Prolonged SARS-CoV-2 shedding in a person living with advanced HIV and diffuse large B-cell Lymphoma: a case report.

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Abstract
The global spread of SARS-CoV-2 has required adequate case isolation with recommended times based on mean times to viral clearance. We present a 28-year-old female living with vertically acquired HIV, undergoing chemotherapy for lymphoma who tested SARS-CoV-2-PCR positive for 164 days. The patient had a history of difficulty taking ARVs, with detectable HIV-RNA and CD4 count below $200x10^6$ for the 8 years prior to presentation with symptoms. She stopped ARVs 10 months prior to experiencing fevers, night sweats and loose stool, with a viral load of 354,000 copies/ml and CD4 count of $30x10^6$. Following no yield on basic investigations, positron emission tomography scan showed diffuse colonic and oesophageal uptake and a caecal biopsy showed diffuse large B-cell lymphoma. She re-started ARVs and underwent five cycles of R-CHOP chemotherapy. Her first positive SARS-CoV-2 PCR test was detected through routine asymptomatic screening. She self-isolated due to repeated positive tests on a further 8 swabs for a total of 164 days until a negative PCR test. She reported feeling low in mood and frustrated by repeated positive tests and the associated lack of social contact or ability to work. Her positive tests prevented in-person review by her HIV team which impacted her ARV adherence leading to an unplanned break in therapy. Our case highlights the challenges to physical and mental health faced by patients with prolonged SARS-CoV-2 shedding and the need to develop surrogate markers for infectivity to enable prompt medical and psychological support and accurate advice about need for isolation.

Introduction
Since the emergence of SARS-CoV-2, globally dissemination has resulted in an ongoing pandemic with devastating physical, psychological and social consequences. In response to this, nations have used a variety of containment and mitigations strategies with contact tracing, case finding and national lockdowns crucial to these efforts. [1] Fundamental to containment is isolation of cases for an adequate time to prevent onward virus transmission. Optimal management of SARS-CoV-2, from diagnosis to prevention and treatment, has been a steep learning curve, with some initial uncertainties successfully evidenced but others still debated or controversial.

Most people with SARS-CoV-2 infection do not have detectable virus in their upper airway by 14 days after symptom onset; this is now reflected in national and international guidelines regarding isolation periods.[2, 3] There are reports of prolonged viral shedding in immunocompromised individuals with cancer, solid organ transplants and human immunodeficiency virus (HIV). [4-8] Questions remain regarding the significance of prolonged viral shedding in these patients, as well as the psychological impact of prolonged isolation requirements, on a background of an already increased prevalence of anxiety and depression. [9] We present a case of asymptomatic SARS-CoV-2 shedding for 164 days in an immunosuppressed individual with advanced HIV and lymphoma and explore the impact on her physical and mental health.

Case Report
A 28-year-old female with vertically acquired HIV was found to have an asymptomatic positive SARS-CoV-2 polymerase chain reaction (PCR) swab during routine screening pre-chemotherapy for diffuse large B-cell lymphoma (DLBCL). She had been on several different antiretroviral (ARV) regimens due to side effects and adherence difficulties since transfer to our service nine years previously. She had never been virologically suppressed nor experienced immune reconstitution to a CD4 count greater than 200 $x10^6$ (nadir 10) prior to diagnosis of DLBCL, despite being managed through a multidisciplinary team in a specialist adolescent HIV clinic. She had no significant past medical, sexual reproductive or family history. Her drug history included dapsone prophylaxis. She does not smoke, drink alcohol or use recreational drugs.

B-symptoms (fevers and night sweats) and diarrhoea developed over a 3-week period. She had stopped her ARVs 10 months prior to symptom onset, with a most recent viral load of 354,000 copies/ml and a CD4 count of 30 $x10^6$. Colonic oedema was identified on cross-sectional imaging as part of work up for opportunistic infection and malignancy. A hybrid computed tomography/positron emission tomography with 2-deoxy-2-fluorine-18-fluoro-D-glucose (CT-^{18}FDG-PET) scan demonstrated diffuse colonic and oesophageal avidity and moderate avidity in lymph nodes above and below the diaphragm. Histology of a caecal erosion biopsy confirmed EBV-positive DLBCL, non-germinal centre subtype.

Following her lymphoma diagnosis, she was re-started on ARVs (tenofovir alafenamide, emtricitabine and dolutegravir), suppressing to an undetectable viral load within 4 weeks. She commenced chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) and one dose of intrathecal methotrexate, completing five cycles in total. CT-^{18}FDG-PET scan after 4 cycles showed metabolic remission,

sustained on CT-^{18}FDG-PET imaging three months later. During the 5th cycle of chemotherapy, she stopped her ARVs resulting in a HIV viral load of 107,000, and thus the planned 6th cycle was omitted. She remains in clinical remission 18 months after cessation of chemoimmunotherapy. She restarted her ARVs after her lymphoma treatment stopped becoming undetectable again 4 weeks after re-starting ARVs and remained virologically suppressed 15 months later.

The timing of her diagnosis and treatment of DLBCL coincided with a substantial increase ("first wave") of SARS-CoV-2 cases in the United Kingdom, resulting in a national lockdown to prevent further transmission, reduce morbidity and mortality, and reduce pressure on the National Health Service (NHS). Medical facilities implemented various infection control practices including symptom screening, temperature checks, hand and respiratory hygiene. Cancer centres included routine SARS-CoV-2 testing, where this patient's first PCR test was positive, Day 0 in Table 1. She had two nucleocapsid antibody tests sent which were negative prior to and during her positive results.

Day	Serology Assay	NAT Assay		Result	Ct Value
-58	Roche ECLIA	-	Nucleocapsid total antibody	Negative	n/a
0	-	Panther Fusion	PCR	Positive	30
15	-	Panther Aptima	TMA	Positive	-
22	-	Panther Aptima	TMA	Positive	-
37	-	Cepheid GeneXpert	PCR	Positive	22
37		Panther Fusion	PCR	Positive	32
48	-	Panther Aptima	TMA	Positive	-
64	-	BGI	PCR	Positive	24
64	Roche ECLIA	-	Nucleocapsid total antibody	Negative	n/a
88	-	Panther Aptima	TMA	Positive	-
142	-	Unknown*		Positive	-
164	-	Panther Aptima	TMA	Negative	-

Table 1 –NAT and serum antibody test results conducted for detection of SARS-CoV-2 during hospital and clinic visits. Days relative to the first positive NAT test taken represented as Day 0.
*Test done via NHS Test and Trace, unknown platform and Ct
NAT= nucleic acid test; PCR = polymerase chain reaction; TMA = transcription-mediated amplification; Ct= cycle threshold

She remained asymptomatic with no fevers or respiratory compromise, but she and her household were advised to self-isolate in line with national guidance. Advice from the virology team was that although she was unlikely to transmit SARS-CoV-2, she should continue to wear a mask, perform hand hygiene and maintain social distance, particularly when visiting the cancer centre. A more cautious approach to infection control was taken due to the lack of data on infection risk in the context of persistently detectable SARS-CoV-2 PCR. Sequencing of samples excluded re-infection. Of note, her household family contacts did not develop symptoms or test positive during this period. She reported feeling low in mood and frustrated by repeated positive tests and having to remain at home. Persistently reactive PCR tests prevented her from accessing in person HIV care, support groups or working and she expressed wanting to be more active but was unable to. She later explained the reason she stopped her ARVs during chemotherapy was due to frustration with her cancer, chemotherapy, and prolonged social isolation on top of the stresses of the pandemic she was already experiencing. With support from her family and HIV team she was able to restart ARVs and remain virologically suppressed.

Discussion

This case highlights the need to understand the ability to transmit virus in those with prolonged viral shedding of SARS-CoV-2, as well as the potential additional impact on physical and psycho-social well-being during a pandemic. There is a paucity of data on SARS-CoV-2 infection in people with HIV and low CD4 counts. Most studies have been retrospective cohort analyses of patients who are more likely to be virally suppressed and less

likely to have low CD4 counts. [7, 10] Our patient had multiple individual risk factors associated with prolonged viral shedding as well as a risk of severe SARS-CoV-2: lymphoma, active chemotherapy, corticosteroid use and advanced HIV (including periods of viraemia) with a low CD4 count but remained asymptomatic throughout.[4-7, 10] She did not mount an antibody response despite detectable virus for 142 days with no change in viral sequence to suggest re-infection. We need to better understand the risk of onward transmission from people with prolonged shedding better inform advice to patients and their contacts, isolation and infection control measures.

Effective isolation of positive cases to prevent onward virus transmission relies on knowledge of the periods of infectious viral shedding. A literature review by Walsh et al found little to no difference in viral load between symptomatic, asymptomatic and pre-symptomatic patients and the median duration of detectable virus on PCR testing was 14.5 days. [2] Detectable virus on PCR cannot be used alone as a surrogate for infectivity as it could be due to detection of non-viable virus or fragments. La Scola et al found no viable virus in culture after day 8 of illness despite ongoing high viral loads. [11] There is evidence of a link between the cycle threshold (Ct) value and successful viral culture suggesting patients with higher Ct values are less likely to be infectious. [11] However the authors caution extrapolating these findings to other centres due to differences in equipment, reagents and procedures and the need for individual centres determining their own threshold for infectivity based on Ct values. Several different assays are used in our diagnostic virology lab (and throughout the UK) reflecting the need for high-volume 24-hour testing. This makes the interpretation of serial positive PCR results challenging. Viral cultures are currently primarily used in research setting and they were never taken for this case. Furthermore, it is unclear if this data on Ct values can be extrapolated to immune suppressed individuals.

Persistent PCR positivity in immune suppressed individuals could indicate infectiousness if they cannot mount an adequate immune response to clear the virus. A positive SARS-CoV-2 PCR and culture was reported 70 days after the first positive PCR test in a HIV negative chronic lymphocytic leukaemia patient by Avanzato et al. [6] The team also observed continuously changing viral genotypes and deletion of the spike gene while the patient remained PCR positive, adding the potential concern of viral mutations in patients with prolonged PCR positivity. [6]

The psychological harms related to the COVID-19 pandemic are well described.[12, 13] For people living with HIV, in addition to increased stress, depression and anxiety, disruption to services and barriers to accessing ARVs are common themes in published literature. [14] Our patient stopped her ARVs during her chemotherapy and prolonged social isolation. She was unable to access in person support from her HIV clinicians or her social network during a stressful period. This break in treatment could be partially attributed to the barriers to accessing in person care and support in addition to the multiple other factors impacting her physical and mental health at the time.

Conclusion

Our case highlights the need to understand the clinical significance of a positive SARS-CoV-2 PCR test persisting longer than national isolation periods and to evaluate surrogate markers for infectivity in HIV patients with low CD4 counts. The impact of prolonged isolation on mental and physical health needs to be assessed to adequately support people in similar situations.

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Ethics Approval

Research ethics committee approval was not sought for this case report in line with NHS Health Research Authority guidance. The patient reviewed the manuscript prior to submission and provided written informed

consent for publication of their clinical details. A copy of the consent form is available for review by the Editor of this journal.

Author Contributions

Data collection and analysis were performed by Nadia Ahmed and Irfaan Maan. The first draft of the manuscript was written by Irfaan Maan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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