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**Title:** Hydroxychloroquine and Remdesivir in COVID-19: A Critical Analysis of Recent Events

**Authors:** Amit Dang1, Vallish B N2, Sumit Dang3

**Author Affiliations:**

1Founder and CEO, MarksMan Healthcare Communications and KYT Adhere, Hyderabad, India [amit.d@marksmanhealthcare.com](mailto:amit.d@marksmanhealthcare.com);

2Associate Consultant, Medical Writing and Biostatistics, MarksMan Healthcare Communications, Hyderabad, India [vallish.bn@marksmanhealthcare.com](mailto:vallish.bn@marksmanhealthcare.com)

3Department of Pediatrics, University of Kentucky, USA [sumitdang@uky.edu](mailto:sumitdang@uky.edu);

**Full address of the institution where the work was carried out:**

MarksMan Healthcare Communications and KYT Adhere

H. No 9-1-67, Plot no. 67, TNGO’s colony

Behind Q City, Financial District

Hyderabad, Telangana – 500032, India

Email: [amit.d@marksmanhealthcare.com](mailto:amit.d@marksmanhealthcare.com)

**Contact information for corresponding author:**

Dr Amit Dang

Founder and CEO

MarksMan Healthcare Communications and KYT Adhere

H. No 9-1-67, Plot no. 67, TNGO’s colony

Behind Q City, Financial District,

Hyderabad, Telangana – 500032, India

Email: [amit.d@marksmanhealthcare.com](mailto:amit.d@marksmanhealthcare.com)

Phone: +91 77383 89300

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**ABSTRACT**

The world is going through an unprecedented medical emergency in the backdrop of not having an effective way to control the infection due to SARS-CoV2 causing COVID-19. Through the principles of drug repurposing, two drugs used for other indications in the past, hydroxychloroquine (HCQ) and remdesivir (RDV) have been undergoing intense scrutiny globally. Both of these drugs have received emergency use authorization by the USFDA; however, the wording and scope of authorization of these two are not entirely identical. In this review, we critically analyse the identification and subsequent events concerning these two drugs as potential treatment options for COVID-19, and conclude with some ethical issues that require serious thoughts from the global scientific community concerned with using these two drugs in the war against COVID-19.

**Key Words:** COVID-19; Hydroxychloroquine; Remdesivir; USFDA; Emergency use authorization

**INTRODUCTION**

The need for drug repurposing has suddenly gone up globally due to the ongoing pandemic of COVID-19. This coronavirus infection, which originated in the Wuhan province of China by the end of 2019, rapidly spread across the globe, and the World Health Organization classified COVID-19 as a pandemic on 12th March 2020.[1] As on 14 May 2020, there are 4.17 million confirmed cases of COVID-19, and 287,525 deaths due to COVID-19, at a mortality rate of 6.88%. With 1.32 million confirmed cases and 79,634 deaths, USA is the worst sufferer in terms of numbers due to COVID-19.[2] Given the sudden and severe nature of the respiratory distress produced by the COVID-19 pneumonia, the speed of spread of the pandemic, and the fact that the development and marketing of a new, safe and efficacious drug is costly and time-consuming, researchers around the world were interested in drug repurposing by which a drug already approved for another condition can be repositioned to treat a new disorder.

The causative agent of COVID-19, SARS-CoV2, is a betacoronavirus which has close genetic resemblance with the SARS-CoV which caused the 2002 SARS outbreak in 30 different countries within 6 months, and the Middle East respiratory syndrome (MERS) CoV which caused the MERS outbreak.[3,4] With this background, the drugs used to treat SARS and MERS were revisited to explore the extent of their activity against SARS-CoV2. Accordingly, a study from China published on 4th February, which tested the in-vitro antiviral activity of seven different drugs, found that chloroquine (CQ) and remdesivir (RDV) potently blocked the SARS-CoV2 infection of Vero E6 cells at low micromolar concentrations with high selectivity.[4]

**CHLOROQUINE AND HYDROXYCHLOROQUINE**

CQ has been used for over 70 years for treating CQ-sensitive malaria and extraintestinal amebiasis,[5] as well as discoid lupus erythematosus and rheumatoid arthritis due to its immunomodulatory properties.[6] The side effects of CQ are relatively few when taken at prescribed doses; at higher doses, chloroquine is associated with concerning ophthalmologic reactions including retinal toxicity, reduced visual acuity, loss of vision, and diplopia, due to the selective binding of chloroquine to melanin in the retinal tissues.[7,8] A 2018 systematic review involving 35,548 patients with malaria who received CQ and quinoline antimalarials found no serious cardiac adverse effects including arrhythmias being reported, with 18,436 participants having underwent ECG evaluation as well.[9] Further, a 2014 study involving 317 SLE patients suggested that CQ has a protective role against an unexpected high rate of cardiac arrhythmias and conduction disturbances.[10] This is not unexpected, because quinidine, a structurally related drug, has been used as a class 1a antiarrhythmic.[11]

HCQ, a less toxic derivative of CQ, has been used orally for a long time for treating conditions such as rheumatoid arthritis, juvenile idiopathic arthritis, and Sjogren's syndrome.[12] The toxicity profile of HCQ is largely similar to that of CQ. Cardiotoxicity is rarely reported with HCQ, and typically manifests as cardiomyopathy or conduction abnormalities.[13] HCQ has been reported to cause cardiotoxicity, neurotoxicity, and gastrointestinal effects after prolonged treatment.[14] Also, HCQ has been documented to be safe during pregnancy.[15]

The most accepted non-specific antiviral mechanism of CQ and HCQ includes inhibition of virus entry, transport, and post-entry events by altering the pH of endosomes.[16] By virtue of lower toxicity compared to CQ, as well as its easy availability and low cost, HCQ was endorsed for usage in the COVID-19 therapy.[17] A lower dose HCQ for prophylaxis of COVID-19 was also proposed.[18]

Because of the sensitive nature of the pandemic, the potential of HCQ in COVID-19 was publicized in media. Anticipating that the indiscriminate usage of the inexpensive HCQ may lead to drug shortages, instil a false sense of security, and potentially cause widespread HCQ toxicity, and in the backdrop of the still unavailable objective evidence of the effectiveness of HCQ against SARS-CoV2, an emphasis for well-designed clinical trials evaluating the same was repeatedly made.[19-23] Simultaneously, various clinical trials exploring the efficacy and safety of HCQ in the treatment and prophylaxis of COVID-19 were also initiated. Though a clinical trial from France strongly suggested that HCQ was associated with viral load reduction/disappearance in COVID-19 patients,[24] concerns were raised with regards to the study methodology.[25] An observational study involving 1376 patients of which 811 (58.9%) received HCQ, found that HCQ administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death. However, this was not a randomized trial, and HCQ-treated patients in this study were more severely ill than those who did not receive HCQ treatment.[26]

On 5th May 2020, a retrospective analysis of 1061 patients with SARS-CoV-2, who were treated for at least three days with a combination of HCQ (200 mg three times daily for ten days) with azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days) reported a good clinical outcome and virological cure within 10 days of treatment in 973/1061 (91.7%) patients, with only one patient having viral PCR positive at day 15. A total of 8/1061 (0.75%) patients died, and cardiac toxicity was not the cause of death in any of these 8. QTc prolongation was observed in only 9 patients, and no arrhythmias or sudden deaths were observed. Adverse events were observed in 2.3% of patients, and were mild, being restricted to GI or skin symptoms, headache, insomnia and transient blurred vision. [27]

On 21st March 2020, the ICMR (Indian Council for Medical Research) issued guidelines approving the usage of HCQ for prophylaxis against SARS-CoV2 infection among healthcare workers and asymptomatic household contacts of laboratory-confirmed cases of COVID-19.[28] CQ was also included in guidelines for the diagnosis and treatment of COVID-19 by the report (6th edition) of the National Health Commission of China, which was published on 19th February 2020.[29] The usage of HCQ was endorsed by the President of the USA as well.[30] This was shortly followed by the USFDA issuing an emergency use authorization (EUA) of HCQ to treat ‘patients who are hospitalized with COVID-19, for whom a clinical trial is not available, or participation is not feasible’. However, by this time, a large number of clinical trials for COVID-19 had already started, and the inclusion of these conditions meant that those patients already in clinical trials could not be administered HCQ for treating COVID-19, thereby lowering the potential number of recipients of the drug. Furthermore, the letter dated 28th March 2020 also emphasised that there were ‘limited in-vitro and anecdotal clinical data in case series’ regarding the efficacy of HCQ in COVID-19.[31] However, it is interesting to observe that a letter published twelve days prior had reported that chloroquine had acceptable efficacy and safety in treating COVID-19 as seen in several clinical trials involving over 100 patients conducted across various centres in China. In comparison to control treatments, CQ was found to reduce exacerbation of pneumonia, improve lung imaging findings, promote a virus-negative conversion, and shorten the disease course. Based on these findings, a conference of stakeholders representing different aspects of healthcare delivery, including the Government, came to an agreement that CQ has potent activity against COVID-19. This was the basis for the inclusion of CQ in the Chinese guidelines for COVID-19 treatment.[32]

The issuance of guidelines and EUA permitting HCQ usage for COVID-19 management met with criticisms as well.[33,34] There were concerns about a possible increase in rates of rare but serious cardiac adverse effects including QTc prolongation with HCQ usage for COVID-19;[35] contrasting reports about the absence of such cardiac safety concerns were published as well.[36] Concerns that overenthusiastic usage of HCQ, leading to shortage, might inconvenience rheumatology patients were raised.[37] There were criticisms of the quality of clinical trial evidence being generated that support the usage of HCQ in COVID-19 as well.[38]

The dosage recommendation for HCQ has varied widely: the prophylactic regimen recommended by the ICMR suggested HCQ to be given at 400 mg twice on day 1, then 400 mg once a week for 7 weeks (for healthcare workers) or 3 weeks (for asymptomatic contacts).[28] Chinese experts recommended a dosage of CQ at 500 mg twice daily for 10 days, thus the total dose was 10 g over 10 days.[39] The USFDA-approved dose for HCQ is 800 mg on day 1, followed by 400 mg daily for 4-7 days; thus the total dose was 2.4-3.6 g over a week.[40]

At the time of this manuscript, the NIH recommends in its guidelines section that there are insufficient clinical data to recommend either for or against using CQ or HCQ for treating COVID-19, and that when used, patients should be monitored for cardiac effects, specially QTc prolongation.[41]

**REMDESIVIR**

The second potential drug that was taken up seriously for repurposing against COVID was Remdesivir (RDV), after the initial identification in the Wang et al study.[4] RDV is a broad-spectrum antiviral agent that was originally synthesized and developed in 2013-14 by Gilead Sciences for the treatment of hepatitis C virus and respiratory syncytial virus. At the beginning of the 2014 Ebola virus outbreak, the anti-Ebola virus activity of RDV was explored.[42,43] RDV demonstrated activity against Ebola virus in cell lines and in Rhesus monkeys infected with the virus.[44,45] RDV was first clinically administered to a patient with Ebola virus relapse on a compassionate-use basis.[46] A subsequent clinical trial in 681 Ebola virus patients from Congo concluded that administration of monoclonal antibodies (REGN-EB3 and mAB114) was associated with greater survival rates than with RDV.[47] The clinical efficacy of RDV was not conclusively demonstrated in the treatment of Ebola and Marbug infections.[48]

RDV is a nucleotide prodrug of an adenosine analogue, which inhibits viral replication by blocking the function of viral RNA-dependent RNA polymerase, leading to premature termination of viral RNA transcription.[43] RDV has documented activity against SARS-CoV and MERS-CoV through in-vitro and animal studies.[49-51] Being a relatively recent drug, the clinical safety data of RDV is not yet adequate; the documented adverse effects being gastrointestinal symptoms, elevated transaminases, and elevated prothrombin time, and possibly non-significant drug interactions due to co-administration of CYP inducers.[41] Similar to HCQ, many clinical trials are being conducted to explore the efficacy and safety of RDV in COVID-19. The results of RDV administered open-label on compassionate-use basis to 61 patients were published on 10th April 2020, and a clinical improvement was observed in 36/53 patients (in terms of improvement in the category of oxygen support). Out of these 53 patients, 32 patients (60%) developed adverse effects; liver enzyme elevation and renal impairments were observed in 12 and 4 patients respectively. Four patients had to discontinue RDV treatment prematurely. However, the authors noticed that there were no new safety signals of concern.[52] In late April, a randomized controlled trial exploring the efficacy of RDV in 237 Chinese patients with laboratory-confirmed SARS-CoV-2 infection was published. This trial observed that RDV was not associated with statistically significant clinical improvement or time to clearance of virus in patients with serious COVID-19 compared with placebo, and that RDV was stopped early in 18 patients due to adverse events. More importantly, RDV was not associated with significant mortality benefit after 28 days of hospitalization. Further, virological clearance as measured by PCR was observed in only 37/236 (19%) patients with positive baseline PCR results. This trial, which was showing trends of RDV to not have significant clinical benefits, was terminated prematurely, and the reason given by the authors was that there was a difficulty in recruiting COVID-19 patients as the pandemic was brought under control in China.[53] This led to the opinion that while RDV might be helpful, it is not a wonder-drug.[54]

On May 01st 2020, the USFDA granted an EUA for the emergency use of intravenous RDV to treat patients with ‘suspected or laboratory confirmed’ severe COVID-19.[55] This EUA was based on USFDA’s review of topline data from two trials, one randomized, placebo-controlled and conducted by Government-funded NIAID (NCT04280705), and the other, an open-label, Gilead-sponsored trial (NCT04292899). Preliminary study data from the NIAID study suggested that compared to placebo, RDV shortens time to recovery by 31% (from 15 days to 11 days) significantly; however, mortality benefit is not significant.[56] The reviewed data suggested that the potential and known benefits of RDV outweighed the potential and known risks when used to treat patients with severe COVID-19, and the EUA had made no restrictions about the patients’ participation or feasibility to participate in clinical trials for receiving RDV treatment. However, at the time of this manuscript, the data from both of these trials are not available in the public domain, neither has it been peer-reviewed. Concerns about removing ‘death’ from the list of primary outcomes of the NIAID-funded trial drew criticisms on the internet.[57]

**USFDA APPROACH OF RDV vs HCQ: ETHICAL CONCERNS**

Analysing of various studies available at present does not prove a clear and conclusive efficacy benefit for either RDV or HCQ in clinical trials, despite both drugs showing impressive broad-spectrum antiviral as well as specific anti-coronavirus activity in in-vitro studies.[4] HCQ has a few additional advantages over RDV: its long-term and short-term safety profile is better studied because it has been used for a long time to treat various conditions, it is inexpensive, and it is administered orally. RDV, on the other hand, is a relatively new drug whose safety is not well studied, is expensive (as per ICER estimates, a 10-day course of RDV could cost USD 4,500, in contrast to a production cost of USD 10[58]), and is administered intravenously. A head-to-head comparison of both these treatment options has the potential to clear doubts on the efficacy and safety of these two drugs; at the time of writing this manuscript, five such trials have been registered in the clinicaltrials.gov database and four of these studies have started recruiting patients.

In these unprecedented times of global humanitarian crisis, it is expected that the medical community acts in the most ethical manner and works together to explore and come up with a solution to this situation that is beyond all influences of politics, profiteering, and personal views. However, by looking at the differing approach of USFDA towards HCQ and RDV, as evidenced by the words chosen in the respective EUAs, we are not having adequate confidence that the ethical process has been duely followed. Scrutiny of the EUAs and other recent events surrounding these two drugs gives way to a few uncomfortable questions.

1. ***Safety:*** the safety profile of HCQ is well-known since it has been in use for various other conditions as well. On the other hand, RDV has not been regularly used for any other condition, and due to the lack of clinical experience, the entire safety profile is not clear. In the compassionate use study, despite the adverse effects being observed among RDV recipients, the authors observed that there are no safety signals of concern. In our opinion, anticipatory management of known safety risks is better than managing the adverse effects of a drug with an unknown safety profile. However, the EUAs of both HCQ and RDV do not contain any information about these. On the other hand, there has been an interesting surge in reports of HCQ-induced QTc prolongation after the issuance of the HCQ EUA. Further, the number of patients who have received HCQ for COVID-19 in trials reported so far is larger than the number of patients who have received RDV for the same indication; thus, the safety profile of RDV for COVID-19 has not been adequately studied in a good number of patients. Why are the safety risks of HCQ being overplayed and the safety risks of RDV being underplayed?
2. ***Cost:*** Compared to RDV, HCQ is inexpensive by a wide margin. Favouring an expensive drug such as RDV over an inexpensive drug such as HCQ in treating COVID-19 might have significant implications in countries like India where a large proportion of medical expenditure is spent out-of-pocket. With the efficacy of both drugs being uncertain, why is the USFDA downplaying the cost benefit of HCQ?
3. ***Efficacy:*** Both HCQ and RDV were shown to inhibit the in-vitro growth of SARS-CoV2. The inconsistent, albeit non-specific, antiviral activity of HCQ has been documented in the past as well. A recent study has indicated that HCQ co-administered with azithromycin provides virological cure and low mortality with no cardiac toxicity. [27] However, the efficacy of RDV in Ebola virus was not fully established.[48] Also, the preliminary results of the NIAID trial is suggesting that RDV shortens time to recovery by a median of 4 days, without any significant mortality benefit. Finally, virological cure rates as measured by PCR was low in the study published in Lancet involving 237 patients.[53] Why is the USFDA downplaying the average track record of RDV in Ebolavirus treatment, and ignoring the prominently lacking mortality benefit with RDV, while highlighting that only anecdotal evidence exists for the efficacy of HCQ?
4. ***Conflicts of interest:*** A large proportion of HCQ to be used in the USA was procured from India. India is the largest manufacturer and supplier of HCQ, and has received request from over 20 countries for HCQ supply.[59] Being an inexpensive drug, HCQ is expected to not provide much profit to the manufacturers. On the other hand, RDV is produced by Gilead sciences, a US-based pharmaceutical company, which faced criticism after overpricing Sovaldi (Sofosbuvir) at USD 84,000 per treatment course.[60] On March 23 2020, the USFDA granted RDV an ‘orphan drug’ status, which resulted in an increase in share prices of Gilead.[61] After facing criticism, the orphan drug status was withdrawn shortly upon request by Gilead.[62] Using the EUA as the basis, Gilead has started getting marketing approval for RDV in other countries.[63] Gilead has also signed pacts with five generic drug makers to make and sell RDV in 127 countries, also using the EUA as basis.[64] By permitting the EUA of RDV even before the results of two clinical trials are made public through peer-reviewed journals, has the USFDA made sure that there are no conflicts of interest in supporting RDV and suppressing HCQ?
5. ***Conditions of use of HCQ and RDV:*** The EUA conditions of HCQ restrict that only patients with ‘known’ COVID-19, who are not part of clinical trials are to be administered HCQ; however, RDV may be administered to patients with ‘suspected’ or confirmed COVID-19, and there are no clinical trial restrictions. What is the basis for these two restrictions imposed only on HCQ and not on RDV?
6. ***Prevention versus treatment:*** Though it was suggested that HCQ can be used for COVID-19 prophylaxis at low and safe doses, the USFDA recommended higher and toxic doses intended for therapy and not prevention. With higher doses, toxic effects are also observed more often, as reported by an interim analysis of a randomized trial,[65] and this is in line with the principles of toxicology. Interestingly, USFDA recommended that HCQ is not to be used outside of hospital settings or a clinical trial in its communication on 24th April 2020, thereby preventing the possible prophylactic usage of HCQ in at-risk people.[66] Such a prophylactic usage, if proven effective, had a potential to reduce the number of people with serious COVID-19, the indication for which RDV is being positioned. Why did the USFDA not consider issuing guidance towards using a lower dose of HCQ prophylactically, like how the ICMR did? Also, why did the USFDA not put its efforts in generating evidence supporting prophylactic usage of HCQ?

**CONCLUSIONS AND WAY AHEAD**

In times of crises such as the present, it is essential for all to rise above everything and let humanity take precedence over everything else, including political affiliation, profit making, and any other conflicts of interest. The ethical concerns raised by us through scrutiny of the events surrounding HCQ and RDV need a serious consideration by all concerned. It might be possible that these concerns and doubts have already started to linger among the medical fraternity. It is essential to ascertain that there are no conflicts of interests behind granting drug approvals, because such undisclosed conflicts of interests may have far-flung impact in countries such as India. It is high time that the USFDA comes clean with a proper explanation and resolves the turbidity.

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