Antiviral agents for the treatment of COVID-19: Progress and challenges

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https://doi.org/10.1016/j.xcrm.2022.100549

The COVID-19 pandemic has seen clinical development and use of antiviral therapies at an unprecedented speed. Antiviral therapies have greatly improved the clinical outcome in COVID-19 patients, especially when administered early after diagnosis. Here, we discuss the successes and challenges of COVID-19 antiviral therapies and lessons for future pandemics.

Antiviral therapies for COVID-19: Current status

The COVID-19 pandemic has seen clinical development and use of antiviral therapies on a scale unprecedented for an acute viral infection. Although antivirals have been used effectively on a large scale to treat chronic virus infections like HIV and hepatitis C virus, their use to treat acute viral infections has been limited until now by a lack of effective antiviral therapies and a small window of opportunity to apply treatment and improve patient outcomes.1 Two years after the emergence of SARS-CoV-2, antiviral therapies are available that can be administered early after diagnosis in patients at risk of developing severe disease, as are therapies to improve outcome once severe disease has developed (Figure 1).2 These treatments are generally divided into two classes: direct-acting antivirals and host-directed therapies. Direct-acting antivirals are those therapies that target components of the virus and inhibit its replication. For these direct-acting antivirals to be effective, they must be administered early during infection before the virus reaches its replication peak and are therefore used to prevent progression to severe disease.3 Host-directed therapies on the other hand either target components of the host cell required for replication of the virus or aim to dampen the dysregulated inflammatory response to infection; in the case of COVID-19, only the latter class of host-directed therapies are currently available. These target the outsize inflammatory response involved in severe COVID-19 disease manifestations. These manifestations—ranging from dyspnea and hypoxia to acute respiratory distress syndrome and multi-organ failure—occur later during infection. Therefore, host-directed therapies are used during the later stages of COVID-19 disease, when virus replication is typically past its peak and the patient is hospitalized and requires respiratory support.3

There are currently no uniform, global COVID-19 treatment guidelines; for the purpose of clarity, this article mainly focuses on the current USA treatment guidelines.2 Remdesivir, a nucleotide analog, was the first direct-acting antiviral to receive FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 patients just months after the COVID-19 pandemic was declared,4 based on data showing a reduced time to recovery in hospitalized COVID-19 patients. Next, a neutralizing monoclonal antibody, bamlanivimab, was shown to reduce symptoms of COVID-19 and hospitalization rates; it received EUA for the treatment of COVID-19 patients.5 This monoclonal antibody was followed by several other monoclonal antibodies and cocktails thereof (Figure 1); other neutralizing monoclonal antibodies are in use outside the USA, and many monoclonal antibodies are still being evaluated in clinical trials. In December 2021, two orally available direct-acting antivirals with clinical benefit in preventing progression to severe disease, hospitalization, and/or death received FDA EUA: molnupiravir, a nucleotide analog, and Paxlovid, a protease inhibitor.6 Together, the direct-acting antivirals have greatly improved the outlook of COVID-19 patients known to be at risk of developing severe COVID-19 due to underlying conditions (Table 1).

In patients that have already progressed to more severe disease, host-directed treatments are used to achieve general immune suppression through use of dexamethasone or other corticosteroids. Other therapies involve a more targeted manipulation of the immune response by using inhibitors of IL6, one of the hallmarks of severe COVID-19 identified early in the pandemic, or by inhibiting Janus kinase and thereby cytokine signaling (Figure 1).7 Although these immunomodulators have resulted in a decreased mortality in severe cases of COVID-19, the effect of these late-stage treatments is much smaller than that of direct-acting antivirals administered in the early disease stage (Table 1). Therefore, patient survival depends heavily on advanced supportive care including prone positioning, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO).2

Several therapeutics (direct-acting and host-directed) are still in the preclinical and clinical stages of development8 and more treatment options will hopefully become available before too long. For example, clinical trial data for fluvoxamine recently showed a clinical benefit in preventing disease progression6 through a currently unknown mechanism. Through the investment of an inordinate amount of money and time, as well as unprecedented collaborations between scientists, clinicians, and the biopharmaceutical industry, we now have several effective antiviral therapies to treat COVID-19.2
However, we must also acknowledge that many severe cases of COVID-19 still occur and more antiviral therapies are needed. A critical assessment of gaps in treatment success is necessary so we can define ways to speed up recovery, reduce the long-term effects of SARS-CoV-2 infection, and increase the rate of survival in severe COVID-19 patients. We should also look beyond COVID-19 and draw lessons from this pandemic that will prepare us better for future pandemics that will undoubtedly emerge.

### Challenges for development of direct-acting antivirals

The value of administering direct-acting antivirals to at-risk patients early after diagnosis is clear from Table 1: the majority of severe COVID-19 cases can be prevented through timely administration of (a combination of) direct-acting antivirals. Currently, these direct-acting therapeutics are only used in patients at known risk for severe COVID-19 due to the presence of risk factors such as age and obesity, or comorbidities like diabetes and heart conditions. Ideally, direct-acting antivirals would be used on an even larger scale, in symptomatic patients not known to be at risk of severe disease, to reduce the time to recovery, potentially reduce long-lasting effects of infection, and potentially even reduce onward transmission of the virus. Due to the nature of direct-acting antivirals, their efficacy increases even with small reductions in time to treatment initiation. Therefore, the availability of rapid diagnostics with a low limit of detection, combined with a low threshold for prescription, and availability in local pharmacies are essential to get the largest possible clinical benefit from direct-acting antivirals.

Another important consideration is the administration route of direct-acting antivirals. As mentioned above, remdesivir was the first antiviral therapy to receive FDA EUA and the only fully licensed antiviral therapy to date. However, remdesivir treatment is complicated by the need to administer it intravenously on 5 consecutive days. Therefore, use of remdesivir has so far mostly been limited to patients already hospitalized with COVID-19. A recent clinical trial studying the effect of outpatient treatment with remdesivir (i.e., sooner after diagnosis) showed a much larger beneficial effect of remdesivir with this early administration. Thus, efforts should be made to develop direct-acting antivirals that can be self-administered, preferentially orally, or subcutaneously or intranasally if oral administration is not feasible. Alternatively, facilities and protocols that can ensure daily outpatient treatment administration could be developed; this has occurred for monoclonal antibody administration and would be possible for other treatments, even if those antiviral therapies might have to be administered on several consecutive days. However, at-home use of antivirals puts a high bar on these drugs: they must lack significant side effects or negative interactions with other medications since patients taking them would not be under continuous medical supervision.

### Treatment of patients upon diagnosis rather than at the time of hospitalization

Treatment of patients upon diagnosis rather than at the time of hospitalization means treating a significantly larger number of people, since most patients never progress to severe disease, even without treatment. Therefore, next-generation antiviral therapies may be needed to treat a larger number of people, and more direct-acting antivirals are required to be administered early after diagnosis.
Table 1. Efficacy and mechanism of action of COVID-19 antiviral therapies depicted in Figure 1

| Therapeutic | Mode of action | Reduction in hospitalization |
|-------------|----------------|-------------------------------|
| Remdesivir  | nucleotide analog | 87%*                          |
| Molnupiravir | nucleotide analog | 30%                           |
| Paxlovid     | protease inhibitor | 90%                           |
| Bamlanivimab and etesevimab | neutralizing mAbs | 70%                           |
| Casirivimab and imdevimab | neutralizing mAbs | 66%                           |
| Sotrovimab   | neutralizing mAb  | 85%                           |
| Tixagevimab and cilgavimab | neutralizing mAbs | 77%                           |
| Regdanvimab  | neutralizing mAb  | 70%                           |
| Amubarivimab and romlusevimab | neutralizing mAbs | 80%                           |
| Dexamethasone or other corticosteroid | immune suppression | 17%–21%                       |
| Baricitinib or tofacitinib | Janus kinase inhibitor | 18%                           |
| Tocilizumab or sarilumab | IL6 inhibitor | 13%                           |

*Efficacy observed with outpatient treatment.

VOC is posing even larger problems, since most monoclonal antibody treatments under FDA EUA have reduced neutralizing capacity against this VOC in vitro. Combination treatments consisting of two or more direct-acting antivirals from a different class (e.g., a nucleotide analog plus monoclonal antibody) will likely reduce the chance of escape variants to emerge and may improve the clinical benefit of treatment. Combination treatment should therefore be investigated in clinical trials.

**Challenges for development of host-directed therapies**
Severe lower respiratory tract infections have historically been extremely difficult to treat, and COVID-19 is no exception. As explained above, direct-acting antivirals have very limited effect once severe disease manifests because the virus replication is already much reduced. Rather, the disease is driven by the host’s hyperinflammatory response to infection, resulting in acute respiratory distress and multi-organ failure. Although a few immunomodulatory therapies have led to an increase in survival in COVID-19 patients, they are ineffective in a large subset of patients (Table 1). Moreover, the administration of these therapeutics in relation to disease progression must be timed correctly to avoid negative effects on patient outcome. Thus, one major remaining challenge is to identify additional host-directed therapies for the treatment of severe COVID-19. Unfortunately, a clear path forward for host-directed therapies has not emerged from either years of research on acute respiratory distress syndrome and multi-organ failure or many clinical trials evaluating potential therapeutics. We must use this pandemic, and the unprecedented amount of patient information acquired so far, to advance our understanding—and treatment—of viral lower respiratory tract disease. Never before have researchers had access to such a large data and clinical sample set derived from patients and animal models that can be used as the basis for this research. Additionally, technological innovations like single-cell transcriptomics and the use of respiratory tract organoids are tools that have not been applied to this problem before but could lead to significant discoveries. Combining these tools with the data and samples available from COVID-19 patients will result in a mechanistic understanding of the cascade of specific cellular processes underlying severe disease, as well as biomarkers indicating which phase of the cascade patients are in. Individual components of this cascade form novel targets for time-resolved host-directed therapies. This will require large investments in terms of research funding, but the added benefit of this investment would be that it will likely result in effective treatments for pneumonia and acute respiratory distress from causes other than SARS-CoV-2 infection as well.

Research also needs to focus on the effects of COVID-19 in convalescent patients, as long-lasting effects of COVID-19 are common. While this issue may have been overlooked early on, when the focus was on finding treatments for acute disease, the enormous number of convalescents with persisting problems is now too urgent to ignore. One obvious area of study is lung regeneration, since many patients who recover from severe COVID-19 will have long-lasting damage to their lungs such as pulmonary fibrosis that may negatively impact recovered patients’ quality of life.
Another area that requires additional clinical and mechanistic research is post-acute COVID-19 syndrome (PACS; also known as “long COVID”). Many recovered COVID-19 patients experience long-lasting effects of COVID-19 infection with problems arising from many different organ systems besides the lung, regardless of the severity of the acute stage of SARS-CoV-2 infection and without evidence of continued virus replication.\(^{13}\) More clinical research on patients with PACS is urgently needed to understand this syndrome better and find effective therapeutics to treat it.

**Future directions: Pandemic preparedness**

Clinicians and scientists from all medical and scientific disciplines redirected their focus to COVID-19 in the past 2 years, resulting in rapid progress in the prevention and treatment of COVID-19 and a significantly reduced disease burden on the level of the individual patient. However, it is clear from the above that we need additional antiviral therapies in our COVID-19 arsenal. Now that pandemic response and pandemic preparedness are high on everyone’s agenda, a thorough analysis of the antiviral therapy research and development pipeline needs to be conducted to identify bottlenecks that impede the clinical development of antiviral therapies. For example, treatments like molnupiravir and Paxlovid were developed years before the emergence of SARS-CoV-2 as potential antiviral therapies for SARS and influenza, respectively. Still, it has taken almost 2 years since the emergence of SARS-CoV-2 for these drugs to receive FDA EUA for COVID-19. Why did this take so long, and could this have been accomplished faster? Why do all the now-approved treatments use a mechanism of action found in previously approved antiviral therapies (i.e., nucleotide analogs, protease inhibitors, monoclonal antibodies) while novel therapeutics like siRNA have lagged behind? Funding for direct-acting antivirals against a specific virus often lapses once the immediate threat of an outbreak is over and the causative agent disappears from the news; how can we ensure continued development of promising antiviral therapies despite a reduced public interest in the infection they would treat? Although obvious bottlenecks are the lack of a long-term research agenda and pre-existing clinical trial networks, a thorough analysis could result in new insights into additional bottlenecks hampering the progression of new antiviral therapies into the clinic and measures to reduce or eliminate them.

At least as important as the therapeutics that worked are the ones that did not. Clinical trials are usually tracked in public databases, so once a therapeutic makes it into clinical trials it is clear whether it had a clinical benefit in patients. Negative outcomes during preclinical development are often not reported, but it is safe to assume that many more potential antiviral therapies for COVID-19 failed in the preclinical development phase than we know of. Yet, much knowledge could be gained from analyzing which compounds were found to be ineffective during preclinical development, why they were ineffective (if known), which assays were used to include the compound in preclinical studies, and which assays were used to exclude them later. A repository of compounds that were ineffective during preclinical development containing this information could be a great tool to streamline the preclinical development of antiviral therapies since it would allow us to define assays with the best predictive value for the efficacy of potential antiviral therapies. Assays with low predictive value could then be replaced with more predictive ones. One important example in this context is the use of Vero cells for the screening of direct-acting antivirals. Chloroquine performed well in these cells, but it was later shown not to be effective in more representative primary cells and multiple animal models. Thus, the chloroquine debacle could have been avoided if a better initial screening assay had been used.\(^{14}\) A more streamlined preclinical development pipeline would likely greatly reduce the number of potential antiviral therapies that successfully make it through the pipeline.

Countless previously unknown viral genomes have been discovered in recent years\(^ {15}\) representing new members of virus families known to have zoonotic potential. In response, there is an ongoing search for broad-acting antivirals that are effective against multiple viruses within one family, or even against viruses from different families. However, we also need to invest in research that will help us determine which of these newly discovered viruses form a pandemic threat. We can then apply the lessons learned from the COVID-19 pandemic to pre-emptively develop direct-acting antivirals against these viruses to supplement the broad-acting antivirals. Only then can we hope to fare better in the next pandemic.

**ACKNOWLEDGMENTS**

We would like to thank Rose Perry-Gottschalk for help with figure design, and Vincent Munster, Sonja Best, and Heinz Feldmann for critically reading the manuscript. M.S. and E.d.W. are supported by the Intramural Research Program of NIAID, NIH. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

**AUTHOR CONTRIBUTIONS**

Conceptualization and writing: M.S. and E.d.W.

**DECLARATION OF INTERESTS**

The authors declare no competing interests.

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