AIDS PATIENT CARE and STDs
Volume 34 Number 6, 2020

DOI: 10.1089/apc.2020.29005.com

**COMMENTARY**

# Why Aren't People Living with HIV at Higher Risk for Developing Severe Coronavirus Disease 2019 (COVID-19)?

Jeffrey Laurence, MD



There is a profound enigma arising from studies identifying risk groups most vulnerable to severe disease after infection with severe acute respiratory distress syndrome-associated coronavirus-2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19). These analyses may offer insight into novel interventions, particularly as seen in the context of HIV infection and its therapy.

By early May, there were >3.45 million SARS-CoV-2 infections worldwide,[1] and this astounding figure is almost certainly an underestimate. The test currently used to document infection, a nasopharyngeal swab in a reverse transcriptase-polymerase chain reaction assay, is associated with a false negative rate as high as 30%, possibly due to respiratory tract sampling error.[2] There have been >244,000 deaths.[1] Organ dysfunction, particularly progressive respiratory failure and acute kidney injury, is associated with the highest rates of mortality.[3,4] These manifestations have been linked to a systemic microvascular thrombosis and generalized coagulopathy, associated with a marked inflammatory response and persistent complement activation.[5] Severe disease usually occurs in the setting of certain comorbidities: obesity, diabetes mellitus, hypertension, advanced age, and male gender at any age.[3,4]

Given those risk factors, and the spread of SARS-CoV-2 by close contact, COVID-19 was expected to affect a disproportionate number of people in lower socioeconomic classes. First, these individuals may be less able to socially distance because of housing situation, or occupation, or both. Similar circumstances also facilitate the spread of HIV worldwide, as highlighted in the discussion of COVID-19, HIV, and migrant workers in this issue of the journal.[6] But they also suffer a second vulnerability: obesity, diabetes, and hypertension are prominent health disparities among the disenfranchised, including people of color.[7]

What was unexpected is the under-representation of people living with HIV (PLWH) among severe COVID-19 cases. In an earlier series from Wuhan, China, only 1.4% involved PLWH.[3] Among 16,749 patients with COVID-19 hospitalized in the United Kingdom, 1% involved PLWH, but HIV did not adversely impact survival.[4] A study of 5700 patients hospitalized with COVID-19 in the New York City area, an epicenter not only of CoV-2 infection but of HIV as well, found that only 0.8% involved HIV.[8] Finally, in a smaller series from Barcelona, of the 62 of 543 consecutive patients with COVID-19 requiring hospital admission, 5 were PLWH: 3 males, 2 transgender, 4 of them on effective antiretroviral therapy (ART).[9] None expired.

One obvious hypothesis as to this apparent lack of HIV-related risk for the development of severe or critical COVID-19 is protection afforded by ART. In vitro, ritonavir-boosted lopinavir suppresses CoV-2 replication, although it had no impact on COVID-19 in vivo, at least in the setting of severe disease.[10] The recent report of a modest but significant effect of the antiviral drug remdesivir on CoV-2 has now directed focus on another ART drug, tenofovir. Hospitalized patients with COVID-19 and lung involvement who received remdesivir had a 31% faster time to recovery than those on placebo, 11 days versus 15 days, with a trend to improved survival.[11] Tenofovir, one of the most widely prescribed anti-HIV medications for both HIV treatment and HIV pre-exposure prophylaxis, blocks the critical RNA-dependent RNA polymerase of CoV-2, and it is structurally related to remdesivir.[12]

A second insight into the under-representation of severe COVID-19 among PLWH derives from a different demographic group also expected to be vulnerable, the cancer patients. Many of these individuals are treated chronically with immune suppressive regimens. Yet, although they comprised 7.2% of the COVID-19 cohort from Wuhan, they were not over-represented among the severe cases.[3] Malignancy was a risk factor for mortality in the U.K. series, but it was of very modest impact, with a relative risk of 1.19-fold.[4] Given that multiple proinflammatory cytokines and innate immune factors appear to play a dominant role in promoting severe COVID-19,[5,13] it is conceivable that the immune suppression characteristic of cancer chemotherapy, and the persistent immune dysregulation that accompanies HIV infection despite effective ART,[14] may suppress CoV-2 pathology as well. This hypothesis is supported by a mouse model of SARS-CoV-1 infection. A mouse-adapted strain of CoV-1 leads to respiratory dysfunction and death in wild-type mice, but after genetic knockout of their complement system, the disease is markedly attenuated.[15] This occurred despite equivalent viral loads in the lung of both types of mice.[15]

Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York, New York, USA.

In conclusion, although complement and perhaps other proinflammatory cytokines do not appear to play a major role in controlling CoV-1 replication, they may have a critical role in its pathogenicity. This is likely to hold true for CoV-2 as well. CoV-2 may be much less capable of invoking these immune responses in the setting of the immune dysregulation characteristic of HIV/ART or cancer. The leads suggested by these observations among PLWH or cancer may provide important insights into the design of novel COVID-19 interventions.

### Funding Information

This study was supported by a grant from the Angelo Donghia Foundation.

### References

1. cdc.gov/coronavirus/2019.ncov (Last accessed May 4, 2020).
2. Yang Y, Yang M, Shen C, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. medRxiv preprint DOI: https://doi.org/10.1101/2020.02.11.20021493.
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–1069.
4. Docherty AB, Harrison EM, Green CA, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO clinical characterization protocol. medRxiv preprint DOI: https://doi.org/10.1101/2020.04.23.20076042.
5. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res 2020;1931:30070.
6. Lodge W II, Kuchukhidze S. COVID-19, HIV, and migrant workers: The double burden of the two viruses. AIDS Patient Care STDs 2020;34:249–250.
7. Yancy CW. COVID-19 and African Americans. JAMA 2020;DOI: 10.1001/jama.2020.6548.
8. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;DOI:10.1001/jama.2020.6775.
9. Blanco JL, Ambrosioni J, Garcia F, et al. COVID-19 in patients with HIV: Clinical case series. Lancet HIV 2020; DOI.org/10.1016/S2352-3018(20)30111-9.
10. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Eng J Med 2020;DOI:10.1056/HEJMoa2001282.
11. NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. Available at: NIAIDNews@niaid.nih.gov (Last accessed April 29, 2020).
12. Elfiky AA. Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. Life Sci 2020;DOI.org/10.1016/j.lfs.2020.117592.
13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054–1062.
14. Korencak M, Byrne M, Richter E, et al. Effect of HIV infection and antiretroviral therapy on immune cellular functions. JCI Insight 2019;4:e126675.
15. Gralinski LE, Sheahan TP, Morrison TE, et al. Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. mBio 2018;9:e01753–18.

Address correspondence to:
*Jeffrey Laurence, MD*
*Division of Hematology and Medical Oncology*
*Weill Cornell Medical College*
*1300 York Avenue*
*New York, NY 10065*
*USA*

*E-mail:* jlaurenc@med.cornell.edu