Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

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Contributors list

Fight AIDS and Infectious Diseases Foundation, Badalona, Spain

Albert Tuldrà PhD, Xavi Serrano MSc, Estefany Uría BASc, Cristina Herrero BPharm, Sílvia Gel BSc, Alberto Alomar BM, Ricard Esteve BM, Anna Maria Soley BM, Clara Muntaner-Virgili BM, Alejandro Hueso-Mor BM, Laura Calvo BM, Itziar Gamboa BM, Anna I. Garcia-Diaz PhD, Kilian Griñan BM, Sara Castells-Büchle BM, Alex Alonso-Vallés MSc, Carolina Rebato BN, Mercè Juan BN, Dolors Palacín BN, José López BN, Elisenda Molas BN, Anna Serra BN, Sílvia Sarrà BN, Enric Fericgla BN, Laura Latorre BN, Guillem Turmo BM, Rosa López BN, Vanesa Villa BN, Laura Martín BN, Cristina Aragón BN, Mireia Vilageli BN, Paula Martínez BN, Cristina Naqui BN, Judith Martínez BN, Paula Puche BN, Emma Yana BN, Magalí Urrea BN, Carmen Barjau BN, Roser Utrillo BN, Joan Enric Torra PhD, Marta Gilabert BN, Carme Domènech BN, Judit Cartiel BN, Israel López BN, Olga Pérez BN, Santiago Rosell BN, Patricia Cobarsi BN, Cristina Miranda BN, Míriam López BN, Anna Martínez BN, Toni Jou BM, Cristina Segundo BN, Nalia López BN, Carla Estany MSs, Deborah Paris MA, Sonia Clemares BA, Lara Teruel BSc, Jorge Romaní BM, Lourdes Mateu PhD, Roger Paredes PhD.

IrsiCaixa AIDS Research Institute, Badalona, Spain

Eulàlia Grau BsC, Cristian Ramírez BsC, Cecilia Cabrera PhD, Francesc Cunyat PhD, Roger Badia PhD, Jordi Senserrich PhD, Ana Jordán PhD, M. Lluïsa Rodríguez PhD, Ferran Tarrés BSc, Carlos Ávila BSc, Àngel Bayón BSc, Raquel Ortiz BSc, Ana Barajas BSc, Sònia Pedreño BSc.

Trial Form Support Clinical Contract Research Organization, Barcelona, Spain

Emma Albacar MSc, Xavier Núñez MSc.

Equip d'atenció primària de Sarrià, Barcelona, Spain

Roger Vinyeta MD, Norma Caritg MD, Rosa Bosch BN, Natàlia Martí BN, Paola Castro BN.

Associació Catalana d'Entitats de Salut

Lluís Monset BM.

CAP Centelles, Centelles, Spain

Dolors Molera BN, Dagda Bermúdez BN, Clara Moliner BN, Gemma Tobajas RA.

Gastrointestinal Physiology Laboratory. Hospital de Mataró, Mataró, Spain

Mireia Bolívar-Prados BM, Pere Clavé PhD.

Centre of Epidemiological Studies of HIV/AIDS and STI of Catalonia (CEEISCAT), Catalan Institute of Oncology (ICO)-Departament de Salut, Generalitat de Catalunya, Badalona, Spain

Laia Egea-Cortés MsC, Yesika Díaz MsC, Sergio Moreno-Fornés MsC, Marcos Montoro-Fernández MsC.

Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Barcelona, Spain

Borja Velasco-Regúlez MsC, Didier Domínguez MsC.

Equip d'Atenció Primària Especialitzada CAP Sant Andreu, Barcelona, Spain

Lourdes Pons BN, Juan Carlos Becerra BN, Esther Diaz Soler BN.

Methods S1. Recruitment strategy, randomization, and selection criteria

Study candidates were screened using the electronic registry of the Epidemiological Surveillance Emergency Service of Catalonia (SUVEC) of the Department of Health. During the Covid-19 outbreak in Catalonia, a public health ordinance required all patients who tested positive for Covid-19 in any of the designated diagnostic laboratories to be notified to the SUVEC.[1]

Randomization was performed remotely by a member of the study team not involved in participants' enrollment. Following ring randomization, we verified the selection criteria of individual candidates and obtained informed consent for enrollment. The allocation was revealed to participants after providing written consent on day 1 (baseline).

Inclusion criteria

1. Asymptomatic individuals exposed to a PCR confirmed COVID19 case within 7 days as either a healthcare worker, a household contact, a nursing home worker or nursing home resident.
2. Aged ≥18 years male or female.
3. In women of childbearing potential, negative pregnancy test and commitment to use contraceptive method throughout the study.
4. Willing to take study medication.
5. Willing to comply with all study procedures.
6. Able to provide oral, informed consent and/or assent.

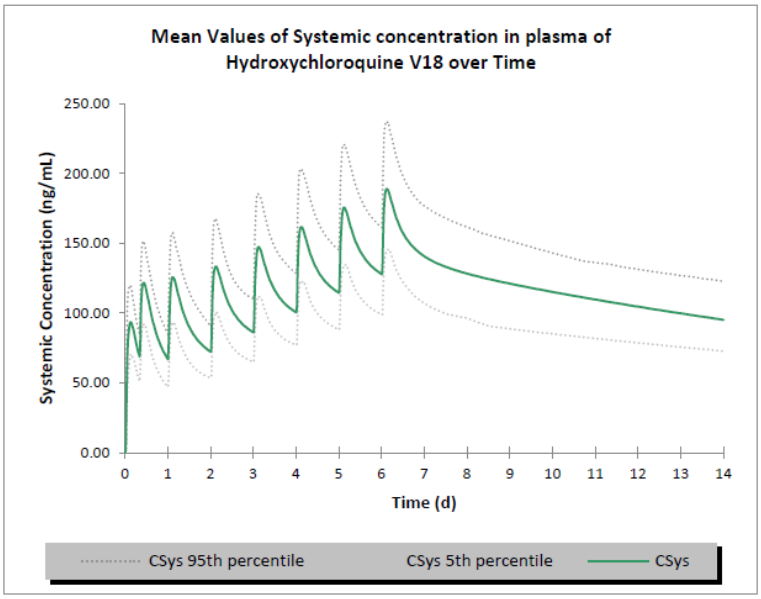
Exclusion Criteria

1. With known history of cardiac arrhythmia (or QT prolongation syndrome).
2. Unable to take drugs by mouth.
3. With significantly abnormal liver function (Child Pugh C)
4. Need of dialysis treatment, or GFR≤30 mL/min/1.73 m^2.
5. Participants with psoriasis, myasthenia, hematopoietic and retinal diseases, CNS-related hearing loss or glucose-6-phosphate dehydrogenase deficit.
6. Persons already treated with any of the study drugs during the last 30 days.
7. Pregnant or lactating women.
8. Any contraindications as per the Data Sheet of Hydroxychloroquine.

Methods S2. Rationale for hydroxychloroquine dosing and schedule

Hydroxychloroquine (HCQ) (Dolquine®) was administered at a dose of 800 mg on day 1, followed by 400 mg once daily for six days. The dose and regimen of HCQ were chosen based on pharmacokinetic simulations to achieve plasma and lung concentrations above the SARS-CoV-2 half-maximal effective concentration (IC50) observed in-vitro[2] for 14 days. According to pharmacological modelling conducted a total dose regimen 3,2g (OHCQ 800mg d1, 400mg d2-7) would give sufficient plasma levels (Fig A) and corresponding lung levels (Fig B) above the in vitro IC50 estimate (orange dots line). Plasma troughs would be nearer to 100ng/ml, compared to 70ng/ml for a lower dose regimen (total dose 2,0g; OHCQ 800mg d1, 400mg d2-4). Lung concentrations would be much higher (2-2.5 log higher), but the free log concentration in lung epithelial cells are what would matter, and this data is not known.

A



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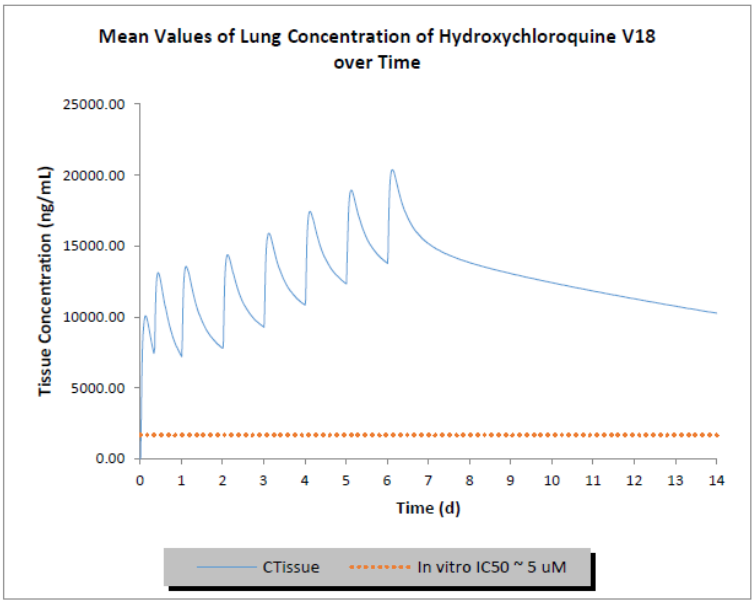


Methods S3. Summary of measurements and procedures performed at each study visit

All visits were performed by dedicated outbreak field teams of trained nurses and paramedical staff (Open Arms, Non-Governmental Organization). By the time of trial conduct, quarantine was mandatory for all exposed contacts, according to the National Department of Health guidelines; hence the likelihood that a participant could be exposed to other cases was low. Covid-19 index cases that generated the rings were enrolled in a nested trial aimed at investigating the efficacy of early treatment with hydroxychloroquine as therapeutic intervention for Covid-19 outpatients.[3]

Day 1

- Verification of selection criteria.
- Collection of written informed consent.
- Administration of a short questionnaire for symptoms of Covid-19
- Nasopharyngeal swab collection for SARS-CoV-2 PCR test.
- Epidemiological investigation: no. of days exposed to the index contact, place of contact, use of mask (both, index case and contact).

Study medications were dispensed free of charge to participants allocated in the intervention arm by the hospital pharmacy.

Days 3 and 7

- Phone call assessment of general health status, treatment compliance, and adverse events.

Any time during the entire follow-up

- Participants were provided with a phone number linked to a passive surveillance reporting system. When a participant reported Covid-19-like symptoms within the 14-day study period, the field team visited the participant at home for a general examination and nasopharyngeal swab collection for SARS-CoV-2 PCR.

Day 14

- Evaluation of health status, adverse events, and treatment compliance.
- Nasopharyngeal swab collection for SARS-CoV-2 PCR test.
- Finger-prick for IgM/IgG rapid test

SAE assessment

Safety outcomes included the frequency and severity of adverse events (AE), serious AE (SAE), and AE of special interest (e.g., cardiac) up to 28 days from treatment start. Causality was assessed by an external panel of pharmacovigilance consultants. SAEs were graded for causality and expectedness and reported immediately to the Contract Research Organization of the study sponsor and the trial pharmacovigilance consultancy (Asphalion, Barcelona) for independent adjudication of relatedness.

Adherence to treatment and crossover

Adherence was assessed using self-reports in telephone interviews (e.g., treatment and number of doses taken between interviews). Crossover was defined as unplanned conversion of control to intervention.

Data collection and cleaning

Study data were recorded electronically by the CTU during phone interviews, and on paper case record forms by the outbreak field teams during home visits and then entered into an electronic database by the data entry team of the sponsor. Data validation and cleaning were done by trial researchers with the support of a trial data management consultancy (Trial Form Support, Barcelona).

Rationale for the secondary outcomes

The secondary outcome was the incidence of SARS-CoV-2 infection, defined as either the RT-PCR detection of SARS-CoV-2 in a nasopharyngeal specimen or the presence of any symptom compatible with Covid-19: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorder(s), or diarrhea). The rationale for this outcome was to encompass definitions of Covid-19 used elsewhere[4,5] and all possible viral dynamics. We, therefore, assumed that if clinical suspicion is high, infection should not be ruled out based on a negative PCR alone—particularly early in the course of infection.[4]

Methods S4. Identification and quantification of the SARS-CoV-2 virus

The detection of the SARS-CoV-2 virus was performed from nasopharyngeal swabs at SYNLAB Diagnostics (Barcelona, Spain). RNA was extracted using an automated workstation (Hamilton Star, Hamilton, US) and subsequently amplified by PCR using TaqMan™ 2019-nCoV Assay Kit according to the manufacturer's protocol (Catalog number: A47532, Thermo Fischer Scientific Inc.). Positivity was recorded when an amplification curve with a Cycle threshold (Ct) < 40 was detected.

Viral load was quantified from nasopharyngeal swabs at IrsiCaixa laboratory (Badalona, Spain). RNA extraction was performed by using the Viral RNA/Pathogen Nucleic Acid Isolation kit, optimized for a KingFischer® instrument, following manufacturer's instructions (Catalog number: 4462359, Thermo Fischer). PCR amplification was based on the 2019-Novel Coronavirus Real-Time RT-PCR Diagnostic Panel guidelines and protocol developed by the American Center for Disease Control and Prevention (CDC).[6] Briefly, a 20 µL PCR reaction was set up containing 5 µL of RNA, 1.5 µL of N3 primers and probe (2019-nCov CDC EUA Kit, catalog no. 10006770, Integrated DNA Technologies) and 5 µL of TaqPath 1-StepRT-qPCR Master Mix (Thermo Fischer). Thermal cycling was performed at 50 ºC for 15 min for reverse transcription, followed by 95°C for 2 min and then 45 cycles of 95°C for 3 sec, 55°C for 30 sec, in the Applied Biosystems 7500 or QuantStudio5 Real-Time PCR instruments (Thermo Fischer). For absolute quantification, a standard curve was built using 1/5 serial dilutions of a SARS-CoV2 plasmid (2019-nCoV_N_Positive Control, catalog no. 10006625, $2x10^5$ copies/µL, Integrated DNA Technologies) and run in parallel with 300 study samples. The viral load of each sample (in copies/mL) was extrapolated from the standard curve and corrected by the corresponding dilution factor. Quantitative data from Covid-19 cases were used to assess PCR linearity and efficiency, fitting in a linear regression model and confirming the high reproducibility and efficiency of the assay. To assess the accuracy and feasibility of a qualitative estimate (i.e., positive vs negative) of SARS-Cov-2 viral load in contacts, 300 samples were determined using both, the quantitative and qualitative approaches and the correlation of Ct values obtained with the two approaches was calculated and plotted (Figure S2). Once confirmed the feasibility of the qualitative approach, the viral load of contacts was estimated from the corresponding Ct values.

Methods S5. Determination of IgM and IgG

The detection of SARS-CoV-2 antibodies was performed from fingertip blood on the day-14 visit using the VivaDiag™ COVID-19 lgM/IgG Rapid Test (VivaChek Biotech Co., Ltd, Hangzhou, China). The test is a colloidal gold immunochromatography detection kit that detects IgG and IgM antibodies against SARS-CoV-2 antigens. The test is CE-marked as meeting the Directive 98/79/EC of the European Parliament and of the Council on in-vitro diagnostic medical devices.

According to the manufacturer, sensitivity (IgM and IgG) was 81.3% for infection time 4-10 days, and 97.1% for infection time 11-24 days; specificity was 100%.[7,8] Clinical performance of the assay was also established by an independent evaluation using a specimen set of 288 plasma or serum samples (including 128 from PCR positive individuals). The results of the independent evaluation are summarized in the table below.

	IgM				**IgG**				**IgM or IgG**			
	Total N	**positive**	**%**	**95%CI**	**Total N**	**Positive**	**%**	**95%CI**	**Total N**	**positive**	**%**	**95%CI**
Sensitivity												
1 to 5 days	25	7	28.0	12.1-49.4	25	7	28.0	12.1-49.4	25	7	28.0	12.1.49.4
6-10 days	35	22	62.9	44.9-78.5	35	22	62.9	44.9-78.5	35	22	62.9	44.9-78.5
11-15 days	30	26	86.7	69.3-96.2	30	25	83.3	65.3-94.4	30	26	86.7	69.3-96.2
16-20 days	19	15	78.9	54.4-93.9	19	14	73.7	48.8-90.9	19	15	78.9	54.4-93.9
Specificity	99	5	94.9	88.6-98.3	99	4	96.0	90.0-98.9	99	5	94.9	88.6-98.3

We carried out the Rapid Test using 10μL of blood and following to the manufacturer instructions.[8] The result was determined by the observation of red test lines (IgM and IgG) and control line; the visible red IgM and/or IgG lines and C line indicated positive result, whereas only red C line appearance meant negative.

Table S1. Sensitivity analysis of study outcomes: complete-case analysis

	Control arm Events (%)	**Intervention arm Events (%)**	**RR* (95% CI)**
Primary outcome	N=1,198	N=1,116	
Overall (N = 2,314)			
PCR confirmed symptomatic Covid19**	74 (6.2%)	64 (5.7%)	0.86 (0.52, 1.42)
Clinical and laboratory criteria	60 (5.0%)	49 (4.4%)	
Hospital or vital records criteria	14 (1.2%)	15 (1.3%)	
PCR (-) at baseline (N =2,000)	N=1,042	N=958	
PCR-confirmed symptomatic Covid19	45 (4.3%)	29 (3.0%)	0.68 (0.34, 1.34)
Clinical and laboratory criteria	37 (3.6%)	24 (2.5%)	
Hospital or vital records criteria	8 (0.8%)	5 (0.5%)	
PCR (+) at baseline (N=314)	N=156	N=158	
PCR-confirmed symptomatic Covid19	29 (18.6%)	35 (22.2%)	1.02 (0.64, 1.63)
Clinical and laboratory criteria	23 (14.7%)	25 (15.8%)	
Hospital or vital records criteria	6 (3.9%)	10 (6.3%)	
Secondary outcomes (N= 2,000) †	N=1,042	N=958	
Covid19 either symptomatically compatible or PCR positivity regardless of symptoms	185 (17.8%)	179 (18.7%)	1.03 (0.77, 1.38)
Laboratory criteria ‡	67 (6.4%)	58 (6.1%)	
Clinical criteria ‖	150 (14.4%)	144 (15.0%)	
Hospital or vital records criteria	8 (0.8%)	5 (0.5%)	
Serology positivity on day 14	91 (8.7%)	137 (14.3%)	1.57 (0.94, 2.62)
IgM positivity	70 (6.7%)	100 (10.4%)	
IgG positivity	82 (7.9%)	118 (12.3%)	

RR: Risk ratio. **CI**: confidence interval.
***** Risk ratios are adjusted for contact-level variables (age, gender, region, and time of exposure).
† Excluding PCR positive at baseline.
** Marginal estimates for the primary outcome were 6.3% control, and 5.6% intervention (risk difference 0.6%)
† Excluding PCR positive at baseline.
‡ PCR confirmed either symptomatic or asymptomatic.
‖ Symptoms compatible with Covid-19 regardless of PCR result
The components of the primary and secondary outcomes are not mutually exclusive.

Table S2. Sensitivity analysis of study outcomes: PP population analysis

	Control arm Events (%)	Intervention arm Events (%)	RR* (95% CI)
Primary outcome	N=1,186	N=1,064	
Overall (N =2,250)			
PCR confirmed symptomatic Covid19	74 (6.2%)	61 (5.7%)	0.87 (0.52, 1.45)
Clinical and laboratory criteria	60 (5.1%)	48 (4.5%)	
Hospital or vital records criteria	14 (1.2%)	13 (1.2%)	
PCR (-) at baseline (N =1,946)	N=1,031	N=915	
PCR-confirmed symptomatic Covid19	45 (4.4%)	28 (3.0%)	0.68 (0.34, 1.36)
Clinical and laboratory criteria	37 (3.6%)	24 (2.6%)	
Hospital or vital records criteria	8 (0.8%)	4 (0.4%)	
PCR (+) at baseline (N=304)	N=155	N=149	
PCR-confirmed symptomatic Covid19	29 (18.7%)	33 (22.1%)	1.02 (0.62, 1.69)
Clinical and laboratory criteria	23 (14.8%)	24 (16.1%)	
Hospital or vital records criteria	6 (3.9%)	9 (6.0%)	
Secondary outcomes (N= 1,946) †	N=1,031	N=915	
Covid19 either symptomatically compatible or PCR positivity regardless of symptoms	184 (17.8%)	166 (18.1%)	1.00 (0.74, 1.37)
Laboratory criteria ‡	67 (6.5%)	58 (6.3%)	
Clinical criteria ‖	111 (10.8%)	106 (11.6%)	
Hospital or vital records criteria	6 (0.6%)	2 (0.2%)	
Serology positivity on day 14	91 (8.8%)	127 (13.9%)	1.58 (0.93, 2.68)
IgM positivity	70 (6.8%)	95 (10.4%)	
IgG positivity	82 (8.0%)	109 (11.9%)	

RR: Risk ratio. **CI**: Confidence interval.
***** Risk ratios are adjusted for contact-level variables (age, gender, region, and time of exposure).
† Excluding PCR positive at baseline.
‡ PCR confirmed either symptomatic or asymptomatic.
‖ Symptoms compatible with Covid-19 regardless of PCR result
The components of the primary and secondary outcomes are not mutually exclusive.

Table S3. Primary outcome measured at unscheduled PCR testing performed when ill versus PCR testing performed at day 14 (ITT population)

	Control arm Events (%)	**Intervention arm Events (%)**
N = 2,314	N=1,198	N=1,116
PCR-confirmed symptomatic Covid19	74 (6.2%)	64 (5.7%)
Unscheduled PCR testing performed when ill	44 (3.7%)	26 (2.3%)
PCR testing performed at day 14	16 (1.3%)	23 (2.1%)
Hospital or vital records criteria	14 (1.2%)	15 (1.3%)

Table S4. Viral load increase from baseline in participants who developed or did not develop Covid-19 (ITT population)

		Overall		**Control arm**		**Intervention arm**	
	N	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
		log_{10} copies/mL (SD)		log_{10} copies/mL (SD)		log_{10} copies/mL (SD)	
Did not develop Covid-19	2,176	3.02 (0.30)	3.40 (1.24)	3.01 (0.26)	3.36 (1.16)	3.02 (0.34)	3.44 (1.29)
Developed Covid-19	138	3.98 (1.74)	7.40 (2.22)	3.81 (1.53)	7.16 (2.21)	4.18 (1.98)	7.72 (2.25)

Legend. Specimens with negative PCR (undetectable viral load) were assigned a value of 3 Log_{10} copies per mL for the purpose of statistical analysis.
*Baseline PCR result was not available for 32 participants who did not develop Covid-19 and 3 participants who developed Covid-19.

SD: standard deviation.

Table S5. Distribution of symptoms observed among virologic confirmed disease versus symptomatic Covid-19 compatible illness (ITT population)

	PCR (+) and Symptoms N=138	PCR (-) and Symptoms N=307
Dyspnea, N (%)	25 (18.1%)	38 (12.3%)
Fever or chills, N (%)	71 (51.4%)	50 (16.1%)
Cough, N (%)	67 (48.6%)	95 (30.6%)
Olfactory or taste disorder, N (%)	37 (27.5%)	39 (12.6%)
Rhinitis, N (%)	20 (14.5%)	22 (7.1%)
Odynophagia, N (%)	8 (5.8%)	36 (11.6%)
Myalgia, arthralgia, fatigue or general malaise, N (%)	35 (25.4%)	34 (11.0%)
Headache, N (%)	17 (12.3%)	59 (19.0%)

Table S6. Descriptive summary of Adverse Events by symptoms (Safety population)

	Control arm N=1,300		**Intervention arm** N=1,197	
Abdominal pain	12	0.9%	197	16.5%
Ageusia	1	0.1%	6	0.5%
Anorexia	1	0.1%	5	0.4%
Anosmia	1	0.1%	8	0.7%
Arthralgia	0	0.0%	2	0.2%
Asthenia	7	0.5%	96	8.0%
Back pain	0	0.0%	3	0.3%
Black stools	0	0.0%	1	0.1%
Blurry vision	1	0.1%	7	0.6%
Chest pain	0	0.0%	2	0.2%
Chills	0	0.0%	1	0.1%
Constipation	0	0.0%	9	0.8%
Darkened skin	0	0.0%	1	0.1%
Death	3	0.2%	2	0.2%
Decompensation. cardiac	1	0.1%	0	0.0%
Diarrhea	22	1.7%	383	32.0%
Drowsiness	10	0.8%	109	9.1%
Dyspepsia	0	0.0%	2	0.2%
Dyspnea	0	0.0%	1	0.1%
Ear pain	0	0.0%	2	0.2%
Eczema	0	0.0%	1	0.1%
Flatulence	1	0.1%	20	1.7%
Headache	21	1.6%	188	15.7%
Hypoglycemia	0	0.0%	1	0.1%
Hypotension	0	0.0%	1	0.1%
Insomnia	0	0.0%	8	0.7%
Itchy rash	8	0.6%	51	4.3%
Localized itching	0	0.0%	2	0.2%
Malaise	0	0.0%	6	0.5%
Muscular pain	0	0.0%	9	0.8%
Nausea / Vomiting	11	0.8%	129	10.8%
Odynophagia	0	0.0%	7	0.6%
Palpitations	1	0.1%	5	0.4%
Pneumonia	12	0.9%	15	1.3%
Polyuria	1	0.1%	0	0.0%
Psoriasis flare-up	0	0.0%	1	0.1%
Rhinorrhea	1	0.1%	9	0.8%
Road traffic accident	1	0.1%	0	0.0%
Sores mouth	0	0.0%	2	0.2%
Stomach burning sensation	0	0.0%	12	1.0%
Stomach heaviness	0	0.0%	1	0.1%
Tachycardia	0	0.0%	0	0.0%
Tingling	7	0.5%	14	1.2%
Tinnitus	0	0.0%	8	0.7%
Urinary infection	2	0.2%	2	0.2%
Vertigo	0	0.0%	4	0.3%
Xerostomia	0	0.0%	3	0.3%

Note. A participant could have reported more than one AE during follow-up

Table S7. Serious adverse events descriptive table (Safety population)

	Study group	Age	SAE criteria	SAE description	ECG (QTc, ms.)	Days from enrollment	Adjudication
1	Intervention	84	Death	Pneumonia	Sinus rhythm (400)	7	Not related
2	Intervention	86	Hospitalization	Pneumonia	Atrial fibrillation (320)	7	Not related
3	Intervention	92	Death	Pneumonia	NA	11	Not related
4	Intervention	48	Hospitalization	Pneumonia	Sinus rhythm (360)	9	Not related
5	Intervention	66	Hospitalization	Pneumonia	Sinus rhythm (360)	12	Not related
6	Intervention	92	Hospitalization	Pneumonia	Atrial fibrillation (400)	8	Not related
7	Intervention	83	Death	Pulmonary embolism	Sinus rhythm (420)	13	Not related
8	Intervention	93	Death	Pneumonia	NA	9	Not related
9	Intervention	98	Death	Unknown death cause*	NA	2	Not related
10	Intervention	62	Hospitalization	Pneumonia	NA	0	Not Related
11	Intervention	24	Hospitalization	Pneumonia	NA	10	Not related
12	Intervention	60	Hospitalization	Pneumonia	Sinus rhythm (400)	5	Not related
13	Intervention	27	Hospitalization	Pneumonia	Sinus rhythm (380)	5	Not related
14	Intervention	97	Hospitalization	Heart failure exacerbation due to Covid-19	Sinus rhythm, negative T aVR (380)	8	Not related
15	Control	66	Hospitalization	Pneumonia	Sinus rhythm (380)	11	Not related
16	Control	62	Hospitalization	Pneumonia	Sinus rhythm (500)	18	Not related
17	Control	99	Death	Pneumonia	NA	3	Not related
18	Control	39	Hospitalization	Motorcycle accident	NA	11	Not related
19	Control	40	Hospitalization	Pneumonia	NA	14	Not related
20	Control	56	Hospitalization	Pneumonia	Sinus rhythm (430)	8	Not related
21	Control	77	Hospitalization	COPD exacerbation	NA	2	Not related
22	Control	77	Death	Pneumonia	NA	2	Not related
23	Control	74	Hospitalization	Pneumonia	Sinus rhythm (380)	3	Not related
24	Control	85	Death	Pneumonia	NA	8	Not related
25	Control	87	Death	Unknown death cause	NA	6	Not related
26	Control	95	Death	Unknown death cause	NA	3	Not related
27	Control	74	Hospitalization	Pneumonia	Sinus rhythm (410)	4	Not related
28	Control	86	Death	Urinary Sepsis	NA	3	Not related
29	Control	85	Death	Unknown death cause	NA	9	Not related
30	Control	92	Death	Pneumonia	NA	1	Not related
31	Control	54	Hospitalization	Pneumonia	Sinus rhythm (410)	10	Not related

*The patient did not take any dose of the study medication.
NA = not available

Remarks:

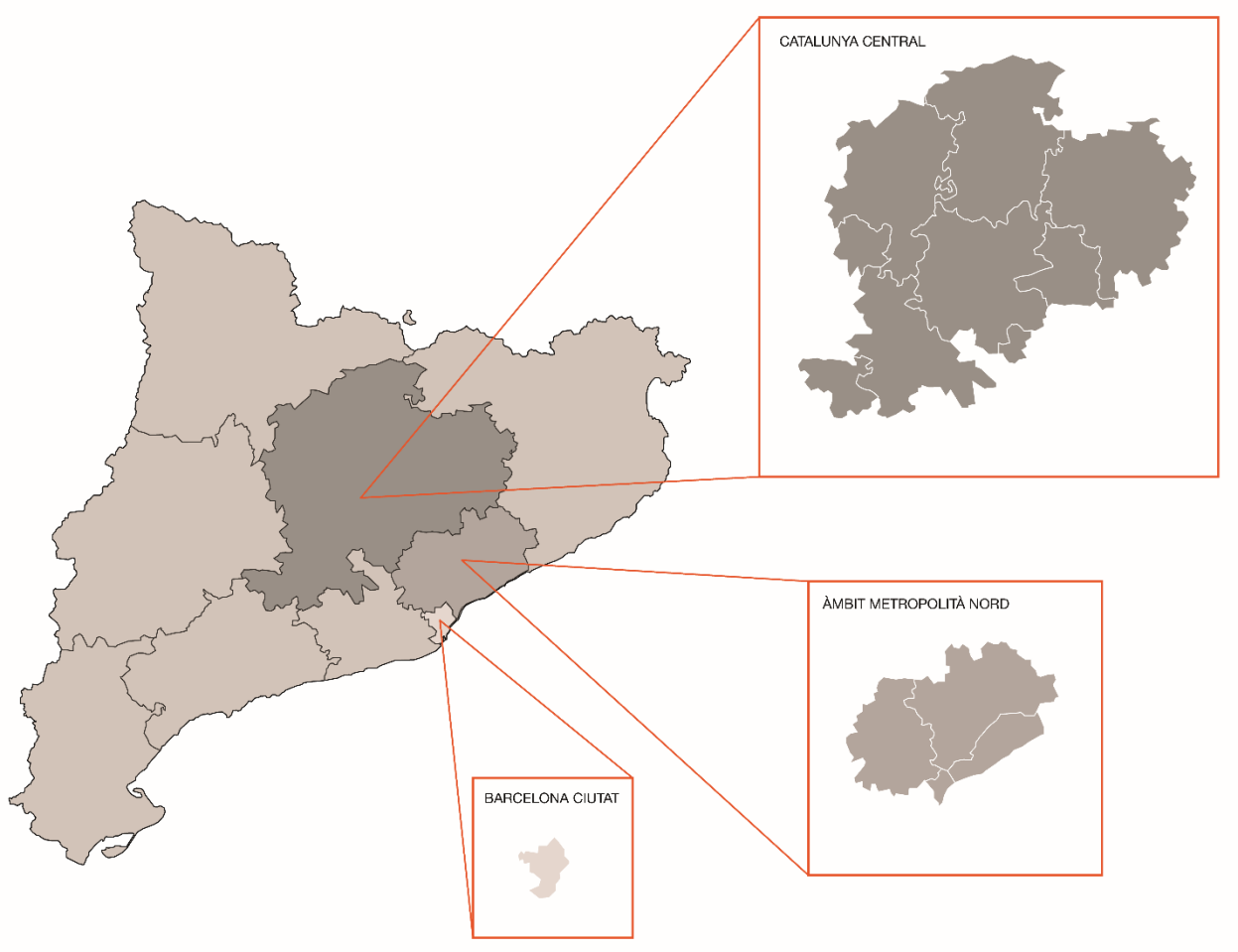
1. ECGs were not planned at entry or as follow-up procedure in the trial. ECG were retrieved from medical records once a SAE or AESI were reported.
2. Exclusion criteria for enrolment comprised known long QT and contraindicated medications with HCQ.
3. To investigate relatedness with experimental drug, former ECG were investigated for long QT congenital syndrome and for current medications likely to interfere with HCQ.
4. Recorded episodes are described according to the timing of HCQ intake and its possible relatedness.
5. Relatedness to the study drug and adjudication were assessed by an external pharmacovigilance board.

Table S8. Adverse events of special interest (Safety population)

	Study group	Age (Sex)	Adverse Event (duration)	Severity	Previous historic ECG	Remark	Relationship to study drug*	Action taken
1	Intervention	51 (F)	Palpitations (minutes)	Mild	Normal	Previous similar episodes anxiety-related	Unlikely	Self-limited
2	Intervention	93 (F)	Palpitations (minutes)	Severe	Normal	COVID-19 related symptoms Respiratory failure Death (12/04/20)	Unlikely	Hospital admission
3	Intervention	45 (F)	Palpitations (recurrent for 14 days)	Mild	Normal	No syncope or vegetative response during the episodes	Possible	Self-limited
4	Intervention	37 (F)	Palpitations (minutes)	Mild	NA	Single episode	Possible	Self-limited
5	Intervention	59 (F)	Palpitations (minutes)	Mild	NA	Anxiety, dizziness, and chest discomfort	Possible	Investigational medical product stopped by the patient
6	Control	40 (F)	Palpitations (minutes)	Mild	NA	Anxiety, dizziness, and chest discomfort	Not applicable	Self-limited

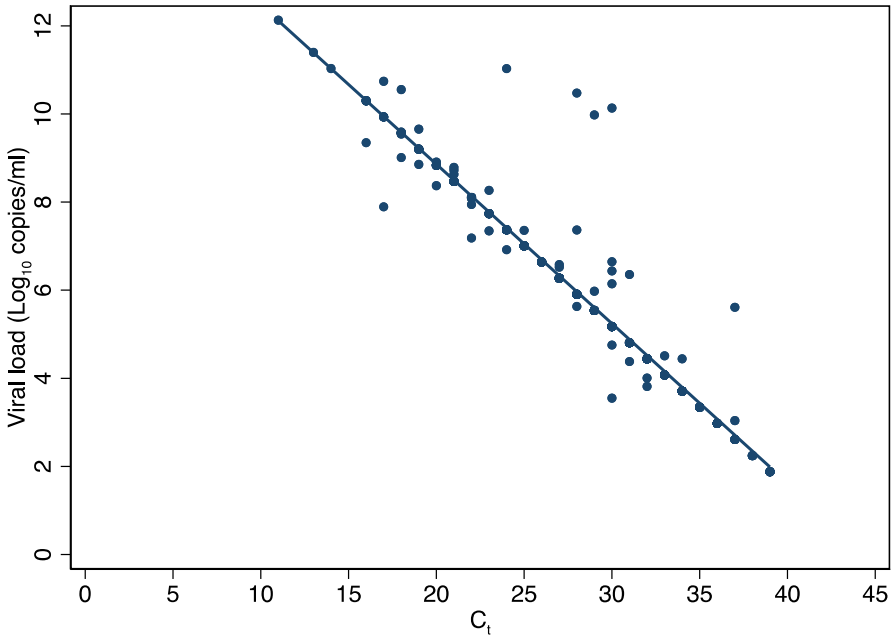
*Relatedness to the study drug and adjudication were assessed by an external pharmacovigilance board.
NA: Not Available, **bpm**: beats per minute

Figure S1. Map of the study areas



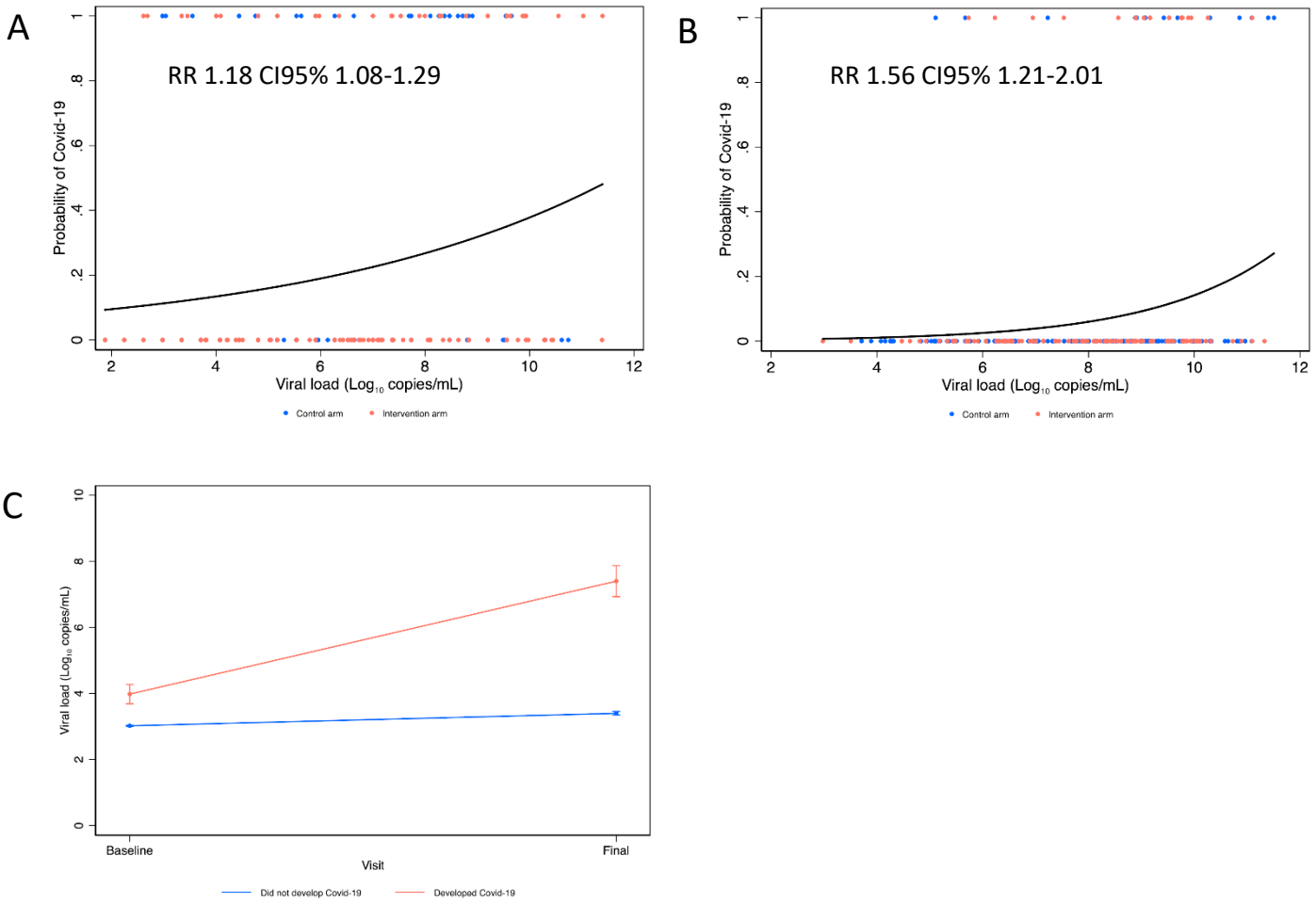
Legend. Three health regions (darker-brown shadowed) out of 9 health regions in Catalonia covering 4,206,440 inhabitants (i.e., 60% of the Catalan population): *Catalunya central*, *Àmbit Metropolità Nord*, and *Barcelona Ciutat.*

Figure S2. Determination of qPCR efficiency and linearity based on quantitative data of patient samples



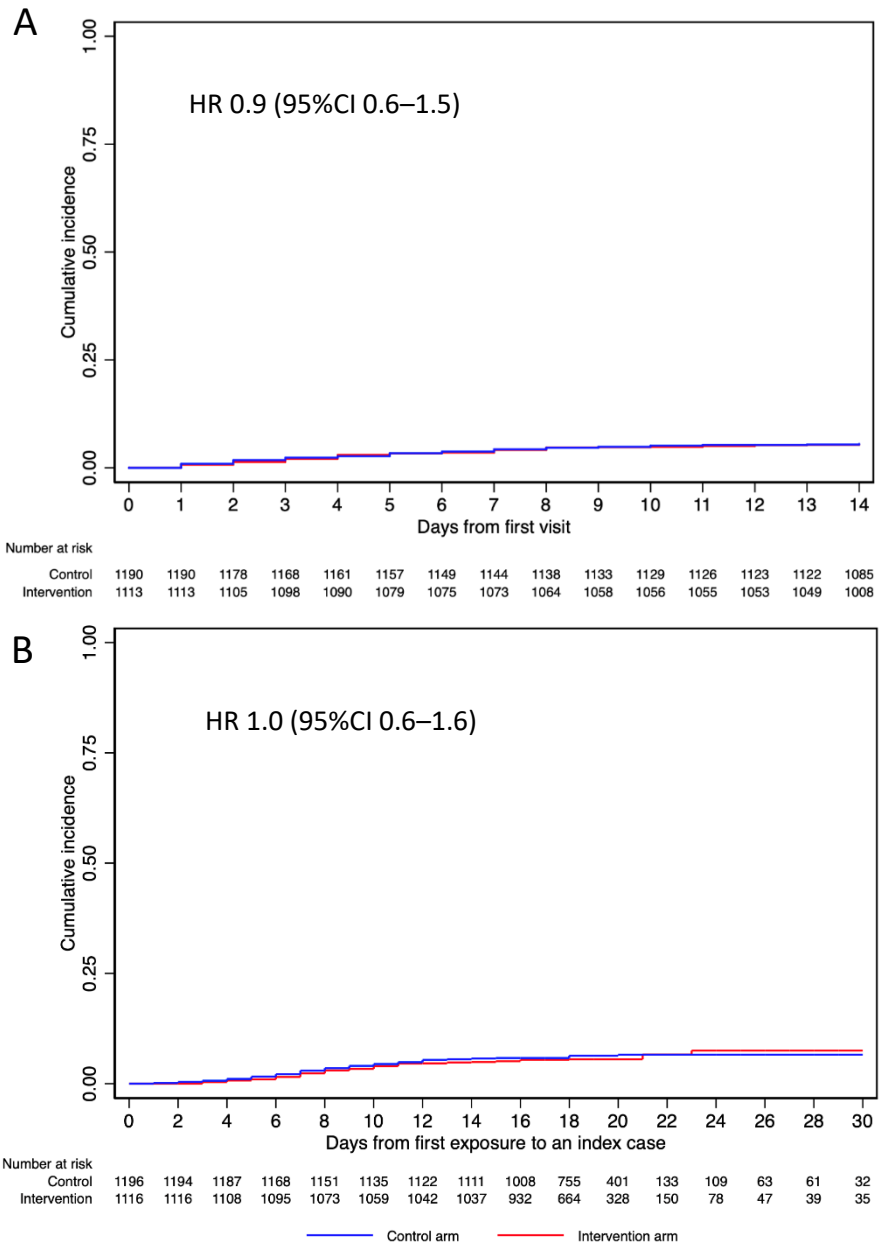
Legend. Correlation between Ct of qualitative SARS-CoV2 determinations (Y-axis) and quantitative data (x-axis) from 300 samples determined with both methods. A correlation coefficient of 0.93 was obtained, allowing the use of qualitative Ct data for the estimation of viral load in contacts.

Figure S3. Association of baseline viral load of participants and index cases with breakthrough Covid-19 events (ITT population)



Legend. Panels A and B show the association of the baseline viral load of participants (A) and the index case (B) with the likelihood of developing PCR-confirmed symptomatic Covid-19 in the overall modified intention-to-treat population (aggregated data for the control and intervention arms). The dots are participants with (=1) or without (=0) the primary outcome of PCR-confirmed Covid-19. Panel C shows the viral load increase from baseline in participants who developed or did not develop Covid-19 (details are provided in Table S4).

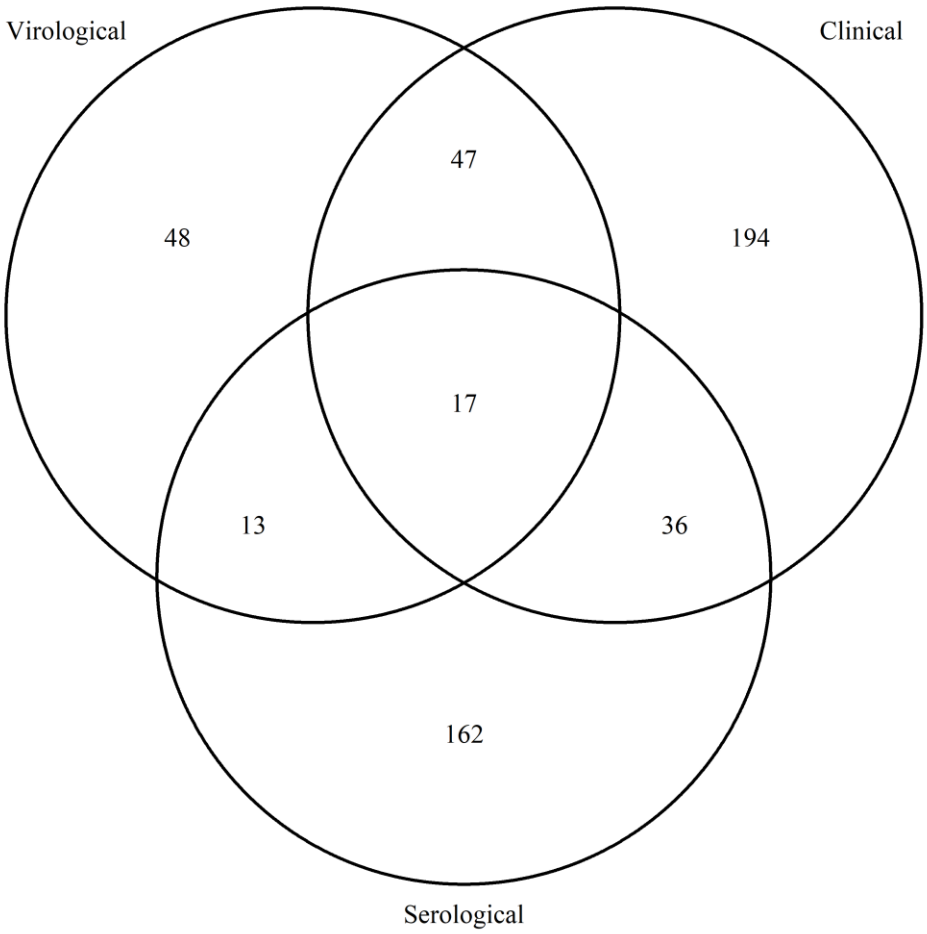
Figure S4. Time to primary outcome (ITT population)



Legend. Panel A shows time to onset of symptomatic illness from visit on day 1 (median 5.0 days, control arm vs 4.0 days, intervention arm). Panel B shows time to onset of symptomatic illness from initial exposure to an index case (median 8.0 days, control arm vs 8.0 days, intervention arm)

Note. Primary outcome events were recorded at unscheduled PCR testing performed when ill (n=67) or tested on day 14 (n=39). For this analysis we recorded the time of onset of symptomatic illness rather than the date of PCR collection.

Figure S5. Overlap of PCR positive, symptoms positive, and antibody IgM/IgG positive events (ITT population)



Legend. The Venn diagram shows the overlap of PCR positive (virological criteria), symptoms positive (clinical criteria), and antibody IgM/IgG positive (serological criteria) in the overall ITT population (aggregated data of the control and intervention arms).

Appendix references

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