VIEWPOINT

Therapy for Early COVID-19
A Critical Need

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While coronavirus disease 2019 (COVID-19) is predominantly self-limited, up to 20% of symptomatic individuals will progress to severe or critical disease with clinical manifestations including pneumonia, acute respiratory distress syndrome, multiorgan system dysfunction, hypercoagulation, and hyperinflammatory manifestations. There have been more than 47 million cases of COVID-19 globally resulting in more than 1.2 million deaths. Additionally, a growing body of data suggests that some patients with COVID-19, including individuals with mild symptoms, will have a variably prolonged course of recovery including fatigue, cognitive impairment, and cardiopulmonary dysfunction.[1] While treatment options for patients with severe disease requiring hospitalization are now available, with corticosteroids emerging as the treatment of choice for critically ill patients, interventions that can be administered early during the course of infection to prevent disease progression and longer-term complications are urgently needed.[2,3]

Recent attention has been focused on the potential of early treatment for individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at high risk for serious outcomes. Yet, there is a noteworthy absence of treatments proven to be efficacious for patients with early or mild infection. Immediate benefits of such treatments include improvement of patient outcomes and prevention of hospitalizations. Longer-term benefits may include prevention of the chronic sequelae of infection as well as prevention of transmission by shortening the period of infectiousness. Outpatient treatments for COVID-19, coupled with an effective vaccine, would have significant implications for the ability to end this pandemic.

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Recent successes in the development of effective treatments for moderately to severely ill hospitalized patients have been reported. The Adaptive COVID-19 Treatment Trial (ACTT), a phase 3, randomized, placebo-controlled trial, demonstrated that the antiviral agent remdesivir was effective in reducing time to recovery in adults hospitalized with COVID-19.[4] These findings helped to support Food and Drug Administration approval for use of remdesivir in hospitalized patients. Additionally, the RECOVERY trial, a large, adaptive trial designed to evaluate efficacy of several therapeutic interventions, compared with standard of care, revealed that dexamethasone reduced mortality in hospitalized patients requiring mechanical ventilation or high-flow oxygen.[5] Both remdesivir and dexamethasone have now been endorsed globally by multiple COVID-19 treatment guideline committees and have led to improvements in patient outcomes among those requiring hospitalization.

However, effective treatments for people with mild to moderate disease have been more elusive. Remdesivir requires daily infusions for up to 10 days[4] and is not suitable for an ambulatory setting. Dexamethasone has not been tested in early, mild disease, but its immune-suppressive effects could potentially worsen clinical outcomes in this setting. Several drugs, such as hydroxychloroquine, have failed to show efficacy in rigorous clinical trials despite early uncontrolled studies suggesting a positive effect.[6] Moreover, the risk-benefit calculus in mild to moderate disease differs from that of severe disease. Treatments for outpatients with mild disease must be safe with few adverse effects, easy to administer, and scalable. Despite these hurdles, a cadre of new treatments has now entered the clinical development pipeline.

Several antivirals approved or in development for other viral infections, such as HIV, hepatitis C virus, and ebolaviruses, are under investigation for early treatment of COVID-19. These investigations have not yet yielded clinically actionable results; however, many trials are ongoing. Examples of antivirals in trials for early treatment of COVID-19 are MK-4482 (EIDD-2801), an orally bioavailable ribonucleoside inhibitor that was originally developed for influenza (NCT04575597); SNG001, a nebulized formulation of interferon-β1a developed for viral infections in patients with chronic obstructive pulmonary disease (NCT04385095); and camostat mesylate, a serine protease inhibitor approved for treatment of chronic pancreatitis and postoperative reflux esophagitis (NCT04353284).

Immune-modulating drugs are being extensively examined for treatment of moderate to severe COVID-19. Even though these agents are less likely to be as beneficial as antivirals during early infection, this approach is also being explored for early, mild disease. Additionally, approaches to prevent some of the more severe complications of COVID-19 are being tested. Several clinical trials, including the National Institutes of Health–sponsored ACTIV-4 trial (COVID-19 Positive Outpatient Thrombosis Prevention Trial [NCT04498273]) are

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testing factor Xa inhibitors and other anticoagulant strategies to prevent thromboembolic complications.

SARS-CoV-2–specific approaches, such as antiviral antibodies, are also being developed. Convalescent plasma, hyperimmune γ-globulin, and polyclonal antibody products are being tested in a wide range of studies including in participants with mild to moderate disease. Additionally, monoclonal antibodies are in development by several companies and academic investigators. Early-phase clinical trials sponsored by Eli Lilly (Ly-CoV555) and Regeneron (REGN-COV2) have yielded promising results suggesting that monoclonal antibodies may be effective in decreasing viremia and improving clinical outcomes in patients with early COVID-19.[7,8] Although these initial monoclonal antibody interventions are administered intravenously and, therefore, present challenges for the outpatient setting, alternative routes of administration, such as inhalation and subcutaneous or intramuscular injection, are also being developed and would be more practical for use in early disease.

Given the duration and severity of the COVID-19 pandemic, investments into targeted de novo drug design approaches for early treatment are also warranted. Although this effort will be lengthy and more costly than repurposing, discovery of novel targeted antivirals may prove useful not only for COVID-19, but also in future pandemics. Lessons can be drawn from successful development of antivirals against other viruses such as HIV and hepatitis C. As with those viruses, combinations of antivirals may be needed for the most effective therapy and to avoid development of resistance.

While the current pipeline of treatments provides hope that effective, early–COVID-19 therapeutics may soon be available, much work remains to be done. Continued research is needed to refine current treatment candidates and develop new drugs that can be dosed without requiring intravenous infusions or other complex maneuvers. Effective treatments that require infusion may be the first approved for clinical use and will have a significant public health impact. However, for the greatest benefit, treatments will need to be administered easily and made available widely at low cost.

Furthermore, rigorous clinical trials will be needed to provide the data to confidently prescribe treatments for individuals and properly implement interventional strategies at the public health level. At best, these trials are difficult to implement. They require large sample sizes and a complex infrastructure to ensure participant and staff safety. Shortages of medications, medical supplies, and staff and overburdened health systems resulting from the pandemic further amplify the challenge. To address these difficulties, and in partnership with Operation Warp Speed, the National Institutes of Health has established multiple clinical trials as part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership. The ACTIV-2 trial (Adaptive Platform Treatment Trial for Outpatients with COVID-19 [NCT04518410]), in particular, is a platform protocol designed to evaluate promising antivirals starting with a phase 2 trial and seamlessly progressing into a phase 3 trial for treatment of early COVID-19 in the outpatient setting. The platform design allows the pooling of resources to efficiently evaluate multiple interventions simultaneously and ensure that effective therapies are moved forward into the clinic.

From drug discovery to rigorous clinical trials, these challenges demand a significant level of commitment and effort from all parties involved including pharmaceutical companies, scientists, clinical trialists, and study volunteers. Preventing hospitalizations and the chronic sequelae of COVID-19 will not only save lives, but also will help restore medical systems and other institutions that are overburdened by the effects of the pandemic. Effective, early treatments will also mitigate gaps left by previous and current prevention strategies and curtail forward transmission. It is encouraging that effective outpatient treatments for early COVID-19 are on the horizon; these efforts deserve the full support of the medical community and the public.

ARTICLE INFORMATION

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Additional Information: Dr Kim is Director of the Therapeutics Research Program in the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH; Dr Read is Deputy Director of DAIDS; and Dr Fauci is Director, NIAID.

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