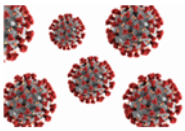


# COVID-19 Treatment

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## Introduction

The research pipeline of potential treatments for COVID-19 comprises over a thousand clinical trials that cannot feasibly all be detailed here (see available online tracking tools and the excellent summary page from *STAT News*). As outlined in an article in *STAT News*, there is a lack of overall coordination and many studies are small in size and unlikely to offer conclusive data on the efficacy of the interventions being assessed.

The responsibility for generating sufficiently robust results to alter clinical care for people with COVID-19 has fallen on a handful of large research programs, most prominently the RECOVERY trial being conducted in the United Kingdom. Additional significant efforts include the World Health Organization's Solidarity trial and the U.S. government sponsored Adaptive COVID-19 Treatment Trial 2 (ACTT-II).

## Antiviral Drugs

Most pharmaceutical interventions—drugs—are usually small molecule inhibitors of specific proteins. It's usually proteins that carry out functions for a cell or virus, including structural functions like viral particle assembly or catalytic functions like facilitating needed chemical reactions.

Small molecules are smaller than proteins, DNA, or RNA, around the size of biological molecules like hormones and vitamins. This makes the small molecules more bioavailable, or able to be taken up via ingestion or injection into cells and tissues.

While some drugs are proteins (like the antibody molecule infliximab/Remicade) or peptides (small proteins, like insulin), most antiviral medications are small molecules. These drugs typically specifically inhibit a viral protein that isn't conserved in human cells (viral proteins that act unlike human proteins).

For example, a number of HIV drugs inhibit the viral reverse transcriptase enzyme that's needed to copy its genetic material. Human cells do not have reverse transcriptase, which reduces the potential for drug toxicity. Other HIV drugs inhibit the viral protease that's required to create functional HIV proteins in the cell. The influenza drug Tamiflu—

oseltamivir phosphate—is a specific inhibitor of neuraminidase, a protein enzyme the flu virus needs to bud, or leave, cells. Sofosbuvir, a drug for hepatitis C, blocks the action of NS5B, a protein needed to copy the virus' genes for efficient viral replication. If a drug can block viral replication or budding or a protease the virus needs and the virus can't copy itself, the immune system may eventually clear or control the virus. For HIV and herpes viruses, drugs are required consistently to keep viral replication in check, whereas other viruses—like hepatitis C—can be cured.

**SARS-CoV-2 Drug Targets**

SARS-CoV-2, the cause of COVID-19, is a novel coronavirus that emerged into humans in late 2019. Coronaviruses are single-stranded RNA viruses that bind to a receptor on the human cell's surface, release an infectious RNA molecule into the cell, and replicate entirely in the cell's cytoplasm. This implies that all the activities that would normally occur in a cell's nucleus—where the genetic material of the cell, its DNA, is kept—must be performed by viral machinery.

Coronaviruses therefore have several targets for antiviral therapy: the enzymes they use to copy and transcribe their RNA (RNA-dependent RNA polymerase); the machinery needed to cleave proteins into their functional units (proteases); and other enzymes the virus needs to replicate, including RNA capping enzymes and the spike protein needed to bind to cells. All of these unique viral enzymes are good targets for small molecule inhibitors that may be effective against SARS-CoV-2.

In addition to these virus-specific therapeutic targets, the immune system response to SARS-CoV-2 infection can be modulated by a large number of additional drugs. Severe disease initially seemed to correlate with immune system overactivation (sometimes called a 'cytokine storm'), and many immunomodulators, particularly immunosuppressants, are in use to treat hospitalized COVID-19 patients.

**FDA-Approved Drugs**

SARS-CoV-2 spread worldwide within the first few months of human-to-human transmission, infecting millions and killing hundreds of thousands. The rapid need to develop therapeutics led scientists to initially test drugs that were already approved by the U.S. Food and Drug Administration (FDA) for safe use in human patients, also called drug repurposing.

The process of drug development through FDA approval takes 12 years on average, although review can be expedited in emergency cases. Even in the most rapid case, many months or a year would be needed to test a drugs' safety before beginning trials to see whether the drug is efficacious in treating COVID-19.

For these reasons, the first drugs tested in people with COVID-19, the first therapeutics chosen for large-scale clinical trials, and the first libraries of small molecules tested against SARS-CoV-2 replication in cells were all drugs with previous FDA approval for use in humans (either for research or full approval for marketing).

**Remdesivir**

Remdesivir is a small molecule drug developed to treat hepatitis C by inhibiting the RNA polymerase the virus uses for replication. After failing to block hepatitis C virus replication, it was added to a screen for use against other viral pathogens. Researchers at Gilead Sciences, the U.S. Centers for Disease Control and Prevention (CDC), the U.S. National Institutes of Health, and U.S. Army Medical Research Institute of Infectious Diseases found potent antiviral activity against the Ebola virus. Remdesivir inhibits the RNA dependent RNA polymerase the virus uses to copy its genome.

The bioavailability of the chemical precursor of remdesivir was low. Low bioavailability—the ability of a drug to be soluble and accessible in a patient's cells where the virus is active—can prevent even a potent antiviral molecule from becoming a viable therapy in patients. To increase the bioavailability of the small molecule, researchers at Gilead developed a pro-drug, which is a molecule that is altered by the metabolism of a cell into its active form. The drug is therefore only active after being taken up by cells.

Remdesivir is the resulting pro-drug. It completed phase I and phase II clinical trials, demonstrating safety, but—after years of development—it did not show efficacy as a treatment for Ebola virus.

Research by the EcoHealth alliance studying coronaviruses in bat reservoirs led to researchers testing remdesivir against the human coronaviruses SARS-CoV-1 and MERS, in addition to novel bat coronaviruses in 2017, before the emergence of SARS-CoV-2. Remdesivir showed potent antiviral activity against all these coronaviruses *in vitro*. Upon sequencing of SARS-CoV-2, the virus is clearly related to bat coronaviruses.

Remdesivir was therefore considered a likely therapeutic intervention against SARS-CoV-2. It had been FDA approved for human testing and showed potent activity directly against SARS-CoV-2 *in vitro*.

Doctors treating COVID-19 patients began using remdesivir on a compassionate use/expanded access basis early in the COVID-19 pandemic, outside of clinical trials. Gilead released results from 53 patients treated with the drug under compassionate use guidelines,

A study in non-human primates showed significantly reduced viral loads of SARS-CoV-2 and less severe illness after remdesivir treatment. Initial anecdotal results prompted qualified hope and the upscaling of large-scale clinical trials with randomized control arms.

The U.S. National Institute of Allergy and Infectious Diseases (NIAID) sponsored the largest randomized controlled trial of remdesvir versus placebo completed to date, the Adaptive COVID-19 Treatment Trial 1 (ACTT-I). The target population was adults hospitalized with COVID-19 who had evidence of lower respiratory tract involvement. After an initial controversial announcement of the results on April 29, 2020 that contained little information, a more detailed "preliminary report" was published in the *New England Journal of Medicine* on May 22, 2020.

Among 1,059 participants (538 randomized to remdesivir and 521 to placebo), remdesivir was associated with a slight but statistically significant improvement in recovery time: 11 days compared to 15 days for placebo recipients. There was a trend toward a reduction in the risk of death but it did not reach statistical significance, with Kaplan-Meier estimates of mortality by 14 days of 7.1% in the remdesivir arm and 11.9% in the placebo arm. The hazard ratio for death in the remdesivir arm compared to placebo was 0.70 with a 95% confidence interval (CI) of 0.47 to 1.04. The 95% CI is a measure of the uncertainty around a result and for statistical significance to be achieved the upper bound would have to be less than 1.

The ACTT-I trial administered a 200 mg loading dose of remdesivir on day one followed by 100 mg daily for up to nine additional days, or placebo for up to 10 days. Rates of adverse events were similar between the arms. The most common grade 3 or 4 adverse event among remdesivir recipients were anemia or decreased hemoglobin and kidney toxicities.

Another trial in China with a placebo arm found a non-significant effect of remdesivir use on the duration of COVID-19 symptoms, but was stopped early because declining numbers of local COVID-19 cases precluded meeting the original enrollment target.

Published results from research sponsored by Gilead (the SIMPLE study) demonstrated that the use of remdesivir lead to statistically significant improvement in symptom severity after a five-day course of treatment compared to placebo, with the response to a ten-day course of treatment with remdesivir nearing but not reaching statistical significance. There was no increase in adverse effects compared to the control group in this study.

On May 1, 2020, the FDA issued an Emergency Use Authorization for the use of remdesivir to treat COVID-19, based on the preliminary results of ACTT-I and the Gilead sponsored study.

To date, no high-quality trial has yet found a significant impact of remdesivir use on the likelihood of death in mild, moderate, or severe disease. Furthermore, there are no data demonstrating effectiveness of remdesivir in mild or moderate COVID-19.

Remdesivir is so far only available as an intravenous injection and not as a soluble pill. Gilead has initiated a trial of an inhaled solution as a possible approach to outpatient treatment of COVID-19 with the drug.

On August 10, 2020, Gilead filed a new drug application with the FDA seeking approval of remdesivir (trade name Veklury) for the treatment of COVID-19.

**Antiretroviral Drugs**

Some researchers have proposed repurposing certain antiretroviral drugs as COVID-19 treatments based on limited evidence of their potential to inhibit SARS-CoV-2 replication derived from laboratory and modeling studies. The FDA-approved protease inhibitor lopinavir/ritonavir (Kaletra) has been the most extensively tested candidate in clinical trials, but the accumulated results have definitively ruled out any benefits. The first indication was a small study published in the *New England Journal of Medicine* but more recently the

RECOVERY trial and WHO Solidarity trial have both announced the discontinuation of lopinavir/ritonavir arms due to lack of efficacy.

A growing number of reports in the scientific literature indicate that people with HIV experience COVID-19 outcomes similar to comparable HIV-negative individuals, with little evidence of any preventative or disease-modulating effects of antiretrovirals. There are some exceptions, including a cohort analysis suggesting tenofovir/emtricitabine (Truvada) may have had a protective effect against severe outcomes in 21 people with HIV (compared to people with HIV receiving other antiretrovirals). However, the numbers involved are small and there is a strong likelihood that confounding factors could explain the result. A study testing Truvada as pre-exposure prophylaxis (PrEP) against COVID-19 in healthcare workers is ongoing in Spain.

**Hepatitis C Drugs**

The combination of sofosbuvir and daclatasvir, two approved hepatitis C drugs, is being investigated in several COVID-19 trials in Iran (where a locally produced combination pill with the trade name *Sovodak* is the recommended first-line treatment for hepatitis C). Sofosbuvir is a nucleotide inhibitor of viral RNA polymerase while daclatasvir inhibits the hepatitis C NS5A protein. A study indicating both drugs have activity against SARS-CoV-2 is available in preprint form (meaning it has not yet undergone peer review).

Preliminary results from the Iranian trials were reported at the 2020 IAS COVID-19 Virtual Conference. The presentation offered limited evidence of faster recovery and reduced mortality in a relatively small number of participants. A 600-person double-blind, placebo-controlled trial named DISCOVER is underway with the aim of providing definitive information on the efficacy of the combination—results are anticipated in September 2020.

For background on the research effort to develop sofosbuvir and daclatasvir as potentially cheap treatments for COVID-19, see Terri Wilder's interview with Andrew Hill for TheBodyPro.com.

**Hydroxychloroquine**

Early in the COVID-19 pandemic, there were reports from small clinical studies that the antimalarial drug hydroxychloroquine was an effective treatment, alone or in combination with an antibiotic such as azithromycin. Hydroxychloroquine modulates the immune system by increasing the pH of lysosomes in cells, decreasing their activity. Early hypotheses about COVID-19 suggested that altering the biology of lysosomes in this way may inhibit SARS-CoV-2.

The addition of azithromycin, a potent antibiotic and common treatment for bacterial pneumonia, was thought to be useful to help clear or keep clear secondary bacterial infections in the lung. Azithromycin may also accumulate in endosomes to block viral entry and/or modulate the host immune response.

Along with remdesivir, early studies showed that chloroquine and hydroxychloroquine inhibited SARS-CoV-2 infection in Vero cells. Fluorescent microscopy showed an inhibition

of viral entry, in agreement with the hypothesis that these molecules block SARS-CoV-2's use of the cell's lysosomes to infect the cell.

The off-label use of hydroxychloroquine for COVID-19 treatment became routine in critical care situations. However, as soon as larger clinical trials with control groups were published or the original data were reanalyzed, it became clear that hydroxychloroquine did not decrease the likelihood of death or shorten the duration of symptoms.

The hydroxychloroquine arms of both the RECOVERY trial and WHO Solidarity trial have been terminated due to lack of benefit. The FDA has revoked the Emergency Use Authorization allowing hydroxychloroquine use to treat SARS-CoV-2 infections in the United States.

**Monoclonal Antibodies (mAb, Neutralizing Antibodies)**

Antibodies—Y-shaped proteins that are produced by the host adaptive immune system in response to infection—can bind to and neutralize a pathogen upon reinfection. Many vaccines function by raising a specific antibody response to a virus or bacteria without requiring infection, thus leading to protection.

Using current biomedical technologies, antibodies against a pathogen can be isolated from humans or animal models, including mice, sheep, cows, llamas, rats, and rabbits. Polyclonal antibodies include a complex mix of antibodies against a specific antigen—a portion of a virus or bacteria. Monoclonal antibodies require the selection of one specific antibody—ideally one that has strong neutralizing capabilities against the antigen—and its production in a cell line.

In the absence of a viable SARS-CoV-2 vaccine, it may be possible to produce antibodies *in vitro*, in a lab, that could be injected into patients to neutralize the virus and prevent its activity.

Early in the COVID-19 pandemic, scientists solved the structure of the spike protein, which sits on the SARS-CoV-2 outer membrane and is required for cellular entry. The spike protein is a target of the host immune response and blocking its activity may inhibit infection. Researchers have reported that polyclonal antibodies against the spike protein prevented infection in a cell-based model. Subsequent work demonstrated that a monoclonal antibody could bind to the spike protein and prevent infection in a cell-based model. Other reported monoclonal antibodies block the binding of the spike protein to its cellular receptor (ACE2) altogether.

Several clinical trials currently listed in clinicaltrials.gov are evaluating the use of monoclonal antibodies blocking the spike protein in treating COVID-19. The company Regeneron Pharmaceuticals is sponsoring mid-stage treatment trials of a monoclonal antibody cocktail and plans to launch a phase III evaluation of the preventive efficacy of the antibodies in adult household contacts of individuals who have tested positive for SARS-CoV-2. Researchers have published a preprint describing evidence of efficacy of these antibodies in macaque and ferret models. The Regeneron product has been added the RECOVERY trial protocol in the U.K.

The NIH is initiating multiple studies of LY-CoV555, a monoclonal antibody against the SARS-CoV-2 spike protein developed by Eli Lilly and Company in collaboration with AbCellera. The treatment trials include ACTIV-2, which will investigate outpatient administration, and ACTIV-3 for people hospitalized with COVID-19. The preventive efficacy of LY-CoV555 will be assessed in a phase III trial conducted in partnership with the NIH's COVID-19 Prevention Network (CoVPN). The target populations are residents and staff at long-term care facilities in the U.S.

On September 16, 2020, Eli Lilly and Company issued a press release stating that LY-CoV555 administration significantly reduced the risk of hospitalization or emergency room visits in people with mild to moderate COVID-19 in a phase II clinical trial (BLAZE-1). The results are not yet published.

A partnership between the biotechnology company Vir and GlaxoSmithKline is initiating an efficacy study of a monoclonal antibody, VIR-7831, in people with early symptomatic COVID-19. Approximately 1,300 participants will be enrolled and the primary endpoint is prevention of hospitalization.

Alex Renn and colleagues have published a helpful open access summary of the antibody pipeline (as of July 28, 2020) in *Trends in Pharmacological Sciences*.

Monoclonal antibodies are expensive and difficult to produce, particularly at large scale. Whether this will limit their use for COVID-19 treatment and prevention is unclear. On August 10, 2020, IAVI and the Wellcome Trust issued a timely report outlining issues that will need to be addressed to expand global access to monoclonal antibody-based products.

**Convalescent Plasma**

People with COVID-19 also produce antibodies against the virus as part of their immune response. While the levels of various antibodies (IgA, IgG, and IgM) vary widely between individuals, current research shows that most or all people with COVID-19 eventually seroconvert. Seroconversion describes the ability to detect antibodies against a virus, a clear, molecular marker that someone has been infected with SARS-CoV-2.

People with COVID-19 show remarkably different levels not only of antibodies, but of neutralizing antibodies. Not all antibodies bind to and block viral infection equally. They may target different portions of the spike protein or other proteins, and some of these interactions may not have an impact on the ability of the virus to infect cells. Researchers are working to better understand the reasons for the different levels of antibodies and neutralizing antibodies between individuals.

Early in the COVID-19 epidemic, doctors hypothesized that plasma from people who had recovered from the disease (convalescent plasma) may be a viable treatment. Plasma is a blood product with the cells and clotting factors removed. It's easy to make from blood samples and contains the antibodies circulating in an individual.

Small studies on the SARS-CoV-2 virus suggested a significant use of convalescent plasma to shorten hospital stay and decrease mortality.

Convalescent plasma has been used to tread COVID-19 in countries around the world. Some researchers, but not all, are testing the plasma's ability to neutralize SARS-CoV-2 before use. In early 2020, very small studies (involving 10, six, and five participants, most severely ill) described a potential benefit of this treatment. No large-scale clinical trial data are currently available for the treatment of COVID-19 with convalescent plasma. Many trials are underway.

On August 23, 2020, convalescent plasma became the latest COVID-19 therapeutic candidate to be dishonestly politicized by the Trump administration (on the eve of the Republican National Convention). Despite extremely limited data, which includes no positive findings from randomized, controlled clinical trials, the FDA announced the issuance of an Emergency Use Authorization. The FDA press release used wildly inappropriate language lauding the current administration and referring to the therapy as "promising." Even worse, the FDA commissioner Stephen Hahn joined other administration spokespeople in lying egregiously to the public about a "35% mortality reduction" reported in a retrospective, observational analysis of convalescent plasma recipients.

The analysis is contained in preprint paper authored by proponents of convalescent plasma, which has not been peer reviewed. Among over 35,000 people with COVID-19 who received convalescent plasma through an expanded access program, a small subset had information available on levels of antibodies in the plasma prior to administration. An exploratory analysis comparing 515 recipients who received plasma with "high" antibody levels to 561 recipients with "low" antibody levels found that mortality was lower in the former group after seven days (relative risk of 0.65 with a wide confidence interval of 0.47-0.92) and, to a lesser extent, after 30 days (relative risk of 0.77 with a confidence interval of 0.63-0.94).

The relative risk of 0.65 at day seven is the source of the false claim of a 35% reduction in mortality. The claim is false because:

- It only relates to a small subset of people who received convalescent plasma containing antibody levels the researchers defined as "high," and thus it cannot in any way be applied to all recipients of convalescent plasma. This gives the lie to the statement that 35 out of every 100 recipients of convalescent plasma would survive COVID-19 due to the treatment. This false statement has been made by Stephen Hahn, FDA commissioner, Michael Caputo, the spokesperson for the Department of Health and Human Services (DHHS), and Emily Miller, the FDA spokesperson.
- The comparison isn't with a control group that didn't receive convalescent plasma, but with a group that received plasma containing antibody levels the researchers defined as "low." There could be many differences between these groups with the potential to affect mortality outcomes that the researchers didn't capture (referred to as confounding variables, the bane of observational studies).

Randomized controlled clinical trials remain the only means to assess if convalescent plasma confers any benefits to people with COVID-19. Conducting these trials has been

logistically challenging, and the premature granting of an Emergency Use Authorization by FDA will only make the task more difficult.

**Immunomodulating Drugs for Severe COVID-19**

In severe cases of COVID-19, clinicians rapidly noted a dysregulation of the immune system, with an apparent overreaction of the host response that correlates with bad disease outcomes, including death. This is often referred to as a 'cytokine storm,' as cytokines are small protein effectors of the immune response, and many cytokines are potent activators of innate and adaptive immune cells.

Cells of the innate immune system, such as macrophages, dendritic cells, natural killer cells, and mast cells respond to general signals of viral or bacterial infection. Adaptive immune cells, such as T-cells and B-cells, are selected upon infection with a virus or bacteria to respond specifically to that infectious agent.

The exact nature of the immune reaction and overreaction to SARS-CoV-2 is still a new field and little molecular detail currently exists. It's clear that immunocompromised individuals are at greater risk for severe disease, a seeming contradiction for an overreaction of the immune system. However, it appears that a strong immune response may prevent viral replication early in infection (particularly a T-cell response, potentially due to cross reactivity from other human coronaviruses). In the absence of this robust response, sufficient SARS-CoV-2 replication in the lungs, as well as other organs, promotes the multi-system immune overreaction that is deadly in many patients.

It's therefore critical to note that immunosuppressants are unlikely beneficial in cases of mild or moderate COVID-19 and would be contraindicated as pre-exposure prophylaxis (PrEP) for healthy individuals.

Clinicians started treating these severe COVID-19 cases with immunosuppressants off label in early 2020. These drugs include corticosteroids such as hydrocortisone and dexamethasone, IL-6 inhibitor tocilizumab, IL-1 inhibitor anakinra, and JAK/STAT inhibitors such as jakotinib hydrochloride and ruxolitinib.

**Dexamethasone and Other Corticosteroids**

Dexamethasone is a low-cost corticosteroid steroid anti-inflammatory drug. This class of drug has a general suppressive effect on the immune system and is used to treat a wide variety of allergies and autoimmune diseases.

In a large-scale well-controlled clinical trial at Oxford University, low-dose dexamethasone significantly decreased the incidence of mortality in people with severe COVID-19. The decrease in mortality was one third in patients on ventilators and 20% for those receiving oxygen. There was no effect (and possibly some evidence of harm) in milder patients who were not receiving oxygen, indicating that the drug is only an appropriate intervention for more advanced cases. Dexamethasone was dosed at 6mg once per day and given either by pill or IV. At the time of writing, it is the only medication that has shown a significant effect on mortality in any clinical trial worldwide.

Other corticosteroids including prednisone and hydrocortisone are being routinely used both off label and in clinical trials for severe COVID-19.

**ACE Inhibitors**

Angiotensin-converting enzyme (ACE) inhibitors represent another example of FDA approved drugs being repurposed and tested against COVID-19. Primarily used to treat high blood pressure (hypertension) and heart disease, there were initially concerns that ACE inhibitors might exacerbate COVID-19 due to upregulating expression of the ACE2 receptor that the SARS-CoV-2 virus uses to infect cells. However, researchers have since proposed a countervailing hypothesis that ACE inhibitors may help counteract lung-damaging effects of ACE2 receptor downregulation induced by SARS-CoV-2. A review of the evidence by WHO found no cause to recommend that individuals currently receiving ACE inhibitors alter their treatment in response to the COVID-19 pandemic.

Observational studies in the U.S., United Kingdom, and China have suggested that ACE inhibitors may be associated with reduced COVID-19 disease severity (particularly among seniors), and several studies are more rigorously testing their effects including placebo-controlled trials of ramipril at the University of California, San Diego and inhaled captopril at Hôpitaux de Paris in France.

**IL Blockers**

Interleukins (IL) are a family of small protein cytokines that can activate or suppress the immune response. Activating ILs, such as IL-1, IL-2, and IL-6 have secondary effects that induce inflammation. These molecules can promote autoimmune disorders, and researchers have therefore developed inhibitors of their activity.

ILs are secreted by immune cells and bind to receptors on other cells to mediate their activation of the immune system. Antagonists are molecules or proteins that bind to a protein and block its activity, usually by preventing an interaction between a protein and its receptor or binding partner. IL-modulating drugs work by acting as antagonists to the IL receptors, therefore preventing full immune activation upon cytokine release.

Tocilizumab is a monoclonal antibody that binds to and blocks the receptor for IL-6. Tocilizumab was genetically modified to be long lasting and is administered only by intravenous injection. Clinicians have reported small, uncontrolled, cohort and observational studies in severe COVID-19, and dozens of clinical trials are underway worldwide to test its use.

The first results from a large-scale randomized controlled study demonstrated that tocilizumab (trade name Actemra) offered no significant benefits to people hospitalized with COVID-19. Among 450 participants, there was no evidence of improvements in clinical status or mortality.

Sarilumab (trade name Kevzara), a human monoclonal antibody against the IL-6 receptor, advanced into a large phase III trial but it was stopped due to lack of any evidence of efficacy.

News reports indicate that the U.S government's Biomedical Advanced Research and Development Authority (BARDA) has now stopped supporting the development of Actemra and Kevzara for COVID-19.

Anakinra (Kineret) is an IL-1 receptor antagonist developed from the native human protein that has this same function. A dozen clinical trials worldwide are currently testing its use in severe COVID-19.

**JAK/Stat Inhibition**

When an IL (or other cytokine) binds to its receptor on a cell, a signaling pathway inside the cell mediates the activation. This transmits the signal from the cell membrane, where an IL binds, to the cell's nucleus, where changes in gene expression activate the cell.

Janus kinases (JAK) and signal transducer and activator of transcription proteins (STATs) are the protein effectors of this downstream activation. Therefore, blocking the function of JAK/STAT pathways would similarly inhibit immune activation.

Drugs that block JAK/STAT signaling are called JAK inhibitors and include tofacitinib, ruxolitinib, baricitinib, and peficitinib. There are fewer initial data on these molecules in COVID-19, likely due to the fact that they impact immune signaling much more broadly than IL-1 or IL-6 inhibitors, and there are fears this could increase viral replication. Several clinical studies are underway to evaluate ruxolitinib for the treatment of severe COVID-19.

Preliminary results from a large NIAID-sponsored trial—Adaptive COVID-19 Treatment Trial 2 (ACTT-II)—testing the combination of baricitinib and remdesivir compared to remdesivir alone were described in a press release on September 14, 2020. The addition of baricitinib led to a statistically significant but meager improvement in recovery time of one day. Additional analyses are underway and details on the study outcomes will be reported in a peer reviewed journal.

**Interferons**

Researchers have found evidence that SARS-CoV-2 suppresses production of cytokines called interferons, which are normally an early and important component of the immune response to viruses. Furthermore, studies have shown that defects in interferon-related genes and the presence of anti-interferon antibodies may explain around 14% of severe COVID-19 cases.

A commercially available injectable formulation of beta interferon (interferon β 1a, FDA-approved for multiple sclerosis) has emerged as a lead therapeutic candidate for COVID-19. Several small trials have suggested beneficial effects on viral load, hospital discharge rates, and mortality. The company Synairgen is developing an aerosol formulation of interferon β 1a delivered by nebulizer. In a press release, Synairgen has claimed that the

approach greatly reduced the incidence of severe disease in a study of 101 hospitalized people with COVID-19, but the results are not yet published.

The ongoing WHO Solidarity trial includes an evaluation of injectable interferon β 1a, so more robust results should be forthcoming. The NIH has also announced that subcutaneous interferon β 1a will be tested in combination with remdesivir in the third installment of their Adaptive COVID-19 Treatment Trial (ACTT), which will recruit over 1,000 hospitalized adults.

**Pre-Clinical Coronavirus Studies**

Huge amounts of research are currently underway to develop and test a COVID-19 vaccine and to test existing medicines for activity against SARS-CoV-2 in large, well-controlled clinical trials. For other viral pathogens, including HIV and hepatitis C, vaccines to prevent infection have thus far remained elusive after decades of research. Indeed, for both HIV and hepatitis C, significant pre-clinical research into the basic molecular and cellular biology and biochemistry of the viruses was required to develop potent small molecule inhibitors to treat these viral infections.

These studies included structural biology to solve crystal structures of the HIV viral protease and hepatitis C viral replicase. This work facilitated structural design of small molecule inhibitors in addition to significant high throughput screening of large libraries of small molecules, both with known and unknown function. While these types of studies take significantly more time than repurposing of existing small molecules (or even accelerated vaccine development), the investment is well worth the effort in case vaccine research fails, provides only partial protection, or other novel coronaviruses emerge in the future.

After the emergence of SARS-CoV-1, MERS, and now SARS-CoV-2, it's become clear that the most basic pre-clinical research into this family of viruses is now of the utmost urgency and should be prioritized alongside vaccine, clinical, and translational studies.

**Clinical Trial Design**

The COVID-19 pandemic and subsequent empirical use of off label therapeutics reinforces the need to rapidly respond to a crisis with the best possible science. Out of necessity, much of the early reports on COVID-19 therapies were from small trials without placebo control arms. Only later did large-scale studies reporting on many of these treatments—and the adverse effects associated with them—emerge, leading to a rapidly shifting treatment landscape and to confusion at all levels of the health care system, from doctors to the president of the United States. Many therapies that showed promise in small studies did not turn out to be effective when examined at scale.

Even drugs that are extremely safe in other contexts must be carefully tested in people with COVID-19. Large, well-controlled clinical trials are needed to evaluate the safety, efficacy, and dosing of any therapeutic intervention.

These studies should have well defined endpoints that are determined before the trial starts. Various endpoints have emerged for COVID-19 clinical trials, including length of

hospitalization, severity of disease, incidence of ongoing hospitalization after a certain interval of time, and incidence of mortality. At times these endpoints have shifted mid-study. Researchers must clearly report their endpoints, the size of the study, details of the administration and dose of the intervention, and their confidence intervals (as opposed to just a p-value) in any report on their findings.

The ethical considerations and risk of clinical trials have thus far largely removed some vulnerable populations. Children and pregnant women may have a different response to COVID-19, and therefore therapeutics may act differently in these populations as well. There is a long history of clinical trials with robust informed consent in these high-risk populations, and researchers should be engaging with this literature immediately.

Community engagement in clinical trial design and implementation is critical. Patients with, or who have recovered from, COVID-19, or who are at the highest risk of the disease must be invited to participate at every level of scientific decision making. This includes healthcare workers, essential workers (including those in factories, farms, and meat packing plants), the elderly, those who live in congregate settings, especially nursing homes, those with underlying conditions, and black and brown Americans.

If COVID-19 treatments or vaccines are developed, clinicians and public health officials must be able to reach people at a nearly unprecedented level. This will require trust between the biomedical infrastructure and the communities they serve. This trust must be established now, in part through the ethical, community-based, and science-driven inclusion of the most at need in highly ethical and openly transparent clinical trials. The time for community engagement in clinical trials isn't now; it's yesterday.

COVID-19 is also a global disease, and so clinical trials must be viewed in a global context. This requires coordination at all levels of government and between governments. Activists and advocates can and must play a central role here, led by those at greatest risk and with the closest ties to at-risk communities.