386070[156]	OL, RCTΩ, phIII	Lopinavir/ritonavir, or hydroxychloroquine, or both	No drug treatment	May 2021
NCT04390061[157]	OL, RCT‖, phII	Tofacitinib and hydroxychloroquine	Hydroxychloroquine	September 2020

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NCT04382846[158]	OL, RCTᵠ, phIII	Nitazoxanide and azithromycin	Ivermectin and chloroquine, or ivermectin and nitazoxanide, or nitazoxanide and ivermectin and azithromycin	December 2030
NCT04384458[159]	OL, RCTᵛ	Hydroxychloroquine	No intervention	October 2020
NCT04383717[160]	DB, RCTᵠ, phIII	Levamisole and Isoprinosine	Hydroxychloroquine and azithromycin	August 2020
NCT04390152[161]	DB, RCT≠, phI/II	Wharton's jelly derived Mesenchymal stem cells and standard therapy (hydroxychloroquine and lopinavir/ritonavir, or azithromycin and placebo)	Standard therapy (hydroxychloroquine and lopinavir/ritonavir, or azithromycin and placebo)	November 2020
NCT04381936[162]	OL, RCTΩ, phII/III	Hydroxychloroquine or lopinavir/ritonavir or corticosteroid or azithromycin or tocilizumab	Standard hospital care	December 2020
NCT04410562[163]	DB, RCTʏ, phIII	Hydroxychloroquine	Placebo	May 2021
NCT04405921[164]	OL, RCT☼, phIII	Hydroxychloroquine and azithromycin	Hydroxychloroquine and placebo	December 2020
NCT04414241[165]	OL, RCT~, phIII	Hydroxychloroquine	Standard measures of personal protection	September 2020
NCT04403555[166]	OL, RCTᵠ, phII/III	Ivermectin and doxycycline	Chloroquine	December 2030
NCT04411433[167]	OL, RCT◊, phIII	Favipiravir	Favipiravir and hydroxychloroquine, or favipiravir and azithromycin, or hydroxychloroquine, or hydroxychloroquine and azithromycin	July 2020
NCT04403100[168]	QB, RCTᵛ, phIII	Hydroxychloroquine	Lopinavir and ritonavir, or hydroxychloroquine and lopinavir and ritonavir, or placebo	August 2020
NCT04429867[169]	DB, RCT^, phIV	Hydroxychloroquine	Placebo	December 2020
NCT04428268[170]	DB, RCT#, phII	Chloroquine and losartan	Chloroquine	June 2020
NCT04420247[171]	RCTᵛ, phIII	Hydroxychloroquine or chloroquine	Standard care	May 2020
NCT04421664[172]	QB, RCT^¶, phIII	Hydroxychloroquine	Placebo	July 2020
NCT04435587[173]	RCTΠ, phIV	Ivermectin	Hydroxychloroquine and darunavir and ritonavir	June 2021
2020/00561[174]	OL, RCT†, phIII	Hydroxychloroquine	Ivermectin or povidone-iodine throat spray or zinc and vitamin C	Unknown

DB: double blind, QB: quadruple blind, SA: single arm, OL: open label, MC: multicentre, SC: single centre, RCT: randomised controlled trial, ph: phase.
Study sites in †Singapore, *China, #Mexico, ^United States, ᵛBrazil, §Norway, ¶Canada, ᵛPakistan, ⁻France, ◊Turkey, ∅South Korea, ΣIsrael, ʏSpain,ΠThailand, ΩUnited Kingdom, ΨDenmark, ¤Poland, ωAustralia, ϴIreland, ɣSouth Africa, βVietnam , ςAustria, ᵠEgypt, ϰColombia, ÞNew Zealand, ЖGermany, ДIraq, ▼Netherlands, ♦Czech Republic, ⚑Iran, ☼Tunisia, ǂQatar, ֍Hong Kong, ♠Russia, ǂJordan, ≛Slovenia, ╚Philippines, ‖Italy, ≡Switzerland, ᵅBahrain, ᴬSaudi Arabia, ᵚSenegal, ᶜTaiwan, ≠Colombia, ~Peru

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