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Protecting Frontline Health Care Workers from COVID-19 with Hydroxychloroquine Pre-exposure Prophylaxis: A structured summary of a study protocol for a randomised placebo-controlled multisite trial in Toronto, Canada

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Abstract

Objectives: *Primary Objective*: To determine if pre-exposure prophylaxis (PrEP) with 400mg hydroxychloroquine (HCQ), taken orally once daily reduces microbiologically confirmed COVID-19 among front line health care workers at high risk for SARS-CoV-2 exposure.
Secondary Objectives: To compare the following between study arms: adverse events; symptomatic COVID-19; duration of symptomatic COVID-19; days hospitalized attributed to COVID-19; respiratory failure attributable to COVID-19 requiring i) non-invasive ventilation or ii) intubation/mechanical ventilation; mortality attributed to COVID-19, number of days unable to work attributed to COVID-19, seroconversion (COVID-19 negative to COVID-19 positive over the study period); ability of participant plasma to neutralize SARS-CoV-2 virus *in vitro;*
To describe short-term psychological distress associated with risk of COVID-19 exposure at 1, 60, 120 days of the study.
To explore laboratory markers within participants with confirmed COVID-19: including circulating markers of host immune and endothelial activation in participant plasma and their correlation with disease severity and outcome

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Trial design: The HEROS study is a two-arm, parallel-group, individually randomized (1:1 allocation ratio), placebo controlled, participant and investigator-blinded, multi-site superiority trial of oral HCQ 400 mg taken once daily for 90 days as PrEP to prevent COVID-19 in health care workers at high risk of SARS-CoV-2 exposure. At 90 days, there is an open label extension wherein all participants are offered a one-month course of HCQ 400mg once daily for PrEP of COVID-19.

Participants: Frontline HCWs aged 18 years of age or older, at high risk of SARS-CoV-2 exposure (including staff of emergency departments, intensive care units, intubation teams, COVID-wards, and staff deployed to Long Term Care facilities) of five academic hospitals in downtown Toronto, Canada.
Exclusion criteria include: currently pregnant, planning to become pregnant during the study period, and/or breast feeding; known hypersensitivity/allergy to hydroxychloroquine or to 4-aminoquinoline compounds; current use of hydroxychloroquine; known prolonged QT syndrome and/or baseline resting ECG with QTc>450 ms and/or concomitant medications which simultaneously may prolong the QTc that cannot be temporarily suspended/replaced; known pre-existing retinopathy, G6PD deficiency, porphyria, liver disease including cirrhosis, encephalopathy, hepatitis or alcoholism, diabetes on oral hypoglycemics or insulin, or renal insufficiency/failure; disclosure of self-administered use of hydroxychloroquine or chloroquine within 12 weeks prior to study; confirmed symptomatic COVID-19 at time of enrollment.

Intervention and comparator: Intervention: hydroxychloroquine, 400mg (2 tablets) orally per day. Comparator: placebo, two tablets visually identical to the intervention, orally per day

Main outcomes: The primary outcome is microbiologically confirmed COVID-19 (i.e. SARS-CoV-2 infection). This is a composite endpoint which includes positive results from any validated SARS-CoV-2 diagnostic assay including detection of viral RNA, and/or seroconversion.
Participants will be assessed at baseline, and then undergo monthly follow-up at day 30, 60, and 90, 120. At each visit, participants will provide an oropharyngeal sample, blood sample, and will undergo electrocardiogram monitoring of the QTc interval.
Secondary outcome measures include: adverse events; symptom duration of COVID-19; days of hospitalization attributed to COVID-19; respiratory failure requiring ventilator support attributed to COVID-19; mortality attributed to COVID-19; total days off work attributed to COVID-19; seropositivity (reactive serology by day 120); and short term psychological impact of exposure to SARS-CoV-2 at day 1, 60, 120 days using the K10, a validated measure of non-specific psychological distress.

Randomisation: Within each site, participants will be individually randomized to either the intervention arm with HCQ or the placebo arm using a fixed 1:1 allocation ratio using an interactive web-based response system to ensure concealment of allocation. Randomization schedules will be computer-generated and blocked using variable block sizes.

Blinding (masking): All participants, research coordinators, technicians, clinicians and investigators will be blinded to the participant allocation group.
Numbers to be randomised (sample size) N=988, randomised into two groups of 494 patients.

Trial Status: This summary describes protocol version No. 1.6, May 15, 2020. Recruitment is ongoing - started April 20, 2020 and anticipated end date is July 30, 2021

Trial registration: ISRCTN.com Identifier: ISRCTN14326006, registered April 14, 2020.

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.
The study protocol has been reported in accordance with the Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines (Additional file 2).

Keywords: COVID-19, Randomised placebo controlled trial, protocol, hydroxychloroquine, viral PCR, serology, psychological distress

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-020-04577-8.

Additional file 1.

Additional file 2.

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Authors' contributions

ML and KK are the co-Principal Investigators and Study Sponsors. JKW, ML, KCK, DHST and SLW conceived and designed the trial, and prepared the study protocols for REB review. GT directed the statistical analysis plan. The Applied Health Research Centre of St. Michael's Hospital (AHRC) (PJ and DK) developed the data management plan and study database. TM is the lead microbiologist responsible for sample processing and SARS-CoV-2 PCR. SM will lead the virus neutralization studies. RC is the Project Manager. MG is the cardiology consultant. SLW/JH/EO (University Health Network), DHST/CS (St. Michael's/Unity Health), IC/AC (Sunnybrook Health Sciences Center), BB/SM (Sinai Health System), serve as the Study Site leads and implemented the study protocols at their respective institutions. LD and FH are the study pharmacists.

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The funding bodies have had / will have no role in the design of the study, data collection, analysis, interpretation, or dissemination of study findings to either journals, general public or scientific meetings.

Availability of data and materials

Data will be made available from the author on reasonable request. Please contact Dr. Megan Landes (corresponding author).

Ethics approval and consent to participate

Ethical approval was granted by Clinical Trials Ontario (CTO) (Project ID: 2132). Initial approval was granted 8 April 2020. The Board of Record is the University Health Network (UHN) Research Ethics Board (REB). The public listing of the study can be found here: https://www.ctontario.ca/covid-19-clinical-trial-resources/ The HEROS trial received ethical approval from an appropriate ethical committee as described above. This study will be conducted in accordance with the ICH-GCP Guidelines and the principles in the Declaration of Helsinki. Potential participants are invited to view an online information video outlining the risks, benefits and procedures of the trial, and then will be invited to provide written informed consent prior to being enrolled.

Consent for publication

Not applicable.

Competing interests

The authors declare that they do not have any competing interests.

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