



## FLASH INFO ERN-EYE COVID N°001 v1.0

DATE : 3<sup>TH</sup> APRIL 2020

AUTHORS : Pr Susan M Downes, Oxford University Hospitals Foundation NHS Hospitals Trust, Oxford, UK  
Pr Bart P Leroy, Ghent University Hospital, Ghent, BELGIUM  
Pr Helene Dollfus, Hôpitaux Universitaires de Strasbourg, Strasbourg, FRANCE

---

### *Overview of the retinal risks concerning Hydroxychloroquine/Chloroquine therapy during the COVID-19 pandemic*

---

#### INTRODUCTION:

This statement is about Hydroxychloroquine (HCQ) as well as the closely related chloroquine (CQ) and the potential risks to the retina due to:

- 1) Its novel use as prophylaxis or treatment of complications or their prevention in the context of COVID-19 infection
- 2) The specific risks of use of HCQ/CQ either as prophylaxis or treatment for COVID-19 in patients with inherited retinal degenerations such as retinitis pigmentosa or macular dystrophies.
- 3) The postponement of HCQ/CQ retinal screening/monitoring during the COVID-19 epidemic

#### MAIN QUESTIONS:

Hydroxychloroquine, and more rarely now chloroquine, are drugs currently used in the treatment of rheumatological and dermatological conditions(1), but since late December 2019, it has been proposed as treatment or prevention for the complications of COVID-19 and also as a potential prophylaxis against COVID-19(2).

Questions relating to this topic include:

1. Is a patient with an **inherited retinal dystrophy** such as **retinitis pigmentosa** or macular dystrophy at a higher risk of visual impairment by taking HCQ/CQ therapy?
2. **Is there a potential risk of developing retinopathy in the group of patients with inherited retinal dystrophies for:**
  - a. Participants in trials evaluating the role of HCQ/CQ in short term treatment of complications of COVID-19 or in prophylaxis against COVID-19?
  - b. Individuals who have been prescribed, or are self-prescribing HCQ/CQ without monitoring and unknown doses and who have potential other co-morbidities potentially making HCQ/CQ retinopathy a higher risk?
3. Is there a **potential risk of missing early HCQ/CQ retinopathy** due to the current postponement of retinal screening and monitoring during the COVID-19 epidemic?  
Mostly HCQ/CQ is usually avoided in patients with pre-existing retinal conditions. However, many patients without pre-existing retinal conditions take HCQ on a regular basis as treatment for rheumatological and dermatological conditions. Their screening visits may be considered as non-essential visits in these COVID-19 times.





## FACTS and ANALYSIS

Hydroxychloroquine (HCQ) is used widely in treatment of rheumatological and dermatological disorders(1,2). It was first synthesized in 1946 by introducing a hydroxyl group into the older drug chloroquine (CQ), which has been abandoned due to its higher frequency of retinal toxicity, which is thought to be due to CQ's higher lipid affinity and consequent accumulation in the retinal pigment epithelium (RPE)(3–5). In addition, since early 2020, HCQ/CQ have made headlines recently as potential treatment or prevention for pulmonary complications of COVID-19 infection. Moreover, a potential prophylactic role in preventing infection in COVID negative individuals has also been proposed (6–8).

Early clinical observations have reported a potential beneficial effect of HCQ, with a decrease in viral load and carriage duration in COVID-19 patients receiving HCQ (600 mg/day during ten days), with enhanced effects in combination with azithromycin(7). At present we await the results of larger trials, as this trial comprised a small sample size, without a randomized control arm, with no clinical benefit analysis and only short-term follow-up. Since 2020, there have been > 20 publications regarding HCQ/CQ and COVID-19. There is a widespread view in the public domain, fuelled by high profile parties, albeit without any sound scientific basis that HCQ/CQ can be used prophylactically to prevent COVID-19 infection, or once infected, HCQ/CQ could reduce morbidity/mortality.

This has led to recommendations in some countries to take prophylaxis in high-risk groups,(9). It has also led to self-medication in some individuals with attendant risks.

It is important to realize that HCQ/CQ has a narrow therapeutic index and potential severe systemic complications may occur for example for patients with heart conditions especially with repolarisation problems, with auto-immune myasthenia, with G6PD deficiency, and other co-morbidities.

In addition, it is well known that the risk of HCQ retinal toxicity is related to duration and amount of the drug used and is higher in patients with some co-morbidities (eg renal impairment, tamoxifen treatment among others) (1,2)

Regarding HCQ retinal toxicity we make the following observations:

1) a) If an individual is participating in one of the recently started trials testing the efficacy of HCQ/CQ either in prophylaxis against developing COVID-19, or for addressing life-threatening complications of COVID-19, the likelihood of retinal toxicity is expected to be very low, as the risk tends to be in long-term users. (1,2) In addition, these patients will be undergoing careful monitoring with careful consideration of their co-morbidities, lowering general toxicity risks.

b) Physicians should be aware that self-medication may be occurring, and not only does this have systemic risks, but retinal toxicity may occur earlier if high doses are being taken and if there are concomitant co-morbidities as described above. (1,2)

2) If a patient with an inherited retinal degeneration (IRD), including retinitis pigmentosa and macular degeneration, is prescribed HCQ to treat COVID-19 symptoms, the moderate dose and short duration of treatment (10 days with 600mg per day) would not be expected to affect the vision.

3) Most patients already taking (or starting) HCQ for rheumatological/ dermatological disorders are enrolled into screening and monitoring programs. It is unlikely that many patients with IRDs are prescribed





HCQ/CQ for these conditions, as it is generally avoided in patients with pre-existing retinal disease. Most Eye Departments/Units during the COVID-19 crisis, have advised that only patients with sight-threatening eye problems should be seen. Their planned appointments are being postponed until the end of the COVID-19 outbreak. However, if a patient reports a new deterioration in vision, then he/she would be seen as per the local emergency guidelines for any patients reporting visual loss or vision disturbance.

## CONCLUSIONS

---

- **Medical advice and evaluation is always required before taking HCQ/CQ** as there are contra-indications and not taking these into account may lead to life-threatening events.
  - **Short courses of HCQ** taken as part of current trials to evaluate potential beneficial effect of HCQ/CQ in COVID19 would **not be expected to confer a significant risk of HCQ/CQ retinal toxicity**. However, this does come with a caveat; there are specific groups in the general population in whom a more rapid retinal toxicity may be seen. Also, in such cases we strongly recommend the use HCQ and not CQ, in all patients.
  - Having an inherited retinal dystrophy such as **retinitis pigmentosa is not considered to be a contra-indication per se for short term HCQ/CQ treatment** (unless the individual has in addition, a pre-existing susceptibility, or a co-morbidity, or medication that predisposes the individual to HCQ retinal toxicity). Again, we strongly recommend the use of HCQ and not CQ, in all patients.
  - Ophthalmologists should be aware that **self-prescription of HCQ/CQ may be occurring with unknown doses** in individuals who are self-medicating with HCQ/CQ as they believe it is a prophylaxis against COVID-19. These individuals may have co-morbidity risk factors (kidney failure, liver failure, as well as a list of specific co-medications that are contra-indicated) and thus run an increased risk of retinal toxic side effects during the COVID-19 epidemic.
  - Patients requiring **HCQ for usual indications screening and monitoring as per local protocols are being postponed** in most units to reduce their risk of acquiring COVID-19, but should be informed to report back urgently if they notice a decrease in vision.
  - Some **specific genetic/rare conditions can represent a contra-indication** to this prescription, including but not limited to G6PD deficiency, intermediate porphyria, congenital or acquired heart disorders such as repolarization anomalies (Long QT), myopathy and myasthenia gravis.
- 





## MAIN SOURCES and REFERENCES:

1. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. *Eye Lond Engl*. ;31(6):828-45; **2017**.
2. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF, American Academy of Ophthalmology. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology*. 123(6):1386-94; **2016**.
3. McChesney EW. Animal toxicity and pharmacokinetics of hydroxychloroquine sulfate. *Am J Med*.;75(1A):11-8; **1983**.
4. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol*.16(3):155-66; **2020**.
5. Rynes RI, Bernstein HN. Ophthalmologic safety profile of antimalarial drugs. *Lupus*. 2 Suppl 1:S17-19; **1993**.
6. Mégarbane B. Chloroquine and hydroxychloroquine to treat COVID-19: between hope and caution. *Clin Toxicol Phila Pa*.1-2; **2020**.
7. Gautret P, Lagier J-C, 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*. 105949; **2020**.
8. 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*. 14(1):72-3; **2020**.
9. Ravindranath P. COVID-19: Doctors cautious over use of malaria drug as prophylaxis [Internet]. *Science Chronicle*. Available: <https://journosdiary.com/2020/03/24/covid-19-hydroxychloroquine-prophylaxis-icmr/>; **2020 [cited 9 avr 2020]**.

