Barnabas et al. Trials (2020) 21:475
https://doi.org/10.1186/s13063-020-04446-4

Trials

LETTER Open Access

Efficacy of hydroxychloroquine for post-exposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among adults exposed to coronavirus disease (COVID-19): a structured summary of a study protocol for a randomised controlled trial

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Abstract

Objectives: Primary Objective
• To test the efficacy of Hydroxychloroquine (HCQ) (400 mg orally daily for 3 days then 200 mg orally daily for an additional 11 days, to complete 14 days) to prevent incident SARS-CoV-2 infection, compared to ascorbic acid among contacts of persons with SARS-CoV-2 infection
Secondary objectives
• To determine the safety and tolerability of HCQ as SARS-CoV-2 Post-exposure Prophylaxis (PEP) in adults
• To test the efficacy of HCQ (400 mg orally daily for 3 days then 200 mg orally daily for an additional 11 days, to complete 14 days) to prevent incident SARS-CoV-2 infection 2 weeks after completing therapy, compared to ascorbic acid among contacts of persons with SARS-CoV-2 infection
• To test the efficacy of HCQ to shorten the duration of SARS-CoV-2 shedding among those with SARS-CoV-2 infection in the HCQ PEP group
• To test the efficacy of HCQ to prevent incident COVID-19

(Continued on next page)

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Trial design: This is a randomized, multi-center, placebo-equivalent (ascorbic acid) controlled, blinded study of HCQ PEP for the prevention of SARS-CoV-2 infection in adults exposed to the virus.

Participants: This study will enroll up to 2000 asymptomatic adults 18 to 80 years of age (inclusive) at baseline who are close contacts of persons with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 or clinically suspected COVID-19 and a pending SARS-CoV-2 PCR test. This multisite trial will be conducted at seven sites in Seattle (UW), Los Angeles (UCLA), New Orleans (Tulane), Baltimore (UMB), New York City (NYU), Syracuse (SUNY-Upstate), and Boston (BMC).

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Men or women 18 to 80 years of age inclusive, at the time of signing the informed consent
2. Willing and able to provide informed consent
3. Had a close contact of a person (index) with known PCR-confirmed SARS-CoV-2 infection or index who is currently being assessed for COVID-19

Close contact is defined as:

a. Household contact (i.e., residing with the index case in the 14 days prior to index diagnosis or prolonged exposure within a residence/vehicle/enclosed space without maintaining social distance)
b. Medical staff, first responders, or other care persons who cared for the index case without personal protection (mask and gloves)

4. Less than 4 days since last exposure (close contact with a person with SARS-CoV-2 infection) to the index case
5. Access to device and internet for Telehealth visits
6. Not planning to take HCQ in addition to the study medication

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known hypersensitivity to HCQ or other 4-aminoquinoline compounds
2. Currently hospitalized
3. Symptomatic with subjective fever, cough, or shortness of breath
4. Current medications exclude concomitant use of HCQ
5. Concomitant use of other anti-malarial treatment or chemoprophylaxis, including chloroquine, mefloquine, artemether, or lumefantrine.
6. History of retinopathy of any etiology
7. Psoriasis
8. Porphyria
9. Known bone marrow disorders with significant neutropenia (polymorphonuclear leukocytes <1500) or thrombocytopenia (<100 K)
10. Concomitant use of digoxin, cyclosporin, cimetidine, amiodarone, or tamoxifen
11. Known moderate or severe liver disease
12. Known long QT syndrome
13. Severe renal impairment
14. Use of any investigational or non-registered drug or vaccine within 30 days preceding the first dose of the study drugs or planned use during the study period

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Intervention and comparator: Households will be randomized 1:1 (at the level of household), with close contact participants receiving one of the following therapies:
•HCQ 400 mg orally daily for 3 days then 200 mg orally daily for an additional 11 days
•Placebo-like control (ascorbic acid) 500 mg orally daily for 3 days then 250 mg orally daily for 11 days

Main outcomes: The primary outcome of the study is the incidence of SARS-CoV-2 infection through day 14 among participants who are SARS-CoV-2 negative at baseline by randomization group.

Randomisation: Participants will be randomized in a 1:1 ratio to HCQ or ascorbic acid at the level of the household (all eligible participants in 1 household will receive the same intervention). The randomization code and resulting allocation list will be generated and maintained by the Study Statistician. The list will be blocked and stratified by site and contact type (household versus healthcare worker).

Blinding (masking): This is a blinded study.
HCQ and ascorbic acid will appear similar, and taste will be partially masked as HCQ can be bitter and ascorbic acid will be sour.
The participants will be blinded to their randomization group once assigned. Study team members, apart from the Study Pharmacist and the unblinded statistical staff, will be blinded. Laboratory staff are blinded to the group allocation.

Numbers to be randomised (sample size): The sample size for the study is *N*=2 000 participants randomized 1:1 to either HCZ (*n*=1 000) and ascorbic acid (*n*=1 000).

Trial status: Protocol version: 1.2
05 April 2020
Recruitment is ongoing, started March 31 and anticipated end date is September 30, 2020.

Trial registration: ClinicalTrials.gov, Protocol Registry Number: NCT04328961
Date of registration: April 1, 2020, retrospectively registered

Full protocol: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

Keywords: COVID-19, Randomised controlled trial, protocol, hydroxychloroquine, post-exposure prophylaxis, household contact, health care worker

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-020-04446-4.

Additional file 1. Full study protocol.

Acknowledgements
Not applicable

Authors' contributions
RVB wrote the first draft of the letter. All authors contributed critically to the design of the protocol and to reviewing and approving the finalized copy.

Funding
The study is funded by the Bill and Melinda Gates Foundation (INV-016204). A funding agency staff member (RSM) is a co-author of the manuscript. Sandoz donated the study drug. The funders had no separate role, beyond that of other authors, in study design; writing of the letter; or in the decision to submit for publication. The corresponding author had full access to the study protocol and had final responsibility for the decision to submit for publication.

Availability of data and materials
Data from the study will be available from the study oversight committee on request (rbarnaba@uw.edu). The final dataset will be available through open access.

Ethics approval and consent to participate

- Name of ethics committee: Western Institutional Review Board
- File number/reference number: 1281603
- Date of approval: 20 March 2020

I certify that this trial has received ethical approval from the appropriate ethical committee as described above. The study will be conducted according to Good Clinical Practice, the Belmont Report, and the Declaration of Helsinki. The principles of informed consent in the current edition of the Declaration of Helsinki will be implemented in each clinical study before any protocol-specified procedures or interventions are carried out. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, and this fact will be documented in the participant's record.

Consent for publication
Not applicable

Competing interests
AB reports personal fees from Gates Ventures. CC reports personal fees from Gilead Sciences and Merck, outside the submitted work. JMB reports personal fees from Gilead Sciences, Merck, and Janssen, outside the submitted work. HC reports grants from Sanofi-Pasteur, Ellume, Cepheid, and Genentech; and personal fees from GSK and Merck, outside the submitted work. All other authors declare that they have no competing interests.

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Received: 29 April 2020 Accepted: 23 May 2020
Published online: 03 June 2020

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