1 Paxlovid and Molnupiravir Approved to Manage COVID-19: A Countdown for SARS
2 CoV-2 Variant Apocalypse.

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Dear Editor,

In two subsequent days, the US FDA has issued an emergency use authorization for Pfizer's Paxlovid (nirmatrelvir and ritonavir) and Merck's molnupiravir to be used orally for mild to moderate COVID-19. The instructions included prompt administration after diagnosis of COVID-19 and within five days of symptom onset. Furthermore, it allowed Paxlovid to be administered to adults and children 12 years of age and older weighing at least 40 kilograms or about 88 pounds while molnupiravir was not authorized for use in patients younger than 18 years of age because to avoid impairment of bone and cartilage growth. Notably, the USA FDA has admitted failure of molnupiravir when it was administered to manage hospitalized COVID-19 patients. I wish to challenge this approval for both drugs while discussing the risk benefit ratio of each if used in mild to moderate COVID-19 patients.

The use of protease inhibitors, the group to which nirmatrelvir and ritonavir belong, to manage RNA viral infection e.g., HIV and HCV has been constantly associated with a risk of resistance that was described as an inevitable outcome under the selective pressure of therapy as these viruses are known with high adaptability due to high genome replication rates, high intrinsic RNA polymerase error rate, accumulating mutations in the viral genome will eventually lead to resistance associated variants due to class cross-resistance mutations and polymorphisms [1-4]. However, second generation protease inhibitors, as Paxlovid, was shown to have an advantage of a raised genetic barrier towards resistance with multiple needed mutations, yet this barrier is not immune in over a quarter of sampled cases [5] especially when used in resource limited setting with less frequent monitoring[6] as the virus might evolve to upgrade the required need mutations or even develop novel alternative resistance mechanisms[7]. Alarminglly, molnupiravir is primarily acting through promotion of SARS CoV-2 RNA mutagenesis[8] which could also affect mammalian cells[9].

We wish to suggest that the risk benefit ratio to use either Paxlovid or molnupiravir for mild to moderate COVID-19 patients is outbalanced considering that SARS CoV-2 is much more adaptable than both HIV and HCV, we risk the evolution of multi-drug resistant SARS CoV-2 variants especially if some physicians used both drugs together. Moreover,

it is not unusual to encounter post marketing toxicity reports for Paxlovid as occurred before with some members of protease inhibitors and both acute short term and serious long term serious adverse effects should be closely monitored with molnupiravir.

Finally, I wish to recommend not to approve either Paxlovid or molnupiravir in those countries that are still considering their license, to revoke the emergency use authorization in those countries that issued it, and it is very unfortunate for humanity that safe, generic and highly effective Kelleni's African protocol used to manage pediatric, adult and pregnant COVID-19 patients [10] is not, yet, adopted by those countries where COVID-19 is wasting thousands of lives daily and I humbly suggest the reasons for this long-lasting ignorance are not medical or scientific.

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Conflict of interests

None

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