A High Percentage of People with HIV on Antiretroviral Therapy Experience Detectable Low-Level Plasma HIV-1 RNA Following COVID-19

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Dear Editor,

We read with interest the recent article by Geretti *et al.* (October 2020) in which among adults under the age of 60 with acute SARS-CoV-2 infection, HIV seropostivity was shown to be significantly associated with 28-day mortality, even when adjusted for age and other potentially important factors (1). As the authors discuss in detail, these data contrast with an earlier study recently published in Clinical Infectious Diseases by Sigel *et al.* of people with HIV (PWH) who were hospitalized for acute SARS-CoV-2; in this study, there were no differences in adverse outcomes compared to a demographically similar HIV-seronegative group (1). While a number of case series and retrospective studies have also shown no differences in COVID-19 mortality or severity in PWH (2-7), there is emerging evidence for exacerbations of lymphocyte dysfunction and aberrant immune activation in the setting of SARS-CoV-2/HIV coinfection (8). Furthermore, COVID-19 often leads to increased markers of immune activation, inflammation and immune dysregulation, regardless of concomitant chronic infections (9). It is therefore plausible that, in addition to HIV modulating SARS-CoV-2 infection, COVID-19 may have a short or longer-term impact on HIV disease following acute SARS-CoV-2 infection in PWH on effective antiretroviral therapy (ART). As a result, we sought to identify if SARS-CoV-2/HIV-1 coinfection may lead to an increase the frequency of detectable, but low-level plasma HIV-1 RNA levels that would not necessarily be detected by clinical viral load assays.

We tested large volumes of plasma for HIV-1 RNA using a highly sensitive single copy assay (SCA) from 12 PWH on ART using a replicate (9x) technology as previously described (10) with PCR-confirmed, convalescent SARS-CoV-2 infection a median of 37 days since onset of COVID-19 symptoms, and from 17 PWH on ART with plasma collection prior to COVID-19 (March 2018 – October 2019). **Table 1** summarizes participant demographics, ART use and low-level residual HIV-1 RNA. Whereas 83.3 percent of PWH had detectable HIV-1 RNA by SCA, only 58.8 percent of PWH had detectable HIV-1 RNA prior to the COVID-19 pandemic despite similar input plasma volumes. The median HIV-1 RNA copies/mL was 1.59 in PWH

with recent COVID-19 compared with 0.38 in the pre-COVID-19 group. Four COVID-19+ participants that all had detectable blips had subsequent testing a median of 75 days after onset of symptoms (interquartile range: 58-90 days); three had persistence of detectable HIV-1 plasma RNA (median 1.95 copies/mL, IQR 0.1-14.53).

Although sample sizes were modest and there were no significant differences between COVID-19+ and pre-COVID-19 groups, the above results suggest that lasting perturbations of immune function and systemic inflammation may impact the natural course of HIV infection, potentially months following HIV infection. Whereas these low-level viremic episodes are unlikely to have direct clinical implications for patients, larger, prospective studies will be needed in order to fully understand the long-term impact of COVID-19 on HIV dynamics and viral immune responses.

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Potential Conflicts of Interest

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Table 1. Characteristics of PWH on ART with Recent COVID-19 and Prior to COVID-19 Including Detectable Low-Level Plasma HIV-1 RNA

	PCR+ COVID-19	Pre-COVID-19
Group N	12	17
Median Time from onset of COVID-19 symptoms to initial sampling (IQR)	37 (29, 62)	N/A
Hospitalized for COVID-19 [N (%)]	2 (16.7%)	N/A
Median Age in Years (IQR)	57 (53, 64)	63 (57, 69)
Male Sex [N (%)]	12 (100%)	16 (94%)
White	10 (83.3%)	14 (82.3%)
Black/African American	1 (8.3%)	3 (17.6%)
Asian/Pacific Islander	1 (8.3%)	-
INSTI Use	11 (91.7%)	12 (70.6%)
NNRTI Use	1 (8.3%)	3 (17.6%)
PI-Based Use	2 (16.7%)	2 (11.8%)
Leronlimab Use	0 (0%)	2 (11.8%)
CD4 T Cell Count [median cells/μL (IQR)]	658 (540, 804)	537 (457, 827)
Detectable Plasma HIV-1 RNA (SCA+) N (%)[1]	10 (83.3%)	10 (58.8%)
No Detectable Plasma HIV-1 RNA (SCA-) N (%)[2]	2 (16.7%)	7 (41.2%)
Median Plasma HIV-1 RNA copies/mL (IQR)	1.59 (0.39, 6.95)	0.38 (0.0, 5.67)

IQR = interquartile range; ART = antiretroviral therapy; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SCA = HIV-1 Single Copy Assay (plasma RNA)

[1] No significant difference between recent COVID-19+ and COVID-19- participants using Fisher Exact test (P=0.23)

[2] No significant difference between recent COVID-19+ and COVID-19- participants using Mann-Whitney test (P=0.36)