



Should chloroquine or hydroxychloroquine be used in the prophylaxis of COVID-19?

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This rapid review summarizes the available evidence on the efficacy and safety of chloroquine or hydroxychloroquine in the prevention of COVID-19. This may change as new evidence emerges.

KEY FINDINGS

There is insufficient evidence to support the routine use of hydroxychloroquine as prophylaxis for COVID-19. Low quality evidence from 1 RCT was inconclusive for benefit but showed an increased risk for adverse events among patients given HCQ as postexposure prophylaxis.

- In-vitro studies have shown that chloroquine (CQ) and hydroxychloroquine (HCQ) are potent inhibitors of SARS-CoV2. HCQ has been used off-label as COVID-19 prophylaxis.
- Based on one RCT, HCQ did not significantly reduce laboratory-confirmed or probable COVID-19 infection among participants given HCQ as postexposure prophylaxis compared to placebo (RR 0.83, 95% CI: 0.58 to 1.18). There was an increased risk for adverse events among those who received HCQ compared to placebo (RR 2.39, 95% CI 2.83 to 3.11). Reported adverse events included gastrointestinal (nausea, abdominal discomfort or vomiting, diarrhea), and neurologic reactions (irritability, dizziness or vertigo), and headache.
- The Indian Medical Council of Medical Research recommends prophylaxis with HCQ for asymptomatic healthcare workers, asymptomatic frontline workers involved COVID-19 activities and asymptomatic household contacts, and strongly warns against a false sense of security when on chemoprophylaxis. The US-NIH does not recommend any agent for pre- or post- exposure prophylaxis for COVID-19. The Philippine Society for Microbiology and Infectious Disease (PSMID) does not recommend HCQ or CQ as preventive therapy for COVID-19.
- As of June 20, 2020, there were at least 58 clinical trials registered on ClinicalTrials.gov, which included one trial in the Philippines (NCT04364815).

DISCLAIMER: *The aim of this rapid review is to retrieve, appraise, summarize and update the available evidence on COVID-related health technology. This review has not been externally peer-reviewed; it should not replace individual clinical judgement and the sources cited should be checked. The views expressed represent the views of the authors and not necessarily those of their host institutions. The views are not a substitute for professional medical advice.*

RESULTS

Characteristics of Included Studies

We found one (1) randomized, double-blind, placebo-controlled trial (NCT04308668) on the use of hydroxychloroquine as post-exposure prophylaxis, which was conducted in the United States and Canada [1]. This trial included 821 asymptomatic adult participants with household or occupational exposure to a person with confirmed COVID-19 at a distance of less than 6 ft for more than 10 minutes wearing neither a face mask nor an eye shield or while wearing a face mask but no eye shield. Hydroxychloroquine was given as 800 mg once, then 600 mg 6 to 8 hours later, then 600 mg daily for 4 more days. The primary outcome was the incidence of either PCR-confirmed or symptomatically compatible cases of Covid-19 after 14 days of follow-up.

Appraisal of Included Studies

The study had a low risk for selection, performance and detection bias. Randomization and allocation concealment were done. The participants and outcome assessors were blinded to the treatment assignment. Intention to treat analysis was done. However, the study had a significant drop-out rate (52/821, 6.3%). Overall quality of the evidence was downgraded to low due to risk of bias and imprecision (Table 1).

Effectiveness outcome

There was no significant difference in laboratory-confirmed or probable COVID-19 infection among participants exposed to COVID-19 who received hydroxychloroquine prophylaxis compared to placebo (RR 0.83, 95% confidence interval: 0.58 to 1.18)). It should be noted that majority of the participants were diagnosed with COVID-19 based on clinical manifestations and did not undergo laboratory confirmation. There was no significant difference in hospitalization rate between the two treatment groups. No deaths were reported (Table 1).

Table 1. Summary of outcomes of hydroxychloroquine as post-exposure prophylaxis

Outcome	HCQ (%)	Placebo (%)	RR	Quality
Lab-confirmed or probable COVID infection	49/414 (11.8)	58/407 (14.3)	0.83 (0.58 to 1.18)	Low ^a
Lab-confirmed COVID	11/414 (2.7)	9/407 (2.2)	1.20 (0.50 to 2.87)	Low ^a
Symptoms compatible with COVID	48/414 (11.6)	55/407 (13.5)	0.95 (0.68 to 1.33)	Low ^a
Any hospitalization	1/414 (0.2)	1/407 (0.2)	0.98 (0.06 to 15.66)	Low ^a
Death	0	0	-	-
Adverse events	140/349 (40.1)	59/351 (16.8)	2.39 (2.83 to 3.11)	Moderate ^b

^aDowngraded 2 steps for risk of bias (significant drop-out rate) and imprecision (wide CI)

^bDowngraded 1 step for risk of bias (significant drop-out rate)

Safety Outcomes

The results of the RCT showed that HCQ significantly increased the risk for adverse events compared to placebo (RR 2.39, 95% confidence interval: 2.83 to 3.11). Common adverse events reported were gastrointestinal (nausea, abdominal discomfort or vomiting, diarrhea), neurologic (irritability, dizziness or vertigo), and headache.

Ongoing Studies

As of June 20, 2020, there were at least 58 clinical trials registered on ClinicalTrials.gov, which included one trial in the Philippines (NCT04364815). Three (3) have been withdrawn or suspended. [2-59]

Recommendations from Other Guidelines

The ministry of health of India recommends HCQ as prophylaxis for COVID-19 in the following high-risk groups:

- All asymptomatic healthcare workers involved in containment and treatment of COVID-19 and asymptomatic healthcare workers working in non-COVID hospitals/non-COVID areas of COVID hospitals/blocks
- Asymptomatic frontline workers, such as surveillance workers deployed in containment zones and paramilitary/police personnel involved in COVID-19 related activities.
- Asymptomatic household contacts of laboratory confirmed cases.

It also emphasized that prophylaxis should be coupled with infection prevention and control measures, and should not instill a false sense of security[60].

Other guidelines (WHO, CDC, Canadian, European, Australian, Chinese, Korean, Japanese) have no recommendations on chemoprophylaxis against COVID-19 because of the lack of data.

As of April 21, 2020, the US-NIH does not recommend the use of any agent as pre- and post- exposure-prophylaxis for COVID-19 outside the setting of a clinical trial [61]. The Philippine Society for Microbiology and Infectious Disease (PSMID) also does not recommend HCQ or CQ as preventive therapy for COVID-19 [62].

CONCLUSION

There is insufficient evidence to support the use of HCQ as chemoprophylaxis for COVID-19. However, HCQ showed an increased risk for adverse events. Infection prevention and control measures are still the primary methods for prevention against COVID-19.

Declaration of Conflict of Interest

LPV is participating in the ACT-COVID trial, which will investigate various therapies for COVID-19. It originally included HCQ as one of the study arms, but has since removed HCQ as a treatment after the release of the RECOVERY trial results. IGC has no relevant conflicts of interest.

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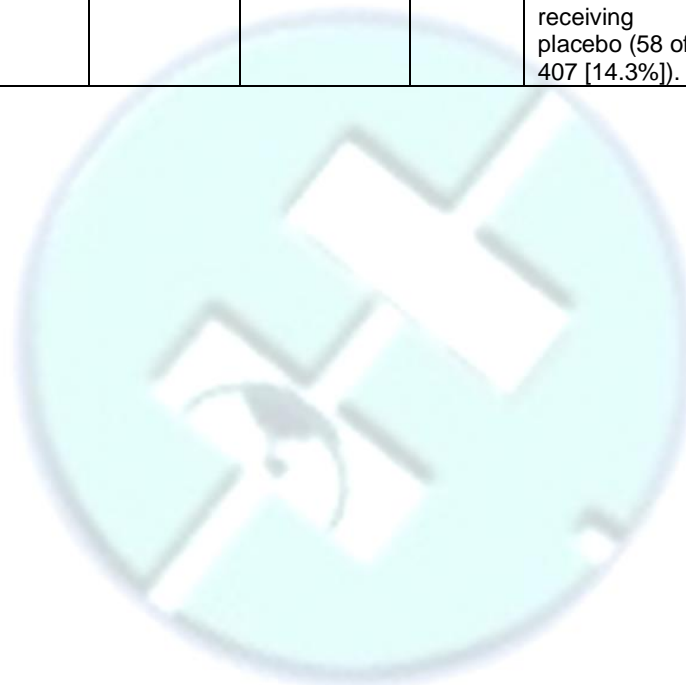
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Appendix 1: Summary of included trials

Title	Study Design	Population	Interventions	Comparator	Outcomes	Locations	Key Findings
A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19	Randomized, double-blind, placebo-controlled trial	Participants with household or occupational exposure to a person with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield or while wearing a face mask but no eye shield.	Hydroxychloroquine sulfate: 800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 3 tablets daily for 4 more days for a total course of 5 days.	Placebo folate tablets.	Symptomatic illness confirmed by a positive molecular assay or if testing was unavailable, Covid-19 related symptoms.	United States, Canada	The incidence of new illness compatible with Covid-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]).



Appendix 2: Summary of ongoing clinical trials

NCT Number	Title	Status	Interventions	Completion Date	Locations
NCT04435808	Efficacy of Hydroxychloroquine Prophylaxis for Health Care Workers at High Risk for COVID-19	Recruiting	Drug: Hydroxychloroquine	April 14, 2025	United States
NCT04421664	Preemptive Therapy for SARS-Coronavirus-2 (COVID-19 PEP Canada)	Recruiting	Drug: Hydroxychloroquine Drug: Placebo oral tablet	August 26, 2020	United States, Canada
NCT04414241	Hydroxychloroquine to Prevent SARS-CoV-2 Infection	Not yet recruiting	Drug: Hydroxychloroquine	Oct-20	Peru
NCT04410562	Hydroxychloroquine Efficacy and Safety in Preventing SARS-CoV-2 Infection and COVID-19 Disease Severity During Pregnancy	Recruiting	Drug: Hydroxychloroquine Drug: Placebo	August 1, 2021	Spain
NCT04408456	Efficacy of Hydroxychloroquine (HCQ) as Post Exposure Prophylaxis (PEP) for Prevention of COVID-19	Recruiting	Drug: HCQ Other: Standard therapy	June 30, 2020	India
NCT04400019	Prevention of COVID19 Infection in Nursing Homes by Chemoprophylaxis With Hydroxychloroquine (PREVICHARM)	Not yet recruiting	Drug: Hydroxychloroquine Only Product in Oral Dose Form	April 1, 2021	Spain
NCT04397328	COVID-19 PEP- High-risk Individuals in Long-term and Specialized Care - Canada	Not yet recruiting	Drug: Hydroxychloroquine Drug: Placebo	April 30, 2021	Canada
NCT04389359	PROphylaxis for paTIEnts at Risk of COVID-19 infecTion	Not yet recruiting	Drug: Hydroxychloroquine Sulfate 200 MG	Aug-25	United Kingdom
NCT04385264	#StayHome: Early Hydroxychloroquine to Reduce Secondary Hospitalisation and Household Transmission in COVID-19	Not yet recruiting	Drug: Hydroxychloroquine Drug: Mannitol	Oct-20	Switzerland

NCT04 384458	COVID-19 Prophylaxis With Hydroxychloroquine Associated With Zinc For High-Risk Healthcare Workers	Not yet recruiting	Drug: Hydroxychloroquine	Oct-20	Brazil
NCT04 381988	A Study of Hydroxychloroquine vs Placebo to Prevent COVID-19 Infection in Patients Receiving Radiotherapy	Recruiting	Drug: Hydroxychloroquine Other: Placebo Radiation: Radiation therapy	May-21	United States
NCT04 377646	A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers	Not yet recruiting	Drug: Hydroxychloroquine Drug: Hydroxychloroquine (placebo) Drug: Zinc Drug: Zinc (Placebo)	July 31, 2020	Tunisia
NCT04 374942	Does Hydroxychloroquine Before & During Patient Exposure Protect Healthcare Workers From Coronavirus?	Enrolling by invitation	Drug: Hydroxychloroquine Drug: Placebo oral tablet	January 30, 2022	Canada
NCT04 372017	Hydroxychloroquine as Post-Exposure Prophylaxis Against COVID-19 Infection	Active, not recruiting	Drug: Hydroxychloroquine Dietary Supplement: Vitamin D	June 4, 2021	United States
NCT04 371926	Prophylactic Benefit of Hydroxychloroquine in COVID-19 Cases With Mild to Moderate Symptoms and in Healthcare Workers With High Exposure Risk	Withdrawn	Drug: Hydroxychloroquine Sulfate	Jul-21	United States
NCT04 371523	Hydroxychloroquine to Prevent COVID-19 Disease Amongst Healthcare Workers	Not yet recruiting	Drug: Apo-Hydroxychloroquine Drug: Matched Placebo	August 30, 2020	Canada
NCT04 370015	Hydroxychloroquine Chemoprophylaxis for COVID-19 Infection in High-risk Healthcare Workers.	Not yet recruiting	Drug: Hydroxychloroquine Drug: Placebo oral tablet	October 15, 2020	Pakistan
NCT04 364815	The University of the Philippines Hydroxychloroquine PEP Against COVID-19 Trial	Not yet recruiting	Drug: Hydroxychloroquine plus standard preventive measures Drug: Placebo plus standard preventive measures	May-21	Philippines

NCT04 364022	Efficacy of Pragmatic Same-day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland	Recruiting	Drug: Hydroxychloroquine Sulfate 200 MG [Plaquenil] Drug: Lopinavir/ritonavir	Oct-20	Switzerland
NCT04 363827	Protect: Study With Hydroxychloroquine for Prevention and Early Phase Treatment of Coronavirus Disease (COVID-19)	Recruiting	Drug: Hydroxychloroquine	Mar-21	Italy
NCT04 363450	Hydroxychloroquine as Prophylaxis for COVID-19 in Healthcare Workers (HCQPreP)	Recruiting	Drug: Hydroxychloroquine Drug: Placebo	August 3, 2020	United States
NCT04 359537	Efficacy of Various Doses of Hydroxychloroquine in Pre-Exposure Prophylaxis for COVID 19	Recruiting	Drug: Hydroxychloroquine Sulfate 200 MG Other: Placebo	September 25, 2020	Pakistan
NCT04 354870	COVID-19 PrEP HCW HCQ Study	Recruiting	Drug: Hydroxychloroquine (HCQ)	September 1, 2020	United States
NCT04 354597	Hydroxychloroquine and Azithromycin as Prophylaxis for Healthcare Workers Dealing With COVID19 Patients	Not yet recruiting	Drug: HCQ & AZ	October 15, 2020	Jordan
NCT04 353037	PATCH 2&3:Prevention & Treatment of COVID-19 (Severe Acute Respiratory Syndrome Coronavirus 2) With Hydroxychloroquine	Recruiting	Drug: Group A HCQ Drug: Group B Control	June 15, 2021	United States
NCT04 352946	HEalth Care Worker pROphylaxis Against COVID-19: The HERO Trial	Not yet recruiting	Drug: Hydroxychloroquine Pre-Exposure Prophylaxis Drug: Placebo oral tablet	August 24, 2020	United States
NCT04 352933	PROLIFIC Chemoprophylaxis Trial (COVID-19)	Recruiting	Drug: Hydroxychloroquine - Daily dosing Drug: Hydroxychloroquine - Weekly Dosing Other: Matched Placebo Hydroxychloroquine	Apr-21	United Kingdom
NCT04 351191	PRophylaxis of Exposed COVID-19 Individuals With Mild Symptoms Using chloroquinE Compounds	Recruiting	Drug: Hydroxychloroquine Sulfate Regular dose Drug: Hydroxychloroquine Sulfate Loading	June 30, 2020	Pakistan

			Dose Drug: Chloroquine Drug: Placebo		
NCT04 349592	Qatar Prospective RCT Of Therapy Eliminating Covid Transmission	Not yet recruiting	Drug: Hydroxychloroquine + Azithromycin Drug: Hydroxychloroquine + Placebo Other: Placebo + Placebo	May 30, 2020	Qatar
NCT04 349228	Assessment of the Efficacy and Safety of (HCQ) as a Prophylaxis for COVID19 for Health Professionals	Recruiting	Drug: Hydroxychloroquine (HCQ) Drug: Placebo oral tablet	July 15, 2020	Tunisia
NCT04 347889	Preventing COVID-19 in Healthcare Workers With HCQ: A RCT	Not yet recruiting	Drug: Hydroxychloroquine Other: Vitamin C	December 30, 2020	United States
NCT04 346667	Post-Exposure Prophylaxis for Asymptomatic SARS- CoV-2 COVID-19 Patients With chloroquinE Compounds	Recruiting	Drug: Hydroxychloroquine Sulfate Regular dose Drug: Hydroxychloroquine Sulfate Loading Dose Drug: Chloroquine Drug: Placebo	June 30, 2021	Pakistan
NCT04 346329	Immune Monitoring of Prophylactic Effect of Hydroxychloroquine in Healthcare Providers Highly Exposed to COVID-19	Not yet recruiting	Drug: Hydroxychloroquine Drug: Placebo oral tablet	October 1, 2020	Colombia
NCT04 345653	Hydroxychloroquine as Chemoprevention for COVID-19 for High Risk Healthcare Workers	Active, not recruiting	Drug: Hydroxychloroquine Sulfate (HCQ)	April 8, 2021	United States
NCT04 344951	Chloroquine Phosphate Against Infection by the Novel Coronavirus SARS-CoV-2 (COVID- 19): The HOPE Open- Label, Non Randomized Clinical Trial	Recruiting	Drug: UNIKINON (Chloroquine phosphate) 200mg tablets	April 30, 2021	Greece
NCT04 344379	Prevention of SARS- CoV-2 in Hospital Workers s Exposed to the Virus	Suspended	Drug: hydroxychloroquine Drug: azithromycin Drug: hydroxychloroquine placebo	July 15, 2020	France

NCT04 342156	Safety And Efficacy Of Hydroxychloroquine For At Risk Population (SHARP) Against COVID-19	Not yet recruiting	Drug: Hydroxychloroquine Sulfate 200 milligram (mg) Tab	Oct-20	Singapore
NCT04 340349	Low-dose Hydroxychloroquine and Bromhexine: a Novel Regimen for COVID-19 Prophylaxis in Healthcare Professionals	Enrolling by invitation	Drug: Hydroxychloroquine Sulfate Drug: Bromhexine 8 MG	August 20, 2020	Mexico
NCT04 336748	HCQ for Primary Prophylaxis Against COVID19 in Health-care Workers	Not yet recruiting	Drug: Hydroxychloroquine	Aug-20	Austria
NCT04 335084	A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection	Not yet recruiting	Drug: Hydroxychloroquine Dietary Supplement: Vitamin C Dietary Supplement: Vitamin D Dietary Supplement: Zinc	Aug-21	United States
NCT04 334928	Randomized Clinical Trial for the Prevention of SARS-CoV-2 Infection (COVID-19) in Healthcare Personnel	Recruiting	Drug: Emtricitabine/tenofovir disoproxil Drug: Hydroxychloroquine Drug: Placebo: Emtricitabine/tenofovir disoproxil Placebo Drug: Placebo: Hydroxychloroquine	July 31, 2020	Spain
NCT04 334148	Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine	Recruiting	Drug: Hydroxychloroquine Drug: Placebo oral tablet	Jul-20	United States
NCT04 333225	Hydroxychloroquine in the Prevention of COVID-19 Infection in Healthcare Workers	Active, not recruiting	Drug: Hydroxychloroquine	July 30, 2020	United States
NCT04 331834	Pre-Exposure Prophylaxis With Hydroxychloroquine for High-Risk Healthcare Workers During the COVID-19 Pandemic	Recruiting	Drug: Hydroxychloroquine Drug: Placebos	October 30, 2020	Spain

NCT04 330495	Randomized, Controlled, Double-blind Clinical Trial Comparing the Efficacy and Safety of Chemoprophylaxis With Hydroxychloroquine in Patients Under Biological Treatment and / or JAK Inhibitors in the Prevention of SARS-CoV-2 Infection	Not yet recruiting	Drug: Hidroxicloroquina Drug: Control group	November 6, 2020	Spain
NCT04 330144	Hydroxychloroquine as Post Exposure Prophylaxis for SARS-CoV-2(HOPE Trial)	Not yet recruiting	Drug: Hydroxychloroquine as post exposure prophylaxis Other: Others(No intervention)	March 30, 2022	Korea
NCT04 329923	The PATCH Trial (Prevention And Treatment of COVID-19 With Hydroxychloroquine)	Recruiting	Drug: Hydroxychloroquine Sulfate 400 mg twice a day Drug: Hydroxychloroquine Sulfate 600 mg twice a day Drug: Hydroxychloroquine Sulfate 600 mg once a day Drug: Placebo oral tablet	December 1, 2021	United States
NCT04 329611	ALBERTA HOPE COVID-19 for the Prevention of Severe COVID19 Disease	Suspended	Drug: Hydroxychloroquine	September 30, 2020	Canada
NCT04 328961	Hydroxychloroquine for COVID-19 Post-exposure Prophylaxis (PEP)	Recruiting	Drug: Hydroxychloroquine Sulfate Drug: Ascorbic Acid	October 31, 2020	United States
NCT04 328467	Pre-exposure Prophylaxis for SARS-Coronavirus-2	Active, not recruiting	Drug: Hydroxychloroquine Other: Placebo	Aug-20	United States
NCT04 328285	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers	Active, not recruiting	Drug: Hydroxychloroquine Drug: Placebo of Hydroxychloroquine Drug: Lopinavir and ritonavir Drug: Placebo of LPV/r Tablets	November 30, 2020	France
NCT04 326725	Proflaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia	Recruiting	Drug: Plaquenil 200Mg Tablet	September 1, 2020	Turkey
NCT04 322396	Proactive Prophylaxis With Azithromycin and hydroxyChloroquine in Hospitalized Patients With COVID-19	Recruiting	Drug: Azithromycin Drug: Hydroxychloroquine Drug: Placebo oral tablet	March 31, 2021	Denmark

NCT04 318444	Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)	Recruiting	Drug: Hydroxychloroquine Drug: Placebo oral tablet	Mar-22	United States
NCT04 318015	Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)	Recruiting	Drug: Hydroxychloroquine Drug: Placebo oral tablet	March 31, 2021	Mexico
NCT04 304053	Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention	Active, not recruiting	Drug: Treatment and prophylaxis Other: Standard Public Health measures	June 15, 2020	Spain
NCT04 303507	Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting	Active, not recruiting	Drug: Chloroquine or Hydroxychloroquine Drug: Placebo	Apr-21	Thailand