HYDROXYCHLOROQUINE/CHLOROQUINE

RECOMMENDATION

We recommend against the use of hydroxychloroquine/chloroquine, with or without azithromycin among patients with COVID-19 infection. *(Moderate quality of evidence; Strong recommendation)*

Consensus Issues

None raised during panel meetings.

EVIDENCE SUMMARY

Should hydroxychloroquine/chloroquine be used for the treatment of COVID-19?

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Key Findings

Twenty-two trials showed that hydroxychloroquine (HCQ)-containing treatment did not significantly improve the outcomes of patients with COVID-19 disease compared with placebo or standard of care. Eleven (11) trials provided evidence of low certainty that the use of HCQ for the treatment of COVID-19 infection was significantly associated with a higher risk of adverse events (i.e., diarrhea, headache, rashes, and fatigue). There was very limited evidence with low to very low certainty which showed that treatment with HCQ combined with azithromycin does not show any significant difference from placebo in any of the efficacy outcomes. Adverse events were more frequent with the hydroxychloroquine with azithromycin group compared to placebo.

Introduction

Anti-malarial and anti-inflammatory drugs from the 4-quinolone family, particularly hydroxychloroquine (HCQ) and chloroquine (CQ), have been proposed as possible effective treatments or even prophylaxis for SARS-CoV-2 infections. HCQ and CQ are immune modulators which block the production of inflammatory cytokines and suppresses cytokine storms which are critical in the pathogenesis of COVID-19 infections [1]. Some studies have also shown that CQ and HCQ cause glycolysation of ACE 2 receptors, making cells refractory to SARS-CoV-2 infection.[2] HCQ and CQ have previously been used in the treatment of other viral illness such

as HIV, Dengue and Zika virus, with the former having lesser toxic effects of retinopathy, myopathy, neuropathy and cardiomyopathy.

Review Methods

A search for systematic reviews and meta-analysis was done on Pubmed on the treatment of COVID-19 infection, whether on hydroxychloroquine specifically or for all types of medications. The search terms used were “systematic reviews” and “COVID-19.” Identified reviews were assessed based on the Painless EBM systematic review appraisal form. Additional search for trials was done on March 17, 2021 using the Living OVerview of Evidence (L·OVE) platform, using hydroxychloroquine as the intervention and “RCT” and “with reported data” as additional filters to identify new trials that may not have been included in the living reviews.

Results

Four (4) living systematic reviews were identified after a comprehensive search on PubMed: The Living Project [3] reviewed all treatments for COVID, with 33 RCTs incorporated its September 2020 publication, including 12 with HCQ in one arm. No active website could be found for an updated status of this review. One review was limited to studies on severe COVID cases [4], with regular updates as ePublications. Two other living systematic reviews, one by the Cochrane Collaboration [5,6,7], and the other by the McMaster University [8,9], have active websites that are updated regularly, covering all treatments for COVID-19. A search of the COVID living evidence registry, iloveevidence.com for relevant systematic reviews did not yield any additional living review. Based on a comparative appraisal of these living systematic reviews, the trials included in this rapid review were mainly from the trials identified by the Covid-nma project [7] with its last update on March 8, 2021. For this review, the COVID-nma project was accessed on March 16, 2021.

Additional search of a living evidence registry, iloveevidence.com, on March 9, 2021 yielded 4 additional studies that were not included in the COVID-NMA evidence base as of March 16, 2021. (10)(11)(12)(13)

Twenty two (22) RCTs [10,11,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32] compared hydroxychloroquine-containing therapy with either placebo or standard of care alone. Three (3) trials compared hydroxychloroquine combined with azithromycin with placebo. [11,17,27] A total of 4682 patients were randomized to receive HCQ, and 435 were randomized to HCQ with azithromycin. Seven (7) RCTs (one of which had two different active control groups) compared HCQ-containing treatment with another treatment (azithromycin[33], ivermectin[13,34], ivermectin with doxycycline[35], febuxostat[36], favipiravir with interferon-beta[37], lopiravir/ritonavir [15], lopiravir/ritonavir with interferon-beta[15]). One trial compared chloroquine with favipiravir[38].

Characteristics of these included studies are detailed in Appendix 1.

Most of the trials in the review were assessed to be with high risk of bias because of being open labeled trials, although this was not deemed to impact their conclusions as outcomes were

objective. One was quasi-randomized. Several trials were pre-terminated due to restrictions by regulators on the conduct of HCQ trials after publication of several studies showing lack of benefit and concerns regarding the unfavorable risk/benefit ratio.

The GRADE profile and summary of findings table is presented in Appendix 2.

Comparison 1: Hydroxychloroquine versus placebo or standard of care

Fifteen (15) trials provided high certainty evidence that hydroxychloroquine treatment did not reduce mortality rates when compared to placebo or standard of care (RR 0.99, 95% CI 0.45-2.18) (see Appendix 2). Moreover, several trials also showed no significant difference between HCQ and placebo or standard of care in terms of other treatment outcomes such as viral negative conversion, clinical improvement, and clinical recovery.

Ten (10) trials provided evidence of low certainty that the use of HCQ for the treatment of COVID-19 infection was significantly associated with a higher risk of adverse events (RR 1.83, 95%CI 1.12-2.97). The common side effects associated with HCQ reported in the trials include diarrhea, headache, rashes, and fatigue.

Comparison 2: Hydroxychloroquine + azithromycin versus placebo or standard of care

Three trials [11,17,27] provided very limited evidence with low to very low certainty that treatment with HCQ combined with azithromycin did not show any significant difference from placebo in any of the efficacy outcomes. Adverse events were more frequent with the hydroxychloroquine with azithromycin group compared to placebo (RR 1.42 95%CI 1.08, 1.87). One trial (17) provided data for most of the outcomes evaluated.

Comparison 3: Hydroxychloroquine/Chloroquine-containing treatment versus other active treatments

Results from six trials [15,33,35,38,36,37] also showed that treatment with HCQ did not show any significant difference from the other active treatments (azithromycin, ivermectin + doxycycline, febuxostat, favipiravir + interferon-beta, liponavir + ritonativir, liponative/ritonavir + interferon-beta) in the different outcomes measured (see Appendix 4a-h). One study showed significantly higher risk for mortality at 28 days with HCQ treatment, compared with ivermectin among patients with severe COVID-19 infection.[34]

Recommendations from Other Groups

The US-NIH recommends against the use of HCQ/CQ with or without azithromycin in the treatment of COVID-19 in hospitalized and non-hospitalized patients. [39] The Infectious Disease Society of America likewise recommends against HCQ/ HCQ with azithromycin for COVID-19 treatment.[40]

Early Termination of Clinical Trials

The major clinical trials investigating the effects of HCQ for COVID-19 infection, upon recommendation of their respective independent review committees, terminated participant recruitment after unblinded review of the results. On June 2020, the US NIH stopped the Outcomes Related to COVID-19 treated with hydrochloroquine among In-patients with

symptomatic Disease study, or the ORCHID Study.[41] The chief investigators of the Recovery trial stopped enrolling participants to the HCQ arm of the trial after the review of the data by the Independent Data Monitoring Committee on the same month.[42] WHO, upon recommendation from the Solidarity Trial's International Steering Committee, discontinued the trial's HCQ arm in July 2020. [43]

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Appendix 1: Characteristics of Included Studies

HCQ / HCQ+Azithro vs placebo / standard of care

Study ID	Patients	Intervention (HCQ)	Comparator	Outcomes
Abd-Elsalam(14)	Suspected and confirmed	HCQ 400mg BID on D1 then 200 mg	Standard care : paracetamol, antibiotic,	Recovery within 28 days, need for mechanical

	COVID, all severities	BID x 15 days (n=97)	oseltamivir x 5 days (n=97)	ventilation, death, mean duration to negative PCR, mean time to clinical improvement, mean time to discharge, outcome at D28
Ader (Discovery) (15)	>= 18 yo, hospitalized with PCR proven SARS-COV-2 infection and pulmonary rales, sPaO2 <=94%, or requiring supplemental O2	SOC plus HCQ 200mg to 400mg twice on D1 then 400mg OD x 9 days (n= 145)	Standard of Care (SOC) (n=148) SOC + lopinavir 400mg /ritonavir 100mg Q 12h x 14 days (n=145) SOC + lopinavir 400mg / ritonavir 100mg Q12 x 14 days + IFN-Beta 44ug SQ on D1, 3,6 (n=145) SOC + remdesivir 200mg IV on D1 then 100 mg OD x 10 days (n=145)	Clinical status at D15 (WHO Master protocol), at D29, time to an improvement of 2 categories or hospital discharge until D29, time to NEWS2 <= or hospital discharge until D29, 29-day mortality, viral load, grade 3 or 4 AE, SAE, premature suspension of patients or discontinuation of treatment
Amaravadi (16)	COVID positive at home (Cohort 1)	HCQ 400mg BID x 14days (C1)	Placebo (C1)	Time to release from quarantine; rate of hospitalization; treatment-related AE
	COVID positive hospitalized (Cohort 2)	High dose HCQ 600 mg BID x 14day	Low dose HCW 600 mg OD x 7 days	Time to discharge, rate of discharge at 14 days,
Bernal-Gonzales (13)	RT-PCR positive with pneumonia diagnosed by xray or CT with a pattern suggesting involvement from coronavirus with recently established hypoxemic respiratory failure or acute clinical deterioration of preexisting lung or heart disease; excluded those requiring high oxygen volumes	HCQ 400mg q 12H on D1 then 200mg q12H x 4 days (n=33) (later in trial, coadministered with dexamethasone 6mg IV q 24H x 10 days)	Placebo – calcium citrate 2 tabs q 12H on D1 then 1 tab q 12H x 4 days (n=37) Ivermectin 12 mg for those weighing <80 kg and 18 mg for those above 80kg (n= 36) (later in trial, coadministered with dexamethasone 6mg IV q 24H x 10 days)	Duration of hospitalization, respiratory deterioration, death, SOFA, CORADS

Cavalcanti (17)	18 years or older, hospitalized with suspected or confirmed COVID (not all with (+) PCR ; mild or moderate	HCQ 400mg BID x 7 days (n=221) HCQ 400mg BID plus azithromycin 500 mg OD x 7 days (n=217)	Standard case (immunomodulators, antibiotics, antivirals) (n=227)	Clinical status at D15 (score 1-7), clinical status at D7, indication for intubation at D15, supplemental oxygen within 15 days, LOS, inhospital death, AKI, respirator days
Chen C (18)	20-79 years, confirmed COVID, mild to moderate	HCQ 400mg D1 and 200mg BID x 6 days (n= 21)	Standard care (with antibiotics, oseltamivir) (n=12)	Proportion of negative PCR at D14; median time to negative PCR; time to clinical revocery, proportion of discharges at D14, mortality; safety
Chen J (19)	>=18 years, confirmed COVID	HCQ 400mg x 5 days (n=15)	Standard of care (n=15)	Viral clearance on Day 7; Mortality; radiological progression on CT,
Chen L (20)	18-75 years, positive PCR or with lung changes od COVID; moderate disease	Chloroquine 1000QD on Day 1 then 500mg QD x 9 days (n = 25->18); HCQ 200mg BID x 10 days, (n=28->18)	n=14 ->12	Clinical recovery time; Adverse events; Time to RNA negativity; LOS, changes on chest CT, duration of supplemental oxygenation, clinical status, mortality
Chen Z (21)	>=18 years; confirmed COVID mild disease	HCQ 400mg x 5 days (n=31)	Standard of care (n=31)	Severe AE, time to clinical recovery, changes in chest CT (pulmo recovery)
Dubee (22)	18 years and older, PCR positive or with CT findings, with risk factor; mild and moderate	HCQ 200mg BID x 9 days(n=123)	Placebo (n=124)	Composit of death and need for mechanical ventilation at da14;SAE at D28; clinical improvement ad D14 and D28, mortality at D14 and D28; PCR positive at D5 and D10
Hernandez-Cardenas (10)	Over 18 yo, <14 days from symptom onset of confirmed diagnosis of COVID-19 by RT PCR requiring hospitalization, requiring respiratory support	HCQ 200mg Q 12 H x 10 days (n= 106)	Sucrose-placebo x 10 days (n=108)	Mortality, proportion requiring ventilatory support after admission, duration of hospitalization, severe adverse events leading to treatment discontinuation, intervention or death
Horby (Recovery) (23)	At least 18yo, hospitalized, clinically	HCQ 400mg x 10 days (n=1561)	Standard care (n- 3155)	Mortality at 28D; time to discharge, % discharge at

	suspected or confirmed COVID			D28; composite of mech vent, ECMO and death,

Kamran (24)	18-80 years, mild COVID, hospitalized	HCQ 400mg BID on D1 then 200 mg BID x 5 days (n=349)	Standard of care (n= 151) = vit C 2gms, vit D, paracetamol, Zinc	Disease progression ; PCR negative at d7 and d14
Johnston (11)	18-80 years old, lab confirmed SARS-CoV-2 infection, subgrouped to high and low risk cohorts	HCQ 400 mg BID on D1 then 200mg BID x 9 days + Folic acid (n=63) HCQ as above + Azitho 500mg on D1 then 250mg OD x 4 days (n= 74)	Ascorbic acid + Folic acid (n=80)	Development of LRTI (SpO2<93%) D14, COVID-related hospitalization, death, time to COVID symptom resolution, adverse vents, SAEs,
Lyngbakken (25)	18 years and above, PCR positive cases, moderate to severe	HCQ 400mg x 7 days (n=26)	Standard of care (n-27)	Rate of decline of viral load; in hospital death; clinical status at D14, LOS,
Mitja (26)	18 years or more, mild COVID, PCR-confirmed	HCQ 800mg on D1 then 400mg x 6 days (n-184), 157 PP	Standard care (n=169), 136 PP	Reduction of vidal load at day 3 and day 7; AE and SAE, clinical progression, time to resolution of symptoms
Omrani (27)	18 years and older, PCR positive, non-hospitalized, mild	HCQ 600mg x 7 days (n= 152) HCQ 600mg x 7 days plus Azithro 500mg then 250mg day 2-5 (n=152)	Placebo (n=152)	PCR negative at day6
Pan (28)	18 years and older, hospitalized with COVID 19; mild and moderate	HCQ 400mg x 10 days (n=909)	Standard care (n=954)	In hospital mortality; initiation of mech vent, LOS,
Self (29)	18 years and older; hospitalized, PCR positive, mild to severe	HCQ 400mg BID x 1 day then 200 mg BIDx 4 days (n=242)	Placebo x 5 days (n = 237)	Clnical status (covid who scale) at d14; covid score at D2.7.28, mortality ad D14 and D28, time to recovery, composite of death or ECMO, safety,
Skipper (30)	Non hospitalized; symptomtic covid case within 4 days of diagnosis, OR symptomatic high risk exposure	HCQ 800mg once then 600mg 6 to 8 hours later on D1 then 600mg OD x 4 days (n=244) PP = 212	Placebo (folic acid 400mcg / lactose) (n=247) PP = 211	Adverse events; hospitalization / ICU or detah at D14; symptom severity score

Tang (31)	>18 years, PCR positive mixed population, all severities	HCQ 1200mg x 3 days then 800mg x 14 days (n=75)	Standard of care (n=75)	PCR conversion at D28, 4, 7, 10,14,21, adverse events, alleviation of clinical symptoms

Ultrich (32)	PCR positive, hospitalized	HCQ 200mg x 5 days (n=61)	Placebo : calcium citrate 200mg x 5 days (n=67)	Progression to severe at 14 days, serious AEs, grade 3 or 4 AEs, change in COVID score, LOS,

HCQ vs other treatments

Study ID	Patients	Intervention	Comparator	Outcomes
Ader (Discovery) (15)	>= 18 yo, hospitalized with PCR proven SARS-COV-2 infection and pulmonary rales, sPaO2 <=94%, or requiring supplemental O2	HCQ 200mg to 400mg twice on D1 then 400mg OD x 9 days plus SOC (n= 145)	Standard of Care (SOC) (n=148) SOC + lopinavir 400mg /ritonavir 100mg Q 12h x 14 days (n=145) SOC + lopinavir 400mg / ritonavir 100mg Q12 x 14 days + IFN-Beta 44ug SQ on D1, 3,6 (n=145) SOC + remdesivir 200mg IV on D1 then 100 mg OD x 10 days (n=145)	Clinical status at D15 (WHO Master protocol), at D29, time to an improvement of 2 categories or hospital discharge until D29, time to NEWS2 <= or hospital discharge until D29, 29-day mortality, viral load, grade 3 or 4 AE, SAE, premature suspension of patients or discontinuation of treatment
Bernal-Gonzales (13)	RT-PCR positive with pneumonia diagnosed by xray or CT with a pattern suggesting involvement from coronavirus with recently established hypoxemic respiratory failure or acute clinical deterioration of preexisting lung or heart disease; excluded those requiring high oxygen volumes	HCQ 400mg q 12H on D1 then 200mg q12H x 4 days (n=33) (later in trial, coadministered with dexamethasone 6mg IV q 24H x 10 days)	Ivermectin 12 mg for those weighing <80 kg and 18 mg for those above 80kg (n= 36) Placebo (n=37) (later in trial, coadministered with dexamethasone 6mg IV q 24H x 10 days)	Duration of hospitalization, respiratory deterioration, death, SOFA, CORADS
Brown (33)	>18 years, hospitalized, lab-confirmed COVID, all severities	HCQ 400mg BID on D1 then 200mg x 4 days (n=43)	Azithro 500mg on D1 then 250mg x 4 days (n=42)	COVID ordinal scale on D14, adverse event, mortality at D28

Chowdhury (35)	PCR positive, O2sat >95%, normal chest xray	HCQ 400mg D1 then 200 mg BID x 9 days with azithro 500 mg OD x 5 days (n= 56)	Ivermectin 200ug/kg single dose + doxycycline 100mg BID x 10 days (n=60)	Negative PCR, time to negative PCR, adverse events

Dabbous (38)	18-80 years Mild or moderate COVID, PCR confirmed,	HCQ 400mg 12 hourly D1 then 200 mg 12 hourly x 9 days + Osaltamivir 75mg 12 hourly x 10 days + (n=	Favipiravir 3200 mg (1600mg 12 hourly) D1 then 1200mg (600mg 12 hourly) x 9 days	Time to viral negative conversion, radiological imporvement ad D14, discharge rate out of hspital
Davoodi (36)	With CT findings compatible with COVID 19, symptoms of respiratory tract infection	HCQ 200mg BID (n= 30)	Febuxostat 80 mg OD (n = 30)	Rate of hospitalization, rate of ICU admission, mortality rate, clinical improvement and improvement of CT findings at D14
Elgazzar (34)	18-80 yo, with mild, moderate or severe COVID, PCR confirmed	Mild-Mod : HCQ 400mg Q 12H on D1 then 200mg Q 12H x 5 days (n=100) Severe : HCQ 400mg Q 12H on D1 then 200mg Q 12H x 9 days (n=100) Plus SOC (Azithro, Paracetamol, Lactoferrin, Acetylcysteine)	Ivermectin 0.4mg/kg , max of 4 tabs (6mg/tab) OD x 4 days (n=200)	Clinical and lab improvement and /or 2 consecutive negative PCR taken at least 48 hrs apart, adverse events, mortality, hospital stay, recovery time
Khamis (37)	18-75 years, confirmed COVID, moderate to severe	HCQ 400mg BID on D1 then 200 mg BID x 7 days (n-44)	Favipiravir 1600mg D1 then 600mg BID x 10 days+ interferon beta-1b (600mg/8million IU (0.25g) x 5 days (n= 45)	Time to clinical recovery, ICU admission, mortality at D14

Appendix 2: Methodological Quality Assessment of Included Studies

Study ID	R1	R2	R3	R4	R5	Overall	Comments
HCQ/CQ vs Placebo							
Abd-Elsalam	L	U	H	L	L	H*	Unblinded
Ader	L	L	H	L	L	H*	Unblinded
Amravadi	U	U	H	H	L	H	Unpublished, data reported only in trial registry, pre-terminated; Cohort 2 is open label
Bernal Gonzales	U	U	L	H	L	H	Randomization and allocation concealment not described, pre-terminated
Cavalcanti	L	L	H	L	L	H*	Unblinded
Chen CP	L	U	H	L	L	H*	Unblinded
Chen L	U	U	H	H	L	H	Unblinded; >5%of randomized without data,
Chen J	H	H	H	L	L	H	Randomization based on the parity of the patient's medical record; unblinded
Chen Z	L	U	U	L	L	L	Patient blinded but outcome assessor unclear if blinded
Dubee	L	L	L	L	L	L	Trial prematurely stopped after 250 pxs due to slowdown of pandemic
Horby	L	L	H	L	L	H*	unblinded
Johnston	L	L	L	L	L	L	
Kamran	L	U	H	H	U	H	Unblinded; many missing data
Lyngbakken	L	H	H	L	L	H	Unblinded, no allocation concealment
Mitja	U	U	H	L	L	H	Open label; high lost to follow up but equally distributed
Omrani	L	L	L	L	L	L	
Pan	L	L	H	L	L	H*	Unblinded
Self	L	L	L	L	L	L	
Skipper	L	L	L	H	L	H	68 patients with missing data / lost to ffup
Tang	L	U	H	L	L	H*	Unblinded
Ultrich	U	U	H	H	L	H	Patient and investigator blinded but unblinding allowed, only 48% of patients with viral conversion data, 25% for mortality data

HCQ+Azi vs Placebo							
Cavalcanti	L	L	H	L	L	H*	Unblinded
Omrani	L	L	L	L	L	L	
HCQ/CQ vs Other treatments							
Ader	L	L	H	L	L	H*	Unblinded
Brown	U	L	H	L	L	H*	Method of randomization not specified unblinded
Chowdhury	H	H	H	L	L	H	Quasi-RCT (odd-even), unblinded
Dabbous	L	U	U	L	U	U	
Davoodi	L	L	L	L	L	L	
Elgazzar	U	U	U	L	L	U	
Khamis	L	U	H	L	U	H*	Unblinded

*H – assessed as high because of lack of blinding; but may be low risk for objective outcomes (eg. mortality)

R1- sequence generation
R2 – allocation concealment
R3 – blinding
R4 – incomplete outcome data
R5 – selective outcome reporting

L – low risk of bias
H – high risk of bias
U – uncertain / no information

Appendix 3: GRADE Evidence Profile

COMPARISON : Hydroxychloroquine versus Placebo / Standard of Care
NOTE : All included studies are Randomized Controlled Trials

Quality Assessment						Summary of Findings				
						Number of patients		Effect		
No. of studies	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Hydroxy-chloroquine**	**Placebo/ Standard of Care**	**Relative Risk**	**Risk Difference**	**Certainty**
Incidence of Viral negative conversion D7										
7	Not serious	Not serious	Not serious	Serious (wide confidence interval)	Not assessed	125/377 (33.2%)	120/352 (34.1%)	0.94 (0.83, 1.07)	20 fewer per 1000	+++ Moderate
Clinical improvement D28										
6	Serious (unblinded)	Not serious	Not serious	Not serious	Not assessed	1469/2243 (65.5%)	2524.3833 (65.8%)	0.97 (0.93, 1.01)	20 fewer per 1000 (from 46 fewer to 7 more)	+++ Moderate
WHO progression score (level 7 or above) D28										
10	Not serious	Not serious	Not serious	Serious (wide confidence interval)	None	91/1113 (8.2%)	95/1116 (8.5%)	0.96 (0.73, 1.25)	3 fewer per 1000 (from 23 fewer to 21 more)	+++ Moderate
Mortality D28										
16	Not serious	Not serious	Not serious	Not serious	None	589/4149 (14.2%)	941/5690 (16.5%)	1.08 (0.98, 1.18)	13 fewer per 1000 (from 3 fewer to 30 more)	++++ High

Adverse events										
11	Serious (unblinded)	Serious (significant heterogeneity)	Not serious	Not serious	none	547/1153 (47.4%)	344/1156 (29.8%)	1.71 (1.10, 2.67)	211 more per 1000 (from 30 more to 497 more)	++ Low
Serious adverse events										
12	Serious (unblinded, randomization)	Not serious	Not serious	Serious (wide confidence interval)	none	102/1254 (8.1%)	89/1242 (7.2%)	1.14 (0.90, 1.44)	10 more per 1000 (from 7 fewer to 32 more)	++ Low

COMPARISON : Hydroxychloroquine+Azithromycin versus Placebo / Standard of Care
NOTE : All included studies are Randomized Controlled Trials

Quality Assessment						**Summary of Findings**				
						Number of patients		**Effect**		
No. of studies	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Hydroxy-chloroquine + Azithromycin**	**Placebo/ Standard of Care**	**Relative Risk**	**Risk Difference**	**Certainty**
Incidence of Viral negative conversion D7										
1	Not serious	Not assessed	Not serious	Serious (single study, wide confidence interval)	Not assessed	16/152 (10.5%)	18/147 (12.2%)	0.86 (0.46, 1.62)	17 fewer per 1000 (from 66 fewer to 76 more)	+ Very Low
Clinical improvement D7										
1	Some concern (allocation concealment)	Not serious	Not serious	Serious (wide confidence interval)	Not assessed	120/217 (55.3%)	117/229 (51.1%	1.08 (0.91, 1.29)	41 more per 1000 (from 46 fewer to 148 more)	++ Low
Clinical improvement D14 – D28										

1	Serious (allocation concealment)	Not serious	Not serious	Serious (wide confidence interval)	Not assessed	184/217 (84.8%)	195/229 (85.2%)	1.0 (0.92, 1.08)	0 fewer per 1000 (from 68 fewer to 68 more)	++ Low
WHO progression score (level 6 or above) D7										
1	Serious (unblinded)	Not assessed	Not serious	Serious (wide CI)	Not assessed	19/217 (8.8%)	17/229 (7.4%)	1.8 (0.63, 2.21)	13 fewer per 1000 (from 27 fewer to 90 more)	+ Very Low
WHO progression score (level 6 or above) D14-28										
1	Serious (unblinded)	Not assessed	Not serious	Serious (wide CI)	Not assessed	13/217 (6.0%)	15/229 (6.6%)	0.91 (0.45, 1.88)	6 fewer per 1000 (from 36 fewer to 58 more)	+ Very Low
WHO progression score (Level 7 or above) D7										
1	Not serious	Not assessed	Not serious	Serious (single study))wide CI)	Not assessed	16/217 (7.4%)	13/229 (5.7%)	1.30 (0.64, 2.64)	17 more per 1000 (from 20 fewer to 93 more)	+ Very Low

WHO progression score (level 7 or above) D14-28										
1	Not serious	Not assessed	Not serious	Serious (wide CI) (single study)	Not assessed	13/217 (6.0%)	13/229 (5.7%)	1.06 (0.50, 2.23)	3 fewer per 1000 (from 28 fewer to 70 more)	++ Very Low
Mortality D7										
2	Not serious	Not assessed	Not serious	Serious (wide CI)	Not assessed	1/366 (0.3%)	3/375 (0.8%)	0.35 (0.04, 3.36)	5 fewer per 1000 (from 8 fewer to 19 more)	++ Low
Mortality D14-28										
2	Not serious	Not assessed	Not serious	Serious (wide CI)	Not assessed	3.366 (0.8%)	6/375 (1.6%)	0.53 (0.13, 2.08)	8 fewer per 1000 (from 14 fewer to 17 more)	++ Low
Adverse events D14-28										
1	Serious (unblinded)	Not assessed	Not serious	Serious (single study, wide confidence interval)	Not assessed	82/217 (37.8%)	61/229 (26.6%)	1.42 (1.08, 1.87)	112 more per 1000	+ Very Low
Serious adverse events D14-28										
2	Some concerns (allocation concealment, unblinded)	Not serious	Not serious	Serious (wide confidence interval)	Not assessed	3/217 (1.4%)	3/229 (1.3%)	1.06 (0.22, 5.17)	1 more per 1000 (from 10 fewer to 55 more)	+ Very Low

Appendix 4: Summary of Findings Tables for Hydroxychloroquine versus Other Treatment

Appendix 4a: HCQ vs Azithromycin (33)

	HCQ	Azithromycin	RR (95% CI)
Mortality D14 to D28	6/42 (14.3%)	1/43 (2.3%)	6.14 (0.77, 48.87)
Adverse events	39/42 (92.9%)	42/43 (97.7%)	0.95 (0.86, 1.05)
Serious adverse events	39/42 (92.9%)	42/43 (97.7%)	0.95 (0.86, 1.05)

Appendix 4b: HCQ vs Ivermectin (13)(34)

	HCQ	Ivermectin	RR (95%CI)
Mortality D28 (Mild/Moderate)	6/133 (4.5%)	5/136 (3.7%)	1.23 (0.38, 3.92)
Mortality D28 (Severe)	20/100 (20%)	2/100 (2%)	10.0 (2.4, 41.66)

Appendix 4c: HCQ +Azithromycin vs Ivermectin-Doxycycline (35)

	HCQ +Azithromycin	Ivermectin + Doxycycline	RR (95% CI)
Viral negative conversion D7	60/63 (95.2%)	54/62 (87.1%)	1.09 (0.98, 1.22)
Adverse events	26/62 (41.9%)	19/63 (30.1%)	1.39 (0.86, 2.24)
Time to negative PCR	9.33 (5-15 days)	8.93 (8-13 days)	Na
Mean duration of symptomatic recovery / Time to recovery	6.99 (4-12 days	5.93 (5-10 days)	na
Clinical recovery D7	71.4%	83.6%	na

Appendix 4d: HCQ vs Febuxostat (36)

	HCQ	Febuxostat	RR (95% CI)
Mortality, D7 and D14to D28	0/30	0/30	Not evaluable

improvement in Chest CT Scan/ X-ray,	47.4% improvement	58.5% improvement	NA

Appendix 4e: HCQ vs Favipiravir + Interferon Beta (37)

	HCQ	Favipiravir + interferon Beta	RR (95%CI)
Clinical improvement D14-28	31/45	29/44	1.05 (0.78, 1.4)
Mortality D14-28	6/45	5/44	1.17 (0.39, 3.57)

Appendix 4f: HCQ vs Lopinavir/Ritonavir (15)

	HCQ	Lopinavir/Ritonavir	RR (95%CI)
WHO score 7 at D28	27/151 (17.9%)	31/150 (20.7%)	0.87 (0.54, 1.38)
Viral negative conversion D7	50/81 (61.7%)	53/80 (66.3%)	0.93 (0.74, 1.18)
Mortality at D28	11/151 (7.3%)	14/150 (9.3%)	0.78 (0.37, 1.66)
Adverse events	109/151 (72,2%)	119/150 (79.3%)	0.91 (0.80, 1.03)
Serious adverse events	63/151 (41.7%)	76/150 (50.7%)	0.82 (0.64, 1.05)

Appendix 4g: HCQ vs Lopinavir/Ritonavir + Interferon-beta (15)

	HCQ	Lopi/Rito + IFBeta	RR (95% CI)
WHO score 7 at D28	27/151 (17.9%)	37/150 (24.7%)	0.72 (0.47, 1.13)
Viral negative conversion D7	50/81 (61.7%)	60/81 (74.1%)	0.83 (0.67, 1.03)
Mortality at D28	11/151 (7.3%)	18/150 (12.0%)	0.61 (0.30, 1.24)
Adverse events	109/151 (72.2%)	117/150 (78.0%)	0.93 (0.81, 1.05)

Serious adverse events	63/151 (41.7%)	78/150 (52.0%)	0.80 (0.63, 1.02)

Appendix 4h: CQ vs Favipiravir (38)

	Chloroquine (+ osaltamivir)	**Favipiravir**	**RR (95%CI)**
Mortality D28	2/48 (4.7%)	1/48 (2.1%)	2.0 (0.19, 21.33)
Time to viral negative conversion	8.1 days	8.3 days	na
Viral negative conversion D7	55%	48%	na
CT improvement/recovery D7	21/50 (52%)	21/50 (52%)	1.0 (0.63, 1.59)
Duration of hospitalization	15.89 +/- 4.75	13.29 +/- 5.86	na