Medical staff treat a patient with the novel coronavirus this month in Wuhan, China.

PHOTO: STR/AFP/GETTY IMAGES

IN DEPTH

INFECTIOUS DISEASES

Race to find COVID-19 treatments accelerates

WHO launches megatrial to test repurposed drugs and experimental drug candidates

By **Kai Kupferschmidt** *and* **Jon Cohen**

With cases of the new coronavirus disease 2019 (COVID-19) climbing steeply everywhere from Madrid to Manhattan, overwhelming one hospital after another and pushing the global death toll past 17,000, the sprint to find treatments has dramatically accelerated. Drugs that stop the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), could save the lives of severely ill patients, protect health care workers and others at high risk of infection, and reduce the time patients spend in hospital beds.

The World Health Organization (WHO) last week announced a major study to compare treatment strategies in a streamlined clinical trial design that doctors around the world can join. Other trials are also underway; all told, at least 12 potential COVID-19 treatments are being tested, including drugs already in use for HIV and malaria, experimental compounds that work against an array of viruses in animal experiments, and antibody-rich plasma from people who have recovered from COVID-19. More than one strategy may prove its worth, and effective treatments may work at different stages of infection, says Thomas Gallagher, a coronavirus researcher at Loyola University Chicago's Health Sciences Campus. "The big challenge may be at the clinical end determining when to use the drugs."

Researchers want to avoid repeating the mistakes of the 2014–16 West African Ebola epidemic, in which willy-nilly experiments proliferated but randomized clinical trials were set up so late that many ended up not recruiting enough patients. "The lesson is you start trials now," says Arthur Caplan, a bioethicist at New York University's Langone Medical Center. "Make it a part of what you're doing so that you can move rapidly to have the most efficacious interventions come to the front."

To that end, WHO on 20 March announced the launch of SOLIDARITY, an unprecedented, coordinated push to collect robust scientific data rapidly during a pandemic. The study, which could include many thousands of patients in dozens of countries, has emphasized simplicity so that even hospitals overwhelmed by an onslaught of COVID-19 patients can participate. WHO's website will randomize patients to local standard care or one of the four drug regimens, using only ones available at the patient's hospital. Physicians will simply record the day the patient left the hospital or died, the duration of the hospital stay, and whether the patient required oxygen or ventilation. "That's all," says Ana Maria Henao Restrepo, a medical officer at WHO's Department of Immunization Vaccines and Biologicals.

The design is not blinded: Patients will know they received a drug candidate, and that could cause a placebo effect, Henao Restrepo concedes. But it is in the interest of speed, she says. "We are doing this in record time." The agency hopes to start to enroll patients this week.

Rather than taking years to develop and test compounds from scratch, WHO and others want to repurpose drugs that are already approved for other diseases and have acceptable safety profiles. They're also looking at experimental drugs that have performed well in animal studies against the other two deadly coronaviruses, which cause SARS and Middle East respiratory syndrome (MERS). And they are focusing on compounds plentiful enough to treat a substantial number of patients.

For its study, WHO chose an experimental antiviral called remdesivir; the malaria medication chloroquine (or its chemical cousin hydroxychloroquine); a combination of the HIV drugs lopinavir and ritonavir; and that combination plus interferon-beta, an immune system messenger that can help cripple viruses. The treatments would stop the virus by different mechanisms, but each has drawbacks.

Remdesivir, developed by Gilead Sciences to combat Ebola and related viruses, shuts down viral replication by inhibiting a key viral enzyme, the RNA polymerase. It didn't help patients with Ebola in a test during the 2019 outbreak in the Democratic Republic of the Congo. But in 2017, researchers showed in test tube and animal studies that the drug can inhibit the SARS and MERS viruses.

The drug, which is given intravenously, has been used in hundreds of COVID-19 patients in the United States and Europe under what's known as compassionate use, which required Gilead to review patient records; some doctors have reported anecdotal evidence of benefit, but no hard data. Gilead says it is now starting to supply remdesivir under a simpler "expanded use" designation. Five other clinical trials underway in China and the United States are testing it and may have preliminary results soon. Of the drugs in the SOLIDARITY trial, "remdesivir has the best potential," says Shibo

Jiang of Fudan University, who works on coronavirus therapeutics.

Like most drugs for acute infections, remdesivir may be much more potent if given early, says Stanley Perlman, a coronavirus researcher at the University of Iowa—and that could be a challenge. "What you really want to do is give a drug like that to people who walk in with mild symptoms," he says. "And you can't do that because it's an [intravenous] drug, it's expensive, and 85 out of 100 people don't need it" because they won't develop severe disease.

Chloroquine and hydroxychloroquine have received intense attention because of positive results from small studies and an endorsement from President Donald Trump, who said, "I feel good about it." The drugs decrease acidity in endosomes, compartments that cells use to ingest outside material and that some viruses co-opt during infection. But SARS-CoV-2's main entryway is different: It uses its so-called spike protein to attach to a receptor on the surface of human cells. Studies in cell culture have suggested chloroquine can cripple the virus, but the doses needed are usually high and could cause severe toxicity. "Researchers have tried this drug on virus after virus, and it never works out in humans," says Susanne Herold, an expert on pulmonary infections at the University of Giessen.

Results from COVID-19 patients are murky. Chinese researchers who treated more than 100 patients touted chloroquine's benefits in a letter in *BioScience*, but they did not publish data. And WHO says "no data has been shared" from more than 20 other COVID-19 studies in China using chloroquine or hydroxychloroquine. French microbiologist Didier Raoult and colleagues published a study of hydroxychloroquine in 20 COVID-19 patients that concluded the drug had reduced viral load in nasal swabs. (It seemed to work even better with the antibiotic azithromycin.) But the trial, reported in the *International Journal of Antimicrobial Agents*, was not randomized, and it didn't report clinical outcomes such as deaths.

Hydroxychloroquine might actually do more harm than good. It has many side effects and can, in rare cases, harm the heart—and people with heart conditions are at higher risk of severe COVID-19, says David Smith, an infectious disease physician at the University of California, San Diego. "This is a warning signal, but we still need to do the trial," he says. There have also been reports of chloroquine poisoning in people who self-medicated.

Many coronavirus researchers are similarly skeptical of the lopinavir-ritonavir combination. Abbott Laboratories developed the drugs to inhibit the protease of HIV, an enzyme that cleaves a long protein chain during assembly of new viruses. The combination has worked in marmosets infected with the MERS virus, and has also been tested in patients with SARS and MERS, though those results are ambiguous. But the first trial with COVID-19 was not encouraging. When doctors in Wuhan, China, gave 199 patients standard care with or without lopinavir-ritonavir, the outcomes did not differ significantly, they reported in *The New England Journal of Medicine* on 15 March. The authors say the patients were very ill and treatment may have started too late.

The fourth arm of SOLIDARITY combines these two antivirals with interferon-beta, a molecule involved in regulating inflammation that has lessened disease severity in marmosets infected with MERS. But interferon-beta might be risky for patients with severe COVID-19, Herold says. "If it is given late in the disease it could easily lead to worse tissue damage, instead of helping patients," she cautions.

SOLIDARITY is designed to provide a quick, useful verdict, based on the outcomes that are the most relevant for public health, says virologist Christian Drosten of the Charité University Hospital in Berlin. More detailed data could come from an add-on trial in Europe, announced on 23 March by the French biomedical research agency INSERM. To include 3200 patients, it will test the same drugs, including hydroxychloroquine but not chloroquine, and collect additional data such as blood gas levels or lung imaging.

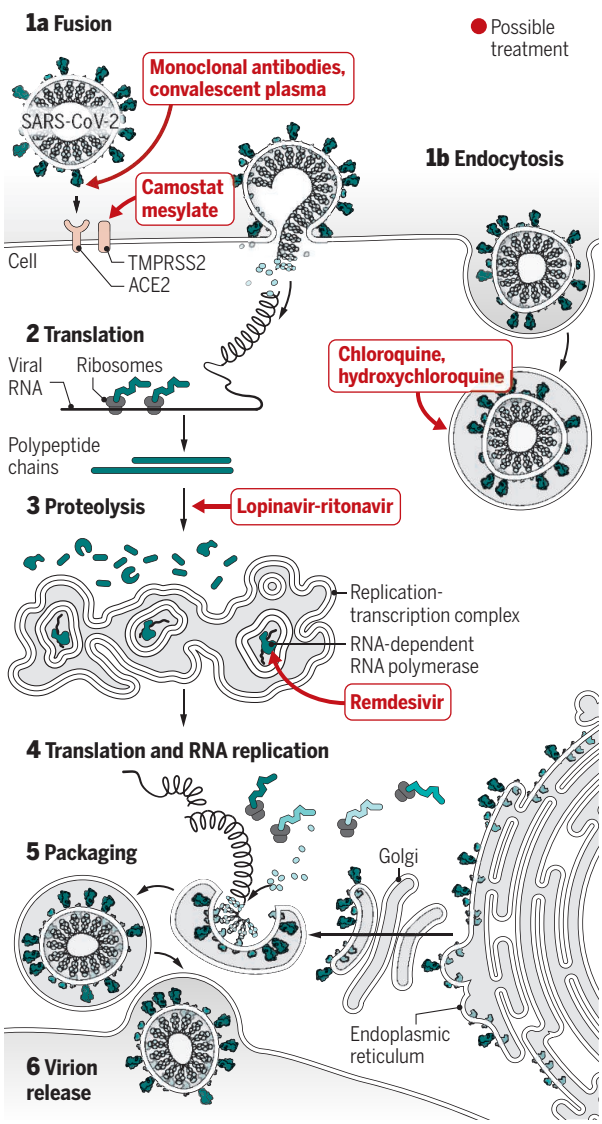
Other approved and experimental treatments are in testing against coronavirus or likely soon to be. They include drugs that can reduce inflammation, such as corticosteroids and baricitinib, a treatment for rheumatoid arthritis. Some researchers have high hopes for camostat mesylate, a drug licensed in Japan for pancreatitis, which inhibits a human protein involved with infection. Other antivirals will also get a chance, including the influenza drug favipiravir and additional HIV antiretrovirals. Researchers also plan to try to boost immunity with "convalescent" plasma from recovered COVID-19 patients or monoclonal antibodies directed at SARS-CoV-2.

Perlman says the smartest way to test the drugs is in people in early stages of disease who doctors think are most likely to get much worse. How would you determine that? "That is the key question," he says. Researchers might find a biomarker in blood that helps them predict disease course.

Crucially, doctors and researchers around the world are tackling the problem with urgency, Henao Restrepo says. "This is a crisis like no other and we will have to work together," she says. "That is the only way perhaps we are going to find a solution." ■

Lines of attack

Experimental treatment strategies attempt to interfere with different steps (numbered) in the coronavirus replication cycle.



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