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Review Article

Assessing Preventive Effects of Chloroquine or Hydroxychloroquine against COVID-19: What is the Rationale and what Clinical Trials are Running?

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Abstract

Chloroquine (CQ) and hydroxychloroquine (HCQ) have garnered considerable attention for their potential to treat or prevent the novel coronavirus disease 2019 (COVID-19) due to in vitro data and preliminary results from certain clinical studies in China and France. These molecules have a long history of use including prophylaxis. Confronted with serious complications leading to intensive care admissions and deaths, these medicines have been recommended and implemented in some risk populations. Our aim was to present the rationale for use of these medicines in chemoprophylaxis pre-exposure or post-exposure and list the clinical trials in progress to evaluate the efficacy for using these two drugs in prevention. Out of the 1324 trials registered on clinical trial.gov, 44 were devoted to CQ or HCQ in chemoprophylaxis. Most pre-exposure setting refer to the recommended dose for treatment of rheumatoid arthritis while very few refer to the recommended dose for malaria prophylaxis.

Keywords: *Corona Virus; Chloroquine; Hydroxychloroquine; Chemoprophylaxis*

The world is facing a pandemic of COVID-19, a highly contagious disease caused by a coronavirus recently discovered in China in Wuhan, Hubei province called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). As of April 26, 2020, nearly 3 million people have been diagnosed with COVID-19 and 200,000 deaths have been registered worldwide [1]. More than 80% of COVID-19 cases have been observed in Europe and the United States, which has put most health systems in difficulty. Until now, the absence of complete data on the pathophysiology of COVID-19, has meant that there is still no consensus in the scientific and medical community as regards the most effective treatment regimen. With an increasing death toll worldwide, there is an urgent need to develop treatments that can be used quickly to prevent further COVID-19 infections, transfers to intensive care and death. In addition to barrier measures to prevent the spread of the virus, chemoprevention is increasingly recommended especially in high risk populations, such as health workers. Several countries have adopted chloroquine or hydroxychloroquine and azithromycin as the standard treatment. To better protect health workers, several governments around the world, especially those developing countries with reduced capcity to monitor intensive care patients, have adopted chloroquine or hydroxychloroquine in chemoprophylaxis, whether pre-exposure or post-exposure. Chloroquine and the 4-aminoquinoline drug hydroxychloroquine belong to the same molecular family. Hydroxychloroquine differs from chloroquine by the presence of a hydroxyl group at the end of the side chain: the N -ethyl substituent is β- hydroxylate. Hydroxychloroquine has pharmacokinetics similar to that of chloroquine, with rapid gastrointestinal absorption and renal elimination [2].

We aim to present the rationale for use of these medicines in chemoprophylaxis pre-exposure or post-exposure and to list of the clinical trials in progress to evaluate effectiveness of the effective strategy for using these two molecules in prevention.

Chloroquine and hydroxychloroquine historical use

Chloroquine is a 9-aminoquinoline that has been known since 1934. Specifically, synthesized to be used as an antimalarial agent, chloroquine was subsequently shown to have immunomodulatory properties that have led to its application in the treatment of autoimmune diseases such as rheumatoid arthritis. For this specific pathology, chloroquine and its hydroxy-analogue hydroxychloroquine have represented a valid contribution to the available pharmacological tools, since they proved able to slow down the progress of the disease while showing limited toxicity [3]. For decades, chloroquine was a front-line drug for the treatment and prophylaxis of malaria and is one of the most prescribed drugs worldwide. It is an antimalarial agent with proven chemoprophylaxis properties in malaria [4].

In vitro, chloroquine appears as a bioactive agent also known to possess antiviral activity on RNA viruses such as poliovirus HIV, hepatitis A and C virus, influenza A and B viruses, influenza A H5N1 virus, Chikungunya virus, Dengue virus, Zika virus, Lassa virus and Ebola virus, as well as on DNA viruses such as hepatitis B virus and herpes simplex virus [2].

The antiviral properties of chloroquine described *in vitro* have sometimes been observed when administered to virus-infected patients but these observations have not been confirmed in clinical trials. This has mainly to do with the ways that there have been varying controls over the disease being treated, the concentration of chloroquine used, the duration of treatment and the clinical team in charge of the trial. Thus, to date, despite many promising leads *in vitro*, chloroquine or hydroxychloroquine have not demonstrated any real clinical efficacy in the treatment or prevention of viral infections [5].

Chloroquine/hydroxychloroquine interest for chemoprophylaxis in COVID-19 pandemic

Chloroquine and hydroxychloroquine are drugs that have shown activity *in vitro* on the replication of certain coronaviruses. *In vitro* experiments showed a strong antiviral effect of chloroquine on a recombinant HCoV-O43 coronavirus and Middle East respiratory syndrome coronavirus (MERS-CoV) [6,7]. In the current context of the SARS-CoV-2 coronavirus pandemic, the potential efficacy of chloroquine-based treatments, is being thoroughly examined once again. *In vitro* studies have shown that chloroquine as well as hydroxychloroquine, exhibit antiviral activity against SARS-CoV-2, with a lower EC50 for hydroxychloroquine (0.72 μM vs 5.47 μM) suggesting a more powerful effect of the drug [8]. Chloroquine has been shown to block viral infection by increasing the endosomal pH required for virus/cell fusion, as well as by interfering with the glycosylation of cellular SARS-CoV-2 receptors [2]. As regards the mechanism of action, it may be hypothesised that chloroquine also interferes with ACE2 receptor glycosylation thus preventing SARS-CoV-2 binding to target cells.

Today, preliminary data indicate that chloroquine interferes with SARS-CoV-2 attempts to acidify the lysosomes and presumably inhibits cathepsins, which require a low pH for optimal cleavage of SARS-CoV-2 spike protein, a pre-requisite to the formation of the autophagosome [9,10].

These medicines also have anti-inflammatory and immunomodulatory activity by regulating the production of TNFα, interferon and certain cytokines. HCQ or CQ are likely to attenuate the severe progression of COVID-19, inhibiting the cytokine storm by suppressing T cell activation.

These multiple possible mechanisms of action propel chloroquine and hydroxychloroquine to the rank of prominently prospective candidates for the prevention of infection by SARS-Cov-2 and thus highlighting these old and inexpensive drugs for the management of COVID-19 particularly for chemoprophylaxis adopted by many countries.

Several clinical trials are currently underway around the world to examine the effect of hydroxychloroquine or chloroquine in preventing infection.

As of May 08, 2020, out of the 1324 trials registered on clinical trial .gov website, 44 were devoted to evaluating the efficacy and safety of CQ or HCQ in chemoprophylaxis. Most pre-exposure prevention trials refer to the recommended dose for management of autoimmune

diseases such as long-term treatment of rheumatoid arthritis while very few refer to the recommended dose for prophylaxis of the malaria. One trial administered Hydroxychloroquine/Chloroquine based off of *in-vitro* pharmacokinetics study of optimal dosage for efficacy against SARS-CoV-2. In post-exposure prophylaxis setting, 800 mg loading dose followed in 6 hours by 600 mg, then 600 mg daily for 4 more days was most used (Table 1).

How did we proceed?

We downloaded the clinical trial.gov COVID-19 database on 08 May 2020 and applied our data cleaning and extraction code for covid19.trialstracker.net. Cross-registrations are removed to avoid double-counting and fields are normalized to common terms. For all current and planned studies in the final dataset (n= 1324) we extracted all interventions explicitly mentioned in the relevant registry fields. For this report card, we included every trial that mentioned CQ/HCQ as an intervention, and extracted key trial characteristics (Title, Interventions, Dose, Types of prophylaxis (pre-exposure prophylaxis (PREP), or post-exposure prophylaxis (PEP)), allocation (randomization, Non-Randomization), blinding, start date, expected completion date and the locations.

ClinicalTrials.gov Identifier	Title	Interventions	Dose	Types of prophylaxis	Allocation	Masking	Start Date	Expected Completion Date	Locations
1.NCT04364815	The University of the Philippines Hydroxychloroquine PEP Against COVID-19 Trial	Hydroxychloroquine Vs Placebo	Hydroxychloroquine loading dose of 400mg two times per day on Day 1 then 400 mg once a day for Day 2-10	PEP	Randomized	Randomized allocation concealment	May 2020	May 2021	University of the Philippines
2.NCT04364022	Efficacy of Pragmatic Same-day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland (COPEP)	Hydroxychloroquine Sulfate Vs Lopinavir/ritonavir	Hydroxychloroquine Sulfate 200 mg Single dose (PO) of 800 mg	PEP	Randomized	None (Open Label)	April 2020	October 2020	Geneva, Switzerland
3.NCT04328285	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers (COVIDAXIS)	1-Hydroxychloroquine Vs Placebo of Hydroxychloroquine 2-Lopinavir/ritonavir (LPV/r) Vs Placebo	Hydroxychloroquine 200 mg: 2 tablets on the evening at Day 1 and 2 tablets on the morning at Day 2 and 1 tablet once daily afterwards daily afterwards.	PEP	Randomized	Triple (Participant, Investigator, Outcomes Assessor)	April 14, 2020	November 30, 2020	France

4.NCT04352933	PROLIFIC Chemoprophylaxis Trial (COVID-19)	Hydroxychloroquine Vs Placebo	Daily (loading phase: 800mg for first 2 days; maintenance phase: 1 x 200mg tablet every day) for approximately 90 days/ Weekly dosing Hydroxychloroquine weekly (loading phase: 800mg for first 2 days; maintenance phase: 2 x 200 mg tablets every 7th day/ weekly) for approximately 90 days.	PrEP	Randomized	Double-blind	April 2020	April 2021	Cambridge, England
5.NCT04329923	The PATCH Trial (Prevention and Treatment of COVID-19 With Hydroxychloroquine)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine 600 mg once a day for 2 months	PEP	Randomized	Triple (Participant, Care Provider, Investigator)	April 9, 2020	December 1, 2021	University of Pennsylvania Philadelphia, Pennsylvania, United States
6.NCT04304053	Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention (HC-Q4COV19)	Hydroxychloroquine	Hydroxychloroquine (200 mg tablets) 800 mg on day 1, and 400 mg on days 2, 3, 4	PEP	Randomized	None (Open Label)	March 18, 2020	June 15, 2020	Barcelona, Spain

7.NCT04333225	Hydroxychloroquine in the Prevention of COVID-19 Infection in Healthcare Workers	Hydroxychloroquine	Hydroxychloroquine 400 mg twice a day (two 200 mg tabs twice a day) on day 1 followed by two 200 mg tablets once a week for a total of 7 weeks.	PEP	Non-Randomized	None (Open Label)	April 3, 2020	July 30, 2020	Texas, United States
8.NCT04354597	Hydroxychloroquine and Azithromycin as Prophylaxis for Healthcare Workers Dealing with COVID19 Patients (MOPHYDA)	Hydroxychloroquine and Azithromycin	Weekly HCQ 400mg X 1 Day and AZ 500m X 3 Days; weekly for 16 weeks.	PreEP	Randomized	None (Open Label)	May 1, 2020	October 15, 2020	Amman, Jordan
9.NCT04331834	Pre-Exposure Prophylaxis with Hydroxychloroquine for High-Risk Healthcare Workers During the COVID-19 Pandemic (PrEP_COVID)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine 400 mg daily during the first 4 days, followed by 400 mg weekly during 6 months	PrEP	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	April 3, 2020	October 30, 2020	Barcelona, Spain
10.NCT04371926	Prophylactic Benefit of Hydroxychloroquine in COVID-19 Cases with Mild to Moderate Symptoms and in Healthcare Workers With High Exposure Risk (PREVENT)	Hydroxychloroquine	HCQ sulfate 400mg/ week for 4 weeks	PEP	Randomized	Single (Investigator)	June 2020	July 2021	Texas, United State

11.NCT04354870	COVID-19 PrEP HCW HCQ Study	Hydroxychloroquine	Loading dose: 600 mg,1day Maintenance dose: 200 mg, daily, for 90 days	PrEP	Non-Randomized	None (Open Label)	April 3, 2020	September 1, 2020	New York, United States
12.NCT04372017	Randomized, Double-Blind,Controlled Trial of Hydroxychloroquine as Post-Exposure Prophylaxis Against COVID-19 Infection	Hydroxychloroquine Vs Placebo	Hydroxychloroquine 800 mg on day 1 followed by 400 mg on days 2-5. Hydroxychloroquine 800 mg on day 1 followed by 400 mg on days 2-5.	PEP	Randomized	Double (Participant, Investigator)	April 30, 2020	April 20, 2023	Sanford Health, South Dakota, USA
13.NCT04347889	Preventing COVID-19 in Healthcare Workers With HCQ: A RCT	Hydroxychloroquine and Vitamin C	Hydroxychloroquine 800 mg on day 1 followed by 400mg on days 2-5/ Vitamin C Oral Vitamin C 1,000 mg daily for three months	PrEP	Randomized	Single (Outcomes Assessor)	April 20, 2020	December 30, 2020	Stony Brook University, New York, USA
14.NCT04318444	Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine Two tablets (400mg) twice daily on day 1; for days 2-5, one tablet (200mg) twice daily.	PEP	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	March 29, 2020	March 2022	Columbia University Irving Medical Center New York, New York, United States

15.NCT04318015	Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine 200 mg per day for 60 days/Hydroxychloroquine 200 mg per day for 60 days	PrEP	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	April 14, 2020	December 31, 2020	Mexico, City, Mexico
16.NCT04377646	A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers (COVID-Milit)	Hydroxychloroquine Vs Placebo, Zinc Vs Placebo	Hydroxychloroquine 400 mg at day 1 and day 2, then a weekly dose of 400 mg up to 2 months. Zinc 15 mg at daily dose up to 2 months	PEP	Randomized	Triple (Participant, Care Provider, Investigator)	May 4, 2020	July 31, 2020	Military Hospital of Tunis Tunis, Tunisia
17.NCT04330144	Hydroxychloroquine as Post Exposure Prophylaxis for SARS-CoV-2(HOPE Trial)	Hydroxychloroquine	1 day: Hydroxychloroquine 800 mg; 2-5dy: Hydroxychloroquine 400 mg	PEP	Randomized	Single (Outcomes Assessor)	April 1, 2020	March 30, 2022	Gangnam Severance Hospital, Gangnam, South Corea
18.NCT04359537	Efficacy of Various Doses of Hydroxychloroquine in Pre-Exposure Prophylaxis for COVID 19 (CHEER)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine 400mg twice a day on day 1 followed by 400 mg once a week for a total of 12 weeks./ Hydroxychloroquine 400 mg on day 1 followed by 400 mg once every 3 weeks for at total of 12 weeks./ Hydroxychloroquine 200 mg on day 1 followed by 200 mg once every 3 weeks for a total of 12 weeks.	PrEP	Randomized	Single (Participant)	April 25, 2020	September 25, 2020	

19.NCT04345653	Hydroxychloroquine as Chemoprevention for COVID-19 for High Risk Healthcare Workers	Hydroxychloroquine	HCQ 400mg (2x 200mg tablets) by mouth 6-12 hours apart on day 1, followed by 3 weeks of weekly 400mg (2x 200mg tablets) by mouth	PEP	Single Group Assignment	None (Open Label)	April 14, 2020	April 8, 2022	Hackensack Meridian Health -JFK Medical Center Edison, New Jersey, United States
20.NCT04341441	Will Hydroxychloroquine Impede or Prevent COVID-19 (WHIP COVID-19)	Hydroxychloroquine Vs Placebo	Day 1 dose of 400 mg once. Following by 200 mg daily for for 7 weeks/ Hydroxychloroquine 6.5 mg/kg per dose (maximum of 400 mg per dose) weekly for 7weeks.	PrEP	Randomized	Masking: Triple (Participant, Care Provider, Investigator)	April 7, 2020	April 30, 2021	United States, Michigan Henry Ford Hospital
21.NCT04333732	CROWN CORONATION: Chloroquine repurposing to health Workers for Novel coronavirus mitigation (CROWN CORONA)	Chloroquine Vs Placebo	Low-dose (300mg chloroquine base weekly)/Medium-dose (300mg chloroquine base twice weekly)/ High-dose (150 mg chloroquine base daily) for 3 months each arm;	PrEP	Randomize	Masking: Double (Participant, Investigator)	May 2020	February 2021	United States, Missouri

22.NCT04351191	Prophylaxis of Exposed COVID-19 individuals with mild symptoms using chloroquine compounds (PRECISE)	Hydroxychloroquine/ Chloroquine Vs Placebo	Hydroxychloroquine loading dose (400 mg BID for 2 days) followed by 200 mg BID for 4 days or Chloroquine 500 mg BID for 5 days	PEP	Randomized	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	April 15, 2020	June 30, 2020	Pakistan
23.NCT04328961	Hydroxychloroquine for COVID-19 PEP	Hydrochloroquine Vs Ascorbic acid	Hydrochloroquine 400 mg for 3 days, then 200 mg daily for an additional 11 days **Vs** Ascorbic acid 500 mg orally daily for 3 days, then 250 mg orally daily for 11 days	PrEP	Randomized	Masking: Double (Participant, Investigator)	March 31, 2020	October 31, 2020	United States, California, University of California Los Angeles
24.NCT04356495	Treatments to Decrease the Risk of Hospitalization or Death in Elderly Outpatients with Symptomatic SARS-CoV-2 Infection (COVID-19) (COVERAGE)	Hydroxychloroquine Vs vitamin supplement («AZINC forme et vitalité®")	Hydroxychloroquine 2 tablets twice a day on the first day (day 0) then 2 tablets daily from day 1 to day 9/	PEP	Randomized	None (Open Label)	April 15, 2020	August 15, 2020	France
25.NCT04346667	Post-Exposure Prophylaxis for Asymptomatic SARS-CoV-2 COVID-19 Patients With chloroquine Compounds (PEACE)	Hydroxychloroquine/ Chloroquine Vs Placebo	Hydroxychloroquine loading dose (400 mg BID for 2 days) followed by 200 mg BID for 4 days/ Chloroquine 500 mg BID for 5 days	PEP	Randomized	Masking: Double (Participant, Outcomes Assessor)	April 14, 2020	June 30, 2021	Pakistan

26.NCT04303507	Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV)	Chloroquine or Hydroxychloroquine Vs Placebo	A loading dose of 10 mg base/ kg followed by 155 mg daily (250mg chloroquine phosphate or 200mg of hydroxychloroquine sulphate) for 3 months	PrEP	Randomized	Masking: Double (Participant, Investigator)	April 2020	April 2021	Asia Europe and Africa
27.NCT04334148	Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine (HEROHCQ)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine 600mg bid loading dose on day 1 followed by 400mg on days 2-30.	PrEP	Randomized	Masking: Triple (Participant, Care Provider, Investigator)	April 2020	July 2020	Duke University
28.NCT04350450	Hydroxychloroquine Treatment of Healthcare Workers with COVID19 Illness at Montefiore	Hydroxychloroquine Vs None treatment	HCQ dosing regimen of 400mg every 12 hours x 24 hours, then 400mg daily for remaining 4 days	PEP	Interventional	None (Open Label	April 2020	August 2020	United States, New York
29.NCT04363450	Hydroxychloroquine as Prophylaxis for COVID-19 in Healthcare Workers (HCQPreP) (HCQPreP)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine loading 400mg (2 capsules) twice 12 hours followed by 200mg (1 capsule) twice weekly during 12 weeks	PrEP	Randomized	Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	April 27, 2020	August 3, 2020	United States, Louisiana
30.NCT04370015	Hydroxychloroquine Chemoprophylaxis for COVID-19 Infection in High-risk Healthcare Workers.	Hydroxychloroquine Vs Placebo	hydroxychloroquine 400 mg twice a day (four 200 mg tablets) on day 1 followed by 400mg (two 200 mg tablets) once a week for 11 weeks.	PrEP	Randomized	Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	May 15, 2020	October 15, 2020	Pakistan

31.NCT04344379	Prevention of SARS-CoV-2 in Hospital Workers s Exposed to the Virus (PREP-COVID)	Hydroxychloroquine Vs Placebo Vs Azithromycin	hydroxychloroquine 200 mg BID per day during 40 days	PrEP	Randomized	Masking: Double (Participant, Investigator)	April 15, 2020	August 31, 2020	France
32.NCT04330495	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	Hydroxychloroquine Vs Placebo	hydroxychloroquine at a dose of 200 mg twice a day for 6 months.	PrEP	Randomized	Masking: Double (Participant, Investigator)	April 6, 2020	November 6, 2020	Spanish
33.NCT04335084	A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection (HELPCOVID-19)		Hydroxychloroquine Prophylaxis treatment for COVID-19 Dietary Supplement: Vitamin C Prophylaxis treatment for COVID-19 Dietary Supplement: Vitamin D Prophylaxis treatment for COVID-19 Dietary Supplement: Zinc Prophylaxis treatment for COVID-19 during 24 weeks	PrEP	Observational		April 2020	July 2021	ProgenaBiome Ventura, California, United States

34.NCT04340349	Low-dose Hydroxychloroquine and Bromhexine: a Novel Regimen for COVID-19 Prophylaxis in Healthcare Professionals (HCQINRLGII)	Hydroxychloroquine + Bromhexine Vs Placebo Bromhexine only	200 mg of Hydroxychloroquine daily for 2 months 8 mg of Bromhexine every 8 hrs for 2 months	PrEP	Randomized	Triple (Participant, Care Provider, Investigator)	April 10, 2020	July 10, 2020	Mexico
35.NCT04342156	Safety and efficacy of hydroxychloroquine for at risk population (SHARP) against COVID-19 (SHARP COVID-19)	Hydroxychloroquine Vs Untreatment group	Hydroxychloroquine sulfate. Dose: 800 mg (4 pills of 200mg) in two divided doses on day 1 followed by 400mg (2 pills of 200mg) in two divided doses on day 2, 3,4, 5.	PEP	Randomized	Masking: None (Open Label)	April 2020	October 2020	Tan Tock Seng Hospital
36.NCT04349228	Assessment of the efficacy and Safety of (HCQ) as a Prophylaxis for COVID19 for Health Professionals (COVID_2Pro)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine (HCQ) (200 mg/day) for at least 2 months	PrEP	Randomized	Open-label	April 28, 2020	July 15, 2020	Tunisia
37.NCT04342650	Chloroquine diphosphate in the prevention of SARS in Covid-19 Infection (CloroCOVID19II)	Chloroquine Vs Placebo	CQ 450 mg twice daily (3 tablets of 150 mg, every 12 hours) on day 1, followed by CQ 450 mg once daily (3 tablets of 150 mg) from D2 to D5.	PEP	Randomized	Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	April 8, 2020	September 2020	Brazil

38.NCT04308668	Pre-exposure prophylaxis for SARS-Coronavirus-2	Hydroxychloroquine Vs Placebo	800 mg once, followed in 6 to 8 hours by 600 mg, then 600 mg once a day for 4 consecutive days	PEP	Randomized	Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	March 17, 2020	May 14, 2020	United States, Minnesota
39.NCT04328467	Pre-exposure prophylaxis for SARS-Coronavirus-2	Hydroxychloroquine Vs Placebo	400 mg once, followed by 400 mg 6 to 8 hours later, thereafter 400mg weekly for the duration of follow up, up to 12 weeks/400 mg once, followed by 400mg 6 to 8 hours later, thereafter 400 mg twice weekly for the duration of follow up, up to 12 weeks	PrEP	Randomized	Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	April 6, 2020	August 2020	United States, Minnesota
40.NCT04322123	Safety and efficacy of hydroxychloroquine associated with azithromycin in SARS-Cov-2 Virus (COVID-19) (Coalition-I)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine [400 mg 2x/day, 12/12h] for 07 days. Hydroxychloroquine [400 mg 2x/day, 12/12h] + azithromycin [500 mg 1x/day]) for 07 days.	PEP	Randomized	None (Open Label)	April 1, 2020	August 30, 2020	Hospital Geral Clériston Andrade Feira De Santana, BA, Brazil

41.NCT04353037	PATCH 2&3: Prevention & treatment of COVID-19 (Severe acute respiratory syndrome coronavirus 2) with hydroxychloroquine	Hydroxychloroquine Vs Placebo	Hydroxychloroquine 600 mg once a day (three 200 mg tablets once a day) for up to 2 months	PrEP	Randomized	Masking: Double (Participant, Care Provider)	April 7, 2020	June 15, 2021	United States, New York
42.NCT04336748	HCQ for primary prophylaxis against COVID19 in health-care workers	Hydroxychloroquine Vs Placebo	Low dose (200 mg) Hydroxychloroquine once daily for 4 weeks	PrEP	Randomized	Masking: Triple (Participant, Care Provider, Investigator)	April 2020	August 2020	No Contacts or Locations Provided
43.NCT04374942	Does hydroxychloroquine before and during patient exposure protect healthcare workers from coronavirus? (HEROs)	Hydroxychloroquine Vs Placebo	400 mg hydroxychloroquine orally once a day for three months (Day 1-90).	PrEP	Randomized	Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	April 30, 2020	January 30, 2022	Canada, Ontario
44.NCT04346329	Immune monitoring of prophylactic effect of hydroxychloroquine in healthcare providers highly exposed to COVID-19 (Chloroquine UN)	Hydroxychloroquine Vs Placebo	Hydroxychloroquine with a loading dose of 800 mg of hydroxychloroquine the first day followed by 400 mg/ week for 90 days		Randomized	Masking: Double (Participant, Care Provider)	April 20, 2020	October 1, 2020	Colombia

Table 1: *Summary of ongoing clinical trials for chemoprophylaxis with Hydroxychloroquine or Chloroquine up to April, 8th, 2020. PEP: Post-Exposure-Prophylaxis; PrEP: Pre-Exposure-Prophylaxis.*

Conclusion

Chloroquine and hydroxychloroquine have the capacity to inhibit the pH-dependent entry of SARS-Cov-2 into host cells, or even to block the replication of enveloped virus by inhibiting the glycosylation of envelope proteins. They also have anti-inflammatory and immunomodulatory activity. In addition, CQ and HCQ are cheaper and more readily available. These properties support strategies using Chloroquine or hydroxychloroquine in pre-exposure or post exposure chemoprophylaxis. Several clinical trials are currently underway around the world to confirm or refute this indication. However, the favorable natural course of COVID-19 infection in more than 80% of cases can make it difficult to demonstrate a possible protective effect of these two drugs.

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