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If Not Now, When ? --- Chlroroquine/Hydroxychloroquine dosage for COVID-19 should be clarified especially in view of higher mortality in the elderly.

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The pandemic associated with the virus SARS-CoV-2, started in December 2019, has initially taken the health community off-guard and has rapidly spread from Wuhan (China) to several Asiatic, European, African and American Countries (**[1], [2]**). It was somehow unexpected (although predictable **[1]**), since SARS-CoV in 2003 and limited outbreaks of MERS-CoV in 2012 were considered isolated events **[1]**. However, appropriate measures of social distancing have shown some efficacy in disease containment in China, South Korea, Italy and other Countries **[2]**. Still, mortality rates- either CFR or IFR- are particularly high in Northern Italy, where CFRs of 11% or more were registered **[3]**. This is in striking contrast with values of around 1% in Germany and values even < 1% in Israel **[2]**. Although older average age in Italy as compared to China or other Countries was often given as one explanation **[3]**, the over-65 population in Italy has been previously ranked as one of the healthiest and with better life-expectancies **[4]**. A viral-genetic explanation is unlikely as all the sequencing data indicate scarce variability and mutation rates for SARS-CoV-2, an encouraging news for future vaccine developments **[1]**. However, a rather precise estimate of CFR and IFR especially in an older population (such as the one in a cruise-ship) can be obtained from the well-known events on board of the Diamond Princess, where 3711 people were on board: 705 became ill, also testing virus-positive, and 7 died, with a CFR of .99% **[2]**. Alternative epidemiological explanations for dramatic differences in mortality rates have been suggested such as the Original Antigenic Sin (OAS) theory of immune response **[5]**, but have not been addressed as yet in the COVID-19 pandemics.

In considering type and dosage of pharmacological/antiviral treatments and national/international guidelines for facing COVID-19, we noticed a potential uncertainty and confusion for dosage of the synthetic analogues of quinine: Chloroquine (CQ) and Hydroxy-Chloroquine (HCQ).

A lower dosage of **200 mg/day HCQ** is indicated in a recent publication from Italy **(Table 1)**. This would be approximately 3 fold lower than Chinese and French standard, potentially explaining some confusion witnessed in the last few weeks. It is not clear to us at the present time, whether this lower dosage was also employed in Northern Italy.

However, the official reference in IT appears to be a document by the Italian Society for Infectious and Tropical Diseases (SIMIT): this suggests for COVID-19 a dosage of 200mg BID (i.e., *bis in die* or twice a day) or **400 mg/day HCQ,** which would be only 2/3 of the internationally accepted dosage **(Table 1)**.

The higher dosage of **600 mg/day HCQ,** which appears to be equivalent per specific weight/efficacy to **1000 mg/day of CQ,** is the dosage preferred in clinical trials from China, France

and Holland. Chinese trials preferentially employed CQ at the higher concentration (1 gr/day, **Table 1)**, while other groups in Europe employ HCQ, generally less toxic than CQ, at a concentration of 600 mg/day for 10 days or less. **(Table 1)**.

In a study from South Korea also with an effective dosage of **600 mg/day HCQ** (nominal dose 400 mg/day for low body weight/frail patients), a potentially interesting prophylactic effect was demonstrated: Post-Exposure Prophylaxis, PEP **(Table 1).**

A higher dosage of **1.2 gr (loading dose)** for 3 days followed by **800 mg of HCQ** for the remaining days till 2 or 3 weeks (mild/moderate or severe disease and with start at 16 days post disease-incipit) has been utilized in a slightly larger, open label but randomized clinical trial (75 patients and 75 controls), recently published from China. It has demonstrated increased alleviation of clinical symptoms, greater decline of CRP and faster recovery from lymphopenia.

Since it is expected that the majority of patients in IT has been/will be treated with HCQ instead of CQ, this could be associated with under dosage of this antiviral, HCQ, for COVID-19 patients in Italy or elsewhere **(Table 1)**.

i) This letter suggests that the problem of HCQ dosage for COVID-19 patients should be reconsidered and rectified, since discrepancies and potential confusion is evident.

ii) In view of better results at higher doses, we suggest that a dosage of at least 600 mg/day HCQ or 1000 mg/day CQ should be employed. Both doses appear to be safe and tolerable **(Table 1)**.

iii) It further suggests that recommended CQ dosage should be carefully monitored and made comparable to HCQ standards, in view of CQ potential toxicities especially in the elderly.

Although the real efficacy of HCQ/CQ compounds as antivirals in contrasting the COVID-19 pandemics will be addressed and answered exclusively by RCTs, effective dosages for the less toxic HCQ of at least 600 mg/day should be strongly considered, especially now, in the midst of a pandemics with higher lethality in the elderly.

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Antiviral Drug Dosage Used	Initially reported in: (reference / year)	Models in vitro/in vivo :	Effective in clinical trials:	Counter-indication–longer treatment
HCQ 200 mg/day	(Cortegiani, Ingoglia et al. 2020)	NO	insufficient	Tolerable (Savarino, Di Trani et al. 2006)
HCQ 400 mg/day	SIMIT (IT) (Accessed 07-04-2020) but see Cortegiani 2020 http://www.simit.org/medias/1555-covid19-linee-guida-trattamento-01mar.pdf	NO	Shown as insufficient in clinical trial: (CHEN Jun 2020)	Tolerable (Savarino, Di Trani et al. 2006)
HCQ 400 mg*/day Post-exposure prophylaxis * to be considered 600 mg/day in view of patients low body weight (40 kg)	(Lee, Son et al. 2020) Tested after previous exposure of 205 residents in Long Term Care Hospital, South Korea	(Liu, Cao et al. 2020) (Yao, Ye et al. 2020)	Effective PEP(=0 cases compared to 21 new cases predicted, see (Lee, Son et al. 2020) Appendix-sup.material)	Tolerable (Savarino, Di Trani et al. 2006)
HCQ 600 mg/day	-- CDC (NL) (Accessed 07-04-2020)https://lci.rivm.nl/covid-19/bijlage/behandeladvies -- (Wei Tang, Zhujun Cao et al. 2020) -- see also (Alia and Grant-Kels 2020) -- (Gautret 2020)	(Liu, Cao et al. 2020) (Yao, Ye et al. 2020) (La Scola, Le Bideau et al. 2020) (Andreani, Le Bideau et al. 2020)	Effective - (Wei Tang, Zhujun Cao et al. 2020): 75 pts. + 75 cnts. (Gautret 2020): Effective-80 p.	Tolerable: (Devaux, Rolain et al. 2020) (Savarino, Di Trani et al. 2006)
CQ 1000 mg/day	(Huang, Tang et al. 2020)	(Liu, Cao et al. 2020) (Wang, Cao et al. 2020)	(Huang, Tang et al. 2020) Effective (10 pts)	Tolerable. (Huang, Tang et al. 2020) Some adverse events

Table 1. Different doses of HCHLQ/CHLQ recommended for treatment of COVID-19 patients according to recent references (autors-date) or official sites (Internet URLs). References for Table 1:

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