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BRIEF REPORT

Clinical Outcomes and Immunologic Characteristics of Coronavirus Disease 2019 in People With Human Immunodeficiency Virus

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We performed a retrospective study of coronavirus disease 2019 (COVID-19) in people with human immunodeficiency virus (PWH). PWH with COVID-19 demonstrated severe lymphopenia and decreased $CD4^+$ T cell counts. Levels of inflammatory markers, including C-reactive protein, fibrinogen, D-dimer, interleukin 6, interleukin 8, and tumor necrosis factor α were commonly elevated. In all, 19 of 72 hospitalized individuals (26.4%) died and 53 (73.6%) recovered. PWH who died had higher levels of inflammatory markers and more severe lymphopenia than those who recovered. These findings suggest that PWH remain at risk for severe manifestations of COVID-19 despite antiretroviral therapy and that those with increased markers of inflammation and immune dysregulation are at risk for worse outcomes.

Keywords. HIV; people living with HIV; COVID-19; SARS-CoV-2; coronavirus; inflammation.

The impact of coinfection with severe acute respiratory syndrome coronavirus (SARS-CoV-2) in people with human immunodeficiency virus (PWH) is incompletely understood [1–3]. Data on clinical outcomes in large and diverse cohorts of PWH are needed to understand the manifestations, including immunologic outcomes, of this novel coinfection.

Manifestations of coronavirus disease 2019 (COVID-19) range from asymptomatic infection to acute respiratory distress syndrome and multiorgan failure [4]. Case series have demonstrated severe disease in a variety of immunocompromised populations, including those who have received solid organ transplants and those on chronic immunosuppression [5, 6]. In 2 recent reports of suspected or confirmed COVID-19 in PWH, most cases were described as mild [2, 3].

Human immunodeficiency virus (HIV) infection is characterized by a chronic inflammatory state and varying degrees of immune dysfunction, even in the presence of suppressive antiretroviral therapy (ART) [7]. There are several mechanisms by which HIV may impact outcomes of SARS-CoV-2 coinfection. First, COVID-19 is associated with perturbations in immune function, most notably lymphopenia [4]. While the underlying mechanisms are unclear, PWH may be particularly vulnerable and the implications of severe lymphopenia in this population are unknown. Second, limited reports of PWH with COVID-19 initially led to suggestions that PWH could be at lower risk of severe disease, either due to epidemiologic factors or a limited ability to mount the uncontrolled inflammatory response associated with poor outcomes [8]. However, PWH are capable of generating pronounced inflammatory responses to other coinfections, leading to the possibility that such responses during SARS-CoV-2 coinfection could be severe. Third, some antiretroviral drugs may exhibit activity against SARS-CoV-2. Reverse transcriptase inhibitors (eg, tenofovir) are being investigated [9], whereas current US Food and Drug Administration–approved protease inhibitors have little effect [10]. All of these factors could potentially modify the disease course of COVID-19 in PWH.

METHODS

Study Population

We systematically identified all individuals with a diagnosis of HIV infection presenting to 5 New York City emergency departments between 2 March 2020 and 15 April 2020 who had a positive nucleic acid amplification test for SARS-CoV-2.

Performing a manual records review of the electronic medical record, 1 clinician-reviewer recorded demographic data, HIV history, presenting symptoms and signs, general laboratory and HIV parameters during the COVID-19 presentation, and outcomes for all patients. A second clinician-reviewer independently reviewed each data field.

Case Definitions

We recorded HIV history including the duration of infection, self-reported or clinician-reported nadir $CD4^+$ T-cell count if noted in the medical record, and the most recent $CD4^+$ T-cell count and plasma HIV RNA level from the pre-COVID period in the subset of individuals for whom these data were available. We defined the pre-COVID period as the time period between 1 January 2019 and 31 December 2019. We recorded the most recent documented ART regimen and noted whether

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the regimen contained either tenofovir disoproxil fumarate or tenofovir alafenamide, or a protease inhibitor (including darunavir, lopinavir, atazanavir, or ritonavir).

We tabulated comorbid disease, home medications, and smoking status as noted in the past medical history and clinical notes. We tabulated the presence of key symptoms of COVID-19 in the initial emergency department note and admission note; symptoms were recorded as present or absent/not recorded. We recorded whether the initial vital signs in the emergency department were abnormal, defined as temperature ≥38.0°C (≥100.4°F), systolic blood pressure <90 mm Hg, and whether oxygen saturation by pulse oximetry measured <92%.

We recorded laboratory values including HIV parameters during the presentation, nadir blood cell counts, peak levels of liver function tests and inflammatory markers, the results of other microbiology tests, and the results of the initial chest radiograph.

We recorded whether the patient was discharged from the emergency department or admitted. For those admitted, we recorded the highest level of care received (intensive care unit [ICU] vs general medical ward), the highest level of oxygen support administered (nasal canula or facemask, high-flow oxygen or noninvasive positive pressure ventilation, mechanical ventilation, or extracorporeal membrane oxygenation), and the administration of COVID-19–related therapies. We tabulated whether admitted patients died or recovered and were discharged from the hospital. Data were reviewed until an outcome could be recorded.

Statistical Analyses

We summarized presenting characteristics using descriptive statistics. For patients who had HIV parameters available from the pre-COVID period, we performed within-subject comparisons of results from the period prior to the pandemic and those during the COVID-19 presentation using the Wilcoxon matched-pairs signed-rank test. To compare PWH who died and recovered, we used χ^2 or Fisher exact tests for categorical variables and Mann–Whitney tests for continuous variables. Analyses were performed using Stata version 15.1SE software and results displayed using GraphPad Prism version 8.1.2 software.

Regulatory Approval

This study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board.

RESULTS

Demographics and HIV Disease Characteristics

Table 1 shows the demographics and HIV disease characteristics of patients included in the study. Of 93 patients, 67 (72%) were male, and the median age was 58 years (interquartile range [IQR], 52–65 years). Thirty-eight were black (40.9%) and 29 were Hispanic/Latinx (31.2%). In the subset for whom historical data were available, median duration of HIV infection was 20 years (IQR, 15–26 years [n = 57]) and nadir $CD4^+$ T-cell count was 320 cells/μL (IQR, 139–490 cells/μL [n = 81]). In the year preceding the COVID-19 presentation, median proximal $CD4^+$ T-lymphocyte count was 554 cells/μL (IQR, 339–752 cells/μL [n = 63]) with a percentage of 33% (IQR, 25%–38% [n = 59]), and 57 of 68 individuals (83.8%) had quantitative HIV-1 RNA measurements <50 copies/mL. Twenty-three (24.7%) had a prior documented opportunistic infection, 62 of 89 (69.6%) were on an ART regimen that included tenofovir, and 12 of 89 (13.5%) were on a regimen including a protease inhibitor. Fourteen (15.0%) were current smokers, 37 (39.8%) were former smokers, 32 (34.4%) had diabetes, 17 (18.3%) had heart disease, and 25 (26.9%) had underlying lung disease.

Presenting Clinical and Laboratory Parameters

Table 1 shows clinical and laboratory parameters of the study cohort at the time of presentation. Sixty-one (65.6%) reported fever, 71 (76.3%) reported cough, and 57 (61.3%) reported shortness of breath. PWH with COVID-19 demonstrated significant lymphopenia and decreased $CD4^+$ T-cell counts and percentages. Levels of inflammatory markers, including C-reactive protein (CRP), fibrinogen, D-dimer, interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor α were commonly elevated; IL-1β was a notable exception. In the subset of individuals with available data from the year prior to the COVID-19 presentation, we noted significant declines in median $CD4^+$ T-cell count (464 vs 188 cells/μL; $P < .0001$ [n = 30]), $CD4^+$ T-cell percentage (28% vs 23%; $P = .0012$ [n = 26]), and absolute lymphocyte count (1.9 vs 0.9×10^3 cells/μL; $P < .0001$ [n = 62]) (Figure 1).

Outcomes of Those Admitted

Of 72 PWH hospitalized with COVID-19 during the study period, 19 (26.4%) required ICU-level care and 15 (20.8%) required mechanical ventilation. A substantial proportion was treated with azithromycin (77.8%) or hydroxychloroquine (73.6%). In all, 19 individuals (26.4%) died and 53 (73.6%) recovered.

Comparison of Those Who Died and Recovered

Supplementary Table 1 compares those who died (n = 19) with those who recovered (n = 53). Those who died were more likely to require ICU care (68.4% vs 11.3%; $P < .0001$) and ventilator support (57.9% vs 7.6%; $P < .0001$), and to have a lower nadir absolute lymphocyte count (0.4 vs 0.9×10^3 cells/μL; $P = .0005$). Inflammatory markers including CRP, IL-6, and IL-8 were significantly higher among subsets of those who died compared with those who recovered for whom these measurements were performed ($P = .0004$, $P = .03$, and $P = .02$, respectively; Supplementary Table 1, Supplementary Figure 1). No difference was observed in age; sex; obesity; duration of HIV infection; nadir, preceding, or presenting $CD4^+$ T cell count; or

Table 1. Demographics, Human Immunodeficiency Virus (HIV) History, and Disease Characteristics of People With HIV Presenting With Confirmed Coronavirus Disease 2019

Characteristic	No. (%)
Age, y, median (IQR)	58 (52–65)
Sex	
Male	67/93 (72.0)
Female	23/93 (24.7)
Transgender	3/93 (3.2)
Race	
White	21/93 (22.6)
Black	38/93 (40.9)
Not specified/unknown	34/93 (36.7)
Ethnicity	
Hispanic/Latinx	29/93 (31.2)
Not Hispanic/Latinx	64/93 (68.8)
HIV history	
Duration of infection, y (n = 57), median (IQR)	20 (15–26)
Nadir CD4$^+$ T-cell count noted in record, cells/μL (n = 81), median (IQR)	320 (139–490)
CD4$^+$ T-cell count preceding COVID-19 diagnosis, cells/μL (n = 64), median (IQR)	554 (339–752)
CD4% preceding COVID-19 diagnosis (n = 59), median (IQR)	33 (25–38)
Plasma HIV RNA <50 copies/mL preceding COVID-19 diagnosis (n = 68)	57/68 (83.8)
Documentation of prior OI in record	23/93 (24.7)
ART prescription documented in record	89/93 (95.7)
Documented ART contains tenofovir (TAF or TDF)	62/89 (69.6)
Documented ART contains protease inhibitor (LPV, ATV, or DRV)	12/89 (13.5)
Comorbidities	
Disease documented in record	
Autoimmune disease	4/93 (4.3)
Cancer	8/93 (8.6)
Diabetes	32/93 (34.4)
Heart disease, CAD, or CHF	17/93 (18.3)
Hypertension	49/93 (52.7)
Lung disease, asthma, or COPD	25/93 (26.9)
Chronic kidney disease	16/93 (17.2)
End-stage renal disease	7/93 (7.5)
Solid organ transplant	5/93 (5.4)
Home medications documented in record	
ACE inhibitor	10/93 (10.8)
Angiotensin receptor blocker	3/93 (3.2)
Steroids	5/93 (5.4)
Nonsteroidal immunosuppressant	4/93 (4.4)
Smoking status	
Current smoker	14/93 (15.0)
Former smoker	37/93 (39.8)
Never smoker or not listed	42/93 (45.2)
Presenting signs and symptoms	
Symptoms recorded at presentation[a]	
Fever	61/93 (65.6)
Altered mental status	10/93 (10.8)
Congestion	13/93 (14.0)
Sore throat	18/93 (19.4)
Cough	71/93 (76.3)
Shortness of breath	57/93 (61.3)
Myalgia	33/93 (35.5)
Anosmia	2/93 (2.2)
Diarrhea	18/93 (19.4)
Headache	17/93 (18.3)
Initial vital signs at presentation[b]	
Fever, ≥38.0°C (≥100.4°C)	31/93 (33.3)
Hypoxia, SpO_2 <92%	43/92 (46.7)
Hypotension, SBP <90 mm Hg	5/92 (5.4)
BMI, kg/m^2 (n = 86), median (IQR)	26.7 (23.8–29.6)
Disposition from emergency department	
Admitted to hospital	72/93 (77.4)
Discharged from emergency department	21/93 (22.6)
Diagnostic parameters during COVID-19 illness	
Blood counts	
Initial CD4$^+$ T-cell count, cells/μL (n = 53), median (IQR)	220 (132–372)
Initial CD4% (n = 51), median (IQR)	23 (17–30)
Plasma HIV RNA <50 copies/mL (n = 46)	41/46 (89.1)
Nadir WBC, ×10^3 cells/μL (n = 84), median (IQR)	5.1 (3.6–6.9)
Nadir ALC, ×10^3 cells/μL (n = 81), median (IQR)	0.9 (0.6–1.2)
Nadir ANC, ×10^3 cells/μL (n = 81), median (IQR)	3.5 (2.1–4.8)
Peak liver function tests, median (IQR)	
ALT, U/L (n = 78)	45 (27–94)
AST, U/L (n = 78)	61 (38–113)
Total bilirubin, mg/dL (n = 78)	0.7 (0.5–0.9)
Alkaline phosphatase, U/L (n = 77)	96 (76–128)
Peak inflammatory markers	
CRP (n = 69)	
Median CRP, mg/L, median (IQR)	137.0 (91.7–240.0)
CRP elevated (ULN 5.0 mg/dL)	69/69 (100)
Fibrinogen (n = 43)	
Median fibrinogen, mg/dL, median (IQR)	626 (481–790)
Fibrinogen elevated (ULN 450 mg/dL)	36/43 (83.7)
D-dimer (n = 64)	
Median D-dimer, μg/mL, median (IQR)	2.6 (1.2–10.3)
D-dimer elevated (ULN 0.5 μg/mL)	57/64 (89.0)
IL-6 (n = 48)	
Median IL-6, pg/mL, median (IQR)	57.6 (30.5–130.9)
IL-6 elevated (ULN 5.0 pg/mL)	47/48 (97.9)
IL-8 (n = 22)	
Median IL-8, pg/mL, median (IQR)	42.2 (30.6–68.5)
IL-8 elevated (ULN 5.0 pg/mL)	22/22 (100)
TNF-α (n = 22)	
Median TNF-α, pg/mL, median (IQR)	21.8 (16.3–38.5)
TNF-α elevated (ULN 22.0 pg/mL)	11/22 (50)
IL-1β (n = 21)	
Median IL-1β, pg/mL, median (IQR)	0.3 (0.3–0.5)
IL-1β elevated (ULN 5.0 pg/mL)	0 (0)
Other microbiology	
RVP positive (n = 15)	0/15 (0)
Blood culture positive (n = 69)	1/69 (1.4)
Radiology	
CXR in first 24 h abnormal (n = 90)	71/90 (78.9)
Clinical management of hospitalized PWH with COVID-19	
Highest level of care in those hospitalized (n = 72)	
ICU	19/72 (26.4)
Hospital ward	53/72 (73.6)
Highest level of oxygen support in those hospitalized (n = 72)	

Table 1. Continued

Characteristic	No. (%)
No oxygen support needed	6/72 (8.3)
Standard nasal canula	34/72 (47.2)
HFNC or NIPPV	17/72 (23.6)
Mechanical ventilation	15/72 (20.8)
ECMO	0/72 (0)
Treatment in those hospitalized (n = 72)	
Hydroxychloroquine	53/72 (73.6)
Steroids	12/72 (16.7)
Azithromycin	56/72 (77.8)
Trial of investigational agent	3/72 (2.7)
Outcomes in those hospitalized (n = 72)	
Recovered	53/72 (73.6)
Died	19/72 (26.4)

N = 93 unless otherwise indicated. Data are presented as No. (%) unless otherwise indicated.

[a]Symptoms not documented as present in the clinical record were recorded as absent.

[b]One patient did not have some initial vital signs recorded in the medical record.

Abbreviations: ACE, angiotensin-converting enzyme; ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; ART, antiretroviral therapy; AST, aspartate aminotransferase; ATV, atazanavir; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CXR, chest radiograph; DRV, darunavir; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal canula; HIV, human immunodeficiency virus; ICU, intensive care unit; IL, interleukin; IQR, interquartile range; LPV, lopinavir; NIPPV, noninvasive positive pressure ventilation; OI, opportunistic infection; PWH, people with human immunodeficiency virus; RVP, respiratory viral panel; SBP, systolic blood pressure; SpO_2, oxygen saturation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TNF, tumor necrosis factor; ULN, upper limit of normal; WBC, white blood count.

viral suppression preceding or during the COVID-19 presentation. There was no statistical difference in the proportion of individuals on tenofovir-containing regimens (73.6% vs 55.5%; $P = .15$).

DISCUSSION

These findings indicate that PWH, particularly those with prolonged duration of HIV infection and medical comorbidities, remain at risk for severe manifestations of COVID-19 despite suppressive ART and immune reconstitution. Substantial inflammation and immune dysregulation occurred in a subset of individuals who experienced poor outcomes. Additional work is needed to determine whether and how the pathophysiology of COVID-19 in PWH differs from that in the general population.

The high prevalence of comorbidities and the presenting syndrome of COVID-19 are similar to reports in people without HIV [11, 12] and in recent series of PWH [1–3]. The degree of lymphopenia was striking, with on average a 50% reduction in absolute lymphocyte count and $CD4^+$ T-cell count compared to historical values, although CD4 percentages remained relatively stable. Furthermore, mortality was associated with more severe lymphopenia, in agreement with the general observation that lymphopenia may predict COVID-19 severity [13]. Recent data suggest that perturbations in T-cell subsets might affect the cellular immune response to SARS-CoV-2 [14]. While the clinical significance of these observations remains unknown, PWH may be particularly vulnerable to such effects given residual immune dysregulation even in the presence of suppressive ART [7].

A substantial proportion of PWH died. Fatality rates among the general population with COVID-19 in New York during the study period vary from 10.2% to 24.5% [11, 12]. While the proportion here is similar to that described in transplant recipients and those on immunomodulatory agents [5, 6], it is higher than that reported among PWH with confirmed or suspected COVID-19 in Spain and Germany [2, 3]. Larger studies with HIV-negative comparators will be essential to determine whether the risk in PWH, or specific subpopulations of PWH (eg, those with detectable viremia), is elevated.

PWH who died had higher levels of soluble markers of immune activation and inflammation than those who survived. Inflammation has been closely tied to disease severity in COVID-19 [15]. The frequency and degree of elevations in

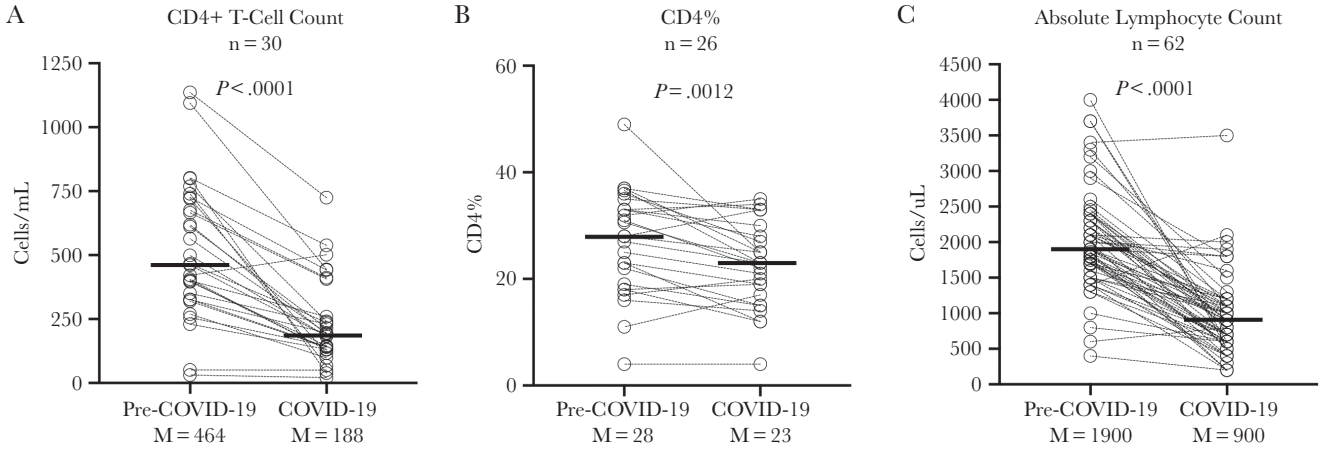

Figure 1. Changes in blood counts in the subset of patients with paired data from 2019 and the coronavirus disease 2019 (COVID-19) presentation available. *A*, $CD4^+$ T-cell count. *B*, $CD4^+$ T-cell percentage. *C*, Absolute lymphocyte count. Each connected pair represents 1 patient. Solid lines reflect medians for the sample. Medians are reported (M). *P* values calculated utilizing Wilcoxon matched-pairs signed-rank test.

the hospitalized group suggest that PWH remain capable of mounting a profound inflammatory reaction in response to SARS-CoV-2 coinfection that is similar to that in other populations [8]. The relationship between markers of inflammation and non-AIDS-defining morbidity and mortality in treated HIV infection is well known, and inflammation may be even more strongly associated with adverse outcomes in PWH than in the general population [16]. While it remains unclear whether inflammatory pathways are exacerbated or potentiated in PWH, our findings indicate that at least a subset of PWH are capable of severe inflammatory responses. It is notable that the majority of patients maintained virologic suppression below commercial assay limits despite broad immune activation. Additional work is needed to clarify the mechanisms underlying these responses, including the effects of ART, persistent immune activation, and nadir or presenting $CD4^+$ T-cell counts in the setting of COVID-19.

It has been suggested that PWH treated with tenofovir might benefit from this agent's potential activity against the SARS-CoV-2 RNA polymerase [9]. We did not find a statistical difference in the use of this agent between those who died and recovered. Further work in larger populations of PWH experiencing a broader spectrum of COVID-19 severity will be needed to determine whether there is any protective effect of this agent.

This study has some limitations. First, this was a retrospective records review limited to 1 hospital system. Complete HIV history was not available on all patients, and laboratory markers were obtained at the discretion of treating physicians. Second, a matched HIV-negative comparison group was not available and comparisons to published data are potentially confounded by disease and epidemiologic factors. Third, high rates of HIV suppression prevented us from drawing conclusions about the risk of severe COVID-19 in viremic PWH. Fourth, the SARS-CoV-2 pandemic has strained the US healthcare system, and testing in many locations has been limited. During the study period, testing was prioritized for sicker patients and this biased the sample toward those with more severe disease, who might be predisposed to worse outcomes. Fifth, data on race and ethnicity were limited. Disparities based on these factors are likely to be of great importance [17], particularly in populations of PWH.

This analysis reveals that a subset of PWH develop severe COVID-19 associated with a profound inflammatory response. Prospective studies with carefully matched control groups to identify determinants of severe COVID-19 in PWH will be crucial to understanding the biological mechanisms and clinical impact of SARS-CoV-2 coinfection in this population.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. H. H. obtained institutional review board approval. H. H. and M. J. P. designed the data abstraction instrument. H. H. and C. M. performed the data abstraction. H. H. and M. J. P. analyzed the de-identified data, which were interpreted by all authors. H. H., M. J. P., C. M., J. A. A., and M. P. M. wrote the manuscript, with input from all authors. All authors edited the manuscript.

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