LETTER TO THE EDITOR

HIV and SARS-CoV-2 coinfection: A case report from Uganda

To the Editor,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the coronavirus disease 2019 (COVID-19), has been reported in over 3.6 million individuals worldwide including at least 35 000 people in Africa as of 7 May 2020.[1] Fever, cough, fatigue, and shortness of breath are the predominant clinical manifestations of COVID-19, with the disease taking on a severe course in 25% of individuals.[2] Advanced age (>60 years) and having a chronic underlying condition have been reported to be associated with severe disease, lack of clinical improvement, and mortality among patients with COVID-19.[3]

Sub-Saharan Africa accounts for more than 70% of the global burden of HIV infection, and the coinfection with SARS-CoV-2 among HIV-infected patients is inevitable in this region, albeit with yet to be known clinical consequences.[4] There are few case reports on HIV/SARS-CoV-2 coinfection. From Wuhan, China, Zhu et al reported a severe case of a newly diagnosed HIV/SARS-CoV-2 coinfected male with diabetes who presented with fever, hypoxemia, lymphopenia, and chest computed tomography (CT) abnormalities, who was managed on oxygen therapy, the HIV antiviral agent lopinavir/ritonavir, moxifloxacin, gamma-globulin, and methyl prednisone.[5] Blanco et al also reported five cases of HIV/SARS-CoV-2 coinfection–of whom four were virologically suppressed on antiretroviral therapy (ART)–from Spain, who invariably presented with cough and fever.[6] Two of these had other comorbidities while one was newly diagnosed with advanced HIV (CD4 of 13 cells/mm^3 and concurrent infection with *Pneumocystis jiroveci*). Characterization of HIV/SARS-CoV-2 coinfection is important not only because of the possible variations in the clinical presentation but also HIV co-infection may delay the detection of plasma SARS-CoV-2 anti-bodies, and therefore affect the fidelity of SARS-CoV-2 serological tests.[7] There are no reports of HIV/SARS-CoV-2 co-infection from resource-limited settings. A case of HIV/SARS-CoV-2 coinfection who was successfully managed at Entebbe Regional Referral Hospital, a tertiary public health care facility in Uganda, is presented in this case report.

A 34-year-old female with a history of travel to Turkey in early March 2020 was put under institutional quarantine upon return to Uganda as part of the government's measures instituted in late March 2020 to prevent importation of SARS-CoV-2 infections. She presented with no complaint. A nasopharyngeal swab was taken off and a real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay performed at the Uganda Virus Research Institute confirmed the presence of SARS-CoV-2 by amplifying the betacoronavirus E gene and the SARS-CoV-2 specific RdRp gene. The patient was HIV-positive on antiretroviral therapy (ART)–tenofovir disoproxil fumarate, lamivudine, and efavirenz–for 5 years. She did not report any other chronic illnesses. She was admitted for isolation at Entebbe Regional Referral Hospital. On admission (day 1), she was in a good general condition with no symptoms. There was no wasting, lymphadenopathy, or pallor and her temperature was 36.4°C) (normal). She had a blood pressure of 110/80 millimeters of mercury (mm Hg) and a pulse rate of 84 beats per minute (b/min), both of which were normal. The respiratory exam was significant for tachypnea (a respiratory rate of 26 breaths per minute (breaths/min)) with normal oxygen saturation (SPO$_2$) of 96% on ambient air. There was no respiratory distress, and auscultation of the chest was normal. On day 3, she reported headache, chest pain, anorexia, and muscle aches but no cough or shortness of breath. Her vitals were normal, except for a respiratory rate of 24 breaths/min and a pulse rate of 97 b/m. The same day, she was initiated on oral azithromycin (500 mg daily for 5 days), hydroxychloroquine (400 mg twice on day 3 and 200 mg twice daily for the subsequent 5 days), and paracetamol (1 gram three times a day for 5 days). On day 6, she developed watery non-bloody diarrhea without vomiting, abdominal pain or fevers. Clinically, she had dry mucus membranes and the blood pressure was 96/60 mm Hg. The abdominal examination was unremarkable. Oral ciprofloxacin (500 mg twice daily for 5 days) and oral rehydration salts were initiated by the attending physician on clinical suspicion of a superimposed gastrointestinal bacterial infection. The serum chemistry measured on day 10 was significant for elevated alkaline phosphatase (ALP) of 128.4 units per liter (U/L) while the direct and total bilirubin and other hepatic transaminases were normal. Serum creatinine, urea, albumin, uric acid, and total protein were normal. The full blood count (FBC) was also normal, including a white blood cell count of 5.4×10^9 per liter (L), lymphocyte count of 1.68×10^9/L, hemoglobin level of 12.2 grams per deciliter (g/dL) and a platelet count of 278×10^9/L. Her CD+ cell count and CD4+ T- lymphocyte percentage measured on day 12 were 965 cells/mm^3 and 40.1% respectively. The HIV viral load performed (HIV-1 RT-PCR) on a dry blood spot was <1000 copies/mL, that is, below the threshold of detection. The urine lipoarabinomannan, for tuberculosis, was negative. A repeat FBC on day 11 was normal. All symptoms had resolved by day 12. The respiratory rate was 16 b/min, the pulse rate was 80 b/min, and she had a blood pressure of 126/88 mm Hg.

Throughout the admission period, her SPO$_2$ was >96% on ambient air and the temperature ranged between 35.4°C and 37.0°C. The follow-up SARS-CoV-2 RT-PCR tests were positive on day 3 and

6. On day 18 and 21, two consecutive negative SARS-CoV-2 RT-PCR tests were registered. The patient was subsequently discharged on day 24.

This is the first case report of HIV/SARS-CoV-2 co-infection from sub-Saharan Africa. This case report highlights important clinical aspects of the co-infection. The patient did not have fever or cough, the two commonest symptoms of COVID-19.[8] Rather, she developed gastrointestinal symptoms that occur in only 12% of patients with mild COVID-19.[9] At the moment, it is unclear whether HIV-infected patients are likely to present with the less common symptoms of COVID-19 although "atypical" CT scan findings have been reported in an HIV-infected patient.[10] In a case series from Spain, all HIV/SARS-CoV-2 coinfected patients had cough and fever.[6] However, unlike the patient reported in this case report, they had other comorbid conditions, with one having concurrent *Pneumocystis jiroveci* pneumonia (PJP). One similarity to this case report is that four of the five patients in the case series also presented with headache. Also, similar to this patient, the HIV coinfected patient who had good adherence to ART and a suppressed viral load, presented with weakness and nonbloody diarrhea with no significant clinical signs and laboratory abnormalities in a case series from Turkey.[11] It appears that HIV patients who are well optimized on ART without other comorbid conditions experience different symptoms, few clinical signs, and laboratory abnormalities of COVID-19. However, clinical manifestations of COVID-19 need to be characterized among HIV patients by larger studies to facilitate early clinical suspicion, diagnosis, and treatment.

The presentation with chest pain, tachypnea, normal auscultation findings, and tachycardia raises the possibility of alternative diagnoses that could mimic COVID-19. Specifically, PJP and pulmonary embolism can present in a similar manner, and have been reported among patients with COVID-19.[6,12] In this patient, PJP was unlikely owing to an apparently normal CD4 count, normal oxygen saturation and the lack of fever. The lack of a CT scan at the treatment site precluded CT angiogram imaging to rule out pulmonary embolism. A chest X-ray was not performed for this patient either. However, its diagnostic accuracy for COVID-19, PJP, and pulmonary embolism is low.[13] Elsewhere, imaging findings among HIV/SARS-CoV-2 coinfected findings include normal imaging findings, basal interstitial infiltrates, ground-glass appearance- and pleural effusion, all of which can occur with pulmonary embolism.[6,11,14] A high index of clinical suspicion for concurrent chest pathology due to other diseases among HIV/SARS-CoV-2 coinfected is needed.

Save for the elevated ALP, the laboratory work up of this patient was unremarkable. The elevated ALP, a marker of bone resorption due to osteoblastic activity, is most likely caused by tenofovir rather than a unique feature of HIV/SARS-CoV-2 co-infection.[15] Normal laboratory works up in an HIV patient with COVID-19 has been reported in China and Turkey especially in the setting of controlled HIV.[7,10,11] Laboratory abnormalities observed elsewhere are elevated lactate dehydrogenase, C-reactive protein (CRP), D-dimers, fibrinogen and ferritin, thrombopenia, leucocytosis- and lymphopenia.[5,6] Unfortunately, CRP, D-dimers, fibrinogen and ferritin are not routinely performed at our facility. Alongside the unavailability of advanced imaging, the lack of diagnostic capacity for COVID-19 prognostic biomarkers in low resource settings is likely to affect the optimization of care among HIV patients with COVID-19. Similar to this patient, normal CD4 counts and suppressed HIV viral load were almost invariably reported by Blanco et al among HIV/SARS-CoV-2 coinfected patients who were ART experienced. It is unclear how SARS-CoV-2 might affect CD4 counts among ART naïve HIV infected patients.

Optimal treatments for HIV/SARS-CoV-2 coinfection are unknown. The successful use of hydroxychloriquine, quinolones, and azithromycin has also been reported by other case reports.[5,6] Larger studies are needed to evaluate the benefits and risks of hydroxychloroquine with or without antibiotics among HIV/SARS-CoV-2 coinfected. The optimal ART among HIV patients with COVID-19 is not established yet. This patient had been taking tenofovir, which has been showed to be effective against SARS-CoV-2 by binding RNA polymerase.[16] The EPICOS trial (NCT04334928) will hopefully provide evidence for the role of coadministration of hydroxychloroquine with tenofovir. The benefit of lopinavir/ritonavir combination has been questioned among patients with severe COVID-19.[17]

The HIV/SARS-CoV-2 coinfected cases in literature took on a varied clinical course raging from mild to severe, although cure was realized in most of the cases.[5,6,10,11] It is unclear whether HIV infection is protective against severe COVID-19 due to lack of a hyperactive immune response.[18] The patient presented herein had a normal CD4 count and seems to have experienced a moderate course of the disease. Sensitive prognostic scores for low resource settings are needed to predict the clinical course of COVID-19 among HIV patients.[19]

In conclusion, HIV/SARS-CoV-2 co-infection is likely to become a common phenomenon in countries with a high HIV prevalence. There is a need for larger prospective studies to characterize clinical manifestations of COVID-19 among HIV patients and determine optimal treatments, including appropriate ART regimens. Low resource settings need to build diagnostic capacity for COVID-19 "mimics" and prognostic biomarkers.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

JBB: Design, data accrual, methodology, manuscript writing and final approval. SM: Design, methodology, manuscript revision and final approval. GI, CS, and MM: Data accrual, methodology, manuscript revision and final approval.

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