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Descriptive Analysis of Patients Living with HIV Affected By COVID-19

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Running title: Patients with HIV Affected by COVID-19

Abstract

Background: COVID-19 disease has spread globally and was declared a pandemic on March 11, 2020 by the World Health Organization. On March 10th, the State of Michigan confirmed its first two cases of COVID-19 and since then the number of confirmed cases has reached 47,182 as of May 11, 2020 with 4,555 deaths.

Setting: Currently, little is known if patients living with HIV (PLWH) are at higher risk of severe COVID-19 or if their antiretrovirals are protective. This study presents epidemiologic and clinical features of COVID-19 infected PLWH in Detroit, Michigan.

Methods: This is a case series that included 14 PLWH with laboratory-confirmed COVID-19 infection who were evaluated at Henry Ford Hospital (HFH) in Detroit, Michigan between March 20 and April 30, 2020.

Results: 14 PLWH were diagnosed with COVID-19. Twelve patients were male and two were female; 13 of the 14 patients were virally suppressed. Eight patients were hospitalized, and six patients were told to self-quarantine at home following their diagnoses. Three patients who were admitted expired during their hospital stay. No patient required bilevel positive airway pressure or nebulizer use in the emergency department and none developed acute respiratory distress syndrome, pulmonary embolism, deep venous thrombosis, or a cytokine storm while on therapy for COVID-19.

Conclusion: Although the clinical spectrum of COVID-19 among PLWH cannot be fully ascertained by this report, it adds to the data that suggests that HIV-positive patients with SARS-CoV-2 infection are not at a greater risk of severe disease or death as compared to HIV-negative patients.

Keywords: HIV, COVID-19, SARS-CoV-2, cART, tenofovir

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus first detected in December 2019 in Wuhan, Hubei Province, China [1]. Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animals [2]. SARS-CoV-2 was then identified on January 7, 2020 by the Chinese Center for Disease Control and Prevention, which then disclosed the genomic sequence on January 11, 2020 [3]. The World Health Organization named the infection caused by SARS-CoV-2, COVID-19. Since the initial detection of COVID-19, the disease has spread globally and was declared a pandemic on March 11, 2020 by the World Health Organization [4]. In the United States, Detroit, Michigan had become a ”hotspot” of COVID-19 infected patients with the number of confirmed cases reaching 47,182 as of May 8, 2020 with 4,555 deaths in Michigan (fourth most deaths in the U.S.) [5]. Currently, little is known if people living with HIV (PLWH) are at higher risk of severe COVID-19 or if antiretroviral medications used to treat HIV are protective against severe COVID-19. Tenofovir has been shown in vitro to tightly bind to the SARS-CoV-2 RNA-dependent RNA polymerase [6]. Alternatively, lopinavir-ritonavir has already been shown to have no benefit beyond standard care in a large randomized control trial [7,8]. Additionally, little is known if and how frequently PLWH mount the intense cytokine response leading to cytokine storm and severe COVID-19. We describe our single-center experience in Detroit, Michigan of COVID-19 in patients infected with HIV-1. We reviewed patients' demographics, clinical characteristics of both their HIV and COVID-19 co-infections, the antiviral and antiretroviral treatments they received, and their clinical outcomes.

Methods

This is a case series that included 14 PLWH who were evaluated in the Henry Ford Hospital (HFH) emergency department for laboratory-confirmed COVID-19 infection, between March 20 and April 30, 2020. A confirmed case of COVID-19 was defined by a positive result on a reverse transcriptase-polymerase chain reaction assay of a nasopharyngeal swab sample. Patients were identified and clinical data were collected from electronic medical records. All laboratory tests and radiological assessments were performed at the discretion of the treating physician. Categorical variables were analyzed using the chi-square test. Approval from the Henry Ford Health System Institutional Review Board was obtained.

Results

From March 20, 2020 to April 30, 2020, 7,372 people tested positive for COVID-19 at HFH. Of this group, 14 were PLWH. Twelve patients were male and two were female. Twelve were African American and 2 were Hispanic. Six patients were discharged from the emergency department to self-quarantine. Eight patients were admitted to the general practice unit, one of whom required supplemental oxygenation. Two of the 8 patients were admitted to the intensive care unit and required invasive mechanical ventilation. The average duration of symptoms prior to admission was 12 days. The most common presenting complaints were fever (N = 7; 50%), shortness of breath (N = 7; 50%), cough (N = 10; 70%), diarrhea (N = 4; 29%), and loss of taste and smell (N = 4; 29%). One patient endorsed prior travel to Texas and two patients endorsed exposure as healthcare workers. Baseline characteristics of the patients are shown in Table 1. The most common comorbidities included obesity (N = 8; 57%), hypertension (N = 8; 57%), diabetes (N = 6; 43%), chronic kidney disease (N = 5; 36%) and end-stage renal disease

requiring hemodialysis (N = 2; 14%). Past or present smoking and alcohol use was noted in the medical histories of seven patients. One patient was previously on an angiotensin-converting enzyme inhibitor, 2 patients were on an angiotensin II receptor blocker, and 4 patients were on inhaled steroids for either chronic obstructive pulmonary disease or asthma.

Thirteen patients had suppressed HIV viral loads (Table 1) on combination antiretroviral therapy (cART) regimens. One patient was not on cART at presentation. All patients but one on cART had a regimen with a tenofovir component, and only 1 patient was on a protease inhibitor-based regimen with cobicistat-boosted darunavir. Two patients had a history of an AIDS defining illness in the past.

In the emergency department, antibiotics for community-acquired pneumonia were initiated for 4 of the 14 patients, intravenous fluids were given to 3 patients, and systemic corticosteroids were given to 3 patients. No patient required bilevel positive airway pressure or nebulizer use in the emergency department, and none developed acute respiratory distress syndrome, pulmonary embolism, deep venous thrombosis, or a cytokine storm while on therapy for COVID-19. Two patients were transferred to the intensive care unit during their admission; both expired: one from respiratory failure secondary to multifocal pneumonia, and the second one from cardiac arrest and had an extensive history of congestive heart failure. The third patient died while on the general practice unit from cardiac arrest. Five patients were discharged home. All admitted patients received hydroxychloroquine 400 mg PO twice a day for 2 doses followed by 200 mg PO twice a day for 4 days. The administration of hydroxychloroquine was consistent with our institution’s treatment guidelines during that time period. At 30 days following their COVID-19 diagnoses, 11 of the 14 PLWH were still alive.

Because of cardiac-associated mortality concern in the 3 patients who expired, a further medical record review was undertaken with a focus on COVID-19 and hydroxychloroquine associated causes. Patient 13 died from worsening heart failure that was severe prior to a COVID-19 diagnosis. The patient expired in the intensive care unit from pulseless electrical activity arrest with no documentation of torsades de pointes noted on cardiac monitoring. Patient 9 expired on the general practice unit from a cardiac arrest. He was found pulseless and unresponsive by a nurse. This patient had multiple co-morbidities including metastatic cancer, heart failure, lung disease requiring oxygenation and end stage renal disease. It is unclear if COVID-19 contributed to his cardiac arrest. Patient 1 expired from multifocal pneumonia 14 days from a COVID-19 confirmed diagnosis; this death was potentially attributable to late complications from COVID-19 (Table 1).

Discussion

Although the clinical spectrum of COVID-19 among PLWH cannot be ascertained by this report, the course of infection among those described in this report is similar to what has been described in the literature [1]. A case series from Germany presented 33 virally suppressed PLWH infected with COVID-19 with 76% having mild infection, 27% patients having severe infection, and 3% patients expiring [9]. These findings were also consistent with our results. An observational prospective study from Madrid, Spain analyzed 51 PLWH diagnosed with COVID-19 of whom 69% required hospitalization, 63% had one co-morbidity and 12% were critically ill. The authors of this study noted that PLWH should not be considered to be protected from COVID-19 or to have a lower risk of severe disease. Therefore, they should receive the same treatment approach applied to the general public [10]. PLWH at HFH had similar comorbidities and hospital

admissions compared to non-HIV patients admitted with COVID-19. In a recent publication of 463 patients infected with COVID-19, but without known HIV, the investigators from HFH found that the three most common comorbidities were hypertension (63.7%), obesity (57.6%) and diabetes (38.4%). Patients in the HFH study also had a 16% overall 30-day mortality rate [11]. These comorbidities were also the three most common in our population (57%, 57% and 43% respectively) with a 21% overall 30-day mortality rate. Our case series, the current published literature on HIV and SARS-CoV-2, and the published data from HFH on COVID-19 patients without known HIV supports the theory that there is not an excess morbidity and mortality among PLWH affected by COVID-19 compared to the general public.

There are many hypotheses as to why PLWH might have favorable outcomes to COVID-19. One hypothesis is that the majority of these patients are on tenofovir-based regimens. Tenofovir has been described as having the capacity to bind to SARS-CoV-2 RNA-dependent RNA polymerase [6]. This mechanism of action is similar to the antiviral drug remdesivir, which has been approved for treatment for COVID-19 through emergency use by the FDA. However, the affinity for the binding substrate was lowest in tenofovir, compared to galidesivir, remdesivir, and ribavirin [6]. Tenofovir-emtricitiabine was also recently shown to reduce virus titers in a highly susceptible ferret infection model [12]. In a Spanish study, PLWH receiving emtricitabine and tenofovir disoproxil fumarate were found to have a lower risk for COVID-19 and related hospitalization than those receiving other nucleoside reverse transcriptase inhibitors [13]. Whether the tenofovir-based regimen resulted in a reduction in the severity of response to COVID-19 will need to be studied further, but this regimen did not protect our patients from acquiring the infection.

Early cART can blunt the cytokine response in acute HIV infection [14]. In addition, tenofovir has been shown to have anti-inflammatory effects in cells and tissue from HIV-uninfected donors

[15,16]. The impact on COVID-19 of ART, early therapy for SARS-CoV-2, or pre-existing immunodeficiency is unknown. However, none of these patients developed a clinical syndrome compatible with a cytokine storm. While it is of interest that CD4 and CD8 counts fall with SARS-CoV-2 infection, it is unknown whether this change exacerbates or dampens the cytokine response associated with COVID-19 or leads to an increased risk of secondary infections. The absence of reports of COVID-19 among immunosuppressed hosts is striking. The susceptibility, disease course, and outcome among PLWH have not been described. Given the role of the "cytokine storm" in the outcome of COVID-19 infection, some immunodeficient states may be protective in terms of reducing the severity of infection. However, Guan et al. in a review of 1,590 patients found that any malignancy was associated with poor clinical outcomes regardless of an individual's HIV status [17]. The COVID-19 outbreak in Detroit is at a plateau as of May 10, 2020, but the total number of PLWH who have been diagnosed with COVID-19 is unknown as universal testing is not consistently performed [18]. The Michigan Department of Health and Human Services reported that as of 6/30/2020, 278 of the 17,093 (1.6%) known PLWH in Michigan tested positive for COVID-19 with 8% expiring, 21% requiring hospitalization and 5% requiring ventilation (Table 2) [19]. This is similar to the 1.7% prevalence of confirmed COVID-19 in Detroit [5]. Of the approximately 1500 PLWH followed in our HIV clinic in Detroit, MI, 14 HIV-positive individuals were diagnosed with COVID-19 in our laboratories. Others have self-reported to have been diagnosed elsewhere, but due to a lack of clinical information these individuals have not been included in this series..

Our study had some limitations. We had a small sample size, and it is unclear if our findings can be applied to a larger number of patients. All patients also received hydroxychloroquine which was consistent with our institution's guidelines during that time period prior to the Emergency

Use Authorization being rescinded. However, data remains limited on co-infection with HIV and COVID-19, and it is important to share experiences between health care professionals in order to enhance our knowledge about COVID-19.

In conclusion, even though in our series all patients co-infected with HIV and SARS-CoV-2 were either African American or Hispanic, they experienced a clinical course that was similar to that reported in the literature for individuals not infected with HIV. In this small group of individuals, we did not observe an unexpected increase in disease severity or mortality. It is possible that PLWH are more likely to take precautions to prevent exposure, more likely to seek medical care, or more likely to be tested for COVID-19, which may skew data to earlier and less symptomatic infection. Nevertheless, we have seen no signals yet to suggest that care for patients co-infected with HIV and SARS-CoV-2 should be different from care for patients with COVID-19 who are not infected with HIV.

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Table 1. Characteristics Among our Co-infected COVID 19 and HIV Patients at Presentation

Patient	Age (years)	Gender	Race/ Ethnicity	CD4 cells/mm^3	BMI (kg/m^2)	HIV-1 Viral Load (copies/mL)	CRP (mg/dL)	ALC (K/uL)	Co-Morbidities	Disposition From ED
1	74	Male	Black	523	28.8	<20	21.5	0.2	HTN, DM, CKD	GPU to ICU*
2	57	Male	Black	982	55.82	<20	2.1	2.1	COPD, HTN, DM, CHF	GPU
3	65	Female	Black	21	33.32	1646	5.1	1	DM	GPU
4	58	Female	Black	482	33.45	<20	N/A	N/A	DM, CKD	Home
5	39	Male	Black	1291	28.7	<20	N/A	N/A	None	Home
6	64	Male	Black	523	34	<20	11.3	0.3	HTN	GPU
7	48	Male	Hispanic	516	36.26	<20	11.4	1.5	None	GPU
8	54	Male	Hispanic	280	32.92	<20	N/A	0.4	HTN, DM, CKD	Home
9	63	Male	Black	242	20.71	26	20.7	0.3	COPD on 2L O2, HTN, CHF, ESRD on HD	GPU*
10	45	Male	Black	1756	25.73	<20	N/A	N/A	None	Home
11	56	Male	Black	806	31.2	<20	14.4	0.8	CKD, DM, HTN	GPU
12	36	Male	Black	463	23.9	<20	N/A	N/A	None	Home
13	64	Male	Black	145	31.2	35	11.9	1.1	HTN, ESRD on HD, COPD, CHF	GPU to ICU*
14	64	Male	Black	540	23	<20	N/A	N/A	HTN	Home

ALC, absolute lymphocyte count; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CKD, chronic kidney disease; CRP, C-reactive protein; DM, diabetes mellitus; ED, emergency department; ESRD on HD, end stage renal disease on hemodialysis; GPU, general practice unit; HTN, hypertension; ICU, intensive care unit; N/A, not available. *, Patient expired

Table 2. Summary of Total Number of COVID-19 Cases in Michigan With and Without HIV

Characteristic	COVID-19 Patients	PLWH	Co-Infection with COVID-19 and HIV
Total Cases	65,271	17,093	278
Gender			
Males	47%	79%	81%
Females	53%	21%	19%
Age			
Mean	52	46	49
Median	52	48	51
Race/Ethnicities			
Hispanic	7%	6%	9%
Black	32%	56%	68%
White	39%	34%	16%
Unknown	23%	4%	7%
Deaths (N, %)	5942 (9%)	---	23 (8%)
Hospitalization (%)	20%	---	21%
Requiring Ventilation (%)	3%	---	5%