

Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 Delta Variant Shedding in a Patient With AIDS: Case Report and Review of the Literature

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We describe the case of a patient with AIDS who had persistent infection with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta variant for >80 days. The variant contained mutations that were not present in other Delta viruses in our hospital. Prolonged infection in immunosuppressed individuals may lead to evolution of SARS-CoV-2 lineages.

Keywords. COVID-19; SARS-CoV2; PLWH; HIV.

A 45-year-old partially vaccinated man with a history of untreated human immunodeficiency virus (HIV) infection presented to an outside hospital in December 2021 with 3 days of fever, chills, nonproductive cough, dyspnea, left-sided chest pain, nausea, and emesis. He was afebrile and mildly tachycardic with normal oxygen saturation. He had received a single dose of the Pfizer BNT162b messenger RNA severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine 8 months earlier. Upon hospital presentation, SARS-CoV-2 polymerase chain reaction (PCR) was positive. Chest radiography was unremarkable. He was not given antiviral therapy or monoclonal antibodies in the emergency department and was discharged with instructions to isolate. His symptoms improved over the course of a few days, but repeat SARS-CoV-2 testing was not performed.

He was transferred to our tertiary care center for treatment of orbital cellulitis in February 2022. A SARS-CoV-2 PCR

test was positive with a cycle threshold (Ct) value of 21.8, 72 days after the initial positive test. His symptoms included severe frontal headache and throbbing periorbital pain, but he denied other symptoms of coronavirus disease 2019 (COVID-19) infection. His oxygen saturation was normal and his chest radiograph was unremarkable. He was admitted to a negative-pressure room for treatment of orbital cellulitis.

CD4⁺ T-cell count and HIV viral load were found to be 2 cells/ μ L and 56 200 copies RNA/mL, respectively. SARS-CoV-2 immunoglobulin G and immunoglobulin A levels were below the limit of detection. Viral sequencing was performed on the SARS-CoV-2 isolates from February 2022 and was consistent with the Delta variant, which was no longer circulating in February 2022 in Baltimore [1]. He had not traveled outside the city since his initial infection, making it likely that he had persistent viral infection since December 2021. He received 3 transfusions of high-titer convalescent plasma, which was collected in August and September 2021 in Florida (One Blood). SARS-CoV-2 PCR testing with Ct determination was performed and the Ct value was 37.3 (Figure 1A). He was started on antiretroviral therapy and was discharged to an isolation unit. He did not follow through with repeat testing after 20 days of isolation.

This case is an example of prolonged viral replication in a patient with advanced HIV infection. The low Ct value at the time of his admission in February suggests that substantial viral replication was occurring >2 months after his initial diagnosis. Phylogenetic analysis revealed that his complete genome sequences belonged to clade 21J (Delta) and lineage AY.100 (Figure 1B). Additionally, the phylogenetic tree showed that this strain was more evolved than other strains of the AY.100 lineage sequenced at Johns Hopkins Hospital during the same period. This observation is in line with a prior study in which phylogenetic analysis confirmed a persistent infection with accelerated viral evolution, with the majority of mutations occurring in the spike protein and receptor-binding domain (RBD) [2]. In addition, infrequently encountered amino acid changes such as V3G, L18F, H245P, and E484K were observed in the spike of our strain compared to other Delta variant isolates from our hospital (Supplementary Figures 1 and 2). The E484K mutation, which improves the affinity of the spike protein RBD for angiotensin-converting enzyme 2 [3], is rarely seen in the Delta variant [4] and the V3G mutation is now commonly seen in the Omicron BA.4 sublineage [5]. Thus, these mutations could be a sign of viral evolution in this patient. Interestingly, he did not seroconvert despite partial vaccination and prolonged infection. This is probably due to his advanced HIV infection, as partial vaccination has been shown to induce

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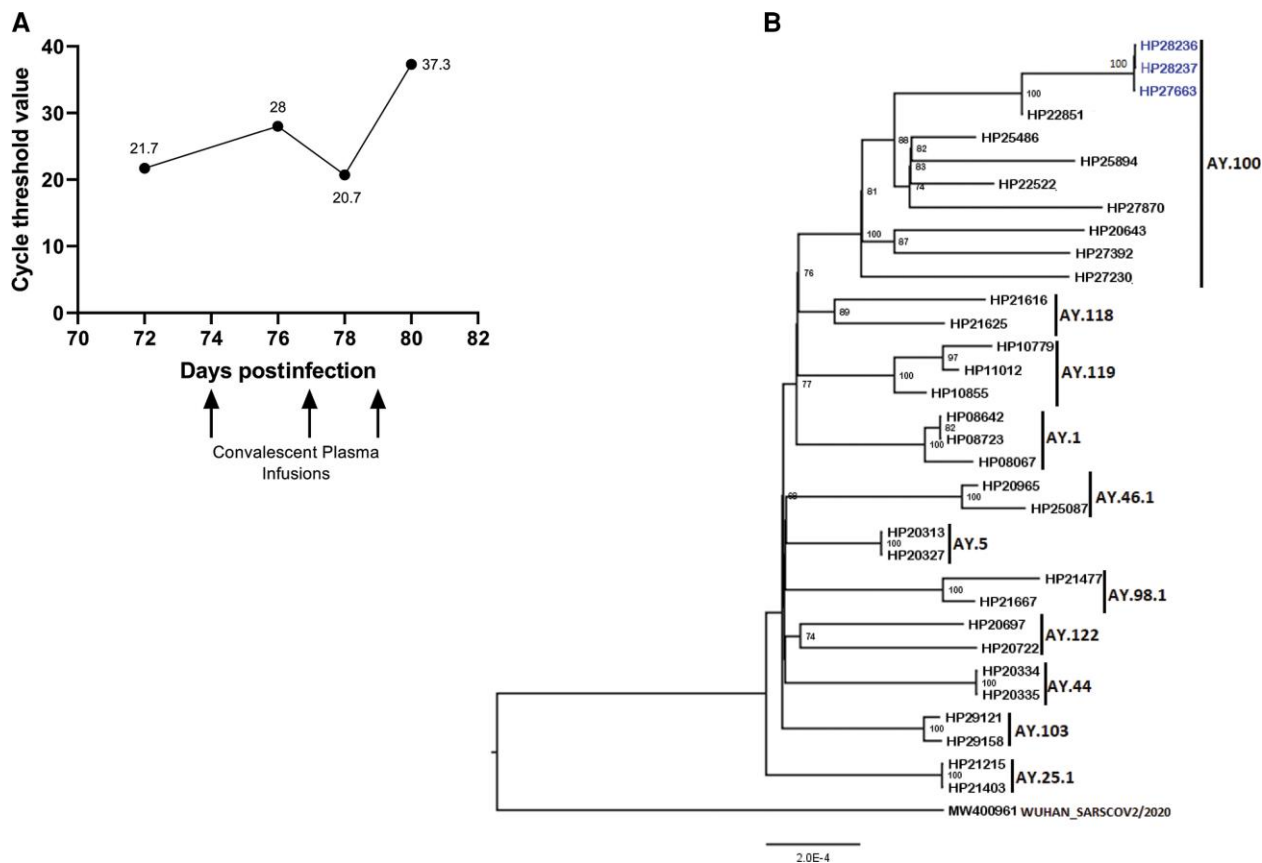


Figure 1. A, Trend of severe acute respiratory syndrome coronavirus 2 cycle threshold values with infusions of convalescent plasma. B, Whole-genome sequence analysis of the virus isolated from the patient. The phylogenetic tree was generated using a maximum likelihood algorithm with the GTR + F nucleotide substitution model using IQ-TREE 2 to estimate the evolutionary distances. The statistical significance was tested by 1000 bootstrapping replicates. Bootstrap values >70% are shown at the branch nodes. The whole-genome sequence of isolates from our patient is colored blue and the other Delta complete genome from the laboratory is colored black. The tree is rooted by the Wuhan strain genome.

detectable antibody responses in healthy donors [6, 7]. A recent small case series reported that treatment with convalescent plasma was not effective in people living with HIV (PLWH) [8]. However, the convalescent plasma given to our patient, obtained from patients who were probably infected during the Delta variant surge, was effective at inhibiting SARS-CoV-2 replication.

REVIEW OF THE LITERATURE

Persistence of SARS-CoV-2 in immunosuppressed patients has been reported. For example, an early case report by Choi et al described an immunosuppressed individual with severe antiphospholipid syndrome complicated by diffuse alveolar hemorrhage with persistent SARS-CoV-2 who ultimately died on day 154 of infection [2]. Similar reports of prolonged SARS-CoV-2 shedding have been described in patients with hematologic malignancies [9, 10]. There have been several reports of persistent SARS-CoV-2 infection in PLWH [11–27]. One

cohort study in China found the median duration of SARS-CoV-2 shedding in PLWH was 30 days [11]. The majority of PLWH with prolonged shedding described in case reports have advanced HIV infection. In 13 cases where clinical information was available, the patients had a median CD4 count of 6 cells/ μ L and median viral load of 378 000 copies/mL (Table 1). This is consistent with the findings in a cohort in South Africa where prolonged shedding of high levels of virus (defined as Ct value <30) in PLWH was associated with low CD4⁺ T-cell counts (median duration >27 days in patients with CD4 counts <200 cells/ μ L vs 7 days in patients with CD4 counts >200 cells/ μ L) and uncontrolled viral replication (median duration of 26 days in patients with viral loads >400 copies/mL vs 6 days in patients with viral loads <400 copies/mL) [26].

Three patients described in case reports were diagnosed with Kaposi sarcoma [13, 21, 23], and 2 patients had diffuse large B-cell lymphoma with 1 receiving chemotherapy [14, 20]. Opportunistic infections were common, with *Pneumocystis*

Table 1. Cases of Persistent Severe Acute Respiratory Syndrome Coronavirus 2 Shedding in the Literature

Time of SARS-CoV-2 RNA Positivity	Age	Sex	CD4 Count, Cells/ μ L	Viral Load, Copies/mL	ART Regimen at Symptom Onset	Treatment	Author
9 mo	22	F	91	5.07 log ₁₀	None	ART	Maponga et al [12]
147 d	54	M	25	930 000	None	Remdesivir, ART	Giubelan et al [13]
92 d	30	M	49	<20	Lamivudine, dolutegravir	Prednisone, remdesivir, convalescent plasma, sotrovimab	Montejano et al [14]
66 d	28	M	3	563 000	None	ART	Álvarez et al [15]
98 d	30	M	5	109 859	None	NA	Wenlock et al [16]
85 d	28	M	3	NA	None	ART	Yousaf et al [17]
216 d	Late 30s	F	6	34 151	Tenofovir, emtricitabine, and efavirenz	Dexamethasone, new ART regimen	Karim et al [18]
109 d	NA	NA	3	558 000	None	ART, Pfizer vaccine, bamlanivimab, and etesevimab	Quaranta et al [19]
164 d	28	F	NA	NA	Regimen not specified	ART	Maan et al [20]
3 mo	38	M	<1	980 000	None	ART, convalescent plasma	Ketels et al [21]
232 d	38	M	663	<20	Regimen not specified	None	Cunha et al [22]
107 d	26	F	2	198 000	None	Dexamethasone, ART, convalescent plasma, bamlanivimab, and etesevimab	Spinicci et al [23]
34 d	49	F	>600	<20	Lamivudine, zidovudine, efavirenz	Interferon, ribavirin, abidol	Menghua et al [24]
2 mo	40s	NA	19	975 000	None	ART	Ridell et al [25]
3 mo	40s	NA	NA	NA	Regimen not specified	New ART regimen	Ridell et al [25]
8.5 mo	30s	NA	NA	NA	Regimen not specified	New ART regimen, remdesivir	Ridell et al [25]

Abbreviations: ART, antiretroviral therapy; F, female; M, male; NA, information not available in manuscript; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

jirovecii diagnosed in 2 cases [15, 16, 21] and suspected in another 4 [16, 17, 18, 25]. There were also 2 cases of *Mycobacterium avium-intracellulare* infection [15, 25] as well as oral and esophageal candidiasis [13, 23], central nervous system toxoplasmosis [23], cytomegalovirus reactivation [23], and cryptosporidiosis [25]. However, in addition to these severely immunocompromised patients, there have been reports of patients with high CD4⁺ T-cell count and undetectable HIV viral loads with prolonged SARS-CoV-2 shedding [22, 24].

Antiretroviral therapy was initiated in most patients (Table 1), and several patients received antivirals [13, 14, 24, 25]. Passive antibody therapy likely assisted in lowering the viral quantity in some cases. Convalescent plasma with high titers of neutralizing antibodies is most effective when provided early in the disease course [28]. It was effective in our patient and was associated with an increase in Ct values over a 7-week course in another patient [21] but was ineffective in 2 other cases [14, 23]. The combination of bamlanivimab and etesevimab was given to 2 patients [19, 23] and in 1 case was associated with clearance 3 weeks later [23]. Sotrovimab was associated with clearance over a 2-week period in a case where remdesivir and convalescent plasma had been ineffective [14].

It has been proposed that highly mutated variants evolving in immunocompromised persons could be a key factor in the

emergence of new variants of concern [29]. There have been several reports of the accumulation of SARS-CoV-2 mutations in PLWH with prolonged shedding [12, 19, 22, 25]. Karim et al documented persistent SARS-CoV-2 infection confirmed by phylogenetic analysis of whole genomes at 7 time points across 6 months in a patient with AIDS in South Africa [18]. The ancestral virus found in the patient accumulated mutations present in the Omicron variant and eventually developed resistance to neutralization by vaccine-elicited antibodies [27]. These cases illustrate how persistent infection can lead to immune escape and potentially to new variants.

CONCLUSIONS

This phenomenon of persistent SARS-CoV-2 infection has important public health implications including the need to vaccinate PLWH. COVID vaccination results in robust antibody responses [30–33] and a relatively low rate of breakthrough infections [34] in PLWH on suppressive ART regimens. Patients with advanced HIV disease are more likely to have persistent infection; thus, efforts should be made to minimize transmission of SARS-CoV-2 from these individuals. There is a need for additional research on therapeutic strategies to inhibit persistent viral replication.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Patient consent. Informed consent was obtained from the patient. The study protocol was approved by the Johns Hopkins University Institutional Review Board.

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