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Therapeutic use of chloroquine and hydroxychloroquine in COVID-19 and other viral infections: A narrative review

Anwar M. Hashem[a,b,**,1], Badrah S. Alghamdi[c,d,*,1], Abdullah A. Algaissi[e,f], Fahad S. Alshehri[g], Abdullah Bukhari[h], Mohamed A. Alfaleh[b,i], Ziad A. Memish[j,k]

[a] Department of Medical Microbiology and Parasitology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[b] Vaccines and Immunnotherapy Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
[c] Department of Physiology, Neuroscience Unit, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[d] Pre-Clinical Research Unit, King Fahad Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
[e] Department of Medical Laboratories Technology, College of Applied Medical Sciences, Jazan University, Jazan, Saudi Arabia
[f] Medical Research Center, Jazan University, Jazan, Saudi Arabia
[g] Department of Pharmacology and Toxicology, College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia
[h] Department of Medicine, Faculty of Medicine, Imam Mohammed Ibn Saud Islamic University, Riyadh, Saudi Arabia
[i] Faculty of Pharmacy; King Abdulaziz University, Jeddah, Saudi Arabia
[j] King Saud Medical City, Research & Innovation Center, Ministry of Health, Saudi Arabia; Al-Faisal University, Riyadh, Saudi Arabia
[k] Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

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ABSTRACT

The rapidly spreading Coronavirus Disease (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2), represents an unprecedented serious challenge to the global public health community. The extremely rapid international spread of the disease with significant morbidity and mortality made finding possible therapeutic interventions a global priority. While approved specific antiviral drugs against SARS-CoV-2 are still lacking, a large number of existing drugs are being explored as a possible treatment for COVID-19 infected patients. Recent publications have re-examined the use of Chloroquine (CQ) and/or Hydroxychloroquine (HCQ) as a potential therapeutic option for these patients. In an attempt to explore the evidence that supports their use in COVID-19 patients, we comprehensively reviewed the previous studies which used CQ or HCQ as an antiviral treatment. Both CQ and HCQ demonstrated promising in vitro results, however, such data have not yet been translated into meaningful in vivo studies. While few clinical trials have suggested some beneficial effects of CQ and HCQ in COVID-19 patients, most of the reported data are still preliminary. Given the current uncertainty, it is worth being mindful of the potential risks and strictly rationalise the use of these drugs in COVID-19 patients until further high quality randomized clinical trials are available to clarify their role in the treatment or prevention of COVID-19.

1. Coronaviruses and the COVID-19 pandemic

Coronaviruses (CoVs) are important human and animal pathogens that have the ability to emerge and cross the species barrier, causing novel and occasionally fatal diseases [1,2]. They belong to the subfamily *Coronavirinae* of the *Coronaviridae* family in the order *Nidovirales* [3]. According to the International Committee on the Taxonomy of Viruses (ICTV), coronaviruses are classified into four genera including, *alphacoronavirus*, *betacoronavirus* (contains 4 lineages A, B, C and D), *gammacoronavirus* and *deltacoronavirus* [4]. They are large enveloped viruses with a large single-stranded RNA, 5′-capped, non-segmented genome with positive polarity ranging from 26 to 32 kb in size [5]. While CoVs from all genera infect a large number of mammals and birds, bats are proposed to be their natural reservoir [6,7]. In humans, on the other hand, only alpha and beta CoVs have been associated with diseases ranging from mild common cold to fatal severe respiratory infections. Two human alpha CoVs (hCoV-229E and hCoV-NL63) and two beta CoVs (hCoV-OC43 and hCoV-HKU1) are associated with

* Corresponding author. Department of Physiology, Neuroscience Unit, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia,
** Corresponding author. Department of Medical Microbiology and Parasitology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.
E-mail addresses: amhashem@kau.edu.sa (A.M. Hashem), basalghamdi@kau.edu.sa (B.S. Alghamdi), AAlgaissi@jazanu.edu.sa (A.A. Algaissi), fsshehri@uqu.edu.sa (F.S. Alshehri), aibukhari@imamu.edu.sa (A. Bukhari), maalfaleh@kau.edu.sa (M.A. Alfaleh), zmemish@yahoo.com (Z.A. Memish).
[1] equal contribution.

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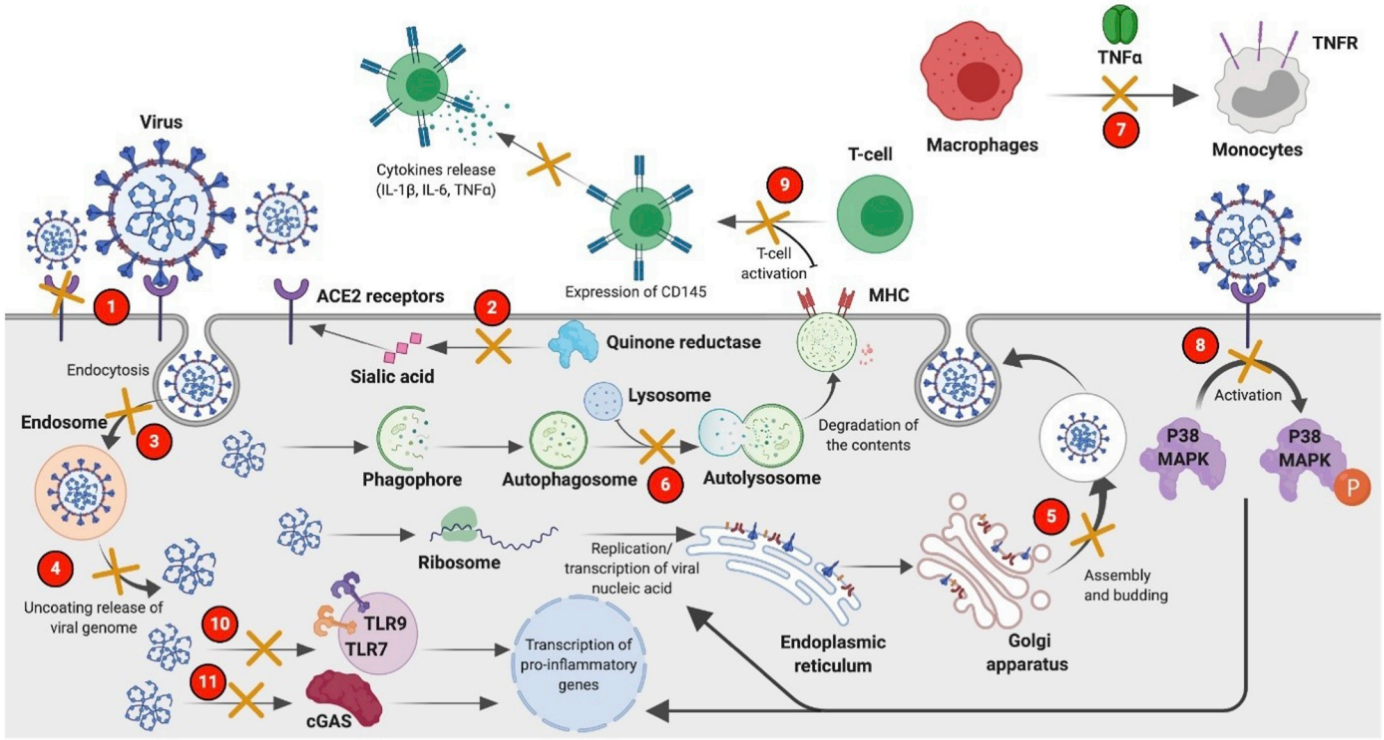

Fig. 1. Cellular and molecular possible sites of action of CQ ± HCQ as antiviral agents. (X) Represents the site of inhibition by CQ ± HCQ. (1) CQ and HCQ inhibit virus binding to its cell surface receptor, (2) CQ inhibits sialic acid biosynthesis through suppressing quinone reductase 2 activity which affect ACE2 receptor activity, (3) CQ and HCQ inhibit virus pH-dependent endocytosis through increasing pH, (4) CQ interferes with virus uncoating, (5) CQ interferes with assembly/budding leading to accumulation of viral vesicles within trans-Golgi network, (6) CQ interferes with lysosomal protein degradation and lysosomal fusion with autophagosomes. HCQ can interfere with lysosomal activity and prevent major histocompatibility complex (MHC) class II expression, (7) CQ interferes with TNF release and binding from macrophages and/to monocytes, (8) CQ inhibits phosphorylation of P38 MAPK and caspase in Th1 cells which in turn inhibits pro-inflammatory cytokines production and virus replication, (9) HCQ blocking of MHC expression prevents T cell activation, expression of CD145 and cytokines release, (10) HCQ impairs TLR signaling through increasing endosomal pH and interfering with TLR7 and TLR9 binding to their DNA/RNA ligands thereby inhibiting transcription of pro-inflammatory genes, (11) HCQ inhibits the binding of DNA to the cGAS and therefore reduce cytokines transcription and production. ACE2: Angiotensin converting enzyme 2; MHC: Major histocompatibility complex; TLR: Toll-like receptors; cGAS: Cyclic GMP-AMP synthase; MAPK: Mitogen-activated protein kinase. This figure was created with BioRender.com.

Table 1
CQ and HCQ pharmacokinetic parameters.

Pharmacokinetic parameters	CQ	HCQ
Bioavailability	89 ± 16%	74 ± 13%
Half-life	30–60 days	30–52 days
Peak plasma time	2–4 h	
Metabolism	Liver CYP-450	
Excretion	Kidney and liver (40–60%) unchanged or metabolized	

common cold [8–11]. In 2002 and 2012, two novel highly pathogenic beta CoVs known as the severe acute respiratory syndrome-CoV (SARS-CoV) and the Middle East respiratory syndrome-CoV (MERS-CoV) emerged in China and Saudi Arabia, respectively [12–15]. These two viruses have spread widely and were associated with severe respiratory diseases with mild to severe and fatal outcomes. More recently, a novel human CoV known as severe acute respiratory syndrome-CoV-2 (SARS-CoV-2) emerged in December 2019 in Wuhan, the capital city of Hubei province in China as the third known highly pathogenic human beta CoV [16].

Since its emergence, SARS-CoV-2, which causes the Coronavirus Disease (COVID-19), has rapidly spread to more than 214 countries around the world, causing a large-scale global pandemic. Until April 10th, more than 1.6 million COVID-19 confirmed cases have been reported globally, including more than 100,000 deaths. There are currently no vaccines or specific antiviral drugs for SARS-CoV-2 [17]. The rapid global spread of this virus and the worrisome associated mortality rate encouraged the medical community and policy makers to expediate the process of exploring all available and potential interventions to control and mitigate this outbreak [18]. Several interventional treatment options for COVID-19 have been suggested with unclear efficacy and safety considerations [19]. Recent publications have suggested using chloroquine (CQ), a broadly used antimalarial drug, and its derivative hydroxychloroquine (HCQ) as a treatment for COVID-19 patients [20–22]. In this review, we explore the antiviral activities of CQ and HCQ against CoVs and non-CoVs in the majority of previously published *in vitro*, *in vivo* and clinical trial studies with an aim to find evidence that supports their use in COVID-19 patients.

2. Possible mechanisms of CQ and HCQ antiviral activities

Both CQ and HCQ, known antimalarial and antirheumatic drugs, have closely related chemical structures [22]. However, their mechanisms of action are still not fully elucidated. Several studies have revealed that both drugs have antiviral activity *in vitro* through different mechanisms [23–25]. In particular, CQ has been shown to interfere with different stages of the viral life cycle as shown in Fig. 1 [26–29]. Different studies have reported the ability of CQ to inhibit viral entry [30–32], uncoating [33], assembly and budding [34,35]. One of the suggested mechanisms by which CQ can affect the entry step of viruses is by inhibiting quinone reductase 2 [36], which is required for the biosynthesis of sialic acid [37]. Sialic acid was found to be involved in virus attachment and entry into host cells by several viruses including hCoV-OC43 and MERS-CoV [38,39]. Moreover, CQ was

Table 2
In vitro antiviral activity of CQ and its derivatives on CoVs.

Drug	Virus	Cells	EC_{50} (μM)	SI	Main findings	Year	Ref
CQ	SARS-CoV	Vero E6	8·8 ± 1·2	30	↓ viral replication	2004	[104]
CQ	SARS-CoV	Vero E6	4.4 + 1·0	–	↓ viral replication	2005	[37]
CQ	SARS-CoV	Vero 76	1–5	2–20	↓ viral replication	2006	[105]
CQ	SARS-CoV	Vero	6.5 ± 3.2	> 15	↓ viral replication	2006	[106]
CQ	SARS-CoV	Vero E6	4.1 ± 1.0	> 31	↓ viral replication	2014	[107]
CQ-MP	SARS-CoV	Vero 76	4–6	3–8	↓ viral replication	2006	[105]
CQ-DP	SARS-CoV	Vero 76	3–8	2–10	↓ viral replication	2006	[105]
AMD	SARS-CoV	Vero 76	3–10	2–10	↓ viral replication	2006	[105]
HCQ	SARS-CoV	Vero	34 ± 5	> 3	Ineffective	2006	[106]
FQ	SARS-CoV	Vero	1.4 ± 0.1	15	↓ viral replication	2006	[106]
HFQ	SARS-CoV	Vero	1.9–4.9	4–17	↓ viral replication	2006	[106]
CQ	MERS-CoV	Huh7	3.0 ± 1.1	19.4	↓ viral replication	2014	[107]
CQ	MERS-CoV	Vero E6	6.3	–	Ineffective	2018	[116]
CQ	SARS-CoV-2	Vero E6	1.13	> 88.5	↓ viral replication	2020	[113]
CQ	SARS-CoV-2	Vero	5.47	–	↓ viral replication	2020	[112]
CQ[a]	SARS-CoV-2	Vero E6	2.71–7.36	37.12–100.81	↓ viral replication	2020	[114]
HCQ	SARS-CoV-2	Vero	0.72	–	↓ viral replication	2020	[112]
HCQ[a]	SARS-CoV-2	Vero E6	4.06–17.31	14.41–61.45	↓ viral replication	2020	[114]
CQ	HCoV-229E	L132	–	–	↓ viral replication	2008	[109]
CQ	HCoV-229E	Huh7	3.3 ± 1.2	> 15	↓ viral replication	2014	[107]
CQ	HCoV-OC43	HRT-18	0.3 ± 0.0	1369	↓ viral replication	2009	[108]
CQ	MHV4	Murine cells	–	–	Ineffective	1991	[117]
CQ	MHV3	Murine MΦ	–	–	↓ viral replication	1966	[115]
CQ	F–CoV	CRFK	> 0.8	–	↓ viral replication	2006	[106]
HCQ	F–CoV	CRFK	28 ± 27	–	Ineffective	2006	[106]
FQ	F–CoV	CRFK	2.9 ± 1.2	–	↓ viral replication	2006	[106]
HFQ	F–CoV	CRFK	> 4	–	Weak effect	2006	[106]
CQ	FIPV	fcwf-4	–	–	↓ viral replication	2013	[110]
CQ	PHEV	Neuro-2a	–	–	↓ viral replication	2017	[111]

CQ: Chloroquine; **CQ-MP**: Chloroquine monophosphate; **CQ-DP**: Chloroquine diphosphate; **AMD**: Amodiaquine; **HCQ**: Hydroxychloroquine; **FQ**: Ferroquine; **HFQ**: Hydroxy ferroquine; **SARS-CoV**: Sever acute respiratory syndrome-coronavirus; **MERS-CoV**: Middle East respiratory syndrome-coronavirus; **SARS-CoV-2**: Sever acute respiratory syndrome-coronavirus 2; **MHV4**: Mouse hepatitis virus Type 4; **F–CoV**: Feline coronavirus; **FIPV**: Feline infectious peritonitis virus; **PHEV:** Porcine hemagglutinating encephalomyelitis virus; **Vero cells**: African green monkey kidney epithelial cells; **Huh7 cells**: Human hepatocyte-derived carcinoma cells; **L132**: human epithelial lung cells; **HRT-18**: Human ileocecal colorectal adenocarcinoma cells; **MΦ**: macrophages; **CRFK cells**: Crandell–Reese feline kidney cells; **fcwf-4 cells**: Felis catuswhole fetus-4 cells; **Neuro-2a**: murine neuroblastoma cells; **EC_{50}**: 50% Effective concentration; **SI**: Selectivity index defined as the ratio of drug efficacy to cytotoxicity.

[a] Tested at different multiplicities of infections (MOIs) of 0.01–0.8.

shown to potently inhibit entry of SARS-CoV into cells by interfering with the glycosylation of its cellular receptor angiotensin converting enzyme 2 receptor (ACE2). SARS-CoV-2 also uses ACE2 as a receptor for cell entry, suggesting a possible similar effect of CQ on SARS-CoV-2 at this step of virus replication [40]. CQ can also affect early stage of virus replication by inhibiting virus-endosome fusion, likely via increasing endosomal pH [41]. CoVs such as SARS-CoV were shown to be able to enter target cells via pH-dependent mechanism in which the acidic pH of the lysosome triggers fusion of the viral and endosomal membranes resulting in viral particle uncoating and subsequent release of viral nucleic acid into the cytoplasm [42]. CQ can also impair posttranslational modifications of viral proteins through interfering with proteolytic processes [43] and inhibition of glycosylation via specific interactions with sugar-modifying enzymes or glycosyltransferases [28]. CQ can also hamper lysosomal protein degradation and lysosomal fusion with autophagosomes [44–46]. Moreover, it has been suggested that CQ has the ability to affect the cytotoxic mechanisms and works as anti-autophagy agent *in vitro* [47]. CQ works as anti-inflammatory agent through reducing tumor necrosis factor (TNFα) release and suppressing TNF receptors on monocytes [26,28].

On the other hand, HCQ has similar effects to CQ in interfering with the glycosylation of ACE2, blocking virus/cell fusion and inhibiting lysosomal activity by increasing pH [22]. HCQ can also impede major histocompatibility complex (MCH) class II expression which inhibits T cell activation, expression of CD145 and cytokines release [48–50]. Furthermore, HCQ has been shown to impair Toll-like receptors (TLRs) signaling through increasing endosomal pH and interfering with TLR7 and TLR9 binding to their DNA/RNA ligands thereby inhibiting transcription of pro-inflammatory genes [51–53]. The aforementioned immunomodulatory properties of CQ and HCQ have raised the interest in using these drugs in COVID-19 patients at risk of cytokines release syndrome (CRS) [22].

3. CQ and HCQ pharmacokinetics

The fact that both CQ and HCQ are considered for the management of COVID-19 patients clearly highlights the need to better understand their pharmacokinetics (PK) parameters. However, a full understanding of these parameters has been challenging despite the numerous reported studies. Generally, PK parameters for CQ and HCQ are comparable (Table 1) [54,55]. Following oral administration of CQ and HCQ, their bioavailability can reach up to 80% with plasma peak time around 2–4 h [56–58]. Thus, parenteral administration, if available, might be a better route especially that oral administration has shown huge interpatient variability [56,59,60]. The long half-life of both CQ and HCQ which could range from 30 to 60 days is likely attributed to their large volume of distribution (200–800 L/kg) and extensive tissue uptake [61–68]. CQ and HCQ are metabolized via CYP-450 enzymes to other active compounds, which are responsible for the extended pharmacological actions and increased toxicity [61,69]. Up to 60% of CQ and HCQ is primarily excreted renally as unchanged or metabolized forms, and the remaining (40%) is usually cleared through the liver, feces and skin or stored in other lean body tissues [54,69–74]. It's important to note that CQ and HCQ have a chiral center, which produces two enantiomers R(−) or S(+) forms or isomers [75], in which little is known about the differences in their pharmacological activity and their corresponding metabolites. Most clinically used CQ and HCQ exist as a racemic mixture (50:50) of both isomers which complicates the

Table 3
In vitro antiviral activity of CQ and its derivatives on non-CoVs.

Drug	Virus	Cells	EC_{50} (μM)	SI	Main findings	Year	Ref
CQ	HIV-1	HL3Tl	–	–	↑ viral replication[p]	1988	[126]
CQ	HIV-1	H-9	–	low toxicity	↓ viral replication	1990	[118]
CQ[a]	HIV-1	H-9	–	No toxicity	↓ viral replication	1998	[119]
CQ[a]	HIV-1	U-937	–	No toxicity	↓ viral replication	1998	[119]
CQ[b]	HIV-1	H-9	0.9	No toxicity	↓ viral replication	1999	[120]
CQ[b]	HIV-1	U-937	0.4	No toxicity	↓ viral replication	1999	[120]
CQ[b]	HIV-1	T cells[k]	0.9	No toxicity	↓ viral replication	1999	[120]
CQ[b]	HIV-1	Monocytes[k]	0.2	No toxicity	↓ viral replication	1999	[120]
CQ[b]	HIV-1	U-1[l]	0.1	No toxicity	↓ viral replication	1999	[120]
CQ[b]	HIV-1	ACH-2[m]	1	No toxicity	↓ viral replication	1999	[120]
CQ[c]	HIV-1	U-937	0.4	No toxicity	↓ viral replication	2001	[121]
CQ[c]	HIV-1	H-9	0.9	No toxicity	↓ viral replication	2001	[121]
CQ[c]	HIV-1	T cells[k]	0.9	No toxicity	↓ viral replication	2001	[121]
CQ[c]	HIV-1	MΦ[k]	0.2	No toxicity	↓ viral replication	2001	[121]
CQ[c]	HIV-1	U-1[l]	0.1	No toxicity	↓ viral replication	2001	[121]
CQ[c]	HIV-1	ACH-2[m]	1	No toxicity	↓ viral replication	2001	[121]
CQ[d]	HIV-1	H-9	1–10	No toxicity	↓ viral replication	2004	[122]
CQ	HIV-1	MT-4	8.86 ± 1.18	6	↓ viral replication	2006	[106] [r]
HCQ	HIV-1	U-937	1	low toxicity	↓ viral replication	1993	[123]
HCQ	HIV-1	CEM	10	low toxicity	↓ viral replication	1993	[123]
HCQ	HIV-1	63	0.01	No toxicity	↓ viral replication	1996	[124]
HCQ	HIV-1	SP	0.1	No toxicity	↓ viral replication	1996	[124]
HCQ	HIV-1	63_{HIV}	–	–	↓ viral replication	1996	[124]
HCQ	HIV-1	SPH	–	–	↓ viral replication	1996	[124]
HCQ	HIV-1	MT-4	> 12	–	Ineffective	2006	[106] [r]
FQ	HIV-1	MT-4	> 2.4	–	Ineffective	2006	[106] [r]
HFQ	HIV-1	MT-4	2.9 ± 1.1	3	↓ viral replication	2006	[106]
CQ[d]	HIV-2	MT-4	1–10	No toxicity	↓ viral replication	2004	[122]
CQ	IAV H1N1	MDCK	–	–	↓ viral replication	1981	[127]
CQ	IAV H1N1	MDCK	3.60	–	↓ viral replication	2006	[128]
CQ	IAV H1N1	A549	–	–	↓ viral replication	2007	[129]
CQ	IAV H1N1	MDCK	1.26	–	↓ viral replication	2007	[130]
CQ	IAV H3N2	MDCK	0.84	–	↓ viral replication	2006	[128]
CQ	IAV H3N2	MDCK	1.53	–	↓ viral replication	2007	[130]
CQ	IAV H3N2	A549	–	–	↓ viral replication	2007	[129]
CQ	IAV H5N1	A549	–	–	↓ viral replication	2013	[29]
CQ	IAV H5N9	MDCK	14.38	–	↓ viral replication	2007	[130]
CQ	IAV H7N3[f h]	MDCK	> 20	–	Ineffective	2007	[130]
CQ	IAV H7N3[g h]	MDCK	14.39	–	↓ viral replication	2007	[130]
CQ	Flu B	MDCK	–	–	↓ viral replication	1983	[131]
CQ	DENV-2	BHK	–	–	↓ viral replication[q]	1990	[43]
CQ	DENV-2	Vero	–	No toxicity	↓ viral replication	2013	[141]
CQ	DENV-2	C6/36	–	No toxicity	Ineffective	2013	[141]
CQ	DENV-2	U-937	–	No toxicity	↓ viral replication	2014	[140]
CQ	ZIKV	Vero	9.82	No toxicity	↓ viral replication	2016	[135]
CQ	ZIKV	hBMECs	14.20	No toxicity	↓ viral replication	2016	[135]
CQ	ZIKV	NSCs	12.36	No toxicity	↓ viral replication	2016	[135]
CQ	ZIKV	NSs	–	–	↓ viral replication	2016	[135]
CQ	ZIKV	Vero	4.15	–	↓ viral replication	2017	[134]
CQ	ZIKV	Huh7	1.72–2.72	–	↓ viral replication	2017	[134]
CQ	ZIKV	NSs	10	–	↓ viral replication	2017	[136]
AMD	ZIKV	Vero	–	–	↓ viral replication	2017	[134]
CQ	CHIKV	HeLa	–	–	↓ viral replication	2007	[132]
CQ pre	CHIKV	Vero	7.0 ± 1.5	37.14	↓ viral replication	2010	[41]
CQ post	CHIKV	Vero	17.2 ± 2.1	15.29	↓ viral replication	2010	[41]
CQ con	CHIKV	Vero	10.0 ± 1.2	26	↓ viral replication	2010	[41]
CQ	CHIKV	MDM[n]	–	low toxicity	↓ viral replication	2018	[133]
CQ	CHIKV	Fibroblasts[n]	–	high toxicity	↓ viral replication	2018	[133]
CQ	EBOV[i]	HEK 293T	4.7	–	↓ viral replication	2013	[139]
CQ	EBOV[j]	Vero 76	16	–	↓ viral replication	2013	[139]
HCQ	EBOV[i]	HEK 293T	9.5	–	↓ viral replication	2013	[139]
HCQ	EBOV[j]	Vero 76	22	–	↓ viral replication	2013	[139]
AMD	EBOV[i]	HEK 293T	2.6	–	↓ viral replication	2013	[139]
AMD	EBOV[j]	Vero 76	8.4	–	↓ viral replication	2013	[139]
AQ	EBOV[i]	HEK 293T	4.3	–	↓ viral replication	2013	[139]
AQ	EBOV[j]	Vero 76	21	–	↓ viral replication	2013	[139]
CQ	EBOV	MRC-5	–	low toxicity	↓ viral replication	2015	[137]
CQ	EBOV	Vero E6	1.77[o]	–	↓ viral replication	2015	[138]
CQ	SINV	BHK-21	–	–	↓ viral replication	1981	[142]
CQ	VSV	BHK-21	–	–	↓ viral replication	1981	[142]
CQ	VSV	B104	–	–	↓ viral replication	2010	[149]
CQ	Rabies	NS-20	–	–	↓ viral replication	1984	[143]
CQ	PICV	BHK-21			↓ viral replication	1989	[147]
CQ	Poliovirus	HeLa	–	–	Ineffective	1991	[151]

(*continued on next page*)

Table 3 (*continued*)

Drug	Virus	Cells	EC_{50} (μM)	SI	Main findings	Year	Ref
CQ	SLE	BHK	–	–	↓ viral replication[q]	1990	[43]
CQ	POW	BHK	–	–	↓ viral replication[q]	1990	[43]
CQ	NiV	Vero	–	–	↓ viral replication	2009	[150]
CQ	NiV	HeLa	0.62	–	↓ viral replication	2010	[148]
CQ	HeV	Vero	–	–	↓ viral replication	2009	[150]
CQ	HeV	HeLa	0.71	–	↓ viral replication	2010	[148]
CQ	EBV	HH514-16	–	–	↑ viral replication	2017	[125]
CQ[e]	HCV	Huh-7	0.22	–	↓ viral replication	2010	[144]
CQ	DHBV	PDH	–	–	↓ viral replication	1990	[145]
CQ	DHBV	PDH	–	No toxicity	↓ viral replication	1991	[146]
CQ	JEV	B104	–	–	↓ viral replication	2010	[149]
CQ	MARV[i]	HEK 293T	5.5	–	↓ viral replication	2013	[139]
CQ	MARV[j]	Vero 76	15	–	↓ viral replication	2013	[139]
HCQ	MARV[i]	HEK 293T	9.8	–	↓ viral replication	2013	[139]
HCQ	MARV[j]	Vero 76	18	–	↓ viral replication	2013	[139]
AMD	MARV[i]	HEK 293T	2.3	–	↓ viral replication	2013	[139]
AMD	MARV[j]	Vero 76	8.3	–	↓ viral replication	2013	[139]
AQ	MARV[i]	HEK 293T	4.3	–	↓ viral replication	2013	[139]
AQ	MARV[j]	Vero 76	42	–	↓ viral replication	2013	[139]
CQ	CCHFV	Vero E6	–	–	↓ viral replication	2015	[150]
CQ	CCHFV	Huh7	–	21.3	↓ viral replication	2015	[150]

CQ: Chloroquine; **HCQ**: Hydroxychloroquine; **FQ**: Ferroquine; **HFQ**: Hydroxy ferroquine; **AMD**: Amodiaquine; **Pre**: pre-treatment; **Post**: post-treatment; **Con**: concurrent; **AQ:** Aminoquinoline; **HIV:** Human immunodeficiency viruses; **IAV**: Influenza A virus; **Flu B**: Influenza B virus **DENV-2:** Dengue virus 2; **ZIKV**: Zika virus; **CHIKV:** Chikungunya virus; **EBOV:** Ebola virus; **SINV**: Sindbis virus; **VSV**: Vesicular stomatitis virus; **PICV**: Pichinde virus; **SLE:** St. Louis encephalitis virus**; POW:** Powassan virus; **NiV:** Nipah virus; **HeV**: Hendra virus; **EBV**: Epstein-Barr virus; **HCV:** Hepatitis C virus**; DHBV**: Duck hepatitis B virus; **JEV:** Japanese encephalitis virus; **MARV:** Marburg virus**; CCHFV:** Crimean-Congo hemorrhagic virus; **HL3Tl**: HeLa derivative cells; **H-9:** Human T lymphocytic cells; **U-937**: Human promonocytic cells; **U-1**: Human promonocytic cells; **ACH-2**: Human T lymphocytic cells; **MΦ**: macrophages; **MT-4 cells**: HTLV-I-transformed T-cell line; **CEM**: Human T lymphoblast cells; **63**: Human macrophage hybridoma; **SP**: T-cell line derived from the pleural fluid of an HIV- 1-infected individual; **63_{HIV}**: 63 cells infected by HIV; **SPH:** SP cells infected by HIV; **MDCK**: Madin Darby canine kidney; **A549 cells**: Human adenocarcinomic alveolar basal epithelial cells; **BHK/BHK-21 cells**: Syrian golden Syrian golden fibroblast cells; **Vero cells**: African green monkey kidney epithelial cells; **C6/36:** Aedes albopictus cell line; **hBMEC**: Human brain microvascular endothelial cells; **NSCs**: Neural stem cells; **NS**: Neurospheres; **Huh7 cells**: Human hepatocyte-derived carcinoma cells; **HeLa**: Human epithelial cell line; **MDM**: Monocyte-derived macrophages; **HEK 293T**: Human embryonic kidney cells; **MRC-5**: Human normal lung fibroblasts; **MRC-5**: Medical Research Council cell strain 5; **B104:** Rat neuroblastoma cell; **NS-20**: Murine neuroblastoma; **HH514–16**: Burkitt lymphoma cell line; **PDH:** Primary duck hepatocytes; **EC_{50}**: 50% Effective concentration; **SI**: selectivity index defined as the ratio of drug efficacy to cytotoxicity (when no SI value was reported, level of toxicity was indicated if available).

[a] Either alone or combined with hydroxyurea (HU1) + didanosine (ddI).

[b] In combination with hydroxyurea (HU1) + didanosine (ddI).

[c] In combination with hydroxyurea (HU1) + didanosine (ddI) or with hydroxyurea (HU1) + zidovudine (ZDV).

[d] Enhanced inhibition against HIV-1 and HIV-2 in combination with HCQ in H9 and MT-4 cells; and against HIV-1 in combination with indinavir (IDV), saquinavir (SQV) or ritonavir (RTV) in MT-4 cells or peripheral blood mononuclear cells (PBMCs).

[e] Synergistic inhibitory effect of CQ with IFN-α.

[f] A/Mallard/It/43/01 (H7N3).

[g] A/Ty/It/220158/02 (H7N3).

[h] The haemagglutinins (HAs) of the two avian H7N3 strains differ in two amino acid residues (261 in the HA1 subunit and 161 in HA2 subunit) and display different pH requirements.

[i] Viral entry (viral pseudotype assay).

[j] Viral replication.

[k] Primary cells.

[l] Cells stimulated with LPS.

[m] Cells stimulated with PMA.

[n] Primary non-human primates derived cells.

[o] EC_{50} in μg/mL.

[p] Suggested enhanced replication and protection of tat from proteolytic degradation with CQ.

[q] Suggested inhibition of virus replication based on increased prM protein in progeny virions rather than M protein due to inhibition of proteolytic process.

[r] CQ, HCQ and FQ showed no significant activity against parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus, Punta Toro virus, respiratory syncytial virus (RSV), herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), vaccinia virus, vesicular stomatitis virus (VSV), and influenza A virus (H3N2).

understanding of their PK and associated toxicity as they could behave differently inside the body [57,75–77].

4. CQ and HCQ adverse effects and related toxicities

The most common CQ and HCQ adverse effects are gastrointestinal symptoms such as nausea, vomiting and abdominal discomfort [78], and uncommonly worrisome fulminant hepatic failure [79], toxic epidermal necrolysis (TEN) [80] and cardiotoxicity that could manifest with QT abnormality [81–83]. Nevertheless, over the years CQ and HCQ have maintained a good safety profile when used in several chronic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Despite some animal experiments suggesting that HCQ is probably less toxic than CQ, there is a lack of high quality evidence from clinical trials supporting this claim [74,84–87]. These toxicities could be related to the very long half-life and the large volume of distribution of both drugs. One of the significant toxic effects of CQ and HCQ is the possible ocular pigmentation due to their binding to melanin, which could lead to damage in different parts of the eye including the cornea, ciliary body and retina [88]. Notably, the incidence of such ocular toxicity is usually rare. For instance, it was shown that only 0.5% out of ~400 patients treated with HCQ (≤6.5 mg/kg/day) for 6 years due to RA or SLE had developed ocular related complications [89]. Most studies have shown that such complications might only

Table 4
In vivo animal studies on the antiviral activity of CQ and its derivatives on CoVs and non-CoVs.

	Drug	Virus	Model	Dose (mg/kg)	Route	Main findings	Year	Ref
CoVs	CQ	SARS-CoV	Mice	1–50	i.p or i.n.	Tolerated; ineffective	2006	[105]
	AMD	SARS-CoV	Mice	9.4–75	i.p or i.n.	Tolerated; ineffective	2006	[105]
	CQ	HCoV-OC43	Mice	15 (daily)	s.c.	Effective[c]	2009	[108]
	CQ	HCoV-OC43	Mice	30 then 15	s.c.	Effective	2019	[152]
	CQ	FIPV	Cat	10/3 days	s.c.	Not significant effect	2013	[110]
Non CoVs	CQ	IAV H1N1	Mice	12.5 (daily)	i.t. or oral	Toxic; ineffective	2007	[129]
	CQ	IAV H3N2	Mice	12.5–37.5 (daily)	i.t. or oral	Toxic; ineffective	2007	[129]
	CQ	IAV H3N2	Ferrets	10 (daily)	oral	Ineffective	2007	[129]
	CQ	IAV H5N1	Mice	50	i.p.	Effective[d]	2013	[29]
	CQ	EBOV	GUPI	33.75(2 daily)	i.v. or oral	Toxic; ineffective	2015	[137]
	CQ	EBOV	Mice	90	i.p.	Toxic; ineffective	2015	[138]
	CQ	EBOV	Hamsters	90	i.p.	Toxic; ineffective	2015	[138]
	CQ[a]	EBOV	Hamsters	50	i.p.	Tolerated; ineffective	2015	[138]
	CQ	EBOV	Mice	90	i.p	Effective	2013	[139]
	CQ	NiV	Ferrets	25 (daily)	–	Ineffective	2009	[153]
	CQ[b]	NiV	Hamsters	50	i.p.	Ineffective[e]	2010	[148]
	CQ[b]	HeV	Hamsters	50/2 days	i.p.	Ineffective[e]	2010	[148]
	CQ	LASV	Mice	90	i.p	Ineffective	2013	[139]
	CQ	ZIKV	Mice	100	i.g.	Effective[f]	2017	[134]
	CQ	ZIKV	Mice	50 (5 days)	oral	Effective[g]	2017	[136]
	CQ	CHIKV	NHP	14 (daily)	s.c.	Toxic; ineffective[h]	2018	[133]
	CQ	SFV	Mice	~10	i.p	Toxic; ineffective	1991	[154]

CQ: Chloroquine; **AMD**: Amodiaquine; **SARS-CoV**: Sever acute respiratory syndrome-coronavirus; **FIPV**: Feline infectious peritonitis virus; **IAV**: Influenza A virus: **EBOV:** Ebola virus; **NiV:** Nipah virus; **HeV**: Hendra virus; **LASV:** Lassa fever viruses; **ZIKV:** Zika virus; **CHIKV:** Chikungunya virus; **SFV:** Semliki Forest Virus; **GUPI**: Guinea pig; **NHP**: non-human primate; **i.p:** intraperitoneal; **i.n**: intranasal; **s.c.**: subcutaneous; **i.t**: intratracheal; **i.v**: intravenous; **i.g**: intragastric.

[a] Combined with doxycycline (2.5 mg/kg) and azithromycin (50 mg/kg).

[b] Either alone or combined with ribavirin.

[c] Dose-dependent protection of infected pups when given to mothers prepartum or postpartum (placental and maternal milk transfer).

[d] therapeutically but not prophylactically.

[e] Disease exacerbation.

[f] in both wild type and IFNAR deficient mice. Also, protected infected pups from infection and microcephaly when given to mothers.

[g] CQ extended the average lifespan of ZIKV-infected AG129 mice, and suppresses vertical transmission from pregnant infected mice.

[h] Disease exacerbation correlating with increased type I IFN response and delayed immune response.

occur with long term treatment of chronic diseases which extends for more than 5 years with doses above or equal to 6.5 mg/kg/day [90,91]. However, ocular toxicity and changes could still occur with shorter treatments. Other complications such as development of proximal myopathy associated with respiratory failure have also been reported in patients treated with either CQ or HCQ [92–95]. Nonetheless, most of these complications were seen in elderly patients with an average age of 70 years suffering from chronic RA or autoimmune diseases. Both CQ and HCQ were also shown to be associated with rare but life-threatening cardiomyopathy [96–98]. Other less reported CQ and HCQ toxicities include urticaria [99], ototoxicity [100,101] and some neurological effects [102,103].

5. *In vitro* antiviral activity of CQ and HCQ

The antiviral effects of CQ were suggested at least 50 years ago [23,25]. Since then, several studies have tested the ability of CQ and HCQ to inhibit the replication of a wide range of CoVs and non-CoV viruses *in vitro* as shown in Tables 2 and 3, respectively. The majority of these studies have revealed a substantial ability of CQ and HCQ as well as some of their derivatives to inhibit viral replication with no to low toxicity. Specifically, CQ has been shown to inhibit the replication of different CoVs including SARS-CoV, MERS-CoV and SARS-CoV-2 among others in several studies (Table 2) [37,104–115]. Only two studies showed no significant inhibitory effects of CQ on MERS-CoV and mouse hepatitis virus (MHV4) [116,117]. Other CQ derivatives such as amodiaquine (AMD), ferroquine (FQ), hydroxy ferroquine (HFQ) have been also shown to exerts some antiviral activity [105,106]. Interestingly enough, while HCQ does not seem to have a significant effect in reducing SARS-CoV and Feline CoV replication [106], it was recently shown to have a potent *in vitro* inhibitory effects against SARS-CoV-2 replication [112,116].

Similarly, these compounds have shown excellent *in vitro* antiviral activity against several non CoV (mostly RNA viruses) with low toxicity in most cases (Table 3). For instance, HIV was shown to be inhibited by CQ alone or in combination with HCQ, hydroxyurea (HU1), didanosine (ddI), zidovudine (ZDV), indinavir (IDV), saquinavir (SQV) or ritonavir (RTV) [106,118–122]. While other derivatives such as HCQ and HFQ have been also shown to inhibit HIV replication [106,123,124], one study showed no effect of HCQ and FQ on HIV [106]. Similarly, it was found that CQ could enhance Epstein-Barr virus replication [125]. Furthermore, another study has suggested possible enhanced HIV replication with CQ treatment through protection of tat protein from proteolytic degradation [126]. Influenza A and B viruses have also been shown to be inhibited by CQ [27,127–131] although contradicting results have been seen for some subtypes and strains such as avian H7N3 strains (A/Mallard/It/43/01 and A/Ty/It/220158/02) [106,130]. Several other studies have also reported *in vitro* inhibitory effect of CQ on multiple viruses such as chikungunya virus (CHIKV) [41,132,133], zika virus (ZIKV) [134–136], Ebola virus (EBOV) [137–139], dengue viruses (DENV) in mammalian cells [43,140,141] but not insect cells [141] as well as several others [43,139,142–150]. Nonetheless, some reports failed to observe antiviral activity of CQ, HCQ and FQ on several other viruses including polio virus, reovirus, respiratory syncytial virus (RSV), herpes simplex viruses, coxsackie virus, vesicular stomatitis virus (VSV), vaccinia virus, sindbis virus, parainfluenza-3 virus and Punta Toro virus [106,151].

6. *In vivo* animal antiviral activity of CQ and HCQ

There are limited studies established to investigate the possible antiviral effects of CQ or HCQ in animal models (Table 4). In general, studies showed no significant effect of CQ on CoVs including SARS-CoV and feline infectious peritonitis virus (FIPV) replication or clinical

Table 5
Main findings of clinical trials on the antiviral activity of CQ and its derivatives on CoVs and non-CoVs.

Drug	Virus	Design	Dose mg/day	Total No.	Main Findings	Year Ref
HCQ + AZT	SARS-CoV-2	SAOLS	600 mg/day (10 days)	42	↓ viral load[a]	2020 [162]
HCQ	SARS-CoV-2	RCT	400 mg/day (5 days)	62	↓ Recovery time	2020 [163]
HCQ	SARS-CoV-2	Pilot	400 mg/day (5 days)	30	Ineffective[b]	2020 [165]
HCQ + AZT	SARS-CoV-2	OS	600 mg/day (10 days)	80	↓ viral load	2020 [164]
HCQ + AZT	SARS-CoV-2	SAOLS	600 mg/day (10 days)	11	Ineffective[c]	2020 [166]
CQ	Influenza A/B	RDBPCS	500 mg/day (1 week) Once a week (11 weeks)	1516	Ineffective	2011 [155]
CQ	DENV	RDBPCS	600 mg/day (day 1 and 2) 300 mg/day (day 3)	307	Ineffective[d]	2010 [156]
CQ	DENV	RDBPCS	500 mg/day BID (3 days)	37	Ineffective[e]	2013 [158]
CQ	CHIKV	RDBPCS	600 mg (day 1) 300 mg (BID, days 2 and 3) 300 mg (days 4 and 5)	54	Ineffective[f]	2008 [157] 2018 [133]
HCQ	HIV 1	Case report	600 mg/day	2	↓ viral load[g]	1996 [169]
HCQ	HIV 1	RDBPCS	800 mg/day (8 weeks)	40	↓ viral load Stable $CD4^+$ level ↓ serum IL-6 & IgG	1995 [170]
HCQ	HIV 1	RDBS	800 mg/day (16 weeks)	72	↓ viral load Stable $CD4^+$ level ↓ serum IL-6 & IgG	1997 [159]
HCQ	HIV	RDBPCS	400 mg/day (42 weeks)	83	Ineffective ↑ viral load ↓ $CD4^+$ level	2012 [161]
CQ- ART	HIV	RDBPCS	250 mg/day (12 weeks)	33	↑ viral replication	2016 [171]
CQ + ART	HIV	RDBPCS	250 mg/day (12 weeks)	37	↓ Immune cell activation	2016 [171]

HCQ: Hydroxychloroquine; **AZT:** Azithromycin; **CQ:** Chloroquine; **ART**: Antiretroviral therapy; **SARS-CoV-2**: Sever acute respiratory syndrome-coronavirus 2; **DENV**: Dengue Virus; **CHIKV**: Chikungunya virus; **HIV**: Human immunodeficiency virus; **SAOLS**: Single arm open labelled study; **RCT:** Randomized clinical trial; **OS:** Observational study; **RDBPCS**: Randomized double blind placebo controlled study; **RDBS**: Randomized double blinded study; **BID**: Twice per day.

[a] Small sample size study, 1 death and 3 transferred to ICU among 26 patients treated with HCQ + AZT.
[b] 1 patient developed to sever stage.
[c] 1 death, 2 transferred to ICU, 1 complained of QT interval prolongation among 11 patients treated with HCQ + AZT.
[d] Longer duration of DENV viremia, CQ was associated with a significant reduction in fever clearance time.
[e] Temporary improvement in the quality of life.
[f] Delayed immune response and more frequent arthralgia in treated group.
[g] In one patient.

scores in mice and cats, respectively [105,110]. However, it has been found that CQ significantly reduced HCoV-OC43 dissemination and replication in mice central nervous system (CNS) [152] and increased the survival rate of HCoV-OC43 infected newborn mice when their mothers treated by CQ most probably through placental and maternal milk transfer [108].

On the other hand, CQ administration has shown contradicting outcomes when used against non-CoVs RNA viruses in different animal models. Some studies have demonstrated antiviral efficacy of CQ in influenza A virus H5N1, ZIKV and EBOV infected mice [29,134,139]. Interestingly, CQ was effective against ZIKV in both wild type and IFNAR deficient mice, and protected infected suckling pups from infection and microcephaly when given to their mothers [29,134,136]. However, several other studies showed no significant antiviral effect of CQ against influenza A H1N1 and H3N2 viruses in mice and Ferrets, respectively [129]. Similarly, CQ was ineffective against EBOV in guinea pigs, mice and hamsters [137,138], Nipah virus (NiV) in Ferrets and hamsters [148,153], Hendra virus (HeV) in hamsters [148], CHIKV in cynomolgus macaques [133], Lassa virus (LASV) in mice [139] and Semliki Forest Virus (SIV) in mice [154]. Importantly, most of these previous *in vivo* studies showed toxicity in animals [129,133,137,138,154]. Furthermore, it was shown that CQ could lead to disease exacerbation correlating with increased type I IFN response and delayed immune responses in CHIKV infected macaques [133], increased mortality rate of SFV-infected mice [154] and NiV or HeV infected hamsters [148].

7. Use of CQ and HCQ as antiviral agents in clinical trials

There are very limited published clinical trials that studied the possible antiviral effects of CQ or HCQ in CoV and non-CoV infected patients (Table 5). These published clinical trials have clearly shown no significant benefit of using CQ in the prevention or treatment against influenza, DENV or CHIKV infections in patients [133,155–158]. In fact, in one study, patients treated with CQ were more likely to develop adverse effects such as arthralgia at day 200 post-treatment [157]. On the other hand, few studies have reported that HCQ could decease HIV-1 viremia, stabilize CD4 T cell count and reduce IL-6 and IgG levels in infected patients [159], although others showed contradicting finding of increased HIV RNAemia in HCQ treated patients [160,161]. Interestingly, while few clinical studies have suggested that the use of HCQ alone or with azithromycin (AZT) could be beneficial for COVID-19 patients as it reduces viral shedding and time to clinical recovery [162–164], others have reported no effect in infected patients [165,166]. However, it is important to note that most of these studies have several limitations in study designs with small sample sizes. Nonetheless, around 104 clinical trials are ongoing in different countries to asses and evaluate the therapeutic and prophylactic effects of both CQ and/or HCQ in COVID-19 patients (Table 6).

8. Conclusion

The COVID-19 pandemic has spread out of control and has caused considerable morbidity and mortality in several countries. In this unprecedented situation, clinicians have tried all kinds of treatments in an effort to stem the progression of this disease. One treatment that has received huge attention was the empirical use of anti-malarial CQ/HCQ. While there is no strong and enough scientific and clinical data to support their use, several countries have already included CQ/HCQ in COVID-19 treatment protocols [167,168], not only as a treatment option for severely ill patients but also as a prophylactic measure.

Table 6
Characteristics of ongoing clinical trials studying the efficacy and safety of CQ and HCQ in patients with COVID-19.

Drug	Design	Status	Group(s)	Total No	Primary outcomes	Country Registration No.
HCQ	Interventional ROLCS	Completed	Conventional treatment HCQ	360	Viral clearance	China ChiCTR2000029868
HCQ	Interventional ROLCS	Recruiting	Conventional treatment HCQ	78	Clinical status	China ChiCTR2000029740
HCQ	Interventional RDBS	Recruiting	Placebo HCQ	300	Viral clearance T cell recovery time	China ChiCTR2000029559
HCQ	Retrospective Observational	Not yet recruiting	HCQ	1200	Pneumonia incidence	China ChiCTR2000031782
HCQ	Interventional ROLS	Completed	Conventional treatment HCQ	30	Viral clearance Mortality	China NCT04261517
CQ	Interventional RROLCS	Recruiting	Control CQ	80	Clinical recovery time	China ChiCTR2000030718
CQ	Interventional RCT	Recruiting	Placebo CQ/FAV FAV	150	Improvement or recovery Viral clearance	China ChiCTR2000030987
CQ	Interventional RRSBCS	Recruiting	Placebo CQ	300	Viral clearance	China ChiCTR2000031204
CQ	Interventional ROLCS	Not yet recruiting	HCQ Arbidol	320	No. patients progressed to suspected/confirmed	China ChiCTR2000029803
CQ	Interventional RSBCS	Recruiting	Conventional/CQ CQ	100	Length of hospital stay	China ChiCTR2000029939
CQ	Interventional SAOLS	Recruiting	Conventional/CQ	100	Length of hospital stay	China ChiCTR2000029935
CQ	Interventional OLS	Not yet recruiting	LPV/RTV CQ/LPV/RTV CQ	205	Viral clearance	China ChiCTR2000029609
CQ	Interventional cohort study	Recruiting	Conventional treatment CQ	20	Viral clearance Mortality	China ChiCTR2000029542
CQ	Interventional ROLCS	Recruiting	LPV/RTV CQ	112	Clinical status Mortality Viral clearance	China ChiCTR2000029741
CQ	Interventional OLS	Recruiting	Control CQ	80	Clinical recovery time	China ChiCTR2000029988
CQ	Interventional SAOLS	Not yet recruiting	CQ	10	Viral clearance Mortality	China ChiCTR2000029975
CQ	Interventional RDBPCS	Recruiting	Placebo FAV CQ/FAV	150	Time to and frequency of improvement or recovery Viral clearance	China NCT04319900
CQ	Interventional ROLCS	Not yet recruiting	Carrimycin CQ LPV/RTV Arbidol	520	Fever HRCT Viral clearance	China NCT04286503
HCQ CQ	Interventional ROLCS	Recruiting	CQ HCQ	100	Clinical recovery time	China ChiCTR2000029899
HCQ CQ	Interventional ROLCS	Recruiting	CQ HCQ	100	Clinical recovery time	China ChiCTR2000029898
HCQ CQ	Interventional ROLS	Not yet recruiting	Conventional treatment HCQ CQ	100	Clinical recovery time	China ChiCTR2000030054
HCQ CQ	Interventional ROLS	Not yet recruiting	Conventional treatment CQ HCQ	100	Clinical recovery time Viral clearance	China ChiCTR2000029992
HCQ	Interventional RCT	Not yet recruiting	Placebo HCQ	1600	No. symptomatic confirmed cases	USA NCT04318444
HCQ	Interventional ROLS	Not yet recruiting	Standard of care HCQ AZT HCQ/AZT	500	Clinical status	USA NCT04335552
HCQ	Interventional OLS	Not yet recruiting	HCQ Vit C Vit D Zinc	600	Viral clearance Blood pressure Presence of side effects	USA NCT04335084
HCQ	Interventional RCT	Recruiting	HCQ Vit C	1250	Hospitalization IMV	USA NCT04334967
HCQ	Interventional OLS	Not yet recruiting	HCQ/AZT/Vit C/Vit D/Zinc	60	Symptoms resolution Viral clearance Safety	USA NCT04334512
HCQ	Interventional ROLS	Recruiting	HCQ AZT	1550	Hospital admission	USA NCT04334382
HCQ	Interventional RDBPCS	Recruiting	Placebo HCQ	210	Viral clearance	USA NCT04333654
HCQ	Interventional OLS	Recruiting	HCQ Control	360	Rate of positivity	USA NCT04333225

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Table 6 (*continued*)

Drug	Design	Status	Group(s)	Total No	Primary outcomes	Country Registration No.
HCQ	Interventional ROLS	Not yet recruiting	Standard of care HCQ HCQ/AZT	160	Viral clearance	USA NCT04336332
HCQ	Interventional RDBPCS	Recruiting	Placebo HCQ	510	Clinical status	USA NCT04332991
HCQ	Interventional RDBPCS ROLCS	Not yet recruiting	Placebo HCQ	400	Quarantine release rate Hospital discharge rate Infection rate	USA NCT04329923
HCQ	Interventional RCT	Recruiting	Placebo HCQ	3500	Survival/recovery	USA NCT04328467
HCQ	Interventional RDBPCS	Recruiting	Placebo HCQ LPV/RTV LST	4000	Clinical status	USA NCT04328012
HCQ	Interventional ROLS	Recruiting	HCQ AZT	300	Clinical status	USA NCT04329832
HCQ	Interventional RSBS	Not yet recruiting	Ascorbic Acid HCQ	2000	Viral clearance	USA NCT04328961
HCQ CQ	Interventional ROLCS	Recruiting	HCQ HCQ/AZT CQ CQ/AZT	500	Recovery	USA NCT04341727
HCQ	Interventional RCT	Recruiting	Placebo HCQ	3000	Incidence in asymptomatic Severity	USA/Canada NCT04308668
HCQ CQ	Interventional RDBPCS	Not yet recruiting	Placebo CQ HCQ	55000	Disease severity	USA, Australia, Canada, Ireland, South Africa, UK NCT04333732
HCQ	Interventional OLS	Not yet recruiting	Standard of care LPV/RTV HCQ Baricitinib Sarilumab	1000	Clinical status	Canada NCT04321993
HCQ	Interventional RDBPCS	Not yet recruiting	Placebo HCQ	1660	Hospitalization IMV Mortality	Canada NCT04329611
CQ	Interventional ROLCS	Not yet recruiting	Standard of care CQ/AZT	1500	Outpatients: admission or death Inpatients: IMV or death	Canada NCT04324463
HCQ	Interventional RDBPCS	Not yet recruiting	Placebo HCQ LPV/RTV	1200	Confirmed infection in HCW	France NCT04328285
HCQ	Interventional RDBPCS	Recruiting	Placebo HCQ	1300	Mortality IMV	France NCT04325893
HCQ	Interventional ROLS	Recruiting	Standard of care RDV LPV/RTV LPV/RTV/IFβ-1a HCQ	3100	Clinical status	France NCT04315948
HCQ	Interventional ROLCS	Recruiting	RDV LPV/RTV IFβ-1a HCQ	3100	Clinical status	France EudraCT 2020-000936-23
HCQ	–	Recruiting	HCQ	25	Viral clearance	France EudraCT 2020-000890-25
HCQ	Interventional OLCS	Recruiting	Standard of care HCQ/AZT	1000	Incidence Mortality	France EudraCT 2020-001250-21
HCQ	Interventional RDBPCS	Recruiting	Placebo HCQ	1300	IMV Death	France EudraCT 2020-001271-33
HCQ	–	Recruiting	HCQ	50	HCQ pharmacokinetics	France EudraCT 2020-001281-11
CQ	Interventional CSS	Recruiting	Any drug used to treat Covid-19 including CQ	1000	Renal failure	France NCT04314817
CQ	Interventional ROLCS	Recruiting	Standard of care CQ analogue NIVO TCZ	273	Survival rate	France NCT04333914
HCQ	Interventional RDBS	Not yet recruiting	HCQ/LPV/RTV HCQ/LPV/RTV/LEV/BUD/FORM	30	Chest CT-scan Viral clearance	Iran NCT04331470
HCQ	Interventional ROLCS	Recruiting	HCQ/LPV/RTV HCQ/LPV/RTV/IFβ-1b	30	Clinical status Lab/radiological findings Adverse reactions	Iran IRCT20100228003449N27
HCQ	Interventional ROLCS	Recruiting	HCQ/LPV/RTV HCQ/LPV/RTV/IFβ-1a	30	Clinical status Lab/radiological findings Adverse reactions	Iran IRCT20100228003449N28

(*continued on next page*)

Table 6 (*continued*)

Drug	Design	Status	Group(s)	Total No	Primary outcomes	Country Registration No.
HCQ	Interventional ROLCS	Recruiting	HCQ/LPV/RTV HCQ/LPV/RTV/SOF/LDV	50	Clinical status Lab/radiological findings Adverse reactions	Iran IRCT20100228003449N29
HCQ	Interventional SAOLS	Recruitment completed	HCQ/OTV/LPV/RTV/IFβ-1a	20	Clinical status	Iran IRCT20151227025726N12
HCQ	Interventional SAOLS	Recruiting	HCQ/LPV/RTV HCQ/ATV/RTV	50	Clinical status Lab/radiological findings Adverse reactions	Iran IRCT20100228003449N30
HCQ	Interventional ROLCS	Not yet recruiting	Standard of care HCQ HCQ/AZT	630	Clinical status	Brazil NCT04322123
HCQ	Interventional ROLS	Recruiting	HCQ HCQ/AZT	440	Clinical status	Brazil NCT04321278
HCQ	Interventional OLS	Not yet recruiting	HCQ/AZT	400	Evolution of ARS, SpO2, hemodynamic stability	Brazil NCT04329572
CQ	Interventional RDBS	Recruiting	Low Dose CQ High Dose CQ	440	Mortality	Brazil NCT04323527
HCQ	Interventional OLCS	Not yet recruiting	RDV HCQ HCQ/RDV	700	Mortality	Norway NCT04321616
HCQ	Interventional ROLCS	Recruiting	Standard of care HCQ	202	Viral clearance	Norway NCT04316377
HCQ	Interventional RCT	Recruiting	Standard of care HCQ/RDV	443	Safety and efficacy	Norway EudraCT 2020-000982-18
HCQ	Interventional ROLCS	Recruiting	Standard of care HCQ	200	Viral clearance	Norway EudraCT 2020-001010-38
HCQ	Interventional ROLCS	Recruiting	Standard measures HCQ/DRV/COBI	3040	Incidence of secondary cases	Spain NCT04304053
HCQ	Interventional RDBPCS	Not yet recruiting	Placebo HCQ TDF/FTC HCQ/TDF/FTC	4000	Confirmed symptomatic infections	Spain NCT04334928
HCQ	Interventional RDBPCS	Recruiting	Placebo HCQ	440	No. confirmed cases	Spain NCT04331834
HCQ	Interventional ROLCS	Recruiting	HCQ/AZT HCQ/AZT/TCZ	276	Mortality IMV	Spain NCT04332094
HCQ	Interventional ROLCS	Recruiting	LPV/RTV Dexamethasone IFβ-1a HCQ	2000	Mortality	UK EudraCT 2020-001113-21[a]
HCQ	Interventional ROLCS	Recruiting	Standard of care HCQ	350	Change in SpO2/FiO2	UK EudraCT 2020-001270-29
HCQ	Interventional RPCS	Recruiting	Placebo HCQ	3000	Hospital admission Mortality	UK EudraCT 2020-001209-22
HCD CQ	Interventional RDBPCS	Not yet recruiting	Placebo CQ or HCQ	40,000	No. symptoms Severity	UK NCT04303507
HCQ	Interventional ROLCS	Recruiting	No intervention control LPV/RTV HCQ	150	Viral clearance	Korea NCT04307693
HCQ	Interventional ROLCS	Not yet recruiting	Control CIC HCQ/CIC	141	Viral clearance	Korea NCT04330586
HCQ	Interventional RCT	Not yet recruiting	Control HCQ	2486	Incidence	Korea NCT04330144
HCQ	Interventional RPCS	Not yet recruiting	Placebo HCQ	2700	Clinical status	Germany NCT04340544
HCQ	Interventional RPCS	Recruiting	Placebo HCQ	220	Viral clearance	Germany NCT04342221
HCQ	Interventional RPCS	Not yet recruiting	Placebo/HCQ HCQ/COBI	334	Hospital admission	Germany NCT04338906
HCQ	Interventional RDBPCS	Ongoing	Placebo HCQ	220	Viral clearance	Germany EudraCT 2020-001224-33
HCQ	SAOLS	Recruiting	HCQ	150	Dose optimization	Australia ACTRN12620000447954
HCQ	Interventional RCT	Not yet recruiting	Control HCQ LPV/RTV HCQ/LPV/RTV	2500	No. patients not admitted to ICU	Australia ACTRN12620000445976
CQ	Interventional ROLCS	Not yet recruiting	CQ	680	Sick days of HCW	Australia ACTRN12620000417987
HCQ	Interventional RTBCS	Not yet recruiting	Placebo HCQ	400	Infection rate	Mexico NCT04318015
HCQ	Interventional RDBPCS	Not yet recruiting	Placebo HCQ	500	Mortality	Mexico NCT04315896

(*continued on next page*)

Table 6 (*continued*)

Drug	Design	Status	Group(s)	Total No	Primary outcomes	Country Registration No.
HCQ	Interventional ROLCS	Not yet recruiting	Control HCQ	1116	Development of severe infection or death	Israel NCT04323631
CQ	Interventional ROLS	Not yet recruiting	Standard of care CQ	210	Viral clearance Clinical status	Israel NCT04333628
HCQ	Observational CCPS	Recruiting	HCQ	80	Protection	Turkey NCT04326725
HCQ	Interventional ROLCS	Not yet recruiting	Convalescent Plasma/HCQ/AZT HCQ/AZT	80	Viral clearance IgM titers IgG titers	Colombia NCT04332835
HCQ	Interventional ROLS	Not yet recruiting	Quarantine/no treatment HCQ/OTV OTV/LPV/RTV HCQ/OTV/DRV/RTV FAV/LPV/RTV HCQ/FAV/DRV/RTV	80	Viral clearance	Thailand NCT04303299
HCQ	Interventional SAOLS	Recruiting	HCQ/LPV/RTV ± OTV	50	CRP level	Japan jRCTs031190227
CQ	Interventional OLS	Recruiting	CQ	60	Symptoms reduction Pneumonia prevention	Greece EudraCT 2020-001345-38
CQ	Interventional ROLCS	Not yet recruiting	Standard of care CQ	250	Viral clearance	Vietnam NCT04328493
HCQ CQ	Interventional RSBCS	Not yet recruiting	Natural Honey LPV/RTV Arbidol HCQ CQ OTV ± AZT	1000	Viral clearance Fever Resolution of lung inflammation	Egypt NCT04323345
HCQ	Interventional RSBCS	Not yet recruiting	Placebo HCQ/AZT HCQ	75	Clinical status	Pakistan NCT04328272
HCQ	Observational Randomized Trial	Not yet recruiting	Control HCQ AZT OTV HCQ/AZT HCQ/OTV AZT/OTV HCQ/AZT/OTV	500	Viral clearance	Pakistan NCT04338698
HCQ CQ	Interventional ROLCS	Not yet recruiting	Standard of care HCQ CQ	950	Disease progression Admission to ICU or death	Netherlands Trial NL8490
HCQ	Interventional RDBPCS	Recruiting	Placebo HCQ/AZT	226	Survival Hospitalization	Denmark NCT04322396
HCQ	Interventional ROLCS	Recruiting	Control HCQ HCQ/LPV/RTV Wide range of drugs[b]	6800	Mortality Days alive and outside ICU	New Zealand NCT02735707
HCQ	Interventional RDBPCS	Not yet recruiting	Placebo HCQ	440	Viral clearance	Austria NCT04336748
CQ	Interventional ROLCS	Not yet recruiting	CQ/OTV RTV/DRV/OTV LPV/RTV/OTV FAV/LPV/RTV CQ/RTV/DRV/OTV CQ/RTV/DRV/FAV Quarantine	440	Viral clearance	Austria NCT04303299
CQ	Interventional ROLCS	Not yet recruiting	Standard of care CQ	400	Hospitalization or all causes of death	Poland NCT04331600

ROLCS: Randomized open label controlled study; **RDBS**: Randomized double blind study; **ROLS**: Randomized open label study; **RROLCS**: Retrospective randomized open label controlled study; **RCT**: Randomized clinical trial; **RRSBCS**: Retrospective randomized single blind controlled study; **RSBCS**: Randomized single blind controlled study; **SAOLS**: Single arm open label study; **OLS**: Open label study; **RDBPCS**: Randomized double blind placebo controlled study; **RSBS**: Randomized single blind study; **OLCS**: Open label controlled study; **CSS**: Cross-sectional study; **RPCS**: Randomized placebo controlled study; **RTBCS**: Randomized triple blind controlled study; **CCPS**: Case-control prospective study.

HCQ: Hydroxychloroquine; **CQ**: Chloroquine; **FAV**: Favipiravir; **LPV**: Lopinavir; **RTV**: Ritonavir; **AZT**: Azithromycin; **Vit C**: Vitamin C; **Vit D**: Vitamin D; **LST**: Losartan; **RDV**: Remdesivir; **IFß-1a**: Interferon β-1a; **NIVO**: Nivolumab; **TCZ**: Tocilizumab; **LEV**: Levamisole; **BUD**: Budesonide; **FORM**: Formoterol; **SOF**: Sofosbuvir; **LDV**: Ledipasvir; **OTV**: Oseltamivir; **ATV**: Atazanavir; **COBI**: Cobicistat; **TDF**: Tenofovir disoproxil fumarate; **FTC**: Emtricitabine; **CIC**: Ciclesonide; **DRV**: Darunavir. **HRCT**: Pulmonary inflammation resolution time, **IMV**: invasive mechanical ventilation; **HCW**: Healthcare workers;; **ARS**: Acute respiratory syndrome; **SpO2/FiO2**: oxygen saturation/fraction of inspired oxygen ratio; **ICU**: Intensive Care Unit; **CRP**: C-reactive protein.

Data were obtained from NIH. U.S. National Library of Medicine (https://www.clinicaltrials.gov/); the Chinese Clinical Trial Registry (http://www.chictr.org.cn/); the European Union Clinical Trials Registry (https://www.clinicaltrialsregister.eu); ISRCTN registry (http://www.isrctn.com/); Netherlands Trial Registry (https://www.trialregister.nl/); Iranian Registry for Clinical Trials (IRCT) (https://en.irct.ir/); Japanese Registry for Clinical Trials (JRCT) (https://jrct.niph.go.jp/) and the Australian New Zealand Clinical trial Registry (ANZCTR) (https://www.anzctr.org.au/).

[a] The same study was registered in ISRCTN registry (registration no. ISRCTN50189673) with a total number of 5000 patients.

[b] Hydrocortisone, Ceftriaxone, Moxifloxacin or Levofloxacin, Piperacillin-tazobactam, Ceftaroline, Amoxicillin-clavulanate, Macrolide, OTV, IFβ-1a, and Anakinra.

In this comprehensive review of the antiviral effects of CQ and HCQ on SARS-CoV-2 as well as other viruses, we show a broad variation in the research outcomes. Both CQ and HCQ demonstrated promising *in vitro* results, however, such data have not yet been translated into meaningful *in vivo* studies. While few clinical trials have suggested some beneficial effects of CQ and HCQ in COVID-19 patients, most of the reported data are still preliminary [20,162,163]. Furthermore, at least 7 of the ongoing trials were canceled or stopped and it is not yet clear if this was due to possible adverse effects, ineffectiveness or other reasons.

There are several toxicities associated with these drugs [78–80], the one that is foremost concerning is the possibility of QT prolongation and the risk of Torsades de pointes, which is a potentially life-threatening arrhythmia [81–83]. Nevertheless, while our literature review showed that this is quite rare, it is not yet evident whether there would be any additive or possible synergistic risk when these drugs are combined with other medications such as AZT [83]. In fact, it is challenging to base a treatment decision in the absence of a complete research cycle and a clear vision of drug efficacy and safety. Given the current uncertainty, it is worth being mindful of the potential risks and strictly rational the use of these drugs in COVID-19 patients until further high quality randomized clinical trials are available to clarify their role in the treatment or prevention of COVID-19.

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Declaration of competing interest

None declared.

References

[1] Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11:222. https://doi.org/10.1038/s41467-019-13940-6.

[2] Dhama K, Sharun K, Tiwari R, Dadar M, Malik YS, Singh KP, et al. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Hum Vaccines Immunother 2020:1–7. https://doi.org/10.1080/21645515.2020.1735227. 0.

[3] Tyrrell DA, Almeida JD, Cunningham CH, Dowdle WR, Hofstad MS, McIntosh K, et al. Coronaviridae. Intervirology 1975;5:76–82. https://doi.org/10.1159/000149883.

[4] de Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, et al. Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol 2013;87:7790–2. https://doi.org/10.1128/JVI.01244-13.

[5] Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol 2009;7:439–50. https://doi.org/10.1038/nrmicro2147.

[6] Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science 2005;310:676–9. https://doi.org/10.1126/science.1118391.

[7] Gloza-Rausch F, Ipsen A, Seebens A, Gottsche M, Panning M, Drexler JF, et al. Detection and prevalence patterns of group I coronaviruses in bats, northern Germany. Emerg Infect Dis 2008;14:626–31. https://doi.org/10.3201/eid1404.071439.

[8] Higgins PG, Ellis EM. Further observations on the use of organ cultures in the study of acute respiratory-tract infections. J Med Microbiol 1973;6:177–85. https://doi.org/10.1099/00222615-6-2-177.

[9] Hamre D, Procknow JJ. A new virus isolated from the human respiratory tract. Proc Soc Exp Biol Med 1966;121:190–3. https://doi.org/10.3181/00379727-121-30734.

[10] Van der Hoek L, Pyrc K, Jebbink MF, Vermeulen-Oost W, Berkhout RJ, Wolthers KC, et al. Identification of a new human coronavirus. Nat Med 2004;10:368–73. https://doi.org/10.1038/nm1024.

[11] Woo PC, Lau SK, Chu CM, Chan KH, Tsoi HW, Huang Y, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol 2005;79:884–95. https://doi.org/10.1128/JVI.79.2.884-895.2005.

[12] Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319–25. https://doi.org/10.1016/S0140-6736(03)13077-2.

[13] Drosten C, Gunther S, Preiser W, van der Werf S, Brodt HR, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003;348:1967–76https://www.nejm.org/doi/full/10.1056/NEJMoa030747.

[14] Fouchier RA, Kuiken T, Schutten M, van Amerongen G, van Doornum GJ, van den Hoogen BG, et al. Aetiology: koch's postulates fulfilled for SARS virus. Nature 2003;423:240. https://doi.org/10.1038/423240a.

[15] Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367:1814–20https://www.nejm.org/doi/full/10.1056/NEJMoa1211721.

[16] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33. https://doi.org/10.1056/NEJMoa2001017.

[17] Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. Severe acute respiratory syndrome-related coronavirus: the species and its viruses – a statement of the Coronavirus Study Group. bioRxiv 2020. 2020.02.07.937862 https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1.

[18] Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol 2020;92:401–2. https://doi.org/10.1002/jmv.25678.

[19] Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends 2020;14:69–71. https://doi.org/10.5582/bst.2020.01020.

[20] Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72–3. https://doi.org/10.5582/bst.2020.01047.

[21] Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents 2020:105932. https://doi.org/10.1016/j.ijantimicag.2020.105932.

[22] Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother 2020. https://doi.org/10.1093/jac/dkaa114. dkaa114.

[23] Inglot AD. Comparison of the antiviral activity in vitro of some non-steroidal anti-inflammatory drugs. J Gen Virol 1969;4:203–14. https://doi.org/10.1099/0022-1317-4-2-203.

[24] Miller DK, Lenard J. Antihistaminics, local anesthetics, and other amines as antiviral agents. Proc Natl Acad Sci U S A 1981;78:3605–9. https://doi.org/10.1073/pnas.78.6.3605.

[25] Shimizu Y, Yamamoto S, Homma M, Ishida N. Effect of chloroquine on the growth of animal viruses. Arch Gesamte Virusforsch 1972;36:93–104. https://doi.org/10.1007/BF01250299.

[26] Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis 2003;3:722–7. https://doi.org/10.1016/S1473-3099(03)00806-5.

[27] Romanelli F, Smith KM, Hoven AD. Chloroquine and hydroxychloroquine as inhibitors of human immunodeficiency virus (HIV-1) activity. Curr Pharmaceut Des 2004;10:2643–8. https://doi.org/10.2174/1381612043383791.

[28] Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. Lancet Infect Dis 2006;6:67–9. https://doi.org/10.1016/S1473-3099(06)70361-9.

[29] Yan Y, Zou Z, Sun Y, Li X, Xu KF, Wei Y, et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. Cell Res 2013;23:300–2. https://doi.org/10.1038/cr.2012.165.

[30] Gonzalez-Dunia D, Cubitt B, de la Torre JC. Mechanism of Borna disease virus entry into cells. J Virol 1998;72:783–8.

[31] Ros C, Burckhardt CJ, Kempf C. Cytoplasmic trafficking of minute virus of mice: low-pH requirement, routing to late endosomes, and proteasome interaction. J Virol 2002;76:12634–45. https://doi.org/10.1128/JVI.76.24.12634-12645.2002.

[32] Diaz-Griffero F, Hoschander SA, Brojatsch J. Endocytosis is a critical step in entry of subgroup B avian leukosis viruses. J Virol 2002;76:12866–76. https://doi.org/10.1128/JVI.76.24.12866-12876.2002.

[33] Bishop NE. Examination of potential inhibitors of hepatitis A virus uncoating. Intervirology 1998;41:261–71. https://doi.org/10.1159/000024948.

[34] Ferreira DF, Santo MP, Rebello MA, Rebello MC. Weak bases affect late stages of Mayaro virus replication cycle in vertebrate cells. J Med Microbiol 2000;49:313–8. https://doi.org/10.1099/0022-1317-49-4-313.

[35] Harley CA, Dasgupta A, Wilson DW. Characterization of herpes simplex virus-containing organelles by subcellular fractionation: role for organelle acidification in assembly of infectious particles. J Virol 2001;75:1236–51. https://doi.org/10.1128/JVI.75.3.1236-1251.2001.

[36] Kwiek JJ, Haystead TA, Rudolph J. Kinetic mechanism of quinone oxidoreductase 2 and its inhibition by the antimalarial quinolines. Biochemistry 2004;43:4538–47. https://doi.org/10.1021/bi035923w.

[37] Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69. https://doi.org/10.1186/1743-422X-2-69.

[38] Tortorici MA, Walls AC, Lang Y, Wang C, Li Z, Koerhuis D, et al. Structural basis for human coronavirus attachment to sialic acid receptors. Nat Struct Mol Biol 2019;26:481–9. https://doi.org/10.1038/s41594-019-0233-y.

[39] Li W, Hulswit RJ, Widjaja I, Raj VS, McBride R, Peng W, et al. Identification of sialic acid-binding function for the Middle East respiratory syndrome coronavirus spike glycoprotein. Proc Natl Acad Sci U S A 2017;114:E8508–17. https://doi.org/

10.1073/pnas.1712592114.
[40] Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80. https://doi.org/10.1016/j.cell.2020.02.052. e8.
[41] Khan M, Santhosh SR, Tiwari M, Lakshmana Rao PV, Parida M. Assessment of in vitro prophylactic and therapeutic efficacy of chloroquine against Chikungunya virus in vero cells. J Med Virol 2010;82:817–24. https://doi.org/10.1002/jmv.21663.
[42] Yang ZY, Huang Y, Ganesh L, Leung K, Kong WP, Schwartz O. pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN. J Virol 2004;78:5642–50. https://doi.org/10.1128/JVI.78.11.5642-5650.2004.
[43] Randolph VB, Winkler G, Stollar V. Acidotropic amines inhibit proteolytic processing of flavivirus prM protein. Virology 1990;174:450–8. https://doi.org/10.1016/0042-6822(90)90099-D.
[44] Carew JS, Espitia CM, Ja2nd Esquivel, Mahalingam D, Kelly KR, Reddy G, et al. Lucanthone is a novel inhibitor of autophagy that induces cathepsin D-mediated apoptosis. J Biol Chem 2011;286:6602–13. https://doi.org/10.1074/jbc.M110.151324.
[45] Savarino A. Use of chloroquine in viral diseases. Lancet Infect Dis 2011;11:653–4. https://doi.org/10.1016/S1473-3099(11)70092-5.
[46] Wang H, Jiang C. Influenza A virus H5N1 entry into host cells is through clathrin-dependent endocytosis. Sci China C Life Sci 2009;52:464–9. https://doi.org/10.1007/s11427-009-0061-0.
[47] Golden EB, Cho HY, Hofman FM, Louie SG, Schönthal AH, Chen TC. Quinoline-based antimalarial drugs: a novel class of autophagy inhibitors. Neurosurg Focus 2015;38:E12. https://doi.org/10.3171/2014.12.FOCUS14748.
[48] Wu SF, Chang CB, Hsu JM, Lu MC, Lai NS, Li C, et al. Hydroxychloroquine inhibits CD154 expression in CD4(+) T lymphocytes of systemic lupus erythematosus through NFAT, but not STAT5, signaling. Arthritis Res Ther 2017;19:183. https://doi.org/10.1186/s13075-017-1393-y.
[49] van den Borne BE, Dijkmans BA, de Rooij HH, le Cessie S, Verweij CL. Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. J Rheumatol 1997;24:55–60.
[50] Lotteau V, Teyton L, Peleraux A, Nilsson T, Karlsson L, Schmid SL, et al. Intracellular transport of class II MHC molecules directed by invariant chain. Nature 1990;348:600–5. https://doi.org/10.1038/348600a0.
[51] Kuznik A, Bencina M, Svajger U, Jeras M, Rozman B, Jerala R. Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. J Immunol 2011;186:4794–804. https://doi.org/10.4049/jimmunol.1000702.
[52] Ewald SE, Lee BL, Lau L, Wickliffe KE, Shi GP, Chapman HA, et al. The ectodomain of Toll-like receptor 9 is cleaved to generate a functional receptor. Nature 2008;456:658–62. https://doi.org/10.1038/nature07405.
[53] Hacker H, Mischak H, Miethke T, Liptay S, Schmid R, Sparwasser T, et al. CpG-DNA-specific activation of antigen-presenting cells requires stress kinase activity and is preceded by non-specific endocytosis and endosomal maturation. Embo j 1998;17:6230–40. https://doi.org/10.1093/emboj/17.21.6230.
[54] Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. Dermatol Ther 2007;20:160–74. https://doi.org/10.1111/j.1529-8019.2007.00131.x.
[55] Albert DA, Debois LK, Lu KF. Antimalarial ocular toxicity a critical appraisal. J Clin Rheumatol 1998;4:57–62https://scite.ai/reports/10.1097/00124743-199804000-00004.
[56] Gustafsson LL, Walker O, Alvan G, Beermann B, Estevez F, Gleisner L, et al. Disposition of chloroquine in man after single intravenous and oral doses. Br J Clin Pharmacol 1983;15:471–9. https://doi.org/10.1111/j.1365-2125.1983.tb01532.x.
[57] Furst DE. Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. Lupus 1996;5:11–5. https://doi.org/10.1177/096120339600501041.
[58] Tett SE, Cutler DJ, Day RO, Brown KF. Bioavailability of hydroxychloroquine tablets in healthy volunteers. Br J Clin Pharmacol 1989;27:771–9. https://doi.org/10.1111/j.1365-2125.1989.tb03439.x.
[59] Bothwell B, Furst DE. Hydroxychloroquine. Antirheumatic therapy: actions and outcomes Springer; 2005. p. 81–92. https://doi.org/10.1007/978-3-7643-7726-7_5.
[60] Tett S, Cutler D, Day R. Antimalarials in rheumatic diseases. Bailliere's Clin Rheumatol 1990;4:467–89. https://doi.org/10.1016/S0950-3579(05)80004-4.
[61] Ducharme J, Farinotti R. Clinical pharmacokinetics and metabolism of chloroquine. Focus on recent advancements. Clin Pharmacokinet 1996;31:257–74. https://doi.org/10.2165/00003088-199631040-00003.
[62] Cutler DJ, MacIntyre AC, Tett SE. Pharmacokinetics and cellular uptake of 4-aminoquinoline antimalarials. Agents Actions Suppl 1988;24:142–57. https://doi.org/10.1007/978-3-0348-9160-8_13.
[63] Rainsford KD, Parke Ann L, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology 2015;23:231–69. https://doi.org/10.1007/s10787-015-0239-y.
[64] Banks CN. Melanin: blackguard or red herring? Another look at chloroquine retinopathy. Aust N Z J Ophthalmol 1987;15:365–70. https://doi.org/10.1111/j.1442-9071.1987.tb00097.x.
[65] Frisk-Holmberg M, Bergqvist Y, Termond E, Domeij-Nyberg B. The single dose kinetics of chloroquine and its major metabolite desethylchloroquine in healthy subjects. Eur J Clin Pharmacol 1984;26:521–30. https://doi.org/10.1007/BF00542151.
[66] Wetsteyn JC, De Vries PJ, Oosterhuis B, Van Boxtel CJ. The pharmacokinetics of three multiple dose regimens of chloroquine: implications for malaria chemoprophylaxis. Br J Clin Pharmacol 1995;39:696–9. https://doi.org/10.1111/j.1365-2125.1995.tb05731.x.
[67] Hovorka R, Powrie JK, Smith GD, Sonksen PH, Carson ER, Jones RH. Five-compartment model of insulin kinetics and its use to investigate action of chloroquine in NIDDM. Am J Physiol 1993;265:E162–75. https://doi.org/10.1152/ajpendo.1993.265.1.E162.
[68] Yamada Y, Hidefumi K, Shion H, Oshikata M, Haramaki Y. Distribution of chloroquine in ocular tissue of pigmented rat using matrix-assisted laser desorption/ionization imaging quadrupole time-of-flight tandem mass spectrometry. Rapid Commun Mass Spectrom 2011;25:1600–8. https://doi.org/10.1002/rcm.5021.
[69] McChesney EW, Fitch CD. Antimalarial drug II: current antimalarial and New drug developments. Berlin Heidelberg: Springer; 1984. p. 3–60. https://doi.org/10.1007/978-3-642-69254-3.
[70] Bernstein HN. Ocular safety of hydroxychloroquine. Ann Ophthalmol 1991;23:292–6.
[71] Berliner RW, Earle DP, Taggart JV, Zubrod CG, Welch WJ, Conan NJ, et al. Studies on the chemotherapy of the human malarias. VI. The physiological disposition, antimalaril activity, and toxicity of several derivatives of 4-aminoquinoline. J Clin Invest 1948;27:98–107. https://doi.org/10.1172/JCI101980.
[72] Titus EO. Recent developments in the understanding of the pharmacokinetics and mechanism of action of chloroquine. Ther Drug Monit 1989;11:369–79. https://doi.org/10.1097/00007691-198907000-00001.
[73] Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. Am J Med 1983;75:40–5. https://doi.org/10.1016/0002-9343(83)91269-X.
[74] McChesney EW. Animal toxicity and pharmacokinetics of hydroxychloroquine sulfate. Am J Med 1983;75:11–8. https://doi.org/10.1016/0002-9343(83)91265-2.
[75] Iredale J, Fieger H, Wainer IW. Determination of the stereoisomers of hydroxychloroquine and its major metabolites in plasma and urine following a single oral administration of racemic hydroxychloroquine. Semin Arthritis Rheum 1993;23:74–81. https://doi.org/10.1016/S0049-0172(10)80011-3.
[76] Brocks DR, Mehvar R. Stereoselectivity in the pharmacodynamics and pharmacokinetics of the chiral antimalarial drugs. Clin Pharmacokinet 2003;42:1359–82. https://doi.org/10.2165/00003088-200342150-00004.
[77] Salazar-Bookaman MM, Wainer I, Patil PN. Relevance of drug-melanin interactions to ocular pharmacology and toxicology. J Ocul Pharmacol 1994;10:217–39. https://doi.org/10.1089/jop.1994.10.217.
[78] Munster T, Gibbs JP, Shen D, Baethge BA, Botstein GR, Caldwell J, et al. Hydroxychloroquine concentration–response relationships in patients with rheumatoid arthritis. Arthritis Rheum 2002;46:1460–9. https://doi.org/10.1002/art.10307.
[79] Makin AJ, Wendon J, Fitt S, Portmann BC, Williams R. Fulminant hepatic failure secondary to hydroxychloroquine. Gut 1994;35:569–70. https://doi.org/10.1136/gut.35.4.569.
[80] Murphy M, Carmichael AJ. Fatal toxic epidermal necrolysis associated with hydroxychloroquine. Clin Exp Dermatol 2001;26:457–8. https://doi.org/10.1046/j.1365-2230.2001.00857-3.x.
[81] Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. Clin Toxicol (Phila) 2006;44:173–5. https://doi.org/10.1080/15563650500514558.
[82] Stas P, Faes D, Noyens P. Conduction disorder and QT prolongation secondary to long-term treatment with chloroquine. Int J Cardiol 2008;127:e80–2. https://doi.org/10.1016/j.ijcard.2007.04.055.
[83] Chorin E, Dai M, Shulman E, Wadhwani L, Bar Cohen R, Barbhaiya C, et al. The QT interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin. medRxiv 2020. https://doi.org/10.1101/2020.04.02.20047050. 2020.04.02.20047050.
[84] Goldman L, Preston RH. Reactions to chloroquine observed during the treatment of various dermatologic disorders. Am J Trop Med Hyg 1957;6:654–7. https://doi.org/10.4269/ajtmh.1957.6.654.
[85] Wallace DJ, Gudsoorkar VS, Weisman MH, Venuturupalli SR. New insights into mechanisms of therapeutic effects of antimalarial agents in SLE. Nat Rev Rheumatol 2012;8:522. https://doi.org/10.1038/nrrheum.2012.106.
[86] Dubois EL. Antimalarials in the management of discoid and systemic lupus erythematosus. Semin Arthritis Rheum 1978;8:33–51. https://doi.org/10.1016/0049-0172(78)90033-1.
[87] Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. Lancet Infect Dis 2006;6:67–9. https://doi.org/10.1016/S1473-3099(06)70361-9.
[88] Yam JC, Kwok AK. Ocular toxicity of hydroxychloroquine. Hong Kong Med J 2006;12:294–304.
[89] Mavrikakis I, Sfikakis PP, Mavrikakis E, Rougas K, Nikolaou A, Kostopoulos C, et al. The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine: a reappraisal. Ophthalmology 2003;110:1321–6. https://doi.org/10.1016/S0161-6420(03)00409-3.
[90] Michaelides M, Stover NB, Francis PJ, Weleber RG. Retinal toxicity associated with hydroxychloroquine and chloroquine: risk factors, screening, and progression despite cessation of therapy. Arch Ophthalmol 2011;129:30–9. https://doi.org/10.1001/archophthalmol.2010.321.
[91] Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis

Care Res 2010;62:775–84. https://doi.org/10.1002/acr.20133.
[92] Siddiqui AK, Huberfeld SI, Weidenheim KM, Einberg KR, Efferen LS. Hydroxychloroquine-Induced toxic myopathy causing respiratory failure. Chest 2007;131:588–90. https://doi.org/10.1378/chest.06-1146.
[93] Kwon JB, Kleiner A, Ishida K, Godown J, Ciafaloni E, Looney RJ. Hydroxychloroquine-Induced myopathy. J Clin Rheumatol 2010;16:28–31. https://doi.org/10.1097/RHU.0b013e3181c47ec8.
[94] Abdel-Hamid H, Oddis CV, Lacomis D. Severe hydroxychloroquine myopathy. Muscle Nerve 2008;38:1206–10. https://doi.org/10.1002/mus.21091.
[95] Becerra-Cuñat JL, Coll-Cantí J, Gelpí-Mantius E, Ferrer-Avellí X, Lozano-Sánchez M, Millán-Torné M, et al. [Chloroquine-induced myopathy and neuropathy: progressive tetraparesis with areflexia that simulates a polyradiculoneuropathy. Two case reports]. Rev Neurol 2003;36:523–6. https://doi.org/10.33588/rn.3606.2002407.
[96] Soong TR, Barouch LA, Champion HC, Wigley FM, Halushka MK. New clinical and ultrastructural findings in hydroxychloroquine-induced cardiomyopathy—a report of 2 cases. Hum Pathol 2007;38:1858–63. https://doi.org/10.1016/j.humpath.2007.06.013.
[97] Cotroneo J, Sleik KM, Rodriguez ER, Klein AL. Hydroxychloroquine-induced restrictive cardiomyopathy: correlation between clinical, Echocardiographic and pathologic findings. Eur J Echocardiogr 2007;8:247–51. https://doi.org/10.1016/j.euje.2006.02.002.
[98] Muthukrishnan P, Roukoz H, Grafton G, Jessurun J, Colvin-Adams M. Hydroxychloroquine-induced cardiomyopathy: a case report. Circ Heart Fail 2011;4:e7–8. https://doi.org/10.1161/CIRCHEARTFAILURE.110.959916.
[99] Balamurugesan K, Davis P, Ponprabha R, Sarasveni M. Chloroquine induced urticaria: a newer adverse effect. J Fam Med Prim Care 2019;8:2545–7. https://doi.org/10.4103/jfmpc.jfmpc_413_19.
[100] Johansen PB, Gran JT. Ototoxicity due to hydroxychloroquine: report of two cases. Clin Exp Rheumatol 1998;16:472–4.
[101] Seckin U, Ozoran K, Ikinciogullari A, Borman P, Bostan EE. Hydroxychloroquine ototoxicity in a patient with rheumatoid arthritis. Rheumatol Int 2000;19:203–4. https://doi.org/10.1007/s002960000054.
[102] Sahoo S, Kumar M, Sinha VK. Chloroquine-induced recurrent psychosis. Am J Therapeut 2007;14:406–7. https://doi.org/10.1097/MJT.0b013e31802e4b0e.
[103] Malcangi G, Fraticelli P, Palmieri C, Cappelli M, Danieli MG. Hydroxychloroquine-induced seizure in a patient with systemic lupus erythematosus. Rheumatol Int 2000;20:31–3. https://doi.org/10.1007/s002960000066.
[104] Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 2004;323:264–8. https://doi.org/10.1016/j.bbrc.2004.08.085.
[105] Barnard DL, Day CW, Bailey K, Heiner M, Montgomery R, Lauridsen L, et al. Evaluation of immunomodulators, interferons and known in vitro SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. Antivir Chem Chemother 2006;17:275–84. https://doi.org/10.1177/095632020601700505.
[106] Biot C, Daher W, Chavain N, Fandeur T, Khalife J, Dive D, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. J Med Chem 2006;49:2845–9. https://doi.org/10.1021/jm0601856.
[107] De Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, Van Nieuwkoop S, Bestebroer TM, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother 2014;58:4875–84. https://doi.org/10.1128/AAC.03011-14.
[108] Keyaerts E, Li S, Vijgen L, Rysman E, Verbeeck J, Van Ranst M, et al. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob Agents Chemother 2009;53:3416–21. https://doi.org/10.1128/AAC.01509-08.
[109] Kono M, Tatsumi K, Imai AM, Saito K, Kuriyama T, Shirasawa H. Inhibition of human coronavirus 229E infection in human epithelial lung cells (L132) by chloroquine: involvement of p38 MAPK and ERK. Antivir Res 2008;77:150–2. https://doi.org/10.1016/j.antiviral.2007.10.011.
[110] Takano T, Katoh Y, Doki T, Hohdatsu T. Effect of chloroquine on feline infectious peritonitis virus infection in vitro and in vivo. Antivir Res 2013;99:100–7. https://doi.org/10.1016/j.antiviral.2013.04.016.
[111] Ding N, Zhao K, Lan Y, Li Z, Lv X, Su J, et al. Induction of atypical autophagy by porcine hemagglutinating encephalomyelitis virus contributes to viral replication. Front cell infect microbol 2017;7:56. https://doi.org/10.3389/fcimb.2017.00056.
[112] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa237. ciaa237.
[113] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269–71. https://doi.org/10.1038/s41422-020-0282-0.
[114] Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell discov 2020;6:1–4. https://doi.org/10.1038/s41421-020-0156-0.
[115] Mallucci L. Effect of chloroquine on lysosomes and on growth of mouse hepatitis virus (MHV-3). Virology 1966;28:355–62. https://doi.org/10.1016/0042-6822(66)90046-8.
[116] Cong Y, Hart BJ, Gross R, Zhou H, Frieman M, Bollinger L, et al. MERS-CoV pathogenesis and antiviral efficacy of licensed drugs in human monocyte-derived antigen-presenting cells. PloS One 2018;13:e0194868https://doi.org/10.1371/journal.pone.0194868.
[117] Gallagher TM, Escarmis C, Buchmeier MJ. Alteration of the pH dependence of coronavirus-induced cell fusion: effect of mutations in the spike glycoprotein. J Virol 1991;65:1916–28.
[118] Tsai WP, Nara PL, Kung HF, Oroszlan S. Inhibition of human immunodeficiency virus infectivity by chloroquine. AIDS Res Hum Retrovir 1990;6:481–9. https://doi.org/10.1089/aid.1990.6.481.
[119] Boelaert JR, Sperber K. Antiretroviral treatment. Lancet 1998;352:1224–5. https://doi.org/10.1016/S0140-6736(05)60566-1.
[120] Boelaert JR, Sperber K, Piette J. Chloroquine exerts an additive in vitro anti-HIV type 1 effect when associated with didanosine and hydroxyurea. AIDS Res Hum Retrovir 1999;15:1241–7. https://doi.org/10.1089/088922299310133.
[121] Boelaert JR, Sperber K, Piette J. The additive in vitro anti-HIV-1 effect of chloroquine, when combined with zidovudine and hydroxyurea. Biochem Pharmacol 2001;61:1531–5. https://doi.org/10.1016/S0006-2952(01)00576-7.
[122] Savarino A, Lucia MB, Rastrelli E, Rutella S, Golotta C, Morra E, et al. Anti-HIV effects of chloroquine: inhibition of viral particle glycosylation and synergism with protease inhibitors. J Acquir Immune Defic Syndr 2004;35:223–32. https://doi.org/10.1097/00126334-200403010-00002.
[123] Sperber K, Kalb TH, Stecher VJ, Banerjee R, Mayer L. Inhibition of human immunodeficiency virus type 1 replication by hydroxychloroquine in T cells and monocytes. AIDS Res Hum Retrovir 1993;9:91–8. https://doi.org/10.1089/aid.1993.9.91.
[124] Chiang G, Sassaroli M, Louie M, Chen H, Stecher VJ, Sperber K. Inhibition of HIV-1 replication by hydroxychloroquine: mechanism of action and comparison with zidovudine. Clin Therapeut 1996;18:1080–92. https://doi.org/10.1016/S0149-2918(96)80063-4.
[125] Li X, Burton EM, Bhaduri-McIntosh S. Chloroquine triggers Epstein-Barr virus replication through phosphorylation of KAP1/TRIM28 in Burkitt lymphoma cells. PLoS Pathog 2017;13:e1006249https://doi.org/10.1371/journal.ppat.1006249.
[126] Frankel AD, Pabo CO. Cellular uptake of the tat protein from human immunodeficiency virus. Cell 1988;55:1189–93. https://doi.org/10.1016/0092-8674(88)90263-2.
[127] Yoshimura A, Kuroda K, Kawasaki K, Yamashina S, Maeda T, Ohnishi S. Infectious cell entry mechanism of influenza virus. J Virol 1982;43:284–93.
[128] Ooi EE, Chew JS, Loh JP, Chua RC. In vitro inhibition of human influenza A virus replication by chloroquine. Virol J 2006;3:39. https://doi.org/10.1186/1743-422X-3-39.
[129] Vigerust DJ, McCullers JA. Chloroquine is effective against influenza A virus in vitro but not in vivo. Influenza Other Respir Viruses 2007;1:189–92. https://doi.org/10.1111/j.1750-2659.2007.00027.x.
[130] Di Trani L, Savarino A, Campitelli L, Norelli S, Puzelli S, D'Ostilio D, et al. Different pH requirements are associated with divergent inhibitory effects of chloroquine on human and avian influenza A viruses. Virol J 2007;4:39. https://doi.org/10.1186/1743-422X-4-39.
[131] Shibata M, Aoki H, Tsurumi T, Sugiura Y, Nishiyama Y, Suzuki S, et al. Mechanism of uncoating of influenza B virus in MDCK cells: action of chloroquine. J Gen Virol 1983;64:1149–56. https://doi.org/10.1099/0022-1317-64-5-1149.
[132] Sourisseau M, Schilte C, Casartelli N, Trouillet C, Guivel-Benhassine F, Rudnicka D, et al. Characterization of reemerging chikungunya virus. PLoS Pathog 2007;3:e89. https://doi.org/10.1371/journal.ppat.0030089.
[133] Roques P, Thiberville SD, Dupuis-Maguiraga L, Lum FM, Labadie K, Martinon F, et al. Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. Viruses 2018;10:268. https://doi.org/10.3390/v10050268.
[134] Li C, Zhu X, Ji X, Quanquin N, Deng Y-Q, Tian M, et al. Chloroquine, a FDA-approved drug, prevents zika virus infection and its associated congenital microcephaly in mice. EBioMedicine 2017;24:189–94. https://doi.org/10.1016/j.ebiom.2017.09.034.
[135] Delvecchio R, Higa LM, Pezzuto P, Valadão AL, Garcez PP, Monteiro FL, et al. Chloroquine, an endocytosis blocking agent, inhibits zika virus infection in different cell models. Viruses 2016;8:322. https://doi.org/10.3390/v8120322.
[136] Shiryaev SA, Mesci P, Pinto A, Fernandes I, Sheets N, Shresta S, et al. Repurposing of the anti-malaria drug chloroquine for Zika Virus treatment and prophylaxis. Sci Rep 2017;7:15771. https://doi.org/10.1038/s41598-017-15467-6.
[137] Dowall SD, Bosworth A, Watson R, Bewley K, Taylor I, Rayner E, et al. Chloroquine inhibited Ebola virus replication in vitro but failed to protect against infection and disease in the in vivo Guinea pig model. J Gen Virol 2015;96:3484–92. https://doi.org/10.1099/jgv.0.000309.
[138] Falzarano D, Safronetz D, Prescott J, Marzi A, Feldmann F, Feldmann H. Lack of protection against ebola virus from chloroquine in mice and hamsters. Emerg Infect Dis 2015;21:1065–7. https://doi.org/10.3201/eid2106.150176.
[139] Madrid PB, Chopra S, Manger ID, Gilfillan L, Keepers TR, Shurtleff AC, et al. A systematic screen of FDA-approved drugs for inhibitors of biological threat agents. PloS One 2013;8:e60579https://doi.org/10.1371/journal.pone.0060579.
[140] Farias KJ, Machado PR, de Almeida Junior RF, de Aquino AA, da Fonseca BA. Chloroquine interferes with dengue-2 virus replication in U937 cells. Microbiol Immunol 2014;58:318–26. https://doi.org/10.1111/1348-0421.12154.
[141] Farias KJ, Machado PR, da Fonseca BA. Chloroquine inhibits dengue virus type 2 replication in Vero cells but not in C6/36 cells. Sci World J 2013;2013:2827–34. https://doi.org/10.1155/2013/282734.
[142] Coombs K, Mann E, Edwards J, Brown DT. Effects of chloroquine and cytochalasin B on the infection of cells by Sindbis virus and vesicular stomatitis virus. J Virol 1981;37:1060–5.
[143] Tsiang H, Superti F. Ammonium chloride and chloroquine inhibit rabies virus infection in neuroblastoma cells. Brief report. Arch Virol 1984;81:377–82. https://doi.org/10.1007/bf01310010.
[144] Mizui T, Yamashina S, Tanida I, Takei Y, Ueno T, Sakamoto N, et al. Inhibition of hepatitis C virus replication by chloroquine targeting virus-associated autophagy. J Gastroenterol 2010;45:195–203. https://doi.org/10.1007/s00535-009-0132-9.

[145] Civitico G, Wang YY, Luscombe C, Bishop N, Tachedjian G, Gust I, et al. Antiviral strategies in chronic hepatitis B virus infection: II. Inhibition of duck hepatitis B virus in vitro using conventional antiviral agents and supercoiled-DNA active compounds. J Med Virol 1990;31:90–7. https://doi.org/10.1002/jmv.1890310205.
[146] Offensperger WB, Offensperger S, Walter E, Blum HE, Gerok W. Inhibition of duck hepatitis B virus infection by lysosomotropic agents. Virology 1991;183:415–8. https://doi.org/10.1016/0042-6822(91)90157-7.
[147] Glushakova SE, Lukashevich IS. Early events in arenavirus replication are sensitive to lysosomotropic compounds. Arch Virol 1989;104:157–61. https://doi.org/10.1007/bf01313817.
[148] Freiberg AN, Worthy MN, Lee B, Holbrook MR. Combined chloroquine and ribavirin treatment does not prevent death in a hamster model of Nipah and Hendra virus infection. J Gen Virol 2010;91:765–72. https://doi.org/10.1099/vir.0.017269-0.
[149] Zhu YZ, Xu QQ, Wu DG, Ren H, Zhao P, Lao WG, et al. Japanese encephalitis virus enters rat neuroblastoma cells via a pH-dependent, dynamin and caveola-mediated endocytosis pathway. J Virol 2012;86:13407–22. https://doi.org/10.1128/jvi.00903-12.
[150] Ferraris O, Moroso M, Pernet O, Emonet S, Ferrier Rembert A, Paranhos-Baccala G, et al. Evaluation of Crimean-Congo hemorrhagic fever virus in vitro inhibition by chloroquine and chlorpromazine, two FDA approved molecules. Antivir Res 2015;118:75–81. https://doi.org/10.1016/j.antiviral.2015.03.005.
[151] Kronenberger P, Vrijsen R, Boeye A. Chloroquine induces empty capsid formation during poliovirus eclipse. J Virol 1991;65:7008–11.
[152] Niu J, Shen L, Huang B, Ye F, Zhao L, Wang H, et al. Non-invasive bioluminescence imaging of HCoV-OC43 infection and therapy in the central nervous system of live mice. Antivir Res 2020;173:104646. https://doi.org/10.1016/j.antiviral.2019.104646.
[153] Pallister J, Middleton D, Crameri G, Yamada M, Klein R, Hancock TJ, et al. Chloroquine administration does not prevent Nipah virus infection and disease in ferrets. J Virol 2009;83:11979–82. https://doi.org/10.1128/jvi.01847-09.
[154] Maheshwari RK, Srikantan V, Bhartiya D. Chloroquine enhances replication of Semliki Forest virus and encephalomyocarditis virus in mice. J Virol 1991;65:992–5.
[155] Paton NI, Lee L, Xu Y, Ooi EE, Cheung YB, Archuleta S, et al. Chloroquine for influenza prevention: a randomised, double-blind, placebo controlled trial. Lancet Infect Dis 2011;11:677–83. https://doi.org/10.1016/s1473-3099(11)70065-2.
[156] Tricou V, Minh NN, Van TP, Lee SJ, Farrar J, Wills B, et al. A randomized controlled trial of chloroquine for the treatment of dengue in Vietnamese adults. PLoS Neglected Trop Dis 2010;4:e785. https://doi.org/10.1371/journal.pntd.0000785.
[157] De Lamballerie X, Boisson V, Reynier JC, Enault S, Charrel RN, Flahault A, et al. On chikungunya acute infection and chloroquine treatment. Vector Borne Zoonotic Dis 2008;8:837–9. https://doi.org/10.1089/vbz.2008.0049.
[158] Borges MC, Castro LA, Fonseca BA. Chloroquine use improves dengue-related symptoms. Mem Inst Oswaldo Cruz 2013;108:596–9. https://doi.org/10.1590/s0074-02762013000500010.
[159] Sperber K, Chiang G, Chen H, Ross W, Chusid E, Gonchar M, et al. Comparison of hydroxychloroquine with zidovudine in asymptomatic patients infected with human immunodeficiency virus type 1. Clin Therapeut 1997;19:913–23. https://doi.org/10.1016/s0149-2918(97)80045-8.
[160] Jacobson JM, Bosinger SE, Kang M, Belaunzaran-Zamudio P, Matining RM, Wilson CC, et al. The effect of chloroquine on immune activation and interferon signatures associated with HIV-1. AIDS Res Hum Retrovir 2016;32:636–47. https://doi.org/10.1089/AID.2015.0336.
[161] Paton NI, Goodall RL, Dunn DT, Franzen S, Collaco-Moraes Y, Gazzard BG, et al. Effects of hydroxychloroquine on immune activation and disease progression among HIV-infected patients not receiving antiretroviral therapy: a randomized controlled trial. JAMA 2012;308:353–61. https://doi.org/10.1001/jama.2012.6936.
[162] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.
[163] Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020:20040758. https://doi.org/10.1101/2020.03.22.20040758.
[164] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Trav Med Infect Dis 2020:101663. https://doi.org/10.1016/j.tmaid.2020.101663.
[165] Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ - Sci A 2020;49. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03. 0-0.
[166] Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Maladies Infect 2020. https://doi.org/10.1016/j.medmal.2020.03.006.
[167] Lenzer J. Covid-19: US gives emergency approval to hydroxychloroquine despite lack of evidence. BMJ 2020;369:m1335. https://doi.org/10.1136/bmj.m1335.
[168] Indian Council for Medical Research. Recommendation for empiric use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection. https://www.icmr.gov.in/index.html Accessed 9 April 2020.
[169] Ornstein MH, Sperber K. The antiinflammatory and antiviral effects of hydroxychloroquine in two patients with acquired immunodeficiency syndrome and active inflammatory arthritis. Arthritis Rheum 1996;39:157–61. https://doi.org/10.1002/art.1780390122.
[170] Sperber K, Louie M, Kraus T, Proner J, Sapira E, Lin S, et al. Hydroxychloroquine treatment of patients with human immunodeficiency virus type 1. Clin Therapeut 1995;17:622–36. https://doi.org/10.1016/0149-2918(95)80039-5.
[171] Jacobson JM, Bosinger SE, Kang M, Belaunzaran-Zamudio P, Matining RM, Wilson CC, et al. The effect of chloroquine on immune activation and interferon signatures associated with HIV-1. AIDS Res Hum Retrovir 2016;32:636–47. https://doi.org/10.1089/aid.2015.0336.