COVID-19 in HIV-infected patients: A case series and literature review

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Abstract
During the current COVID pandemic, there is growing interest to identify subsets of the population that may be at a higher than average risk of infection. One such group includes people living with HIV (PLWH). While immune deficiency could increase the risk of acquiring viral infections, reports suggest that defective cellular immunity could paradoxically bode better outcomes in COVID-associated cytokine dysregulation. Furthermore, antiretroviral drugs (protease inhibitors [PIs]), are being tested as a therapeutic option owing to their potential to inhibit the 3-chymotrypsin-like protease of COVID.1-3 This case series reviews the clinical and laboratory characteristics of COVID in PLWH admitted to a community hospital.

COVID in PLWH raises certain unique concerns because older PLWH have a higher risk of comorbidities compared with uninfected individuals of the same age, while younger PLWH are more likely to be noncompliant with antiretroviral therapy (ART), thereby leading to reduced HIV viral suppression.4 It may also multiply pre-existent issues in PLWH, such as access and adherence to ART, mental health burden, substance use, food insecurity, and so forth.5 While social isolation slows the spread of COVID, its implications on the above-mentioned issues remains to be seen. Socioeconomic and ethnic disparities can affect clinical outcomes and there is a need for more data to make any definitive conclusions.6 This retrospective analysis identified PLWH among all COVID inpatients in our institution from March to April 2020. HIV diagnosis was based on prior testing within the health system and COVID was confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR). At admission, patients were categorized as mild, moderate, severe, or critical based on the NIH guidelines as follows:

1. Mild—any signs/symptoms of COVID without dyspnea/abnormal chest imaging.
2. Moderate—lower respiratory disease by clinical assessment or imaging and SpO2 ≥94% on room air.
3. Severe—respiratory frequency >30/min, SpO2 <94% on room air, PaO2/FiO2 <300 mmHg, or lung infiltrates >50%.
4. Critical—respiratory failure, septic shock, or multiorgan dysfunction (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-COVID/).

We compiled demographics, clinical, and laboratory characteristics of all patients. Descriptive statistics like simple frequencies, percentages, and mean were calculated. This study was approved by the institutional review board. All six patients were African-American, reflecting the majority demographic that our hospital caters to. One patient was female, while the rest identified as male. The average BMI was 24 and the mean age was 64 years. All patients had at least one comorbidity. Half the patients had an active mental health problem/cognitive impairment and 33% had an active substance use problem. Five of the six were noted to be compliant with their ART preadmission. Majority of the patients were on INSTIs.
In one patient, ART was discontinued as per the discretion of the supervising physician; others were continued on their home ART regimen. The mean CD4 count was 765, with only one patient having a detectable viral load. The distribution of COVID severity was one mild, three moderate, one severe, and one critical. Two patients expired due to post-cardiac arrest syndrome and worsening hypoxic respiratory failure, respectively. Of the remaining four, two required supplemental oxygen during admission and the other two did not. One patient was discharged on home-oxygen. The average duration of hospitalization was 7.5 days. Other clinical/diagnostic findings are in Tables 1-3. Our case series was set in a community hospital in Philadelphia from March to April 2020 and this period was picked because it had a rapid increase in COVID cases. To date, Philadelphia has had approximately 25,000 cases and 1500 deaths, with a peak of 603 new cases in a single day on April 15, 2020. With regard to impact in immunosuppression/immunodeficiency, a systematic review demonstrated that both had increased severity of COVID illness, 3.29- and 1.55-fold, respectively, but this difference was not statistically significant. With regard to HIV, Table 4 summarizes the available evidence.

Available data does not point to HIV being an independent risk factor for poor prognosis in COVID but PLWH are at a higher risk for the noncommunicable comorbidities that are associated with worse clinical outcomes. In our case series, we noted that the two patients who died had more medical comorbidities. These two patients also had elevated procalcitonin. Although both received broad-spectrum antibiotics, there was no growth in their blood/sputum cultures. Hence, it is difficult to assess if they truly had a superadded bacterial infection making them sicker or if it was a nonspecific finding.

Richardson et al. looked at an exclusive inpatient COVID population in New York and found that mortality was 21% overall but as high as 88% in critically ill patients with underlying comorbidities. These two patients also had elevated procalcitonin. Although both received broad-spectrum antibiotics, there was no growth in their blood/sputum cultures. Hence, it is difficult to assess if they truly had a superadded bacterial infection making them sicker or if it was a nonspecific finding.

### Table 1 Patient demographics

| Patient | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---------|-----------|-----------|-----------|-----------|-----------|
| General demographics | | | | | |
| Age | 62 | 59 | 45 | 74 | 57 | 87 |
| Sex | Male | Female | Male | Male | Male | Male |
| Race | African American | African American | African American | African American | African American | African American |
| Body mass index | 25 | 21 | 21 | 22 | 32 | 24 |
| Sick contact | + | + | - | - | + | - |
| Past medical history | | | | | |
| Active mental health problems | Dementia | - | Depression | - | - | Dementia |
| Active substance use | - | Tobacco | Cocaine | - | - | - |
| Chronic obstructive pulmonary disease | - | + | - | - | + | - |
| Diabetes mellitus | + | - | - | + | - | + |
| End-stage renal disease on dialysis | + | - | - | - | - | - |
| Coronary artery disease | - | + | + | - | - | - |
| Hypertension | + | + | - | + | + | + |
| Hyperlipidemia | - | + | - | + | + | + |
| Peripheral vascular disease | - | + | - | - | - | - |
| HIV-related values | | | | | |
| Last CD4 (cells/mm³) | 491 | 1500 | 500 | 772 | 678 | 651 |
| HIV viral load (copies/ml) | 10,000 | Undetectable | Undetectable | Undetectable | Undetectable | Undetectable |
| ART regimen adherence | + | + | + | + | + | + |
| ART regimen preadmission | RPV/ral/3TC | ABC/EFV/3TC | BIC/TAF/FTC | BIC/TAF/FTC | EVG-c/TAF/FTC | EFV/TDF/FTC |
| ART regimen during admission | ART held | Same continued | Same continued | Same continued | Same continued | Same continued |

Abbreviation: ART, antiretroviral therapy.
illness, and ventilator needs, the mortality rate in our case series is comparable with other studies.

Contrary to the concern for worse outcomes in HIV, some data suggest favorable outcomes for COVID in PLWH, perhaps due to the protective effect of ART. However, PIs (lopinavir–ritonavir, darunavir) tested in clinical trials did not show increased efficacy compared with standard supportive care. Current guidelines do not recommend any change in ART to boosted PI-containing regimen. In vitro studies show that remdesivir was the most effective against COVID when compared against medications like tenofovir, lamivudine, emtricitabine, and so forth. Tenofovir though has anti-RNA-dependent RNA polymerase activity akin to remdesivir and hence its protective effect cannot entirely be ruled out.

Despite the largely reassuring data regarding COVID in PLWH in terms of disease severity and mortality, there are many aspects that are yet to be studied. Some data demonstrates that there is a more pronounced decline of CD4 count in the PLWH population with severe COVID and that the lymphopenia can take several weeks to return to baseline. It is unclear if this translates into an increased risk of opportunistic infections and need to be studied. Studying these long-term effects is challenging, given the variable degree of control in PLWH. The spectrum includes viral suppression to a degree that it is undetectable and untransmittable (U = U), HIV-associated comorbidities/virological failure, and severe immunodeficiency/AIDS-defining illnesses. Larger studies are needed to ensure adequate representation of all these categories of PLWH.

### TABLE 2 Admission laboratory values

|                          | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|--------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| Hemoglobin (g/dl)        | 12.3      | 7.1       | 13.6      | 13.9      | 12.2      | 8.6       |
| Leukocyte count (x1000/µl) | 5.72      | 20.64     | 6.1       | 7.03      | 3.3       | 8.55      |
| Neutrophil (%)           | 60.9      | 88.2      | 65        | 81.4      | 72.7      | 84.4      |
| Lymphocyte (%)           | 17.7      | 8.6       | 20        | 11.2      | 17        | 7.3       |
| Absolute lymphocyte count (x1000/µl) | 1.01      | 1.77      | 1.22      | 0.78      | 0.56      | 0.62      |
| Platelets                | 275       | 560       | 170       | 278       | 124       | 268       |
| Baseline creatinine (mg/dl) | 8         | 1         | NA        | 1.6       | 0.8       | 1         |
| Creatinine (mg/dl)       | 8.6       | 1         | 1.2       | 3.1       | 1.1       | 1.8       |
| Peak creatinine (mg/dl)  | 11.9      | 1.9       | 1.2       | 3.1       | 1.1       | 1.8       |
| LDH                      | 338       | 520       | 214       | 508       | 499       | 258       |
| Ferritin (ng/ml)         | 1944      | 171       | NA        | NA        | 7469      | 241       |
| Peak ferritin (ng/ml)    | 2879      | 171       | NA        | NA        | 7469      | 347       |
| AST (IU/ml)              | 24        | 72        | NA        | 52        | 73        | 38        |
| ALT (IU/ml)              | 6         | 42        | NA        | 22        | 67        | 22        |
| Total bilirubin (mg/dl)  | 0.2       | 0.2       | NA        | 0.8       | 1.1       | 0.4       |
| Direct bilirubin (mg/dl) | 0.1       | 0.1       | NA        | 0.4       | 0.7       | 0.3       |
| INR                      | 1.3       | 1.7       | NA        | NA        | 1.2       | 1.2       |
| D-dimer (ng/ml)          | 1970      | 12,940    | 340       | NA        | 2690      | 1170      |
| Fibrinogen (mg/dl)       | 586       | 341       | NA        | NA        | NA        | 677       |
| CRP (mg/L)               | 274       | 243.8     | NA        | 178.6     | 74        | 277.2     |
| Procalcitonin (ng/ml)    | 5.83      | 2.74      | NA        | NA        | 0.1       | 0.42      |
| Lactate (mmol/L)         | 1.8       | 11.19     | NA        | 1.1       | 1.2       | 1.8       |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase.
|                          | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|--------------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| FiO2 at admission        | 21        | 100       | 21        | 21        | 28        | 21        |
| Chest radiograph at admission | +, <50% infiltrates | +, >50% infiltrates | -          | +, <50% infiltrates | +, >50% infiltrates | +, <50% infiltrates |
| COVID severity at admission | Moderate  | Critical  | Mild      | Moderate  | Severe    | Moderate  |
| Highest FiO2 during admission | 100%      | 100       | 21        | 21        | 35        | 28        |
| New supplemental O2 during admission | +          | +         | -         | -         | -         | +         |
| Length of stay (days)    | 14        | 6         | 3         | 4         | 8         | 10        |
| Intubation               | -         | 6 days    | -         | -         | -         | -         |
| NRB/high flow            | 6 days    | -         | -         | -         | -         | -         |
| Discharged on new O2     | Expired   | Expired   | -         | -         | +         | -         |
| Disseminated intravascular coagulation | -         | -         | -         | -         | -         | -         |
| New deep vein thrombosis/pulmonary embolism | -         | -         | -         | -         | -         | +         |
| Gastrointestinal bleed   | -         | -         | -         | -         | -         | -         |
| Required pressors        | -         | 4 days    | -         | -         | -         | -         |
| Hydroxychloroquine (HCQ) | +         | +         | -         | -         | +         | +         |
| Steroids                 | -         | +         | -         | -         | -         | -         |
| Tocilizumab              | -         | -         | -         | -         | -         | -         |
| Remdesivir               | -         | -         | -         | -         | -         | -         |
| Azithromycin             | -         | -         | -         | +         | +         | -         |
| Other antibiotics        | +         | +         | -         | +         | +         | -         |
| Outcome                  | Expired   | Expired   | Discharged | Discharged | Discharged | Discharged |

Abbreviation: NRB, non-rebreather mask.
| Design, duration, and authors of the study | Number of cases | Mean age and demographics | Mean CD4 and immune status | Severity of COVID illness | Deaths | Home ART regimen | Other treatment (Rx) | Other findings |
|------------------------------------------|----------------|--------------------------|---------------------------|--------------------------|--------|------------------|---------------------|------------------|
| Gervasoni et al.\(^1\) Italy February 21–April 16, 2020 Retrospective | 47 | 51 ± 11 years 76% male | 636 ± 290/mm\(^3\) 3 detectable viral load | 13 admitted 6 severe 2 ventilation | 2 | 80% INSTI 11% PI 42% tenofovir | <50% received hydroxychloroquine/azithromycin/lopinavir–ritonavir 1 tocilizumab and remdesivir 1 tocilizumab | 64% patients—at least 1 comorbidity Mean age was 10 years lower than HIV-negative population |
| Blanco et al.\(^2\) Spain February to March 9, 2020 Retrospective | 5 cases | 38 years 3 male 2 transgenders | 563.6/mm\(^3\) 2 ICU 1 NIV 1 ventilation | 0 | 1 patient was not on ART 1 PI 3 INSTI | 2 interferon 4 hydroxychloroquine 2 steroids 1 tocilizumab 3 azithromycin 3 broad-spectrum antibiotics | All five patients were put on a boosted PI regimen during admission |
| Harter et al.\(^3\) Germany March 11–April 17, 2020 Retrospective; 12 centers | 33 cases | 48 years 30 male | 670/mm\(^3\) 2 detectable viral load 4 CD4 count < 350 | 14 admitted 6 ICU 4 ventilation 1 NIV 76% mild, 24% severe/critical | 3 | All patients were on ART NRTIs 31 INSTI 20 NNRRTIs 9 PIs 4 NRTI–tenofovir/emtricitabine/lamivudine | Unknown | 60% patients had at least 1 comorbidity 5. HBV coinfection; 4 resolved/1 chronic Hep B 1 cured HCV |
| Ozlem et al.\(^10\) Turkey March–April 2020 Retrospective | 4 patients | 37 years All male | 627 cells/mm\(^3\) 1 detectable viral load | 1 ICU | 1 | 1 newly started on TDF/FTC + LPV/r 2 PI 1 INSTI | 1 patient got PCP Rx with TMP-SMX as well and discharged on PCP and MAC prophylaxis 1 HCQ, azithromycin | 1 HBV coinfection 1 DM, COPD, HTN |
| Suwanwongse et al.\(^11\) New York March 25–April 20, 2020 Retrospective | 9 patients | 58 years 7 male 2 female | 616 cells/mm\(^3\) (excluding one patient with unknown CD4) | 5 ventilation 6 INSTI 1 PI All patients were on tenofovir and emtricitabine | 7 | 8/9 were on ART 6/9 got antibiotics 4 azithromycin 4 got HCQ | All patients had at least 1 other medical comorbidity 5 hypertension 3 diabetes mellitus 4 COPD |
| Karmen-Tuohy et al.\(^12\) New York March 2–April 23, 2020 | 21 HIV 42 non-HIV | 60 years 19 male | 298 cells/m\(^3\) (2 unknown CD4) 1 CD4 < 200 and viral load > 50 | 6 - ICU 5 ventilation 6 died/transfered to hospice | All patients were on HAART 1 PI | 3 HIV and 1 non-HIV patient received antibiotics for superimposed bacterial pneumonia | HIV patients—higher absolute lymphocyte count (\(p = .043\)) and higher CRP | (Continues) |
| DESIGN, DURATION, AND AUTHORS OF THE STUDY | NUMBER OF CASES | MEAN AGE AND DEMOGRAPHICS | MEAN CD4 AND IMMUNE STATUS | SEVERITY OF COVID ILLNESS | HOME ART REGIMEN | OTHER TREATMENT (RX) | OTHER FINDINGS |
|------------------------------------------|-----------------|----------------------------|---------------------------|--------------------------|-----------------|---------------------|----------------|
| 4 hospitals Retrospective, observational Matched with non-HIV patients | 31 patients     | 60.7 years 24 male         | 396 cells/mm³             | 2 ICU                    | 24 hydroxychlorquine | 16 azithromycin    | Greater % of HIV patients had an abnormal chest radiograph |
| Shalev et al.¹³ New York March 15–April 15, 2020 Retrospective | 51 patients     | 53 years 8 female          | Unknown mean              | 28 admitted              | 41 INSTI            | 30 HCQ               | Trend toward HIV-positive patients having longer hospital stay, higher ICU admission, mechanical ventilation but not statistically significant |
| Vizcarra et al.¹⁴ Spain Until April 30, 2020 Observational prospective study | 30 patients     | 60.7 years 24 male         | 396 cells/mm³             | 2 ICU                    | 24 hydroxychlorquine | 16 azithromycin    | No significantly worse outcomes in HIV compared with matched non-HIV patient |

Abbreviations: ART, antiretroviral therapy; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; HAART, highly active antiretroviral therapy; HCQ, hydroxychloroquine; HBV, hepatitis B virus; HCV, hepatitis C virus; HTN, hypertension; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PCP, pneumocystis pneumonia; PLWH, people living with HIV; SMX, sulfamethoxazole; TMP, trimethoprim.
This case series shows that despite a higher mean age and all our patients having at least one other medical illness, the morbidity and mortality were comparable to other previously conducted studies. The limitation of this study is that it is a single-center retrospective analysis and bigger prospective studies with longer follow-up are needed to assess the effect of HIV and ART in COVID and also look at its other long-term sequelae.

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