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Clinical studies based potent drug therapy of 7-chloro-4-(Diethylamino)-1-methylbutyl amino quinidine and 2-[4-[(7-chloroquinolin-4-yl) amino]pentyl]-ethylamino ethanol for treatment of COVID-19 patients

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Abstract
Coronavirus 2 (Severe acute respiratory syndrome coronavirus 2), can also be a rapidly emerging infection that causes coronavirus disease 2019 (COVID-19). 4QAs have gained unprecedented attention as a potential therapeutic agent against COVID-19 after numerous small clinical trials and uncontrolled case series and name recall. While there is a growing body of scientific data, there's also a priority for harm, particularly QTc prolongation and cardiac arrhythmias. Here, we conduct a quick narrative review and discuss the strengths and limitations of existing laboratory and clinical studies. We use evidence from additional randomized controlled trials prior to the broad incorporation of 4QAs into national and international treatment guidelines.

Keywords: chloroquine, coronavirus, COVID-19, Hydroxychloroquine, SARS-CoV-2.

Introduction
Suicide is derived from the Latin word for "self-murder." It is a fatal act that represents the person's wish to die. A suicide attempt is a behavior that the individual has undertaken with at least some intent to die. The behavior might or might not lead to death, injury or serious medical consequences. Several factors can influence the medical consequences of the suicide attempt, including poor planning, lack of knowledge about the lethality of the method chosen, low intentionality or ambivalence, or chance intervention by others after the behavior has been initiated [1]. Determining the degree of intent can be challenging. Individuals might not acknowledge intent, especially in situations where doing so could result in hospitalization or cause distress to loved ones. Markers of risk include degree of planning, including selection of a time and place to minimize rescue or interruption; the individual's mental state at the time of the behavior, with acute agitation being especially concerning; recent discharge from inpatient care; or recent discontinuation of a mood.
Preliminary reports of the novel southeast respiratory syndrome coronavirus 2 (SARS-CoV-2), form which coronavirus disease 2019 (COVID-19) originated in Wuhan, China, in early December 2019. Since then, the virus has spread out crossed national borders, now infected more than 200 countries and territories have more than one million confirmed cases and 1009,270 deaths confirmed by October 2020 [1]. Consider of compressed personal protective equipment, absence of intensive care unit such as ventilators, and lake of healthcare worker have become unfortunate daily realities as researchers have identify strategies to disrupt communication between transmission and treat the disease. More than three hundreds ongoing clinical research trials on potential therapeutic options for the prevention and treatment of COVID-19 [2]. 4QAs have been identified as the active “game-changers” in the popular press for COVID-19 [1-3]. During this review, we discuss these drugs, their pharmacology, the potential mechanisms of action, significant dosage form, adverse drug reaction across SARS-CoV-2, and the evidence of *in vitro* and clinical reports that have published to date. We discuss their strengths and boundary, and we call for supplementary large scale randomized clinical trials accordingly powered to show a demonstrable impact on meaningful clinical outcomes before national and international guidelines conform all over the place use of hydroxychloroquine/chloroquine for COVID-19 [4].

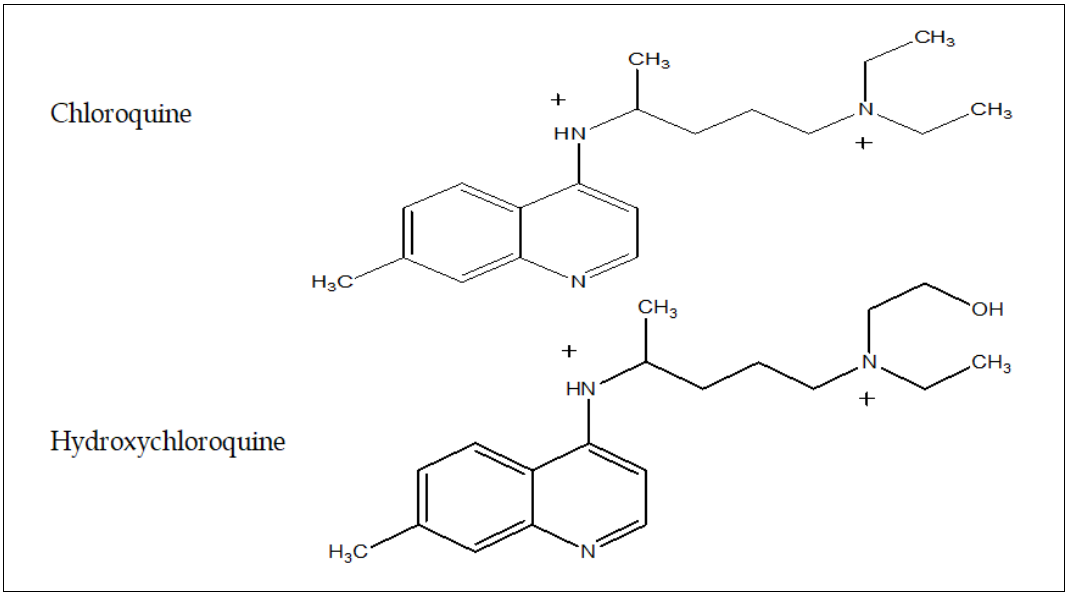

Fig 1: Chloroquine and hydroxychloroquine

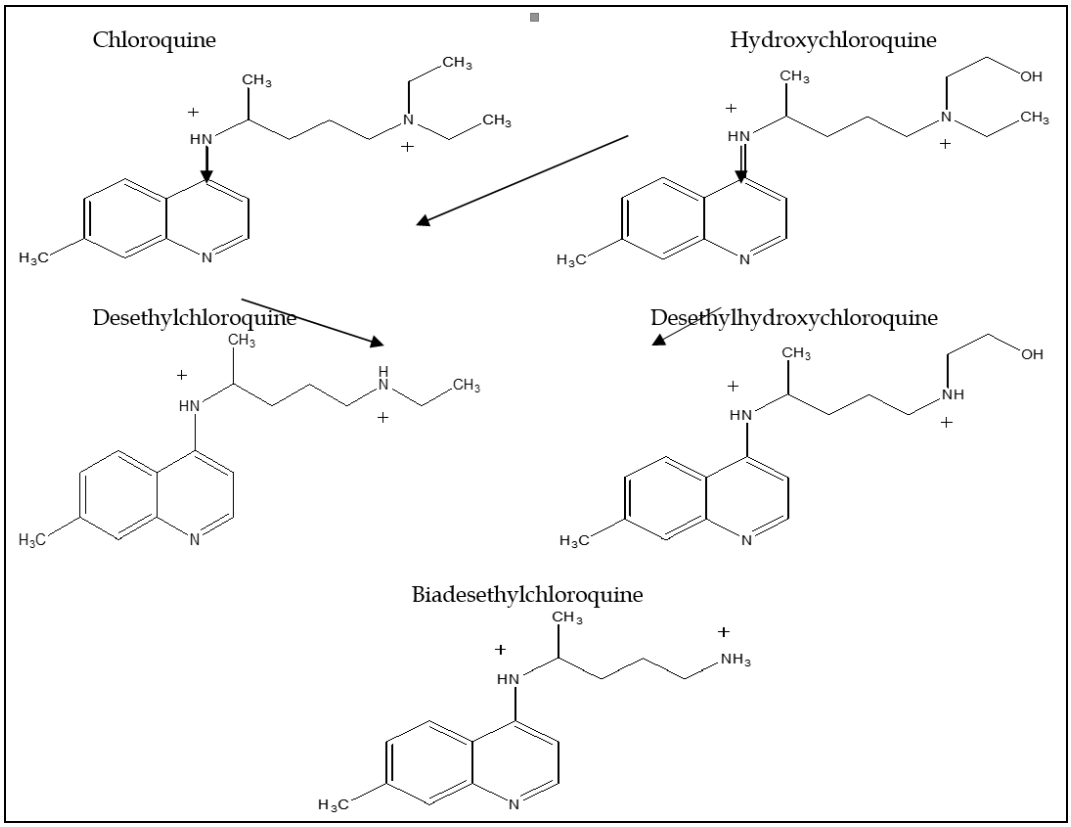

Fig 2: Metabolism of chloroquine and hydroxychloroquine by dealkylation.

Clinical pharmacokinetics of chloroquine and hydroxychloroquine

Chloroquine [7-chloro-4-(diethylamino)-1-methylbutyl] amino quinidine is a 4-aminoquinoline (4QAs) compound discovered in Germany in 1934 as port of a research programmed to developed new antimalarial drugs [5, 6]. Hydroxychloroquine in which one of the ethyl groups in the alkyl side chain hydroxylated, was synthesized in 1946 (Figure 1) [7]. Even in the 1940s, when drug measurement was in its infancy, it was clear that the 4-aminoquinolone had unusual pharmacokinetics properties. Normally complete absorption of 4QAs (chloroquine and hydroxychloroquine) after the oral dose occur with 2-4 hours [8-11]. In fasting subjects the absorption of oral chloroquine was 89±16% and of hydroxychloroquine was 74±13% [11]. An absorption is relatively unaffected by concentration of ingestion of food. The pharmacokinetics data are near to chloroquine to 4QAs [12-16] Plasma volume of distribution up to 65000 litters for chloroquine and 44253 litters for hydroxychloroquine have been described [11,12]. The peak plasma concentration after an oral dose of chloroquine is 3-12 hours [17, 18]. Around 33 to 70% of the drug in plasma protein bound [9, 12, 15, 19, 20]. A useful way to recognize the dissimilar distribution of 4AQs across various tissues is to consider ratios of concentration in tissues compared to plasma concentration (Table 1). The principle

metabolism of 4AQs is by dealkylation in the liver [7] (Figure 2). To set on metabolisms of chloroquine, corbon-14-labeled chloroquine was administered to monkeys, after which 12 labelled metabolites were detected. The two principal were desethyl chloroquine and dbisdrsrthyl chloroquine, both of which have pharmacological potency and are through to be around as toxic as the parent compound [7]. The variety of efficacy and toxicity of metabolise of 4AQs has not been studies, but a suggestion has been made that desthlhydroxychloroquine might have a higher therapeutic ratio than the parent compound hydroxychloroquine [16]. The two most important forms were desethyl chloroquine and bisdeethyl chloroquine, both of which have pharmacological activity and are nearly as toxic as the parent compound. The differentiation of 4AQS has not been studied, but it has been suggested that diethyl hydroxychloroquine may have a higher therapeutic ratio than the main compound hydroxychloroquine [17]. 4AQS is excreted by the kidneys and liver[24]. For both chloroquine and hydroxychloroquine, approximately 40-60% is excreted unchanged or metabolized by the kidneys, 8-25% is excreted unchanged or altered from the face, 5% is excreted through the skin and 25% is 45% stored in Long term in lean body tissues [9, 10, 12, 13, 15, 20, 25].

Pharmacology of chloroquine and hydroxychloroquine

Chloroquine was first synthesized in 1934 (Figure 1) and widely ordered enormously for the cure and treatment of malaria furthermore because the treatment of autoimmune disorder, like arthritis and systemic lupus [4, 26]. Hydroxychloroquine was departed introduced in 1955 and rapidly became recommending because of its higher-degree safety profile [4]. The mechanism of action of those drugs somewhat related to the interaction to the plasmodium parasites with DNA polymerization and direct inhibition of heme polymerization [27, 28]. The immunomodulatory activity of hydroxychloroquine is present to a broad spectrum of the immune system discussed extensively in other work [26, 29, 30]. In extension to activity against rheumatic diseases, the two anti-malarial agents have also disclose therapeutic activity or immunomodulatory activity during a actual broad spectrum of other diseases such as antiphospholipid syndrome, amebiasis, HIV/AIDS, and some cancers [31-34]. These drugs are formed in tablets for oral administration as an active drug of chloroquine phosphate 500 mg (analogue to 300 mg of chloroquine base) and hydroxychloroquine sulfate 200 mg (analogue to 155 mg of hydroxychloroquine base) per tablet, respectively. Dosage varies by treatment indication studies or guidelines [4, 27, 28, 35-40] (Table 1). High doses of 2000 mg 4QAs have been used for the critical treatment of malaria. Both 4QAs are exceptional for their long finishing and elimination half-lives of 22 and 20–60 days respectively [27, 28, 41]. Hydroxychloroquine can be found in the urine up to three months after the last dose [27]. Hydroxychloroquine reaches its maximum peak plasma concentration within three to four hours[27], while chloroquine can reach maximum peak plasma concentration within half an hour [41].

Table 1: Volume of distribution of chloroquine and hydroxychloroquine between different tissue/organs

Experiment/model	Organ/Tissue	Tissue plasma concentration ratio	Reference
Human	Fat, tendon, bone	0.1	[10, 13]
Albino rat, Human	Erythrocytes	1.9-4.0	[9-11, 21]
Albino rat	Whole blood	3.7	[6]
Albino rat	Bran	4-31	[6, 10]
Albino rat	Muscle	4-41	[6, 10]
Human	Skin	6-200	[19, 22, 23]
Albino rat	Heart	150	[6]
NG	Leukocytes	100-300	[10, 18]
Albino rat	Kidney	670	[6]
Albino rat	Lung	640	[6]
Albino rat	Liver	420	[6]

NG (Not given)

Adverse effects

The most common side effects of 4QAs are gastrointestinal irritation, nausea, vomiting and diarrhea [35-37]. In a study that estimated chloroquine use approximately 24% of patients reported nausea, abdominal cramps, and 17% with diarrhea. Up to 50% of patients taking hydroxychloroquine reported gastro-intestinal effects; it depends on the dose and often has a loading dose of 800 mg or more [42]. Table 2 contains a variety of adverse drug reactions involving 4QAs. Retinopathy is the most usually recognized, severe, and irreversible side effects associated with high-dose (>5mg/kg) and long time use (>5 years) of 4QAs [40]. Chloroquine is greater potential to have retinopathy than hydroxychloroquine [22, 43] however, it has nothing to do with short-term dosing [44]. The most serious and serious complications with the use of 4QAs are the risk of closure of QTc prolongation and ventricular arrhythmia [4]. The frequency of QTc prolongation during this setting of 4QAs use is unknown because it is well accustomed to baseline EKG findings, with risks associated with QTc prolongation drug use. During the study of healthy volunteers, an average volume of 600 mg chloroquine was associated with a mean QTc increase of 16ms (95% CI: 9–23ms), while 1500 mg chloroquine was associated with an increase of 28ms (95% CI: 18-38ms), the most important QTC prolongation is four hours after the following dose [45].

Table 2: Studies/Guidelines for the various doses associated chloroquine and hydroxychloroquine in the COVID-19.

Studies/Guidelines	Dose (adults)
Expert consensus from Department of Science and Technology and Health Commission of Guangdong province, China [42]	Chloroquine phosphate 500 mg BID for 10 days
Central Clinical Task Force, Korea [43]	Moderate to severe COVID-19: Lopinavir 400mg/Ritonavir 100 mg BID or Chloroquine 500 mg orally per day or Hydroxychloroquine 400 mg orally per day for 7 to10 days.
Centre for Disease Control and Prevention, Atlanta, MICC Version 1 (March 12, 2020) [44]	URTI plus positive PCR: Chloroquine phosphate 500 mg BID for 5 days. Oseltamivir 150 mg BID for 5 days. COVID-19 Pneumonia: Chloroquine phosphate 500 mg BID for 5 days plus Darunavir 800 mg/Cobicistat 150 mg OD for 2 weeks.
The Dutch Center of Disease Control [45]	Atazanavir 400 mg OD for 2 weeks plus Oseltamivir 150 mg BID for 5 days. The Dutch Center of Disease Control24 600 mg of Chloroquine base followed by 300 mg after 12 h on day 1, then 300 mg 2/day per person on days 2e5.
Italian Society of Infectious and Tropical Diseases (Lombardy Section) [46]	Mild to moderate COVID-19: Lopinavir/ritonavir plus Chloroquine 500 mg 2/day or Hydroxychloroquine 200 mg per day for 10 days. Severe or critical COVID-19: Remdesivir plus Chloroquine 500 mg 2/day or Hydroxychloroquine 200 mg per day for 10e20 days.
Mount Sinai Health System, Canada[47]	Moderate to severe COVID-19: Hydroxychloroquine 400 mg BID x 2 doses then 12 h later start 400 mg OD for 5e10 days.
Surviving Sepsis Campaign, The Society of Critical Care Medicine and the European Society of Intensive Care Medicine [46]	Insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19 at this point of time.
Clinical guidance for patients with suspected or confirmed COVID-19 in Belgium [48]	Mild/Moderate/Severe COVID-19: Hydroxychloroquine 400 mg at diagnosis, 400 mg 12 h later, followed by 200 mg BID for 5 days, Or, Chloroquine 600 mg at diagnosis and 300 mg 12 h later followed by 300 mg BID for 5days (Consider lopinavir 400 mg/ritonavir 100 mg BID for 14 days as a second choice only if HCQ and chloroquine is contraindicated, provided it can be administered within 10 days after onset of symptoms) Critical COVID-19: Remdesivir 200 mg loading dose i.v within 30 min followed by 100 mg OD for 2e10 days (Hydroxychloroquine is second option if Remdesivir is unavailable)
Clinical guidance for patients with suspected or confirmed COVID-19 in Netherland [49]	Mild/moderate/severe COVID-19: Chloroquine 600 mg on day 1, then 300 mg BID for 5 days (lopinavir/ritonavir as second option) Critical COVID-19: Remdesivir for 10 days plus chloroquine for 5 day
Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial [50]	Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th, to receive 600 mg of hydroxychloroquine daily for 10 days.

OD-once daily, BID-twice daily, TID-thrice daily, URTI- upper respiratory tract infection, PCR-polymerase chain reaction, i.v - intravenous.

Studies of hydroxychloroquine and QTc prolongation have been largely limited to reports of long-term use [46, 68]. EKG surveillance is not part of the standard practice for the use of rheumatology for the treatment of malaria or as monotherapy. Chloroquine and hydroxychlorine, including notable drug interactions are essential for the prevention of dioxin, antiepileptic, antacids, cyclosporine, amiodarone, azithromycin, moxifl [48].

The combination of azithromycin and hydroxychloroquine regularly extends the QTc interval as a clinically important pattern and increases over time. In a continuous set of 84 patients, 18% of patients increased their QTc interval from 40 to 60 ms and 12% to 60%, with 11% having a total QTc > 500 ms [50]. The most undesirable effects of acute use of 4QAs are, but are not limited to: hypoglycemia in patients with diabetes, neurotoxicity such as tinnitus, headache and mental disorders and hemolytic anemia in people with G6PD deficiency [27].

Mechanism of 4QAs on SARS-COV-2

The mechanism of action of 4QAs as opposed to SARS-CoV-2 is not yet fully clear. Chloroquine was first detected in SARS-CoV, causing the 2002–2003 SARS coronavirus epidemic [61, 96]. SARS-CoV accepts 79% genetic similarity to SARS-CoV-2 but is thought to result in more significant infection with a case of fatality rate of 10% vs. 3% for SARS-CoV-2 [62, 63]. Based on studies essentially conduct on SARS-CoV, it is believed that SARS-CoV-2 enters cells by attaching to the angiotensin-converting enzyme II (ACE-II) receptor, and can be preventing by allowing chloroquine virus to bind from this eceptor by inhibiting last glycosylation [61]. New research suggests that hydroxychloroquine may prevent SARS-COV-2 from binding to gangliosides, which may prevent viral contact with the angiotensin-II receptor [64]. Both hydroxychloroquine and chloroquine also can include into endosomes and lysosomes, resulting in a higher pH of the intracellular compartments. These organelles generally require lower pH or an acidic environment for homeostasis. Ultimately, this higher in pH lead to protein depletion, endocytosis, and exocytosis needed for viral infection, replication and proliferation [65]. Prior work has shown that coronaviruses can use proteins present on the surface of endosomes and endolysosomes, those protein help viral entry into host cells [66], is similar in the cytoplasm of infected host cells [67]. Overall, 4QAs is able of determine certain cellular pathways and therefore may have certain mechanisms of action against SARS-CoV-2.

***In-vitro* data of chloroquine and hydroxychloroquine in the treatment of SARS-COV-2**

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In-vitro data of chloroquine and hydroxychloroquine in the treatment of SARS-COV-2

At the beginning of the 2019 SARS-CoV-2 andemic, *in vitro* rematch studies indicated that the ability of chloroquine to inhibit SARS-CoV viral genomic replication (**Table 3**). In these studies, authors find that by pretreating cells with chloroquine at a concentration of 10μM, chloroquine inhibited SARS-CoV viral genomic replication as determined by secondary immunofluorescence [70]. When considered an effective post-exposure treatment, the 50% effective dose of chloroquine (ED50) was observed to be 4.4 ± 1 μM [71]. Another study, chloroquine concentrations of 8.8 ± 1.2μM caused theoretically viral replication by 50%, though the exact infectious viral dose used in this study was unclear [68]. In year 2006, Biot *et al.* show that chloroquine was higher than hydroxychloroquine *in vitro* at inhibiting SARS-CoV genomic replication in a Vero cell study model (EC50 6.5 ± 3.2μM vs 34 ± 5μM, respectively) [69]. Last March, Yao *et al*. Results of antiviral action using SARS-CoV-2 infected Vero cell lines have been published. Contrary to the results reported above with SARS-CoV, hydroxychloroquine has been found to be more effective against SARS-CoV-2 [72]. This experiment suggests that hydroxychloroquine is more effective in weakening viral replication than chloroquine, with a 48-hour EC50 of 0.72μM and 5.47μM hydroxychloroquine for chloroquine and after infection [72]. In addition, hydroxychloroquine is more potent than chloroquine, which inhibits SARS-COV-2 viral replication when given immunity; the 48-hour EC50 for hydroxychloroquine and chloroquine was 5.85μM and 18.01μM, respectively [72]. Extra work related chloroquine *in vitro* antiviral extracts only [73]. To identify potential drug regulation for use in humans, physiologically based pharmacokinetic model has been used by Yao *et al.* hey take into account drug administration, physiological parameters (i.e., intestinal absorption and penetration of lung tissue) and biochemical properties of the drug. The published simulation states the lung lung fluid concentrations but does not provide all the details used in the model [73, 74]. Based on this model the most effective diet for the treatment of COVID-19 is an initial dose of 400 mg hydroxychloroquine twice daily and a maintenance dose of 200 mg twice daily for four days [73]. 95% confidence interval was not provided for the estimate of EC50 and, therefore, should be carefully understood again as this dose is miscalculated. Using the same antiviral action at four different times of infection as previously described. Demonstrate that the severity of viral replication is higher than that of 4QAs at all coefficients of infection. However, it is only statistically significant at a multiplicity of 0.01 and 0.2 infections [75]. To assess the specific virus entry in the path of SARS CoV-endosome lysosome degeneration 2, Liu *et al*. Colonization immunofluorescence assay was used. They found that cells treated with hydroxychloroquine or chloroquine contained multiple viruses that were localized in early endosomes and less localized in endosomes when isolated from untreated virus-infected cells [75]. Together, this detection recommenced that 4QAs are effective at inhibition SARs-CoV-2 genomic replication *in vitro*.

Clinical studies data of chloroquine and hydroxychloroquine in the treatment of COVID-19

As of August 30, 2020, published evidence on the successfulness of 4QAs for managing and treating COVID-19 in humans is restricted to several studies personal report [76-81] (Table 4). Chen *et al*. the outcome of the first study on hydroxychloroquine in COVID-19 patients has been published [78]. In this short randomized controlled trial, researchers found that those with and without hydroxychloroquine (87% clearance) received viral clearance based on their level of care in 30 hospitalized patients compared to hydroxychloroquine [82]. No statistically significant difference was found by time, this is (93%, p> 0.05) and they did not distinguish between clinical results (i.e., duration of fever and changes in lung imaging). Although they did not comment on the severity of the reported disease, those on hydroxychloroquine and control weapons showed symptoms for seven and six days, respectively. Within two weeks, all patients underwent negative viral DNA testing. On March 16, 2020, Gao *et al* collected data from 100 patients with confirmed COVID-19 virus from ongoing hospital studies in China and reported improvement in patients using chloroquine [81]. The authors state that chloroquine is superior to standard therapy in helping to reduce clinical recovery time and improve lung imaging results; however, no data have been published to support these results, and no clinical information, including disease severity and outcome, has been provided, and no statistical analysis has been presented in this brief report [81]. On March 20, 2020, Gouret *et al*. The results of a non-randomized, open-label study in France reported that hydroxychloroquine was predictable compared to standard care treatments, which attracted great attention [80]. Twenty-six patients at the hospital were attend with hydroxychloroquine (600 mg for ten days), six of whom attend azithromycin (500 mg, then 250 mg for five days). Sixteen patients included in the study did not receive service inclusion criteria as controls for the study [82]. At the time of enrolment, approximately 17% of patients were asymptomatic, 61% had upper respiratory symptoms, and 22% had symptoms of pneumonia or bronchitis. In the unfair analysis, the author found a significant reduction in viral titres compared with those receiving hydroxychloroquine on day 6 (70% vs. 12.5%, p>0.001); however six volunteers in the hydroxychloroquine treatment arm (23%) were excluded from the analysis because they had to be admitted to intensive care, died, dropped out of the study, or lost in the follow-up [82]. Due to the small sample size of the comprehensive study and the inclusion of these six participants in the absence of an analysis that should be deliberately treated, the results are very biased and should

not lead to a decision. Long-term outcome data from this study are not available and the reported viral filtration results may not be a good choice for significant patient-centered outcome such as the need for mechanical ventilation or mortality. The six patients who received azithromycin plus hydroxychloroquine, all patients underwent a negative SARS-CoV-2 PCR test on day 6 without comparing appropriate controls [82]. Goutret *et al*. another open-label study recently published the results to assess the combination of hydroxychloroquine and azithromycin in 80 hospitalized patient using the same dosing schedule previously described [80]. Six patients including in this analysis were including in the original study. 58% of these patients have at least one chronic condition. Four patients were asymptomatic at baseline, with 41% having upper respiratory symptoms and 54% with symptoms of pneumonia or bronchitis. 92% of patients have a low national early warning score, indicating that the overall disease severity is low in this population. They reported that 83% of patients had an unwanted pharyngeal viral load for 7 days per day; however, there is no comparison group and therefore it is almost impossible to understand the results. In this study, 81% (65/80) of patients were discharged; three patients in need of intensive care, one died and 11 were still hospitalized. On March 31, 2020, Chen *et al*. Publication of randomized, parallel-group trial results in which 62 hospital participants were randomly assigned to receive 400 mg of hydroxychloroquine for five days in addition to standard care or standard care [78].

Table 3: Various adverse drug reactions associated with chloroquine and hydroxychloroquine.

System/Organ specific disorders	Adverse drug reactions
Connective tissue & Musculoskeletal disorder	Skeletal muscle myopathy or neuro-myopathy, depression of tendon reflexes, sensor motor disorder, abnormal nerve conduction, progressive weakness and atrophy of proximal muscles [51].
Neurological and psychiatric side effects	Neurological side effects include headache, dizziness, muscular weakness, diplopia, dyskinesia, seizures, myasthenic syndrome, and (with long-term use) neuromyopathy. Psychiatric side effects include sleeplessness, agitation, psychosis, depression, anxiety, aggressiveness and confusion [52].
Cardiac system disorders	Reported cardiac side effects of CQ/HCQ include conduction disturbances (bundle-branch block, incomplete or complete atrioventricular block, QT prolongation and subsequent torsade de pointes) and cardiomyopathy (hypertrophy and congestive heart failure) [53, 54].
Retina disorders	Photophobia, blurred vision, decreased dark adaptation, bull's eye appearance(Irreversible retinopathy with retinal pigmentation changes), color vision abnormalities, visual disturbances (visual acuity), and visual field defects (paracentral scotomas), maculopathies (macular degeneration) corneal changes (edema and opacities) [55, 56].
Hepatic disorders	Acute hepatic failure, abnormal Liver function tests [57].
GIT & general disorders	Finally, gastrointestinal symptoms (nausea and diarrhoea) have been reported and are the presenting complaint in some cases. In 393 patients admitted to two hospitals in New York, diarrhoea and nausea or vomiting was reported in 23.7% and 19.1% of patients, respectively. To these patients, treatment with drugs having potential gastrointestinal side effects could be problematic [58].
Metabolic disorders	Hypoglycemia, porphyria, appetite decreased, weight decreased [59].
Skin disorders	Skin rashes and photosensitivity, pruritus, exfoliate-dermatitis, AGEP, Stevens-Johnson syndrome, and toxic epidermal necrolysis, pigmentation disorders in skin & mucous membranes, DRESS syndrome, Dermatitis bullous eruptions including erythema multiform, etc. [60].

GIT (Gastro Intestinal Tract), AGEP (Acute Generalized Exanthematous Pustulosis), DRESS Syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms), CQ (Chloroquine), HCQ (Hydroxychloroquine)

Table 4: In-vitro studies of chloroquine and hydroxychloroquine in SARS-CoV-2 infection.

Type of studies	Drugs	Study gropes	Design/experiment	Outcomes
In-vitro studies	CQ	Vero E6 cell model	Immunofluorescence assay	A dose-dependent decrease in virus antigen-positive cells was observed starting at 0.1 µM chloroquine, and concentrations of 10 µM completely abolished SARS-CoV infection [61].
In-vitro studies	CQ, HCQ and FQ	Vero cell model	CQ-sensitive HB3 strain and the CQ-resistant W2 strain	All compounds, except for HCQ, were effective inhibitors of SARS-CoV replication in Vero cells within the 1-10 µM concentration range [69].
In-vitro studies	CQ, HCQ	Vero E6 cell model	Physiologically-based pharmacokinetic models (PBPK)	Hydroxychloroquine was found to be more potent than C8 SARS-Cov-2 *in vitro* [68].
In-vitro studies	CQ, RV	Vero E6 cell model	CCK8 assay	Potential block viral infaction at low micromolar concentration and show high SI (selective index) [70].
In-vitro studies	CQ	American type culture/ HRT-18 cells model	RT-PCR/qRT-PCR/Cytotoxicity assay	Inhibition of HCoV-OC43 replication by chloroquine is more potent [71].
In-vitro studies	HCQ	Vero cells model	Physiologically-based pharmacokinetic models (PBPK)	Hydroxychloroquine (EC50=0.72 µM) was found to be more potent than chloroquine (EC50=5.47 µM) *in vitro* [72].
In-vitro studies	HCQ, CQ	Vero E6 cell model	CCK-8 assays	In the presence of CQ or HCQ, significantly more virions (35.3% for CQ and 29.2% for HCQ; $P < 0.001$) [73].

FQ (ferroquine), CQ (Chloroquine), HCQ (Hydroxychloroquine), µM (Micrometer), RV (Remdesivir), CCK8 (Cell counting kit 8), PBPK (Physiologically-based pharmacokinetic models), RT-PCR (Real-time reverse transcription polymerase chain reaction)

Table 5: Clinical studies of chloroquine and hydroxychloroquine in SARS-CoV-2 infection.

Authors	Drugs	Type of study	Trial registration	Participants	Outcomes
[76]	HCQ	Randomized/multi-center clinical trial	NCT04261517	30 participants	The prognosis of COVID-19 moderate patients is good.
[77]	AZ, HCQ	Randomized/clinical trial	EUN2020-000890-25.	20 participants	Hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients
[78]	HCQ	Randomized/clinical trial	ChiCTR2000029559	62 participants	HCQ could significantly shorten TCR and promote the absorption of pneumonia.
[79]	AZ, HCQ	Randomized/clinical trial	NG	10 participants	Prophylaxis with sometimes a deleterious effect on viral replication
[80]	AZ, HCQ	Randomized/clinical trial	EUN2020 207 - 000890-25	80 participants	(i) an aggressive clinical course requiring oxygen therapy or transfer to the ICU after at least three days of treatment,(ii) Contagiousness as assessed by PCR and culture, and (iii) length of stay in the ID ward.
[81]	CQ	Randomized/multi-center clinical trial	NG	100 participants	The anti-viral and anti-inflammatory activities of chloroquine may account for its potent efficacy in treating patients with COVID-19 pneumonia.
[83]	HCQ	Randomized/multi-center clinical trial	ISRCTN14326006	n=988 participants	Positive results from SARS-CoV-2 diagnostic assay including detection of viral RNA, and/or seroconversion.
[84]	AZ, HCQ	Randomised/ multi-center clinical trial	NCT04339816	240 participants	Decrease virus replication reduces the damage to the lungs Viral load at day 8 (no. of viral RNA copies/milliliter of blood)
[85]	HCQ	Randomized/multi-center clinical trial	NCT04410562	Symptomatic (n=100)/ Asymptomatic (n=100)	The primary outcome is the number of PCR-confirmed infected pregnant women assessed from collected nasopharyngeal and oropharyngeal swabs at day 21 after treatment start (one week after treatment is completed).
[89]	HCQ	Randomized/multi-center clinical trial	EUN 2020-001331-26	1000 participants	Time to diagnosis of positive COVID-19 disease (defined by record of date of symptoms onset and confirmed by laboratory test)
[86]	HCQ	Randomized/multi-center clinical trial	NCT04328961	2000 participants (asymptomatic)	The primary outcome of the study is the incidence of SARS-CoV-2 infection through day 14 among participants who are SARS-CoV-2 negative at baseline by randomization group.
[87]	AZI, HCQ	Randomized/multi-center clinical trial	NCT04322396	226 participants	Number of days alive and discharged from hospital within 14 days
[87]	HCQ	Randomized/single-center clinical trial	EUN 2020-001704-42	450 participants	Number and percentage of healthcare personnel presenting symptomatic and asymptomatic infection (see"Diagnosis of SARS CoV2 infection" below) by the SARS-Cov2 virus during the study observation period (8 weeks) in both treatment arms.

AZI (Azithromycin), CQ (Chloroquine), HCQ (Hydroxychloroquine), PCR (polymerase chain reaction), n (Numbers), RNA (Ribonucleic acid), ICU (Intensive care unit), TCR (T-cell receptor), NG (Not given)

Placebo was not used in this study. The standard of care is defined as corticosteroids with or without oxygen, antiviral agents, antibacterial agents and immunoglobulins. Only co-certified pneumonia and mild illnesses are allowed in patients with SaO2/SpO2> 93% or PaO2/FiO2> 300 mmHg. However, the researchers found that a large percentage of those receiving hydroxychloroquine had clinically improved pneumonia (80% vs. 55%, $p<0.04$) as determined by a chest CT scan. Zero to this day. On the sixth day, the method was not explained. The results may be based on the physician's personal opinion, which may not be taken into account in optimizing treatment. Cough duration (2.0 vs. 3.1 days, $p<0.001$) and shorter clinical recovery time were also reduced in patients receiving hydroxychloroquine compared with controls; However, only 48% (15/31) of them were randomly assigned to obtain hydroxychloroquine and 71% (22/31) had pre-controlled cough and did not know how long. Although four patients in the control group became critically ill, no serious illness was identified. No primary comorbidity with the patient has been investigated and may be an overall confusion variable. In addition, the antiviral and antibacterial drugs used as part of standard treatment have not been identified and the results may be affected. In general, as in previous studies, there are serious limitations and the results of this non-coupled study need to be understood with reasonable care. On April 3, Molina *et al*. Cartort reported the results of 11 hospitalized patients in response to [67]. These patients received similar doses and duration of hydroxychloroquine and azithromycin due to the goutrit study. Eight of the registered patients had significant comorbidities and were receiving supplemental oxygen at 11/10 registration. They found that 80% (95% CI: 49–94%) of patients who survived for five to six days still had pharyngeal smears for SARS-CoV-2, indicating a decrease in viral titers unlike other results. In this small group, two patients were transferred to medical care, one patient died and another was discontinued due to a long QT break. In contrast to the Gourett study, these debilitated patients were included in the analysis. It is important to note that these 6 studies have several significant limitations that prevent inclusion in clinical guidelines. Not all studies are small enough to demonstrate clinical or statistical difference in

sample size (<100 participants) and results. Only two studies had a group of patients from randomized controlled trials, two open, randomized, and non-blind, one prospective ensemble, and the other an ongoing clinical trial, in which a statistical evaluation was not available. Four of the five studies shared a single dose with hydroxychloroquine (400 mg hydroxychloroquine for five days); however, supported laboratory data suggest that effective doses of up to 800 mg, if not more than 400 mg in humans, may be effectively eliminated after several days of running [72]. Despite concerns about the text, only 1 of the six studies has been officially reviewed [81]. It should therefore be understood that these studies are merely hypothesis-producing and will not be used to support the widespread inclusion of hydroxychloroquine/chloroquine in clinical guidelines. Because all of those studies reported differences in disease severity, the full patient population may not be comparable. In the future researchers should report disease severity and use the scientific severity criteria for the COVID-19 supported symptomatic period. Although there is little evidence of efficacy and COVID-19 is under on national health system many official guidelines already include hydroxychloroquine and chloroquine in the proposed treatment for COVID-19 patients [82, 90]. The following increase in prescription led to a deficiency of hydroxychloroquine, threatening the availability of this drug for autoimmune patients with systemic autoimmune disorder and autoimmune disease. The inclusion of those drugs in NTG has several consequences. Although chloroquine and hydroxychloroquine are safe drugs; they are harmless and have significant adverse effects. Through side effects with these drugs are not common the rare side effects of the drug that are commonly prescribed without strong evidence are dangerous to the population. Any significant side effects cannot be justified if the effective drug is not effective. In view of the side effects of the common use of those drugs in the absence of strong data, the euro medicine agency refused to approve chloroquine for COVID-19 and limited its use through clinical trials or national emergency use programs [91]. Currently there has been no study of hydroxychloroquine as a treatment for COVID-19, which demonstrates efficacy or causes no harm. Currently, more than 1 million COVID-19 cases have been identified. If all patients were given chloroquine and hydroxychloroquine, QT prognosis and arrhythmia would appear in 0.1% of the population, for example, which could lead to 1,000 adverse events. Drug use is useless but it is not acceptable. Gouterte and Molina reviewed COVID-19 treatment with a mixture of hydroxychloroquine and azithromycin, which many physicians are now taking to prescribe on a patient basis, simultaneously, without evidence. In these studies, this mixture was used in a hospital setting, possibly with some degree of cardiac monitoring. Azithromycin and hydroxychloroquine alone, but more importantly together, increase the likelihood of chronic QT and lead to malignant arrhythmia [4, 27]. A reconsideration population study of 60,000 patients receiving hydroxychloroquine for arthritis found that hydroxychloroquine was associated with azithromycin (50 deaths) compared with hydroxychloroquine and amoxicillin (25 deaths) (ratio: 2.19). So the risk of heart death increased, 95% confidence interval: 1.22 to 3.94); However, deaths from all causes are the same (accident ratio 1.34) [92]. The risk is much higher when considering the use of selective serotonin reuptake inhibitors, tricyclic antidepressants, various other antipsychotic and antimicrobial drugs that have the ability to prolong QT interval. These small studies do not show sufficient evidence to support the regular use of hydroxychloroquine and azithromycin outside of clinical trials with adequate cardiac monitoring. Finally, Chinese authorities are recommending the employment of Lopinavir/Ritonavir, a widely available antiviral agent for the treatment of disease, with HIV *in vitro* activity against SARS-Cove infection. Recent randomized, open-label, 14-day, randomized trial of Lopinavir/Ritonavir treatment in hospitalized patients with COVID-19, hospitalized, without viral load of SARS-CoV-2 beyond standard care. Clinical improvement and error are not shown inside [93]. Despite these adverse effects, Lopinavir/ Ritonavir are popular in some areas for the treatment of COPID and is often combined with 4QAs. It is important to note that P450 has the potential to increase plasma concentrations of Lopinavir/ Ritonavir chloroquine by increasing the risk of malignant arrhythmia by inhibiting the enzymatic metabolism of CYP2D6. In addition, other factors such as myocarditis and myocardial ischemia may be associated with COVID-19 [94], or, hypoxia and electrolyte abnormalities often observed in the acute phase of acute COVID-19 may further contribute to the occurrence of severe arrhythmia [95]. Therefore, treatment with COVID-19 requires careful use of QT-prolactin drugs such as lopinavir/ritonavir and hydroxychloroquine and azithromycin.

Conclusion

Further studies are urgently needed to investigate 4QAs the prevention and treatment of COVID-19. Due to t he limited evidence available, large controlled trials are needed to determine whether there is a clinical important to hydroxychloroquine/chloroquine in COVID-19. Many ongoing randomized clinical trials are actively recruiting participants to provide a good answer to this question. These randomized tests are designed to show a reduction in significant clinical outcomes such as the development of COVID-19 in preventive testing, hospitalization or intensive care requirements or death on treatment tests. The results of these tests will help determine if these two anti-malarial drugs are effective and if so, how safe the dosage and duration of the guidelines should be. Additional Data Additional documents are available in the Open Forum for Infectious Diseases on the Internet. The data provided by the authors are designed for the benefit of the readers. Published documents are not copied and are the sole responsibility of the authors, so questions or comments should be sent to the relevant author

Abbreviations

QTc: corrected QT interval; DNA: deoxyribonucleic acid; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; EKG: electrocardiogram; G6PD: glucose-6-phospate- dehydrogenase; ACE-2: angiotensin-converting enzyme – II; ED50: median effective dose; EC50: half maximal effective concentration; μM: micrometer; SaO2: oxygen saturation; PaO2: partial pressure of oxygen; FiO2: fraction of inspired oxygen; P450: cytochromes monooxygenases (450 nm); CYP2D6: cytochromes P450 2D6; NTG: national treatment guideline; 4QAs: chloroquine and hydroxychloroquine

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Conflict of Interest
The authors declare no conflict of interest.

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