

Safety of Hydroxychloroquine Among Outpatient Clinical Trial Participants for COVID-19

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Background. Use of hydroxychloroquine in hospitalized patients with coronavirus disease 2019 (COVID-19), especially in combination with azithromycin, has raised safety concerns. Here, we report safety data from 3 outpatient randomized clinical trials.

Methods. We conducted 3 randomized, double-blind, placebo-controlled trials investigating hydroxychloroquine as pre-exposure prophylaxis, postexposure prophylaxis, and early treatment for COVID-19 using an internet-based design. We excluded individuals with contraindications to hydroxychloroquine. We collected side effects and serious adverse events. We report descriptive analyses of our findings.

Results. We enrolled 2795 participants. The median age of research participants (interquartile range) was 40 (34–49) years, and 59% (1633/2767) reported no chronic medical conditions. Overall 2544 (91%) participants reported side effect data, and 748 (29%) reported at least 1 medication side effect. Side effects were reported in 40% with once-daily, 36% with twice-weekly, 31% with once-weekly hydroxychloroquine, compared with 19% with placebo. The most common side effects were upset stomach or nausea (25% with once-daily, 19% with twice-weekly, and 18% with once-weekly hydroxychloroquine, vs 11% for placebo), followed by diarrhea, vomiting, or abdominal pain (23% for once-daily, 17% twice-weekly, and 13% once-weekly hydroxychloroquine, vs 7% for placebo). Two individuals were hospitalized for atrial arrhythmias, 1 on placebo and 1 on twice-weekly hydroxychloroquine. No sudden deaths occurred.

Conclusions. Data from 3 outpatient COVID-19 trials demonstrated that gastrointestinal side effects were common but mild with the use of hydroxychloroquine, while serious side effects were rare. No deaths occurred related to hydroxychloroquine. Randomized clinical trials, in cohorts of healthy outpatients, can safely investigate whether hydroxychloroquine is efficacious for COVID-19.

ClinicalTrials.gov Identifier. NCT04308668 for postexposure prophylaxis and early treatment trials; NCT04328467 for pre-exposure prophylaxis trial.

Keywords: COVID-19; hydroxychloroquine; safety; SARS-CoV-2; side effects.

Hydroxychloroquine has in vitro antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. While in vitro data suggest that both chloroquine and hydroxychloroquine have activity against SARS-CoV-2 replication, the latter is generally considered less toxic and better tolerated. However, clinical data to date demonstrate no conclusive efficacy of hydroxychloroquine for the treatment or prevention of coronavirus disease 2019 (COVID-19) [3–5]. Both

chloroquine and hydroxychloroquine impede SARS-CoV-2 replication [2]. Several randomized placebo-controlled clinical trials are underway to evaluate hydroxychloroquine's safety and efficacy in the prevention and treatment of COVID-19 in both inpatient and outpatient populations [6].

In late March 2020, hydroxychloroquine had substantial positive coverage in the media. However, the tide rapidly turned due to concerted efforts to inform physicians and patients about the potential risks of taking the drug outside of clinical trial settings [7]. Several inpatient treatment studies then went on to show increased cardiac side effects with hydroxychloroquine and azithromycin [8, 9]. On April 24, 2020, the US Food and Drug Administration (FDA) issued a caution against chloroquine and hydroxychloroquine in the treatment of COVID-19 outside of hospital settings or clinical trials [10]. The FDA stated, "Hydroxychloroquine and chloroquine can cause abnormal heart rhythms such as QT interval prolongation and... ventricular tachycardia." The FDA noted that QT prolongation

Received 17 July 2020; editorial decision 13 October 2020; accepted 15 October 2020.

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Open Forum Infectious Diseases® 2020

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DOI: 10.1093/ofid/ofaa500

was more common among persons receiving azithromycin and those with prior heart problems or kidney disease.

Hydroxychloroquine nonetheless has a 65-year track record of safety when prescribed at recommended doses in populations with normal liver and kidney function and without preexisting cardiac arrhythmias [11]. In the medical specialties of tropical medicine and rheumatology, chloroquine and hydroxychloroquine have routinely been prescribed without baseline laboratory testing or electrocardiogram (EKG) monitoring. Whether these tests should be performed in the setting of hydroxychloroquine for COVID-19 is controversial. As it stands, a number of ongoing clinical trials have been paused or halted by regulatory authorities over concerns related to the potential for QT prolongation. Importantly, these safety concerns have risen from reports of hydroxychloroquine use in hospitalized patients, who are more likely to have severe infections, significant comorbidities, and be on multiple concurrent medications [12].

There are some features of the SARS-CoV-2 virus that may predispose individuals with COVID-19 to be more likely to have complications from drugs that prolong the QT than healthy individuals. SARS-CoV-2 itself can enter cardiomyocytes and may cause direct cardiac injury [13–15]. Multiple reports of increased arrhythmias in individuals with COVID-19 without other causes suggest that SARS-CoV-2 itself may cause arrhythmias [15]. Alternatively, elevated cytokines, directly or in concert with cardiomyocyte damage, may predispose to arrhythmias [16]. Additionally, COVID-19 is associated with significant electrolyte imbalances, including sodium, potassium, and calcium, as well as renal failure, each of which also predisposes individuals to arrhythmias [15, 17]. Therefore, testing the safety of hydroxychloroquine in individuals with COVID-19 specifically is valuable.

The safety of hydroxychloroquine use for COVID-19 in outpatients has not been established but is believed to be less risky in outpatients than inpatients [18]. To address current knowledge gaps regarding the safety and tolerability of hydroxychloroquine in the outpatient prevention and treatment of COVID-19 and to inform its future usage in the setting of clinical trials, we present the safety data from 3 randomized placebo-controlled clinical trials of hydroxychloroquine in North America.

METHODS

Study Design

We conducted 3 randomized, double-blind, placebo-controlled trials investigating hydroxychloroquine as prophylaxis and treatment for COVID-19 disease. The first 2 trials evaluated (1) postexposure prophylaxis (PEP) and (2) preemptive early treatment (PET; ClinicalTrials.gov Identifier: NCT04308668) [3, 19]. Trial enrollment began on March 17, 2020, and concluded on May 6, and follow-up was completed on May 20,

2020. The third trial assessed pre-exposure prophylaxis (PREP) for COVID-19 (ClinicalTrials.gov Identifier: NCT04328467). Enrollment for this third trial began April 6 and ended May 26, 2020, with follow-up concluding on July 13, 2020 [20].

In each of these trials, participants were randomized to receive placebo or hydroxychloroquine. The PEP trial required participants to have a known exposure to a lab-confirmed COVID-19 case within 4 days either as a household contact or as a health care worker or first responder. The PET trial enrolled persons with COVID-19 symptoms of 4 or fewer days' duration and either lab-confirmed SARS-CoV-2 or high-risk exposure to a known case within 14 days of symptom onset. The PREP required persons to be high-risk health care workers or first responders with ongoing occupational exposure to COVID-19.

Hydroxychloroquine dosing for both the PEP and PET trials was 800 mg load dosing, followed by 600 mg 6–8 hours later, and then 600 mg daily for 5 days in total. Participants were instructed to split their follow-up dosing in the event of gastrointestinal upset. In designing the trials, investigators chose doses within the existing FDA-approved dosing range that were modeled to achieve therapeutic concentrations from days 1 through 10 [21]. Hydroxychloroquine dosing for PREP was dosed at 400 mg orally once, followed by 400 mg 6 to 8 hours later, and thereafter 400 mg weekly or twice weekly for the duration of follow-up, up to 12 weeks. The placebo was dosed similarly.

Study Participants

Participants were enrolled in the 3 trials via internet-based surveys throughout the United States and selected Canadian provinces. Full details are online (ClinicalTrials.gov Identifiers: NCT04308668, NCT04328467) [3]. Participants were excluded if they were <18 years old, had an allergy to hydroxychloroquine, retinal eye disease, known glucose-6 phosphate dehydrogenase (G6PD) deficiency, known chronic kidney disease that was stage 4 or 5 or receiving dialysis, known porphyria, weight <40 kg, known QT prolongation, or receiving chemotherapy. Current use of hydroxychloroquine, azithromycin, or cardiac arrhythmia medicines (flecainide, amiodarone, digoxin, procainamide, propafenone, or sotalol) was also an exclusion criterion. On April 20, 2020, the FDA required additional exclusions of structural or ischemic heart disease and personal or family history of cardiac QT prolongation and medications that prolong the QTc interval.

Health Canada mandated additional exclusions for Canadian participants. Women who were pregnant or breastfeeding were excluded, as were patients with severe diarrhea or vomiting; known cirrhosis with a history of encephalopathy or ascites; known prolonged cardiac QTc interval, history of ventricular arrhythmia, or history of sudden cardiac death; patients taking additional medicines that had a high risk of prolonging the electrocardiogram QTc interval in conjunction with hydroxychloroquine. The Institutional Review

Board (IRB) in Ontario also mandated that a physician perform a complete review of medications for participants above age 65, to exclude those with important drug–drug interactions.

Participants in the PEP and PET trials completed follow-up email surveys on days 1, 3, 5, 10, and 14, whereas participants in the PREP trial completed weekly follow-up surveys. Surveys obtained self-report of study drug adherence, side effects, new COVID-19 symptoms, new COVID-19 testing, and hospitalization. For participants who stopped their study drug due to side effects or for other reasons, we encouraged them to continue observational follow-up and completion of self-report surveys.

Statistical Analysis

The analysis presented is primarily descriptive, summarizing the frequency of reported medication side effects and medication-related serious adverse events, such as hospitalization, life-threatening events, or deaths.

Patient Consent Statement

The participant's written consent was obtained. IRB approval of the design of the work occurred at McGill University, Clinical Trials Ontario, the University of Manitoba, the University of Alberta, and the University of Minnesota.

RESULTS

A total of 2795 individuals were enrolled into the 3 trials. The combined median age (interquartile range [IQR]) was 40 (34–49) years, and 51% were women. The median weight (IQR) was 79 (66–91) kg. The majority of participants (74%) were health care workers and first responders. Approximately 66% of the participants were taking no chronic medications, and 59% had no chronic medical conditions. Demographic data are displayed in Table 1.

Postexposure Prophylaxis and Early Treatment Trials

Of 1312 ($n = 821$ PEP; $n = 491$ PET) participants randomized, 87% ($n = 1139$) started the study drug and completed follow-up surveys. Of 130 participants who started the drug but did not complete follow-up, vital status was obtained for 32% (42/130), and all were alive. For the remainder, we performed an internet search for death records and found none.

Of 1139 who started the study drug and reported side effect data, 29% reported 1 or more side effects, with more side effects reported among those on hydroxychloroquine (40%) vs placebo (18%) (Table 2). The most common side effects reported were upset stomach or nausea (25% on hydroxychloroquine vs 9% on placebo), followed by vomiting, diarrhea, or other gastrointestinal (GI) symptoms (23% on hydroxychloroquine vs 6% on placebo), and neurologic reactions, such as lightheadedness or dizziness (7% on hydroxychloroquine vs 5% on placebo). Self-reported allergic reactions occurred in 7 participants (6 on

Table 1. Baseline Demographics for all 3 Cohorts: Postexposure Prophylaxis, Preemptive Early Treatment, and Pre-exposure Prophylaxis

Demographic	No. (%) or Median [IQR]
No. of participants	2795
Age, y	40 [34–49]
Weight, kg	79 [66–91]
Women	1423 (51.4)
Ethnicity (all that apply)	
White or Caucasian	1972 (71.3)
Black or African American	72 (2.6)
Asian or South Asian	527 (19.0)
Hispanic or Latino	132 (4.8)
Native American or Pacific Islander	36 (1.3)
Other or not stated	68 (2.5)
Health care worker or first responder	2059 (74.4)
Current smoker	80 (2.9)
No chronic medications listed	1825 (66.0)
No chronic medical conditions	1633 (59.0)

Abbreviation: IQR, interquartile range.

hydroxychloroquine and 1 on placebo). There were no reported episodes of arrhythmias or sudden cardiac death.

Only 46 participants (4%) from the PEP and PET trials reported that they stopped the 5-day treatment course due to side effects. The distribution of side effects was similar among both trials. No serious adverse events, resulting in hospitalization, attributable to medication side effects were reported.

As gastrointestinal issues are known to occur in COVID-19, we compared side effects between the placebo groups in the PEP group vs those who had COVID-19 in the PET group. We did not identify a statistical difference in the incidence of nausea/upset stomach reports in those with COVID-19 vs those exposed (11% vs 8%; $P = .12$). Similarly, the incidence of diarrhea, abdominal pain, vomiting, or other gastrointestinal issues did not differ between those with COVID-19 vs those exposed (7% vs 4%; $P = .14$). The risk of having any side effects did not differ by sex, age group, weight, or whether the participant was a health care worker (Table 3).

Pre-exposure Prophylaxis Trial

Of 1483 randomized, 1405 had follow-up data. Overall, 416 (30%) individuals experienced at least 1 side effect during the study (Table 4). Side effects were higher for those receiving hydroxychloroquine: 36% of those on twice-weekly dosing, 31% on weekly dosing, and 21% on placebo reported at least 1 side effect. Similar to the other trials, the most common side effects reported were upset stomach or nausea (19% on hydroxychloroquine twice weekly, 18% on hydroxychloroquine weekly, and 12% on placebo), followed by vomiting, diarrhea, or other GI symptoms (17% on hydroxychloroquine twice weekly, 13% on hydroxychloroquine weekly, and 8% on placebo). Two participants experienced atrial arrhythmias. One participant

Table 2. Combined Side Effects During Days 1–5 in the Postexposure Prophylaxis and Early Treatment Cohorts

	Hydroxychloroquine, No. (%)	Placebo, No. (%)	PValue
No. randomized	658	654	
Started study medication	576 (87.5)	563 (86.1)	.46
Any side effect (days 1–5) ^a	231 (40.1)	101 (17.9)	<.001
Side effects ^a			
Nausea or upset stomach	146 (25.3)	53 (9.4)	<.001
Diarrhea, abdominal pain, vomiting	131 (22.7)	35 (6.2)	<.001
Irritability, dizziness, vertigo	39 (6.8)	26 (4.6)	.13
Tinnitus	16 (2.8)	8 (1.4)	.15
Headache	15 (2.6)	8 (1.4)	.21
Visual changes	7 (1.2)	5 (0.9)	.77
Skin reaction	10 (1.7)	4 (0.7)	.18
Taste change or dry mouth	3 (0.5)	3 (0.5)	>.99
Allergic reaction	6 (1.0)	1 (0.2)	.12
Hot flashes, night sweats, or palpitations	2 (0.3)	1 (0.2)	>.99
Fatigue	1 (0.2)	1 (0.2)	>.99
Panic	0 (0.0)	1 (0.2)	.49
Other	1 (0.2)	2 (0.4)	.62

P values were calculated using the chi-square test.

^aOf those who started study medication.

on placebo was hospitalized twice with atrial fibrillation. Another participant on hydroxychloroquine twice weekly was hospitalized after a syncopal event and was found to have a supraventricular tachycardia. No ventricular arrhythmias were reported.

In total, across the 3 cohorts, 34 individuals were hospitalized (1% incidence). The PEP trial had 2 individual hospitalizations, 1 in each arm, and no deaths. The PET trial had 14 hospitalizations and 2 deaths. With hydroxychloroquine, 4 hospitalizations and 1 nonhospitalized death occurred. With placebo, 10 hospitalizations occurred, with 1 hospitalized death. Two hospitalizations were for non-COVID-19-related, non-study medication-related reasons, while the remaining 12 hospitalizations were due to COVID-19. Eighteen individuals were hospitalized from the PREP study, 2 for COVID-19, 2 for arrhythmias (1 on hydroxychloroquine twice daily and 1 on placebo), and the other 7 individuals were hospitalized for non-study-related reasons. No sudden unexplained deaths have been reported in any of the 3 trials. Full details are available in [Supplementary Table 1](#).

DISCUSSION

Among 2544 participants reporting side effects from 3 randomized clinical trials investigating the efficacy of hydroxychloroquine in outpatient COVID-19 prevention and treatment, 29% reported at least 1 medication-related side effect. We captured 1 episode of supraventricular tachyarrhythmia with syncope in an individual on hydroxychloroquine and 2 episodes of atrial fibrillation in 1 individual on placebo. Whether hydroxychloroquine was responsible for or contributed to the development of the supraventricular tachycardia is unclear. Hydroxychloroquine prolongs the QT interval and therefore is associated with an increased risk of ventricular arrhythmias, not atrial arrhythmias. Regardless, atrial arrhythmias were rare in both arms, and there were no episodes of ventricular arrhythmia or sudden death in ~50 000 patient-days of cumulative exposure.

As expected, the most common side effects were nausea and gastrointestinal upset. In addition to hydroxychloroquine, COVID-19 is also known to cause gastrointestinal upset. However, when we compared the rate of gastrointestinal upset among those receiving

Table 3. Odds of Side Effects in the Postexposure Prophylaxis and Early Treatment Cohorts

Group	Odds Ratio of Any Side Effect	95% CI	PValue
Women vs men	1.163	0.827–1.637	.39
Health care worker vs not	0.796	0.570–1.111	.18
Age <35 y compared with 35–50 y	1.055	0.707–1.576	.79
Age >50 y compared with 35–50 y	0.726	0.457–1.151	.17
Weight <64 kg compared with 64–87 kg	1.421	0.911–2.218	.12
Weight >87 kg compared with 64–87 kg	0.744	0.470–1.179	.21

P value was calculated using the chi-square test.

Table 4. Side Effects from Pre-exposure Prophylaxis Cohort

	Hydroxychloroquine 2x Per Week, No. (%)	Hydroxychloroquine 1x Per Week, No. (%)	Placebo	PValue
No. randomized	495	494	494	
No. with completed surveys	463	473	469	
Any side effect	168 (36.4)	148 (31.3)	100 (21.4)	<.001
Side effects				
Nausea or upset stomach	90 (19.4)	83 (17.5)	57 (12.2)	.03
Diarrhea, abdominal pain, or vomiting	79 (17.1)	61 (12.9)	35 (7.5)	<.001
Palpitations	6 (1.3)	4 (0.8)	8 (1.7)	.51
Irritability, dizziness, vertigo	24 (5.2)	27 (5.7)	22 (4.7)	.80
Tinnitus	7 (1.5)	10 (2.1)	5 (1.1)	.44
Fatigue	5 (1.1)	1 (0.2)	1 (0.2)	.10
Visual changes	4 (0.9)	7 (1.5)	3 (0.6)	.41
Skin reaction	23 (5.0)	13 (2.7)	11 (2.3)	.07
Allergic reaction	4 (0.9)	2 (0.4)	3 (0.6)	.70
Sleep disturbance	7 (1.5)	10 (2.1)	7 (1.5)	.71
Myalgia	2 (0.4)	7 (1.5)	2 (0.4)	.11
Arrhythmias	1 (0.2)	0 (0.0)	1 (0.2)	–
Other, <1% each	11 (2.3)	11 (2.3)	8 (1.7)	–

P values were calculated using the chi-square test. The percentages of side effects are from participants who completed surveys since starting medication. The median number of side effects is among those reporting side effects. Of arrhythmias in the hydroxychloroquine group, this was a new supraventricular tachycardia resulting in syncope and hospitalization. In the placebo group, new atrial fibrillation occurred in 1 person, resulting in 2 hospitalizations.

placebo in the postexposure prophylaxis cohort vs those in the symptomatic cohort, reported gastrointestinal side effects were not significantly more frequent. Most participants regarded gastrointestinal upset as tolerable and completed the course of medication.

Medications causing QT prolongation are feared due to the risk of inducing ventricular arrhythmias, yet reports of arrhythmias due to hydroxychloroquine use are most often reported in the setting of co-ingestion, chronic use, or overdose [22–24]. The FDA does not recommend the use of hydroxychloroquine with other agents that prolong the QTc [11], such as azithromycin [25]. In 2017, the World Health Organization (WHO) reported that there has never been a reported sudden cardiac death attributable to chloroquine when prescribed at malaria treatment doses [26]. Despite the long history of chloroquine/hydroxychloroquine for malaria treatment and rheumatological diseases such as lupus, there have been increasing concerns around side effects in patients with COVID-19, especially related to arrhythmias [27, 28]. The FDA has now changed their emergency use authorization recommendation for hydroxychloroquine in COVID-19 treatment and prevention for this reason, among many others [10].

For context, a perspective on dosing is needed to understand potential risks associated with chloroquine/hydroxychloroquine. Decades of safety data are available for the standard doses of chloroquine used for malaria prophylaxis (500 mg [300 mg chloroquine base] weekly) and malaria treatment (2.5 g [1.5 g chloroquine base] total over 3 days). Cardiac conduction alterations were mostly seen when using much higher doses in hospitalized patients with COVID-19 (12 g chloroquine base over 10 days) [9]. The cumulative dose of hydroxychloroquine base used in our PEP and PET trials is

3.8 g (2.9 g base) total over 5 days. This is in line with established safe dosing strategies and below the doses shown to cause harmful effects [29, 30]. The Outcomes Related to COVID-19 Treated with Hydroxychloroquine among In-patients with Symptomatic Disease (ORCID) trial used 400 mg twice on day 1 followed by 200 mg twice daily for 5 days total (ClinicalTrials.gov Identifier: NCT04332991). They enrolled 479 individuals and also found no significant safety concerns at that dose. Similarly, the RECOVERY trial used 2.4 g (1.86 g base) in 4 divided doses over 24 hours, followed by 800 mg (620 mg base) for an additional 9 days or until discharge, and they reported no significant safety concerns in 11 000 hospitalized patients with COVID-19 randomized to hydroxychloroquine or placebo [31].

Our trials additionally excluded participants taking azithromycin and other QT-prolonging drugs to enhance safety further. Other risk factors for QT prolongation, such as hypokalemia or hypomagnesemia, are uncommon in outpatients [32, 33]. Mercurio et al. found QTc prolongation at 2.4-g courses of hydroxychloroquine over 5 days, but only clinically concerning side effects when combined with azithromycin, and side effects were more common among those already on loop diuretics [8]. Our data showed 1 potential cardiac complication (atrial arrhythmia) in 1 individual on hydroxychloroquine and 1 on placebo. Our potential rate of atrial arrhythmias due to hydroxychloroquine is <1 in 1000. Many commonly used drugs, including antibacterial, antifungal, and other antimalarial drugs, are known to prolong the QT, and thereby are rarely associated with arrhythmias [34]. The risk of QT prolongation has not precluded the use of drugs such as ciprofloxacin or fluconazole in most patients, but has required that clinicians exercise caution.

Limitations

Despite the innovative design of these clinical trials, several limitations remain. A significant limitation of our studies is related to their pragmatic nature, which relied on self-reporting. We did not prospectively record or evaluate for laboratory abnormalities or QTc changes. While we have outcome data on 91% of participants who have completed the studies, it is possible, given the passive nature of self-reported follow-up, that those lost to follow-up may have had an adverse event that was not reported to our study team or their designated emergency contacts.

Additionally, our cohorts are relatively young, with a median age of 40. Given that our studies were internet-based and advertised initially through social media, an internet-savvy population with a median age of 40 years was recruited. Our participants had few comorbidities and were on few medications. They were also predominantly health care workers, comprising a population of individuals with high health literacy. All of these factors make our outpatient research participants healthier than most hospitalized cohorts. Finally, our study exclusively included outpatients. Patients admitted to the hospital are generally older and have more comorbidities. They also are more likely to have cardiac complications of COVID-19 and thus may be more susceptible to developing adverse effects from hydroxychloroquine. Our data are most likely to be informative for relatively healthy outpatients.

CONCLUSIONS

While efforts toward the development of a vaccine continue, agents that can prevent or treat COVID-19 are important. There are still hydroxychloroquine trials ongoing against COVID-19 for early treatment or prevention. Thus, timely completion of randomized placebo-controlled clinical trials is essential. Thus, large-scale clinical trials to carefully evaluate the limited potential therapeutics that have been identified and perhaps even to replicate results of completed trials are imperative to our public health response. Ongoing clinical trials can safely continue, with research participants and regulatory bodies reassured as to the general safety of hydroxychloroquine when using appropriate exclusion criteria among a similar generally healthy outpatient population such as ours. Safety data using hydroxychloroquine among older patients with COVID-19 and multiple comorbidities would need to come from other studies or be inferred from the decades-long experience with hydroxychloroquine. Importantly, hydroxychloroquine will continue to be used for infectious diseases and rheumatologic conditions other than COVID-19, and providers should be reassured by the general safety profile.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility

of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

The authors thank the Dean of the University of Minnesota School of Medicine, Dr. Jakub Tolar, for his support of our COVID-19 work.

Financial support. This work was supported by Jan and David Baszucki, Steve Kirsch, the Alliance of Minnesota Chinese Organizations, the Minnesota Chinese Chamber of Commerce, and the University of Minnesota. Personnel was supported through the Doris Duke Charitable Foundation through a grant supporting the Doris Duke International Clinical Research Fellows Program at the University of Minnesota. Katelyn Pastick and Elizabeth Okafor are Doris Duke International Clinical Research Fellows. Sarah Lofgren is supported by the National Institute of Mental Health (K23MH121220). Caleb Skipper is supported by the Fogarty International Center (D43TW009345). Drs. Melanie Nicol, Radha Rajasingham, and Matthew Pullen are supported by the National Institute of Allergy and Infectious Disease (K08AI134262, K23AI138851, T32AI055433). Margaret Axelrod is supported by NIH T32GM007347 and F30CA236157. Drs. Lee and McDonald receive salary support from the Fonds de Recherche du Québec-Santé. Canadian funding was received from various sources. In Quebec, funds were received from the Clinical Practice Assessment Unit of the McGill University Health Centre and the McGill Interdisciplinary Initiative in Infection and Immunity's Emergency COVID-19 Research Funding. In Manitoba, the Manitoba Medical Service Foundation provided research support. In Alberta, support was provided by Northern Alberta Clinical Trials and Research Centre. In Ontario, support was provided by the Research Institute of St. Joseph's Hamilton, the St. Joseph's Hospital Foundation in London, and Bridge to Health Medical and Dental. Purolator Canada provided in-kind courier support for Canadian sites participating in the postexposure and early treatment trials. Apotex Pharmaceuticals Canada provided a donation of some of the hydroxychloroquine tablets used. Rising Pharmaceutical donated some of the medicine for US trials. COVID-19 Emergency Supplement funding was requested from the National Institutes of Health for each of the 3 trials.

Potential conflicts of interest. The authors are actively involved in clinical trials to prevent or treat COVID-19. No author has a financial interest in remote EKG monitoring products or services. Gilead, which makes remdesivir, has provided grants and Ambisome to the Infectious Disease Institute in Uganda and Meningitis Foundation for meningitis-related research. No co-author has had any personal financial interests or payments from Gilead, and no one associated with Gilead was involved in our hydroxychloroquine work. Dr. Boulware collaborates with multiple pharmaceutical companies who provide novel antifungal medicines for cryptococcal meningitis, without any financial interests or payments from these companies. Dr. Cheng has worked as a scientific advisory board member with GENIE Lifesciences. There are no other potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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