



## Letter to the Editor

# Coronavirus disease 2019 (COVID-19) oral antivirals stewardship: Establishing game rules

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*To the Editor*—Vaccines against coronavirus disease 2019 (COVID-19) are the cornerstone of preventive strategies during this pandemic.<sup>1</sup> However, COVID-19 vaccine immunity wanes over time,<sup>2</sup> while specific population groups, such as the immunocompromised, may not be able to mount an adequate immune response to COVID-19 vaccination.<sup>3</sup> In addition, new variants with spike-protein mutations continue to emerge, raising concerns about immune escape and breakthrough infections in vaccinated individuals.<sup>4</sup>

Recently, based on the results of relevant clinical trials, an emergency use authorization was granted by the FDA for 2 new oral antivirals against COVID-19: molnupiravir by Merck and Ridgeback Biotherapeutics and Pfizer’s nirmatrelvir-ritonavir. These antivirals, when administered within 5 days of symptom onset in adult patients with mild to moderate COVID-19, reduced the risk of hospitalization and death.<sup>5,6</sup> Both target specific enzymes and functions other than the spike protein and can complement vaccines. Nevertheless, the urgent need for effective outpatient treatment amid ongoing transmission entails the risk of irrational use of these antivirals. Thus far, data regarding the potential to induce resistance in case of inappropriate use are lacking. Cost should also be taken into consideration because each treatment course costs hundreds of dollars.<sup>7,8</sup>

For these reasons and to optimize their use, antiviral stewardship initiatives are necessary. These initiatives should target various sectors and levels of the medication prescription chain, including the healthcare system, prescriber and patient education, prescription practices, patient monitoring and feedback, communication, and diagnostics (Fig. 1).

From a healthcare system perspective, administration monitoring via electronic prescription is an efficient way to control antiviral usage. For instance, electronic health system templates could automatically preauthorize administration only within the first 5 days after symptom onset. National healthcare authorities should adjust electronic prescribing systems so that essential clinical information is required in the form of a checklist before allowing submission of the prescription. Such information could include patient age, symptoms and date of onset, date of laboratory confirmed diagnosis, prior COVID-19 history, vaccination status,

chronic medical conditions predisposing to severe disease, and exclusion of contraindications (eg, pregnancy). Currently, limited drug availability and high treatment cost dictate these antivirals should only be given to high-risk outpatients. Postprescription review and feedback according to predetermined criteria can help improve outcomes; several studies have shown that audit and feedback is a more effective stewardship tool than prior authorization and restriction.<sup>9</sup>

It is the physician’s responsibility to inform patients about the indications as well as the dose and duration of therapy, and to urge them to start their treatment on time and to complete their course of medication. In addition, feedback from patients is beneficial regarding information about symptom attenuation, possible adverse effects or disease progression, in parallel with organized pharmacovigilance activities. For example, an electronic platform connected to the online prescription system could be completed by patients who receive antiviral medication, while healthcare systems obtain, analyze, and communicate this information to prescribers, patients, and the public. Such information could contain type of treatment, time of initiation, adverse events, drug interactions, time to symptom improvement, need for hospital admission, and other patient outcomes. Continuous surveillance will allow for early identification of opportunities for improvement through targeted interventions.

The aforementioned tools are directed toward optimization of organizational, surveillance, and prescribing preparedness. However, to ensure a minimum competency skill set for all prescribers, prompt, accessible, and effective educational resources are necessary.<sup>10</sup> This is particularly critical during the early phase of disposal of these antiviral medications to promote appropriate prescribing practices. Training should include prescription criteria, basic pharmacology, drug interactions, and guidance regarding patient monitoring. Ease of access to specific tools should be ensured, including clinical guides, checklists, and data resources. Evidence-based and effective communication for prescribers and patients should be provided. It is also important to continue to emphasize the significant differences between prevention of disease through vaccination and treatment of disease with medications.<sup>1</sup> Communication extends to public awareness campaigns that inform, present data, and enhance trust in the scientific and medical community.

The evolution of diagnostics is a relevant and important field, necessary for effective stewardship.<sup>11</sup> Early diagnosis guides

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**Fig. 1.** Antiviral stewardship initiatives for the judicious use of the new oral treatments against COVID-19.

appropriate management, including administration of antiviral treatment in those in need. This factor is pivotal in the case of the antivirals discussed here, which are more effective during the early stages of COVID-19. Countries that are investing in these medications are expected to enhance their diagnostic yield by supporting their testing capacity (either molecular or antigen testing or both) to meet the expected needs of prompt diagnosis.

In conclusion, health services around the world are overwhelmed by the ongoing pandemic, and new oral antiviral medications represent an important addition in our limited armamentarium against COVID-19. Early implementation of antiviral stewardship interventions is required to ensure their appropriate use and to monitor their real-world effectiveness until we can determine their true role in the fight against the COVID-19 pandemic.

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