

Insult to Injury-Potential Contribution of Coronavirus Disease-19 to Neuroinflammation and the Development of HIV-Associated Neurocognitive Disorders

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Abstract

Severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 is responsible for a new coronavirus disease known as coronavirus disease-19 (COVID-19). SARS-CoV-2 reports neurotropic properties and may have neurological implications, and this creates another health burden for people living with HIV. As yet, the impact of COVID-19 on (neuro)inflammation and the development of HIV-associated neurocognitive disorders (HAND) is not fully known. Here, we reviewed preliminary evidence that provides clues that COVID-19 may exacerbate inflammatory mechanisms related to the development of HAND.

Keywords: COVID-19, SARS-CoV-2, coronaviruses, HIV-associated neurocognitive disorders, HAND, inflammation

Introduction

HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND) are consequences of the effects of HIV-1 within the central nervous system (CNS).^{1,2} HAND are classified according to impairment severity, namely, asymptomatic neurocognitive impairment, mild neurocognitive impairment, or HIV-associated dementia.^{3,4}

In the modern antiretroviral therapy (ART) era, the more severe forms of HAND have significantly decreased, however, milder forms are persisting in 50% of people living with HIV (PLWH).⁵ Currently, the underlying neuropathophysiological mechanisms of HAND remain unclear. However, the common hypothesis for the persistence of HAND in the modern ART era is the continued immune activation and low-grade inflammation experienced by PLWH.⁶ Regardless of viral suppression and CD4 count, HIV-positive participants report dysregulated inflammatory levels and the dysregulated levels are associated with HAND.^{7–11}

Therefore, low-grade neuroinflammation may be a key pathway in the development of HAND. What are the implications for the development of HAND if another virus were to enter the CNS, eliciting a major immune response such as a cytokine storm and exacerbating the current low-grade inflammation in PLWH?

Since the first reported coronavirus disease-19 (COVID-19) case in December 2019, several studies have reported on the

neurological implications of COVID-19.^{12–18} Among several neurobiological mechanisms, increasing evidence suggests that COVID-19 may have an underlying neuroinflammatory pathology. Considering the large global (37.9 million) and African HIV populations (25.6 million),¹⁹ it is important to assess the potentially detrimental effects of COVID-19 in these populations. This is especially true for neurocognitively impaired PLWH. The purpose of this review was to assess the potential contribution of COVID-19 to (neuro)inflammation and the development of HAND in PLWH.

HAND and (Neuro)inflammation

The neuroinvasion of HIV-1 into the CNS is explained by a widely accepted “Trojan-horse hypothesis” which states that HIV-1 is able to cross the blood/brain barrier (BBB) through infected monocytes, which later differentiate into macrophages.^{20,21} HIV-1 is then able to act via several direct^{22–24} and indirect mechanisms^{25,26} to induce neuronal dysfunction and HAND. The neuropathogenesis of HIV-1 is well explained in a review done by González-Scarano and Martín-García.² This review focused on (neuro)inflammation, considering that it is a key pathway in the development of HAND in the modern ART era.

Once HIV-1 enters the CNS, it can further infect resident macrophages and microglia.^{27–29} HIV-1 may also activate astrocytes, macrophages, and microglia resulting in an inflammatory phenotype that contributes to neuronal damage

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and the development of HAND.^{2,25} Dysregulated inflammatory levels were reported in the blood,^{9,30} cerebrospinal fluid (CSF),^{31,32} and postmortem brain tissue^{33,34} of cognitively impaired PLWH, supporting the role of aberrant immune regulation in the development of HAND.

Even with the introduction of ART, inflammatory levels do not return to that matching HIV-negative controls³⁵ and this low-grade inflammation may explain the persistence of milder forms of HAND. Inflammatory markers can impact neuronal health through several mechanisms. As an example, tumor necrosis factor- α (TNF- α) can induce BBB damage, which results in increased migration of infected cells into the brain,³⁶ dysregulate glutamate metabolism,^{37–39} form reactive oxygen species,^{40,41} and apoptosis in neurons.⁴² Therefore, inflammation may directly contribute to neuronal dysfunction and the development of HAND. Furthermore, the presence of another virus within the CNS may contribute to the dysregulated inflammatory profile and exacerbate the development of severer forms of HAND.

Coronaviruses and (Neuro)inflammation

Although human coronaviruses (hCoVs) typically cause various respiratory diseases, coronaviruses (CoVs) are sometimes linked with CNS diseases such as multiple sclerosis and acute disseminated encephalomyelitis.^{43–47} CoVs can target the CNS and cause nerve damage through direct infection pathways (viz blood circulation⁴⁸ and neuronal pathways^{49,50}), hypoxia,⁵¹ immune-mediated injury,^{52,53} angiotensin-converting enzyme 2 (ACE2),^{54,55} and other mechanisms (e.g., biological properties of the CNS).^{56,57} However, this review focused on those mechanisms most relevant to the indirect underlying pathways of HAND (i.e., inflammation).

Middle Eastern respiratory syndrome-CoV and severe acute respiratory syndrome-CoV

Middle Eastern respiratory syndrome (MERS)-CoV was first linked to MERS in 2012.⁵⁸ Patients initially showed nonspecific symptoms, with general malaise, low-grade fever, chills, headache, nonproductive cough, dyspnea, and myalgia the most commonly reported.⁵⁹ However, several case reports have also linked MERS-CoV infections to various neurological disorders, including neuropathy, delirium, and acute cerebrovascular disease.^{60–62} A larger study of 70 MERS patients also reported neurological symptoms, with the most common listed as confusion (18/70) and seizures (6/70). Unfortunately, there is little evidence for the presence of the MERS-CoV in the CSF from patients, making the association between MERS and neurological symptoms tenuous at the moment.⁶³

The first case of severe acute respiratory syndrome (SARS)-CoV was reported in China, November 2002.⁶⁴ Patients generally presented with chills, headaches, muscular pain, diarrhea, and pneumonia.^{65,66} Cases were also reported for neurological complications, which included seizures, dysphoria, vomiting, and stroke.^{44,67–69} Evidence suggests that SARS-CoV can cross the BBB, as viral RNA was detected in the CSF^{44,67} as well as postmortem brain tissue.⁶⁸ Even for SARS-CoV, these are rare clinical presentations, and, in some cases, these neurological symptoms could be possibly linked to a differential diagnosis. However, the detection of viral SARS-CoV RNA—unlike what is reported for

MERS-CoV—in both CSF and autopsied brain tissue points to a neurotropic component for SARS-CoV infections.⁶³

CoVs generally target epithelial cells of the respiratory and gastrointestinal tract⁷⁰ as these cells contain the ACE2 receptor, which is utilized by the virus to enter the host cell. However, invasion is not limited to these cell types alone. The ACE2 is expressed in several brain regions, including the brain stem, subfornical organ, rostral ventrolateral medulla, nucleus of the tractus solitarius, and paraventricular nucleus.⁷¹ Furthermore, ACE2 was found in both neurons and glia.^{71–73} Therefore, SARS-CoV may directly infect cells of the CNS and contribute to neuronal dysfunction. However, SARS-CoV may also affect neuronal health through indirect methods.

The pathology of SARS-CoV has been linked to inflammation. In SARS-CoV-infected mice, elevated levels of inflammatory cytokines were observed, including interleukin (IL)-6, interferon (IFN)- γ , chemokine ligand (CCL)2, and CCL12.^{74–76} Experimental investigations showed that the replication and accumulation of SARS-CoV were integral causes of the elevated levels of inflammatory chemokine markers in wild-type mice.⁷⁷ In SARS-CoV-activated monocytes and granulocytes, alarmin expression was upregulated resulting in increased chemotaxis,⁷⁸ and this primes the cerebral microenvironment for inflammatory processes.⁷⁹ It was also found that in SARS-CoV-infected patients, genes encoding for lipocalin-2 (an acute-phase protein) were upregulated.⁷⁸

In addition to the possibility of glia and astrocytes used for viral replication, resident CNS cells are involved in neuroinflammation.^{80–82} Astrocytes and microglia exposed to CoVs (mouse hepatitis virus) showed that the severity of neurovirulence of the virus associated with its ability to induce the proinflammatory cytokines IL-12 p40, TNF- α , IL-6, IL-15, and IL-1 β .⁸³ Glial cells of a SARS-CoV-infected patient who developed severe CNS invasion reported elevated monokine induced by IFN- γ [MIG/C-X-C motif chemokine ligand (CXCL)9] cytokine levels.⁶⁸ Brain sections showed an intense inflammation with CD68⁺ macrophage infiltration, neuronal necrosis, diffuse brain edema, and reactive gliosis.⁶⁸

Moreover, viral proteins were detected by immunohistochemistry in brain neurons and astrocytes.⁶⁸ Furthermore, CXCL10/IP-10 and CXCL9 were elevated in the blood of this patient.⁶⁸ Taken together, these studies suggest the potential involvement of both glia and astrocytes in the neuroinflammatory processes of SARS-CoV. Due to the novelty of COVID-19 (SARS-CoV-2), findings from these studies may provide clues to the neuroinflammatory mechanisms of SARS-CoV-2 and COVID-19.

Severe acute respiratory syndrome-coronavirus-2

A CoV classified as SARS-CoV-2 is responsible for a new CoV disease known as COVID-19.⁸⁴ COVID-19 frequently presents as a pneumonia syndrome, with symptoms including fever, dry cough, and breathlessness reported most often.⁸⁴ Even though complications associated with the respiratory system are the most common and life-threatening in COVID-19, increasing evidence suggests that COVID-19 pathophysiology may also involve the central and peripheral nervous systems.⁶³

A retrospective study of a possible neurological component to COVID-19 looked at data from more than 200

individuals in China. Due to an as yet unknown cause, patients—in particular those with severe COVID-19—exhibited symptoms that included impaired consciousness, skeletal muscle injury, hypogeusia, hyposmia, and acute cerebrovascular disease. Unfortunately, at the time of publication, all patients were still hospitalized and the association between these neurological symptoms and patient outcome could not be investigated.⁸⁵

In another study, Li *et al.* report the development of acute cerebrovascular disease, including ischemic stroke, cerebral venous sinus thrombosis, and cerebral hemorrhage in a cohort of 13 COVID-positive patients. Interestingly, here again, the neurological symptoms were more common in severe cases of COVID-19, and also in older patients.⁸⁶ A third study, this time from France, also reports various neurological and neuropsychiatric illnesses in 84% of 58 COVID-19-positive patients admitted to hospital with acute respiratory distress syndrome (ARDS). For this cohort of patients with severe COVID-19, the authors report neurological features that include evidence of encephalopathy, corticospinal tract dysfunction, agitation, and delirium. Moreover, two patients had evidence of a small acute ischemic stroke.⁸⁷

Likewise, many individual case reports describing the development of acute neurological disorders in COVID-19-positive patients, ranging from Guillain-Barré syndrome^{88–96} to meningoencephalitis,⁹⁷ ischemic stroke,⁹⁸ acute necrotizing encephalopathy,⁹⁹ and acute hemorrhagic necrotizing encephalopathy,^{97,99,100} are now being published.

How, and if, SARS-CoV-2 infects the CNS in patients has still not been proven definitively. However, Baig *et al.* have speculated that “SARS-CoV-2 neurotropism occurs via a circulatory and/or an upper nasal transcribrial route.” This would enable the virus to reach the brain, where it then binds and engages with the ACE2 receptors via the spike protein, followed by entry into the brain.¹⁰¹

On the contrary, *in vitro* studies are now showing that SARS-CoV-2 can infect and cause pathologies in brain organoid models. In a very recent study, pseudotyped SARS-CoV-2 viral particles were reported to infect human embryonic stem cell-derived brain organoids, as well as monolayer cortical neurons.¹⁰² In another *in vitro* model of human brain organoids, evidence of SARS-CoV-2 infection—with accompanying metabolic changes in the infected and neighboring neurons—was reported.¹⁰³ Interestingly, it was suggested that SARS-CoV-2 preferably targets the soma of cortical neurons, but not neural stem cells, and that SARS-CoV-2 exposure is associated with missorted Tau from axons to soma, hyperphosphorylation, and apparent neuronal death.¹⁰⁴ These too are suggestive of neurodegenerative-like effects.

What are the possible mechanisms of the various neurological symptoms linked to severe COVID-19? Groups speculate that mechanisms could include the following: (1) direct viral neuronal injury; (2) a secondary hyperinflammation syndrome; (3) para- and postinfectious inflammatory or immune-mediated disorders; or (4) a severe systemic disorder with neurological consequences; these mechanisms could possibly act either individually or in combination.^{105–107} On the contrary, even with the mounting evidence, not all researchers are convinced by the data. As an example, Larvie *et al.* question the interpretation of the data and the conclusions made in the report by Helms *et al.*, speculating that the findings “may not definitively

indicate a specific syndrome of brain involvement associated with SARS-CoV-2.”^{87,108}

The neuropathogenesis of COVID-19 is not clearly understood, however, SARS-CoV-2 belongs to the same beta-CoV clade of the previously reported SARS-CoV and MERS-CoV.¹⁰⁹ SARS-CoV-2 also shares several similarities to that of SARS-CoV and prior research of SARS-CoV may provide insight into COVID-19. Similar to SARS-CoV, the neuroinvasion of SARS-CoV-2 into the CNS may be by ACE2.^{110,111} The SARS-CoV-2 receptor-binding domain (RBD) has a higher ACE2 binding affinity than SARS-CoV RBD. The ACE2 binding affinity of the entire SARS-CoV-2 spike is comparable with or lower than that of SARS-CoV spike, which suggests that the SARS-CoV-2 RBD, although more potent, is more occluded than the SARS-CoV RBD.

Compared with SARS-CoV, cell entry of SARS-CoV-2 is preactivated by proprotein convertase furin, and thus, SARS-CoV-2 has reduced dependence on target cell proteases for entry. These suggest that SARS-CoV-2 may maintain efficient cell entry while evading immune surveillance.¹¹² This may explain why SARS-CoV-2 may be a more virulent strain. It has also recently been suggested that SARS-CoV-2 may use integrins as an alternative cell receptor into host cells. SARS-CoV-2 may bind to integrins via a conserved RGD (403–405: arginine/glycine/aspartate) motif that is present in the RBD of the SARS-CoV-2 spike protein. This motif is present in all SARS-CoV-2 sequences analyzed to date.¹¹³

The findings for the presence of SARS-CoV-2 within the CSF have been contradictory. Certain studies show that COVID-19 patient CSF samples were polymerase chain reaction negative for the presence of SARS-CoV-2,^{87,114–116} whereas others report SARS-CoV-2-positive CSF findings.^{97,117,118} Furthermore, SARS-CoV-2 was detected in the capillary endothelial and neuronal cells of frontal lobe post-mortem brain tissue.¹¹⁹ These findings are similar to that reported for SARS-CoV, supporting the potential of the virus to breach the BBB. In patients recovering from ARDS and/or pneumonia, a large number experience cognitive impairment with impaired functional status, often persisting months after hospital discharge.^{120,121} This may suggest an underlying neuropathology and it is postulated that neuroinflammatory processes may also be associated with such neurological complications in COVID-19 patients.^{122,123}

SARS-CoV-2 causes a surge of inflammatory cytokines also known as the cytokine storm syndrome (CSS). Systemic CSS results in a significant release of cytokines, chemokines, and other inflammatory signals. CSS may damage the BBB, which allows further infiltration of cells into the CNS resulting in an amplified neuroinflammatory process.^{123,124} The immune dysregulation¹²⁵ caused by SARS-CoV-2 results in upregulation of several genes that enhance proinflammatory and oxidative responses, resulting in inflammatory stress⁷⁸ and cytokine storm.^{84,126,127}

SARS-CoV-2 is responsible for the persistent release of inflammatory markers, including IL-1 β , IL-1, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-17, IL-18, IL-33, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein-1A (MIP-1A), MIP-1B, macrophage colony-stimulating factor (M-CSF), TNF- α , transforming growth factor- β , IFN- α , IFN- β , IFN- γ , and chemokines, including CCL2, CCL3, CCL5, CCL7, CCL12,

CXCL8, CXCL9, and CXCL10, which are ultimately responsible for the development of CSS.^{84,128–132}

Moreover, the levels of inflammatory markers are related to the severity of COVID-19 infection, with elevated plasma cytokines/chemokines IL-1 β , IFN- γ , CCL2, and IP-10 linked to mild-to-moderate cases and elevated levels of TNF- α , IL-8, IL-10, G-CSF, CCL2, MIP-1A, and IP-10 related to severer cases.^{84,133} Several studies also reported elevated levels of C-reactive protein (CRP) in COVID-19 patients.^{134–136} It was also found that VEGF (immune-related marker associated with inflammation) is dysregulated in COVID-19 patients, and could possibly be related to neuroinflammation and BBB damage.¹³⁷ Interestingly, in the majority of studies, IL-6 is elevated in COVID-19 patients.^{17,84,133,138–140}

It is speculated that SARS-CoV-2 may activate resident astrocytes and glial cells. Currently, there is no evidence for the SARS-CoV-2 presence in astrocytes, however, there is a possibility for infection, activation, as well as astrocytes being viral reservoirs as shown in several studies of CoVs.^{48,68,83,141,142} Similar to other neurotropic viruses,⁵³ SARS-CoV-2 may similarly induce the production of inflammatory markers such as IL-6 from glial cells that result in CSS.⁸³ SARS-CoV-2 within the CNS activates CD4⁺ cells, in turn inducing macrophages to secrete IL-6 by producing GM-CSF.¹³⁰ The effect of SARS-CoV-2 on cells of the CNS is incompletely known, however, based on findings of other CoVs, SARS-CoV-2 may significantly increase inflammation within the CNS.

Potential Contributions of COVID-19 to (Neuro)inflammation in PLWH

Should COVID-19 contribute to (neuro)inflammation, what may this mean for patients with HAND who already experience dysregulated (neuro)inflammatory levels?^{7,9,10,30,143} Preliminary evidence suggests that COVID-19 may exacerbate systemic and neuroinflammation, with common findings reported for IL-6. IL-6 is a predominant component of CSS and the pathway of IL-6 dysregulation may be important in the pathophysiology of COVID-19.^{144,145} Prior HIV studies found dysregulated peripheral^{8,146,147} and CSF¹⁴⁸ IL-6 levels to be associated with HAND. The effect of SARS-CoV-2 within the CSF may result in significantly higher levels of IL-6, which may negatively affect neuronal health in coinfecting PLWH.

It was also shown that HIV-positive participants have elevated GM-CSF in CSF¹⁴⁹ and these elevated levels are associated with HAND.¹⁴⁸ Alternative markers which may also be dysregulated in patients with COVID-19, include CRP,^{134–136} VEGF,¹³⁷ and lipocalin-2.⁷⁸ CRP is an inflammatory marker that has also been associated with domain-based and global HAND.¹⁵⁰ VEGF is suggested to regulate neuroinflammation and BBB dysfunction in COVID-19.¹³⁷ A prior study in PLWH reported that elevated CSF levels of VEGF were associated with HAND.¹⁵¹

Furthermore, lipocalin-2 gene expression was upregulated in SARS-CoV patients and may similarly be reflected in patients with SARS-CoV-2.⁷⁸ Previous work done by our group and others reported that peripheral lipocalin-2 levels were elevated in HIV-positive participants, and were associated with domain-based neurocognitive impairment¹⁵² and thinner bilateral orbitofrontal cortex.¹⁵³ Furthermore, lipocalin-2 was upregulated in the neocortex of HIV-

positive participants with brain pathology.¹⁵⁴ Therefore, the upregulation of lipocalin-2 due to COVID-19 may have detrimental effects in PLWH and HAND. Overall, the effects of COVID-19 may further add insult to injury by contributing to the dysregulated (neuro)inflammatory profile in PLWH. This may increase the likelihood of participants developing severer forms of HAND (i.e., HIV-associated dementia).

Anticytokine therapies and/or immunomodulators are considered potential therapeutic strategies to target the overactive cytokine response. This may provide relief for systemic inflammation, but will the same apply for therapies with limited CNS penetration? Even though a study has shown that treatment with the anti-IL-6 drug, tocilizumab (IL-6 receptor blocker), resulted in improvement of critically ill COVID-19 patients,¹⁵⁵ it may have limited benefit in the CNS if the brain is a viral reservoir for SARS-CoV-2.¹⁵⁶ In a clinical trial of tocilizumab for residual symptoms in schizophrenia,¹⁵⁷ results found no evidence that affects behavioral outcomes in schizophrenia. One potential explanation was the inability of this agent to penetrate the CNS.

Even though unlikely, another concern for SARS-CoV-2 coinfecting PLWH is that the presence of SARS-CoV-2 could potentially result in an immune activation that may promote the reactivation of latent HIV.¹⁵⁸ The immune system may be activated by SARS-CoV-2 antigens, which may promote the reactivation of latent HIV as indicated by the appearance of HIV in ART-experienced PLWH (HIV surge). The HIV surge may increase the HIV reservoir and inflammatory profile and further accelerate the course of HIV-associated comorbidities (e.g., cognitive disorders).

Findings for studies between CoVs and HIV are contradictory. Initial studies reported that SARS-CoV¹⁵⁹ and MERS-CoV¹⁶⁰ coinfecting HIV patients have a lower risk of CoV infection and progression to severe disease. However, the mechanisms responsible for this are not understood and it is not clear whether HIV replication may interfere with CoV replication and/or the effect of ART on CoV disease progression.¹⁵⁹ It was shown that immunosuppressed (low CD4 counts) HIV-positive participants may be protected from developing the cytokine storm observed in patients with COVID-19.¹⁶¹

Opposing views have also been argued and reported that neither the CD4 count¹⁶² nor the use of specific antiretroviral drugs^{161–163} affected the SARS-CoV-2 severity or infection rate. Limited findings exist for studies of SARS-CoV-2 and HIV in general¹⁶⁴ and no studies at this time for SARS-CoV-2 and HAND. Due to this, there is still much controversy and uncertainty, which require further investigation. There is a need for clinical and preclinical studies assessing the following: (1) CoV disease progression in PLWH in general, (2) the effect of ART on CoV disease progression, (3) the immune response (e.g., inflammation) in coinfecting participants, and (4) the inflammatory response of CNS cells exposed to SARS-CoV-2.

Conclusions

Here we reviewed the potential contributions of COVID-19 to the development of HAND. Recent findings suggest that (1) COVID-19 has neurological implications, (2) CoVs (including SARS-CoV-2) may elicit a significant systemic immune response, and (3) may cross the BBB. Last, it may be speculated that CoVs (including SARS-CoV-2) may

similarly elicit inflammatory responses within the CNS and this may exacerbate neuroinflammation in PLWH. Therefore, COVID-19 may exacerbate the underlying neuropathology contributing to the development of severer forms of HAND.

Author Disclosure Statement

The authors declare no conflicts of interest.

Funding Information

M.E.W. was funded by the next Generation of Academics' Program of South Africa (nGAP; Department of Higher Education and Training [DHET]) and the South African Society for Biological Psychiatry. B.C.F. receives funding from the National Research Foundation (NRF). Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors, and therefore, the funders do not accept any liability in regard thereto.

References

- Hong S, Banks WA: Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications. *Brain Behav Immun* 2015;45:1–12.
- González-Scarano F, Martín-García J: The neuropathogenesis of AIDS. *Nat Rev Immunol* 2005;5:69–81.
- De Francesco D, Underwood J, Post FA, *et al.*: Defining cognitive impairment in people-living-with-HIV: The POPPY study. *BMC Infect Dis* 2016;16:617.
- Antinori A, Arendt G, Becker JT, *et al.*: Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007;69:1789–1799.
- Heaton RK, Clifford DB, Franklin DR, *et al.*: HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: Charter Study. *Neurology* 2010;75:2087–2096.
- Harezlak J, Buchthal S, Taylor M, *et al.*: Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral treatment. *AIDS* 2011;25:625–633.
- Williams ME, Ipser JC, Stein DJ, Joska JA, Naudé PJW. Peripheral immune dysregulation in the ART era of HIV-associated neurocognitive impairments: A systematic review. *Psychoneuroendocrinology* 2020;118:104689.
- Ancuta P, Kamat A, Kunstman KJ, *et al.*: Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. *PLoS One* 2008;3:10–20.
- Cohen RA, de la Monte S, Gongvatana A, *et al.*: Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. *J Neuroimmunol* 2011;233:204–210.
- Falasca K, Reale M, Ucciferri C, *et al.*: Cytokines, hepatic fibrosis, and antiretroviral therapy role in neurocognitive disorders HIV related. *AIDS Res Hum Retroviruses* 2017; 33:246–253.
- Kamat A, Lyons JL, Misra V, *et al.*: Monocyte activation markers in cerebrospinal fluid associated with impaired neurocognitive testing in advanced HIV infection. *J Acquir Immune Defic Syndr* 2012;60:234–243.
- Chen N, Zhou M, Dong X, *et al.*: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020;395:507–513.
- Chen T, Wu D, Chen H, *et al.*: Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. *BMJ*. 2020;368.
- Giacomelli A, Pezzati L, Conti F, *et al.*: Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: A cross-sectional study. *Clin Infect Dis* 2020;71:889–890.
- Hopkins C, Surda P, Whitehead E, Kumar BN. Early recovery following new onset anosmia during the COVID-19 pandemic - An observational cohort study. *J Otolaryngol - Head Neck Surg* 2020;49.
- Wan S, Xiang Y, Fang W, *et al.*: Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol* 2020;92:797–806.
- Wang Z, Yang B, Li Q, Wen L, Zhang R: Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis* 2020;71:769–777.
- Yang X, Yu Y, Xu J, *et al.*: Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475–481.
- Joint United Nations Programme on HIV/AIDS (UNAIDS): Global HIV and AIDS statistics 2019 Fact sheet. *Glob HIV AIDS statistics, World AIDS day 2019 Fact Sheet*. 2019;1:1–6.
- An SF, Groves M, Gray F, Scaravilli F: Early entry and widespread cellular involvement of HIV-1 DNA in brains of HIV-1 positive asymptomatic individuals. *J Neuropathol Exp Neurol* 1999;58:1156–1162.
- Davis LE, Hjelle BL, Miller VE, *et al.*: Early viral brain invasion in iatrogenic human immunodeficiency virus infection. *Neurology* 1992;42:1736–1739.
- Meucci O, Fatatis A, Simen AA, Bushell TJ, Gray PW, Miller RJ: Chemokines regulate hippocampal neuronal signaling and gp120 neurotoxicity. *Proc Natl Acad Sci U S A* 1998;95:14500–14505.
- András IE, Pu H, Deli MA, Nath A, Hennig B, Toborek M: HIV-1 Tat protein alters tight junction protein expression and distribution in cultured brain endothelial cells. *J Neurosci Res* 2003;74:255–265.
- Patel CA, Mukhtar M, Harley S, Kulkosky J, Pomerantz RJ: Lentiviral expression of HIV-1 Vpr induces apoptosis in human neurons. *J Neurovirol* 2002;8:86–99.
- Kaul M, Lipton SA: Chemokines and activated macrophages in HIV gp120-induced neuronal apoptosis. *Proc Natl Acad Sci U S A* 1999;96:8212–8216.
- Wesselingh SL, Power C, Glass JD, *et al.*: Intracerebral cytokine messenger RNA expression in acquired immunodeficiency syndrome dementia. *Ann Neurol* 1993;33: 576–582.
- Wiley CA, Schrier RD, Nelson JA, Lampert PW, Oldstone MB: Cellular localization of human immunodeficiency virus infection within the brains of acquired immune deficiency syndrome patients. *Proc Natl Acad Sci U S A* 1986;83:7089–7093.
- Takahashi K, Wesselingh SL, Griffin DE, McArthur JC, Johnson RT, Glass JD: Localization of HIV-1 in human brain using polymerase chain reaction/in situ hybridization and immunocytochemistry. *Ann Neurol* 1996;39:705–711.
- Fischer-Smith T, Croul S, Adeniyi A, *et al.*: Macrophage/microglial accumulation and proliferating cell nuclear antigen expression in the central nervous system in human immunodeficiency virus encephalopathy. *Am J Pathol* 2004;164:2089–2099.

30. Correia S, Cohen R, Gongvatana A, *et al.*: Relationship of plasma cytokines and clinical biomarkers to memory performance in HIV. *J Neuroimmunol* 2013;265:117–123.
31. Yuan L, Qiao L, Wei F, *et al.*: Cytokines in CSF correlate with HIV-associated neurocognitive disorders in the post-HAART era in China. *J Neurovirol* 2013;19:144–149.
32. Mothapo KM, Stelma F, Janssen M, *et al.*: Amyloid beta-42 ($A\beta$ -42), neprilysin and cytokine levels. A pilot study in patients with HIV related cognitive impairments. *J Neuroimmunol* 2015;282:73–79.
33. Tavazzi E, Morrison D, Sullivan P, Morgello S, Fischer T: Brain inflammation is a common feature of HIV-infected patients without HIV encephalitis or productive brain infection. *Curr HIV Res* 2014;12:97–110.
34. Shapshak P, Duncan R, Minagar A, Rodriguez De La Vega P, Stewart RV, Goodkin K: Elevated expression of IFN-gamma in the HIV-1 infected brain. *Front Biosci* 2004;9:1073–1081.
35. Valcour VG, Spudich SS, Sailasuta N, *et al.*: Neurological Response to cART vs. cART plus integrase inhibitor and ccr5 antagonist initiated during acute HIV. *PLoS One* 2015;10.
36. Sharief MK, Ciardi M, Thompson EJ, *et al.*: Tumour necrosis factor- α mediates blood–brain barrier damage in HIV-1 infection of the central nervous system. *Mediators Inflamm* 1992;1:191–196.
37. Jiang ZG, Piggee C, Heyes MP, *et al.*: Glutamate is a mediator of neurotoxicity in secretions of activated HIV-1-infected macrophages. *J Neuroimmunol* 2001;117:97–107.
38. Bezzi P, Domercq M, Brambilla L, *et al.*: CXCR4-activated astrocyte glutamate release via TNF α : Amplification by microglia triggers neurotoxicity. *Nat Neurosci* 2001;4:702–710.
39. Wang Z, Pekarskaya O, Bencheikh M, *et al.*: Reduced expression of glutamate transporter EAAT2 and impaired glutamate transport in human primary astrocytes exposed to HIV-1 or gp120. *Virology* 2003;312:60–73.
40. Bruce-Keller AJ, Barger SW, Moss NI, Pham JT, Keller JN, Nath A: Pro-inflammatory and pro-oxidant properties of the HIV protein Tat in a microglial cell line: Attenuation by 17 β -estradiol. *J Neurochem* 2001;78:1315–1324.
41. Yang D, Elner SG, Bian ZM, Till GO, Petty HR, Elner VM: Pro-inflammatory cytokines increase reactive oxygen species through mitochondria and NADPH oxidase in cultured RPE cells. *Exp Eye Res* 2007;85:462–472.
42. Talley AK, Dewhurst S, Perry SW, *et al.*: Tumor necrosis factor alpha-induced apoptosis in human neuronal cells: Protection by the antioxidant N-acetylcysteine and the genes bcl-2 and crmA. *Mol Cell Biol* 1995;15:2359–2366.
43. Arbour N, Day R, Newcombe J, Talbot PJ: Neuroinvasion by human respiratory coronaviruses. *J Virol* 2000;74:8913–8921.
44. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY: Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis* 2004;10:342–344.
45. Yeh EA, Collins A, Cohen ME, Duffner PK, Faden H: Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. *Pediatrics* 2004;113(Pt 1).
46. Desforges M, Le Coupanec A, Brison É, Meessen-Pinard M, Talbot PJ: Neuroinvasive and neurotropic human respiratory coronaviruses: Potential neurovirulent agents in humans. *Adv Exp Med Biol* 2014;807:75–96.
47. Desforges M, Le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ: Human coronaviruses: Viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res* 2014;194:145–158.
48. Desforges M, Le Coupanec A, Dubeau P, *et al.*: Human coronaviruses and other respiratory viruses: Underestimated opportunistic pathogens of the central nervous system? *Viruses* 2019;12.
49. Gu J, Gong E, Zhang B, *et al.*: Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 2005;202:415–424.
50. Mori I: Transolfactory neuroinvasion by viruses threatens the human brain. *Acta Virol* 2015;59:338–349.
51. Abdennour L, Zeghal C, Dème M, Puybasset L: Interaction cerveau-poumon. *Ann Fr Anesth Reanim* 2012;31:e101–e107.
52. Yin CH, Wang C, Tang Z, Wen Y, Zhang SW, Wang B: Clinical analysis of multiple organ dysfunction syndrome in patients suffering from SARS. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2004;16:646–650.
53. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM: Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci* 2018;12:386.
54. Loganathan SK, Schleicher K, Malik A, *et al.*: Rare driver mutations in head and neck squamous cell carcinomas converge on NOTCH signaling. *Science* 2020;367:1264–1269.
55. Yang P, Gu H, Zhao Z, *et al.*: Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. *Sci Rep* 2014;4:7027.
56. Reinhold A, Rittner H: Barrier function in the peripheral and central nervous system—A review. *Pflugers Arch* 2017;469:123–134.
57. Wüthrich C, Batson S, Koralnik IJ: Lack of major histocompatibility complex class I upregulation and restrictive infection by JC virus hamper detection of neurons by T lymphocytes in the central nervous system. *J Neuropathol Exp Neurol* 2015;74:791–803.
58. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM: Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012;367:1814–1820.
59. Chafekar A, Fielding BC: MERS-CoV: Understanding the Latest Human Coronavirus Threat. *Viruses* 2018;10:93.
60. Arabi YM, Harthi A, Hussein J, *et al.*: Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection* 2015;43:495–501.
61. Algahtani H, Subahi A, Shirah B: Neurological complications of Middle East respiratory syndrome coronavirus: A report of two cases and review of the literature. *Case Rep Neurol Med* 2016;2016:1–6.
62. Kim JE, Heo JH, Kim HO, *et al.*: Neurological complications during treatment of Middle East respiratory syndrome. *J Clin Neurol* 2017;13:227–233.
63. Ng Kee Kwong KC, Mehta PR, Shukla G, Mehta AR: COVID-19, SARS and MERS: A neurological perspective. *J Clin Neurosci* 2020;77:13–16.
64. Xu RH, He JF, Evans MR, *et al.*: Epidemiologic clues to SARS origin in China. *Emerg Infect Dis* 2004;10:1030–1037.

65. Meo SA, Alhowikan AM, Khilaiwi TAL, *et al.*: Novel coronavirus 2019-nCoV: Prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. *Eur Rev Med Pharmacol. Sci.* 2020;24:2012–2019.
66. Hui DSC, Wong PC, Wang C: SARS: Clinical features and diagnosis. *Respirology* 2003;18:S20–S24.
67. Hung ECW, Chim SSC, Chan PKS, *et al.*: Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. *Clin Chem* 2003;49:2109.
68. Xu J, Zhong S, Liu J, *et al.*: Detection of severe acute respiratory syndrome coronavirus in the brain: Potential role of the chemokine MIG in pathogenesis. *Clin Infect Dis* 2005;41:1089–1096.
69. Tsai LK, Hsieh ST, Chang YC: Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan* 2005;14:113–119.
70. Gheblawi M, Wang K, Viveiros A, *et al.*: Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: Celebrating the 20th anniversary of the discovery of ACE2. *Circ Res* 2020;1456–1474.
71. Xia H, Lazartigues E: Angiotensin-converting enzyme 2: Central regulator for cardiovascular function. *Curr Hypertens Rep* 2010;12:170–175.
72. Gowrisankar YV, Clark MA: Angiotensin II regulation of angiotensin-converting enzymes in spontaneously hypertensive rat primary astrocyte cultures. *J Neurochem* 2016;138:74–85.
73. Turner AJ, Hiscox JA, Hooper NM: ACE2: From vasopeptidase to SARS virus receptor. *Trends Pharmacol Sci* 2004;25:291–294.
74. Tseng C-TK, Huang C, Newman P, *et al.*: Severe acute respiratory syndrome coronavirus infection of mice transgenic for the human angiotensin-converting enzyme 2 virus receptor. *J Virol* 2007;81:1162–1173.
75. McCray PB, Pewe L, Wohlford-Lenane C, *et al.*: Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. *J Virol* 2007;81:813–821.
76. Glass WG, Subbarao K, Murphy B, Murphy PM: Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. *J Immunol* 2004;173:4030–4039.
77. Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N: TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. *J Virol* 2019;93:e01815–1818.
78. Reghunathan R, Jayapal M, Hsu LY, *et al.*: Expression profile of immune response genes in patients with severe acute respiratory syndrome. *BMC Immunol* 2005;6.
79. Welcome MO: Neuroinflammation in CNS diseases: Molecular mechanisms and the therapeutic potential of plant derived bioactive molecules. *PharmaNutrition* 2020;11:100176.
80. Graeber MB, Li W, Rodriguez ML: Role of microglia in CNS inflammation. *FEBS Lett* 2011;585:3798–3805.
81. Bachiller S, Jiménez-Ferrer I, Paulus A, *et al.*: Microglia in neurological diseases: A road map to brain-disease dependent-inflammatory response. *Front Cell Neurosci* 2018;12:488.
82. Colombo E, Farina C: Astrocytes: Key regulators of neuroinflammation. *Trends Immunol* 2016;37:608–620.
83. Li Y, Fu L, Gonzales DM, Lavi E: Coronavirus Neurovirulence Correlates with the Ability of the Virus To Induce Proinflammatory Cytokine Signals from Astrocytes and Microglia. *J Virol* 2004;78:3398–3406.
84. Huang C, Wang Y, Li X, *et al.*: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
85. Mao L, Jin H, Wang M, *et al.*: Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683–690.
86. Li Y, Li M, Wang M, *et al.*: Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol* 2020;279–284.
87. Helms J, Kremer S, Merdji H, *et al.*: Neurologic features in severe SARS-COV-2 infection. *N Engl J Med* 2020;382:2268–2270.
88. Esteban Molina A, Mata Martínez M, Sánchez Chueca P, Carrillo López A, Sancho Val I, Sanjuan-Villarreal TA: Guillain-Barré syndrome associated with SARS-CoV-2 infection. *Med Intens* 2020.
89. Khalifa M, Zakaria F, Ragab Y, *et al.*: Guillain-Barré syndrome associated with severe acute respiratory syndrome coronavirus 2 detection and coronavirus disease 2019 in a child. *J Pediatric Infect Dis Soc* 2020;9:510–513.
90. Pelea T, Reuter U, Schmidt C, Laubinger R, Siegmund R, Walther BW: SARS-CoV-2 associated Guillain—Barré syndrome. *J Neurol* 2020:1–4.
91. Sancho-Saldaña A, Lambea-Gil Á, Capablo Liesa JL, *et al.*: Guillain-Barré syndrome associated with leptomeningeal enhancement following SARS-CoV-2 infection. *Clin Med J R Coll Physicians London* 2020;20:E93–E94.
92. Su XW, Palka SV, Rao RR, Chen FS, Brackney CR, Cambi F: SARS-CoV-2-associated Guillain-Barré syndrome with dysautonomia. *Muscle Nerve* 2020;62:E48–E49.
93. Toscano G, Palmerini F, Ravaglia S, *et al.*: Guillain-Barré syndrome associated with SARS-CoV-2. *N Engl J Med* 2020;382:2574–2576.
94. Velayos Galán A, del Saz Saucedo P, Peinado Postigo F, Botia Paniagua E: Guillain-Barré syndrome associated with SARS-CoV-2 infection. *Neurologia* 2020;35:268–269.
95. Virani A, Rabold E, Hanson T, *et al.*: Guillain-Barré Syndrome associated with SARS-CoV-2 infection. *ID-Cases* 2020;20.
96. Zhao H, Shen D, Zhou H, Liu J, Chen S: Guillain-Barré syndrome associated with SARS-CoV-2 infection: Causality or coincidence? *Lancet Neurol* 2020;19:383–384.
97. Moriguchi T, Harii N, Goto J, *et al.*: A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 2020;94:55–58.
98. Beyrouth R, Adams ME, Benjamin L, *et al.*: Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry* 2020;91:889–891.
99. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B: COVID-19-associated acute hemorrhagic necrotizing encephalopathy: Imaging features. *Radiology* 2020;296:E119–E120.
100. Sedaghat Z, Karimi N: Guillain Barre syndrome associated with COVID-19 infection: A case report. *J Clin Neurosci* 2020;76:233–235.
101. Baig AM, Khaleeq A, Ali U, Syeda H: Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci* 2020;11:995–998.
102. Yi SA, Nam KH, Yun J, *et al.*: Infection of brain organoids and 2D cortical neurons with SARS-CoV-2 pseudovirus. *Viruses* 2020;12:1004.

103. Song E, Zhang C, Israelow B, *et al.*: Neuroinvasive potential of SARS-CoV-2 revealed in a human brain organoid model. *bioRxiv* 2020:69946.
104. Ramani A, Müller L, Ostermann PN, *et al.*: SARS-CoV-2 targets cortical neurons of 3D human brain organoids and shows neurodegeneration-like effects. *bioRxiv* 2020:106575.
105. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ: COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–1034.
106. Paterson RW, Brown RL, Benjamin L, *et al.*: The emerging spectrum of COVID-19 neurology: Clinical, radiological and laboratory findings. *Brain* 2020.
107. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S: Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: A review. *JAMA Neurol* 2020;77:1018–1027.
108. Larvie M, Lev M, Hess C: More on neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020;382:e110.
109. Wu A, Peng Y, Huang B, *et al.*: Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. *Cell Host Microbe* 2020;27:325–328.
110. Hoffmann M, Kleine-Weber H, Schroeder S, *et al.*: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271.e8–280.e8.
111. Wan Y, Shang J, Graham R, Baric RS, Li F: Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 2020;94:e00127–20.
112. Shang J, Wan Y, Luo C, *et al.*: Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci U S A* 2020;117:11727–11734.
113. Sigrist CJ, Bridge A, Le Mercier P: A potential role for integrins in host cell entry by SARS-CoV-2. *Antiviral Res* 2020;177:104759.
114. Destras G, Bal A, Escuret V, Morfin F, Lina B, Josset L: Systematic SARS-CoV-2 screening in cerebrospinal fluid during the COVID-19 pandemic. *Lancet Microbe* 2020;1:e149.
115. Espíndola O de M, Siqueira M, Soares CN, *et al.*: Patients with COVID-19 and neurological manifestations show undetectable SARS-CoV-2 RNA levels in the cerebrospinal fluid. *Int J Infect Dis* 2020;96:567–569.
116. Al Saiegh F, Ghosh R, Leibold A, *et al.*: Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. *J Neurol Neurosurg Psychiatry* 2020;91:846–848.
117. Huang YH, Jiang D, Huang JT: SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav Immun* 2020;87:149.
118. Domingues RB, Mendes-Correa MC, de Moura Leite FBV, *et al.*: First case of SARS-COV-2 sequencing in cerebrospinal fluid of a patient with suspected demyelinating disease. *J Neurol* 2020.
119. Paniz-Mondolfi A, Bryce C, Grimes Z, *et al.*: Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol* 2020;92:699–70.
120. Elizabeth Wilcox M, Brummel NE, Archer K, Wesley Ely E, Jackson JC, Hopkins RO: Cognitive dysfunction in ICU patients: Risk factors, predictors, and rehabilitation interventions. *Crit Care Med* 2013;41(Suppl 1):S81–S98.
121. Herridge MS, Moss M, Hough CL, *et al.*: Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. *Intensive Care Med* 2016;42:725–738.
122. Sasannejad C, Ely EW, Lahiri S: Long-term cognitive impairment after acute respiratory distress syndrome: A review of clinical impact and pathophysiological mechanisms. *Crit Care* 2019;23:352.
123. Steardo L, Steardo L, Zorec R, Verkhatsky A: Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiol (Oxf)* 2020;229:e13473.
124. Geng J, Wang L, Zhang L, *et al.*: Blood-brain barrier disruption induced cognitive impairment is associated with increase of inflammatory cytokine. *Front Aging Neurosci* 2018;10:129.
125. Ye Q, Wang B, Mao J: The pathogenesis and treatment of the ‘cytokine storm’ in COVID-19. *J Infect* 2020;80:607–613.
126. Li X, Geng M, Peng Y, Meng L, Lu S: Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal* 2020;10:102–108.
127. Liu B, Li M, Zhou Z, Guan X, Xiang Y: Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *J Autoimmun* 2020;111:102452.
128. Liu K, Fang YY, Deng Y, *et al.*: Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)* 2020;133:1025–1031.
129. Wang W, Liu X, Wu S, *et al.*: Definition and Risks of Cytokine Release Syndrome in 11 Critically Ill COVID-19 Patients With Pneumonia: Analysis of Disease Characteristics. *J Infect Dis*. 2020;222:1444–1451.
130. Chen C, Zhang XR, Ju ZY, He WF: Advances in the research of mechanism and related immunotherapy on the cytokine storm induced by coronavirus disease 2019 [in Chinese]. *Zhonghua Shao Shang Za Zhi* 2020;36:471–475.
131. Chen G, Wu D, Guo W, *et al.*: Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130:2620–2629.
132. Gao Y, Li T, Han M, *et al.*: Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol* 2020;92:791–796.
133. Qin C, Zhou L, Hu Z, *et al.*: Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020;71:762–768.
134. Deng Y, Liu W, Liu K, *et al.*: Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: A retrospective study. *Chin Med J (Engl)* 2020;133:1261–1267.
135. Guan W, Ni Z, Hu Y, *et al.*: Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–1720.
136. Liu W, Tao ZW, Wang L, *et al.*: Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J (Engl)* 2020;133:1032–1038.
137. Zhang R, Wang X, Ni L, *et al.*: COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci* 2020;250:117583.
138. Sun D, Li H, Lu XX, *et al.*: Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: A single center’s observational study. *World J Pediatr* 2020;16:251–259.

139. Zhou F, Yu T, Du R, *et al.*: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* 2020; 395:1054–1062.
140. Chen L, Liu HG, Liu W, *et al.*: Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020;43:203–208.
141. Jacomy H, Fragoso G, Almazan G, Mushynski WE, Talbot PJ: Human coronavirus OC43 infection induces chronic encephalitis leading to disabilities in BALB/C mice. *Virology* 2006;349:335–346.
142. Sun N, Grzybicki D, Castro RF, Murphy S, Perlman S: Activation of astrocytes in the spinal cord of mice chronically infected with a neurotropic coronavirus. *Virology* 1995;213:482–493.
143. Yuan L, Liu A, Qiao L, *et al.*: The relationship of CSF and plasma cytokine levels in HIV infected patients with neurocognitive impairment. *Biomed Res Int* 2015;2015: 506872.
144. Magro G: SARS-CoV-2 and COVID-19: Is interleukin-6 (IL-6) the ‘culprit lesion’ of ARDS onset? What is there besides Tocilizumab? *SGP130Fc. Cytokine X.* 2020;2: 100029.
145. Abbasifard M, Khorramdelazad H: The bio-mission of interleukin-6 in the pathogenesis of COVID-19: A brief look at potential therapeutic tactics. *Life Sci* 2020;257: 118097.
146. Lyons JL, Uno H, Ancuta P, *et al.*: Plasma sCD14 is a biomarker associated with impaired neurocognitive test performance in attention and learning domains in HIV infection. *J Acquir Immune Defic Syndr* 2011;57:371–379.
147. Sattler FR, He J, Letendre S, *et al.*: Abdominal obesity contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. *J Acquir Immune Defic Syndr* 2015;68:281–288.
148. Perrella O, Guerriero M, Izzo E, Soscia M, Carrieri PB: Interleukin-6 and granulocyte macrophage-CSF in the cerebrospinal fluid from HIV infected subjects with involvement of the central nervous system. *Arq Neuropsiquiatr* 1992;50:180–182.
149. Abassi M, Morawski BM, Nakigozi G, *et al.*: Cerebrospinal fluid biomarkers and HIV-associated neurocognitive disorders in HIV-infected individuals in Rakai, Uganda. *J Neurovirol* 2017;23:369–375.
150. Rubin LH, Benning L, Keating SM, *et al.*: Variability in C-reactive protein is associated with cognitive impairment in women living with and without HIV: A longitudinal study. *J Neurovirol* 2018;24:41–51.
151. Kallianpur AR, Gittleman H, Letendre S, *et al.*: Cerebrospinal fluid ceruloplasmin, haptoglobin, and vascular endothelial growth factor are associated with neurocognitive impairment in adults with HIV infection. *Mol Neurobiol* 2019;56:3808–3818.
152. Williams ME, Ipser JC, Stein DJ, Joska JA, Naudé PJW: The association of immune markers with cognitive performance in South African HIV-positive patients. *J Neuroimmune Pharmacol* 2019;14:679–687.
153. Williams ME, Joska JA, Amod AR, *et al.*: The association of peripheral immune markers with brain cortical thickness and surface area in South African people living with HIV. *J Neurovirol* 2020.
154. Ojeda-Juárez D, Shah R, Fields JA, *et al.*: Lipocalin-2 mediates HIV-1 induced neuronal injury and behavioral deficits by overriding CCR5-dependent protection. *Brain Behav Immun* 2020;89:184–199.
155. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ: Cytokine release syndrome in severe COVID-19: Interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents* 2020;55:105954.
156. Matias-Guiu J, Gomez-Pinedo U, Montero-Escribano P, Gomez-Iglesias P, Porta-Etessam J, Matias-Guiu JA: Should we expect neurological symptoms in the SARS-CoV-2 epidemic? *Neurologia* 2020;35:170–175.
157. Girgis RR, Ciarleglio A, Choo T, *et al.*: A randomized, double-blind, placebo-controlled clinical trial of tocilizumab, an interleukin-6 receptor antibody, for residual symptoms in schizophrenia. *Neuropsychopharmacology* 2018;43:1317–1323.
158. Lisco A, Vanpouille C, Margolis L: Coinfecting viruses as determinants of HIV disease. *Curr HIV/AIDS Rep* 2009;6: 5–12.
159. Chen XP, Li GH, Tang XP, Xiong Y, Chen XJ, Cao Y: Lack of severe acute respiratory syndrome in 19 AIDS patients hospitalized together. *J Acquir Immune Defic Syndr* 2003;34:242–243.
160. Shalhoub S, AlZahrani A, Simhairi R, Mushtaq A: Successful recovery of MERS CoV pneumonia in a patient with acquired immunodeficiency syndrome: A case report. *J Clin Virol* 2015;62:69–71.
161. Guo W, Ming F, Dong Y, *et al.*: A survey for COVID-19 among HIV/AIDS patients in two districts of Wuhan, China. *SSRN Electron J* 2020.
162. Vizcarra P, Pérez-Elías MJ, Quereda C, *et al.*: Description of COVID-19 in HIV-infected individuals: A single centre, prospective cohort. *Lancet HIV* 2020;7:e554–e564.
163. Cao B, Wang Y, Wen D, *et al.*: A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. *N Engl J Med* 2020;382:1787–1799.
164. Cainelli F, Dzudzor B, Lanzafame M, Goushchi A, Chhem S, Vento S: HIV and SARS-coronavirus-2 epidemics: Possible interactions and need for studies, especially in Africa. *Front Med* 2020;7:216.

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