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.

available, we were unable to establish the effect of influenza viruses or SARS-CoV-2 vaccination on outcome in monoinfected and co-infected patients.

As public health restrictions are lifted, respiratory virus co-infections are more likely to occur during future winters. The marked increase in risk among patients with co-infection has several implications for policy. First, our results provide further support for vaccination against both SARS-CoV-2 and influenza viruses. Second, they suggest that testing for influenza viruses is important in hospital inpatients with COVID-19 to identify patients at risk and a cohort of patients who might have different responses to immunomodulatory and antiviral therapy.

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1 Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic–United States, Australia, Chile, and South Africa, 2020. *Am J Transplant* 2020; **20:** 3681–85.
2 Gomez GB, Mahé C, Chaves SS. Uncertain effects of the pandemic on respiratory viruses. *Science* 2021; **372:** 1043–44.
3 Kawai S, Fukushima K, Yomota M, et al. Number of patients with influenza and COVID-19 coinfection in a single Japanese hospital during the first wave. *Jpn J Infect Dis* 2021; **74:** 570–72.
4 Dunning JW, Merson L, Rohde GGU, et al. Open source clinical science for emerging infections. *Lancet Infect Dis* 2014; **14:** 8–9.
5 Aitken C, Jeffries DJ. Nosocomial spread of viral disease. *Clin Microbiol Rev* 2001; **14:** 528–46.

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

For more on the **COVID-19 interaction checker** see https://www.covid19-druginteractions.org

Ritonavir and COVID-19: pragmatic guidance is important

We thank Joseph Heskin and colleagues[1] for highlighting the crucial issue of drug–drug interactions (DDIs) with ritonavir, the pharmacoenhancer or booster co-formulated with the novel SARS-CoV-2 protease inhibitor, PF-07321332 (Paxlovid, Pfizer [New York, NY, USA]).[2] Since Paxlovid will be primarily administered to non-hospitalised individuals and prescribed by clinicians who might not routinely manage complex interactions or have access to their full medication list, an awareness of the DDI potential and clear pathways to support safe decision making are essential, ideally led by pharmacists who have speciality knowledge in this area. If managed appropriately, DDI should, in most cases, not necessitate a change in antiviral management.

The onset of ritonavir's inhibitory effect on the CYP3A4 isoenzyme, and to a lesser degree CYP2D6, is rapid, but the inhibition is also lost rapidly after drug cessation, mostly within 2 days.[3] This information is important to guide dose adjustment or pause of concomitant medication where advised. As Heskin and colleagues clearly highlight, ritonavir also induces several cytochrome P450 isoenzymes, but this induction effect is slow to develop and is unlikely to be of clinical importance when used in a short course. However, an important consideration in people established on strong CYP3A inducers, such as carbamazepine, phenytoin, and rifampicin, is that these inducers are likely to reduce nirmatrelvir exposure and, as induction persists for about 2 weeks after cessation, are a contraindication to its use.

The clinical impact of DDIs depends on a number of factors including: the therapeutic window of the co-administered drug; the degree to which co-administered drugs are metabolised via CYP3A4 (ie, higher DDIs magnitudes are anticipated for those extensively metabolised by CYP3A4, for instance simvastatin); and the clinical indication and relative benefit treatment for the individual. We, of course, advise prescribers to consult the relevant summaries of product characteristics, and appropriate prescribing tools. Heskin and colleagues[1] refer to the University of Liverpool HIV drug interaction checker, and, although this is an invaluable tool, we encourage clinicians to refer to their specific COVID-19 interaction checker, as the advice might differ for short-term ritonavir use. However, the real-life effect of known or predicted DDIs, and recommended practice, might differ from prescribing advice, and sources of advice might be inconsistent. Antiretrovirals are

one example of potential DDIs. The current UK patient information leaflet warns that Paxlovid treatment can result in medicines used to treat HIV becoming less effective.[4] However, any resulting DDIs are not considered clinically important, as reflected by the University of Liverpool interaction checker, and the UK prescribing advice does not warn of reduced antiretroviral effectiveness.[5] Another example is anti-platelet agents. Ritonavir reduces exposure to the active metabolite of clopidogrel, resulting in reduced anti-platelet effectiveness. This DDI might be clinically important in the context of a recent vascular stent but the potential interaction is not included in the information for patients or prescribers.[4,5] Conversely, the University of Liverpool COVID-19 interaction checker advises not to co-administer Paxlovid and clopidogrel, but provides more nuanced advice based on clinical indication, advising that the period within 6 weeks after stenting is the highest risk and, beyond that, a transient loss in effectiveness might be acceptable versus a change in drug or less effective antiviral. However, we suggest that the association between COVID-19 and thrombotic events might warrant a more cautious approach and switch to an alternative antiplatelet therapy (such as prasugrel or ticagrelor) or COVID-19 treatment for the first 12 weeks after stent therapy, and potentially longer (up to 6 months in the presence of an acute coronary syndrome).

Careful review of concomitant medication, led where possible by a pharmacist, and clear guidance for prescribers, is essential to facilitate safe and pragmatic decision making. Rapid access to appropriate specialty advice will assist risk–benefit assessment in complex cases, but optimal COVID-19 treatment, with an alternative to Paxlovid if necessary, should not be delayed due to DDI concerns.

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1 Heskin J, Pallett SJC, Mughal N, at al. Caution required with use of ritonavir-boosted PF-07321332 in COVID-19 management. *Lancet* 2022; **399:** 21–22.
2 US Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19. Dec 22, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19 (accessed Feb 25, 2022).
3 Stader F, Khoo S, Stoeckle M, et al. Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. *J Antimicrob Chemother* 2020; **75:** 3084–86.
4 UK Medicines & Healthcare products Regulatory Agency. Summary of product characteristics for paxlovid. Feb 9, 2022. https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid/summary-of-product-characteristics-for-paxlovid (accessed Feb 11, 2022).
5 UK Medicines & Healthcare products Regulatory Agency. Patient information leaflet for paxlovid. Feb 9, 2022. https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid/patient-information-leaflet-for-paxlovid (accessed Feb 11, 2022).

War in Ukraine and barriers to diabetes care

The conflict and violence that followed the military invasion of Ukraine in late February, 2022, has already left substantial scars on the population. The human cost of the combat becomes more evident each passing day. On March 15, 2022, the ongoing hostilities affected hundreds of thousands of inhabitants and substantially damaged crucial civilian infrastructure in eastern Ukraine, including homes, schools, hospitals, and water and gas pipelines. In some southeastern cities, such as Mariupol, people have been facing critical shortages of food, water, and life-saving medicines, which were aggravated by the blockade of humanitarian convoys trying to reach the region with supplies.[1] According to the UN High Commissioner for Human Rights, a total of 691 civilian deaths were confirmed by March 14, 2022—a number that is probably underestimated.[2] In the middle of this social and humanitarian crisis, patients who have chronic diseases perceive health resources deteriorating at an unprecedented rate, raising concerns about their sustainability. For people living with a disease as prevalent as diabetes, the scarce access to essential health resources is even more worrisome. According to the International Diabetes Federation Atlas, there were about 2 325 000 inhabitants with type 2 diabetes in Ukraine in 2021, representing a prevalence of 7·1%. For type 1 diabetes, around 6700 children and adolescents had the diagnosis in the past year.[3]

The effects of the military conflict, which began on Feb 24, 2022, might have the potential to affect different domains of diabetes care. First, some infrastructures such as deliveries and pharmacy services have been disrupted, resulting in shortages and rationing of insulin and supplies for blood glucose control. Without receiving the appropriate treatments, especially in cases of type 1 diabetes, there is a risk of life-threatening complications, such as diabetic ketoacidosis. Notwithstanding, the military conflict brought the need to reallocate resources to support victims of the

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