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HIV & SARS-CoV-2 biochemical interactions may not explain clinical outcomes among adults hospitalized with COVID-19 co-infected with HIV:

Response to "Antagonism between hydrogen bonding and secondary chemical bonding to calcium in viruses"

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We appreciate the interest by Huang et al [1] in our paper on clinical outcomes among people living with HIV hospitalized with COVID-19. We hypothesized that people living with HIV hospitalized with COVID-19 would be at increased risk of mortality and major adverse cardiac events compared to those without HIV, but we did not find evidence of significantly increased risk [2]. From a biochemistry perspective, Huang et al propose that HIV and SARS-CoV-2 do not show mutual interaction due to counteraction of hydrogen bonding and secondary chemical bonding to calcium. They suggest this accounts for the lack of an effect of HIV-1 infection on COVID-19 clinical outcomes among those with SARS-CoV-2 coinfection in our study.

Our study did not investigate whether there are direct viral interactions between HIV and SARS-CoV-2. Nonetheless Huang et al's proposed mechanism is unlikely to explain our findings for the following reasons: (1) HIV targets CD4+ T cells[3, 4], whereas SARS-CoV-2 primarily infects respiratory epithelial cells via the ACE-2 receptor [5, 6]. Respiratory tract tissues most susceptible to SARS-CoV-2 [7] do not overlap with HIV reservoirs [8]. Simply put, SARS-CoV-2 and HIV are not in the same place at the same time. (2) Most individuals with HIV included in our cohort are likely to be treated with antiretroviral therapy and the majority are likely to be virally suppressed (per CDC surveillance data in the US: 96% are on antiretroviral therapy [9], and 85% are virally suppressed [10]). We were not able to assess the proportion in our study treated with antiretroviral therapy or viral suppression, but others have found increased risk among those with lower CD4 counts[11–13]. In other words, most people with HIV in our study likely do not have high levels of circulating HIV especially compared to the levels of SARS-CoV-2 during acute infection.

If there are differences among PLWH in post-acute sequelae of COVID-19 (PASC) or "Long COVID," then chronic inflammation, immune activation, autoantibodies, or microvascular dysfunction are plausible mechanisms that could explain such differences. Viral RNA

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persistence may drive these pathologic processes [14], although HIV co-infection has not been shown to result in differences in RNA persistence. Combining insights from clinical studies with basic science may catalyze advances in understanding and treating these two viral infections, especially when they infect the same host.

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