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COMMENTARY

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Antiviral Therapeutics: Key to Curbing the COVID-19 Pandemic

Well-nigh 2 years into the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the successful abrogation of this global scourge appears increasingly uncertain. Confronted with a fourth wave of infections fueled by the highly transmissible Delta variant, an exhausted planet stands bereft of a clear path forward. Left to ponder waning vaccine-mediated protection, attendant breakthrough infections, and vaccine boosters, governments the world over are in desperate search for solutions. Nonadherence to mitigation measures, anti-vaccination and anti-masking sentiments, as well as growing pandemic fatigue, further compromise what is rapidly becoming an increasingly fragile state of affairs. It is against this backdrop that the growing importance of potent antiviral therapeutics has become glaringly apparent. Calls to address this shortfall were recently issued by both the National Academy of Medicine and the Government Accountability Office.[1,2] In this Commentary we review recent investments of the US government in the development and procurement of short- and long-acting antiviral therapeutics in a quest to complement vaccines and hamper the pandemic.

It is becoming increasingly clear that vaccination and mitigation alone will not suffice if the SARS-CoV-2 pandemic is to be subdued.[1,2] This recognition draws, in part, on the materialization of ever more potent, heretofore unrecognized viral mutants.[1,2] Aided by the multiple challenges of attaining nationwide (let alone global) herd immunity, viral mutants are bound to continue to evolve, leaving ever more human devastation in their wake.[1,2] The outcome of an all-out race to develop vaccines at a pace that matches the viral mutation rate remains uncertain at best. What appears to be called for, at this time, is an investment in the heretofore absent short- and long-term antiviral therapeutics, with an eye toward complementing and fortifying extant antiviral strategies.[1,2] Readily prescribed by primary care providers across the globe, antiviral therapeutics stand to make a world of difference.[1,2] Only in so doing can a weary world regain some semblance of normal pre-pandemic life.

On June 17, 2021, the Department of Health and Human Services announced the intent of the Biden Administration to invest $3 billion from the American Rescue Plan Act of 2021 in the development of the next generation of Coronavirus disease 2019 (COVID-19) therapies.[3] Leading the way will be the Antiviral Program for Pandemics and the constituent components thereof, including the National Institutes for Health (NIH), the National Institute of Allergy and Infectious Diseases (NIAD), the National Center for Advancing Translational Science (NCATS), and the Biomedical Advanced Research and Development Authority (BARDA).[4] The partnership among the NIH, NIAD, NCATS, and BARDA is hardly novel. All have previously collaborated in the development of vaccines, therapeutics, and diagnostics to combat ebola, anthrax, and smallpox.[4] BARDA's record in drug development—over 60 products having achieved US Food and Drug Administration (FDA) approval—is noteworthy as well. With an eye on near-term implementation, the Antiviral Program for Pandemics will focus on the 19 therapeutic agents prioritized by the ACTIV (Accelerating COVID-19 Therapeutics and Vaccines) public−private partnership for "testing in rigorous clinical trials for outpatients and inpatients with COVID-19".[4] The NIH, for its part, "will evaluate, prioritize and advance antiviral candidates to Phase 2 clinical trials . . . to de-risk early stage development with sponsors and guide candidates along development paths".[4]

Earlier this year, on March 16, 2021, the Department of Health and Human Services and the Department of Defense concluded an agreement with AstraZeneca (Cambridge, UK) in support of the late-stage development of AZD7442 and the supply of 700,000 doses thereof.[5] An altogether unique therapeutic, AZD7442 constitutes a long-acting combination of 2 highly modified human monoclonal antibodies, the clinical efficacy of which is being assessed. Backed by a compelling body of preclinical data, AZD7442 is projected to afford long-term (6-12 months) protection against COVID-19 in a manner distinct from that rendered

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by a vaccine.[6] As seen by AstraZeneca, AZD7442 possesses the potential to offer almost immediate protection to those who are immunosuppressed, to prevent the acquisition of the disease, and to treat those who are already infected with the virus.[5] Recent results from a Phase III pre-exposure prophylaxis trial showed AstraZeneca's AZD7442 to have achieved a statistically significant reduction in the trial's primary endpoint, that is, the incidence of symptomatic COVID-19.[7] Subject to approval by the FDA, AZD7442 could well become the first long-acting anti-COVID-19 measure that is not a vaccine.

More recently, on June 9, 2021, the Department of Health and Human Services announced that it will procure "approximately 1.7 million [5-day] courses of the investigational antiviral treatment, Molnupiravir (MK-4482), for COVID-19" from Merck & Co (Kenilworth, NJ).[8] The $1.2 billion purchase is contingent on Molnupiravir being granted emergency use authorization or approval from the FDA.[8] This multiagency initiative comprised BARDA, the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense of the Department of Defense, and the Army Contracting Command.[8] An oral broad-spectrum agent, Molnupiravir prevents viral replication through the induction of genome copying errors.[8] Co-developed with Ridgeback Biotherapeutics (Miami, Fla), Molnupiravir is being studied for its capacity to "reduce the risk of hospitalization or death in non-hospitalized [COVID-19] patients who have symptoms for five days or less and are at high risk for severe illness".[8] Having concluded Phase 1 and Phase 2 studies, Molnupiravir is presently undergoing a randomized double-blind Phase 3 clinical trial (ClinicalTrials.gov Identifier: NCT04575597).[8] Intent on enrolling ≤1850 participants globally, the estimated primary completion date of this Phase 3 clinical trial is November 8, 2021.[9] Subject to the approval of Molnupiravir by the FDA, the federal government plans to allocate this therapeutic to states and US territories.[8] Health care providers will be able to order the product directly from the distributor within those allocations.[8] While the United States and other high-income countries are leading the development charge, one must not lose sight of the global justice imperative. As previously noted for vaccines, commitments to supply low- and middle-income countries that are most in need often buckle under the weight of domestic politics.

With the federal government now firmly enmeshed in the development of short- and long-term antiviral therapeutics, the prospect of modifying the COVID-19 pandemic has been materially advanced. The benefits accrued need not be limited to the present. Extant breakthroughs could well serve as a first line of defense against future pathogens. Planning along these very lines, the American Rescue Plan Act of 2021 has further allocated up to $1.2 billion in support of the creation of collaborative drug discovery groups.[3] The latter, known as the Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern, will draw on the creativity of the national biomedical research community to engender "innovative antiviral drug discovery and development".[3] Focused at first on the coronaviruses, the AViDD centers will, in time, redirect their focus onto other viruses with pandemic potential.[3] Forewarned is forearmed.

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