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Clinical Features and Outcomes of Coronavirus Disease 2019 Among People With Human Immunodeficiency Virus in the United States: A Multicenter Study From a Large Global Health Research Network (TriNetX)

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Background. Human immunodeficiency virus infection (HIV) is a presumed risk factor for severe coronavirus disease 2019 (COVID-19), yet little is known about COVID-19 outcomes in people with HIV (PWH).

Methods. We used the TriNetX database to compare COVID-19 outcomes of PWH and HIV-negative controls aged ≥18 years who sought care in 44 healthcare centers in the United States from January 1 to December 1, 2020. Outcomes of interest were rates of hospitalization (composite of inpatient non-intensive care [ICU] and ICU admissions), mechanical ventilation, severe disease (ICU admission or death), and 30-day mortality.

Results. Of 297 194 confirmed COVID-19 cases, 1638 (0.6%) were HIV-infected, with >83% on antiretroviral therapy (ART) and 48% virally suppressed. Overall, PWH were more commonly younger, male, African American or Hispanic, had more comorbidities, were more symptomatic, and had elevated procalcitonin and interleukin 6. Mortality at 30 days was comparable between the 2 groups (2.9% vs 2.3%, $P = .123$); however, PWH had higher rates hospitalization (16.5% vs 7.6%, $P < .001$), ICU admissions (4.2% vs 2.3%, $P < .001$), and mechanical ventilation (2.4% vs 1.6%, $P < .005$). Among PWH, hospitalization was independently associated with male gender, being African American, integrase inhibitor use, and low CD4 count; whereas severe disease was predicted by older age (adjusted odds ratio [aOR], 8.33; 95% confidence interval [CI], 1.06–50.00; $P = .044$) and CD4 <200 cells/mm^3 (aOR, 8.33; 95% CI, 1.06–50.00; $P = .044$).

Conclusions. People with HIV had higher rates of poor COVID-19 outcomes but were not more at risk of death than their non-HIV-infected counterparts. Older age and low CD4 count predicted adverse outcomes.

Keywords. clinical outcomes; COVID-19; HIV.

As of February 1, 2021, the coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in an estimated 100 million confirmed infections and more than 2 million deaths globally [1]. Black and other racial minority heritage, male gender, age >65 years, obesity (body mass index [BMI] ≥30 kg/m^2), diabetes mellitus, hypertension, severe cardiopulmonary disease, and other chronic conditions have been reported as contributing to poor COVID-19 outcomes, including increased risk of mortality [2–5].

Compared with the general population, people with human immunodeficiency virus (PWH) are presumed to be at greater risk of severe COVID-19 and adverse clinical outcomes [6, 7]. This has been attributed to the observation that PWH tend to have a higher burden of lifestyle-associated risk factors and underlying comorbidities, in addition to having an already heightened systemic inflammatory state at baseline that could potentially enhance or amplify the viral cytokine release syndrome—also referred to as the "cytokine storm"—that has been described in the setting of COVID-19 [6–11].

Notwithstanding, emerging evidence from case report series, early observational studies, and systematic reviews describing the clinical features of COVID-19 among PWH have yielded mixed findings thus far. Several studies from Europe and North America have observed no substantial differences in morbidity and mortality rates among human immunodeficiency virus (HIV) and non-HIV cohorts of patients hospitalized with COVID-19, with the majority of HIV-infected patients in these studies reported

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as stable on antiretroviral therapy (ART) and virally suppressed [12–15]. On the other hand, recent data from 2 large population-based studies from South Africa and the United Kingdom found a 2- and 2.6-fold increase in the risk of COVID-19 death, respectively, among PWH compared with their non-HIV-infected counterparts [16, 17]. In the United Kingdom study by Bhaskaran et al [17], black ethnic minority status was associated with a 4.3-fold higher hazard of COVID-19 death among PWH compared with non-HIV-infected controls. However, crucial questions around the associations (if any) between the degree of immunosuppression, level of virologic control, or class of ART and COVID-19 outcomes in PWH have remained largely unanswered and are the focus of ongoing inquiry into the nature of the interactions between HIV and SARS-CoV-2.

In a multicenter study in the United States using TriNetX (a large global federated health research network), Hadi et al [15] had previously observed a higher crude COVID-19 mortality in 404 PWH, compared with their non-HIV-infected counterparts; however, the study used an earlier time cutoff (July 2020) and, importantly, did not examine the relationship between outcomes of interest and CD4 count, virologic control, and class of ART. In this study, we used a higher time cutoff in TriNetX (to include a larger number of patients) to characterize the clinical features and predictors of adverse COVID-19 among PWH in the United States.

MATERIALS AND METHODS

Study Population and Design

We used the TriNetX database to conduct a retrospective study of adult patients aged ≥18 years with SARS-CoV-2 infection (confirmed by polymerase chain reaction [PCR] or serology) who sought care across 44 healthcare organizations in the United States from January 1, 2020 to December 1, 2020. To safeguard protected health information, TriNetX does not include data on participating healthcare organizations (HCOs). Therefore, we are unable to provide geographic or institutional information. However, a participating HCO typically represents a large health center with main and satellite hospitals, specialty care services, and outpatient clinics.

Data Collection and Definitions

We collected clinical data including patient demographics, comorbidities, lifestyle-associated risk factors (smoking, alcohol use, and illicit drug use), vital signs and symptoms at presentation, laboratory findings, medication use, and healthcare services used—ie, outpatient clinic, emergency room, inpatient non-intensive care (ICU) setting, or ICU admission. We additionally collected the last CD4 count and viral load data (measured by HIV-1 ribonucleic acid [RNA] PCR) within the preceding 12 months. A full description of study definitions and variables used to query the TriNetX database and their corresponding *International Classification of Diseases, Tenth Revision* (ICD-10) codes are provided in the Supplementary Materials.

Our clinical outcomes of interest were the odds of outpatient visit (defined as utilizing ambulatory clinic or emergency department services only), hospitalization (defined as the composite outcome of inpatient non-ICU and ICU service utilization), mechanical ventilation use, severe COVID-19 (ICU admission or death), and mortality rate at 30 days after COVID-19 diagnosis.

We further analyzed COVID-19 severity in the PWH cohort based on hospital services used. Mild disease was defined as having required outpatient services only (ie, ambulatory clinic or emergency department visit). Moderate disease was defined as having required inpatient non-ICU services, whereas severe disease was defined as having required ICU services or death within 30 days of COVID-19 diagnosis.

Statistical Analyses

Summary statistics were generated for all variables at baseline. Continuous data were presented as means and standard deviations and were compared using independent *t*-tests. Categorical data were presented as frequency and proportions and compared using χ^2 or Fisher's exact test, as appropriate. To address possible confounders, we balanced cohorts using 1:1 greedy nearest-neighbor propensity score matching by demographics and key comorbidities associated with poor COVID-19 outcomes as outlined in Table 1. Within the PWH cohort, we explored predictors of outcomes (moderate and severe COVID-19) using multinomial logistic regression models with the main effects of age, race, comorbidities, class of ART, CD4 count, and viral load. For outcomes of interest, we calculated odds ratios (ORs) and 95% confidence intervals (CIs), with $P < .05$ considered statistically significant. All analyses were conducted in the statistical software R version 3.63 (R Core Team, 2020).

Patient Consent Statement

The study was approved by the Institution Board Review committee at Case Western Reserve University/University Hospitals Cleveland Medical Center. Written informed consent from patients was not required because data from the TriNetX system safeguards patient's privacy by reporting deidentified data.

RESULTS

Baseline Characteristics of People With Human Immunodeficiency Virus (HIV) and Non-HIV-Infected Patients

Of 297 194 confirmed COVID-19 cases, 1638 (0.6%) were HIV-infected, with >83% on ART. Among PWH, 229 (14.0%) contributed CD4 count data, with 187 (81.6%) reporting CD4 ≥200 cells/mm^3. Seven hundred fifty-five (46.1%) contributed viral load data, with 617 (81.7%) being virally suppressed (HIV-1 RNA <20 copies/mL) (Table 1).

Table 1. Comparison of Patient Demographics, Comorbidities, Social History, and Treatment Between PWH and Non-HIV-Infected COVID-19 Patients Before and After Propensity Score Matching

	Before Matching			After Matching		
Variables	HIV (N = 1638)	Non-HIV (N = 295 556)	*P* Value	HIV (N = 1635)	Non-HIV (N = 1609)	*P* Value
Age, years (mean ± SD)	43.34 ± 13.59	46.48 ± 18.7	**<.001**	48.34 ± 13.59	49.12 ± 14.89	.116
Gender						
Female	501 (30.6%)	163 318 (55.3%)	**<.001**	500 (30.6%)	1135 (69.4%)	1.000
Male	1137 (69.4%)	130 866 (44.3%)	**<.001**	1135 (69.4%)	1116 (69.4%)	1.000
Race or Ethnicity						
Black or African American	805 (49.1%)	55 264 (18.7%)	**<.001**	804 (49.2%)	791 (49.2%)	.420
White	573 (35.0%)	169 681 (57.4%)	**<.001**	572 (35.0%)	581 (36.1%)	1.000
Hispanic or Latino	297 (18.1%)	44 869 (15.2%)	**.001028**	297 (18.2%)	304 (18.9%)	.851
Asian	25 (1.5%)	7643 (2.6%)	**.0088**	25 (1.5%)	28 (1.7%)	.303
American Indian or Alaska Native	6 (0.4%)	1359 (0.5%)	.7077	6 (0.4%)	5 (0.3%)	.851
Native Hawaiian or other Pacific Islander	2 (0.1%)	801 (0.3%)	.3397	2 (0.1%)	1 (0.1%)	.106
Comorbidities						
Cardiovascular diseases	977 (59.6%)	98 078 (33.2%)	**<.001**	974 (59.6%)	995 (61.8%)	.198
Diabetes mellitus	358 (21.9%)	37 921 (12.8%)	**<.001**	357 (21.8%)	391 (24.3%)	.104
Obesity (body mass index >30 kg/m^2)	404 (24.7%)	43 883 (14.8%)	**<.001**	404 (24.7%)	440 (27.3%)	.095
Liver disease	179 (10.9%)	11 714 (4.0%)	**<.001**	179 (10.9%)	169 (10.5%)	.725
Chronic lower respiratory diseases	392 (23.9%)	39 622 (13.4%)	**<.001**	391 (23.9%)	387 (24.1%)	.960
Neoplasms	450 (27.5%)	39 622 (13.4%)	**<.001**	450 (27.5%)	467 (29.0%)	.323
Chronic kidney disease	264 (16.1%)	15 680 (5.3%)	**<.001**	262 (16.0%)	239 (14.9%)	.382
Asthma	237 (14.5%)	24 299 (8.2%)	**<.001**	237 (14.5%)	228 (14.2%)	.831
Dementia	22 (1.3%)	2299 (0.8%)	**.014**	22 (1.3%	14 (0.9%)	.261
Lifestyle-Associated Risk Factors						
Nicotine-related disorders	301 (18.4%)	16 292 (5.5%)	**<.001**	300 (18.3%)	278 (17.3%)	.453
Alcohol-related disorders	138 (8.4%)	6174 (2.1%)	**<.001**	138 (8.4%)	113 (7.0%)	.149
Cocaine-related disorders	81 (4.9%)	1272 (0.4%)	**<.001**	81 (5.0%)	58 (3.6%)	.070
Opioid-related disorders	77 (4.7%)	2696 (0.9%)	**<.001**	77 (4.7%)	58 (3.6%)	.137
ART Regimens						
NRTIs	896 (54.7%)			895 (54.7%)		
Tenofovir-based	653 (39.9%)			653 (39.9%)		
NNRTIs	148 (9.0%)			148 (9.0%)		
INSTIs	781 (47.7%)			781 (47.7%)		
Healthcare Service Used						
Emergency Department Services	400 (24.4%)	46 866 (15.9%)	**<.001**	399 (24.4%)	372 (23.1%)	.414
Outpatient Office Services	323 (19.7%)	50 299 (17.0%)	**.004**	323 (19.8%)	316 (19.6%)	.782
Inpatient Services	157 (9.6%)	12 174 (4.1%)	**<.001**	156 (9.5%)	116 (7.2%)	**.015**
Critical Care Services	57 (3.5%)	4297 (1.5%)	**<.001**	57 (3.5%)	50 (3.1%)	.499

Bold indicates statistically significant values.
Abbreviations: ART, antiretroviral therapy; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NNRTI, nucleos(t)ide reverse-transcriptase inhibitor; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; PWH, people with HIV; SD, standard deviation.

At entry into the healthcare system, approximately one fifth of PWH versus non-HIV-infected patients presented in the ambulatory clinic setting (19.5% vs 17.0%; $P = .004$), whereas one quarter presented to the emergency department (24.4% vs 15.9%, $P < .001$). Approximately 9.6% and 3.5% of PWH required inpatient services directly upon presentation in the non-ICU and ICU settings, respectively, versus 4.1% and 1.5% of non-HIV-infected patients ($P < .001$).

Compared with their non-HIV-infected counterparts, PWH patients were more commonly younger (43.34 ± 13.59 vs 46.48 ± 18.7 years, $P < .001$), male (69.4% vs 44.3%, $P < .001$), black or African American (49.1% vs 19.7%, $P < .001$), Hispanic (18.1% vs 15.2%, $P < .001$), and more likely to have underlying cardiovascular disease (46.8% vs 26.1%, $P < .001$), obesity (24.7% vs 14.8%, $P < .001$), diabetes mellitus (21.9% vs 12.8%, $P < .001$), and other comorbidities. People with HIV were also significantly more likely to have a history of smoking, alcohol, and drug use (all $P < .001$).

Clinical Presentation and Laboratory Parameters of People With Human Immunodeficiency Virus (HIV) and Non-HIV-Infected Patients

Overall, PWH were more symptomatic at presentation compared with non-HIV-infected patients (Table 2). The most

Table 2. Comparison of Vital Signs and Symptoms at Presentation, Laboratory Findings, and Medical Services Used Between PWH and Non-HIV-Infected COVID-19 Patients Before and After Propensity Score Matching

	Before Matching			After Matching		
Variables	HIV (N = 1638)	Non-HIV (N = 295 556)	*P* Value	HIV (N = 1635)	Non-HIV (N = 1609)	*P* Value
Presenting Vital Signs						
Systolic blood pressure, mmHg (mean ± SD)	124.7 ± 19.3 n = 556	127.3 ± 19.8 n = 80 404	**.002**	124.7 ± 19.3 n = 555	128.5 ± 19 n = 547	**.001**
Diastolic blood pressure, mmHg (mean ± SD)	75.7 ± 12.8 n = 587	75.1 ± 12.8 n = 86 147	.222	75.8 ± 12.8 n = 586	77.1 ± 13.5 n = 577	.075
Heart rate, beats/min (mean ± SD)	85.5 ± 16.1 n = 192	82.2 ± 15.6 n = 23 460	**.004**	85.5 ± 16.1 n = 192	82.4 ± 15.3 n = 181	.058
Respiratory rate, breaths/min (mean ± SD)	17.3 ± 3.1 n = 237	17.0 ± 9.9 n = 23 778	.662	17.3 ± 3.1 n = 237	16.7 ± 3.2 n = 198	**.038**
Oxygen saturation, % (mean ± SD)	80.7 ± 24.2 n = 120	83.0 ± 22.1 n = 12 784	.274	80.6 ± 24.2 n = 119	79.4 ± 25.7 n = 115	.726
Symptoms at Presentation						
Cough	277 (16.9%)	47 080 (15.9%)	.294	277 (16.9%)	273 (17.0%)	1.000
Difficulty breathing	224 (13.7%)	25 438 (8.6%)	**<.001**	224 (13.7%)	211 (13.1%)	.533
Fever (≥100.4°F)	186 (11.4%)	25 553 (8.6%)	**<.001**	186 (11.4%)	166 (10.3%)	.286
Pain in throat and chest	119 (7.3%)	10 957 (3.7%)	**<.001**	118 (7.2%)	90 (5.6%)	.069
Abnormalities of heart beat	93 (5.7%)	7876 (2.7%)	**<.001**	93 (5.7%)	82 (5.1%)	.504
Nausea and vomiting	66 (4.0%)	7753 (2.6%)	**<.001**	66 (4.0%)	68 (4.2%)	.855
Abdominal and pelvic pain	68 (4.2%)	5452 (1.8%)	**<.001**	68 (4.2%)	52 (3.2%)	.192
Malaise and fatigue	66 (4.0%)	13 887 (4.7%)	.223	65 (4.0%)	94 (5.8%)	**.017**
Headache	41 (2.5%)	6669 (2.3%)	.557	41 (2.5%)	36 (2.2%)	.696
Disturbances of smell and taste	43 (2.6%)	7545 (2.6%)	.915	43 (2.6%)	52 (3.2%)	.417
Laboratory Parameters						
Leukocytes, $\times 10^9$/L (mean ± SD)	6.9 ± 4.1 n = 554	7.7 ± 26.3 n = 59 895	.465	6.9 ± 4.1 n = 553	8.3 ± 20.6 n = 472	.118
Neutrophils, $\times 10^9$/L (mean ± SD)	283.5 ± 1977.5 n = 427	206.2 ± 1205 n = 37 953	.197	283.2 ± 1979.8 n = 426	279.7 ± 1282.8 n = 305	**.002**
Lymphocytes, $\times 10^9$/L (mean ± SD)	24.4 ± 14.2 n = 530	20.3 ± 11.7 n = 54 094	**<.001**	24.4 ± 14.2 n = 529	20.6 ± 12.4 n = 422	**<.001**
Hemoglobin, g/dL (mean ± SD)	12.6 ± 2.6 n = 582	12.9 ± 2.2 n = 62 141	**<.001**	12.6 ± 2.6 n = 581	12.8 ± 2.5 n = 489	.086
Platelets, $\times 10^9$/L (mean ± SD)	216.8 ± 91.9 n = 573	229.5 ± 93.1 n = 59 360	**.001**	216.5 ± 91.7 n = 572	231.5 ± 130.9 n = 477	**.030**
Creatinine, mg/dL (mean ± SD)	1.9 ± 2.9 n = 594	1.3 ± 1.7 n = 60 346	**<.001**	1.91 ± 2.91 n = 593	1.68 ± 2.2 n = 482	.155
Glomerular filtration rate, mL/min (mean ± SD)	71.9 ± 35.5 n = 593	78.0 ± 34.8 n = 60 686	**<.001**	71.8 ± 35.5 n = 592	76.1 ± 38.2 n = 486	.058
Prothrombin time, seconds (mean ± SD)	14.9 ± 5.7 n = 177	14.5 ± 6.2 n = 19 708	.311	14.9 ± 5.7 n = 177	15.2 ± 6.2 n = 150	.655
International normalized ratio (mean ± SD)	1.3 ± 0.5 n = 176	1.3 ± 0.7 n = 19 598	.751	1.3 ± 0.5 n = 176	1.3 ± 0.6 n = 151	.710

Table 2. Continued

Variables	Before Matching			After Matching		
	HIV (N = 1638)	Non-HIV (N = 295 556)	*P* Value	HIV (N = 1635)	Non-HIV (N = 1609)	*P* Value
Activated partial thromboplastin time, seconds (mean ± SD)	35.1 ± 11.3 n = 126	32.8 ± 11.9 n = 14 010	**.038**	35.1 ± 11.3 n = 126	33.2 ± 7.0 n = 107	.146
C-reactive protein, mg/dL (mean ± SD)	65.7 ± 73.8 n = 207	80.3 ± 86.0 n = 19 572	**.015**	65.7 ± 73.8 n = 207	85.8 ± 84.8 n = 161	.253
D-dimer, ng/mL (mean ± SD)	276.6 ± 729.4 n = 93	308.6 ± 1142.3 n = 9982	.788	276.6 ± 729.4 n = 93	370.5 ± 824.4 n = 78	.432
Erythrocytes 10^6/µL (mean ± SD)	4.2 ± 0.9 (n = 576)	4.4 ± 0.8 (n = 59 058)	**<.001**	4.2 ± 0.9 (n = 575)	4.5 ± 0.9 (n = 473)	**<.001**
Erythrocyte sedimentation rate, mm/hour (mean ± SD)	56.6 ± 35.5 n = 78	48.3 ± 32.4 n = 6446	**.025**	56.6 ± 35.5 n = 78	49.9 ± 30.1 n = 42	.300
Lactate, mg/dL (mean ± SD)	1.7 ± 1.5 n = 198	1.6 ± 1.2 n = 16 909	.257	1.7 ± 1.5 n = 197	1.5 ± 0.8 n = 150	.100
Lactate dehydrogenase, U/L (mean ± SD)	393.4 ± 367.8 n = 169	410.4 ± 362.9 n = 14 822	.546	393.5 ± 367.8 n = 169	434.3 ± 386.5 n = 142	.341
Ferritin, ng/dL (mean ± SD)	866.7 ± 1000 n = 176	884 ± 1890 n = 16 263	.901	866.7 ± 1000 n = 176	1214 ± 1404.2 n = 140	**.011**
Troponin I (cardiac), mg/dL (mean ± SD)	0.1 ± 0.2 n = 111	0.27 ± 3.1 n = 12 029	.517	0.1 ± 0.2 n = 111	0.1 ± 0.1 n = 105	.091
Procalcitonin, ng/mL (mean ± SD)	2.5 ± 10.1 n = 95	1.3 ± 5.9 n = 8529	**.042**	2.5 ± 10.1 n = 95	3.8 ± 14.0 n = 67	.492
Interleukin-6, pg/mL (mean ± SD)	258.5 ± 642.1 n = 17	98.2 ± 248.7 n = 2160	**.010**	258.5 ± 642.1 n = 17	197.4 ± 475.3 n = 16	.759
CD4 count <200 cells/mm^3	187 (11.4%)			187 (11.4%)		
CD4 count ≥200 cells/mm^3	42 (2.6%)			42 (2.6%)		
HIV-1 RNA >20 copies/mL	617 (37.7%)			616 (37.7%)		
HIV-1 RNA <20 copies/mL	138 (8.4%)			138 (8.4%)		

Bold indicates statistically significant values.

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; PWH, people with HIV; RNA, ribonucleic acid; SD, standard deviation.

common symptoms were cough (16.9% vs 15.9%, $P = .294$), difficulty breathing (13.7% vs 8.6%, $P < .001$), and fever (11.4% vs 8.6%, $P < .001$), with a smaller proportion of patients exhibiting gastrointestinal and neurological symptoms.

On laboratory parameters, PWH were more commonly anemic ($P < .001$), thrombocytopenic ($P < .001$), and had elevated serum creatinine ($P < .001$), procalcitonin ($P = .042$), and interleukin (IL)-6 ($P = .010$) levels. Although C-reactive protein ($P < .0148$) and erythrocyte sedimentation rate ($P < .001$) were lower in PWH, serum levels of other markers of acute systemic inflammation, myocardial injury, and coagulopathy were comparable between the 2 cohorts (Table 2).

Disease Severity and Clinical Outcomes at 30 Days in People With Human Immunodeficiency Virus (HIV) and Non-HIV-Infected Patients

Table 3 displays the differences in 30-day outcomes between PWH and non-HIV patients. People with HIV had higher rates of hospitalization (16.5% vs 7.6%, $P < .001$) and higher rates of severe illness requiring ICU admission (4.2% vs 2.3%, $P < .001$) and mechanical ventilation (2.4% vs 1.6%, $P < .005$). Mortality at 30 days was higher among PWH but did not attain statistical significance (2.9% vs 2.3%, $P = .123$). In propensity score-matched analysis based on demographics and key comorbidities, PWH remained at significantly higher odds of hospitalization (OR, 1.26; 95% CI, 1.04–1.53; $P = .023$).

Predictors of Poor Coronavirus Disease 2019 Outcomes Among People With Human Immunodeficiency Virus

Overall, 511 (31.2%) of PWH had visit data available, 237 (46.4%) of which were classified as having mild COVID-19, 196 (38.4%) had moderate COVID-19, and 78 (15.3%) had severe COVID-19 (Table 4).

In multinomial logistic regression models, moderate COVID-19 in PWH requiring hospitalization was independently associated with being male (adjusted OR [aOR] = 5.40; 95% CI, 1.10–28.18; $P = .048$), black or African American (aOR = 5.28; 95% CI, 1.20–23.18; $P = .028$), integrase strand transfer inhibitor (INSTI) use (aOR = 20.77; 95% CI, 1.54–280.96; $P = .026$), and CD4 < 200 cells/mm^3 (aOR = 12.50; 95% CI, 2.33–100.00; $P = .003$). Severe COVID-19 resulting in ICU admission or death within 30 days of COVID-19 diagnosis was independently associated with older age (aOR = 8.33; 95% CI, 1.06–50.00; $P = .044$) and CD4 <200 cells/mm^3 (aOR = 8.33; 95% CI, 1.06–50.00; $P = .044$). We found no significant effects of tenofovir use, protease inhibitor (PI) use, or viral load on COVID-19 outcomes among PWH (Table 4).

DISCUSSION

In this analysis of approximately 300 000 confirmed COVID-19 cases (0.6% PWH) from the United States, we found that almost half (47.6%) of PWH presented with mild disease (ie, required outpatient care only), 38.3% presented with moderate disease (ie, required inpatient non-ICU services), and 14.1% had severe disease (ie, required ICU admission or died within 30 days of COVID-19 diagnosis). We found no significant difference in COVID-19 mortality rates between PWH and non-HIV-infected patients. The crude death rates were low in both groups (2.9% vs 2.3%, respectively). Our findings are in broad agreement with population-based studies from other high-resource settings with good healthcare infrastructure, where COVID-19 mortality rates have generally been reported at <5% [6–9, 12–20].

Furthermore, we observed that compared with non-HIV-infected patients, PWH were more symptomatic at presentation, more likely to have severe disease, and used more healthcare resources with higher rates of hospitalizations, mechanical ventilation use, and ICU admissions. The high risk for hospitalization of PWH persisted after propensity score matching by key variables. We hypothesize that the reasons for these findings may be related to the combined effects of the high prevalence of underlying comorbidities coupled with the possibility of a more vigorous manifestation of the cytokine release syndrome in PWH [6–11]. It is notable that PWH in this study had a 2- to 2.5-fold higher serum levels of IL-6 and procalcitonin, respectively, compared with non-HIV-infected patients. The role of IL-6 and other cytokines in COVID-19 pathogenesis has been well described. During the early phases of SARS-CoV-2 infection, activated T lymphocytes and macrophages release IL-1, IL-6, tumor necrosis factor-alpha, monocyte chemoattractant

Table 3. Differences in 30-Day Outcomes Between PWH and Non-HIV-Infected COVID-19 Patients

	Before Matching				After Matching			
Outcomes	HIV	Non-HIV	OR (95% CI)	*P* Value	HIV	Non-HIV	OR (95% CI)	*P* Value
Hospitalization	270 (16.5%)	22 398 (7.6%)	2.41 (2.11–2.74)	**<.001**	269 (16.5%)	218 (13.5%)	1.26 (1.04–1.53)	**.023**
Intensive care services	68 (4.2%)	6731 (2.3%)	1.86 (1.45–2.36)	**<.001**	68 (4.2%)	71 (4.4%)	0.94 (0.67–1.32)	.790
Ventilation management	40 (2.4%)	4624 (1.6%)	1.58 (1.13–2.14)	**.005**	40 (2.4%)	46 (2.9%)	0.85 (0.55–1.31)	.536
Mortality at 30 days	47 (2.9%)	6708 (2.3%)	1.28 (0.94–1.69)	.1233	46 (2.8%)	61 (3.8%)	0.74 (0.50–1.08)	.145

Bold indicates statistically significant values.

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PWH, people with HIV.

[a]Results shown both before and after propensity score matching.

Table 4. Multinomial Logistic Regression Model Results for Predictors of Moderate and Severe COVID-19 Among PWH

	Moderate (Hospitalized Non-ICU) N = 196				Severe (ICU Admission or Death) N = 78			
Predictor	Estimates	SE	aOR (95% CI)	*P* Value	Estimates	SE	aOR (95% CI)	*P* Value
Age	0.018	0.03	1.02 (0.96–1.09)	.571	0.121	0.05	1.13 (1.02–1.25)	**.017**
Male	1.69	0.85	5.40 (1.01–28.76)	**.048**	1.66	1.15	5.25 (0.55–49.9)	.149
Black or African American	1.66	0.76	5.28 (1.20–23.18)	**.028**	1.58	0.95	4.85 (0.75–31.29)	.097
Tenofovir use	0.863	0.86	1.55 (0.29–8.43)	.609	−0.541	1.03	0.58 (0.08–4.36)	.598
Protease inhibitor use	1.039	1.05	2.83 (0.36–22.00)	.321	3.25	1.17	3.42 (0.34–34.04)	.295
Integrase inhibitor use	3.03	1.33	20.77 (1.54–280.96)	**.026**	1.59	1.34	4.93 (0.36–67.57)	.223
CD4 <200 cells/mm^3	−2.56	0.88	12.50 (2.33–100.00)	**.003**	−2.14	1.06	8.33 (1.06–50.00)	**.044**
Viral load >20 copies/mL	−0.039	0.96	0.962 (0.15–6.26)	.968	0.217	1.22	1.24 (0.11–13.69)	.859

Bold indicates statistically significant values.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; PWH, people with human immunodeficiency virus; SE, standard error.

protein-1, and other proinflammatory mediators of the so-called cytokine storm that is characterized by tissue damage, endothelial leakage, and the activation of the complement and coagulation pathways [21, 22]. The centrality of IL-1β and IL-6 in particular in immune dysregulation has warranted the exploration of anticytokine antagonists as novel therapies for severe COVID-19 [22–25].

Our study analyzed risk factors associated with poor COVID-19 outcomes in PWH. Male gender and being black or African American were associated with >5-fold increase in the risk of hospitalization, whereas older age was associated with higher odds of ICU admission or death within 30 days of COVID-19 diagnosis. Importantly, even after adjusting for age and comorbidities, Black ethnic minority status remained independently associated with poor COVID-19 outcomes. These findings are consistent with multiple previous reports from the United States and elsewhere that have highlighted the gender, racial, and ethnic disparities associated with the HIV and COVID-19 pandemics [26, 27]. African American, Hispanic, and other minority populations in the United States continue to be disproportionately impacted by a synergy of persistent social and economic barriers that have limited their access to health services and placed them at heightened risk of poor disease outcomes [28, 29]. Public health efforts aiming to address inequities in HIV and COVID-19 outcomes would benefit from implementing policies and actions prioritizing minority and other vulnerable populations.

Similar to other studies, we did not detect any significant effects of HIV viremia on COVID-19 severity [12–15]; however, advanced HIV disease (CD4 count <200 cells/mm^3) and INSTI use were associated with an 8-fold and 20-fold higher risk of poor outcomes, respectively. The association between low CD4 count and poor outcomes was anticipated, but the large effect demonstrated by INSTI use was unexpected. Although it has been widely speculated that some antiretrovirals may have a protective effect against SARS-CoV-2, their role in COVID-19 prevention and treatment remains in dispute. Several HIV-1 PIs (eg, lopinavir, ritonavir, and saquinavir) had demonstrated potent activity against 2 earlier coronaviruses (SARS-CoV and Middle East respiratory syndrome coronavirus) and inhibited their replication in in vitro and animal studies [30–32]; however, a randomized controlled trial of 199 critically ill hospitalized patients failed to show benefit with lopinavir-ritonavir beyond standard of care [33]. Tenofovir and other nucleos(t)ide reverse transcriptase inhibitors (NRTIs) have been shown to inhibit SARS-CoV-2 in in vitro studies by attenuating the effects of IL-8 and IL-10, while promoting the production of interferon-gamma [34–36]. Two recent studies from Spain and South Africa found that compared with other therapies, tenofovir-based ART had a protective effect against COVID-19 death among PWH [16, 37]. In our study, however, NRTI- or PI-based ART did not show mortality benefit among PWH.

Integrase strand transfer inhibitors are preferred first-line ART used in combination with 2 NRTIs and are particularly attractive due to their efficacy, good tolerability profile, and high genetic barrier to resistance [38–40]. However, INSTIs have been associated with significant weight gain in PWH initiating ART [41–43]. There are currently no studies (in vitro or in vivo) describing the direct effects of INSTIs on SARS-CoV-2. We postulate that the adverse effects of INSTIs on COVID-19 in this study likely result indirectly from the metabolic complications of weight gain and increased BMI—a well recognized risk factor for poor COVID-19 outcomes [2, 5].

Our study had several limitations. These included incomplete data on CD4 count, viral load, and other laboratory findings. In addition, we are unable to capture the start date of the symptoms, and as such we cannot exclude the possibility that PWH presented later in the course of COVID-19, which would explain the more frequent symptoms, hospitalizations, and ICU use among PWH with COVID-19. Nonetheless, to the best of our knowledge, this is one of the largest multicenter studies to date from the United States that was sufficiently

powered to detect meaningful differences and statistically significant associations between patient characteristics and outcomes of interest.

CONCLUSIONS

In one of the largest multicenter studies to date from the United States, PWH with COVID-19 had a higher burden of comorbidities and life-style associated risk factors and higher rates of hospitalization, mechanical ventilation, and ICU admissions. Despite this, PWH did not appear to be significantly more at risk of death at 30 days after COVID-19 diagnosis compared with their non-HIV-infected counterparts. Male gender, being black or African American, INSTI use, and low CD4 count were independently associated with adverse COVID-19 outcomes, regardless of HIV virologic control. Similar to previous studies, our findings highlight the need for public health efforts and policy to prioritize PWH, minority, and other vulnerable populations in addressing longstanding social and economic inequities that are being further exacerbated by the HIV and COVID-19 pandemics.

Supplementary Data

Supplementary materials are available at Open Forum 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.

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