Persistent infection with severe acute respiratory coronavirus virus 2 (SARS-CoV-2) in a patient with untreated human immunodeficiency virus (HIV)

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To the Editor— Severe acute respiratory coronavirus virus 2 (SARS-CoV-2) RNA can be detected in the upper-respiratory specimens of patients with coronavirus disease 2019 (COVID-19) for prolonged periods, although the likelihood of recovering replication-competent virus beyond day 10 of illness is very low.[1,2] Among those with severe COVID-19 disease, infectious virus has been detected for up to 20 days following symptom onset.[3] Much greater variability, however, has been observed with severely immunocompromised individuals, making it challenging to determine the potential for prolonged transmission risk and raising questions around the role of ongoing viral replication in generation of SARS-CoV-2 variants.[4–7] We report a case of persistent infection with SARS-CoV-2 in a vaccinated individual with advanced human immunodeficiency virus (HIV) infection for >20 weeks from time of COVID-19 diagnosis, with evidence of minimal virus mutation over time.

Case summary

A 76-year-old man was admitted to hospital after testing positive for SARS-CoV-2 on a nasopharyngeal swab by reverse-transcription polymerase chain reaction (RT-PCR) (Fig. 1).[8] He received 2 doses of the mRNA-1273 COVID-19 vaccine 3 and 4 months prior to admission. He was asymptomatic but was hospitalized for monitoring given his immunocompromised state related to longstanding untreated HIV infection (his CD4 count was 110 cells/mm^3 2 months prior to admission). He remained well throughout his 2-week admission and did not require supplemental oxygen or COVID-19–directed therapies. He was ultimately discharged to a long-term care facility.

The patient was readmitted to hospital on postdiagnosis day 69 with new onset of fever, cough, and dysphagia with evidence of oral thrush on examination. Testing for SARS-CoV-2 by RT-PCR was again positive, which was thought to represent persistent RNA shedding rather than ongoing infection. However, given his immunocompromised state, the nasopharyngeal swab was sent for viral culture. Computed tomography of the chest showed new patchy areas of consolidation at the lung bases for which he received a 7-day course of antibiotics in addition to fluconazole for esophageal candidiasis. He was discharged to the long-term care facility after a 1-week admission with resolved symptoms. Viral culture subsequently revealed the presence of replication-competent virus,[8] confirmed to be SARS-CoV-2 by RT-PCR. However, given the resolution of his respiratory symptoms with antibiotic therapy, no treatment was initiated for COVID-19.

He returned to the hospital on postdiagnosis day 107 after suffering a fall with hip fracture requiring surgical intervention. The postoperative course was complicated by fevers and worsening bibasilar airspace infiltrates on chest radiograph suggestive of aspiration pneumonia, for which he received another 5-day antibiotic course with clinical improvement. He was discharged back to the long-term care facility after a 9-day admission but returned 1 week later with progressive lethargy, poor oral intake, and hypotension. His nasopharyngeal swab on admission was indeterminate for SARS-CoV-2 by RT-PCR. Given his poor functional baseline and guarded prognosis in the context of advanced untreated HIV infection, his care was transitioned to palliative care. Repeat testing on postdiagnosis day 133 was again positive for SARS-CoV-2 with viable virus isolated in culture. He died on postdiagnosis day 142 and a nasopharyngeal swab collected on this date was positive for SARS-CoV-2 by RT-PCR.

Sequencing of viral genomes throughout the clinical course revealed persistent infection with the SARS-CoV-2 α (alpha) variant of concern (VOC) with minimal mutation over time (Fig. 1).[8,9] Genome analysis did not identify any persistently gained mutations or mutations not previously identified in the SARS-CoV-2 α (alpha) VOC. In addition, spike and nucleocapsid serology was negative late in the course of illness despite vaccination and breakthrough infection.

Discussion

We present a case of a severely immunocompromised individual with untreated HIV infection who developed COVID-19 3 months after completing his primary vaccine series and who continued to shed infectious virus until the time of his death nearly 5 months later. This case demonstrates that a time-based approach for determining duration of isolation may be inadequate in severely immunocompromised individuals. Our patient was institutionalized throughout the time of his COVID-19 infection, which allowed for repeat testing to guide decision making regarding isolation precautions. However, tools for determining the duration of infectivity using viral culture (as in this case) are generally inaccessible, making it difficult to operationalize this method on a large scale.

Rising cycle threshold (Ct) values are typically indicative of viral clearance over time, but values from a single test should be

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Cite this article: Zhabokritsky A, *et al.* (2023). Persistent infection with severe acute respiratory coronavirus virus 2 (SARS-CoV-2) in a patient with untreated human immunodeficiency virus (HIV). *Infection Control & Hospital Epidemiology*, 44: 350–351, https://doi.org/10.1017/ice.2022.140

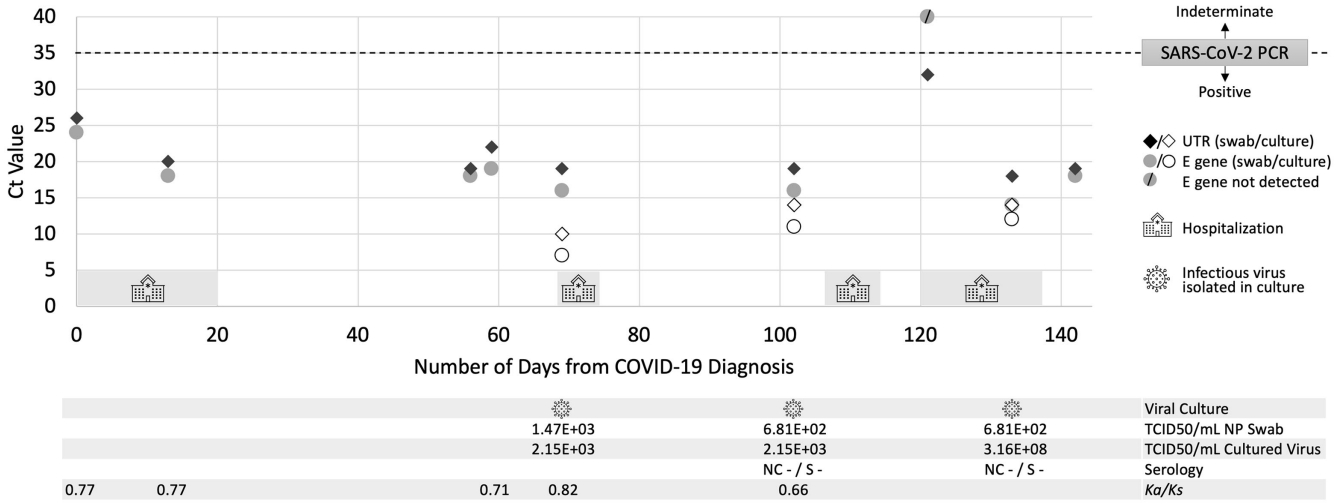

Fig. 1. Summary of patient's clinical and microbiological course from time of COVID-19 diagnosis to time of death. Note. Ct, cycle threshold; PCR, polymerase chain reaction; UTR, untranslated region; E, envelope; TCID50/mL, median tissue culture infectious dose per mL; NC, nucleocapsid antigen; S, spike antigen; *Ka/Ks*, nonsynonymous/synonymous changes per site relative to "USA/CA-CDC-STM-000008272."

interpreted with caution in severely immunocompromised individuals as demonstrated by detection of replication-competent virus in our patient 2 weeks after an indeterminate result. Pairing RT-PCT testing with SARS-CoV-2 serology can help guide decision making regarding isolation precautions. For example, lack of seroconversion with Ct values <30 beyond 20 days in a severely immunocompromised host should raise concern for ongoing infectiousness and may identify individuals that could benefit from prolonged isolation and administration of monoclonal antibodies or antivirals outside the traditional acute infection period.[10]

It has been proposed that ongoing viral replication and mutation in immunocompromised individuals has contributed to development of more pathogenic and transmissible SARS-CoV-2 variants.[6,7] However, we did not observe significant gain of viral diversity in our patient over time, and the only identified mutations were confined to known SARS-CoV-2 α (alpha) VOC diversity, potentially due to lack of selective pressure in the absence of adequate immunologic response due to his profound immunosuppression.

In conclusion, mounting evidence indicates that severely immunocompromised individuals, especially those with nonreversible immunosuppression, can have very prolonged SARS-CoV-2 infection, regardless of vaccination status. Persistent Ct values of <30 beyond 20 days in association with undetectable SARS-CoV-2 antibodies in this population should raise concern for the presence of replication-competent virus.

Acknowledgments. The authors thank all the individuals involved in this patient's care.

Financial support. No financial support was provided relevant to this article.

Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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