With that in mind, the authors found the EC50 was 6.14 micromolar at 24 hours and 0.72 micromolar at 48 hours. In other words, incubation time and possibly accumulation into cells was important.

Now as clinicians we need to take these molar concentration targets and transform them into something we can actually work with. To do that, we use the molecular weight of HCQ and correct for protein binding. When we crunch these numbers, we come up with a total level in plasma of 0.48 mg/L that corresponds to that 48h EC50 and 4.1 mg/L corresponding to the 24h EC50.

I would also like to point out that though complete viral inhibition occurs at an even higher target of 6.7 mg/L.

It is also important to note that there are differences between plasma or serum and whole blood. We make the case that for SARS-COV-2, actually measuring HCQ concentration in plasma or serum is preferred and highlight this discussion in our manuscript.

(Methods)

Now that we defined target concentrations, we evaluated 3 data sources to determine whether patients with rheumatic disease routinely obtain these targets. These three sources allowed us to characterize average drug levels across a wide range of patients with rheumatic disease.

(Results)

And the results of our first aim is presented in this table. So I will focus your attention to the highest dose group of 400 mg daily, here highlighted in yellow. We have here the average HCQ levels observed in the study along with the standard deviation. We found that the average levels were below the lowest target exposure- so here highlighted in red- in all studies. However, consistent with the wide variability in HCQ pharmacokinetics, we do see that a small proportion of patients can reach or exceed the lowest EC50 target. Now importantly, assuming the highest EC50, all studies had approximately one-tenth or less the required exposure for viral inhibition. Now the study also suggests that no patients were able to achieve concentrations needed for complete viral inhibition.

(Methods)

So then next we leveraged a published pharmacokinetic model of pregnant women with rheumatic disease and conducted dosing simulations using one of several regimens being tested for COVID-19. So for this abstract though, I will focus on just the last two dosage regimens.

(Results)

The results are our dosing simulations are noted in these figures. Just to orient you for a moment, the Y axis here is HCQ concentration and X axis is time in hours. This thick black line in the middle is the median drug concentration for this simulated dose. The dashed lines here are the 95th and 5th percentile. This blue dashed line in the middle is the lowest EC50 target and the red line is the surrogate ceiling for safety. This was derived from the clinical study that did the PK model. So we can interpret this data as follows: so for a pregnant women already on

long-term HCQ at a dosage of 400 mg a day, increasing that dose to 600 mg actually would obtained a peak or CMAX target concentration after the first dose and that is seen here and then average concentrations after the second dose.

However, mothers who continue the standard of care dosing of 400 mg once a day would actually not achieve median concentrations.

So the model also supports that, despite using loading doses of HCQ, no patients are able to obtain the levels needed for the higher EC50 or for complete viral inhibition.

(Conclusions and Discussion)

So then in summary, we found that the average patient with rheumatic diseases, including children, pregnant adults, and non-pregnant adults, are unlikely to obtain total serum or plasma concentrations shown to inhibit SARS-CoV-2 in-vitro.

The data therefore suggests that current HCQ dosing strategies, are unlikely to be effective in the setting of SARS-CoV-2 viremia, so this is where the serum most directly mirrors what they did in the in-vitro studies.

However, it is important to note that our data does not entirely preclude a potential benefit for HCQ in the setting of COVID-19. So first, HCQ may have antithrombotic and anti-inflammatory benefits, and these may be mediated at different target concentrations. Second intracellular lung concentrations may be critical for the drug's potential antiviral effect. Studies in rats suggest the lung concentrations are several hundred times higher than plasma. However, because HCQ accumulates in the lungs over several months, it may be the duration of therapy, as opposed to the dose, that is really key to understanding it's potential in COVID-19.

So ultimately, our study really highlights that well-designed clinical trials are urgently needed to characterize the efficacy, mechanism of action, and goal concentrations for HCQ in the target tissues before any specific dosage adjustments can be recommended. I think rheumatologists are well poised to lead these studies.

So with that in mind, on behalf of the authors, I would like to acknowledge our funding sources and thank our collaborators

I have also listed here several key references.

So please check out our article at the Journal of Rheumatology and feel free to e-mail me with any comments or questions. Again, thank you very much for your time and have a great day.