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# Correspondence

## False reassurance or inadequate drug levels?

Sir,

We read with interest the article by Chatterjee *et al*[1] where they concluded that intake of hydroxychloroquine (HCQ) for four or more weekly doses was associated with a significant decrease in SARS-CoV-2 infection rates. We applaud the authors for conducting a timely study, particularly amid the ongoing pandemic. The results of this study are consistent with the findings from other observational studies on systemic lupus erythematosus and rheumatoid arthritis, where HCQ has been shown to be associated with a significantly reduced risk of infections despite being an immunomodulatory agent[2-4]. Being a cost-effective and easily available drug, HCQ may have the potential to alter the course of the pandemic if determined to be effective for pre-exposure prophylaxis of COVID-19. However, we would also like to highlight important limitations of this study. Healthcare workers (HCWs) who have not been infected are more likely to continue HCQ prophylaxis for a longer duration, thus leading to a spurious association between prolonged HCQ prophylaxis and lower infection rates. In this situation, working in non-COVID areas, use of adequate personal protective equipment, awareness about the disease and behavioural patterns may further confound this association. In addition, the relative increase in the infection rates of SARS-CoV-2 in HCWs who had received 2-3 weekly doses of HCQ, as found in this study, is of concern. The authors explain this association by suggesting that HCWs taking 2-3 doses of HCQ may become complacent regarding infection control practices using a condom analogy[1]. However, this is less likely to be the case given numerous negative studies on HCQ as well as the negative press coverage on the same. It has been previously demonstrated in SARS-CoV that short duration treatment of SARS-CoV-infected cells with ammonium chloride (the antiviral mechanism of which is similar to HCQ, *i.e.* increasing endosomal *p*H) paradoxically increased the risk of infection by 2-4 times[5]. Thus, it is biologically plausible that insufficient concentrations of HCQ may paradoxically increase the risk of infection. *In vitro* studies on SARS-CoV-2 have shown significant increase in lung concentrations till day five following a loading dose and subsequent daily dosing[6]. As such, achieving sufficient free lung trough concentrations early and maintaining the drug levels will probably prevent the increased risk of SARS-CoV-2 infections.

We would like to suggest an alternative prophylactic regimen where sufficient drug levels may be achieved early. This would involve a loading dose of 800 mg followed by 400 mg HCQ twice weekly to maintain adequate drug levels[7]. Such a regimen should be first investigated before extending HCQ prophylaxis for a larger population.

***Conflicts of Interest*:** None.

**Praveen Tirlangi, Adil Rashid Khan, Devashish Desai & Manish Soneja***
Department of Medicine, All India Institute of Medical Sciences, New Delhi 110 029, India
**For correspondence*:
manishsoneja@gmail.com

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