

**- Virus**

## The latest in COVID-19 treatment

Here are the new medicines at the forefront in the fight against COVID

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Since the original SARS coronavirus was first discovered in February 2003, scientists have been hard at work looking for effective treatments against deadly coronaviruses. The first promising treatments included convalescent plasma, which is basically serum-containing antibodies from people who had successfully recovered from the disease. A host of different antivirals were being studied, but SARS fizzled out after a few months and completely disappeared in a little over a year, and so proper clinical trials could not proceed. Nevertheless, scientists continued to work on some promising antiviral agents. When the MERS coronavirus showed up in 2012, some of these medications were tried but none showed any promise. MERS has continued to have low level outbreaks of a few hundred cases per year, but antivirals have been difficult to test with such small numbers.



Ever since SARS-CoV-2 emerged in 2020, many drugs have been tested against it. Some were brand new molecules while others were repurposed. Treatments against COVID-19 work through two major mechanisms: antiviral drugs that kill the virus, and immunomodulatory drugs that limit the damage from the inflammation caused by the virus. A third category, monoclonal antibodies, which directly bind to the virus, is already being used in other countries like the US but has not yet made it to the Philippines.

### Antivirals

Antivirals are drugs that kill the SARS-CoV-2 virus. They can do this using one of several mechanisms that disrupt the viral life cycle. Some drugs prevent entry of the virus into the host cells, some interfere with enzymes that are essential for the virus to reproduce, while others introduce defective building blocks into the viral genetic material. Some of the earliest antivirals that were tried against SARS-CoV-2 were hydroxychloroquine and lopinavir-ritonavir. Hydroxychloroquine seemed to interfere with multiple life processes of the virus when used in the laboratory. This did not pan out in real life, however, and some people developed irregular heart rhythms from the drug. Lopinavirritonavir is a repurposed drug used against HIV that interferes with the RNA-dependent RNA polymerase (RdRp), an enzyme that the virus uses to replicate its genetic material. Early studies failed to show any beneficial clinical efficacy as well.

Some antivirals, which were originally used for the influenza virus, have also been tried. Favipiravir is one of these drugs. It has shown some promise if used in moderate COVID-

19. The two most prominent antivirals at the moment are remdesivir and molnupiravir.

### Remdesivir

Remdesivir is the first antiviral to show clinical efficacy against COVID-19. It has had its share of controversies since it does not seem to consistently prevent deaths from COVID-19. It was approved in the US on the basis of its apparent ability to shorten the time to recovery of patients with severe COVID-19 by about five days. A large clinical trial done, however, in different countries that was sponsored by the World Health Organization (WHO) did not show a decrease in deaths and so it was not recommended for use by the WHO.

Subsequent results from other clinical trials showed that remdesivir works best when used early in patients with worsening COVID-19. Its benefit in patients who do not require oxygen is unclear, and those on mechanical ventilators are also less likely to respond. The use of remdesivir therefore needs to be tailored to a “sweet spot,” i.e., sick enough to require oxygen but not sick enough to have critical COVID-19. This variable effect depending on disease status has made it much more difficult to study. A recent paper has shown a significant decrease in risk of death if remdesivir is given before seven days from symptom onset, but not much benefit if it is started late.

Remdesivir is currently only for compassionate use in the Philippines and needs to be given in a hospital setting. Being the only COVID-19 antiviral medication with significant evidence of efficacy, most infectious diseases doctors and pulmonologists will use this drug in patients with severe COVID-19. Side effects include occasional liver enzyme elevation, otherwise it is well-tolerated.

### Molnupiravir

Molnupiravir is an upcoming treatment that recently made headlines when it was shown to substantially decrease the risk of hospitalization from COVID-19 in vulnerable populations. Molnupiravir is a drug that works by mimicking the building blocks of viral genetic material, introducing errors during replication and stopping the virus in its tracks. Molnupiravir is taken as a pill, which makes it much easier to give than remdesivir, which is given intravenously. Early studies on molnupiravir in hospitalized patients with severe COVID-19 failed to show a significant effect. When used in confirmed COVID-19 patients with mild disease but with a high risk for progression to severe disease, however, molnupiravir reduced the risk of hospitalization by 50 percent compared with the control group. There were no deaths in the molnupiravir arm and eight deaths in the placebo arm. This data is from a phase 3 clinical trial in outpatients who were unvaccinated. It is not yet peer-reviewed or published. Per the report, the data was so compelling that the investigators stopped the trial early since it was already clear that the drug was going to save lives. It remains to be seen whether the data will stand up to scrutiny and will be approved for use by the US FDA. If the study results are confirmed, molnupiravir will be a valuable addition to the arsenal we use to treat COVID-19. The trick will be to identify patients who will benefit from it early enough so that they won't require hospitalization.

### Immunomodulators

These are drugs that limit the damage that SARS-CoV-2 does to the target organs, particularly the lungs. In patients who develop severe COVID-19, the body overreacts and cannot

reign in its inflammatory response even after the virus has been defeated. To help the body calm down, steroids and other anti-cytokine treatments are used.

### Steroids

The very first treatment that was shown to decrease the risk of dying was dexamethasone. This drug was used in patients with severe COVID-19. It has been found to cut the risk of dying in half. It did not have a beneficial effect on those who did not require oxygen. Other steroids like hydrocortisone and methylprednisolone have also been shown to help. It is not advisable to use steroids without proper medical evaluation as these can increase the risk of acquiring infections, and can have undesirable metabolic side effects when used inappropriately.

### Anti-cytokine treatments

Tocilizumab is a monoclonal antibody against the inflammatory cytokine interleukin 6 (IL-6). Monoclonal antibodies are antibodies mass-produced in a laboratory, designed to bind to a specific substance, in this case a mediator of inflammation. Tocilizumab was shown to decrease the risk of progression of disease in severe COVID-19 patients. It works by blocking IL-6, which is a key cytokine in the pathophysiology of COVID-19. It is best combined with steroids for maximum effect. Tocilizumab is quite expensive. It can cause immune suppression and so should only be given at the direction of a properly trained and experienced doctor. Baricitinib is a Janus Kinase (JAK) inhibitor, which interferes with activation of IL-6. It can be used as a substitute for tocilizumab. It is a pill, indicated for the same types of patients as tocilizumab. Similar to tocilizumab, it should be used in combination with dexamethasone or another steroid.

Anti-SARS-CoV-2 monoclonal antibodies are not yet available in the Philippines but have been shown to be effective in some populations at high risk for severe COVID-19. These anti-SARS-CoV-2 monoclonal antibodies include bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab. Very expensive, these are in short supply globally. These drugs are expected to become available in the near future but will likely be targeted at very specific patients.

The best and most effective intervention against COVID-19 is still vaccination. Vaccination continues to protect very well against severe disease, despite reports of more breakthrough infections from the Delta variant. Getting vaccinated means that the probability of any of the medications discussed above being needed is much, much lower. It is comforting to know, however, that even if the virus somehow still gets through and causes severe disease, there are now very effective treatments that are available. These medicines when used properly give us a much better fighting chance at surviving COVID-19 and making a full recovery.

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