

Persons with HIV and the COVID-19 Pandemic: A Viral Synergy of Biology and Sociology

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The effects of the COVID-19 pandemic on persons with HIV (PWH) are incompletely understood. As COVID-19 continues to devastate communities worldwide, resulting in nearly 47 million cases and 1.2 million deaths, it is evident that certain populations are differentially impacted. Despite significant advances in the development and implementation of HIV treatment and prevention over the past four decades, our fight against the HIV/AIDS epidemic is long from over. In 2019, there were approximately 38 million PWH living across the globe, with varying access to care and antiretroviral therapy (ART)¹. While PWH represent a heterogeneous population, they share many complex biologic and sociobehavioral factors that warrant careful consideration during a novel viral pandemic and in the context of SARS-CoV-2 infection specifically.

From the onset of COVID-19, HIV clinicians, researchers, and advocates have been curious and concerned about synergism between the concurrent COVID-19/HIV pandemics. In the early days of SARS-CoV-2 propagation, overlap with the global HIV epidemic became apparent: both viruses are originally zoonotic, now transmitted person-to-person, and promote inflammation and immune dysregulation; both infections can be associated with profound stigma; and both pandemics thrive on health disparity and illuminate fatal gaps in our healthcare system². How may these and additional factors converge to affect PWH? In particular: (1) Are PWH at increased risk of SARS-CoV-2 acquisition and/or severe illness compared with persons without HIV? (2) Among PWH, what is the natural history of SARS-CoV-2 infection, and how may general (i.e., age, comorbidities) and HIV-specific factors (i.e., immune status, virologic control, ART) mediate COVID-19 risk and disease course? (3) How do vaccines and therapeutics in development for COVID-19 perform among PWH? And (4) What is the impact of the COVID-19 pandemic on PWH accessing essential services including ART, screening and

treatment for sexually transmitted infections, support for mental health and substance use disorders, management of chronic comorbidities, referrals for housing and food security, etc.?

To address aspects of these questions, several large observational cohorts of PWH in existence prior to COVID-19 (some also including HIV-seronegative controls) are being leveraged throughout the world. Additionally, prospective studies dedicated to enrolling PWH with COVID-19 have initiated in order to rigorously investigate the natural history of SARS-CoV-2/HIV coinfection. It is also paramount that ongoing and future clinical trials of vaccines and treatments for SARS-CoV-2 infection provide PWH the opportunity to participate. Finally, to wholly understand the reach of COVID-19, research priority areas should include the clinical, virologic and immunologic aspects of SARS-CoV-2 infection among PWH as well as implications of the COVID-19 pandemic on underlying social determinants of health and health services delivery for PWH. Data on these many topics are rapidly evolving. While initial descriptions of COVID-19 presentation and outcomes among PWH were limited to single-center case series, more systematic and comprehensive studies are now being published.

In this issue of *Clinical Infectious Diseases*, Geretti *et al* report on the clinical presentation and outcomes of persons with and without HIV that were hospitalized with COVID-19 at 207 centers across the United Kingdom (UK) from January 17 to June 4, 2020³. Leveraging the largest observational prospective COVID-19 outcomes study worldwide, the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO Clinical Characterization Protocol (CCP), the authors analyzed data from 47,592 patients hospitalized with COVID-19 including 122 PWH. Compared with persons without HIV, PWH were nearly two decades younger, had fewer comorbidities, and included a significantly higher proportion of men and individuals of Black race. Age-adjusted 28-day mortality was higher among PWH compared with people without HIV (HR 1.47, 95% CI 1.01-2.14); and this effect persisted after adjusting for sex, race/ethnicity, the presence of 10 major comorbidities and

other key variables. This large and timely study is an important contribution to the growing, somewhat conflicted, evidence base on COVID-19 outcomes among PWH.

In multiple early series from the United States (US) and Europe, the clinical outcomes of PWH with COVID-19 did not appear worse than those of the general population⁴⁻¹⁰. Among patients hospitalized for COVID-19 in New York City, including 88 PWH and >400 HIV-negative matched comparators (by age, sex, race/ethnicity and calendar week of infection), no differences were observed by HIV status in COVID-19 severity on admission, need for mechanical ventilation, or cumulative incidence of death¹¹. Likewise, in a similarly matched analysis using data from the Veterans Aging Cohort Study, COVID-19 outcomes were comparable among patients with and without HIV¹². On the contrary, among ~3.5 million patients in South Africa, HIV was associated with COVID-19 mortality (aHR 2.14, 95% CI 1.70-2.70) in models adjusted for age, sex, comorbidities and clinic location¹³. Data analyzed from the OPENSafely platform in the UK suggested that PWH had nearly 3-fold the risk of COVID-19 death than persons without HIV when age- and sex-adjusted; this finding was attenuated though remained significant after accounting for race/ethnicity and socioeconomic status¹⁴.

It is possible that traditional risk factors (age, comorbidities, social determinants of health) may influence COVID-19 disease severity and outcomes among PWH more so than HIV infection itself or HIV-related variables (degree of immunocompetency, viral suppression, ART regimen). In the general population, persons of older age and those with medical comorbidities are at greatest risk of severe illness from SARS-CoV-2 infection¹⁵. Other demographic factors, including male sex and non-white race, have been associated with a disproportionately high number of infections and deaths from COVID-19 in the US and the UK^{15,16}. Specifically, Black, Hispanic, and South Asian individuals appear to be most affected, likely related to underlying disparities in social determinants of health^{16,17}. Importantly, many of these demographics are common among PWH. In the US, it is estimated that more than half of PWH are aged ≥ 50 years

old¹⁸. Further, aging PWH suffer from a high burden of non-AIDS comorbidities¹⁹ including hypertension, diabetes, cardiovascular and lung disease, cancer and other chronic conditions associated with worse COVID-19 outcomes^{5,6}. HIV disproportionately affects persons of racial and ethnic minorities and therefore the contribution of racial disparities in mediating COVID-19 incidence and outcomes may be exacerbated among PWH. The COVID-19 pandemic is catalyzing our long overdue need to better understand and eliminate drivers of health inequity, such as structural racism, unstable housing and food insecurity, not only for PWH but for all marginalized people.

There are limited data on the effect of CD4 count and HIV viremia on SARS-CoV-2 infection and sequelae among PWH. Most published reports to date include hospitalized PWH with virologic suppression on ART – it is not yet known whether this population is at greater risk of COVID-19 illness severity than persons with advanced HIV not on ART. While data from a US multicenter registry of PWH with COVID-19 suggested worse COVID-19 outcomes among those with CD4 count <200 cell/mm³ (despite HIV suppression), COVID-19 mortality risk among PWH in South Africa was similar across strata of HIV viral load and immunosuppression¹³. Chronic immune activation is well-described in HIV infection (even when suppressed), likely plays a role in aging-related comorbidity development among PWH²⁰, and may intersect with the dysregulated immune response and endothelial inflammation observed in severe COVID-19^{21,22}. Additional studies are needed to better elucidate the virologic-immunologic crossroads of HIV/SARS-CoV-2 coinfection.

The study by Geretti *et al* has many strengths including the sheer number of patients included, ability to compare PWH with HIV-negative persons, prospective data collection using the well-curated ISARIC clinical networks infrastructure – designed to provide a proficient, agile and coordinated research response to infectious diseases outbreaks – and thorough statistical analyses commanding validity to the reported findings. A common methodologic limitation of

COVID-19 hospitalized cohort studies is neglecting hospital discharge as a competing event; while Geretti *et al* primarily used time-to-event methods, a sensitivity analysis employing competing risk methods did not alter the main findings. Of importance, the investigators were not able to adjust for markers of health disparity (e.g. socioeconomic status) in multivariable analyses, nor was the potential for regional variability across the 207 centers explored. Both of these unmeasured factors, and others, may be associated with COVID-19 outcomes and findings should be interpreted in this context. HIV-specific indices including CD4 count and HIV viral load were not routinely collected as part of the ISARIC CCP and therefore not included in the description of COVID-19 presentation for this study.

In conclusion, this important population cohort study by Geretti *et al* suggests that COVID-19 mortality risk is higher among PWH than HIV-negative persons, in a region where the vast majority of PWH are virologically suppressed on ART. Additional study is needed to evaluate COVID-19 risk factors, clinical course and outcomes among diverse groups of PWH including those of varying clinical stability and residing in different geographic settings. Future investigations will be crucial in disentangling the effects of age, comorbidities, immune function, HIV virologic control, ART and social determinants of health on COVID-19 disease as well as vaccine and treatment uptake and responses. Finally, the impact of COVID-19 on our fight against the HIV/AIDS epidemic should be rigorously monitored, evaluated and intervened on so that we can conquer the challenges born of synergized pandemics and deliver accessible care, ART, health and wellbeing for all PWH.

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