

# HIV and COVID-19 co-infection: Mild infection or prolonged transmission – a case series

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**Background.** Comorbid conditions may be associated with severe COVID-19. However, there is no evidence to suggest that people living with HIV have a higher risk of contracting SARS-CoV-2 or, if infected, have more severe disease.

**Objective.** To describe three patients with HIV and COVID-19 co-infection.

**Method.** The study was conducted in a private hospital in Gauteng Province, South Africa. All three patients were known to have HIV disease and were treated with chronic antiretroviral medication. All patients admitted to the unit were screened for chronic conditions such as HIV, tuberculosis, diabetes and hypertension. They were admitted to the hospital after being diagnosed with COVID-19, this being confirmed by positive reverse transcription polymerase chain reaction (RT-PCR) tests.

**Results.** The combination of HIV and SARS-CoV-2 (HIVCO) with comorbidities in case 1 (dialysis-dependent end-stage renal failure and hypertension) resulted in severe illness, a long hospital stay and protracted viral shedding. The protracted shedding pattern (>60 days) was confirmed by multiple positive RT-PCR tests and positive viral cultures obtained after 60 days. Despite comorbidities, case 2 (Takayasu's disease in remission, dyslipidaemia and previous deep vein thrombosis) and case 3 (hypertension and diabetes) presented with mild illness. The mild clinical course and negative RT-PCR tests in cases 2 and 3 indicated resolution of infection.

**Conclusion.** Patients with HIVCO and comorbidities may present with mild or severe illness. Unusually long SARS-CoV-2 shedding is a risk for disease transmission, and its association with HIV, other immunocompromised conditions and comorbidities is unclear. We describe a shedding classification that may assist in identifying and managing infectious subsets of patients. Multiple SARS-CoV-2 tests and viral cultures may be necessary to confirm protracted shedding.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was unknown prior to the outbreak in Wuhan, China, in December 2019.<sup>[1]</sup> The disease is likely to have a zoonotic origin involving the bat and the pangolin as primary and intermediate hosts, respectively.<sup>[2]</sup> In October 2020, the number of infected individuals surpassed 37 million globally, resulting in more than 1 million deaths.<sup>[3]</sup> Hypertension, diabetes, cardiovascular disease and cancer are associated with severe coronavirus disease 2019 (COVID-19) and increased risk of mortality.<sup>[4,5]</sup> Immuno-compromised individuals may be at increased risk for severe COVID-19.<sup>[6]</sup> Reports have also implicated a hyperactive immune

response ('cytokine storm') in severe life-threatening COVID-19.<sup>[7]</sup> In these cases, the benefits of dexamethasone and tocilizumab have recently been documented in randomised controlled studies.<sup>[8,9]</sup> Furthermore, reports suggest that antiretroviral (ARV) drugs such as lopinavir and ritonavir may be beneficial in treating COVID-19.<sup>[10,11]</sup> Currently, there is no evidence to suggest that people living with HIV (PLWH) have a higher risk of contracting SARS-CoV-2, but preliminary data have shown that once they are infected, they may have more severe COVID-19.<sup>[12]</sup> In September 2015, the World Health Organization (WHO) guidelines recommended that all PLWH should receive ARVs irrespective of

their CD4 counts.<sup>[13]</sup> This resulted in a mass rollout of ARVs globally. As of 2019, it was estimated that half the population of PLWH (19.5 million) receive ARVs. Globally, South Africa (SA) has one of the highest burdens of HIV (7.7 million in 2018),<sup>[14]</sup> and with the increasing number of COVID-19 cases (692 471 cases on 12 October 2020),<sup>[15]</sup> it can be assumed that a large number of PLWH will be co-infected with SARS-CoV-2. Therefore it is imperative to understand how the co-existence of these diseases affects afflicted individuals.

The aim of this article is to describe three cases with concurrent HIV and COVID-19 infections (HIVCO) in Gauteng Province, SA.

## Methods

The three cases were identified in a private general hospital (with 200 inpatient beds) in Gauteng Province, SA. During the COVID-19 pandemic, reverse transcription polymerase chain reaction (RT-PCR) tests were routinely used to screen all patients for SARS-CoV-2 infection prior to admission. Case 1 was referred to the hospital for further care after being diagnosed with COVID-19. Cases 2 and 3 were admitted to the hospital after positive RT-PCR tests were obtained by attending doctors at the emergency department. Data were collected from hospital records and the laboratory result sheets. This case series was approved by the Sefako Makgatho Health Sciences University Research Ethics Committee (ref. no. SMUREC/D/117/2020 (J)).

## Results

This case series describes three patients with HIV-COVID-19 co-infection. All three patients were already receiving chronic antiretroviral treatment (ART). Their different comorbidities and clinical courses are shown in Table 1.

Case 1 presented with features of respiratory distress and was categorised as having severe COVID-19. The patient's medical history included dialysis-dependent end-stage renal failure and hypertension. The patient was prescribed steroid therapy. Clinical improvement was noted during the 36 days of hospital admission, which corroborated the progressive decline in biomarkers (C-reactive protein, procalcitonin and neutrophil-lymphocyte ratio) (Fig. 1). Furthermore, there was sustained eosinopenia ( $0.01 - 0.04 \times 10^9/L$ ) during the course of the disease.

From the onset of symptoms, 9 RT-PCR tests were performed over 68 days: 5 were positive on days 1, 18, 23, 28, 35 and 68, and 3 were negative on days 14, 25 and 46. Sixty-eight days after the first positive RT-PCR test, two nasopharyngeal and one throat swab were submitted for viral culture. Low amounts of virus were detected on the swab material. Unusual protracted infectivity was suspected, and the patient was advised to self-isolate (at this stage beyond 75 days).

Case 2 presented with malaise and headache and was categorised as having mild COVID-19. Symptoms lasted for 2 days. Medical history included Takayasu's disease, which was in remission, dyslipidaemia and previous deep vein thrombosis. A second RT-PCR test 10 days after symptom onset was negative.

Case 3 presented with a sore throat that resolved after 24 hours. Comorbidities included hypertension and diabetes. A second RT-PCR test performed 12 days after symptom onset was negative.

## Discussion

The combination of HIVCO and comorbidities in case 1 resulted in severe illness, a long hospital stay and protracted viral shedding (PVS). Despite comorbidities, cases 2 and 3 presented with mild illness and recovered uneventfully. The effects of chronic ART on HIVCO are currently unknown, and require further investigation. It was assumed that their mild clinical courses, biomarker profiles and negative RT-PCR tests indicated cure. However, a protracted viral shedding pattern (presumably due to poor immunity), and the possible false-negative RT-PCR tests observed in case 1, suggest that further monitoring may have been appropriate in cases 2 and 3.

In case 1, the unique protracted SARS CoV-2 infective pattern deserves further interpretation and discussion.

The positive viral cultures eventually clarified the significance of the persistently positive RT-PCR tests. Viral replication and shedding were, therefore, more likely than the presence of mere non-virulent RNA particles. Moreover, viral transmission may have been possible for >60 days. Despite a dynamic improvement in biomarkers, the significantly sustained eosinopenia may have been due to active COVID-19. The conflicting biomarker changes, in association with an apparent false-negative RT-PCR, need further investigation. Similarly, some HIVCO patients may be 'prolonged super-shedders'. Thus, the concept of persistent SARS-CoV-2 viral shedding and transmission warrants further investigation.

Although viral shedding refers to the expulsion and release of virus progeny, the term is loosely applied when an RT-PCR test is positive. By inference, shedding indicates that the person with the disease is contagious. However, this may be inaccurate, as non-infective gene particles may be responsible for the positive test outcome. Reports on influenza viral shedding also indicate a lack of consensus regarding the definition of PVS; therefore, researchers generally accept the timeline to be either beyond 7 days or beyond 14 days.<sup>[16]</sup> The duration of shedding can either be reported from the onset of symptoms to the last positive detection, or the first and last positive detection (usually RT-PCR).<sup>[17]</sup> Therefore, serial sampling is necessary.

There is no consensus on COVID-19 shedding patterns, with wide variation and contradiction reported in some instances. In asymptomatic cases, the reported median duration of viral shedding (from symptom onset and positive RT-PCR test to negative RT-PCR test) varies from 11 days (in children)<sup>[18]</sup> to 19 days (in adults).<sup>[19]</sup> Frequently, severe illness is associated with longer shedding intervals. In symptomatic cases, reported duration of viral shedding varies between 14 days (mild symptoms),<sup>[19]</sup> 17 days,<sup>[18,20]</sup> 31 days<sup>[21]</sup> (severe cases) and up to 42 days.<sup>[22]</sup>

Moreover, the presence of comorbidities was found to affect the duration of viral shedding.

Vizcarra et al.<sup>[23]</sup> report that the median (interquartile range (IQR)) viral clearance was 18 (7 - 28) days in HIVCO patients. Six patients who were severely ill had positive RT-PCR tests at a median (IQR) of 40 (13 - 45) days. In a case report, a renal transplant patient who was on immunosuppressive drugs received positive RT-PCR tests on days 57 and 63 after the onset of symptoms, even though previous IgG/IgM tests had

**Table 1. Clinical details of three HIV-COVID-19 co-infection cases**

Variable	Case 1	Case 2	Case 3
Age (years)	52	41	52
Gender	M	F	M
Comorbidities	Hypertension, ESRF	Hyperlipidaemia, DVT, Takayasu's disease	Diabetes, hypertension
Year of HIV diagnosis	2009	2006	2003
Last CD4 count (cells per $\mu$ L)	325	1 400	594
HIV viral load at or before admission (copies per mL)	Undetectable	Undetectable	Undetectable
ART regimen before admission	Lamivudine, Efavirenz, Tenofovir	Lopinavir, Lamivudine, Abacavir	Tenofovir
Chronic medication	Vitamin C, nifedipine, furosemide	Atorvastatin, rivaroxaban, prednisolone	Metformin, bisoprolol, perindopril, aspirin
Duration of symptoms (days)	15 days	2 days	1 day
Diagnosis	Viral pneumonitis, multi-lobar pneumonia, pulmonary oedema		
Severe COVID-19	Mild COVID-19	Mild COVID-19	
Temperature	38.9°C	36.7°C	36.5°C
Symptoms	Cough, dyspnoea, fever	Malaise, headache	Sore throat
Blood pressure (mmHg)	123/73	125/85	130/80
Respiratory rate (breaths per minute)	30	18	20
Heart rate (beats per minute)	87	78	72
Chest X-ray findings	Bilateral interstitial changes	Normal chest X-ray	Not requested
O <sub>2</sub> saturation in ambient air	80%	96%	94%
WBC ( $10^9$ /L) (range 4.0 - 12.0)	4.97	9.07	6.06
Lymphocyte ( $10^9$ /L) (range 1.0 - 4.0)	0.97	5.13	2.03
Platelets ( $10^9$ /L) (range 150 - 450)	245	254	270
NLR abnormal ( $\geq 4$ )	3.78	1.74	1.58
C-reactive protein (mg/dL) (abnormal $<5$ )	307.4	12.9	8.4
D-dimer (ng/mL) (range 0.005 - 0.5)	Not requested	1.37	0.23
Procalcitonin (ng/mL) Range (0.00 - 0.05)	0.86	Not requested	0.07
Other antiviral treatments	No	No	No
Other antibiotics/medications	Ceftriaxone, solucortef, azithromycin, teicoplanin, piperacillin/tazobactam, chloroquine	Zinc, vitamin C, quercetin	Zinc, vitamin C
Admitted to ICU	Yes	No	No
Invasive or non-invasive mechanical ventilation	No	No	No
Length of hospital stay	36 days	1 day	2 days
Outcomes	Self-isolation	Cured	Cured

ESRF = end-stage renal failure; DVT = deep vein thrombosis; WBC = white blood cell; NLR = neutrophil-lymphocyte ratio; ICU = intensive care unit.

been positive.<sup>[24]</sup> These studies indicate that COVID-19 shedding patterns are unpredictable, and seem to range from 2 weeks to beyond 2 months in different subsets (such as moderately ill, severely ill and immunocompromised patients).

Asymptomatic patients also had lower levels of IgG in the acute phase.<sup>[19]</sup> A recent modelling study determined that if  $<20\%$  of COVID-19 positive individuals are pre-symptomatic or asymptomatic, they can account for 48% and 3.4% of transmission, respectively; thus, isolation of silent infections is required to suppress attack rates.<sup>[25]</sup>

In the absence of laboratories (which can perform routine viral cultures and sensitive antibody tests), it becomes a challenge to determine recovery. In patients with unusually long viral shedding patterns, recommendations regarding infectivity, repeat RT-PCR testing and quarantine/isolation are currently not available. The possibility that a group of immunocompromised, life-long 'super-shedders' exists is of grave concern.

We propose the following COVID-19 shedding classification to facilitate research communication and assist in the identification of infective subsets. The classification categories are based on the

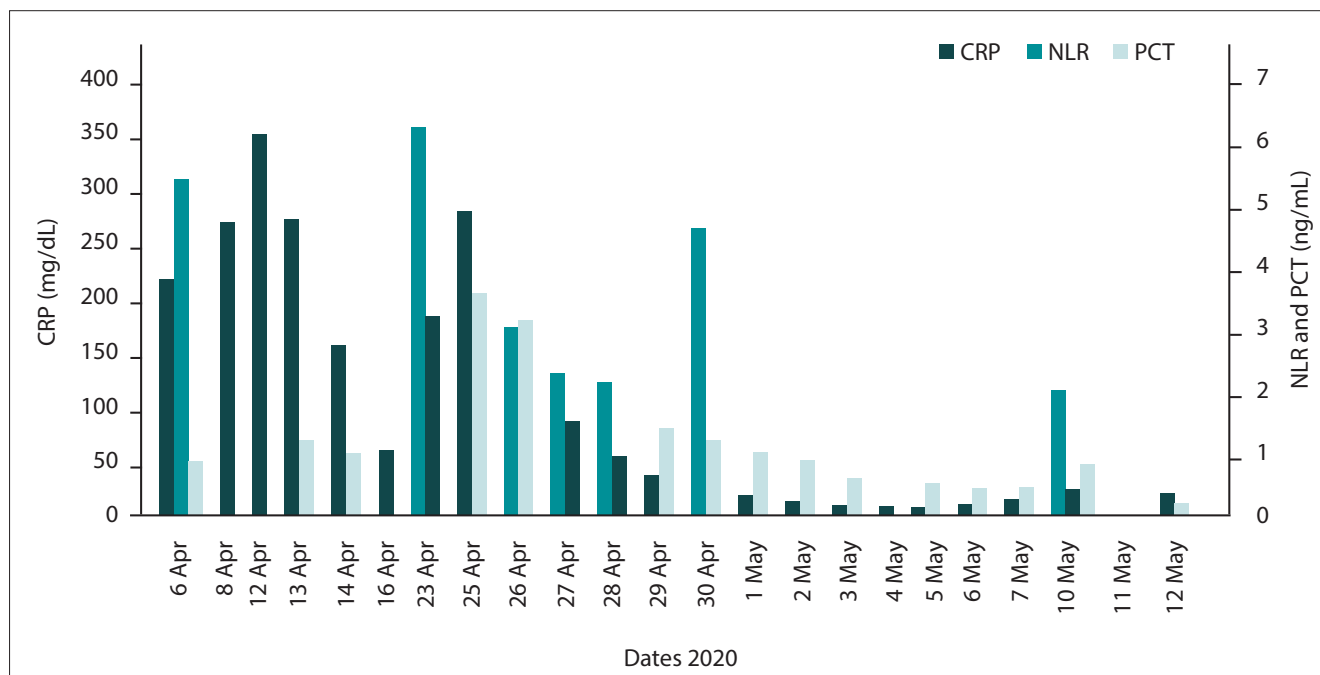


Fig. 1. Changes in C-reactive protein (CRP), procalcitonin (PCT) and neutrophil-lymphocyte ratio (NLR) in case 1.

duration from symptom onset to the last positive RT-PCR test:

- (i) prolonged shedding: 15 - 30 days
- (ii) extended shedding: >30 - 40 days
- (iii) protracted shedding: >40 days.

The current scientific brief of the WHO<sup>[26]</sup> does not recommend routine viral culture in all COVID-19 patients. However, multiple RT-PCR tests, viral cultures and antibody testing may be necessary to define and classify various shedding patterns. Simultaneous assessment of illness severity, immune status and dynamic biomarker values may be beneficial.

## Conclusion

Patients with HIVCO and comorbidities may present with mild or severe illness. Unusually long viral shedding is a risk for disease transmission, and is poorly defined. A shedding classification may assist in identifying and managing infectious subsets of patients.

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