Hydroxychloroquine/Chloroquine Safety During Off-Label Use for COVID-19

- FREQUENTLY ASKED QUESTIONS -

MARCH 30, 2020 (AMENDED APRIL 23,2020)

VA PHARMACY BENEFITS MANAGEMENT SERVICES [PBM] AND CENTER FOR MEDICATION SAFETY [VAMedSAFE]

Q: Is hydroxychloroquine (HCQ) or chloroquine (CQ) approved for treatment of the 2019 novel Coronavirus (COVID-19)?

A: No. No therapy is currently FDA-approved for prophylactic or post-exposure treatment of the 2019 novel Coronavirus (COVID-19). HCQ is indicated for the prophylaxis and treatment of malaria, as well as the treatment of autoimmune diseases (rheumatoid arthritis and systemic lupus erythematosus).[1] CQ is indicated for the treatment of malaria and amebiasis. [2]

Q: What is the mode of action of HCQ/CQ in the treatment of COVID-19?

A: CQ and HCQ are 4-aminoquinoline drugs. HCQ is a derivative of CQ. Due to similar structures, it is suggested that HCQ and CQ inhibit virus infection by elevating endosomal pH required for virus/cell fusion and disrupting the glycosylation of cellular receptors (i.e., ACE2) needed for virus-receptor binding. Activity of CQ and HCQ against COVID-19 was discovered in vitro; HCQ was found to be more potent in activity than CQ in vitro. [3-6]

Q: What data are available for the use of HCQ/CQ in the treatment of COVID-19?

A: Evidence from peer-reviewed randomized clinical trials is lacking. Limited efficacy findings are available at: VHA PBM Information on Investigational and off-label Treatment Options of COVID-19. [7] Further studies are needed.

Q: What are the options for use of HCQ/CQ in the treatment of COVID-19 within the VA?

A: Ideally, use of treatments for COVID-19 would be in the context of a clinical trial. However, in the absence of such a trial, considerations for off-label use should occur using the best available information, in consultation with Infectious Diseases and/or other facility designated experts, and only AFTER evaluating the potential benefits and risks associated with the treatment, customized to the needs of the patient. Discussion of these risks/benefits should be in consultation with the patient, family, and in keeping with the PBM Document entitled: Pharmaceutical Use Outside of Approved Indications Guidance on "Off-Label" Prescribing (August 2013).[7]

Q: What are the dosing considerations associated with the use of HCQ/CQ in the treatment of COVID-19?

A: Optimal dosing and duration of HCQ/CQ for COVID-19 are unknown. Therapeutic index is narrow; the toxic dose is as little as 3-5 times the therapeutic dose. An overdose of HCQ/CQ can cause acute toxicity and death.[1-2]

- The following dosing for off-label treatment of COVID-19 has been studied:
  - HCQ: 400mg twice daily for 1 day, followed by 200mg twice daily x 4 more days.
    Note: if given with azithromycin, 200mg three times daily for 10 days would also be appropriate.
  - CQ: 500mg twice daily for 10 days.
- Compared to CQ, HCQ is preferred based on improved in vitro activity and safety but CQ is an appropriate option if HCQ is not available.
- HCQ/CQ tablets may be crushed to prepare suspensions for NG/OG administration.[8]

See Table 1 (page 2) for additional dosing considerations.

Q: Are there any contraindications against the use of HCQ or CQ?

A: Yes - pre-existing retinopathy of the eye and known hypersensitivity to 4-aminoquinoline compounds.[1-2]

Q: What are the potential risks associated with HCQ/CQ use?

A: Both CQ and HCQ have known safety profiles with side effects that include, but are not limited to:[1-2]

- Cardiac risks: QT prolongation and arrhythmia
- Neuro/psychiatric risks: seizures, delirium, anxiety, depression, psychosis
- Hypersensitivity reactions: rash/pruritis, erythema multiforme
- Hypoglycemia: sometimes profound
- Hematologic: hemolytic anemia with G6PD deficiency
- Gastrointestinal side effects: nausea, abdominal pain and diarrhea
- Possibility that HCQ/CQ may worsen long term outcomes due to immune modulating and anti-inflammatory properties of CQ in vivo. [9]

See Table 2 (page 2) for additional details. While some risks would only be expected with chronic therapy (i.e., cardiomyopathy, retinopathy), safety in this population (i.e., sick, possibly critically-ill patients) HAS NOT BEEN ESTABLISHED.

Q: What are the monitoring recommendations for cardiotoxicity associated with the use of HCQ/CQ within the VA?

A: QT should be monitored prior to initiation and drug avoided if QT > 490 msec. Ideally patients should be on telemetry, and if tele QTc is concordant to EKG QTc, telemetry can be used for further QTc monitoring.

- For patients not on telemetry, a repeat EKG should be taken after starting HCQ/CQ and considered daily if risk factors.
- Discontinue all other QT prolonging agents, if possible.
- If QTc increases by > 50 msec, or absolute QTc > 500 msec, discontinuation should be strongly considered.
- Of note, other modifiable risk factors (K+, Mg++) should be monitored and controlled for.
- **Azithromycin may prolong the QTc and has been shown to increase the risk of sudden cardiac death.** [8]

Q: What drugs should be reviewed for interactions prior to administration of HCQ/CQ?

A: A comprehensive medication review should assess for the following concurrent medications (among others): medications that prolong the QT interval, (including but not limited to Class 1A, 1C, III antiarrhythmics, certain antidepressants, antipsychotics, fluoroquinolones, macrolides, 5-HT3 receptor antagonists) due to increased risk of QT prolongation; drugs metabolized by CYP2D6 (i.e., beta-blockers, antipsychotics, antidepressants) as HCQ/CQ inhibits CYP2D6 and may increase levels of these drugs; antacids due to the potential to reduce the activity of HCQ/CQ (administration should be separated by 4 hours).[1-2] See Table 3 (page 2) for additional details.

Table 1. Dosing considerations for the use of hydroxychloroquine or chloroquine. [1-2]

	HYDROXYCHLOROQUINE (PLAQUENIL®) | [HCQ]	CHLOROQUINE (ARALEN®) | [CQ]
DOSING CONSIDERATIONS	• Daily doses should not exceed 6.5 mg (salt form)/kg ideal (lean) body weight. • Using absolute body weight could result in an overdosage. • Exceeding the recommended daily dose increases risks of retinal toxicity and cardiac arrhythmias. • One 200 mg tablet is equivalent to 155 mg base.	• Daily dose of chloroquine phosphate should not exceed 2.3 mg/kg of actual body weight. • Exceeding the recommended daily dose increases risks of retinal toxicity and cardiac arrhythmias. • Each 500 mg tablet contains the equivalent of 300 mg base.
OVERDOSE	• Symptoms may occur within 30 minutes and include: headache, drowsiness, visual disturbances, cardiovascular collapse, hypokalemia and convulsions, rhythm and conduction disorders, including QT interval prolongation, torsade de pointes, ventricular tachycardia, ventricular fibrillation, width-increased QRS complex, PR interval prolongation, bradyarrhythmias, nodal rhythm, atrioventricular block, followed by sudden potentially fatal respiratory and cardiac arrest. • Treatment is symptomatic and supportive with observation (e.g., ECG monitoring). The ECG may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.	• Symptom onset possible within minutes, including nausea, vomiting, headache, drowsiness, visual disturbances, cardiovascular collapse, convulsions, hypokalemia, rhythm and conduction disorders including QT prolongation, torsade de pointes, ventricular tachycardia and ventricular fibrillation, followed by sudden potentially fatal respiratory and cardiac arrest. Extrapyramidal disorders may occur. • Treatment is symptomatic with immediate evacuation of the stomach by emesis or gastric lavage followed by activated charcoal. Care should include cardio-respiratory and hemodynamic support, monitoring of potassium along with management of arrhythmias and convulsions, as necessary.

Table 2. Risks associated with the use of hydroxychloroquine or chloroquine and precautions to consider. [1-2]

SYSTEM	RISK	PRECAUTION
Cardiovascular	• Cardiomyopathy (Life-threatening and fatal) • Electrocardiogram (ECG) Changes and Potential for Cardiac Arrhythmias (Serious and fatal outcomes, including ventricular arrhythmias, heart blocks, ventricular fibrillation, QTc prolongation, and torsade de pointes) • The magnitude of QT, PR or QRS prolongation is dose-dependent.	• Not recommended in patients with baseline QTc prolongation (e.g., congenital or acquired Long QT Syndrome), second-or third-degree atrioventricular block. • Electrolyte imbalances (e.g. hypokalemia/hypomagnesemia/hypocalcemia) must be corrected prior to use. • Caution in patients with risk factors for torsade de pointes, including, but not limited to: female gender; age ≥ 65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid hemorrhage, stroke, intracranial trauma); diabetes mellitus; autonomic neuropathy • Concomitant use with other QTc, PR or QRS interval prolonging drugs should be avoided or undertaken with particular caution. • If cardiotoxicity is suspected, discontinue use promptly.
Endocrine/Metabolism	Severe hypoglycemia (+/- antidiabetic drugs)	Concomitant antidiabetic therapy may enhance hypoglycemic effects. Closely monitor glucose while on therapy. Lower dose of antidiabetic drugs/insulin as needed
Hematologic	Bone marrow depression	Caution in patients with blood disorders or glucose-6-phosphate dehydrogenase deficiency due to hemolytic anemia (less concern with HCQ than CQ), leukopenia.
Hepatic	Abnormal LFTs and fulminant hepatic failure	Caution in hepatic disease or alcoholism, in whom a reduction in dosage may be necessary, or in conjunction with known hepatotoxic drugs.
Neurologic/Psychiatric	Muscular weakness, extrapyramidal reactions, suicidal behavior/ideation, seizures	Caution or avoid in patients with history of seizures.
Ophthalmologic	Irreversible retinal damage	Retinal toxicity is largely dose-related.
Renal	Potential for adverse events with renal impairment due to long half-life	Caution in renal dysfunction.
Skin	Exacerbation of psoriasis or porphyria; Erythema multiforme (uncommon) and rash/pruritis (common)	Not recommended in psoriasis or porphyria due to possible exacerbation. Recommend discontinuation in setting of severe skin reactions.

Table 3. Drugs that may interact with hydroxychloroquine or chloroquine. [1-2]

DRUGS	INTERACTION
CYP2C8 and CYP3A4 inhibitors (i.e., ketoconazole, itraconazole, erythromycin, aprepitant, fluconazole, clopidogrel, teriflunomide, letermovir)	HCQ/CQ is a **substrate of CYP2C8, 3A4** - Co-administration may increase HCQ/CQ levels.
Drugs metabolized by CYP2D6 (i.e., beta-blockers, antipsychotics, antidepressants)	HCQ/CQ **inhibits CYP2D6** - May increase levels of drugs metabolized by CYP2D6.
Antacids	May reduce absorption of HCQ/CQ. Administer 4-hours apart.
Antidiabetic Drugs and Insulin	May enhance hypoglycemic effect; decrease in dose of antidiabetic drugs/insulin may be required.
Cyclosporine	Levels may increase since HCQ/CQ **inhibits CYP3A4.**
Digoxin	May result in increased serum digoxin levels; monitor digoxin levels closely in concomitant treatment.
Drugs that prolong the QRS and/or QT interval and other arrhythmogenic drugs including, but not limited to, Class IA, IC and III antiarrhythmics; certain antidepressants, antipsychotics, and anti-infectives (i.e., fluoroquinolones, macrolides); domperidone; 5-hydroxytryptamine (5-HT)3 receptor antagonists; kinase inhibitors; histone deacetylase inhibitors beta-2 adrenoceptor agonists	Cardiotoxic effects. *Note:* **Azithromycin may prolong the QTc and has been shown to increase the risk of sudden cardiac death.** Documented in outpatients (not in context of COVID); risk was greatest in those with the highest baseline CV. **Overuse can also lead to C.difficile and antibiotic resistance.**
Drugs that affect electrolytes including, but not limited to, loop, thiazide, and related diuretics, laxatives and enemas, amphotericin B, high dose corticosteroids, and proton pump inhibitors	Cardiotoxic effects.
Tamoxifen/Drugs known to induce retinal toxicity	Concomitant use is not recommended due to retinal toxicity**.**

REFERENCES:

1. PLAQUENIL® (HYDROXYCHLOROQUINE SULFATE TABLETS, USP) [Prescribing Information]. St. Michael, Barbados: Concordia Pharmaceuticals Inc.; June 2018.
2. ARALEN® (Chloroquine Phosphate, USP) [Prescribing Information]. Bridgewater, NJ: sanofi-aventis U.S. LLC; 2017.
3. Wang, M., Cao, R., Zhang, L. *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* **30,** 269–271 (2020). https://doi.org/10.1038/s41422-020-0282-0
4. Liu, J., Cao, R., Xu, M. *et al.* Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* **6,** 16 (2020). https://doi.org/10.1038/s41421-020-0156-0
5. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. 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 Mar 9. pii: ciaa237. doi: 10.1093/cid/ciaa237. [Epub ahead of print]
6. Gao J et al. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bioscience Trends Advance publication. DOI:10.5582/bst.2020.01047Letter.
7. VA Pharmacy Benefits Management Services [PBM]. Literature Summary on Investigational and off-label Medications for COVID-19. *Internal Guidance.* Available at: https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/Clinical%20Recommendations/VHA%20PBM%20Information%20on%20Investigational%20and%20off-label%20Treatment%20Options%20COVID-19.docx . Accessed 03/26/2020.
8. McHenry A, Wemp M, Rice p. Stability of extemporaneously prepared hydroxychloroquine sulfate 25 mg/mL suspension in plastic bottles and syringes. *Int J Pharmaceut Compound* 2017;21:251.
9. Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res. 2020 Mar 5;177:104762. doi: 10.1016/j.antiviral.2020.104762. [Epub ahead of print]