

Available Antiretrovirals in the Treatment and Pre-Exposure Prophylaxis of SARS-CoV-2: Quo Vadis?

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Dear Sir,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has put severe strain on global economies, healthcare systems, and public health. The coronavirus disease 2019 (COVID-19) seems to carry significantly higher mortality compared to the viral respiratory infections we were accustomed to.

Nevertheless, severe COVID-19 in individuals infected with the human immunodeficiency virus (HIV) has been seldomly described, which is unexpected. An article has been published describing no increased incidence of COVID-19 or increased severity in HIV-infected individuals (indeed, in some instances, the incidence of severe disease may be even lower in the presence of HIV infection) and limited evidence showed that under certain antiretroviral therapeutic schemes, namely the ones including lopinavir/ritonavir, no cases of SARS-CoV-2 were detected [1].

This contrasts with the results of Cao et al. [2], where lopinavir/ritonavir showed no significant improvement in the outcomes of a sample of COVID-19 patients. We must note this population had a higher mortality than that usually seen for COVID-19 infection, which may imply that the treatment was offered only to those most se-

verely ill. We cannot ignore that while the disease initiator is a virus, and much of the lung damage seen in severe disease is an inflammatory response. It is plausible that antiviral drugs may be of interest either to prevent or to treat recent onset infections, but fails to add benefit after significant inflammatory response takes place. We hypothesize that antiretroviral therapy in the context of HIV infection or Pre-Exposure Prophylaxis (PrEP) against HIV infection may offer some degree of protection against, at least, severe forms of SARS-CoV-2 infection.

This could be explained by the fundamental role of proteases to viral replication such as C30 endopeptidase (3CLpro), which is inhibited by protease inhibitors used in the treatment of HIV infection [3]. Moreover, Furin, a protein convertase expressed by the host shown to promote SARS-CoV-2 binding to ACE2 receptor [4], could be inhibited by tenofovir disoproxil (TDF) [5], widely used both in the treatment and PrEP of HIV infection, but these data are yet to be peer-reviewed or replicated.

This hypothesis seems to be supported by recent evidence that viral loads of SARS-CoV-2 seem to be lower in ferrets when TDF + emtricitabine (TDF/FTC) is administered [6]. Furthermore, a recent article where 77,950

HIV-positive individuals were followed found reduced incidence of SARS-CoV-2 infection in individuals under TDF/FTC compared to other antiretroviral regimens, and no cases of severe COVID-19 requiring intensive care unit admission or deaths were seen in this subset of patients [7]. Of note, patients under the novel Tenofovir alafenamide + FTC (TAF/FTC) treatment seem to have a higher risk compared to those under TDF/FTC. Considering that the major difference between TDF and TAF pertains to pharmacokinetics, where TAF allows for a higher intracellular concentration of tenofovir with lower plasmatic concentration than TDF [8], if this difference in effect on SARS-CoV-2 infection proves to be true, one may hypothesize that the higher concentrations of plasmatic tenofovir observed after the administration of TDF may play a more significant biological role against SARS-CoV-2 than the higher intracellular concentrations of tenofovir that are reached with TAF. Such a conclusion would further support the hypothesis that TDF effects on SARS-CoV-2 infection may be mostly due to Furin inhibition (or of other yet unknown extracellular host protein) rather than through direct inhibition of intracellular viral replication, which should be most affected by the intracellular concentration of the drug. Even in a reference article where caution is advised when considering HIV-infected individuals to have lower risk of severe COVID-19, we can see that the patients undergoing antiret-

roviral treatment with TDF/FTC did not present poor outcomes [9].

We, thus, propose that further investigation should be carried to investigate the potential merits of common antiretrovirals in the treatment of early COVID-19 infection, or even as PrEP for this infection. It would be fundamental for centers with high number of patients under HIV PrEP to analyze the epidemiology of SARS-CoV-2 in their patients. SARS-CoV-2 PrEP would be invaluable in reducing morbidity and mortality in the most vulnerable populations, until an effective vaccine is available.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Miguel Alpalhão and Paulo Filipe contributed equally to the conception, writing, revision, and final approval of this manuscript. All contributing authors have been listed.

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