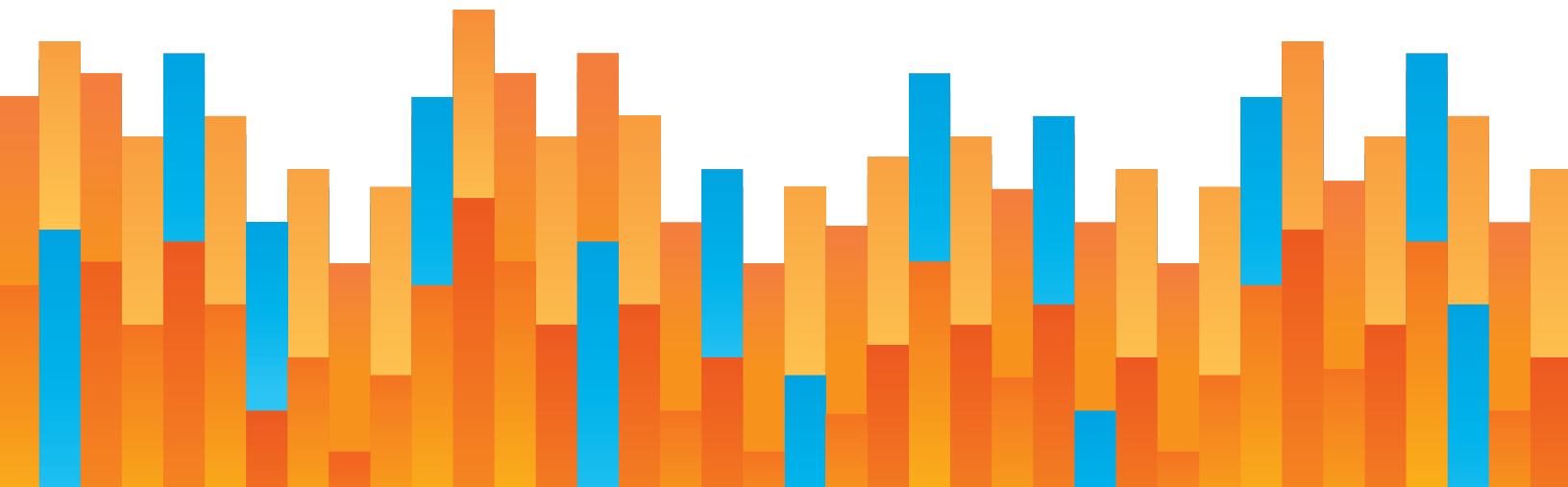




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FREQUENTLY ASKED QUESTIONS ABOUT CHLOROQUINE AND HYDROXYCHLOROQUINE IN TREATING COVID-19

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PART 1

INTRODUCTION

The global spread of novel virus Covid-19¹ has health care professionals scrambling to treat patients of varying severity. Yet currently, no treatment has definitely shown enough promise against Covid-19 to receive U.S. FDA approval for widespread use. Many, including President Trump, have touted the efficacy of two drugs currently in use in China and other countries: chloroquine² (CQ) and hydroxychloroquine (HCQ).³ As a result, many argue that, due to the severe and volatile effects of Covid-19 and the lack of effective therapies, the FDA should streamline, compress or even skip the years-long clinical trials process for these drugs, especially for patients who have a high chance of succumbing to the virus. To evaluate this position, it's necessary to understand why and how clinical trials work and methods for working around them.

¹ While both the disease and the virus are commonly called "Covid-19," as in this paper, the virus is technically named SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2019).

² Also known as chloroquine phosphate or Aralen.

³ Also known as hydroxychloroquine sulfate or Plaquenil.

PART 2

FREQUENTLY ASKED QUESTIONS

1. HOW DO CLINICAL TRIALS WORK?

Clinical trials are designed to vet the safety and effectiveness of developed drugs before they go to mass market through assessment in four distinct phases.

Phase 1: The experimental drug is administered to a small group of people suffering from a particular illness as well as healthy volunteers to look for side effects and determine the best dose for the drug.

Phase 2: The drug is then given to a group of several hundred ill people to evaluate the drug's effectiveness and any side effects not found in Phase 1.

Phase 3: The trial drug is then administered on a large scale—a group of hundreds to thousands of people—with its effects measured against those of a placebo in a randomized manner. This garners the best evidence of how the drug works and its most likely common side effects, and even some of its rare side effects, due to group size. This phase normally takes between one and four years.

Phase 4: The drug is approved for highly monitored use, and evaluated for longer-term side effects.

Due to the clinical trials process, new drugs (and vaccines as well) take years to attain approval for market sales while regulators seek to ensure that drugs are not only effective, but also “do no harm”—or at least no extensive harm that would eclipse their benefit. During a fast-moving pandemic of a highly contagious, often-lethal virus, the value of each step of this safety-assurance process must be weighed against the number of lives potentially saved by fast-tracking authorization for use. To skip the first phases of investigational drug approval, a logical strategy is to examine already approved drugs whose mechanisms are likely to be effective against what we know about Covid-19, because their short- and long-term side effects are already known, leaving only effectiveness to be determined. However, since such use would be “off-label,” or other than the use for which the drug’s efficacy has been tested, the FDA has several tools to sanction use aside from completing the clinical trials process.

2. IS THERE ANY WAY FOR COVID-19 INVESTIGATIONAL DRUGS TO BYPASS THE CLINICAL TRIALS PROCESS, MAKING THEM AVAILABLE FOR DOCTORS TO ADMINISTER?

“Expanded access” (also known as “compassionate use”), as well as “emergency use authorization,” provide for use of drugs that have not completed the clinical trials process.⁴ For “expanded access” to apply, the patient must have a serious and/or life-threatening disease with no known comparable therapy, the patient cannot enroll in a clinical trial, and the use of the drug cannot interfere with the drug’s approval process. For those that do not qualify for expanded access, a similar but less bureaucratic process called “right to try,” is another option. The third option, and the one that’s relevant to CQ and HCQ—“emergency use authorization” (EUA)—applies the FDA’s authority to temporarily approve certain medications for emergency use, bypassing the usual federal requirements. Amid conflicting global reports of CQ and HCQ efficacy and safety, the FDA issued an EUA for CQ and HCQ on March 28, 2020.

⁴ Sullivan, Thomas. “Understanding FDA Regulatory Terminology During COVID-19.” *Policy and Medicine*. 23 April 2020. <https://www.policymed.com/2020/04/understanding-fda-regulatory-terminology-during-covid-19.html>

3. WHAT ARE CHLOROQUINE (CQ) AND HYDROXYCHLOROQUINE (HCQ) AND HOW DO THEY WORK?

CQ, an anti-malarial and anti-amebiasis drug, was developed in 1934. HCQ, also called Plaquenil, is a roughly 40% less toxic derivative that was first approved for use in 1955, primarily for systemic lupus erythematosus and rheumatoid arthritis.⁵ Over the many years of these drugs' approved and widespread use, researchers and health care professionals have learned their side effects and mechanisms. Since these drugs block the specific transport mechanism of viruses that include coronaviruses,⁶ researchers sought them out as potentially effective medication against Covid-19.

While many contract Covid-19 asymptotically, for those who do show symptoms, infection usually begins with acute respiratory infectious illness that can damage multiple organ systems, including heart, lung and blood. Most adults experience fever, cough and fatigue for one to three weeks, with some progressing to pneumonia, respiratory failure, acute respiratory distress syndrome and death. With no proven therapies to prevent progression of Covid-19 to serious, life-threatening stages, these drugs held promise in shutting down the rapid systemic spread in the body. CQ and HCQ are not likely to prevent infection by Covid-19.

4. WHAT ARE THE SIDE EFFECTS OF CHLOROQUINE AND HYDROXYCHLOROQUINE?

It's important to remember that all drugs create side effects of some sort, and the key is identifying them and assessing whether the cure is less harmful than the disease. If so, close medical monitoring of patients, and readiness to intervene when needed, can mitigate the harm of many side effects.

⁵ Liu, Jia et al. "Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro." *Cell Discovery*. Article 16. 18 March 2020.
<https://www.nature.com/articles/s41421-020-0156-0>

⁶ Ibid.

SOME SIDE EFFECTS OF CHLOROQUINE

Common	Potentially serious
• Rash	• Cardiomyopathy
• Reduced hearing or tinnitus	• Seizures
• Headache	• Hypotension
• Increased liver enzymes	• Hepatitis
• Anorexia	• Irreversible retinal damage
• Nausea/vomiting	• Involuntary muscle movement
• Blurred vision	• Depression
• Diarrhea	• Personality changes

Sources: Aralen. Rxlist.com. <https://www.rxlist.com/aralen-side-effects-drug-center.htm>; H. Weniger. "Review of Side Effects and Toxicity of Chloroquine." World Health Organization. 21 June 1979. https://apps.who.int/iris/bitstream/handle/10665/65773/WHO_MAL_79.906.pdf

Accidental ingestion of CQ by younger children has led to fatality in most cases, even in relatively small doses. A 1990 study puts pediatric mortality at 80%, whereas adult mortality is only 10%.⁷ Adult mortality consists chiefly of overdoses as suicide attempts.⁸

SOME SIDE EFFECTS OF HYDROXYCHLOROQUINE

Common	Potentially serious
• Irritability	• Cardiomyopathy
• Headache	• Irreversible retinal damage
• Dizziness	• Bone marrow disorders
• Nausea	• Abnormal liver function
• Weakness	

Sources: Hydroxychloroquine Sulfate, side effects. Drugs.com. <https://www.drugs.com/sfx/hydroxychloroquine-side-effects.html>; "Chloroquine (Aralen) vs. Hydroxychloroquine (Plaquenil): What's the Difference?" Medicine.net. https://www.medicinenet.com/chloroquine_aralen_vs_hydroxychloroquine_plaquenil/article.htm

⁷ H. Weniger. "Review of Side Effects and Toxicity of Chloroquine." World Health Organization. 21 June 1979. https://apps.who.int/iris/bitstream/handle/10665/65773/WHO_MAL_79.906.pdf; Kelly, J.C. et al. "Chloroquine poisoning in a child." *Annals of Emergency Medicine*. January 19, 1990. <https://www.ncbi.nlm.nih.gov/pubmed/2297155>

⁸ Weniger. "Review of Side Effects and Toxicity of Chloroquine."

Not only is HCQ less toxic—it suppresses the immune system. It may seem counter-intuitive to seek out such a medication, but medical professionals globally have detected a high concentration of cytokines, which signals severe overactivity of immune response, in the plasma of critically ill Covid-19 patients. This finding suggests that patients’ spiral into acute respiratory distress may be triggered by a “cytokine storm,” which could be mitigated by immune-suppressants like HCQ. Due to the lower toxicity of HCQ, and its greater availability and its special immune-suppressive properties, health care professionals worldwide sought to try it on Covid-19 patients.⁹

5. IF HYDROXYCHLOROQUINE IS 40% LESS TOXIC THAN CHLOROQUINE, WHY ARE WE EVEN BOTHERING WITH CHLOROQUINE?

While hydroxychloroquine is less toxic than chloroquine, animal testing finds that it’s also less potent, which could have an effect on its virus-transport blocking capability for Covid-19.¹⁰ Moreover, the novel nature of the Covid-19 pandemic suggests that all drugs with potential to mitigate the respiratory distress that often leads to intubation, which alone causes significant damage, and death, should be considered.

Of course, if several drugs make the cut for effectiveness, other criteria also come into play. The drug must be available, especially given the immediacy of the need, as well as low in cost. Market supplies of both drugs have fluctuated over the years, leading to various stored quantities among countries. The U.S. Strategic National Stockpile recently received a donation of millions of doses of both drugs, prompting the FDA to issue an emergency use authorization (EUA) for their use.¹¹ Moreover, it may be that many different drugs will be needed to address various strains of the virus, or the various manifestations of it among different groups or individuals. For all these reasons, as many drugs as are thought to show potential for treatment of Covid-19 should be considered for off-label use.

⁹ Liu et al. “Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro.”

¹⁰ Ibid.

¹¹ HHS Press Release. “HHS accepts donations of medicine to Strategic National Stockpile as possible treatments for COVID-19 patients. March 29, 2020. HHS.gov. <https://www.hhs.gov/about/news/2020/03/29/hhs-accepts-donations-of-medicine-to-strategic-national-stockpile-as-possible-treatments-for-covid-19-patients.html> Donations were received from Novartis and Bayer—the companies that developed them.

6. DO THE DRUGS WORK AGAINST COVID-19?

Since the Covid-19 pandemic led to widespread compassionate use measures of investigational drugs, such as CQ and HCQ, researchers are compiling day-by-day data, but much of these results are not randomized or blind. A French non-randomized clinical trial in early March dosed patients daily with hydroxychloroquine, treated some with azithromycin as well, and used patients who refused the protocol as negative controls. The research found that patients taking hydroxychloroquine showed significantly decreased viral loads, and those taking azithromycin had even greater decreases.¹² This research has led France to experiment with using HCQ.

Some clinical trials in China and anecdotal evidence in the U.S. find these drugs to be effective against Covid-19, yet other trials or data from emergency use have either found little or no benefit, or have been stopped due to a prevalence of serious heart arrhythmias in patients.¹³ A U.S. study of veterans with Covid-19, which ended on April 11, 2020, found that HCQ treatment did not prevent recourse to mechanical ventilation and also led to an increased overall mortality rate.¹⁴ As a result of these and other inconclusive data, on April 24, 2020, the FDA warned against using CQ or HCQ outside of hospitals or clinical trials due to evidence of severe heart arrhythmias.¹⁵ The Journal of the American Medical Association found that “The potential harms [of using hydroxychloroquine] are substantial.

¹² Gautret, Phillippe et al. “Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.” *International Journal of Antimicrobial Agents*. 22 March 2020. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102549/>

¹³ Borba, Mayla Gabriela Silva et al. “Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19) study.” <https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v2>

¹⁴ Magagnoli, Joseph et al. “Outcomes of hydroxychloroquine usage in U.S. veterans hospitalized with Covid-19.” <https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2>

¹⁵ “FDA cautions against use of hydroxychloroquine or chloroquine for covid-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.” [https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or- ; fda press release. “Coronavirus Update: FDA Reiterates Importance of Close Patient Supervision for ‘Off-Label’ Use of Antimalarial Drugs to Mitigate Known Risks, Including Heart Rhythm Problems.” <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-reiterates-importance-close-patient-supervision-label-use>](https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or-)

Hydroxychloroquine is QT prolonging, which poses a risk of sudden cardiac death in certain populations.”¹⁶

As of press time, the latest research conducted in New York City finds no benefit in using HCQ in preventing the infection’s progression to intubation.¹⁷ Such mounting evidence, as well as the FDA warning, compelled Mount Sinai and other hospitals in New York City to stop using HCQ as a standard treatment for Covid-19 patients. As Dr. Thomas McGinn, deputy physician-in-chief at Northwell Health explains, “We know now it probably doesn’t help much. We’re not recommending it as a baseline therapy anymore.”¹⁸

7. WHAT OTHER APPROACHES ARE BEING SOUGHT?

Fighting a novel virus calls for as much innovation in response options as possible. To this end, researchers are looking at several mechanisms. Convalescent plasma is a very old technique that involves harvesting Covid antibodies from recovered patients and injecting them into infected ones. Going further in the direction of antibody harvest is the use of monoclonal antibodies, which provide the infected person with a pre-coded “guided missile” to attack the virus. As well, several companies are pursuing a therapy called “hyperimmunes,” which combines antibodies from numerous people to create a more powerful and broad-ranging serum. Researchers are also looking into stem cell therapies and various immune suppressants, as well as already available antivirals such as remdesivir, which failed against the Ebola virus and is highly toxic, but may show promise against Covid-19.¹⁹ These various mechanisms are undergoing testing already. On May 1, 2020, the FDA issued an EUA for remdesivir. A novel virus means the human population has

¹⁶ DeJong, Colette, MD and Robert M. Wachter, MD. “The Risks of Prescribing Hydroxychloroquine for Treatment of COVID-19—First, Do No Harm.” *Journal of the American Medical Association*, JAMA Network. <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2765360>

¹⁷ Geleris, Joshua et al. “Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19.” *New England Journal of Medicine*. https://www.nejm.org/doi/full/10.1056/NEJMoa2012410?query=RP&fbclid=IwAR0_yam7jJ8axuFJ0XLPtCUc7i9dTf1uho-3qR4yyMwBS5cwkLKQhQeM3OQ

¹⁸ Couza, Bobby. “Why Hospitals in New York City Have Abandoned Hydroxychloroquine.” May 7, 2020. <https://www.ny1.com/nyc/all-boroughs/news/2020/05/07/hospitals-in-nyc-abandon-hydroxychloroquine-treatment-touted-by-trump->

¹⁹ National Institutes of Health. “NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19.” News release. April 29, 2020.

no existing antibodies, so medical professionals and researchers are having to build the boat while at sea, so to speak.

PART 3

CONCLUSION

But for the vast majority of Covid-19 infections, patients will recover and resume their normal lives. This makes long-term side effects like irreversible retinal damage and heart rhythm problems a consideration in determining treatment options. But for those whose lives immediately hang in the balance, side effects, especially long-term ones, must take a back seat to living to fight again tomorrow. Emergency protocols such as emergency use authorization and compassionate use protocols bypass regulatory red-tape that can cost lives and allow patients, doctors and researchers to marshal all available options, while generating informative data for treatment of subsequent infections. Our approaches to defeating the coronavirus should be given the greatest degree of regulatory freedom possible, leaving life and death treatment options to the physicians and their patients.

ABOUT THE AUTHOR

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