Letter

Fighting on two fronts: drug–drug interactions in people living with HIV infected with SARS-CoV-2

People living with HIV (PLWH) who have a normal CD4 T-cell count and suppressed viral load may not be at an increased risk for COVID-19. Nonetheless, the majority of PLWH have other chronic or acute multimorbidity, which increases their risk. Indeed, almost half of the PLWH in Europe are older than 50 years and have comorbidities. Drug–drug interactions are also prevalent in these individuals, and people with drug interactions have an increased risk of morbidity and mortality.[1] It is highly recommended that treatment for COVID-19 in PLWH generally follow the same protocols as for patients without HIV.[2]

Cytochrome P450 (CYP450) enzymes and efflux proteins such as P-glycoprotein (P-gp) are likely to result in drug interactions. Antiretroviral drugs can be divided into three main groups in terms of being the substrate, inhibitors and inducers. Regarding the first group, nucleoside reverse transcriptase inhibitors (NRTIs), raltegravir and maraviroc are not P-gp or CYP450 substrate. Thus, these drugs have a low risk potential for interaction. In the second group, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and cobicistat are inducers or inhibitors of CYP450, and maraviroc, elvitegravir and dolutegravir are a substrate for CYP3A4. In the third group, protease inhibitors are both P-gp and a CYP450 substrate and inhibitor. These drugs have a high potential for pharmacokinetic interaction.[3]

Chloroquine (CQ) and hydroxychloroquine (HCQ) are metabolised by the CYP450 isoenzymes 2C8, 2D6 and 3A4. Co-administration with inhibitor or inducer antiretroviral drugs may increase or decrease exposure to CQ/HCQ, respectively. Azithromycin has a low risk

for CYP450 interactions. Tocilizumab is not metabolised with CYP450 enzymes. However, it has been shown that elevated interleukin-6 (IL-6) levels in inflammatory states inhibit CYP3A4, CYP2C19, CYP2C9 and CYP1A2. In patients treated with tocilizumab, decreased IL-6 levels may reverse this enzyme inhibition and drug interactions may occur. Lopinavir is primarily metabolised by CYP3A enzymes. Ritonavir is a potent inhibitor for CYP3A and CYP2D6. Additionally, lopinavir–ritonavir are inhibitors of drug transporters such as P-gp, breast cancer resistance protein (BCRP) and organic anion transporter protein B1 (OATP1B1). Therefore, lopinavir–ritonavir might increase plasma concentrations of CQ/HCQ and remdesivir, and adverse effects or toxicity will probably increase. Remdesivir is a prodrug predominantly metabolised by hydrolase activity, and is a substrate of CYP2C8, CYP2D6 and CYP3A4 and an inducer of CYP1A2 and CYP2B6 enzymes. Remdesivir is also a substrate of transporters like OATP1B1 and P-gp in vitro. Nevertheless, due to rapid distribution, metabolism and clearance, the potential for clinically significant interactions is low. Remdesivir could be affected by strong inhibitors/inducers, thus coadministration is not recommended. Transporter interactions may be minimised by the parenteral route of administration. Favipiravir is mainly metabolised by aldehyde oxidase and CYP450 enzymes do not contribute to its metabolism. Favipiravir inhibits the CYP2C8 enzyme and is a moderate inhibitor for OAT1 and OAT3 transporters.[4]

CQ/HCQ, azithromycin and efavirenz may prolong the QT interval. Lopinavir–ritonavir may also prolong the PR interval.[4]

It is important to be vigilant for pharmacokinetic and pharmacodynamic interactions when using these drugs together. It is highly recommended to monitor drug blood levels whenever possible. Hence, sources like www.covid19-druginteractions.org should be considered.

Melda Bahap ,[1] **Emre Kara,**[1]
Gulay Sain Guven[2]

[1]Department of Clinical Pharmacy, Hacettepe University Faculty of Pharmacy, Ankara, Turkey
[2]Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey

Correspondence to Melda Bahap, Department of Clinical Pharmacy, Hacettepe University Faculty of Pharmacy, Ankara 06800, Turkey; melda_610@hotmail.com

Check for updates

REFERENCES

1 Marzolini C, Elzi L, Gibbons S, *et al*. Prevalence of comedications and effect of potential drug–drug interactions in the Swiss HIV cohort study. *Antivir Ther* 2010;15:413–23.
2 The Infectious Diseases Society of America and HIV Medicine Association. COVID-19: special considerations for people living with HIV 2020. Available: https://www.hivma.org/globalassets/covid-19-special-considerations [Accessed 12 Apr 2020].
3 Gong Y, Haque S, Chowdhury P, *et al*. Pharmacokinetics and pharmacodynamics of cytochrome P450 inhibitors for HIV treatment. *Expert Opin Drug Metab Toxicol* 2019;15:417–27.
4 University of Liverpool. COVID-19 drug interactions, 2020. Available: https://www.covid19-druginteractions.org [Accessed 12 Apr 2020].