

# COVID-19 Prophylaxis Using Hydroxychloroquine in India: A Review

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## ABSTRACT

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was identified as the etiological agent for pneumonia of unknown cause, which broke out in 2019 in Wuhan city, China. The coronavirus disease (COVID-19) was considered as a pandemic by World Health Organization (WHO) and had caused significant panic globally. Hydroxychloroquine (HCQ) has been advised for prophylaxis against COVID-19 for the prevention of transmission by Indian Council of Medical Research (ICMR) based on *in vitro* studies conducted by National Institute of Virology (NIV), Pune. This article reviews the revised ICMR guidelines on the use of HCQ as prophylaxis against SARS-CoV-2, the proposed mechanism of HCQ prophylaxis, and its efficacy in COVID-19.

**Keywords:** Coronavirus disease, Hydroxychloroquine prophylaxis, *In vitro* testing of hydroxychloroquine, Severe acquired respiratory syndrome coronavirus-2.

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## INTRODUCTION

COVID-19 has been declared as a pandemic by WHO on March 11, 2020. According to WHO globally as of May 25, 2020, confirmed cases of COVID-19 were 5,307,298 with 342,070 deaths, and in India, confirmed cases of COVID-19 were 145,000 with 4,167 deaths and the incidence is growing drastically till date.<sup>1,2</sup> The prevention of transmission among high-risk contacts is need of the hour to curb the spread of the disease. Since there is no approved vaccine or treatment for the disease, prevention is the mainstream for minimizing the spread of the disease. Therefore, measures like social distancing, wearing mask, hand hygiene among community, and using personal protective equipment (PPE) along with above-mentioned measures are recommended for healthcare workers (HCWs) for the prevention of disease spread.

The role of hydroxychloroquine (HCQ) in the prophylaxis against COVID-19 has been proposed due to its *in vitro* activity against SARS-CoV-2 in inhibiting membrane fusion by increasing the pH of endosomes/lysosomes, which in turn affects the viral replication. It also affects the mode of antigen presentation which in turn prevents the cytokine storm.<sup>3-6</sup> Based on the *in vitro* study conducted at NIV, Pune, stated HCQs antiviral property like log reduction of viral RNA copy and infectivity, thus the ICMR guidelines have recommended the use of HCQ as prophylaxis against SARS-CoV-2.<sup>4,7,8</sup>

The justification for HCQ prophylaxis advised by ICMR was based on the results from the retrospective case-control study indicating the relationship between the number of HCQ prophylactic doses and the incidence of COVID-19 in symptomatic HCWs who were tested for SARS-CoV-2 infection. The guidelines were framed based on the studies conducted at three central government hospitals in New Delhi, and an observational prospective study conducted at All India Institute of Medical Science (AIIMS) clearly indicated a decreased occurrence of COVID-19 infection among HCWs working in COVID-19 patient care who received prophylaxis with HCQ.<sup>2,7,8</sup> However, there is a paucity of research in this area because of the unprecedented pandemic.

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The dose-response relationship is of paramount importance in HCQ prophylaxis according to the case-control study conducted by ICMR COVID-19 research team. The efficacy of HCQ prophylaxis against SARS-CoV-2 infection increases not by mere initiation of prophylaxis, but with the consumption of four or more maintenance doses.<sup>9</sup>

## INDICATION FOR HCQ PROPHYLAXIS

According to the previous ICMR guidelines, the indications for HCQ prophylaxis are all asymptomatic HCWs involved in care of suspected or confirmed cases of COVID-19 and asymptomatic household contacts of laboratory-confirmed cases.<sup>7</sup> Additionally, asymptomatic HCWs involved in containment/treatment of COVID-19, those who are working in non-COVID hospitals/non-COVID areas of COVID hospitals/blocks and asymptomatic frontline workers, such as surveillance workers deployed in containment zones and paramilitary/police personnel involved in COVID-19-related activities, have been included in revised ICMR HCQ prophylaxis guidelines.<sup>8</sup>

## CONTRAINDICATIONS FOR HCQ PROPHYLAXIS

Due to adverse drug reactions, the HCQ prophylaxis has been contraindicated in patients with glucose-6-phosphate

deficiency (G6PD) disease, retinopathy, hypersensitivity to HCQ or 4-aminoquinolone compounds, preexisting cardiomyopathy, and cardiac rhythm disorders. According to MoHFW guidelines, HCQ is contraindicated in <15 years for prophylaxis and <12 years for treatment of COVID-19 patients.<sup>2,7,8</sup>

The HCQ prophylaxis has to be given under strict medical supervision with informed consent regarding the side effects of it by a registered medical practitioner. HCQ can rarely cause serious adverse drug reactions like cardiomyopathy and visual disturbances, so the key considerations given in the revised ICMR guidelines have to be followed strictly without any compromise.<sup>2,7,8</sup>

## DOSAGE FOR HCQ PROPHYLAXIS

The revised ICMR guidelines for HCQ prophylaxis have categorized indicated personnel into two categories: category 1 includes asymptomatic household contacts of laboratory-confirmed cases for whom the recommended dosage was 400 mg twice a day (BD) on day 1 followed by 400 mg once weekly for 3 weeks to be taken with meals, whereas category 2 includes personnel such as asymptomatic HCWs involved in containment and treatment of COVID-19 and those who are working in non-COVID hospitals/non-COVID areas of COVID hospitals/blocks and asymptomatic frontline workers, such as surveillance workers deployed in containment zones and paramilitary/police personnel involved in COVID-19-related activities, for whom the dosage recommended was 400 mg BD on day 1 followed by 400 mg once weekly for 7 weeks to be taken with meals.<sup>8</sup> Furthermore, if the HCQ prophylaxis has to be continued beyond 8 weeks period for category 2 personnel, then one ECG should be taken during the course of prophylaxis and in case of presentation with new cardiovascular symptoms like palpitation, chest pain, or syncope as recommended by the ICMR guidelines.<sup>8</sup> In addition to that, monitoring of HCQ prophylaxis may be done using an ECG with the estimation of QT interval before initiating the prophylaxis or for continuing the prophylaxis beyond 8 weeks.<sup>8</sup>

The safety of the HCQ has been assessed as per the data collected from 1323 HCWs, the common adverse drug reactions encountered were nausea (8.9%), abdominal pain (7.3%), vomiting (1.5%), hypoglycemia (1.7%), and cardiovascular effects (1.9%) in revised ICMR guidelines,<sup>8</sup> whereas the pharmacovigilance program of India had reported seven cases of serious adverse drug reactions which includes three cases with prolongation of QT interval on ECG among 214 reported adverse drug reaction cases.<sup>8</sup> However, there is a paucity of research in this area as expected owing to unprecedented pandemic of COVID-19 which requires further randomized double-blinded studies on HCQ prophylaxis.<sup>10</sup> Furthermore, a study conducted on the safety and effectiveness of HCQ in long-term care hospitals in South Korea showed that out of 211 personnel who were initiated on post-exposure prophylaxis with HCQ, 205 personnel have not developed any serious adverse reactions.<sup>10</sup> Moreover, the pharmacokinetic property of HCQ like long half-life and ability to achieve half lung concentration than the plasma concentration makes it a suitable agent for prophylaxis.<sup>11,12</sup> Furthermore, the half-maximal inhibitory concentration (IC<sub>50</sub>) requirement of the drug for inhibition of SARS-CoV replication in Vero E6 cells is 8.8 µmol/L, which results in lower plasma concentrations in humans when compared to the plasma concentrations reached during the course of malaria treatment.<sup>10</sup> The IC<sub>50</sub> for SARS-CoV is 1–3 µmol/L, which is similar

to a dose of 3.6 mg/kg prescribed to treat autoimmune disorders like rheumatoid arthritis with a better drug tolerance.<sup>12,13</sup>

Although HCQ has above-mentioned advantages, HCQ is a known inhibitor of P-glycoprotein (P-gp) and cytochrome P450 (CYP) 2D6. Therefore, the key consideration should be given to drug–drug interactions while co-administering with certain drugs like beta-blockers, antipsychotics, selective serotonin inhibitors, and methadone which are metabolized by cytochrome P450 (CYP) 2D6 and drugs transported by P-gp such as direct acting oral anticoagulants or digoxin.<sup>14–16</sup>

## DOSAGE OF HCQ FOR TREATMENT OF COVID-19

According to the Ministry of Health and Family Welfare (MoHFW), Government of India, based on uncontrolled clinical trials, the revised guidelines recommend the consideration of the following drug combination as the treatment regime for severe cases of COVID-19 requiring intensive care unit (ICU) admission. It includes HCQ 400 mg BD on day 1 followed by 200 mg BD for the next 4 days in combination with azithromycin 500 mg once a day (OD) for the duration of 5 days, as there is a lack of effective specific antiviral drugs which have been approved for COVID-19 treatment. The above-mentioned regime is used along with other symptomatic treatment. According to MoHFW guidelines, HCQ is contraindicated in <15 years for prophylaxis and <12 years for treatment of COVID-19 patients.<sup>2</sup> Although HCQ is a safe and proven effective drug when used for malaria or autoimmune disease, evidence for the use in COVID-19 infection treatment regimens is poorly evaluated because of a paucity of research in this area.<sup>9,17</sup>

## CONCLUSION

The global social and economic crisis due to COVID-19 pandemic can be managed efficiently only if we prevent the transmission of the disease in the population, especially in high-risk personnel, which is the need of the hour. Therefore, the HCQ prophylaxis should be administered with strict adherence to the key considerations mentioned in the revised ICMR HCQ prophylaxis guidelines without compromise.

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