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EDITORIAL COMMENTARY

When Epidemics Collide: Why People With Human Immunodeficiency Virus May Have Worse Coronavirus Disease 2019 Outcomes and Implications for Vaccination

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(See the Major Article by Braunstein et al on pages e1021–9.)

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The coronavirus disease 2019 (COVID-19) pandemic continues to accelerate, stressing healthcare systems and highlighting and exacerbating disparities. As the pandemic surges in the United States, it is increasingly important to identify patients at elevated risk of developing severe disease to inform management decisions, including COVID-19 vaccine prioritization. People with HIV (PWH) have been proposed to be at high risk for severe COVID-19 because of immunodeficiency, comorbidities, and/or societal inequities, such as poverty and lack of access to care. Several studies, including that of Braunstein et al in this issue of *Clinical Infectious Diseases*, are now finding that PWH have worse COVID-19 outcomes; determining why is of utmost importance.

A complex interplay of factors drives the course of COVID-19 [1–6]. Patients with immunodeficiency, such as organ transplant recipients, are at increased risk for severe COVID-19, and prolonged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication has been reported in immunocompromised hosts [7, 8]. In PWH who are not receiving antiretroviral therapy (ART) or have low CD4 cell counts—that is, those who are immunodeficient—there has been concern that SARS-CoV-2 infection will cause severe disease, as is the case for influenza [9]. PWH who are receiving ART are typically not at high risk for other infections, but there are theoretical reasons why they may be more prone to severe COVID-19. PWH on ART continue to have excess inflammation, which has been linked to comorbidities, such as cardiovascular disease [10, 11]. Residual inflammation is most pronounced in PWH with low CD4 cell count nadirs, incomplete CD4 cell reconstitution, or persistently low CD4/CD8 ratios—an immune dysregulation "legacy effect." [12, 13]. Because elevated inflammatory markers have been linked to severe COVID-19 [4], it is important to determine whether the HIV legacy effect "primes the pump" for worse outcomes after SARS-CoV-2 infection. If this is the case, one would predict worse COVID-19 outcomes in PWH, particularly among those with low CD4 cell count nadirs, incomplete CD4 cell count reconstitution, or persistently low CD4/CD8 ratios.

In addition to potential contributions of immune dysregulation, PWH may have worse COVID-19 outcomes because of comorbidities or social determinants of disease. Clinical and sociodemographic factors that are highly prevalent in people with HIV parallel risk factors for severe COVID-19. PWH are aging as a population [14], are frequently black or Hispanic, and have elevated rates of comorbidities including cardiometabolic risk factors (obesity, diabetes, hypertension) and cardiovascular disease [11, 15]; these factors closely mirror risk factors for development of severe COVID-19 [2–4, 16]. Studies of PWH with COVID-19 find high rates of factors that increase severe COVID-19 risk. In a study comparing COVID-19 outcomes in 404 PWH and 49 763 individuals without HIV, PWH had higher rates of obesity, hypertension, diabetes, and chronic kidney disease and were more likely to be African American [17]. PWH with COVID-19 have higher body mass index (BMI) and a higher proportion have at least 1 comorbidity compared with PWH without COVID-19 [18]; in addition, PWH have been shown to have high rates of comorbidities in several case series, including 64% with at least 1 comorbidity in an Italian cohort [19], 83% with at least 1 comorbidity in a Boston cohort [20], and half of patients with at least 5 comorbidities in an Atlanta case series [21].

With these potential contributors as background, what do we know about

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PWH who develop COVID-19? Several studies have failed to show an association of HIV with severe COVID-19 (Table 1). A large US-based study using a multicenter research network and a propensity-matched cohort of COVID-19 patients without HIV showed no difference in mortality after matching for demographics and comorbidities [17]. Several studies in which COVID-19 patients without HIV were compared with PWH with COVID-19 failed to show associations of HIV status with intensive care unit (ICU) admission [22, 23], mechanical ventilation [22–25], or mortality [22–25], although matching factors differed. An as-yet unpublished abstract from the Veterans Aging Cohort Study found that PWH had no increased risk of severe COVID-19 outcomes [26].

By contrast, several large population-based studies have found that PWH are at increased risk of severe COVID-19 (Table 1). Data from a large cohort in South Africa showed HIV to be associated with increased COVID-19 mortality (adjusted hazard ratio [aHR], 2.14), adjusting for some comorbidities but not for BMI, smoking, or socioeconomic status [27]. A United Kingdom population-based study encompassing 1 728 905 patients, including 27 480 with HIV, showed that HIV conferred a >2-fold increased risk of COVID-19 mortality (aHR, 2.59 [adjusting for deprivation, ethnicity, smoking, and obesity]) [28]. A prospective study of patients hospitalized with COVID-19 showed increased 28-day mortality in PWH after adjusting for age (aHR, 1.47); in patients under age 60, mortality rates were higher for PWH compared with HIV-uninfected COVID-19 patients (21.3% vs 9.6%) [29]. A New York City study that did not show an overall effect of HIV on severe COVID-19 showed a significant association of HIV with intubation and mortality among patients ≤50 years of age [23]. A separate New York State study in preprint form demonstrated a standardized mortality ratio for HIV of 1.23 for

Table 1. Selected Comparative Studies Assessing the Association Between Human Immunodeficiency Virus and Severe Coronavirus Disease 2019 Outcomes (Published or Preprint)

Study, First Author [Reference]	Date Published	Population	HIV + COVID-19, No.	COVID-19, No.	Risk Increased?	Effect Size	Outcome	Adjusted[a]	Matched[a]
Karmen-Tuohy [22]	June 2020	NYC hospitalized	21	42	No	...	ICU admission; MV; mortality	No	Yes
Sigel [24]	July 2020	NYC hospitalized	88	405	No	...	MV; mortality	Yes	Yes
Stoeckle [25]	August 2020	NYC hospitalized	30	90	No	...	MV; in-hospital mortality	No	Yes
Boulle [27]	August 2020	South Africa	3978	22 308	Yes	2.14	Mortality	Yes	No
Miyashita [23]	August 2020	NYC	161	8912	No	...	ICU admission; MV; mortality	No	No
Geretti [29]	October 2020	UK hospitalized	122	47 592	Yes	1.47	Mortality	Yes	No
Hadi [17]	November 2020	US multicenter	404	49 763	No	...	Mortality	No	Yes
Bhaskaran [28][b]	December 2020	UK OpenSAFELY			Yes	2.30	Mortality	Yes	No
Braunstein (current issue)	December 2020	NYC	2410	204 583	Yes	1.63	Mortality	No	No
Tesoriero [30]	Preprint (2020)	NY State	2988	375 260	Yes	1.23	Mortality	Yes	No

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; ICU, intensive care unit; MV, mechanical ventilation; NYC, New York City; UK, United Kingdom; US, United States.

[a]Adjustment and matching were based on the following study-specific factors: Karmen-Tuohy [22]: Matched on admission date, age, body mass index (BMI), gender, tobacco history, and a history of chronic kidney disease (CKD), hypertension, asthma, chronic obstructive pulmonary disease (COPD), or heart failure. Sigel [24]: Adjusted for age, sex, race/ethnicity, COVID-19 severity on admission, COPD , smoking, baseline ferritin level, and baseline white blood cell count. Stoeckle [25]: Matched on age, sex, and race/ethnicity. Boulle [27]: Adjusted for age, sex, diabetes, hypertension, CKD, chronic pulmonary disease/asthma, and tuberculosis. Hadi [17]: Matched on sex, BMI, diabetes, hypertension, chronic lung disease, CKD, race, and history of nicotine dependence. Geretti [29]: Adjusted for age, sex, ethnicity, baseline date, 10 comorbidities, indeterminate/probable hospital acquisition of COVID-19, and hypoxia/receiving oxygen at presentation. Bhaskaran [28]: Adjusted for age, sex, index of multiple deprivation, ethnicity, smoking, obesity, diagnosed hypertension, chronic respiratory disease, asthma, chronic cardiac disease, diabetes, nonhematological cancer, hematological cancer, chronic liver disease, stroke, dementia, other neurological disease, reduced kidney function, organ transplant, asplenia, rheumatoid arthritis, lupus, psoriasis, and other immunosuppressive conditions. Tesoriero [30]: Adjusted for age, sex, and region.

[b]No data were available for this study on COVID-19 diagnoses.

in-hospital mortality, but did not adjust for comorbidities [30].

Several factors merit consideration in interpreting studies investigating the impact of HIV on COVID-19 outcomes. First, the ability to adjust for comorbidities may profoundly impact results. Comorbidities are highly prevalent in PWH, typically at higher rates than in non-HIV comparator groups, and increase risk for severe COVID-19. A finding of increased risk of severe COVID-19 conferred by HIV may be attenuated or lose significance after adjustment for relevant comorbidities. Second, findings may reflect the selection of the study population. Studies limited to hospitalized patients may fail to detect a mortality signal if the at-risk group in question is hospitalized at higher rates. Third, by virtue of sociodemographic factors or occupation, some PWH may be at higher risk of COVID-19 exposure [20, 31]. Fourth, the role of inflammation in HIV and COVID-19 outcomes is likely to be complex and may impact outcomes. While several studies have shown higher C-reactive protein (CRP) values in PWH with COVID-19 compared with HIV-uninfected patients [22, 29], another large multicenter study showed no difference in inflammatory markers (CRP, lactate dehydrogenase, erythrocyte sedimentation rate, or ferritin) in PWH compared with HIV-uninfected patients with COVID-19 after propensity score matching [17]. The uncertainty regarding whether HIV affects the inflammatory response in COVID-19 underscores the need for additional research on the impact of inflammatory markers on risk stratification.

In terms of the impact of HIV disease stage or virologic suppression on COVID-19, data from several recent studies are beginning to shed light on this critical question. A study from the University of Missouri showed CD4 count <200 cells/mm^3 to increase risk of a composite outcome of ICU admission, mechanical ventilation, or death >3-fold [32]; a South African population-based study showed CD4 count <200 cells/mm^3 in hospitalized patients to be associated with COVID-19 death [27]; a New York State study showed CD4 count <200 cells/mm^3 to be associated with increased risk of hospitalization [30]; and an Italian series showed nadir CD4 cell count to be lower in hospitalized patients in unadjusted analyses [33]. The New York State study also showed HIV viremia to be associated with increased risk of hospitalization [30].

The current study by Braunstein et al adds to this literature by demonstrating increased rates of severe COVID-19 in PWH. The population-level analysis matched records from the New York City (NYC) Health Department with those from the NYC HIV surveillance registry. Comparison groups included PWH with COVID-19 (n = 2410), PWH without COVID-19 (n = 113 907), and COVID-19 patients without HIV (n = 202 012). PWH with COVID-19 were more likely to be hospitalized (42% vs 26% of all cases), be admitted to the ICU (5% vs 3%), and to die (13% vs 8%) compared with all NYC patients with COVID-19. Among patients who experienced 1 of these 3 outcomes, PWH were older, lived in higher-poverty neighborhoods, and were more likely to be black or Hispanic when compared with all COVID-19 patients (although race/ethnicity data were missing for nearly half of HIV-uninfected COVID-19 patients). Comorbidities were common in PWH, with 64.3% reporting at least 1 comorbidity compared with 35.4% in HIV-uninfected COVID-19 patients; this difference persisted even when PWH who reported immunodeficiency as their single comorbidity were excluded. Notably, >90% of PWH who were admitted to the ICU or died had at least 1 comorbidity documented. While the majority of PWH were virally suppressed, a higher proportion of patients admitted to the ICU had a CD4 count <200 cells/mm^3 compared with those hospitalized but not admitted to the ICU (34.7% vs 23.4%).

These findings corroborate results from several other studies indicating that PWH are at increased risk for severe COVID-19 [27–30]. Because it was not possible to adjust for potentially confounding variables, however, the factors driving this increased risk in HIV cannot be delineated in this study. Notably, higher rates of comorbidities might explain in part the increased risk of hospitalization, ICU admission, and death observed among PWH compared with the non-HIV COVID-19 comparator group. Because of the lack of adjustment and possibility of confounding, this study is certainly not the last word on whether HIV itself leads to worse COVID-19 outcomes.

Although the studies to date have been suggestive, it is important to emphasize that salient knowledge gaps remain regarding the role of HIV in COVID-19 course, and filling in these gaps is needed to inform critical medical and policy decisions, including COVID-19 vaccine prioritization. In particular, we do not have definitive data to answer critical questions, such as: (1) Is HIV a risk factor for severe COVID-19 and mortality independent of comorbidities and socioeconomic factors? and (2) To what extent do CD4 cell count and HIV RNA determine COVID-19 outcomes?

Despite these uncertainties, based on the currently available data, there is growing concern that PWH may be at increased risk for severe COVID-19; indeed, several large studies (but not all) point to a signal of increased COVID-19 mortality in individuals with HIV (Table 1). Exactly why PWH may have worse COVID-19 outcomes is not certain. Is it HIV's legacy effect on immune function or inflammation? Is it because of comorbidities? Is it because of societal inequities and disparities in access to care? Or is it because of a conglomeration of these and potentially other mechanisms? Large and rigorous studies that adequately account for immunologic function (including current and nadir CD4 cell count; CD4/CD8 ratio; and

inflammation), comorbidities (including smoking, BMI, cardiovascular disease), and socioeconomic disparities are needed to once and for all disentangle and delineate what is driving COVID-19 outcomes in people with HIV.

While awaiting these necessary and critical studies to sort out exactly why PWH may have worse COVID-19 outcomes, we must make decisions today about how to apportion vaccines and how best to counsel and manage PWH. Even if increased risk of COVID-19 mortality in HIV is largely limited to individuals with lower CD4 cell counts or active viremia, we do not yet have the data to precisely identify which individuals in this population are at highest risk. Even if risk of severe COVID-19 is mostly driven by comorbidities, these are often underdiagnosed and underrecognized in PWH—particularly as they can manifest at younger ages in this group—and might not be adequately factored into COVID-19 risk stratification. Even if structural inequities long endured by many PWH influence COVID-19 outcomes (and they almost certainly do), this makes vaccination even more pressing because COVID-19 prevention—such as staying home and social distancing—is likely to be more challenging for many PWH due to employment, family obligations, or other unavoidable constraints. For all these reasons, we call for prioritization of people with HIV for COVID-19 vaccination into the same tier as people with other comorbidities that confer increased risk of severe COVID-19, such as those with cardiovascular or chronic pulmonary disease.

The intersecting epidemics of HIV and COVID-19 pose a clear challenge over the coming months. What is our charge in caring for PWH during the COVID-19 era? Maintaining a high degree of vigilance for COVID-19 symptoms and disruptions to care, facilitating frequent communication and outreach, and ensuring equitable and timely access to testing, therapeutics, clinical trial participation, and COVID-19 vaccination must be our highest priorities to reduce disparities and promote the well-being of this vulnerable population.

Notes

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