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## Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect

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Sir,  
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly infectious, causing coronavirus infectious disease 2019 (COVID-19) worldwide.<sup>1</sup> One of the experimental treatments includes the HIV drug lopinavir boosted with ritonavir. Both PIs cause irreversible mechanism-based inhibition (loss of metabolizing enzymes) and induction of metabolizing enzymes in the liver and intestine, which often leads to drug–drug interactions (DDIs) with co-medications.<sup>2</sup> The duration of cytochrome P-450 (CYP) 3A inhibition after stopping lopinavir/ritonavir treatment is not well understood, leading to some uncertainty as to how long to maintain adjusted doses of co-medications or when to restart drug therapies against comorbidities.

We investigated the duration of hepatic and intestinal CYP3A inhibition after stopping lopinavir/ritonavir treatment by a verified modelling approach.<sup>3</sup> Lopinavir/ritonavir (400/100 mg twice daily) was administered for 7 days in a virtual trial to achieve steady-state CYP3A inhibition and the abundance of CYP3A was estimated for 21 consecutive days. The interaction potential after stopping lopinavir/ritonavir was investigated with the CYP3A probe substrate midazolam. Midazolam was administered orally (5 mg once daily) starting on the seventh day of the study. Simulations were performed in the four age categories 20 to 50 years, 60 to 69 years, 70 to 79 years and 80 to 89 years, because severe COVID-19 outcome is more likely in older individuals having comorbidities.<sup>4</sup> Our model takes age-related physiological changes into account.<sup>3</sup> These include a decrease in hepatic and renal blood flow and glomerular filtration rate, which lead to a decline in drug clearance.

Furthermore, body composition changes with advanced ageing, towards more adipose tissue weight and lower body water, which does, however, not affect the volume of distribution.<sup>5,6</sup> In each age group, 100 subjects (50% women) in 10 trials were simulated. The reduction in DDI magnitude for midazolam was calculated using the last day of lopinavir/ritonavir administration as a basis. Results are reported as mean (95% CI).

CYP3A inhibition decreased profoundly 24 h after stopping lopinavir/ritonavir, with a 61% (17%–80%) and 46% (8%–80%) reduction in adults aged 20 to 50 years and 80 to 89 years, respectively [Table 1 and Figure S1 (available as [Supplementary data](#) at JAC Online)]. The temporal decrease in CYP3A inhibition was slower 3 days after stopping lopinavir/ritonavir compared with the first day post-COVID-19 treatment, meaning that the initial novel CYP3A synthesis is fast in the first hours after discontinuing the strong mechanism-based CYP3A inhibitor and becomes saturated after 72 h. In all age groups, there was more than 80% disappearance of CYP3A inhibition 5 days after stopping lopinavir/ritonavir under the consideration of population variability. Complete disappearance of CYP3A inhibition took 21 days in all simulated age groups.

The experimental COVID-19 treatment lopinavir/ritonavir irreversibly inhibits CYP3A. After stopping the treatment, CYP3A needs to be synthesized, which depends on the turnover rate of CYP3A rather than the half-life of lopinavir/ritonavir, leading to a longer inhibition as opposed to competitive inhibition.<sup>7</sup> We demonstrated that the CYP3A inhibitory effect was reduced by 80% after 48 h in adults aged 20 to 50 years and after 72 h in adults at least 60 years old, who are more likely to have severe COVID-19 outcomes and be taking more co-medications.<sup>4</sup> Thus, pre-COVID-19 treatments can be restarted at normal doses 2 to 3 days after stopping lopinavir/ritonavir for most individuals. However, given the physiological variability of COVID-19 patients, which leads to variability in the DDI magnitudes (see the 95% CI in Table 1), we suggest standard doses of co-medication can be safely given on the fifth day after stopping lopinavir/ritonavir to all hospitalized COVID-19 patients.

Lopinavir/ritonavir does not only inhibit CYP3A, but also induces CYP2C9, CYP2C19 and CYP1A2.<sup>2</sup> Induction implies new synthesis of enzymes and therefore resolution can take up to 3 weeks.<sup>8</sup> Narrow therapeutic-index drugs induced by lopinavir/ritonavir, which warrant monitoring, include for instance vitamin K antagonists.

It is also important to note that COVID-19 leads to a cytokine storm with elevated IL-6 concentrations,<sup>9</sup> which may also irreversibly inhibit CYP3A, although to a lesser extent than lopinavir/ritonavir.<sup>10</sup> Thus, careful monitoring of co-medications metabolized by CYP3A is important since doses may need to be adjusted in all hospitalized COVID-19 patients with the return to pre-COVID-19 doses in the same time range as reported here for lopinavir/ritonavir.

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**Table 1.** Disappearance of hepatic and intestinal CYP3A inhibition after stopping lopinavir/ritonavir treatment

Day after stopping lopinavir/ritonavir	Disappearance of hepatic and intestinal CYP3A inhibition (%)							
	20–50 years		60–69 years		70–79 years		80–89 years	
	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI
0	0	0–0	0	0–0	0	0–0	0	0–0
1	61	17–80	51	9–78	50	8–76	46	8–80
2	80	61–91	76	47–91	74	18–89	71	10–92
3	87	77–95	87	72–95	84	53–94	81	12–96
4	91	84–97	91	82–97	89	74–96	88	67–97
5	94	88–98	93	87–98	92	82–97	92	83–98
6	95	91–98	95	90–98	94	87–98	94	89–99
7	96	93–99	96	92–99	96	90–98	95	92–99
14	99	98–100	99	98–100	99	98–100	99	98–100
21	100	100–100	100	100–100	100	100–100	100	100–100

## Transparency declarations

None to declare.

## Supplementary data

Figure S1 is available as [Supplementary data](#) at JAC Online.

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