Comment on “Comparative Population Pharmacokinetics of Darunavir in SARS-CoV-2 Patients vs. HIV Patients: The Role of Interleukin-6”

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We read with interest the manuscript by Cojutti et al. [1], which documented that darunavir clearance and drug trough concentrations were, respectively, 60% lower and five-fold higher in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compared with patients with human immunodeficiency virus (HIV) for the same daily drug dose (800 mg once daily). These results are in agreement with previous findings showing four-fold higher lopinavir trough concentrations in patients with SARS-CoV-2 vs patients with HIV [2–4]. As both HIV protease inhibitors are substrates of cytochrome P450 3A4, the authors hypothesized that the reduced clearance of darunavir and lopinavir in patients with SARS-CoV-2 could have been driven by an impairment of drug metabolism related to the viral infection. Remarkably, interleukin-6 was the only clinical covariate that significantly correlated with darunavir pharmacokinetics. Accordingly, it has been proposed that the acute viral infection perpetrated a pro-inflammatory state that may, in turn, downregulate cytochrome P450 3A4 expression and activity, ultimately resulting in increased darunavir systemic concentrations [1, 5]. As indirect support for this hypothesis, the authors have shown that lower interleukin-6 levels measured in the comparator group of patients with HIV were

associated with higher darunavir clearance compared with patients with SARS-CoV-2.

Taken together, findings from lopinavir and darunavir can be considered as a proof of concept of viral disease–drug interactions, recalling the issue of optimal dose selection of the cytochrome P450 3A4 substrate in patients with SARS-CoV-2. We believe, however, that the study by Cojutti et al. lacks a third mandatory comparator group: the patients co-infected with HIV and SARS-CoV-2. The inclusion of this additional group could allow the characterization of the pharmacokinetics of darunavir in patients with the concomitant presence of chronic and acute inflammatory states related to chronic and acute viral infections, respectively.

To address this issue, we searched through the database of our Clinic of Infectious Diseases for HIV-infected patients with a diagnosis of SARS-CoV-2 infection, given darunavir as maintenance antiretroviral therapy who underwent therapeutic drug monitoring of darunavir trough concentrations during COVID-19. Data on interleukin-6 and/or C-reactive protein were also collected as biomarkers of acute inflammatory progression in patients with SARS-CoV-2. To indirectly verify the comparability of the darunavir trough concentrations in patients with SARS-CoV-2 described by Cojutti et al., with those measured in our patients coinfecting with HIV/SARS-CoV-2, we also considered a control group of patients with HIV not infected with SARS-CoV-2 undergoing therapeutic drug monitoring of darunavir trough concentrations (as done by Cojutti et al. [1]). Data were expressed as median (interquartile range); significance was set at $p < 0.05$.

Six patients with HIV co-infected with SARS-CoV-2 and fulfilling the inclusion criteria were retrieved from the database of our clinic. They were mostly male (four out of six), with a median age of 62 (58–64) years. As shown in Table 1, no significant differences were found when comparing darunavir trough concentrations in patients co-infected with HIV/SARS-CoV-2 with patients mono-infected with HIV (836 [409–1523] vs 1273 [734–1954] ng/mL; $p = 0.861$).

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Table 1 Comparison of darunavir trough concentrations and inflammatory indices in patients with SARS-CoV-2 and/or HIV infection from our cohort vs the Cojutti et al. cohort [1]

	SARS-CoV-2 and HIV	HIV Our cohort	SARS-CoV-2 Cojutti et al. [1]	HIV Cojutti et al. [1]
Patients, <i>n</i>	6	130	30	25
Darunavir trough, ng/mL	836 (409–1523)	1273 (734–1954)	4960 (2015–7951)	1010 (550–2112)
Interleukin-6, pg/mL	17 (4–53)	n.a.	31 (10–115)	2 (2–3)
C-reactive protein, mg/L	21 (10–35)	n.a.	n.a.	n.a.

Data were given as median (interquartile range)

HIV human immunodeficiency virus, n.a. not available, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

We could not make formal statistical comparisons between our datasets and the those from Cojutti et al. (individual darunavir concentrations for the latest study were not available). However, to a visual evaluation, the darunavir trough concentrations measured in patients co-infected with HIV/SARS-CoV-2 and patients mono-infected with HIV from our cohort fully matched to those measured in the comparator group of patients with HIV from the other study (1010 [550–2112] ng/mL), resulting in five-fold lower than darunavir trough concentrations measured in patients mono-infected with SARS-CoV-2 (4960 [2015–7951] ng/mL). No major differences in the inflammatory states were observed between the two cohorts of patients with SARS-CoV-2 (Table 1). Taken together, these findings provide indirect evidence that the observed differences in the darunavir trough concentrations between patients mono-infected with SARS-CoV-2 and patients co-infected with HIV/SARS-CoV-2 were not biased by potential analytical issues (the concentrations of darunavir in patients mono-infected with HIV measured in the two studies were comparable) or affected by key differences in the inflammatory status between the two cohorts (patients co-infected with HIV/SARS-CoV-2 and patients mono-infected with SARS-CoV-2 had comparable interleukin-6 levels). Moreover, the darunavir trough concentrations measured in patients mono-infected with HIV and patients co-infected with HIV/SARS-CoV-2 were similar to those measured previously in healthy volunteers given darunavir at 800 mg at steady state [6, 7]. Hence, combined evidence from our study and the Cojutti et al. study provides two key messages: (a) the increased darunavir exposure can be attributed exclusively to SARS-CoV-2 and (b) this effect is switched off by the presence of concomitant HIV infection.

The mechanism by which HIV is able to mitigate the effects of SARS-CoV-2 on cytochromal enzyme activity and darunavir clearance cannot be derived from the present study given its retrospective naturalistic design. Despite these limitations, we believe that our case series, although small, may add another important piece to the puzzle well described by Cojutti et al. [1], showing that in patients with SARS-CoV-2 co-infected with HIV the presence of a pro-inflammatory

state does not result in increased darunavir exposure. Even though the clinical relevance of these findings remains to be explored, this is a good example of how the co-existence of acute and chronic inflammatory conditions might provide unexpected and unpredictable results on drug disposition.

Declarations

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Conflicts of interest/competing interests Cristina Gervasoni has received personal fees from MSD, ViiV, Gilead, and Janseen Cilag, outside the submitted work. Dario Cattaneo has received personal fees from MSD, ViiV, and Janseen Cilag, outside the submitted work. Mario Corbellino, Valeria Cozzi, and Marta Fusi have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The study was approved by our hospital's ethics committee (Comitato Etico Interaziendale Area 1, Milano, Italy).

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' contributions Conception and study design: DC, CG; data acquisition: MC; data analysis: VC, MF. Each author contributed important intellectual content during manuscript drafting or revision, approved the submitted version of the manuscript, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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