Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Caution required with use of ritonavir-boosted PF-07321332 in COVID-19 management

We read with interest the news that the UK Government has announced deals to procure the oral antivirals for SARS-CoV-2, molnupiravir (Lagevrio, Merck [Branchburg, NJ, USA]) and ritonavir in combination with PF-07321332 (Paxlovid, Pfizer [New York, NY, USA]).[1] Although we welcome further partnership between the government and pharmaceutical industry in the provision of effective agents to manage the COVID-19 pandemic, we urge caution with the widescale use of ritonavir, given its propensity for causing clinically significant drug–drug interactions with commonly prescribed and over-the-counter medications.

PF-07321332 is a SARS-CoV-2 protease inhibitor currently being assessed in phase 3 trials for its safety and efficacy in the treatment of non-hospitalised adult patients with COVID-19 who are not at increased risk of developing severe illness. The drug is also being explored as a post-exposure prophylaxis agent in patients found to have been exposed to SARS-CoV-2. Treatment duration is 5–10 days, and PF-07321332 is co-administered with low-dose ritonavir to boost and maintain plasma concentrations of the novel agent.

Ritonavir is a potent inhibitor of the CYP3A4 isoenzyme and is used widely within HIV antiretroviral therapy to enhance plasma drug concentrations and to prolong the half-life of CYP3A substrates. Launched initially in the mid-1990s as a protease inhibitor designed to treat HIV infection, the use of ritonavir was complicated by high pill burden, poor tolerability, and drug interactions. At doses of 100 mg once or twice daily, ritonavir is well tolerated and effective in enhancing the pharmacokinetic profile of combination agents (eg, protease inhibitors or integrase agents) through inhibition of intestinal and hepatic CYP3A4 and P-glycoprotein (ABCB5 P-gp), resulting in increases in the area under the curve, maximum concentration, and half-life.[2] This strategy has reduced the frequency of dosing in HIV antiretroviral therapy, pill burden, impact of food on bioavailability, and variability of systemic drug exposure, and has improved treatment efficacy.[3]

It is imperative that clinicians are aware of the pharmacokinetic properties of ritonavir. In addition to the drug's potent inhibition of the CYP3A4 isoenzyme, ritonavir shows further inhibitory effects on CYP2D6, CYP2C19, CYP2C8, and CYP2C9. Furthermore, ritonavir inhibits ABCB5 P-gp and the cellular transport mechanism via the efflux pump, which might contribute to the pharmacokinetic boosting effect through disruption of the active transport of concomitant agents out of cells from the intestinal tract, liver, and kidneys. Additionally, ritonavir is a known inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and the UGT family.[4] Other drug transporters inhibited by ritonavir include the breast cancer resistance protein (ABCG2), the organic anion transporting polypeptides (hOCT1) in the liver, and MATE1, which is important in renal drug handling.[5]

Although ritonavir has been expertly managed in the context of combined HIV antiretroviral therapy, the potent boosting and induction effects of the drug have led to various interaction issues with co-medications, encompassing prescribed, over-the-counter, and recreational agents. Concomitant use of ritonavir with some drugs is absolutely contraindicated because of the risk of clinically significant interactions that might lead to life-threatening adverse events. Such agents include statins, steroids, sedative hypnotics, anticoagulants, and antiarrhythmic therapies, many of which are prescribed separately in older populations (aged ≥70 years) at the greatest risk of complications from SARS-CoV-2 infection.

Despite how treatment of patients with COVID-19 with ritonavir-boosted antiviral agents is likely to be a short-term measure, the potential for clinically significant drug–drug interactions remains. For example, inhibitory effects are apparent within short timeframes. We would recommend that all prescribing clinicians become familiar with potential interactions by use of dedicated reference guides, such as the University of Liverpool antiretroviral drug interaction checker and existing antiretroviral treatment guidelines,[6] and by liaising closely with colleagues experienced in the treatment of HIV infection, to reduce the potential for clinically significant iatrogenic adverse or life-threatening events

JH has received funding in the form of a research fellowship from the CW+ charity and The Westminster Medical School Research Trust; and has received honoraria from Gilead, unrelated to this Correspondence. SJCP has received a research grant from the Scientific Exploration Society–Viscount Gough, unrelated to this Correspondence. NM has received speaker fees from Beyer and Pfizer; and received educational support from Eumedica and Baxter. GWD has received consultation fees from DNA Nudge. LSPM has consulted for and received speaker fees from bioMerieux, Pfizer, Eumedica, Shionogi, Pulmocide, Umovis Labs, DNA Electronics, Profile Pharma, and Dairy Crest; and received research grants from the UK National Institute for Health Research (NIHR), LifeArc, and the CW+ charity. RJ has received honoraria, speaker fees, travel support, or research grant funding from Gilead, ViiV Healthcare, Bristol Myers Squibb, Abbvie, Janssen, and Merck. All other authors declare no competing interests. JH acknowledges support from the CW+ charity and The Westminster Medical School Research Trust. LSPM acknowledges support from the NIHR, Imperial Biomedical Research Centre, and the NIHR Health Protection Research Unit in health-care associated infection and antimicrobial resistance at Imperial College London, in partnership with Public Health England. The views expressed in this Correspondence are those of the authors, and not necessarily those of the National Health Service, the NIHR, or the UK Department of Health.

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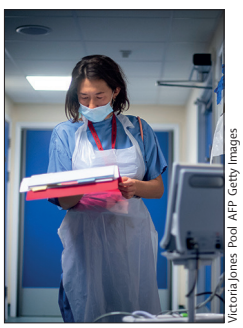

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For more on the **University of Liverpool drug interaction checker** see https://www.hiv-druginteractions.org

For **interaction information on ritonavir** see https://bnf.nice.org.uk/interaction/ritonavir-2.html

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COVID-19 ARDS: getting ventilation right

We read with special interest the Article by Ryan Barbaro and colleagues,[1] describing the evolving outcomes of patients with COVID-19 who required extracorporeal membrane oxygenation (ECMO) during 2020. We were sad to corroborate the same increased mortality we had observed in our own patients. However, we wish to clarify two key aspects that we hope will supplement the conclusions of this important Article.

First, the assumption that a non-invasive ventilation (NIV) strategy can be deleterious for patients with acute respiratory distress syndrome (ARDS) and with COVID-19 has no clinical evidence so far.[2] Furthermore, NIV has been progressively used during the evolving pandemic and is probably more related to the improvement in survival observed in hospitalised patients than to a delay in intubation and hypothetically worse outcome.[3]

And second, when to start ECMO on these patients has probably changed during this period due to a higher use of NIV (the authors do not report days on NIV before intubation). We had never before ventilated so many patients with severe ARDS and we have learned that a so-called wait and see approach in terms of intubation or ECMO, as with many other invasive procedures in critically ill patients,[4] might also be valid. ECMO should be initiated in those patients who cannot be protectively ventilated in the context of extremely severe ARDS.[5] In this scenario, mortality might increase in those patients who finally require ECMO assuming that this delayed strategy will save many more other patients from receiving an intervention that is not free from complications besides its high cost of resources.

We declare no competing interests.

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Authors' reply

We thank Xosé Pérez-Fernández and colleagues for their thoughtful Correspondence regarding our study of extracorporeal membrane oxygenation (ECMO) in COVID-19.[1] We agree that our study does not provide evidence that forms of non-invasive ventilation (NIV), such as high-flow nasal cannula and mask or helmet ventilation, might be deleterious compared with other strategies. Our observational study was not designed to make causal inferences regarding the potential superiority of ECMO or any pre-ECMO support strategy. We showed that the more recent cohort with higher mortality had increased use of NIV and decreased duration of pre-ECMO invasive mechanical ventilation (IMV).[1] We did not measure the initiation time of NIV, however, and so could not test for an association between duration of pre-ECMO NIV and the relative risk of mortality.

Although many patients with severe COVID-19 might benefit from the use of NIV, the subset of patients who ultimately do not respond to NIV and require IMV are precisely those who are likely to have high work of breathing, high transpulmonary pressures, and who are therefore at risk of developing patient self-inflicted lung injury.[2] This situation might select for more severely ill patients receiving IMV and ultimately ECMO. It is one hypothesis out of a number we put forward to help explain the association with increased mortality in those who ultimately do not respond to these levels of support. However, this is not an argument for or against the use of NIV in this setting. Even if the hypothesis is correct, NIV might still be the appropriate therapy for any given patient. A randomised clinical trial is required to fully address this question.

To date, there are no prospective clinical trials evaluating the effect on outcomes of the timing of initiating ECMO support. However, in accord with the suggestion of