Clinical Infectious Diseases: Invited Commentary

Hydroxychloroquine for Prevention of SARS-CoV-2 Infection: challenges to trial conduct during the global pandemic.

Jason D. Goldman, MD, MPH[1,2 *]

1. Swedish Center for Research and Innovation, Swedish Medical Center, Seattle, WA
2. Division of Allergy and Infectious Disease, University of Washington, Seattle, WA

* Correspondence addressed to:
Jason D. Goldman
1124 Columbia Ave, #600
Seattle, WA 98104
jason.goldman@swedish.org

Keywords: SARS-CoV-2, COVID-19, hydroxychloroquine, twitter, pandemic

Since the first days of the Covid-19 pandemic, healthcare workers were at high risk for acquiring SARS-CoV-2 infection, and at risk for death. Dr. Li Wenliang, a physician in Wuhan, China, sounded the alarm on social media about an unexplained viral pneumonia and later succumbed to the infection.[1] As the pandemic quickly spread around the world, a lack of any treatments or preventatives known to be effective, coupled with critical gaps in personal protective equipment (PPE) in the United States and elsewhere left front-line healthcare workers scared and vulnerable. *In vitro* studies suggested that aminoquinolines, such as hydroxychloroquine (HCQ), were effective in inhibiting SARS-CoV-2 infection in a cell culture model,[2, 3] and modeling studies predicted dosing in silico.[4] The putative mechanism of action was unknown, but was speculated to be pleotropic.[5]

In the setting of this uncertainty and risk, Dr. Rajasingham et al. rapidly designed and implemented a double-blind, placebo-controlled RCT to evaluate the use of hydroxychloroquine (HCQ) to prevent Covid-19, as pre-exposure prophylaxis (PrEP), i.e. COVID PrEP trial.[6] They enrolled healthcare workers in front-line positions at high risk for acquiring SARS-CoV-2 (79% performed aerosol generating procedures). Participants were randomized to receive HCQ at 400mg once weekly vs 400mg twice weekly vs placebo for 12 weeks. The primary outcome was incidence of confirmed or probable Covid-19, assessed by self-report. Strengths and novelty of this trial design include remote procedures such as online enrolment, social media recruitment, and overnight shipping for drug dispensing. These procedures were shared with the sister trials for treatment of mild Covid-19,[7] and post-exposure prophylaxis (PEP) for Covid-19,[8] the latter was covered in Paul Sax's blog "in praise of a negative clinical trial".[9] The HCQ COVID PrEP trial planned to recruit and enroll 3,150 participants, but ultimately only 1,483 health care workers were included.

The HCQ COVID PrEP trial documented fewer primary outcome events in the HCQ arms than the placebo arm, but these results were not statistically significant. The point estimates of the hazard ratios for effect of HCQ for PrEP was 0.72 for one weekly and 0.74 for twice weekly dosing, when compared to placebo, but the 95% confidence intervals crossed the null. The authors conclude that PrEP with HCQ at doses studied did not significantly reduce confirmed or probable COVID-19 in this high-risk group. Possible reasons for the negative finding in this trial include no effect of the drug, or inadequate dosing. It is also possible that HCQ is effective at these doses, but the study was underpowered to find a difference if such a difference exists.

Due to concurrent events limiting enthusiasm for trial participation, the COVID PrEP did not fully accrue. In unpacking the possibility that the study was underpowered to see a preventive effect of HCQ if one exists, the authors acknowledge a few important limitations. These include lower than expected primary outcome events, and the inability to definitively diagnose some suspected Covid-19 events with PCR due to limited availability PCR testing in the US during the trial and the high false-negative test rate in early illness. Other study designs could have mitigated the high proportion of events lacking PCR confirmation, including patient self-collect swabs mailed back,[10] though at the time of the study design, home self-collection of swabs for SARS-CoV-2 PCR was not well validated. The failure to definitively diagnose the key primary outcome is the major weakness in the trial which affects interpretability, leaving the possibility that HCQ has an effect when given as PrEP incompletely answered.

As Rajasingham et al. discuss the failure to recruit the intended sample size, the manuscript recalls the epic journey through the trials and tribulations of HCQ during the SARS-CoV-2 pandemic. At the

time of trial start-up, intense interest in HCQ was stoked by public figures promoting the drug despite little supporting evidence. The President of the United States (POTUS) proclaimed on twitter "HYDROXYCHLOROQUINE & AZITHROMYCIN, taken together, have a real chance to be one of the biggest game changers in the history of medicine.", and encouraged use by stating on a televised press conference: "What do you have to lose? Take it."[11] The these statements came after a pre-print was released of a small observational trial with methodological flaws.[12] Following this discourse, patients turned to internet purchasing to obtain HCQ,[13] and shortages ensued which limited access for persons with rheumatologic conditions and a *bona fide* use case for HCQ.[14] Despite the paucity of supporting evidence, the FDA approved Emergency Use Authorization (EUA) for HCQ. Just over a week later, Rajasingham et al. enrolled their first participant to the HCQ COVID PrEP trial on April 6th, 2020. Enrollment was adequate for a few weeks, until further scandals ensued, including alleged political pressuring of a career government scientist at BARDA over HCQ.[15] Observational studies also began to emerge which questioned the effectiveness of off-label treatment programs to prevent disease progression or death,[16-18] and speculated on the risks for cardiac toxicity.[18, 19] When a flawed paper demonstrating harm from HCQ was published in the Lancet (later retracted),[20] the WHO Solidarity trial suspended enrollment. Rajasingham et al terminated enrollment on the HCQ COVID PrEP trial the following day on May 26th, 2020, due to an inability to recruit participants. The FDA subsequently withdrew the EUA.[21] See timeline in the **Figure**.

The shuttering of the HCQ COVID PrEP trial was not an isolated event, and occurred in other HCQ trials due to flagging recruitment.[22] Some trials reduced enrollment goals, including the prevention trials UW COVID-PEP,[23] and HERO-HCQ (NCT04334148), and the two large treatment trials RECOVERY[24] and WHO Solidarity[25] were terminated early due to interim analyses suggesting lack of efficacy. Despite the tumultuous ride, the data from multiple trials agree that HCQ is not effective at the moderate doses tested, for short-term or long-term use for prevention of SARS-CoV-2 as PEP[8, 23] or PrEP.[6] Likewise, conclusions converge that HCQ is not effective for treatment of Covid-19 based on retrospective observational studies[16-18] and prospective clinical trials.[24-26] Given speculation on cardiac risk via QT prolongation,[26] guidelines recommend against the use of HCQ for prevention or treatment.[27, 28] Scientific teams arrived at these conclusions by performing clinical trials during the pandemic which utilized clever designs with remote procedures to side-step the usual processes which would confer additional transmission risk, and allow for more dispersed enrollment. Rajasingham et al. should be commended on their novel and pragmatic trial approach, and for shedding light on the truth, amidst a very chaotic time in the pandemic.

Looking back, the lack of coordinated scientific responses to the pandemic in the US may have hindered the ability to arrive at definitive conclusions about HCQ used as PrEP. In contrast, the RECOVERY trial in the United Kingdom had the full backing of their National Health Service and was able to rapidly recruit trial participants nationwide to definitively determine lack of effectiveness for HCQ as treatment of COVID-19 in hospitalized participants. Premature EUA of HCQ in the US may have displaced participants from participating in proper RCTs of HCQ, as has been speculated for convalescent plasma,[29] effectively imperiling equipoise. The FDA is charged with the process to assure safety and efficacy of biomedical interventions prior to approval, and public trust is needed in the institution to assure uptake of important public health measures, like vaccines and monoclonal antibodies.

While PPE shortages in the US have been mostly mitigated, healthcare workers remain at risk for acquiring SARS-CoV-2 and prophylactics proven to be safe and effective still do not exist. Reviewing the scientific development of HCQ as it was repurposed for SARS-CoV-2 reveals the difficulty of conducting rigorous science during a pandemic. Regulatory agencies may have competing goals to facilitate treatments for this potentially fatal condition and simultaneously study the agent. Yet the tendency to "do something" must be balanced with efforts to first determine safety and efficacy prior to widespread use. Looking forward, society is likely to derive the most benefit if the high-quality science surrounding the SARS-CoV-2 vaccine efforts and monoclonal antibody development programs are left unimpeded by the drama, political meddling, and premature emergency use authorization that has surrounded the study of hydroxychloroquine.

Figure: Timeline of key publications and concurrent events related to use of hydroxychloroquine for SARS-CoV-2. Modified from Sattui et al.[30] Abbreviations: HCQ = Hydroxychloroquine, AZM = Azithromycin, PrEP = Pre-Exposure Prophylaxis, PK = Pharmacokinetic, WHO = World Health Organization, NIH = National Institutes of Health, BARDA = Biomedical Advanced Research and Development Authority, FDA = Federal Drug Administration, EUA = Emergency Use Authorization, POTUS = President of the United States.

Acknowledgments:

The author would like to thank Chris Vanderwarker, MD, MBA, Emily R. Hazan, ARNP, DNP, CNM and Ruanne Barnabas, MBChB, DPhil for helpful discussions about this manuscript.

References:

1. Li Wenliang: Coronavirus kills Chinese whistleblower doctor. Accessed 10/23/20, https://www.bbc.com/news/world-asia-china-51403795
2. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 03 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0
3. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16. doi:10.1038/s41421-020-0156-0
4. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. Mar 2020;doi:10.1093/cid/ciaa237
5. Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. *Int J Antimicrob Agents*. 04 2020;55(4):105945. doi:10.1016/j.ijantimicag.2020.105945
6. Rajasingham R, Bangdiwala AS, Nicol MR, et al. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. Clin Infect Dis, in press. PLACEHOLDER.
7. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial. *Ann Intern Med*. 10 2020;173(8):623-631. doi:10.7326/M20-4207
8. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med*. 08 2020;383(6):517-525. doi:10.1056/NEJMoa2016638
9. Sax P. Hydroxychloroquine Not Effective in Preventing COVID-19 — In Praise of a Negative Clinical Trial. Accessed 10/23/20, https://blogs.jwatch.org/hiv-id-observations/index.php/hydroxychloroquine-not-effective-in-preventing-covid-19-in-praise-of-a-negative-clinical-trial/2020/06/07/
10. McCulloch DJ, Kim AE, Wilcox NC, et al. Comparison of Unsupervised Home Self-collected Midnasal Swabs With Clinician-Collected Nasopharyngeal Swabs for Detection of SARS-CoV-2 Infection. *JAMA Netw Open*. 07 2020;3(7):e2016382. doi:10.1001/jamanetworkopen.2020.16382
11. DeJong C, Wachter RM. The Risks of Prescribing Hydroxychloroquine for Treatment of COVID-19-First, Do No Harm. *JAMA Intern Med*. 08 2020;180(8):1118-1119. doi:10.1001/jamainternmed.2020.1853
12. Goldman JD, Diaz G, Urba WJ. Use of hydroxychloroquine in combination with azithromycin for patients with COVID-19 is not supported by recent literature. IJAA *in press*, PLACEHOLDER.
13. Liu M, Caputi TL, Dredze M, Kesselheim AS, Ayers JW. Internet Searches for Unproven COVID-19 Therapies in the United States. *JAMA Intern Med*. 08 2020;180(8):1116-1118. doi:10.1001/jamainternmed.2020.1764
14. Yazdany J, Kim AHJ. Use of Hydroxychloroquine and Chloroquine During the COVID-19 Pandemic: What Every Clinician Should Know. *Ann Intern Med*. 06 2020;172(11):754-755. doi:10.7326/M20-1334
15. Shear MD, Haberman M. Health Dept. Official Says Doubts on Hydroxychloroquine Led to His Ouster. https://www.nytimes.com/2020/04/22/us/politics/rick-bright-trump-hydroxychloroquine-coronavirus.html?action=click&module=RelatedLinks&pgtype=Article
16. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with COVID-19. *Med (N Y)*. Jun 2020;doi:10.1016/j.medj.2020.06.001
17. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 06 2020;382(25):2411-2418. doi:10.1056/NEJMoa2012410

18. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA*. 06 2020;323(24):2493-2502. doi:10.1001/jama.2020.8630
19. Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw Open*. 04 2020;3(4):e208857. doi:10.1001/jamanetworkopen.2020.8857
20. Mehra MR, Ruschitzka F, Patel AN. Retraction-Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet*. 06 2020;395(10240):1820. doi:10.1016/S0140-6736(20)31324-6
21. Howard J, Azad A, Fox M. FDA revokes authorization of drug Trump touted. Accessed 10/23/20, https://www.cnn.com/2020/06/15/politics/fda-hydroxychloroquine-coronavirus/index.html
22. Doughton S. Clinical trial enrollment plummets as volunteers are scared off coronavirus drugs promoted by Trump. Accessed 10/25/20, https://www.seattletimes.com/seattle-news/health/clinical-trial-enrollment-plummets-as-volunteers-are-scared-off-coronavirus-treatment-pushed-by-trump/
23. Barnabas RV, Brown ER, Bershteyn A, et al. Efficacy of Hydroxychloroquine (HCQ) for Post-exposure Prophylaxis to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Blinded, Randomized, Controlled Trial. IDWeek 2020, Abstract LB-17; OFID. PLACEHOLDER.
24. Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. Oct 2020;doi:10.1056/NEJMoa2022926
25. Pan H, Peto R, Karim QA, et al. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. *medRxiv*. 2020:2020.10.15.20209817. doi:10.1101/2020.10.15.20209817
26. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med*. Jul 2020;doi:10.1056/NEJMoa2019014
27. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis*. Apr 2020;doi:10.1093/cid/ciaa478; https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed on 4/30/20 & 6/30/20.
28. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Accessed 4/30/20 & 6/30/20, https://www.covid19treatmentguidelines.nih.gov/.
29. Lee SJ. ASH Comment on Emergency Use Authorization for Convalescent Plasma. Accessed 10/23/20, https://www.hematology.org/covid-19/commentary-on-eua-for-convalescent-plasma
30. Sattui SE, Liew JW, Graef ER, et al. Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19. *Expert Rev Clin Immunol*. 07 2020;16(7):659-666. doi:10.1080/1744666X.2020.1792778

Figure 1