Therapeutics
Getting to and Sustaining the Next Normal: A Roadmap for Living with Covid

Summary

Newly developed and repurposed therapeutics to treat Covid have saved lives. Despite their expedited development, identification of safe and effective therapies relied on a patchwork of trials and the urgent reconfiguration of existing trial networks to focus on Covid drug development. Many of the drugs are in short supply, cumbersome to administer, or difficult for patients to get. The federal government must sustain and expand its capabilities to conduct large-scale, coordinated clinical trials in a crisis, and intensify efforts to develop more treatments, especially ones that are easier to administer. It must improve access to treatments, especially among patients with underlying risk factors, children, and minority communities. Finally, it should devise a framework to hedge against the emergence of variants that will inevitably become resistant to existing antiviral therapies.

A Quiet Success Story

Efforts to develop effective treatments for Covid have notched some extraordinary successes, a story sometimes overshadowed by controversies surrounding unproven therapies. Among the major advances were the expedited development and December authorizations of Pfizer’s Paxlovid and Merck’s molnupiravir. Both are antiviral pills that patients can take by mouth. If given early, both reduce the risk of progression to severe Covid. Separately, the rapid creation of monoclonal antibodies by numerous other pharmaceutical companies including Roche, Regeneron, Eli Lilly, GlaxoSmithKline, and Vir Biotechnology has been critical in treating people with high risk of severe outcomes from SARS-CoV-2 infection, and these development platforms are designed to enable rapid updates to combat virus evolution.

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In February, the FDA authorized the use of bebtelovimab, a monoclonal antibody developed by Eli Lilly meant to replace two earlier intravenous treatments that were not effective against the Omicron variant. Physicians have also gotten better at using traditional treatments like baricitinib and steroids to treat severely ill patients. But much more is needed.
Accelerating Therapeutic Development, Availability, and Access

Early in the pandemic, efficient therapeutic development was hindered by a multitude of small and competing trials that had little prospect of generating reliable information. The early authorization of convalescent plasma based on unreliable data delayed the development of more promising therapies. The clinical trials infrastructure in the United States, arguably the best in the world, was not designed to execute trials in an expedited and coordinated manner under the pressures of a pandemic. Unlike the United Kingdom, the United States was not able to leverage a coordinated health care system where every patient had the opportunity to volunteer to participate in a clinical trial as a care option.

There were high hopes for monoclonal antibody treatments to rescue sick, hospitalized patients. But clinical trials showed these drugs work best in the outpatient setting even though their intravenous administration make them awkward to give outside of hospitals. While monoclonal antibodies have certainly saved lives and redefined treatment options for SARS-CoV-2-positive individuals, they are cumbersome to manufacture, available in limited supply, and are prone to losing their activity when confronted with a new variant. Omicron rendered all but two of the authorized antibody treatments ineffective. On February 23, the FDA limited the use of one of those final options, the GSK/Vir monoclonal antibody sotrovimab, citing reduced effectiveness against the Omicron BA.2 variant. This rapid evolution of the SARS-CoV-2 virus has shown the need to continually redesign monoclonal antibodies to match evolving variants.

Remdesivir, the first drug authorized by the FDA to treat Covid in hospitalized patients, was recently found to reduce hospitalization if given early in the disease course. But the drug requires multiple days of intravenous administration, a significant barrier to its use in outpatient settings.

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Indeed, major limitations exist with all of the treatments that have either been approved or authorized for use against Covid. For example, only three of the drugs are formulated for oral administration, and only two have been authorized for use in children under 12. None are formulated into an easily administered oral, multi-drug antiviral cocktail that can reduce the risk of drug resistance while effectively reducing the risk of hospitalization and death. And none are yet authorized to address host-targeted inflammatory cascades that can exacerbate illness and lead to death.

Moreover, many challenges have limited the utility of these therapeutics, including viral mutations, in-patient administration, and supply shortages. Poor coordination between Covid testing efforts and the broader health care system has often delayed their deployment. There are significant racial and ethnic disparities with respect to treatment utilization, with Black, Asian, and Hispanic-identifying patients all less likely than Whites to receive monoclonal antibodies.51

Accelerating the Development of High-Value Treatments

There are five primary purposes of Covid therapeutics. First, preventing infection after known exposure. Second, keeping the sickened out of the hospitalized. Third, reducing hospital stays. Fourth, preventing or ameliorating long Covid. And finally, saving lives.

Beyond the present stable of monoclonal antibodies, oral antiviral drugs, and repurposed treatments, there are significant opportunities to accelerate the development of therapies supporting these objectives. The discussion draft of the bipartisan PREVENT Pandemics Act introduced in the U.S. Senate identifies several potential means of incentivizing and accelerating the development of innovative therapeutics, including the establishment of new priority designations for specific biologics and treatments using new platforms.52

This report’s authors believe the federal government should prioritize the development of therapeutics that are easy to manufacture and administer. These include orally administered antiviral drugs, especially those that can be combined into a multi-drug cocktail, and prophylactic monoclonal antibodies that can be administered outside the clinic, potentially via a subcutaneous or intramuscular delivery mechanism. The Milken Institute is currently tracking 332 Covid treatment candidates at various stages of development.53 Of these, 237 are in clinical trials and 95 are in pre-clinical development. Some will be easier to scale than others.

Next, the U.S. government should strengthen the ACTIV public-private partnership and ACTT multinational platform to further accelerate the development of the most promising therapeutics. Building on the ACTIV platform, the NIH should further expand the number of adequately powered trials using private sector contract research organizations and clinical sites to provide strong evidence for or against effectiveness across meaningful outcome measures in participants who are diverse in age, ethnic background, and known co-morbidities.

Such an accelerated effort will require more efficient use of existing resources, as well as rapid increases in total clinical research capacity and throughput. This would require partnering with clinical research organizations and persuading or using funding authorities to mandate academic medical centers that receive federal research funds to prioritize large collaborative projects, rather than undertake small bespoke therapy studies or industry-funded studies outside of the ACTIV portfolio.

Development should focus on four main types of therapeutics: oral multi-drug antiviral cocktails, long-acting monoclonal antibodies, intravenous antiviral treatments, and immune modulators.

The federal government should prioritize the development of therapeutics that are easy to manufacture and administer.

Most of the attention should focus on oral, multi-drug antiviral cocktails, which are easy to administer and are the least likely to encounter viral resistance.

Next on the priority list should be monoclonal antibodies. These medicines tend to have long durations, can be useful in prophylaxis, are often helpful in particularly vulnerable patients, and can reduce the risks of viral resistance or escape when given in combinations.

Finally, immune modulators could be effective in preventing or ameliorating severe outcomes like long Covid and Acute Respiratory Distress Syndrome. Among the targets for these drugs are inflammatory pathways (e.g., complement cascade and pro-and anti-inflammatory cytokines), coagulation cascade regulators, and autoantibodies. For the subset of patients who fail to activate the immune system properly, immune stimulators should also be considered.

Given the lack of pediatric authorizations and studies, the federal government should accelerate clinical trials to establish safety, efficacy, and optimal dosing of therapeutics for children.

Most of the attention should focus on oral multi-drug antiviral cocktails.

Finally, the federal government should do more to promote research into the potential repurposing of existing medications for new Covid-related indications. To be sure, ACTIV led by the Foundation for the National Institutes
of Health is doing this, but these efforts need more urgency, greater resources, and better alignment with drug development efforts across HHS, including BARDA. If any drugs are demonstrated to be safe and effective Covid treatments, the benefits of skipping expensive and time-consuming drug discovery and possibly human safety trials would clearly be welcome.

Anticipating and Combating Emerging Drug Resistance

The introduction of mono-therapy approaches for new antivirals increases the risk of antiviral resistance and potential to further drive viral evolution towards new variants. To monitor for and mitigate this risk, the federal government should require each manufacturer to share all data on antiviral resistance collected during clinical evaluation, including genomic sequences of the viruses and metadata associated with observed genetic changes in viruses collected from people undergoing treatment. Manufacturers should support an independent network for ongoing genomic surveillance for known markers associated with reduced therapeutic efficacy, sharing data publicly in real time.

Finally, the NIH should accelerate clinical studies evaluating combination therapies of available oral treatment options, which is the best approach to reduce the risks of antiviral resistance to any single drug. Such combinations are now the standard of care in treating HIV/AIDS.

Deploying Effective Treatments Quickly

To meet the demand for currently approved treatments, the administration should use every mechanism and incentive possible to rapidly scale up supplies of Paxlovid, Evusheld, bebtelovimab, and sotrovimab. To scale vaccine production, the Biden administration utilized the Defense Production Act. Similar approaches should be used to turbocharge supplies of these effective but scarce medicines.

Notably, the discussion draft of the PREVENT Pandemics Act would launch a new pilot designation to accelerate the development of new drug manufacturing technologies, as well as establish manufacturing surge capabilities within BARDA, both of which are likely to mitigate supply shortages over the long-term.54

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The federal government should not tackle these challenges alone. The NIH and BARDA should work collaboratively with the private sector to prioritize promising, scalable treatments and move them quickly through the research pipeline.

Several companies have developed rapid monoclonal antibody discovery and production platforms. Given that the Omicron variant has escaped the targeted epitopes for most currently authorized antibodies, companies should be incentivized to rapidly update their antibodies to match circulating virus variants. Antigenic cartography and other approaches should be used to create libraries of monoclonal antibodies with potential activity against future variants. Some of these antibodies with desirable characteristics such as predicted resilience to mutations should be moved to advanced preclinical (and possibly clinical) development at risk.

If companies are unable to update their antibodies, they should make their manufacturing facilities and supplies available to enable the scale-up and production of other antibody treatments that remain effective against circulating virus variants.

Finally, there must be an effective test-to-treat platform for all Americans so that everyone who tests positive for Covid is offered appropriate and rapid treatment, whether that test occurs at home, a pharmacy, a hospital, or elsewhere.

Rapid antigen tests have great specificity at detecting active Covid infections and thus can serve as reliable and affordable triggers to initiate health consultations and rapid delivery of prescription medications. The federal government should establish a data tracking system that, for those who participate, will proactively initiate an immediate healthcare consultation and suggest appropriate treatment options or clinical trial enrollment after positive tests.

Outpatient Covid treatments should be widely available at no cost — no deductible, no co-pay, and free for the uninsured—for anyone testing positive for Covid and meeting FDA indications. The federal government should prioritize equitable distribution by investing in outreach to underserved populations, as well as supplying safety net facilities and pharmacies in low-income areas with appropriate supplies of therapeutics. Certain Covid treatments should also be made more readily available for preexposure prophylaxis in high-risk groups, especially those who do not respond to vaccination.
Trump Administration therapeutics proposals: Getting to and Sustaining the Next Normal (a roadmap for living with Covid) - 80

**Therapeutics Strategic Goals**

1. **Direct HHS** (inclusive of CDC, BARDA, the NIH, and the FDA) to prioritize clinical research and development of Covid therapies, using both regulatory and financial incentives.
   
   a. Expand the ACTIV and ACTT platforms to rapidly evaluate existing and novel treatments more quickly in a coordinated manner.
   b. Fund acceleration of clinical trials and review processes for oral antiviral therapies and multi-drug antiviral cocktails.
   c. Fund acceleration of clinical trials and review processes for Covid therapeutics targeted to children.
   d. Strengthen requirements regarding recruitment and inclusion of diverse participants in Covid clinical trials to ensure safety and efficacy for all groups.
   e. Fund accelerated development of host-targeted therapies and immune modulators that can reverse or block cytokine-induced inflammation and treat acute respiratory distress syndrome (ARDS).
   f. Incentivize evaluation of existing therapies that might be repurposed for Covid.
   g. Reward the rapid development of monoclonal antibodies to match currently circulating virus variant(s).
   h. Incentivize additional research into the basis of long Covid, identify new therapeutic targets, and extend efforts in host targeting.

2. The federal government should accelerate the production and distribution of Covid therapies, using both regulatory and financial incentives.
   
   a. Rapidly scale up supplies of currently approved treatments (Paxlovid, Evusheld, bebtelovimab, and sotrovimab) with every mechanism and incentive possible. This should include using the Defense Production Act to expand, prioritize, and expedite supply of raw materials and production facilities to meet the urgent demand.
   b. Invest in additional on-shoring or near-shoring manufacturing capacity and raw material, ancillary, and other supply chain items required for therapeutics.

3. Direct the CDC to launch a comprehensive, publicly accessible, proactive genotypic and phenotypic surveillance system to monitor development of treatment resistance among viruses in the general population and resulting from patients treated with SARS-CoV-2 targeted treatments.
   
   a. Require manufacturers to share antiviral resistance and related genomic sequencing data acquired during clinical evaluations.
   b. Require manufacturers to fund for a period of 5 years and report data to a new independent body conducting ongoing genomic surveillance to detect reduced drug efficacy.
   c. Leverage infrastructure built to combat treatment resistance for SARS-Cov-2 to address broader antimicrobial resistance challenges, potentially in a coordinated effort with BARDA.

4. **Direct HHS to establish a test-to-treat system** that proactively offers clear guidance on self-isolation, therapeutic treatment, and/or clinical trial enrollment to Covid-positive individuals.
   
   a. Fund development of a system linking home- or rapid-test results with immediate clinical consultation and rapid distribution and provision of appropriate antivirals in high-risk individuals.
   b. Prioritize equitable distribution by investing in outreach to underserved populations, as well as supplying safety net facilities and pharmacies in low-income areas with appropriate therapeutics.