Chloroquine & Hydroxychloroquine

A Review of Pertinent Drug Information for SARS-CoV-2

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Data updated August 7, 2020

Updates in this Presentation

- **Efficacy Data:**
  - Multicenter RCT HCQ ± Azithromycin in hospitalized patients
  - RECOVERY Trial Specifics
- **Safety data**
  - From Multicenter RCTs

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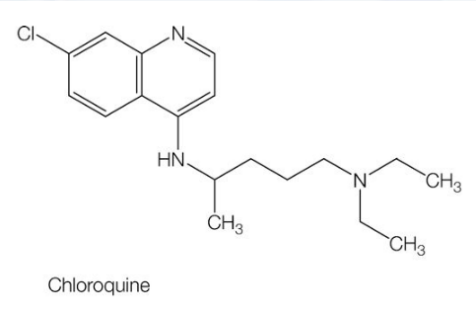
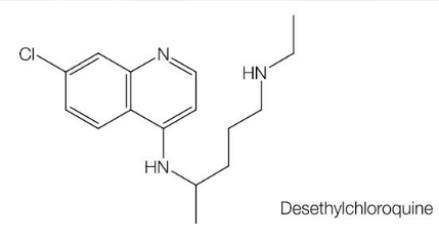
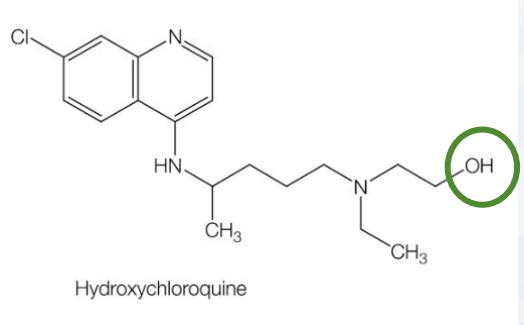
First things First

Chloroquine vs. Hydroxychloroquine







Both possess antiviral activity and are metabolized to the **same active metabolites.** The proportion of metabolite conversion may vary and the relative activity of parent compound vs. metabolite is unknown.

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Barber BE, Eisen DP. "Chloroquine" In Kucers' The Use of Antibiotics Sixth Edition.
Lim H et al. Antimicrob Agents Chemother 2009;53(4):1468-1475.
Projean D et al. Drug Metab Dispos 2003;31(6):748-54.

Dosing (According to the PI)

• Hydroxychloroquine

200 mg tablet (salt form) = 155 mg base
As little as 1-2 grams have proved fatal

Indication	Dose
Malaria Treatment	Adults: LD 800 mg x1 then 400mg daily x 3 (first dose 6-8h after load) Peds (≥6 years): 10mg base/kg x1 then 5mg base/kg x3 (first dose 6h after load)
Rheumatoid arthritis	400-600 mg daily, administered as a single or divided daily dose
Lupus erythematosus	400 mg once or twice daily

• Chloroquine

500 mg tablet (salt form) = 300 mg base
As little as 1 g may be fatal in children

Indication	Dose
Malaria Treatment	Adults: LD 1000 mg x1 then 500mg x3 at 6h, 24h, 36h Peds (≥6 years): 10mg base/kg x1 then 5mg base/kg x3 (first dose 6h after load)

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Plaquenil [Hydroxychloroquine] Package Insert. Last revised Aug 26, 2019. http://products.sanofi.ca/en/plaquenil.pdf.
Aralen [Chloroquine] Package Insert. Last Revised 2017.

HCQ Dosing in COVID-19

Citation	Loading dose	Total daily dose	Regimen
~~FDA~~	~~yes~~	~~400 mg~~	~~800 mg x1 day then 400mg x 4-7 days~~
Yao et al (*in vitro*) NCT 04341727	yes	400 mg	400 mg BID x1 day then 200mg BID x4 days
Gautret et al	no	600 mg	200 mg TID x 10 days
Arshad et al	yes	400 mg	400 mg BID x1 day then 200 mg BID x4 days
Cavalcanti et al	no	800 mg	400 mg BID x7 days
RECOVERY	Yes	1600 mg	800mg x 2 (on day 1) then 400 mg BID x 9 days

EUA Retracted 6.15.20

U.S. Food and Drug Adminsitration (FDA). https://www.fda.gov/media/136537/download. Accessed 4.13.20
Yao X et al. Clin Infect Dis 2020 Mar 9. doi: 10.1093/cid/ciaa237
Gautret et al. Int J Antimicrob Agents. 2020 Mar 20. doi: 10.1016/j.ijantimicag.2020.105949
Arshad S et al. Jul 2 2020. IJID. https://doi.org/10.1016/j.ijid.2020.05.099
Cavalcanti et el. Jul 23 2020. NEJM. DOI: 10.1056/NEJMoa2019014
https://www.fda.gov/media/138945/download. Accessed 6.15.2a0
Horby et al. Jul 15 2020. medRxiv. https://doi.org/10.1101/2020.07.15.20151852

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CQ Dosing in COVID-19

Citation	Loading dose	Total daily dose	Regimen
FDA	yes	1000 mg	1000 mg x1 day then 500 mg daily x4-7 days
Liu et al	no	1000 mg	500 mg BID up to 10 days
NCT04328493 Vietnam	yes	500mg	1200mg x 1 day then 500 mg daily (300mg base) x 9 days
NCT04333628 Israel	no	125 – 1000 mg	125 mg daily (low dose) OR 500 mg BID x7 days
NCT04323527 Brazil	yes/no	450 – 1200 mg	450 mg BID x 1 day then 450 mg daily x 4days (low dose) ~~600 mg BID x 10 days~~
NCT04341727 U.S.A.	yes	1000 mg	1000 mg x1 then 500 mg BID x 5 days total
NCT 04340544	no	600 mg	600mg daily x 7 days

EUA Retracted 6.15.20

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Liu et al. 13 Feb 2020. http://www.chictr.org.cn/showproj.aspx?proj=49263.
https://clinicaltrials.gov/ct2/show/record/NCT04328493. Accessed 4.13.20
https://clinicaltrials.gov/ct2/show/NCT04341727. Accessed 4.13.20
https://clinicaltrials.gov/ct2/show/NCT04333628. Accessed 4.13.20
https://clinicaltrials.gov/ct2/show/NCT04323527. Accessed 4.13.20
https://www.fda.gov/media/138945/download. Accessed 6.15.20

Mechanism of Action

- **Direct antiviral activity**
  - Intracellular alkalinization inhibits pH-dependent steps of viral replication
  - Impaired viral receptor glycosylation
- **Immune modification**
  - Reduces cytokine production, especially IL-1 and IL-6
  - Inhibits toll-like receptor (TLR) signaling

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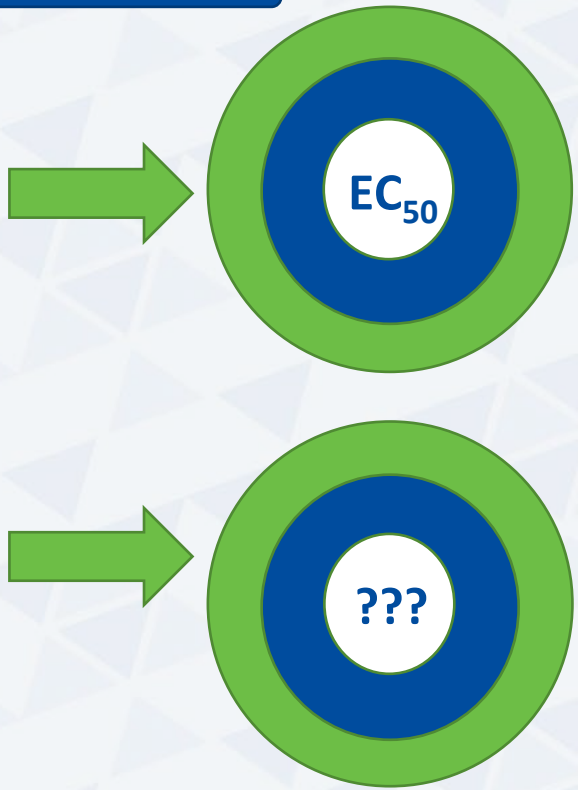
PD Target

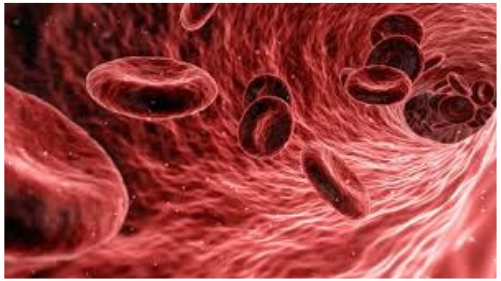


EC50: Drug concentration required to achieve 50% of maximum observed SARS-CoV-2 elimination

Ben-Zvi I et al. Clin Rev Allergy Immunol 2012;42(2):145-53.
Barber BE, Eisen DP. "Chloroquine" In Kucers, 6th Ed.

HCQ Dosing and Pharmacokinetics

- Hydroxychloroquine
  - V_D = 2,851 ± 2,147 liters[Lim]
  - $T_{½}$ = 5-40 days[Perinel]
  - Serum trough concentrations: 0 – 2 mg/L[Perinel]



vs.

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Lim et al. Antimicrob Agents Chemother 2009; 53(4):1468.
Perinel et al. Clin Infect Dis. 07 April 2020. https://doi.org/10.1093/cid/ciaa394.
Arnold S et al. Clin Transl Sci. 2020 Apr 8. doi: 10.1111/cts.12797.

Toxicity: QTc Prolongation

Design	Single center retrospective investigation
Sites	Boston Massachusetts, Mar 1 – Apr 7, 2020
Inclusion	N = 90 Inpatients, +SARS-CoV2 PCR, ≥1 day of HCQ

N = 90

HCQ (n = 37)
400 mg BID day 1
400 mg daily x 4 days

HCQ + Azith (n = 53)

Initial QTc (ms)	Post-Treatment Peak (ms)	QTc > 500 ms	Δ QTc ≥ 60 ms
474 (454-487)	480 (444-502) Δ QTc = 5.5	19%	3%
442 (427-461)	458 (449-492) Δ QTc = 23	21%	13%

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Mercuro NJ et al. JAMA Cardiol. Doi:10:1001/jamacardio.2020.1834
ISMP. Acute Care ISMP Medication Safety Alert. April 9, 2020; 25(7).

Incidence of Cardiac Toxicity Across Randomized Studies

Study	Relevant exclusions	QTc Prolongation			Cardiac Toxicity			
		HCQ	SOC			HCQ	SOC	
RECOVERY 1561 HCQ 3155 SOC	Pts with known prolonged QTc	**Not reported**			**SVT** **Vtach/fib** **AV block** **TdP**	6.9% 0.9% 0.1% 1 case	5.9% 0.7% 0.1% 0 cases	
Cavalcanti et al 239 HCQ + Azith 199 HCQ 177 Control* *neither HCQ nor Azith	History of severe Vtach or QTc ≥ 480	**HCQ + Azith**	**HCQ**	**Control**		**HCQ + Azith**	**HCQ**	**Control**
		QTc > 480/Number Tested			**Arrhythmia**	1.3%	1.5%	0.6%
		17/116 (15%)	13/89 (15%)	1/58 (2%)	**SVT**	0.4%	1%	0%
					Vtach	0%	0%	0%
					MI	0.4%	0%	0%
Lofgren et al 3 RCTs for **PrEP**, PEP, PET 495 HCQ 2x weekly 494 HCQ 1x weekly 494 Placebo	Known prolonged QT Meds for Arrhythmia Structural or ischemic heart disease Family history of >QT Meds that prolong QT	**HCQ**	**Placebo**			**HCQ 2x**	**HCQ 1x**	**Placebo**
		Not collected			**Arrhythmia**	1 (0.2%)	0 (0%)	1 (0.2%)

Cavalcanti et el. Jul 23 2020. NEJM. DOI: 10.1056/NEJMoa2019014
Horby et al. Jul 15 2020. medRxiv. https://doi.org/10.1101/2020.07.15.20151852
Lofgren et al. Jul 23 2020. medRxiv. doi.org/10.1101/2020.07.16.20155531

Incidence of Cardiac Toxicity Across Randomized Studies

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		HCQ	SOC			HCQ	SOC	
RECOVERY 1561 HCQ 3155 SOC	Pts with known prolonged QTc	**Not reported**			**SVT** **Vtach/fib** **AV block** **TdP**	6.9% 0.9% 0.1% 1 case	5.9% 0.7% 0.1% 0 cases	
Cavalcanti et al 239 HCQ + Azith 199 HCQ 177 Control* *neither HCQ nor Azith		17/116 (15%)	13/89 (15%)	1/58 (2%)	**SVT** **Vtach** **MI**	0.4% 0% 0.4%	1% 0% 0%	0% 0% 0%
Lofgren et al 3 RCTs for **PrEP**, PEP, PET 495 HCQ 2x weekly 494 HCQ 1x weekly 494 Placebo	Known prolonged QT Meds for arrhythmia Structural or ischemic heart disease Family history of >QT Meds that prolong QT	**HCQ**	**Placebo**			**HCQ 2x**	**HCQ 1x**	**Placebo**
		Not collected			Arrhythmia	1 (0.2%)	0 (0%)	1 (0.2%)

Cardiac toxicity was a low frequency event and no different between HCQ and Control arms

Cavalcanti et el. Jul 23 2020. NEJM. DOI: 10.1056/NEJMoa2019014
Horby et al. Jul 15 2020. medRxiv. https://doi.org/10.1101/2020.07.15.20151852
Lofgren et al. Jul 23 2020. medRxiv. doi.org/10.1101/2020.07.16.20155531

Available Data

Mar 6: Chen J et al.
1st clinical data published HCQ (N = 30)

Mar 17: Gautret et al.
HCQ + Azith (N = 36)

Mar 27: Gautret et al.
HCQ + Azith observational study (N = 80)

Mar 28: Molina et al.
No evidence for HCQ + Azith in severe infection (N = 11)

Apr 10: Chen et al.
RCT HCQ + SOC vs. SOC alone (N = 62)

Apr 14: Tang et al.
RCT HCQ + SOC vs. SOC alone (N = 150)

Apr 23: Magagnoli et al.
Retrospective multicenter VA study (N = 368)

May 11: Rosenberg et al.
Retrospective multicenter NY study (N = 1438)

Jun 5:
RECOVERY trial, RCT stops enrolling HCQ (N = 1542)

Jul 1: Arshad et al.
Retrospective multicenter Detroit study (N = 2541)

Jul 23: Cavalcanti et al.
RCT HCQ ± Azith in mild/mod disease (N = 667)

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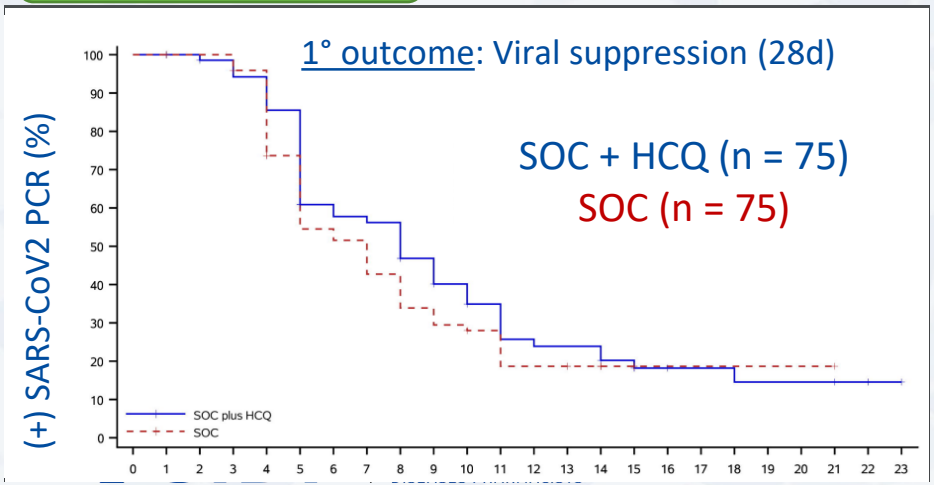
J Zhejiang Univ (Med Sci) 2020, Vol. 49 Issue (1): 0-0 DOI: 10.3785/j.issn.1008-9292.2020.03.03
International Journal of Antimicrobial Agents – In Press 17 March 2020 DOI : 10.1016/j.ijantimicag.2020.105949
Médecine et Maladies Infectieuses 28 Mar 2020 https://doi.org/doi:10.1016/j.medmal.2020.03.006
Chen et al. MedRxiv April 10, 2020. doi.org/10.1101/2020.03.22.20040758
Bhimraj et al. 11 April 2020 https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
Tang et al. MedRxiv. 14 April 2020. https://doi.org/10.1101/2020.04.10.20060558
Magagnoli et al. April 23, 2020. doi.org/10.1101/2020.04.16.20065920
https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19 [Accessed 6.8.20]
Arshad S et al. Jul 2 2020. IJID. https://doi.org/10.1016/j.ijid.2020.06.099
Cavalcanti et el. Jul 23 2020. NEJM. DOI: 10.1056/NEJMoa2019014
https://www.fda.gov/media/138945/download. Accessed 6.15.2a0
Horby et al. Jul 15 2020. medRxiv. https://doi.org/10.1101/2020.07.15.20151852

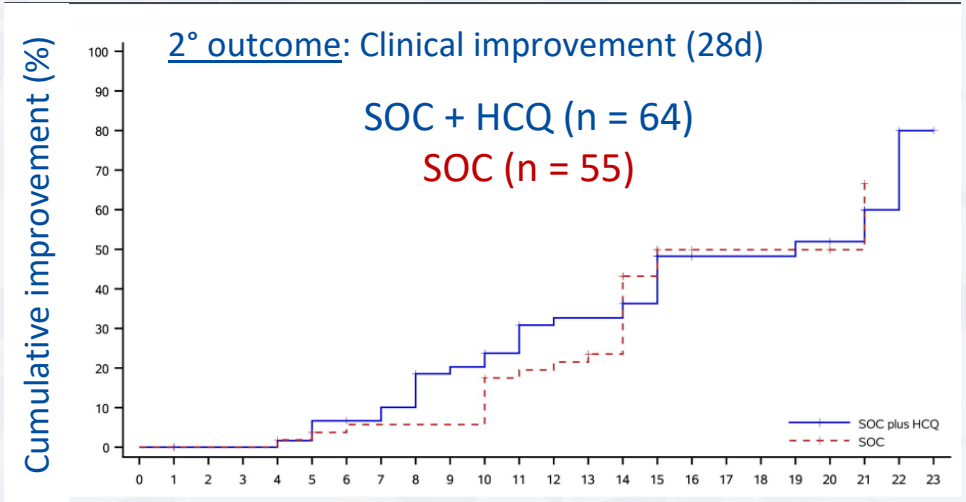
HCQ in COVID-19, An open-label RCT

Design	Multicenter, parallel, open-label, randomized
Sites	16 centers in China (Feb 2020)
Intervention	Treatment: HCQ 1200 daily x 3 days then 800 mg daily x 2-3 weeks + SOC vs. SOC alone

16.6 days from onset to randomization

Tang et al. MedRxiv. 14 April 2020. doi.org/10.1101/2020.04.10.20060558

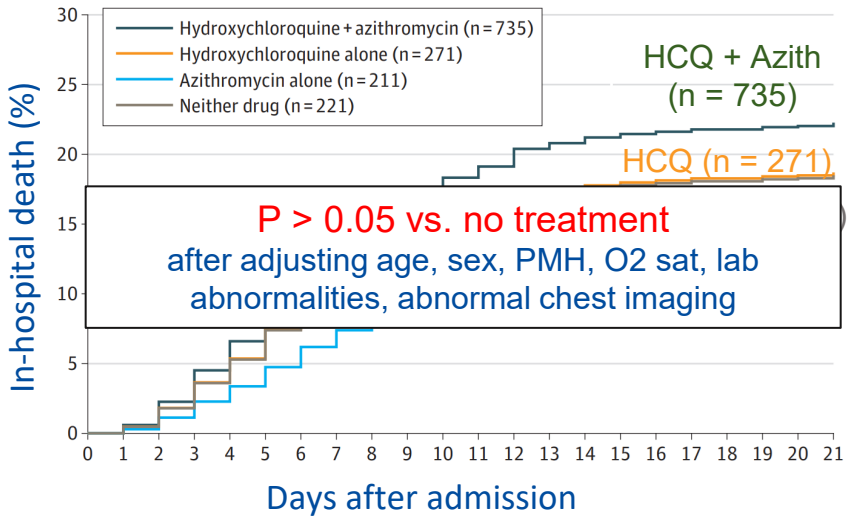




HCQ in COVID-19, New York City Data

Design	Retrospective, multicenter cohort of COVID-19 inpatients
Sites	25 Hospitals in New York Metropolitan Region (Mar 15-28, 2020) N = 7914 patients identified 2362 randomly selected (30% per hospital) 1475 abstracted
Intervention	4 Treatment Arms: Hydroxychloroquine + Azithromycin (51%) / Hydroxychloroquine

1° outcome: In-Hospital Mortality



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2° outcomes: Cardiac arrest, Arrthymia, Prolonged

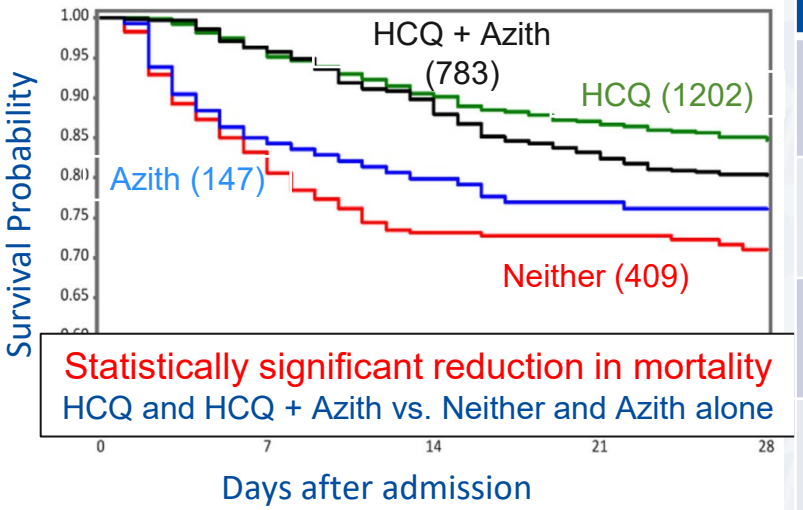
Outcome (OR, 95% CI)	HCQ + Azith	HCQ	Azithromycin	HCQ
Comparator	neither drug	neither drug	neither drug	azithromycin
Cardiac arrest	2.13 (1.12-4.05)	1.91 (0.96-3.81)	0.64 (0.27-1.56)	1.92 (0.99-3.74)
Abnormal ECG	1.55 (0.89-2.67)	1.50 (0.88-2.58)	0.95 (0.47-1.94)	1.58 (0.77-3.24)

Rosenberg ES et al. JAMA. 11 May 2020.
doi:10.1001/jama.2020.8630

HCQ in COVID-19, Detroit Data

Design	**Retrospective, multicenter cohort of COVID-19 inpatients**
Sites	**6 Hospitals in Southeast Michigan (Mar 10 – May 2, 2020) -- N = 2541 patients**
Intervention	**4 Treatment Arms: Hydroxychloroquine + Azithromycin (783) / Hydroxychloroquine (1202)**

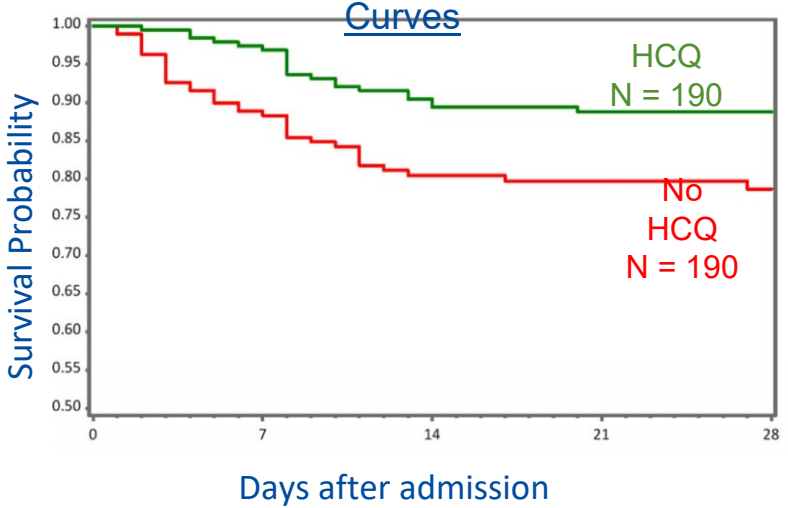
1° outcome: In-Hospital Mortality



Statistically significant reduction in mortality
HCQ and HCQ + Azith vs. Neither and Azith alone

Study Arm	Use of Dexamethasone
HCQ + Azith	74%
HCQ	79%
Azith	39%
Neither	36%

Propensity-Matched Kaplan-Meier Survival Curves



Arshad S et al. IJID. 2 Jul 2020.

RECOVERY Trial:

Randomized Evaluation of COVid-19 thERapY

Randomization A

- No treatment
- Lopinavir/r
- Corticosteroids
- HCQ*
- Azithromycin

±

Randomization B

- No additional treatment
- Convalescent Plasma

±

2nd Randomization for progressive dz

- No additional treatment
- Tocilizumab

*HCQ Dose: 800mg then 800mg after 6h then 400mg q12h x 9 days

5% of participants underwent 2nd randomization

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https://www.recoverytrial.net/files/recovery-protocol-v6-0-2020-05-14.pdf Accessed 6.8.20

Horby et al. Jul 15 2020. medRxiv. https://doi.org/10.1101/2020.07.15.20151852

RECOVERY Trial: Press Release[6.5.20] Preprint[7.15.20]

No Clinical Benefit from use of HCQ

Enrollment

- No treatment (n = 3132)
- Lopinavir/r
- Corticosteroids
- HCQ (n = 1542)
- Azithromycin

	HCQ N = 1561	Control N = 3155
Age	65	65
Female	38%	37%
Any	57%	57%
Comorbidities	27%	27%
DM	27%	25%
Heart disease	21%	23%
Lung disease		
O_2 Supplementation	60%	59%
	17%	17%
Mech vent/ECMO	23%	24%
No O_2 Supplement		
Median tx duration	6 (IQR 3-10)	--
Azithromycin	17%	19%
Dexamethasone	8%	9%

28-day mortality

- No treatment (23.5%)
- HCQ (25.7%)

HR = 1.11
95% CI [0.98-1.26]

https://www.recoverytrial.net/files/recovery-protocol-v6-0-2020-05-14.pdf
Accessed 6.8.20
Horby et al. Jul 15 2020. medRxiv.
https://doi.org/10.1101/2020.07.15.20151852

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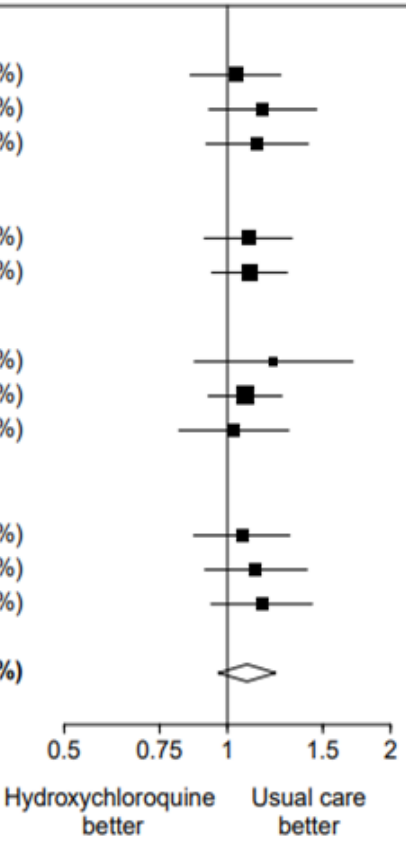
RECOVERY Trial: Study Details

Effects of allocation to HCQ on 28-day mortality

	Hydroxychloroquine	Usual care	RR (95% CI)
Age, years (χ^2_1= 0.4; p=0.51)			
<70	160/925 (17.3%)	314/1874 (16.8%)	1.04 (0.85–1.25)
≥70 <80	126/342 (36.8%)	206/631 (32.6%)	1.16 (0.92–1.46)
≥80	132/294 (44.9%)	268/650 (41.2%)	1.13 (0.91–1.41)
Days since symptom onset (χ^2_1= 0.0; p=0.97)			
≤7	176/622 (28.3%)	338/1275 (26.5%)	1.09 (0.91–1.32)
>7	240/930 (25.8%)	444/1871 (23.7%)	1.10 (0.94–1.29)
Respiratory support at randomization (χ^2_1= 0.6; p=0.45)			
No oxygen received	57/362 (15.7%)	99/750 (13.2%)	1.22 (0.87–1.70)
Oxygen only	251/938 (26.8%)	473/1873 (25.3%)	1.08 (0.92–1.26)
Invasive mechanical ventilation	110/261 (42.1%)	216/532 (40.6%)	1.03 (0.81–1.30)
Baseline risk (χ^2_1= 0.3; p=0.57)			
<30%	145/994 (14.6%)	275/1993 (13.8%)	1.06 (0.87–1.30)
≥30% <45%	135/317 (42.6%)	245/635 (38.6%)	1.13 (0.91–1.40)
≥45%	138/250 (55.2%)	268/527 (50.9%)	1.16 (0.93–1.43)
All participants	**418/1561 (26.8%)**	**788/3155 (25.0%)**	**1.09 (0.96–1.23) p=0.18**



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y et al. Jul 15 2020. medRxiv. doi.org/10.1101/2020.07.15.20151852

Cavalcanti et al

HCQ ± Azithromycin in Mild-Moderate COVID19

Multicenter, randomized, open-label trial

Patients

INCLUDED

≥ 18 years old
≤ 14d from onset
O_2 < 4L/min

EXCLUDED

Use of CQ, HCQ Use of macrolide
QTc > 480
h/o severe Vtach

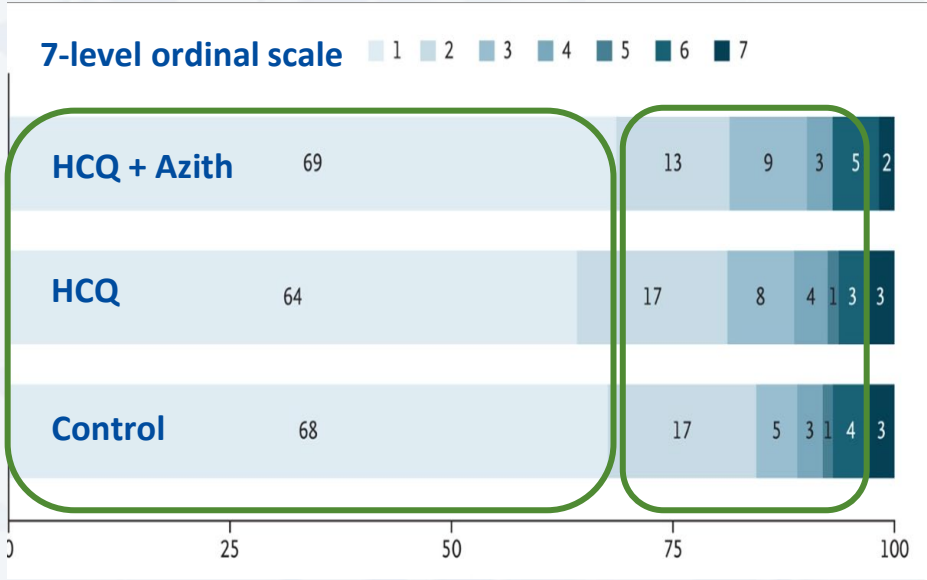
Treatment Groups

HCQ + Azith N=217
HCQ: 400 mg BID x 7d
Azith: 500mg daily x 7d

HCQ N=221
400 mg BID x 7d

CONTROL N = 227
Immunomodulators ± Steroids ± Abx ±Antivirals

Clinical Status on Day 15



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Cavalcanti et al. New Engl J Med. Jul 23, 2020. DOI: 10.1056/NEJMoa2019014

HCQ in Non-hospitalized Adults

Annals of Internal Medicine ORIGINAL RESEARCH

Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19

A Randomized Trial

Caleb P. Skipper, MD; Katelyn A. Pastick, BSc; Nicole W. Engen, MS; Ananta S. Bangdiwala, MS; Mahsa Abassi, DO, MPH; Sarah M. Lofgren, MD; Darlisha A. Williams, MPH; Elizabeth C. Okafor, BSc; Matthew F. Pullen, MD; Melanie R. Nicol, PharmD, PhD; Alanna A. Nascene, BA; Kathy H. Hullsiek, PhD; Matthew P. Cheng, MD; Darlette Luke, PharmD; Sylvain A. Lother, MD; Lauren J. MacKenzie, MD, MPH; Glen Drobot, MD; Lauren E. Kelly, PhD; Ilan S. Schwartz, MD, PhD; Ryan Zarychanski, MD, MSc; Emily G. McDonald, MD, MSc; Todd C. Lee, MD, MPH; Radha Rajasingham, MD; and David R. Boulware, MD, MPH

Background: No effective oral therapy exists for early coronavirus disease 2019 (COVID-19).

Objective: To investigate whether hydroxychloroquine could reduce COVID-19 severity in adult outpatients.

Design: Randomized, double-blind, placebo-controlled trial conducted from 22 March through 20 May 2020. (ClinicalTrials.gov: NCT04308668)

Setting: Internet-based trial across the United States and Canada (40 states and 3 provinces).

Participants: Symptomatic, nonhospitalized adults with laboratory-confirmed COVID-19 or probable COVID-19 and high-risk exposure within 4 days of symptom onset.

Intervention: Oral hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 more days) or masked placebo.

drome coronavirus 2 (SARS-CoV-2) or epidemiologically linked exposure to a person with laboratory-confirmed infection; 56% (236 of 423) were enrolled within 1 day of symptoms starting. Change in symptom severity over 14 days did not differ between the hydroxychloroquine and placebo groups (difference in symptom severity: relative, 12%; absolute, −0.27 points [95% CI, −0.61 to 0.07 points]; $P = 0.117$). At 14 days, 24% (49 of 201) of participants receiving hydroxychloroquine had ongoing symptoms compared with 30% (59 of 194) receiving placebo ($P =$ 0.21). Medication adverse effects occurred in 43% (9 participants receiving hydroxychloroquine versus 211) receiving placebo ($P < 0.001$). With placebo, 10 tions occurred (2 non–COVID-19–related), including 1 hospitalized death. With hydroxychloroquine, 4 hospitalizations occurred plus 1 nonhospitalized death ($P = 0.29$).

Limitations: Only 58% of participants received SARS-CoV-2 testing because of severe U.S. testing shortages.

Limitations

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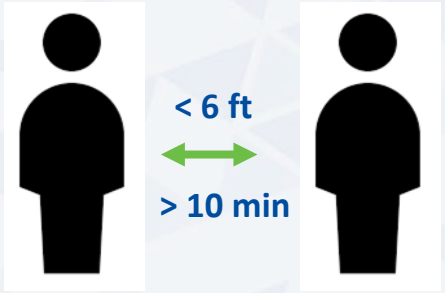
Skipper et al. Ann Intern Med. Jul 16 2020. doi: 10.7326/M20-4207.

HCQ for Post-Exposure Prophylaxis

RCT

Design	Multicenter, double-blind, placebo-controlled trial
Sites	US and Canada
Outcomes	New COVID-19 infection: HCQ (11.8%) Placebo (14.3%) [-2.4% (-7.0%,2.2%)]



Randomized
≤ 4 days of exposure

HCQ (n = 365)
800mg x1,
then 600 mg in 6-8h,
then 600 mg daily x 4 days

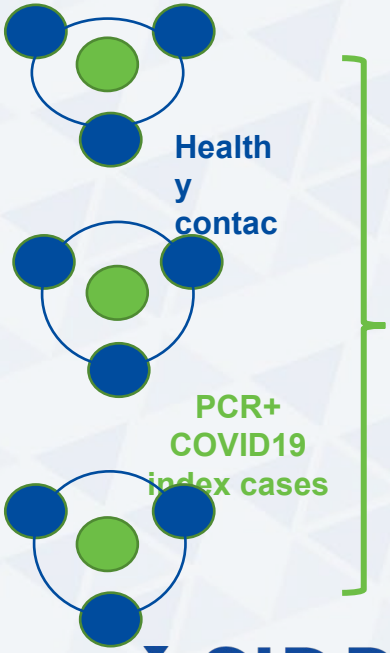
Placebo (n = 354)

Outcomes

Confirmed n = 16	Positive SARS-CoV2 PCR
Probable n = 74	Cough, SOB, difficulty breathing OR ≥2 fever, chills, rigors, myalgia, HA, sore throat, olfactory/taste disorder
Possible n = 13	≥1 of the symptoms compatible with COVID-19

Boulware DR et al. June 3, 2020. DOI:

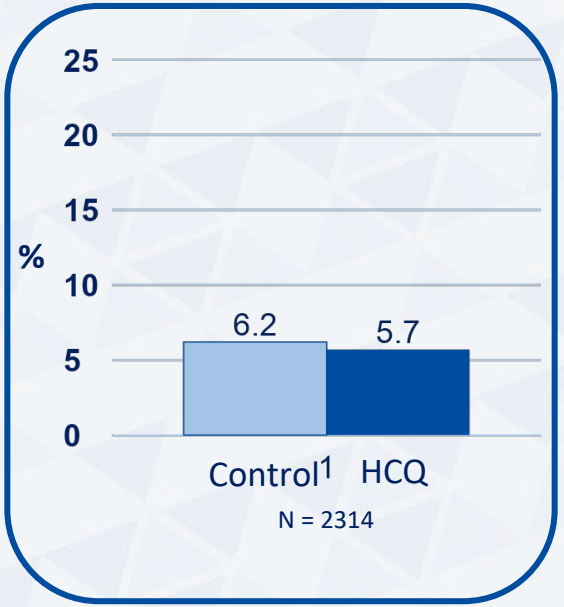
A Cluster RCT of HCQ to Prevent COVID19 Transmission & Disease

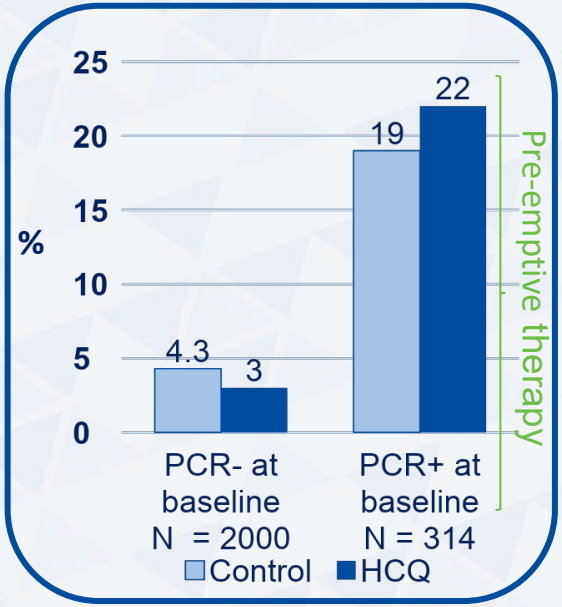


CONTROL
334 Clusters
N = 1300
ITT: 1198

HCQ*
338 Clusters
N = 1225
ITT: 1116

PCR Positive & Symptomatic within 14 days





*HCQ Dose: 800mg x1 then 400 mg daily x 6 days

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Mitja et al. medRxiv. Jul 26 2020. doi.org/10.1101/2020.07.20.20157651

Summary

- RCTs show no evidence of clinical benefit of HCQ in hospitalized patients with COVID-19
- Cluster RCT showed no evidence of clinical benefit of HCQ as post-exposure prophylaxis or early pre-emptive therapy
- We have seen harm: overdose and QTc prolongation. In RCT data, rates of cardiac toxicity were no different between HCQ and control arms
- Retrospective studies have shown possible benefit – which gives hint that just maybe there are specific populations whom this drug may help and/or that placebo is an effective therapeutic

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