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Correspondence

Antiviral pills: A potential game-changing therapy against COVID-19



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Dear Editor,

The entire globe is grave consequences of the coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Many drugs have been repurposed and recorded effectiveness in treatment of COVID-19. However, FDA-approved drugs are still not available against COVID-19. In addition, various research groups have developed a range of vaccines, including intramuscular and intranasal vaccines against COVID-19 [1].

The vaccination drive is in full swing to overcome this pandemic by inoculation of the available COVID-19 vaccines. Recently, these vaccines have also been approved in pregnant women and children to reduce the risk of infection with SARS-CoV-2. Along with a regular vaccination drive, many countries have implemented new vaccine strategies to vaccinate the entire population, e.g., India has recently launched the door-to-door scheme known as “Har Ghar Dastak”, which means immunization of each and every individual at their respective places.

Despite the significant achievements in development of vaccines and drugs to mitigate the deleterious consequences of COVID-19, the emergence of variant of concern (VOC), particularly the Delta and Omicron variants, have posed some serious concerns on the effectiveness of the developed vaccines and drugs [2].

However, recently antiviral drugs such as molnupiravir in the form of oral pills have been suggested as an effective drug in treatment of COVID-19. This drug can be given as pills to take at home. Moreover, it has been estimated that molnupiravir can be 90% effective in prevention of hospitalization and death in high-risk patients in clinical trials. It has also been considered that molnupiravir can work against the highly mutated Omicron variant of SARS-CoV-2, which is viciously gripping the whole world (<https://www.bbc.co.uk/news/health-59681571>).

Hence, this correspondence article aims to examine the safety and reliability of antiviral pills for management of COVID-19. Recently, the Merck’s molnupiravir-the world’s first oral antiviral treatment against COVID-19 was licensed by the UK’s drugs authority. According to the company, the pill can lower the risk of hospitalization or death in

patients with moderate infection. The pill is taken orally and prevents the coronavirus from replicating inside the body. The oral pills usually inhibit replication of certain RNA viruses and have been known to treat COVID-19 in those infected by SARS-CoV-2. Molnupiravir (β -d-N4-hydroxycytidine-5'-isopropyl ester) is a cytidine analog that predominantly works *via* mutagenesis in viruses. It integrates into the new RNA strands, resulting in a slew of mutations during successive replication cycles (Fig. 1). Molnupiravir, also known as MK-4482 and EIDD-2801, is an orally accessible NHC prodrug. Molnupiravir is not a chain terminator can explain how it escapes the exonucleases’ proofreading of SARS-CoV-2 exonucleases. Molnupiravir suppresses the coronaviruses primarily through viral mutagenesis. However, biochemical investigations showed NHC may be converted to deoxy-NHC, which causes DNA alterations in the host cells [3].

Although the time of symptom onset or underlying risk factors were behaved not to affect the drug’s efficacy, a recent clinical study concluded that early treatment with molnupiravir reduced the risk of hospitalization or death in unvaccinated adults with COVID-19 [4]. In the coming days, these contradictions can be rectified with the help of large-scale clinical trials.

Molnupiravir has been reported to reduce the risk of hospitalization or death by roughly 50% compared with placebo in non-hospitalized patients with mild-to-moderate COVID-19 with at least one risk factor for disease progression [5]. Molnupiravir began as a possible therapy for the Venezuelan equine encephalitis virus at the Emory University’s non-profit company DRIVE (Drug Innovation Ventures at Emory) in Atlanta. It was then acquired by the Miami-based company Ridgeback Biotherapeutics, which later partnered with Merck & Co. to develop the drug further. The use of oral pills containing molnupiravir can now be used as an effective therapeutic regimen against COVID-19 amid the emergence of novel variants of SARS-CoV-2 such as Gamma, Delta, Mu, and Omicron. However, these conclusions have been drawn from small-scale clinical trials. There is an urgent need to conduct large-scale clinical trials to confirm the effectiveness of molnupiravir given orally.

Several studies have been conducted, and many are still ongoing to measure the effectiveness of the oral antiviral therapeutic regimens in management of COVID-19. A recent study using PAXLOVID™ (PF-

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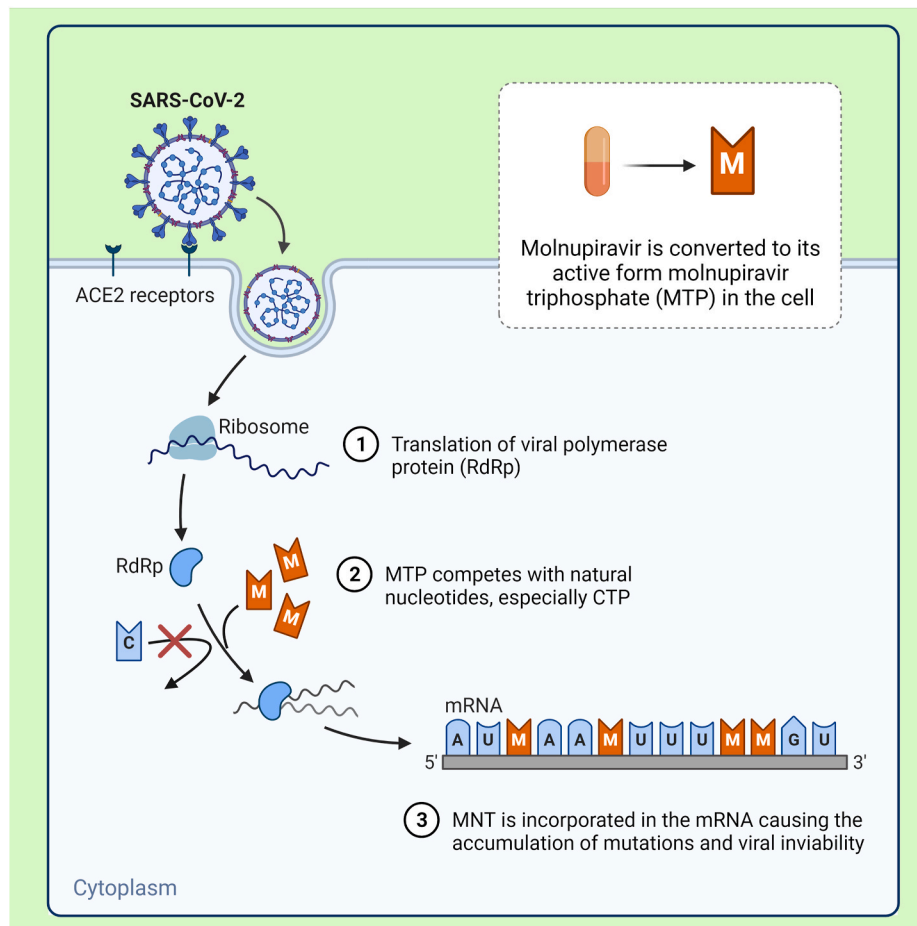


Fig. 1. The schematic representation of action mechanism of molnupiravir. Molnupiravir converted into the active form of the drug in the host cell and competes with the cytidine triphosphate (CTP). Then, molnupiravir integrates into the viral RNA strands and leads to the high number of mutations in the viral RNA. Hence, leads to the blockage of viral reproduction and lower viral load in the patient with SARS-CoV-2 infection. The figure has been adapted from the [BioRender.com](https://www.biorender.com).

07321332; ritonavir) recorded that the antiviral drug reduced the risk of hospitalization or death by 89% compared to placebo in non-hospitalized high-risk adults with COVID-19. In addition, in the overall study population through Day 28, no casualties were reported in patients who received PAXLOVID™ as compared to 10 deaths in patients who received the placebo. In another study, the oral antiviral pills from Merck & Co (MRK.N) and Pfizer Inc (PFE.N) have been shown to significantly blunt the worst outcomes of COVID-19 if taken early enough. Still, clinicians have warned the vaccine-hesitant people not to confuse the benefit of the treatments with prevention afforded by vaccines [3,4].

Although an effective oral antiviral would be a massive help in the battle against COVID-19, it is unclear if molnupiravir would be available to everyone. The estimated cost for a five days course is 700 US\$, and the US government has committed to pay 1.2 billion US\$ for 1.7 million courses of molnupiravir. While analyzing the cost of antiviral pills, Rachel Cohen, executive director at the Drugs for Neglected Diseases Initiative, United States (US) has commented that “Are we going to be in a situation where the price is reasonable in low- and middle-income countries?” There is no doubt that the cost of antiviral pills is far less than the price of remdesivir or monoclonal antibodies (MABs) such as tocilizumab. However, it is still expensive for some developing countries. In addition, Merck, which is co-developing the compound with Ridgeback, has struck licensing agreements with five Indian manufacturers of generic drugs. Those deals allow the manufacturers to set their prices in India and 100 other low- and lower-middle-income countries. But even if the poorer countries can afford the drug, they might not have

the diagnostic capacity to use it properly. Moreover, if molnupiravir needs to be given in the first five days after the onset of symptoms, it would require rapid diagnosis of infected people, which could be a huge challenge for many developing countries and even some wealthy ones [4].

In conclusion, the anti-covid pills have shown promising potential in mitigation of the deleterious consequences of COVID-19. Moreover, the use of antiviral pills to be taken at home could be helpful in controlling the fatality rate, especially amid the emergence of novel variants of SARS-COV-2. As we all know, the health sectors of not only the developing countries but also of the developed countries have suffered significantly in providing treatment to patients with COVID-19 while the cases were on the surge. The emergence of novel variants of SARS-COV-2 has again accelerated the COVID-19 infections in various countries. At this time, antiviral pills can be a game-changer by reducing hospitalization and hence declining the death rates. In addition, these oral antiviral pills could be helpful for countries such as South Africa to control the COVID-19 associated deaths while facing shortage of vaccines. There is no doubt, some contradictions associated with antiviral pills, such as the risk of inducing mutations in the host cell, need to be addressed in the coming future. Finally, it is suggested that patients should consult their doctors before availing of the benefits of these antiviral pills, and the use of antiviral pills should be under strict regulations.

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Manish Dhawan: Conceptualization, Data Curation, Visualization, Writing - Original Draft, Writing - review & editing. **Priyanka:** Conceptualization, Writing - Original Draft, Writing - review & editing. **Om Prakash Choudhary:** Supervision, Writing - Original Draft, Writing - review & editing. All authors critically reviewed and approved the final version of the manuscript.

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Data statement

The data in this correspondence article is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature.

Declaration of competing interest

All authors report no conflicts of interest relevant to this article.

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