Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Eduardo García-Pachón[a,b,*], Lucía Zamora-Molina[a], María J. Soler-Sempere[a], Carlos Baeza-Martínez[a], Justo Grau-Delgado[a], Isabel Padilla-Navas[a], Félix Gutiérrez[b,c]

[a] *Sección de Neumología, Hospital General Universitario de Elche, Elche, Alicante, Spain*
[b] *Departamento de Medicina Clínica, Universidad Miguel Hernández, Elche, Alicante, Spain*
[c] *Servicio de Medicina Interna, Hospital General Universitario de Elche, Elche, Alicante, Spain*

Corresponding author.
E-mail address: eduardo.garciap@umh.es (E. García-Pachón).

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Hydroxychloroquine as Prophylaxis for Coronavirus SARS-CoV-2 Infection: Review of the Ongoing Clinical Trials

Hidroxicloroquina como profilaxis para la infección por coronavirus SARS-CoV-2: revisión de los ensayos clínicos en curso

Dear Editor:

At the time of writing this document the entire planet is facing the pandemic caused by the SARS-CoV-2 virus. Contrary to the initial thoughts that most infected patients had symptoms, according to data from China collected in April 2020, at the time of the diagnosis, up to 80% of those confirmed to have the disease are asymptomatic, becoming an important source of contagion.[1–3] Pan et al. reported that health workers in Wuhan (China) had a significantly higher risk of becoming infected (daily confirmed case rate in local health care workers was 130.5 per million while in the general population it was 41.5 per million).[4]

In this light, the scientific community is discussing the use of chemoprophylaxis in people at higher risk of infection using several alternatives including antimalarials (chloroquine or hydroxychloroquine) and antiretrovirals (lopinavir-ritonavir).[5–10] There is an increased interest in use of chloroquine and hydroxychloroquine, two medications that have experimentally shown to have antiviral capabilities and prophylactic potential.[11,12] Lee et al. recently reported good results in an observational study in South Korea after a large COVID-19 exposure event in a hospital. At the end of quarantine, after receiving post-exposure prophylaxis with hydroxychloroquine (400 mg daily for 14 days) all follow-up PCR tests were negative in 211 individuals exposed to the index case.[13] Certain countries have already adopted chemoprophylaxis schemes; on March 22nd, 2020, the Indian Council of Medical Research's National Task Force for COVID-19 issued a national recommendation to use hydroxychloroquine for prophylaxis against SARS-CoV-2 infection (400 mg twice a day on day 1, followed by 400 mg once weekly for 7 weeks).[14]

We conducted a search (updated to April 15th, 2020) on the website https://clinicaltrials.gov/. Using the keywords COVID-19 and hydroxychloroquine we found a total of 90 projects registered. Twenty-five of those projects included the use of prophylaxis in non-infected population (Table 1)

Institutions from 13 countries are leading those projects, 13 of them from the United States, 2 from Mexico, 2 from Spain and 2 from France. Turkey, Colombia, Austria, South Korea, Singapore, United Kingdom, Thailand, Australia and Canada, have institutions leading one project (there are more institutions than projects, because some have shared leadership).

There is a significant variability in the number of participants among the studies. The estimated number of participants to be enrolled ranges between 45 and 55,000 with an average of $5588 \pm 13{,}139.2$, and a median of 1212 participants. Only 3 (12%) studies plan to enroll more than 4000 participants; those 3 studies will include 70,000 participants which corresponds to 50.1% of the total potential recruitment of the 25 protocols (NCT04334148, NCT04303507 and NCT04333732).

There is a significant variability among protocols regarding hydroxychloroquine maintenance dose, which will be between 200 and 600 mg. The frequency is also highly variable: seventeen protocols will use daily prophylaxis for a period from 4 days to 12 weeks and 9 protocols plan to evaluate weekly use for a period of 3 to 24 weeks. Thirteen (52% of 25) protocols will use an initial loading dose ranging between 400–1400 mg taken on the first day. In three other protocols, 2–4 days of loading doses of 400 mg/day will be indicated.

19 clinical trials will evaluate pre-exposure prophylaxis and 6 post-exposure prophylaxis. In 9 of the pre-exposure prophylaxis studies and 4 of the post-exposure prophylaxis studies, a loading dose of 800 mg of hydroxychloroquine will be started on the first day. In an additional multicenter pre-exposure prophylaxis study, which plans to recruit 15,000 participants (NCT04334148), they will use a higher loading dose on the first day: 1200 mg of hydroxychloroquine.

We evaluated the exclusion criteria among protocols by grouping into several possible categories. Most common criteria used by protocols to exclude patients comprised allergies to 4-aminoquinolines (hydroxychloroquine, chloroquine) in 20 studies (80%); retinopathy in 19 (76%); history of a prolonged QT syndrome, use of medications that prolong the QT/QTc interval or risk factors for torsades de pointe in 17 (68%); nephropathy in 16 (64%); pregnancy or breastfeeding in 14 (56%); concomitant use of other medications with potential pharmacological interaction with 4-aminoquinolines in 13 (52%); liver disease in 13 (52%); psoriasis

Table 1
Clinical studies about chemoprophylaxis for coronavirus disease (COVID-19) registered on ClinicalTrials.gov (April 15th, 2020).

No	Clinical trial	ClinicalTrials.gov Identifier	Intervention (Hydroxychloroquine sulphate dose)	Estimated enrollment	Locations
1	Hydroxychloroquine in the Prevention of COVID-19 Infection in Healthcare Workers	NCT04333225	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.	360	Baylor University Medical Center, Dallas, Texas, United States
2	Pre-Exposure Prophylaxis With Hydroxychloroquine for High-Risk Healthcare Workers During the COVID-19 Pandemic	NCT04331834	400 mg daily during the first 4 days, followed by 400 mg weekly during 6 months	440	ISGlobal, Barcelona, Spain
3	Military COVID-19 Hydroxychloroquine Pre-exposure and Post-exposure Prophylaxis Study	NCT04343677	Daily dosing of hydroxychloroquine (between 200 and 400 mg)	1450	Pentagon Arlington, Virginia, United States
4	Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)	NCT04318444	400 mg twice daily on day 1; for days 2–5, 200 mg twice daily.	1600	Columbia University Irving Medical Center New York, New York, United States
5	The PATCH Trial (Prevention And Treatment of COVID-19 With Hydroxychloroquine) – Cohort 3	NCT04329923	600 mg once a day for 2 months	400	University of Pennsylvania, Philadelphia, Pennsylvania, United States
6	Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)	NCT04318015	200 mg per day for 60 days.	400	National Institute of Respiratory Diseases, Mexico City, Mexico
7	Hydroxychloroquine as Post Exposure Prophylaxis for SARS-CoV-2(HOPE Trial)	NCT04330144	First day: 800 mg. Days 2–5: 400 mg daily	2486	Gangnam Severance Hospital, Seoul, South Korea
8	Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine	NCT04334148	600 mg bid loading dose on day 1 followed by 400 mg on days 2–30.	15,000	Duke University, Durham, North Caroline, United States (multicenter)
9	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers	NCT04328285	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 for 2 months	600	CHU d'Angers, Angers, France. AP-HP – Hôpital Bichat, Paris, France. CHU de Saint-Etienne, Saint-Étienne, France
10	Hydroxychloroquine for COVID-19 PEP	NCT04328961	400 mg orally daily for 3 days, then 200 mg orally daily for an additional 11 days	2000	NYU Langone Health, New York, New York, United States. University of Washington, Coordinating Center, Seattle, Washington, United States. UW Virology Research Clinic Seattle, Washington, United States
11	Hydroxychloroquine as Chemoprevention for COVID-19 for High Risk Healthcare Workers	NCT04345653	400 mg (2× 200 mg tablets) by mouth 6–12 h apart on day 1, followed by 3 weeks of weekly 400 mg (2× 200 mg tablets) by mouth	45	Hackensack Meridian Health - JFK Medical Center, Edison, New Jersey, United States
12	Chloroquine/Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting	NCT04303507	A loading dose 12.9 mg/kg (i.e. usually between 700 and 900 mg). Then 200 mg daily for 3 months	40,000	University of Oxford, Oxford, England. Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand. (multicenter).
13	A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection	NCT04335084	Medication doses are not indicated	600	ProgenaBiome, Ventura, California, United States
14	Will Hydroxychloroquine Impede or Prevent COVID-19	NCT04341441	Daily treatment arm: day 1, 400 mg once and then 200 mg daily for 8 weeks. Once weekly arm: 6.5 mg/kg per dose (maximum of 400 mg per dose) weekly fro 8 weeks.	3000	Henry Ford Hospital, Detroit, Michigan, United States. Detroit Department of Transportation (DDOT) Detroit, Michigan, United States. Detroit Fire Department & Detroit EMS, Detroit, Michigan, United States. Detroit Police Department, Detroit, Michigan, United States
15	Low-dose Hydroxychloroquine and Bromhexine: a Novel Regimen for COVID-19 Prophylaxis in Healthcare Professionals	NCT04340349	Hydroxychloroquine plus Bromhexine: 200 mg of Hydroxychloroquine daily for 2 months and 8 mg of Bromhexine every 8 h for 2 months.	100	National Institute of Rehabilitation, Mexico City, Mexico
16	Safety And Efficacy Of Hydroxychloroquine As COVID-19 Prophylaxis For At-Risk Population (SHARP): A Cluster Randomized Controlled Trial	NCT04342156	800 mg as single dose on day 1 followed by 400 mg single dose on days 2–5.	3000	Singapore: Tan Tock Seng Hospital National Center for Infectious Diseases Singapore Clinical Research Institute Singapore Eye Research Institute. Saw Swee Hock School of Public Health Duke-NUS Graduate Medical School. Netherlands: Ministry of Health, Welfare and Sports.
17	Prophylactic Hydroxychloroquine vs Vitamin C in Healthcare Workers:RCT	NCT04347889	Oral loading dose of 800 mg followed by once weekly 400 mg for 3 months. Active Comparator: Vitamin C 1000 mg daily for three months.	1212	Stony Brook University, New York, United States
18	CROWN CORONATION: Chloroquine RepurpOsing to healthWorkers for Novel CORONAvirus mitigaTION	NCT04333732	Induction dose:1200 mg chloroquine or hydroxychloroquine in 4 divided daily doses, followed by three treatment arms: low-dose (300 mg chloroquine or hydroxychloroquine base weekly); medium-dose (300 mg chloroquine or hydroxychloroquine base twice weekly); and high-dose (150 mg chloroquine or hydroxychloroquine base daily) fo 3 months.	55,000	Washington University School of Medicine Saint Louis, Missouri, United States. Melbourne Medical School Melbourne, Victoria, Australia. Population Health Research Institute Hamilton, Ontario, Canada. (Multicenter)
19	Prevention of SARS-CoV-2 in Hospital Workers s Exposed to the Virus	NCT04344379	200 mg BID per day for 40 days; active comparator: azythromycin.	900	Hôpital GHU Paris Saclay Boulogne-Billancourt, France. Hôpital Saint Antoine Paris, France. Hôpital Broca Paris, France (Multicenter)
20	Proflaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia	NCT04326725	Participants have been started hydroxychloroquine 200 mg single dose repeated every three weeks plus vitaminC including zinc once a day	80	Istinye University Medical School Istanbul, Turkey
21	Randomized Clinical Trial for the Prevention of SARS-CoV-2 Infection (COVID-19) in Healthcare Personnel	NCT04334928	Arm 1: Tenofovir Disoproxil Fumarate 245 mg/Emtricitabine 200 mg + Placebo. Arm 2:Hydroxychloroquine 200 mg once a day + Placebo. Arm 3: Tenofovir Disoproxil Fumarate 245 mg/Emtricitabine 200 mg + Hydroxychloroquine 200 mg (once a day). All the treatments for 12 weeks.	4000	Hospital Universitario Ramón y Cajal, Madrid, Spain
22	HCQ for Primary Prophylaxis Against COVID19 in Health-care Workers	NCT04336748	200 mg once daily for 4 weeks	440	Medical University of Vienna, Vienna, Austria
23	Immune Monitoring of Prophylactic Effect of Hydroxychloroquine in Healthcare Providers Highly Exposed to COVID-19	NCT04346329	Loading dose of 800 mg the first day followed by 400 mg/week for 90 days	86	Facultad de Medicina – Universidad Nacional de Colombia, Bogota, Cundinamarca, Colombia.
24	Pre-exposure Prophylaxis for SARS-Coronavirus-2	NCT04328467	Arm 1: 400 mg orally once, followed by 400 mg 6–8 h later, thereafter 400 mg weekly for the duration of follow up, up to 12 weeks. Arm 2: 400 mg orally once, followed by 400 mg 6–8 h later, thereafter 400 mg twice weekly for the duration of follow up, up to 12 weeks	3500	University of Minnesota, Minneapolis, Minnesota, United States
25	Post-exposure Prophylaxis/Preemptive Therapy for SARS-Coronavirus-2	NCT04308668	800 mg orally once, followed in 6–8 h by 600 mg, then 600 mg once a day for 4 consecutive days	3000	University of Minnesota, Minneapolis, Minnesota, United States.

or porphyria in 11 (44%) and glucose-6-phosphate dehydrogenase deficiency in 9 protocols (36%).

We used only clinicaltrials.gov to search the trials, which is a weakness of our study, because several protocols may be lost (those registered on https://www.clinicaltrialsregister.eu/, http://www.chictr.org.cn/index.aspx or https://apps.who.int/trialsearch/). However, due to the rapidity of the events related to the COVID-19 pandemic, we consider that the initial publication of the review including only those registered on clinicaltrials.gov is warranted, in order to give clinicians a preliminary picture.

According to the World Health Organization, as of April 15th, 2020, there are almost 2 million confirmed cases of SARS-CoV-2 virus in 213 countries and territories, but this is a underestimation, because as mentioned, around 80% of the infected people could be asymptomatic and go undetected.[4] A high infection rate among health care workers would not only exacerbate the impending shortage of health care facilities and health personnel but would also increase the possibility of a more widespread dissemination.[5] However, the current scientific evidence is still not conclusive for institutions and governments to adopt a general recommendation regarding the prophylactic use of hydroxychloroquine chemoprophylaxis in healthcare workers.

Chloroquine and its derivatives (e.g., hydroxychloroquine) have been used for malaria and autoimmune rheumatic diseases for almost 80 years, and both the data from the literature and the experience of clinicians show a low incidence of side effects, which are generally mild to moderate. Retinal toxicity, a serious effect, is related to long-term cumulative dose, and is rarely seen in short-term use (i.e. several weeks).[9,15]

These arguments perhaps tip the balance in favor of using prophylaxis for SARS-CoV-2 virus infection, as long as they are not contraindicated. Nonetheless we are yet to know the results of these clinical trials.

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Virgilio Galvis[a,b,c], Francesca Romana Spinelli[d], Alejandro Tello[a,b,c,*], Claudia L. Sossa[b,c], Juan D. Higuera[b,c], Edgar D. Gómez[b,c], Sergio E. Serrano[c], Paul A. Camacho[b,c], Federico G. Velez[e,f]

[a] *Centro Oftalmológico Virgilio Galvis, Floridablanca, Colombia*
[b] *Fundación Oftalmológica de Santander FOSCAL, Floridablanca, Colombia*
[c] *Faculty of Health Sciences, Universidad Autónoma de Bucaramanga UNAB, Bucaramanga, Colombia*
[d] *Department of Clinical Sciences, Internal Medicine, Anesthesiology and Cardiovascular Diseases – Rheumatology, Sapienza University of Rome, Rome, Italy*
[e] *Department of Ophthalmology, University of California Los Angeles, Los Angeles, California, United States*
[f] *Department of Ophthalmology, Duke University, Durham, North Carolina, United States*

[*] Corresponding author.
E-mail address: alejandrotello@gmail.com (A. Tello).

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