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COMMENTARY

What Might Surviving Coronavirus Disease 2019 Look Like for People Living with HIV?

Rowena Johnston, PhD

THE GOOD NEWS and bad news for people living with HIV (PWH) who acquire severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are that neither HIV nor its treatment with antiretroviral therapy (ART) appears to dramatically alter coronavirus disease 2019 (COVID-19) course. Projections for poorer outcomes were based largely on the prevalence of comorbidities among PWH, as well as underlying immune dysfunction.[1,2] On the flipside, more favorable outcomes were hypothesized on the basis of potential protection by ART, or lower pathological inflammatory responses among PWH due to HIV-associated immune dysregulation.[3]

So far, neither of these hypotheses have been borne out clinically. In a study describing the outcomes of ~7000 SARS-CoV-2-coinfected PWH from around the world,[4] there was no difference in hospitalization or death rates between PWH and the general population. Although PWH were diagnosed with COVID-19 at a higher rate than expected given the underlying prevalence of HIV in their respective populations, a variety of nonbiological factors may explain this finding. These include increased testing due to concern for health, or living under circumstances that are associated with increased susceptibility to infection.[5,6] In addition, no HIV-specific variables—including ART or its absence, HIV viral load or CD4 count—were significantly associated with greater risk of death.

It is important to emphasize that, as is the case for the general population, comorbidities play an important role in predicting PWH COVID-19 outcomes, in particular cardiovascular disease (CVD) and chronic respiratory disease, as well as older age, diabetes, hypertension, and renal disease. This is particularly alarming, given that PWH are living longer, are twice as likely to develop CVD,[7] partly related to the types of ART they are taking,[8] and are at greater risk of chronic respiratory disease[9] and other COVID-19-relevant comorbidities[10,11] compared with the general population. As the COVID-19 pandemic approaches 1 year, mortality rates in general have dropped as our understanding of best treatments has improved. Teasing apart potential differential responses to approved or experimental COVID-19 treatments, and possible differential rates of protection for COVID-19 vaccine candidates, among PWH will be complicated not only by HIV status, but also by underlying multiple comorbidities.

Recovering from SARS-CoV-2 is only the first step. Relatively little has been written in the scientific literature about post-COVID-19 ''long-haulers'' (long-COVID), although this is expected to change with time and increasing number of COVID-19 survivors. A lack of formal definition for long-COVID poses challenges for studying or summarizing it, but symptoms after recovery from acute COVID-19 persist for weeks or months in at least 10%, or maybe one-third or more, of COVID-19 survivors. Patients manifest a range of otherwise unexplained symptoms including respiratory, neurological, and cardiovascular.[12–15] Of 100 patients diagnosed with severe COVID-19, 60% had myocardial inflammation >2 months after diagnosis.[16] Eight weeks after discharge from the hospital, more than half of COVID-19 survivors in another study experienced respiratory difficulty including breathlessness or coughing.[17] A third study highlighted neurological and psychological challenges faced by COVID-19 survivors, including headache, fatigue, and cognitive impairment, as well as a sense of hopelessness and anxiety around the lack of available treatment, or understanding, from their care providers.[18] Even less is known about factors that increase the risk of long-COVID status, although COVID-19 severity does not appear to be among them. Whether pre-existing respiratory, neurological, and cardiovascular conditions predispose to long-COVID, or whether these symptoms manifest regardless of the precipitating cause, it seems reasonable to foresee that long-COVID may be particularly concerning in PWH.

Another potential long-term consequence of SARS-CoV-2 infection pertains to the reservoir of HIV that persists despite virally suppressive ART. Virus within infected cells is thought to persist in a latent or minimally active state that only rarely results in the production of virions. Suppressive ART blocks these occasional virions from productively infecting new cells.[19–21] This reservoir is the primary barrier to an HIV cure, as ART is effective only against actively replicating virus, and nonproductively infected cells are invisible to the immune system. Immune activation has been proposed both to increase the odds of virion production from persistently infected cells and to activate CD4 cells that thus become more susceptible to de novo HIV infection.[22,23] In the context of COVID-19, especially severe disease, the excessive immune activation leads to two hypotheses that result in opposite outcomes as pertains to the reservoir. If ART is sufficient to prevent new HIV infection, activated reservoir cells may die by cytopathic or immune processes, resulting in a contracted HIV reservoir. If, however, ART cannot prevent every new infection event, the COVID-19-associated inflammatory response may result not only in virion production but also create a pool of cells with

amfAR, The Foundation for AIDS Research, New York, New York, USA.

increased susceptibility to HIV infection, thus expanding the HIV reservoir once activated cells revert to a resting state. Intriguingly, HIV viral load was reported to increase after severe, but not mild, COVID-19 in a cohort of PWH on ART.[24] The importance of achieving and maintaining HIV suppression in the COVID-19 era cannot be overstated, but is more challenging than ever when access to medical care and ART delivery is most likely to be disrupted.[25–27]

If the second scenario is borne out, with an expanded post-COVID-19 reservoir, this newly seeded pool of reservoir cells may consist substantially in SARS-CoV-2-specific CD4 T cells. If so, reinfection, or indeed COVID-19 vaccination, may activate them, perhaps resulting in production of HIV and further expansion of the reservoir. Other COVID-19 vaccination scenarios are also of potential concern for PWH. Several COVID-19 vaccine candidates include the use of an adenovirus 5 (Ad5) vector to deliver immunogenic vaccine components. The ill-fated Step and Phambili trials, conducted >10 years ago, tested an Ad5-based vaccine for the prevention of HIV infection, yet resulted in increased HIV infection. Of note, a consensus conference convened by the National Institutes of Health concluded that the use of an Ad5-based vaccine against any infectious pathogen, especially in a setting with high HIV prevalence, risked increasing the spread of HIV.[28]

The nature of immune responses mounted by PWH against SARS-CoV-2 remains largely unknown. A case series in Japan[29] described five PWH with well-controlled HIV infection and mild COVID-19, four of whom developed anti-SARS-CoV-2 antibodies at rates similar to patients without HIV. They concluded that absence of seroconversion in one patient was consistent with reports in mild or asymptomatic COVID-19 among the general population. A study in Russia[30] compared T cell responses in 171 PWH whose ART was interrupted due to the pandemic versus 205 PWH who continued ART. Untreated PWH appeared to have impaired responses against SARS-CoV-2 as demonstrated by limited increases in CD4+ T follicular helper cells and in CD8+ killer T cells, compared with treated PWH and uninfected controls. Further, both groups of PWH had higher baseline T cell expression of programmed death 1 (PD1) than uninfected controls, but untreated PWH experienced a surge in PD1 expression 2 weeks after symptom onset that was absent in treated PWH and HIV-uninfected controls. PD1 expression is widely reported to be elevated in HIV and is normally attributed to T cell exhaustion due to chronic stimulation by HIV, and the author attributed the observation in this study to SARS-CoV-2, compounding the underlying exhaustion due to HIV. It is worth noting, though, that PD1 expression is also an early marker of T cell response, perhaps especially avid response, to pathogen.[31]

As of late November, the United States is approaching 12 million recorded COVID-19 cases,[32] the vast majority of these are among the 210 million adult population, translating to a rate approaching 6%. If the prevalence is the same among PWH, then upwards of 50,000 PWH in the United States alone have experienced COVID-19, perhaps millions around the world, and these numbers will increase. Surviving COVID-19 at the same rate as non-PWH is cause for cautious celebration, but such PWH may be saddled with unknown long-term consequences of living at the intersection of two of the most devastating pandemics of our time.

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Address correspondence to:
Rowena Johnston, PhD
amfAR, The Foundation for AIDS Research
120 Wall Street, 13th Floor
New York, NY 10005
USA

E-mail: rowena.johnston@amfar.org