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Is There such a Thing as Post-Viral Depression?: Implications for Precision Medicine

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Abstract

Viral infections are increasingly recognized as triggers for depressive disorders, particularly following the SARS-CoV-2 pandemic and the rise of long COVID. Viruses such as Herpes Simplex Virus (HSV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), and Human Immunodeficiency Virus (HIV) are linked to depression through complex neurobiological mechanisms. These include immune system dysregulation, chronic inflammation, and neurotransmitter imbalances that affect brain function and mood regulation. Viral activation of the immune system leads to the release of pro-inflammatory cytokines, resulting in neuroinflammation and associated depressive symptoms. Furthermore, specific viruses can disrupt neurotransmitter systems, including serotonin, dopamine, and glutamate, all of which are essential for mood stabilization. The unique interactions of different viruses with these systems underscore the need for virus-specific therapeutic approaches. Current broad-spectrum treatments often overlook the precise neurobiological pathways involved in post-viral depression, reducing their efficacy. This review emphasizes the need to understand these virus-specific interactions to create tailored interventions that directly address the neurobiological effects induced by each type of virus. These interventions may include immunomodulatory treatments that target persistent inflammation, antiviral therapies to reduce the viral load, or neuroprotective strategies that restore neurotransmitter balance. Precision medicine offers promising avenues for the effective management of virus-induced depression, providing patient-specific approaches that address the specific biological mechanisms involved. By focusing on the development of these targeted treatments, this review aims to pave the way for a new era in psychiatric care that fully addresses the root causes of depression induced by viral infections.

Key Words: Viral infection, Depression, Mitochondria, Epigenetics, Neurotransmitter imbalance, Precision medicine

INTRODUCTION

Viral infections have long been associated with a variety of neuropsychiatric conditions, including depression. While the recent COVID-19 pandemic has highlighted the complex interplay between viral diseases and mental health through the phenomenon of Long COVID, this relationship extends beyond a single virus. Long COVID serves as a contemporary example, where individuals, even those with mild initial symptoms, continue to suffer from a range of persistent symptoms including significant psychiatric manifestations such as depression, cognitive derangement, and anxiety. However, the scope of our review extends beyond SARS-CoV-2 to explore the broader implications of various viral infections on mental health. Preclinical and clinical studies regarding the SARS-CoV-2-induced depression as well as its mechanism, are still ongoing. Many reviews cover this issue, and interested readers may consult those works (Leung *et al*., 2022; Premraj *et*

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al., 2022; Zürcher *et al*., 2022).

Multiple studies over decades on different viruses such as herpesvirus, human immunodeficiency virus, cytomegalovirus (CMV), influenza virus, and hepatitis virus have indicated that viral infections can trigger a cascade of physiological, immune, and inflammatory responses, potentially impacting mood and mental health. Such responses include inflammation, neurotransmitter system imbalances, and stress responses, which collectively contribute to the onset of depressive symptoms. Direct viral effects on brain and psychosocial factors also play significant roles. Interestingly, the specific pathogenesis of virus-induced depression may vary significantly between different viruses, suggesting unique virus-specific mechanisms at play.

For instance, research has shown that individuals recovering from some virus like hepatitis C virus (HCV) infection have a notably higher likelihood of developing psychiatric problems, while others have lower probability to induce psychiatric complications. Furthermore, conditions like Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), often linked with various viral infections, underline the potential role of viruses in chronic psychiatric and fatigue syndromes.

The diversity in viral impact on mental health underscores the necessity of a nuanced understanding of the mechanisms through which these infections influence the brain and mood. Such understanding not only promises better control over psychiatric health post-infection but also opens up avenues for developing targeted therapeutic interventions. These interventions are particularly crucial given that a substantial portion of patients do not adequately respond to existing treatments. This review aims to dissect the complex relationships between various viral infections and depression, identifying potential points of intervention that could lead to more effective management of this debilitating condition.

AN OLD CONCERN RAISED BY LONG COVID: THE RELATIONSHIP BETWEEN VIRAL INFECTION AND MENTAL HEALTH, SPECIFICALLY DEPRESSION

Long COVID, also called post-acute sequelae of SARS-CoV-2 infection (PASC), describes a condition where individuals continue to experience a range of symptoms even after recovering from the acute phase of COVID-19, the disease caused by the SARS-CoV-2 virus. Although most people recover from COVID-19 within a few weeks, some, including those who had mild cases, may continue to suffer from persistent and debilitating symptoms for several weeks or even months following their initial infection.

Psychiatric symptoms like depression, unstable mood, social difficulties, cognitive impairment, PTSD, and anxiety form a significant spectrum of symptoms experienced by some individuals suffering from long COVID (Fig. 1) (Schou *et al*., 2021; Leung *et al*., 2022; Lier *et al*., 2022; Premraj *et al*., 2022; Zürcher *et al*., 2022). The COVID-19 Mental Disorders Collaborators noted a significant rise in mental disorders during the pandemic, which may relate to both the infection itself and the associated immobility (COVID-19 Mental Disorders Collaborators, 2021). They estimated 53.2 million new cases of major depressive disorder (MDD) and 76.2 million new cases of anxiety disorders globally in 2020. Other studies observed increased depression prevalence across different age groups, from younger generations to older populations (Beharry, 2022; Silva *et al*., 2023). Conversely, preexisting mental health conditions have been associated with worse COVID-19 outcomes, including higher hospitalization rates and mortality (Ceban *et al*., 2021; Fond *et al*., 2021; Ranger *et al*., 2023). Brain imaging studies reveal structural and functional brain and neural network changes. Direct infection-induced pathological changes, such as blood-brain barrier (BBB) breakdown, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and modulation of neurobiological factors like BDNF and indoleamine 2,3-dioxygenase (IDO-1) (Lorkiewicz and Waszkiewicz, 2021; Kucukkarapinar *et al*., 2022), may contribute to depression post-COVID-19. Moreover, indirect factors like elevated proinflammatory cytokines, stress, and gut-brain axis dysregulation have also been implicated in the heightened prevalence of depression following SARS-CoV-2 infection (Peron, 2023; Zhu *et al*., 2023).

While the physical, psychological, and social consequences of COVID-19—including severe illness, hospitalization, bereavement, financial difficulties, and social isolation—can certainly contribute to depression in affected individuals, research indicates a broader relationship between viral infections and depression. However, the precise mechanisms remain complex and not fully understood. Viral infections can activate physiological, immune, and inflammatory responses that significantly influence mood and mental health. These physiological factors include inflammation, neurotransmitter system imbalances, and stress responses. Various viruses, like herpesvirus, human immunodeficiency virus, CMV, influenza virus, and hepatitis virus, can disrupt these processes (Miller *et al*., 2005; Phillips *et al*., 2008; Pratt *et al*., 2012; Simanek *et al*., 2014; Slavuljica *et al*., 2015).

Interestingly, the mechanisms of virus-induced depression vary among different viruses, indicating virus-specific pathways that lead to depressive symptoms. For instance, individuals recovering from HCV are more prone to depression and other psychiatric conditions, with prevalence rates 1.5 to 4.0 times higher than the general population, reaching about 50% (Adinolfi *et al*., 2015). However, this association is less pronounced for Hepatitis B. Moreover, clearing HCV with antiviral treatment has been linked to improvements in depression and overall quality of life (Fletcher and McKeating, 2012).

ME/CFS, often associated with post-viral fatigue syndromes, presents symptoms like depression and is linked to viral infections (Hwang *et al*., 2023). These infections include DNA, RNA, and retroviruses, emphasizing the potential impact of these infections in developing ME/CFS. The odds ratios of viral infections among ME/CFS patients compared to healthy controls demonstrate a notable association, especially for viruses like parvovirus B19 and coxsackie B viruses, which seem to significantly increase the risk of ME/CFS. This condition often includes symptoms of depression and chronic fatigue.

Patients with depression or under stress are not only susceptible to depression induced by viral infection, but are also at a higher risk of viral infection itself. This vulnerability can further influence the prognosis and pathological consequences of viral infections (Gharbawy *et al*., 2012; Nami *et al*., 2020; Ayling *et al*., 2022). These findings indicate a reciprocal relationship between depression and viral infections, emphasizing the critical importance of understanding the molecular mechanisms underlying these interactions to devise advanced meth-

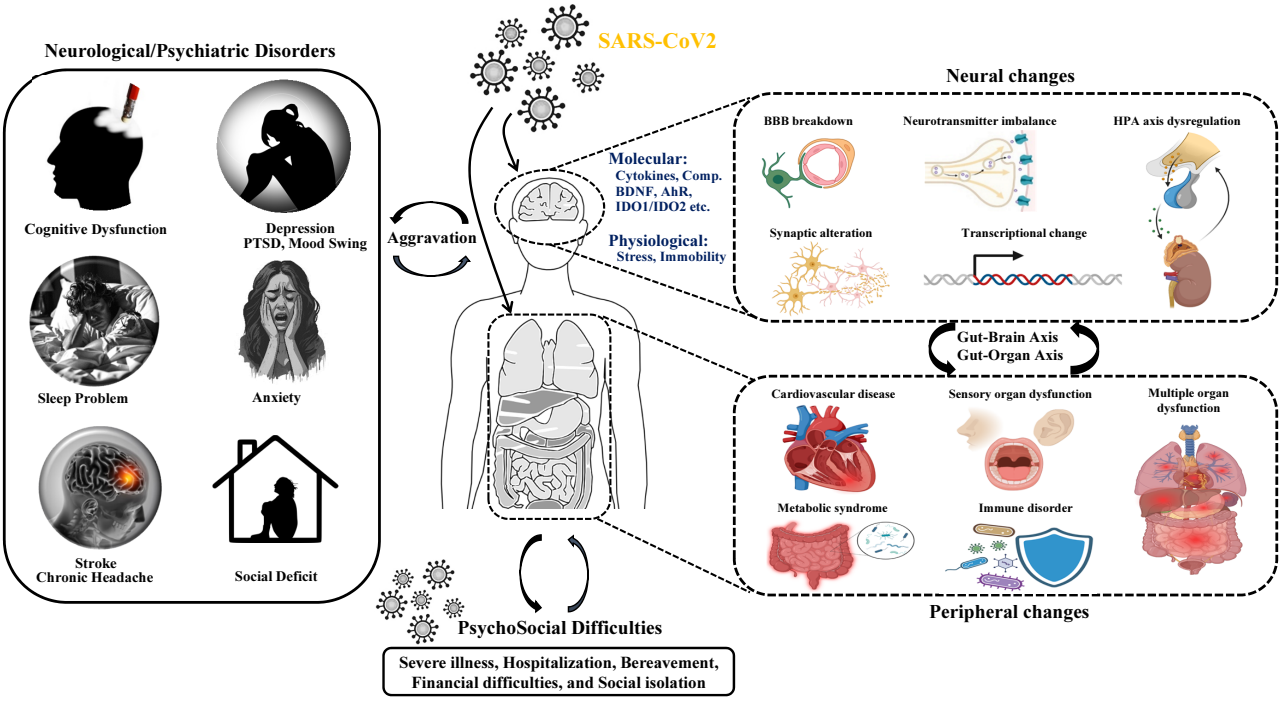

Fig. 1. SARS-CoV-2 infection induces neurological and psychiatric sequelae. SARS-CoV-2 infection leads to a myriad of health problems ranging from cardiovascular diseases to psychiatric symptoms such as depression and cognitive dysfunction. The direct and indirect activation of the immune system in the CNS, as well as the dysregulation of target proteins related to the modulation of neural function (underlying depressive behaviors), such as cytokines, complements, BDNF, AhR (aryl hydrocarbon receptor), IDO1, IDO2, and others, induce neural changes such as BBB breakdown and neurotransmitter imbalance. SARS-CoV-2-induced peripheral diseases and dysregulated physiology can also interact with the brain, further deteriorating its functional and structural integrity. Additionally, psychosocial difficulties encountered during SARS-CoV-2 infection, such as hospitalization and social isolation, may aggravate both central and peripheral defects. All these factors contribute to the manifestation and worsening of neurological and neuropsychiatric adversities. In turn, neurological conditions may also worsen the outcomes of SARS-CoV-2 infection. Figures were created with biorender.com (www.biorender.com).

ods for managing them effectively.

A deeper understanding of the relationship between viral infection and depression can offer improved strategies to manage psychiatric health following viral infections. It may also reveal new therapeutic targets to tackle this challenging neuropsychiatric condition, which remains resistant to existing medications in at least 30% of patients (Fava and Davidson, 1996; Souery *et al*., 2006; Souery, 2023). The pandemic-induced awareness of the association of viral infection with mental health necessitates the investigation of the relationship between specific viral infections and the manifestation of depression as well as the molecular mechanism underlying it, highlighting potential points of intervention for more effective management.

PROMINENT VIRAL MEMBERS RELATED TO THE MANIFESTATION AND PATHOPHYSIOLOGY OF DEPRESSION

Several viral infections have been linked to a heightened risk of developing depression or depressive symptoms, as well as other psychiatric complications (Collins *et al*., 2021; Wouk *et al*., 2021; Büttiker *et al*., 2022; Stefano *et al*., 2022). The following viral members have been particularly implicated in depression.

Herpesviruses

This group of viruses can cause various diseases, including oral and genital herpes, chickenpox (varicella-zoster virus), and shingles (herpes zoster). Herpes simplex virus (HSV) and Epstein-Barr virus (EBV) have been linked to an increased risk of depression (Allen and Tilkian, 1986; Wang *et al*., 2014; Gale *et al*., 2018; Ye *et al*., 2020; Vindegaard *et al*., 2021; Lu *et al*., 2022). However, a Finnish study with an 11-year follow-up found no association between herpes viruses (HSV-1, CMV, EBV) and newly onset depression (Markkula *et al*., 2020), and no difference in serum antibody levels against HSV-1 and HSV-2 in depressed patients (Amsterdam and Hernz, 1993).

HSV-2 infection and possibly CMV infection, but not HSV-1 infection, have been associated with a higher risk of depression in U.S. adults (Gale *et al*., 2018). Regarding general MDD prevalence, females are at a higher risk of depression associated with HSV-2 infection (Lu *et al*., 2023). Conversely, Ye *et al*. (2020) used individual genotypic and phenotypic data from the UK Biobank and found that HSV-1 infection, along with genetic factors, significantly increases the risk of depression.

Emerging evidence suggests that viral infections, such as those caused by human herpesvirus 6 (HHV-6), have been linked to viral infection-associated infertility, is reported to be associated with depression in children (Bayturan *et al*., 2022). HHV-6 sero-positivity, determined by antibody levels, was significantly higher in patients with depression, especially those

exhibiting suicidal ideation, compared to non-suicidal counterparts. This suggests a connection between persistent HHV-6 infections and depressive symptoms, particularly with the etiology of suicidal ideation in childhood depressive disorder (Bayturan *et al*., 2022). Furthermore, HHV-6B has been implicated in disrupting the HPA axis, a key regulator of the stress response, which may raise the risk of depression (Kobayashi *et al*., 2020).

SULF2 is one of the genetic loci most strongly implicated in the association between viral infection and depression. The SULF2 gene encodes an extracellular sulfatase that modulates the structure of heparin sulfate proteoglycans (HSPGs), which are essential for regulating a range of signaling pathways involved in neural development and neuroimmune interactions. HSPGs play a critical role in synaptic organization, axonal guidance, and neurotransmitter receptor function, particularly within the glutamatergic system (Ye *et al*., 2020). In the context of viral-triggered depression, it has been hypothesized that persistent viral infections may influence SULF2 expression or function, thereby altering neurotransmitter receptor-ligand interactions. Specifically, disruptions in glutamate receptor signaling, such as N-methyl-D-aspartate (NMDA) receptor dysregulation, could contribute to the neuropsychiatric symptoms observed in affected individuals. NMDA receptors have been implicated in the pathophysiology and treatment of depression. Notably, autoantibodies against NMDA receptors have been detected in individuals with viral infections, such as varicella-zoster virus, and are associated with NMDA receptor encephalitis, an autoimmune condition characterized by psychiatric and neurological symptoms (Solís *et al*., 2016; Fatma *et al*., 2022; Narasimhappa *et al*., 2024). Although a direct relationship between viral infections and NMDA receptor dysregulation in depression has yet to be conclusively established, the presence of such autoantibodies suggests that viral infection-induced immune responses may contribute to NMDA receptor-mediated neurotoxicity. This may result in excitotoxic damage to neural circuits involved in mood regulation and cognitive dysfunction. And disruption of HPA axis function, as observed in HHV-6 infections, can exacerbate neuroinflammation and contribute to glutamatergic dysregulation through increased glucocorticoid release, which is known to modulate NMDA receptor function. This can lead to overactivation of NMDA receptors, causing excitotoxicity and neuronal damage, thereby exacerbating depressive symptoms, particulary in individuals with pre-existing vulnerabilities related to SULF2-mediated neural development pathways.

Individuals with a history of herpes zoster infection have been found to have a higher risk of developing depression, anxiety, and sleep disorders compared to those without a history of herpes zoster. It is speculated that the inflammatory response triggered by herpes zoster infection could contribute to the development of psychiatric symptoms. A longitudinal study tracking patients from 2000 to the end of 2010 provided strong evidence indicating an almost twofold increase in depression prevalence among people infected with varicella-zoster virus (Chen *et al*., 2014).

Conversely, MDD in elderly adults is linked to a weakened immune response to the varicella-zoster virus (VZV), which might explain the increased risk and severity of herpes zoster in this age group (Irwin *et al*., 2011). The study showed that VZV-specific cell-mediated immunity (CMI), which declines with age, inversely correlates with the severity of depressive symptoms (Irwin *et al*., 2011). Interestingly, antidepressant treatment is linked to higher VZV-CMI levels, suggesting potential therapeutic benefits against decreased VZV immunity in this population (Irwin *et al*., 2011). It was also reported an increased prevalence of herpes zoster in depressed patients, particularly those aged 45 to 54 and those with physical and psychiatric comorbidities (Liao *et al*., 2015). This finding was later confirmed in the Korean population (Choi *et al*., 2019).

Infectious mononucleosis, often caused by EBV and characterized by symptoms like sore throat, fever, rash, swollen spleen and liver, and persistent fatigue, has been linked to a 40% higher hazard ratio (HR) for a future depression diagnosis (Vindegaard *et al*., 2021). Although the precise mechanism is unclear, it's hypothesized that EBV infection may activate autoreactive B and T cells, leading to inflammatory responses that directly attack neurons expressing NMDA receptors or trigger autoantibody reactions that disrupt nervous system functioning. The production of cytokines like interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor (TNF) may play a pivotal role in this process (Pender, 2020).

Herpes viruses can establish latent (dormant) infections in the body, reactivating during periods of stress or immunosuppression, which may affect mood and mental health. A study conducted in Japan found that psychological distress was significantly associated with EBV serological reactivation in women but not in men. In this research, EBV reactivation was independently linked to psychological distress in older women living in the community (Yamanashi *et al*., 2022).

Additionally, it was reported that maternal depressive symptoms in early or late pregnancy were significantly associated with EBV reactivation, potentially mediated by increased stress levels (Haeri *et al*., 2011; Zhu *et al*., 2013).

Several studies have indicated cognitive decline in individuals with herpesvirus infections, regardless of their psychiatric comorbidities like schizophrenia (Thomas *et al*., 2013; Watson *et al*., 2013). Impairments in cognitive functions include abstraction accuracy, mental flexibility, attention, spatial memory, spatial processing and speed, emotional processing, and sensorimotor dexterity. HSV has also recently been associated with the development of Alzheimer's disease. It is hypothesized that recurrent cycles of HSV-1 latency and reactivation could lead to aberrant neuroinflammatory responses and synaptic dysfunction as people age, eventually resulting in pathological changes in synapses and vulnerable brain regions reminiscent of Alzheimer's disease (Piacentini *et al*., 2015; Duarte *et al*., 2019; Mangold and Szpara, 2019; Yong *et al*., 2021; Feng *et al*., 2023; De Francesco, 2024).

It has been suggested that depressive symptoms increase the risk of morbidity and mortality in patients with coronary artery disease, which could be related to increased immune reactivity and vulnerability to viral infections such as CMV, HSV and EBV (Miller *et al*., 2005). In the study, patients in the highest tertile of depressive symptoms had C-reactive protein levels more than 50% higher than other groups and showed twice the evidence of infection with all 3 latent viruses (Miller *et al*., 2005).

Cytomegalovirus (CMV)

CMV is a type of herpes virus commonly infecting the general population that can cause a range of symptoms, from mild to severe, especially in people with weakened immune systems or during certain stages of pregnancy, and can remain

dormant in the body. Some studies have shown a potential association between CMV infection and an increased risk of depression as well as schizophrenia (Gale *et al*., 2018; Frye *et al*., 2019; Ford and Savitz, 2023; Zheng and Savitz, 2023), although more research is needed to understand this relationship.

In a study using blood and dorsolateral prefrontal cortex (DLPFC) postmortem samples to check the presence of anti-CMV antibodies, neuroinflammation, mental illness-related changes in gene expression profiles, as well as microglial density and activation status, sero-positivity against CMV was associated with mood disorders like bipolar disorders and major depression (bipolar disorder: odds ratio [OR]=2.45; major depression: OR=3.70), suicide, elevated markers of neuroinflammation, and microglia activation (Zheng *et al*., 2023). A similar association of sero-positivity against CMV and bipolar disorder has also been reported (Frye *et al*., 2019).

Interestingly, people with higher CMV antibody titers showed a "higher" inflammatory gene expression profile as well as an increased ratio of non-ramified (activated) to ramified (dormant) microglia in the DLPFC, especially in layer 1 (Zheng *et al*., 2023). To examine the persistent pathogenic burdens and incident depression among the older generation, a longitudinal study was performed (Simanek *et al*., 2019). Among several persistent pathogens such as CMV, HSV, Varicella zoster, Helicobacter pylori, and Toxoplasma gondii, only having antibodies against CMV was statistically significantly associated with increased odds of incident depression (OR: 1.38, 95% confidence interval [CI]: 1.00-1.90), which was more prominent in women (OR: 1.70, 95% CI: 1.01-2.86). This linkage was not attributed to the general inflammatory status, as evidenced by the examination of C-reactive protein (CRP) or IL-6 levels (Simanek *et al*., 2019).

Human Immunodeficiency Virus (HIV)

HIV attacks the immune system and can lead to acquired immunodeficiency syndrome (AIDS). HIV has been associated with an increased risk of depression, likely due to the physical, emotional, and social challenges associated with the infection and its impact on the nervous system.

It is fairly common for people with HIV infection to suffer from depression (Ayano *et al*., 2018; Lu *et al*., 2019; Fabrazzo *et al*., 2023). Research indicates a prevalence rate between 11.40 to 45.83% among adolescent with HIV infection/AIDS (for a review see, (Ayano *et al*., 2021)). In their systemic meta-analysis, Ayano *et al*. (2021) suggested that among adolescents with HIV/AIDS, the pooled prevalence estimate for depression stood at 26.07% (95% CI 18.92-34.78) with significant heterogeneity among the studies. Interestingly, females exhibited a higher prevalence of depression (32.15%) compared to males (25.07%), which follows prevalence trends in the general population. Additionally, older adolescents (15-19 years) demonstrated a higher depression prevalence (37.09%) than their younger counterparts (10-14 years) (29.82%). Similarly, a meta-analysis suggested a prevalence rate of 31 % among infected individuals in total (Rezaei *et al*., 2019).

Sustained depression may induce suicidal ideation, and a recent meta-analysis reported that around a quarter of young individuals with HIV/AIDS experienced lifetime suicidal ideation with more than one in ten having current suicidal thoughts. A significant portion of young people with HIV/AIDS reported current (3.75%), 6-month (15.33%), and lifetime (13.05%) suicidal attempts (Tsegay and Ayano, 2020).

In addition to the HIV's impact on immune function, HIV-positive adolescents' vulnerability to stigma, discrimination, and social marginalization as well as higher rates of other mental disorders intensifies their depression risk compared to the general population (Vreeman *et al*., 2017; Kimera *et al*., 2020).

Using the COmorBidity in Relation to AIDS (COBRA) cohort, it has been suggested that MIG and TNF-α in plasma and MIP1-α and IL-6 in CSF are key factors mediating the association between HIV and depressive symptoms (Mudra Rakshasa-Loots *et al*., 2023). The authors did not find an association of other soluble or neuroimaging biomarkers, such as MRI, with depression.

In a prospective longitudinal study conducted in Shenzhen, China, with 247 ambulatory people living with HIV (PLWH) using antiretroviral therapy, an increase in CD4+ T cells over time may not be associated with the sleep quality, depression, and anxiety of PLWH. However, a decrease in CD4+ T cells over time is accompanied by a deterioration of sleep quality and an increase in depression and anxiety in a small proportion of PLWH (11.9%) (Shi *et al*., 2020).

It is also important to note that antiretrovirals, especially older ones, have been linked to neuropsychiatric side effects, including depression. For instance, efavirenz, a commonly used medication, has been associated with psychotropic effects (Zareifopoulos *et al*., 2020a) and higher rates of neuropsychiatric side effects, including mood disturbances and depression (Dalwadi *et al*., 2018; Zareifopoulos *et al*., 2020b), which can also be induced in experimental animals (Cavalcante *et al*., 2017). Although the neuropsychiatric adverse events are still controversial (Li *et al*., 2021a) and are transient nature in most cases, they can be persistent even after the cessation of the treatment.

Similarly, nucleoside reverse transcriptase inhibitors (NRTIs), have been linked to mitochondrial toxicity. NRTIs, such as zidovudine (AZT) or stavudine (d4T), can interfere with the function of the mitochondria by inhibiting enzymes involved in mitochondrial DNA replication. This disruption can lead to mitochondrial dysfunction, affecting energy production and potentially causing various side effects like muscle weakness, neuropathy, or lactic acidosis (Barlow-Mosha *et al*., 2013). Children or adolescents with vertical transmission might have an increased risk of psychiatric complications because they can take NRTIs for a longer period, affecting their mitochondrial function.

Influenza virus

Influenza is a respiratory infection that can cause severe illness in some individuals. Studies have indicated a potential link between influenza infection and an increased risk of depression, though the mechanisms remain unclear.

In an observational case-control study conducted between 2000 and 2013, using the large UK-based Clinical Practice Research Datalink (CPRD), which included 103,307 patients diagnosed with depression, researchers found that influenza infections were linked to a moderately increased risk of developing depression (Bornand *et al*., 2016). Patients with a history of influenza infection were at higher risk of developing depression (OR 1.30, 95% CI 1.25-1.34) than those without such a history. The study also suggested that recent and repeated influenza infections slightly increased the odds of developing

depression (Bornand *et al*., 2016). For instance, viral infections occurring 30-180 days before the depression diagnosis had a higher OR than infections recorded a year earlier.

In a study investigating the neurological and neuropsychiatric effects of post-acute SARS-CoV-2 infection (neuro-PASC), anxiety disorders (affecting 30% of neuro-PASC patients) and depression (affecting 27%) were the most prevalent, similar to findings in the flu cohort (Iosifescu *et al*., 2022). Another study linked influenza infection with heightened brain inflammation, particularly in microglia, and alterations in glutamatergic neurotransmission in the brains of mice, which may lead to impaired brain function and depressive-like behaviors (Düsedau *et al*., 2021). The research indicated that the immune response of the central nervous system (CNS) might play a role in the development of depressive symptoms following influenza infection. The study suggested that the CNS's immune response to influenza infection, particularly involving glial cells such as microglia and oligodendrocytes, may contribute to the onset of depressive symptoms.

Recently, researchers injected PB1-F2, a key virulence molecule from various influenza virus strains, directly into the hippocampal dentate gyrus of mice. This caused depressive-like behavioral phenotypes and disrupted oligodendrocyte development and neural plasticity, providing insight into the cellular and molecular mechanisms underlying post-influenza infection-induced depression (Wang *et al*., 2024c). However, a prospective study with 400 influenza-infected patients found no correlation between depression and antibody titers against influenza (Sinanan and Hillary, 1981). Similarly, a meta-analysis of published articles concluded that depression did not affect the likelihood of influenza infection (Gharbawy *et al*., 2012).

Hepatitis B virus (HBV)

Hepatitis B virus (HBV) primarily affects the liver and can cause inflammation and liver damage over time. Direct evidence linking HBV infection with depression is relatively sparse. However, some studies suggest that individuals with chronic HBV infection might have an increased risk of developing depressive symptoms, likely due to the physical, emotional, and social challenges related to the infection. Chronic hepatitis B can lead to persistent liver inflammation, which may contribute to systemic inflammation and affect mood and mental health.

In the broader context of chronic liver diseases, including HBV, there is a significant association with depression. Studies across various chronic liver conditions, such as non-alcoholic fatty liver disease and chronic hepatitis C (in addition to HBV), consistently show higher rates of depression among patients. These associations highlight the complex interplay between liver disease pathology, involving inflammation and immune response dysregulation, and the development of depressive symptoms (Huang *et al*., 2017).

A study conducted in southern China examined the association between HBV infection and postpartum depression (PPD) among mothers. This research included 3,808 participants and used the Edinburgh Postnatal Depression Scale (EPDS) to assess PPD. The findings indicated that women with HBV infection were more likely to test positive for PPD, but the difference was not statistically significant after controlling for other variables. This suggests that in this population, HBV infection alone did not significantly increase the risk of PPD (Huang *et al*., 2023).

A systematic review examined the bidirectional relationship between HBV infection and comorbid mental health conditions, such as depression and anxiety. The review suggests that shared biological mechanisms could underlie these associations. It highlighted the role of neuroinflammation, cytokine production, and dysregulation of the HPA axis in influencing HBV infection outcomes and mood disorder symptoms (Fabrazzo *et al*., 2023). These findings suggest that the physiological effects of HBV could potentially exacerbate or contribute to mental health problems (Fabrazzo *et al*., 2023).

A study using a large patient database from Taiwan found that patients with HBV and comorbid depression or anxiety experienced significantly higher rates of hepatitis B flares compared to those without these mental health conditions (Tsai *et al*., 2022). This indicates a potential interaction where mental health disorders may impact the clinical progression of HBV, possibly through mechanisms related to stress and immune function.

Hepatitis C virus (HCV)

The relationship between HCV infection and depression is well-documented, with many HCV patients experiencing depressive symptoms (Fletcher and McKeating, 2012; Adinolfi *et al*., 2015). Chronic hepatitis C is a global health issue, affecting millions worldwide, and is the leading cause of liver-related morbidity and mortality in developed countries. Studies have shown a high prevalence of depression among patients with chronic hepatitis C. For instance, one study found that 28% of chronic hepatitis C patients experienced current depressive disorders, more closely linked to the severity of fatigue than liver disease (Dwight *et al*., 2000). Another study with HCV-infected veterans reported that these patients were more likely to have depressive disorders than controls (49.5% vs. 39.1%) (el-Serag *et al*., 2002). Depression in chronic hepatitis C patients has been shown to worsen the illness, increasing physical symptoms, impairing function, and reducing treatment compliance and quality of life.

HCV is believed to interact with endothelial cells in the brain (Fletcher *et al*., 2012). More recently, it has been associated not only with psychiatric symptoms but also with neurodegenerative conditions such as Parkinson's disease and cognitive impairment (Amendola-Pires *et al*., 2023; Yaow *et al*., 2023). The association between depression and liver diseases like HCV, HBV, and chronic alcoholic liver disease suggests that liver function plays a significant role in the manifestation of depression (Huang *et al*., 2017). Dysregulated liver function is also crucial in HCV-induced cognitive impairment (Amendola-Pires *et al*., 2023).

Sickness behavior and depression can be confused, especially in post-viral contexts, due to overlapping behavioral and physical symptoms. The severity of sickness behaviors is largely determined by the extent of inflammatory responses, exemplified by cytokine levels in the blood (Vollmer-Conna *et al*., 2004). Both conditions can involve fatigue, reduced activity, and changes in sleep or appetite. However, they have important differences. In terms of duration and context, sickness behavior is temporary, occurring in acute illness contexts, and resolves as the individual recovers. Depression, in contrast, is persistent, lasting well beyond any physical illness. Regarding symptoms, sickness behavior primarily involves physical and behavioral changes, while depression includes emotional and

cognitive symptoms, such as persistent sadness, hopelessness, and negative self-perception (Maes *et al*., 2012).

Sickness behavior is the body's response to illness, aiming to conserve energy and promote recovery through reduced activity and increased sleep. Depression, however, involves more complex interactions among biological, psychological, and social factors. It affects neuroinflammation, neural transmission, and neural plasticity, requiring active intervention unlike sickness behavior.

A recent special issue of Frontiers in Psychiatry explored the multifaceted nature of sickness behavior as a neurobehavioral consequence of infection. It emphasizes the adaptive aspects of sickness behavior in acute illness but points out that in chronic conditions, these behaviors can become maladaptive and contribute to disease symptoms, resembling depressive states (Kelley and Kent, 2020; Konsman, 2021; Rademacher *et al*., 2021).

Understanding the mechanisms behind MDD following viral infections is crucial. It helps differentiate between sickness behavior and depression for accurate diagnosis and guides tailored treatment and management strategies.

MECHANISM OF VIRAL INFECTION-INDUCED DEPRESSION

Immune imbalance

Viral infections can initiate immune responses that may lead to immune imbalance and inflammation, which can impact the brain and CNS, potentially increasing the risk of developing depression. Although inflammation is a natural defense mechanism, chronic or excessive inflammation may cause immune imbalances that impair brain function. Persistent inflammation and oxidative stress have been linked to depression, as these conditions disrupt normal brain activity and neurotransmission.

The immune response to viral infections starts with the detection of the virus by pathogen recognition receptors (PRRs), such as Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs). These receptors recognize and bind to pathogen-associated molecular patterns (PAMPs), which are unique to viruses, thus triggering an antiviral defense system (Kircheis and Planz, 2023). A key part of this system is the production of interferons, particularly Type I (IFN-α/β) and Type III interferons, which are crucial for controlling viral replication (Mertowska *et al*., 2023; Mihaescu *et al*., 2023). After initial recognition and signaling events, a robust production of cytokines and chemokines occurs, orchestrating further immune responses in various immune cells and target tissues. However, this response can become dysregulated, leading to an excessive or compromised immune response.

Many viruses have evolved ingenious ways to evade host immune systems, resulting in chronic inflammation. Chronic inflammation after viral infection can sustain pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β, contributing to tissue damage and systemic effects that can influence mood and behavior by disrupting neurotransmitter metabolism and signaling pathways. Uncontrolled systemic inflammation can affect the CNS by increasing the permeability of the BBB, allowing inflammatory cytokines and activated immune cells to infiltrate the brain. This infiltration can activate microglia, the resident immune cells of the CNS. While microglia are crucial for maintaining neuronal health, they can also contribute to neuroinflammation and neuronal damage under pathological conditions. Persistent microglial activation has been linked to the production of neurotoxic factors and reactive oxygen species, which can lead to depressive symptoms by disrupting neuronal circuits involved in mood regulation.

Cytokines elevated during chronic inflammation, such as IL-6, TNF-α, and CRP, can cross the BBB and influence brain function. They do so by altering neurotransmitter metabolism, affecting neural plasticity, and modulating neuroendocrine function. For instance, increased IL-6 levels have been correlated with depressive behavior in clinical populations. IL-6 can stimulate the HPA axis, leading to increased cortisol levels, which are often observed in depressed patients. Chronic activation of the HPA axis can lead to several behavioral and physiological alterations associated with depression (Anisman *et al*., 1999; Karlović *et al*., 2012; Lamers *et al*., 2013). Meta-analyses and systematic reviews support the hypothesis that inflammation plays a pivotal role in at least a subset of individuals with depression, particularly those with treatment-resistant forms of the disorder (Bai *et al*., 2020).

There is a plethora of research reports on the clinical changes in inflammation and depressive status in virus-infected individuals. Research has shown that patients recovering from severe influenza sometimes experience persistent mood changes, with elevated levels of cytokines like IL-6 and TNF-α in patients weeks after recovery, correlating with reports of fatigue and depressive symptoms (Taquet *et al*., 2022; Min *et al*., 2023; Chang *et al*., 2024). Increased depression rates among adolescents with HIV might stem from HIV's impact on immunity, lowering CD4 counts and increasing the possibility of opportunistic infection, which may contribute to the increased depression risk (Kaharuza *et al*., 2006; Tesfaw *et al*., 2016; Ayano *et al*., 2018). Epidemiological studies, serological studies, postmortem studies, and neuroimaging studies all suggest the link between peripheral and central inflammation with the neurological, psychiatric and neurodegenerative disorders in the condition of viral infection such as HSV-1, CMV, HIV as well as SARS-CoV-2 (Miller *et al*., 2005; Hellmuth *et al*., 2017; Lu *et al*., 2019; Ellis *et al*., 2020; Yong *et al*., 2021; Lu *et al*., 2022; Fabrazzo *et al*., 2023; Feng *et al*., 2023; Ford and Savitz, 2023; Mudra Rakshasa-Loots *et al*., 2023; Zheng *et al*., 2023). It should also be remembered that viral infections can disrupt the balance of cytokines. Imbalances in cytokines, such as increased levels of pro-inflammatory cytokines, and decreased levels of anti-inflammatory cytokines, which can affect brain function and mood, potentially contributing to the development of depression. For example, HSV infection perturbs cytokine profiles in the patients' blood, which can be affected by the disease progression. The primary infection and reactivation of the latent infection evoke an immune response by modulating the activities of macrophages, CD4+ and CD8+ lymphocytes (Hukkanen *et al*., 2002), which mostly involves a proinflammatory Th1 response but also a Th2 response as well (Hukkanen *et al*., 2002). It has been suggested that an imbalance in cytokine profile and immune responses may be related to the dysregulation of HPA axis, neuroinflammation in cells like microglia, BDNF and other neurotrophic factor production, and abnormal regulation of quinolinic and kynurenic acid metabolic pathways, which play a crucial role in mood regulation (Fabrazzo *et al*., 2023).

Altered stress state and stress response (HPA axis)

Viral infections can impact the body's stress response, which can potentially contribute to the development of depression. The HPA axis, involving the hypothalamus, pituitary gland, and adrenal glands, is a major neuroendocrine system that controls reactions to stress and regulates many body processes, including digestion, the immune system, mood and emotions, sexuality, and energy storage and expenditure. It involves the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which in turn stimulates cortisol release from the adrenal glands.

Viral infections can activate the HPA axis, leading to an increase in the production of stress hormones, such as cortisol. Prolonged activation of the HPA axis due to infections, uncontrollable social and physical stresses, and resulting elevated cortisol levels can disrupt normal brain function, affect mood regulation, and potentially contribute to the development of depression. Cytokines elicited during the immune response to viruses, particularly IL-1 and IL-6, can enhance the hypothalamic secretion of CRH, leading to an overactive HPA axis and elevated cortisol levels, which are often observed in depression (Turk *et al*., 2022; Leng *et al*., 2023). Not only during the active infection period but also during the latent phase of infection of some viruses, such as human herpesvirus 6B (HHV-6B), the HPA axis can be activated, which eventually contributing to the manifestation of depression (Kobayashi *et al*., 2020). During the latent period, HHV-6B can invade olfactory astrocytes and express SITH-1, an HHV-6B latent protein which may induce olfactory bulb apoptosis and activation of HPA axis (Kobayashi *et al*., 2020). Prolonged high levels of cortisol can lead to various health problems, including MDD. Postviral states may exacerbate this through sustained inflammation and immune activation, as seen after viral infections such as COVID-19, SARS and MERS.

Besides CRH, arginine vasopressin (AVP) from the hypothalamus plays a crucial role in stimulating ACTH in response to stress. Research has shown that infections can alter the secretion patterns of AVP and oxytocin, both of which can influence mood and social behavior (Jiang *et al*., 2023; Menke, 2024).

Viral infections can also impact the hypothalamic-pituitary-thyroid (HPT) axis, leading to changes in thyroid hormone levels, which are essential regulators of metabolism and mood. For example, non-thyroidal illness syndrome, characterized by low levels of triiodothyronine (T3) and thyroxine (T4) during systemic infections, including those caused by viruses, can contribute to mood dysregulation (Kjellman *et al*., 1993; Hickie *et al*., 1996; Premachandra *et al*., 2006; Kamyshna *et al*., 2022).

The physical symptoms and discomfort associated with viral infections can augment psychological stress, which may also contribute to an increased risk of depression. Another stress factor associated with viral infections is the deterioration of normal sleep architecture. Viral infections can disrupt normal sleep patterns, leading to sleep disturbances or sleep deprivation (Heeren *et al*., 2014; Morin *et al*., 2022). Sleep plays a crucial role in mood regulation and overall mental health, and disruptions in sleep can potentially contribute to the development of depression (Dollish *et al*., 2024).

Finally, viral infections may require individuals to isolate themselves or experience social distancing measures, which can lead to social isolation and interpersonal stress. Social isolation and interpersonal stress, both in preclinical and clinical studies, have been associated with an increased risk of depression (Zaletel *et al*., 2017), as social connections and support play an important role in mental health.

In conclusion, neuroendocrine disruption following viral infections presents a complex interplay between immune responses and hormonal regulation, which can significantly affect mental health. Understanding these pathways provides critical insights into the pathophysiology of postviral depression and highlights potential targets for therapeutic intervention.

Neurotransmitter imbalance

Viral infections can potentially affect catabolic and metabolic changes in the neurotransmitter system, affecting neurotransmitter concentration, relative concentrations of different neurotransmitters, as well as the pharmacodynamics of neurotransmitter receptors and regulatory proteins, which may contribute to the development of depression. This impact can occur not only through direct invasion of the CNS, oxidative stress, neuronal insults and inflammation but also indirectly through stress, peripheral inflammation and HPA-axis perturbation.

Viral infection-induced inflammation has been associated with reduced levels of serotonin after SARS-CoV-2 infection, a key neurotransmitter often associated with mood regulation (Wong *et al*., 2023). Lower serotonin levels have been linked to an increased risk of depression. It has been suggested that viral infection and type I interferon-driven inflammation reduce serotonin through three mechanisms such as diminished intestinal absorption of the serotonin precursor tryptophan, perturbed serotonin storage mechanisms via platelet hyperactivation and thrombocytopenia, and enhanced metabolism of serotonin by monoamine oxidase (MAO). Tryptophan is a critical precursor for serotonin synthesis. Reduced availability of tryptophan can impair serotonin production, leading to a higher risk of depression. Several studies have demonstrated that tryptophan depletion is associated with mood disturbances, emphasizing its role in maintaining emotional balance. Viral infections that reduce tryptophan absorption may thus exacerbate serotonin deficiency and contribute to depressive symptoms. The reduction in peripheral serotonin levels may disrupt vagus nerve activity and thereby impair hippocampal responses and cognitive function (Wong *et al*., 2023). Thrombocytopenia is a common sequela of HIV-infection and has been associated with reduced levels of BDNF and serotonin, which will lead to poor immune responses and depression-like symptoms (Míguez-Burbano *et al*., 2014). Altered tryptophan levels have also been reported in patients with HCV infection (Cozzi *et al*., 2006; Zignego *et al*., 2007). In patients with HCV infection, the immune response leads to the release of pro-inflammatory cytokines such as IFN-γ, which induces the activation of the IDO. This enzyme shifts tryptophan metabolism towards the kynurenine pathway, reducing the availability of tryptophan for serotonin synthesis in the brain. As a result, serotonin deficiency occurs, which is a well-established mechanism contributing to the development of depressive symptoms. Furthermore, neurotoxic metabolites of the kynurenine pathway, such as quinolinic acid, act as NMDA receptor agonists, leading to excitotoxicity. This excitotoxicity contributes to

neuroinflammation and neuronal damage, both of which are implicated in the pathophysiology of depression. Therefore, altered tryptophan metabolism due to immune activation in HCV infection may exacerbate serotonin depletion and contribute to the onset or worsening of depressive symptoms. Interestingly, rodent offspring born from dams infected with the human influenza virus showed decreased serotonin levels and signaling phenotypes in the brain without affecting dopamine levels (Winter *et al*., 2008; Moreno *et al*., 2011). Considering that serotonin is a precursor of melatonin, one of the key modulators of natural sleep, it is essential to determine whether post viral reduction of serotonin affects sleep architecture and thereby the clinical features of depression. However, the level of serotonin in the periphery can be regulated by multiple factors, including the specific strain of the virus, pathological windows, dietary patterns of patients, and so on; it should be interpreted and studied in the context of individual viral infection status. For example, long-term survivors of HIV infection show different patterns of serotonin and its metabolites in the blood, generally correlated with psychiatric symptoms, predictable from the role of each neurochemical entity (Vadaq *et al*., 2022).

In the case of HSV infection, it has been suggested that tryptophan hydroxylase 2 (TPH2), the neuronal specific rate-limiting enzyme for serotonin synthesis, is the most significantly upregulated gene by HSV, along with other metabolic enzymes and transporters for serotonin signaling. In the ocular system, HSV infection induces the upregulation of serotonin levels, which might be related to augmented viral replication and pathological consequences (Battaglia *et al*., 2022).

Viral infections can affect dopamine metabolism, which may affect pathological sequelae not only for psychiatric symptoms but also viral pathogenesis as well (McLaurin *et al*., 2021; Limanaqi *et al*., 2022). In chronically infected patients, CSF levels of dopamine and the expression level of tyrosine hydroxylase (TH) are decreased in the brains of those infected with HIV (Berger *et al*., 1994; Sardar *et al*., 1996; Silvers *et al*., 2006). In fact, the dopamine concentration in brain is almost consistently decreased in clinical and experimental animal samples, which might be involved in apathy/depression, attentive, and neurocognitive problems in people with chronic HIV infection (Saloner *et al*., 2020; McLaurin *et al*., 2021; Fu *et al*., 2023).

HIV viral TAT protein expression in the brains of mice decreased dopamine turnover in the caudate putamen while it increased serotonin turnover in the hippocampus and tended to increase the conversion of glutamate to glutamine in all regions (Kesby *et al*., 2016). HIV-1 Nef viral protein expression in the microglia of mice induced CCL2 expression together with a reduction of dopamine levels, MAO activity, and dopamine transporter (DAT) expression in the striatum of transgenic animals, resulting in hyperactive behaviors observed in mania and other psychiatric comorbidities common in HIV-infected persons (Acharjee *et al*., 2014).

Recent intriguing evidence suggests that SARS-CoV-2 may interfere immune responses via mechanisms involving the dysregulation of the dopamine system (Khalefah and Khalifah, 2020; Nataf, 2020; Nataf and Pays, 2021; Limanaqi *et al*., 2022). Viral infection may enhance viral entry and life cycle using DA receptors while inducing the downregulation of L-dopa-decarboxylase, the rate-limiting enzyme for converting L-DOPA to dopamine (Nataf and Pays, 2021). Direct injection of HSV-1 virus into the brain of mice resulted in the reduction of dopamine levels and an elevated ratio of homovanillic acid to dopamine without affecting norepinephrine or serotonin levels and their metabolites. Interestingly, the authors did not observe obvious cell death, suggesting the effects were not resulted from the nonspecific cellular damage (Seegal and McFarland, 1988).

In the case of other neurotransmitters, including glutamate, which has a direct association with the manifestation and maintenance of depressive symptoms, there are sparse reports regarding the effects of virus infection (Khoodoruth *et al*., 2022; Horowitz *et al*., 2023). Based on reduced glucose metabolism status evidenced by brain [18F]FDG-PET scans, it may be assumed that dysfunction of astrocytes, which play important roles in the modulation and coupling of brain energy metabolism, glutamatergic neurotransmission, and neuroinflammatory responses, may underlie the neurocognitive symptoms of COVID-19 (Horowitz *et al*., 2023). Whether glutamatergic abnormalities play a key or substantial role in this regard remains to be determined.

Viral infections can affect the expression and function of neurotransmitter receptors and transporters. HIV viral infection upregulates the expression of serotonin transporter in the brain, which may contribute to psychiatric adversity like depression (Shah *et al*., 2019), although another study suggested decreased SERT mRNA levels in the blood of sHIV-infected rhesus macaques (Yu *et al*., 2010). In patients with herpes simplex encephalitis, it has been reported that autoantibodies against NMDA receptor are observed, which might underlie the movement disorder and cognitive dysfunction associated with encephalitis (Prüss *et al*., 2012; Hacohen *et al*., 2014; Mohammad *et al*., 2014; Nosadini *et al*., 2017; Danilenko *et al*., 2022; Cleaver *et al*., 2024). Interestingly, patients with movement disorder symptoms showed detectible levels of NMDA receptor autoantibodies, and anti-immune treatments such as steroids, intravenous immunoglobulin, and cyclophosphamide all improved the behavioral symptoms along with a decrease in the titer of NMDA receptor autoantibodies (Mohammad *et al*., 2014). Considering the importance of NMDA receptors as a therapeutic target against depression, it remains to be determined whether this serves as a pathological mechanism underlying post-viral depression.

Among three groups of CFS/ME patients, namely with three different etiological factors such as Herpesviridae carriers (group V), stress (distress, group D), and the idiopathic (group I), group V had an elevated level of autoantibodies towards voltage-gated calcium channels, while group D had higher levels of dopamine-, glutamate- and GABA-receptor autoantibodies (Danilenko *et al*., 2022). Regarding autoimmunity after viral infection, it is interesting to note that the 5-HT(2A) receptor is upregulated and the mGlu (2) receptor is downregulated along with higher c-fos, egr-1, and egr-2 expression in response to the hallucinogenic drug, DOI, in the frontal cortex of mice born to influenza virus-infected mothers, suggesting autoimmune involvement in schizophrenia-like behavioral changes in prenatally influenza-virus exposed offspring (Moreno *et al*., 2011). Similarly, polyriboinosinic:polyribocytidylic acid (poly I:C) system, a synthetic double-stranded RNA often used in animal models of viral infection administered to pregnant mice, induced an abnormal number of serotonergic neurons and dysregulated serotonin content in the hippocampus, potentially leading to serotonergic dysfunction and autistic behaviors in offspring (Ohkawara *et al*., 2015).

Several viruses, such as HIV, Japanese encephalitis virus, and SARS-CoV-2, may utilize dopaminergic receptors to replicate in the nervous system as well as for viral neuropathogenesis. Co-binding of SARS-CoV-2 to angiotensin-converting enzyme 2 receptors on the surface of neuronal cells and to dopaminergic receptors on neighboring cells using the spike protein of the virus can accelerate its life cycle and exacerbate neurological symptoms. Considering the involvement of the dopaminergic system in regulating the immune-neuroendocrine system and the expression of dopamine receptors in most immune cells suggests that modulation of the dopaminergic system may play a crucial role in post-viral neural and neuro-immune perturbation (Rasmi *et al*., 2024).

Effects of viral infection on neural signaling and synapse

Viral infections, such as Influenza A virus (IAV) and HIV, have been linked to alterations in neurotransmission processes and synaptic function, potentially contributing to depressive-like behaviors. Studies have shown that IAV infection can lead to subtle imbalances in glutamatergic synapse transmission, affecting synaptic pruning and neuronal alterations in the cortex and hippocampus, which may persist for long periods (Averill *et al*., 2022). Similarly, HIV-1 infection has been associated with dysfunctions in serotonergic and dopaminergic neurotransmission, impacting motivational alterations and causing synaptodendritic damage in the nucleus accumbens (Gelman *et al*., 2012). Furthermore, the use of selective serotonin reuptake inhibitors (SSRIs) like escitalopram has shown efficacy in restoring behavioral impairments and synaptodendritic damage induced by HIV-1 (Denton *et al*., 2021), suggesting a potential role for SSRI therapies in repairing viral infection-mediated neuronal damage and restoring synaptic function (Düsedau *et al*., 2021). These findings highlight the intricate relationship between viral infections, neurotransmitter systems, and synaptic dysfunction in the context of depressive-like behaviors.

Some viruses can directly interact with neurons in the brain, affecting their normal function and neurotransmission. For example, herpesviruses, such as HSV and CMV, can infect neurons and disrupt neurotransmitter release and uptake, leading to altered neurotransmission. Research using transgenic mice expressing HIV-1's Tat protein showed a marked reduction in dopamine uptake through dopamine and norepinephrine transporters in the prefrontal cortex (Strauss *et al*., 2020). The interaction between HIV's Tat protein and human DAT (hDAT) highlights a mechanism by which HIV may impair neuronal signaling. Tat binding appears to block dopamine's entry pathway at the transporter, inhibiting its reuptake as well as the dysregulation of cell surface expression of the transporter and exacerbating conditions like HIV-associated neurocognitive disorders (Zhu *et al*., 2009; Midde *et al*., 2012; Bucci, 2015), although a compensatory mechanism may exist as evidenced in a study using HIV-Tg rats (Zhu *et al*., 2016).

In some cases, viruses can interact with neurotransmitter receptors in ways that may either protect or harm neurons, depending on the specific viral and host factors involved. This complex relationship underscores the significant impact viruses can have on neuronal function beyond simple destruction (Gosztonyi and Ludwig, 2001). Viruses can modify synaptic plasticity through various mechanisms, including direct viral action on neurons (Hosseini *et al*., 2018) or through the modulation of immune responses.

Expression of rabies virus glycoprotein enhances both short-term and long-term synaptic plasticity. This suggests that viral components can directly influence synaptic functions and could potentially be harnessed for modifying neuronal connectivity and plasticity in specific neurological conditions (Ghassemi *et al*., 2022). HIV affects synaptic plasticity by disrupting normal neuronal function, which contributes to the cognitive deficits observed in HIV-associated neurocognitive disorders. Research indicates that HIV might impair synaptic plasticity by altering gene expression and dendritic structure, which can exacerbate the severity of HIV-associated neurological disorders (Sagar *et al*., 2016). This disruption can be mediated by direct viral effects or through secondary immune-mediated mechanisms, affecting neurotransmitter systems and synaptic connectivity (Atluri *et al*., 2013; Avdoshina *et al*., 2013; Mocchetti *et al*., 2014; Bétourné *et al*., 2018).

Viral infections can trigger an immune response in the brain, leading to neuroinflammation. Neuroinflammation is characterized by the activation of immune cells in the brain, such as microglia and astrocytes, and the release of pro-inflammatory cytokines and other inflammatory mediators such as TNF-α, IL-1β, and IL-6 as well as BBB breakdown, which prolongs and deteriorates immune perturbation in the brain by facilitating the infiltration of peripheral immune cells into the brain. Neuroinflammation has been implicated in the development and progression of depression, as it can disrupt normal neurotransmission, impair synaptic plasticity, and induce neurotoxic effects.

Astrocytes are implicated in the onset and progression of depression due to their role in maintaining CNS homeostasis. Viruses such as SARS-CoV-2, HIV, HHV-6, ZIKA and BoDv-1 can infect astrocytes as well as microglia with different specificity and selectivity between them (Ellis *et al*., 2022; Yu *et al*., 2023). Oligodendrocytes, responsible for myelination in the CNS, can also be affected by viral infections. Damage to these cells can impair myelin sheath integrity, slowing down or disrupting neuronal signal transmission, which contributes to depressive symptoms (Louie *et al*., 2023). Injection of influenza virus PB1-F2 protein inhibited cell proliferation and oligodendrocyte development, impaired myelin formation, and interfered with synaptic plasticity in the dentate gyrus suggesting the essential role of oligodendrocyte development and synaptic plasticity in the modulation of affective behavior after influenza viral infection (Wang *et al*., 2024b). When activated by viral infections, microglia can switch to a pro-inflammatory state, exacerbating neuroinflammation and potentially leading to depressive symptoms, although it is argued that influenza viral infection can induce activation of microglia, which serves a neuroprotective role (Mori *et al*., 2000; Mori and Kimura, 2001). The release of inflammatory cytokines by activated microglia can further disrupt synaptic plasticity and neuronal function, contributing to the pathophysiology of depression (Düsedau *et al*., 2021).

The microglial inflammasome is a multi-protein complex within microglia that plays a crucial role in the brain's immune defense by detecting pathogenic microorganisms and sterile stressors, leading to the activation of inflammatory responses such as the release of IL-1β and IL-18. In post-viral depression, the heightened inflammatory response mediated by NLRP3 can disrupt neurotransmitter systems and impair neuronal plasticity, factors closely associated with the development of depressive symptoms (Sadasivan *et al*., 2015; Fil-

gueira *et al*., 2021). The continuous activation of the NLRP3 inflammasome in microglia during and after viral infections can maintain a state of chronic neuroinflammation, which is thought to underlie many of the neurocognitive symptoms observed in post-viral syndromes, including mood disturbances and depressive behaviors (Du *et al*., 2024a; Ghaffaripour Jahromi *et al*., 2024; Han *et al*., 2024; Zhou *et al*., 2024).

Overall, immune dysregulation in the brain affects the metabolic and catabolic fate of neurotransmitters such as serotonin, dopamine and glutamate, as well as pharmacodynamic changes in receptor and transporter expression and function, along with the dysregulation of neurotrophic factors like BDNF and NGF and their down-stream signaling. These factors contribute to altered neural function, synaptic plasticity, and synaptic degeneration (Piacentini *et al*., 2015; Ru and Tang, 2017; Maximova *et al*., 2021; Watson and Tang, 2022).

One study showed that peripheral viral mimic injection in mice is sufficient to lead to increased extracellular glutamate levels and enhanced synaptic transmission in the hippocampus, contributing to seizure hypersusceptibility (Hunsberger *et al*., 2016). Another study identified that Borna Disease Virus (BDV) infection selectively blocked activity-dependent enhancement of neuronal network activity, impairing synaptic plasticity relevant for learning and memory (Gonzalez-Dunia *et al*., 2005; Volmer *et al*., 2007), with which mechanism such as dysregulation of astrocytic support of neuron, ionic homeostasis as well as neurotrophic factor signaling are involved. Altered synaptic function and plasticity can be observed in the dysregulated resting and functional connectivity in infected patients with several different types of virus, some of which are normalized by intensive anti-viral therapy (Oriolo *et al*., 2019; Philippi *et al*., 2020; Zhang *et al*., 2020; Zheng *et al*., 2021; Chen *et al*., 2023; Kafali *et al*., 2023; Wang *et al*., 2024a).

Regarding viral infection-induced changes in synaptic plasticity, circuit function and accompanying mood disorders, epigenetic mechanisms are gaining special attention based on the effects of prolonged stress on the epigenetic changes in synaptic plasticity within brain reward circuits (Kwon *et al*., 2022; Yuan *et al*., 2023; Chen *et al*., 2024). Viral infections can lead to epigenetic changes that affect the host's immune response and potentially its neural circuits (Burmeister *et al*., 2022; Li Puma *et al*., 2023; Ma *et al*., 2023; Yao *et al*., 2023; Merz *et al*., 2024). For example, infections from viruses like SARS-CoV-2 have been shown to cause epigenetic alterations that can suppress the immune system and possibly impact neural functions, although the direct effects on stress response, neurotransmission, synaptic plasticity and depression need further investigation (Süt, 2021; Tabano *et al*., 2023). Beyond direct viral effects, infection-induced epigenetic changes can profoundly impact the pathogenesis of diseases, including those affecting mental health. These changes can persist long after the infection has cleared, potentially leading to long-term alterations in behavior and mood as well as other pathological impacts, as seen in various models of chronic viral infections (Adhya and Basu, 2010; Fischer, 2020; Shu *et al*., 2020; Li *et al*., 2021b; Locatelli and Faure-Dupuy, 2023; Krause *et al*., 2024; Lefkowitz *et al*., 2024).

Metabolic and mitochondrial modulation

Considering the essential role of metabolism and energetics, especially mitochondrial function in the modulation of brain function and the pathophysiology of myriad of neurological disorders as well as virus-induced perturbation of those processes, it is reasonable to speculate that virus-induced changes in brain energetics and mitochondrial function may play an essential role in post-viral depression and cognitive derangement (Rappeneau *et al*., 2020; Munshi *et al*., 2024; Wang *et al*., 2024c). A recent comprehensive review summarized how viruses reprogram host cell metabolism to favor viral replication and persistence, drawing parallels with metabolic changes observed in cancer cells (Thaker *et al*., 2019).

Many viruses, such as adenoviruses, herpesviruses, flaviviruses (Dengue and Zika), Influenza viruses upregulate glycolytic metabolism in infected cells, even in the presence of oxygen, a phenomenon known as the Warburg effect. This increased glycolysis provides the necessary energy and building blocks for viral replication (Thai *et al*., 2014). Viruses often stimulate the pentose phosphate pathway to support the generation of nucleotides required for viral replication (Vastag *et al*., 2011). Viruses may also induce alterations in amino acid metabolism to meet the increased demand for protein synthesis during viral replication (Vastag *et al*., 2011). Some viruses manipulate lipid biosynthesis pathways in host cells to generate membranes for viral assembly and replication (Heaton and Randall, 2010; Li *et al*., 2015; Teng *et al*., 2015). In addition, viruses known to cause cancer, such as HPV, HBV, HCV, EBV, KSHV, and HTLV-1, manipulate host cell metabolic pathways, potentially contributing to oncogenesis.

Beyond cytosolic glycolytic pathways, viruses can manipulate various components of the mitochondrial machinery in host cells, leading to significant consequences for cellular metabolism and viral replication. Viruses may modulate mitochondrial respiration to create a favorable metabolic environment for viral replication. For example, decreased mitochondrial respiration has been observed in early EBV infection, which can act as a barrier to cell proliferation (McFadden *et al*., 2016). Viruses can impact autophagic processes in host cells, which play a crucial role in maintaining mitochondrial homeostasis. Imbalances in autophagy induced by viral infections can affect cellular metabolism and contribute to viral pathogenesis (McFadden *et al*., 2016). Some viruses, such as EBV and Kaposi's sarcoma-associated herpesvirus (KSHV), can induce hypoxia responses in host cells. Hypoxia can trigger EBV lytic reactivation and KSHV lytic replication through interactions with hypoxia-inducible factor 1α (HIF-1α), leading to altered gene expression and viral replication (Davis *et al*., 2001; Cai *et al*., 2006; Kraus *et al*., 2017).

Maintaining proper function of mitochondria is essential for energy production, calcium signaling, and the generation of reactive oxygen species (ROS). Patients with depression show impaired mitochondrial gene expression, damage to mitochondrial structures and dynamics, and disrupted activity in the electron transport chain (Khan *et al*., 2023). This dysfunction contributes to higher oxidative stress, neuroinflammation, and apoptosis in both clinical and preclinical models of depression. Mitochondrial dysfunction can lead to neurobiological changes associated with depression, such as reduced neurogenesis, altered neuronal maturation, and decreased synaptic plasticity, which is most prominent in brain regions critical for mood regulation, such as the hippocampus and prefrontal cortex (Mattson *et al*., 2008; Bessa *et al*., 2009; Klinedinst and Regenold, 2015; Allen *et al*., 2018; Gebara *et al*., 2021).

Both clinical and preclinical studies suggest that viral infection can change the mitochondrial proteomics, including

the expression of mitochondrial function-associated proteins and antioxidant enzymes, which may affect inflammatory and chemosensory responses in the infected cells (Tsutsumi *et al*., 2009; Teodorof-Diedrich and Spector, 2018; Cymerys *et al*., 2019; Khan *et al*., 2019; Bartolomeo *et al*., 2022; Surendran *et al*., 2022; Motta *et al*., 2023; Osei *et al*., 2024).

Pan-viral and virus-specific mechanisms inducing depression

Many viral infections trigger immune responses that can become chronic, leading to persistent inflammation. Key inflammatory markers, such as pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), are elevated. These cytokines can cross the BBB, inducing neuroinflammation, which disrupts normal neurotransmission and neuronal circuits involved in mood regulation. This dysregulated immune response can also activate microglia in the brain, leading to neurotoxic effects and disruptions in synaptic plasticity, contributing to depressive symptoms. Similarly, viral infections can stress the HPA axis, leading to an overproduction of cortisol. Mitochondrial dysfunction, disrupted energy metabolism, and oxidative stress are also common consequences of viral infection (Fig. 2). While neurotransmitter imbalances and synaptic alterations are frequently observed following viral infections, the specific dysregulation may vary from virus to virus. For example, HSV has been linked to neurotransmitter disturbances, such as up-regulating serotonin signaling. Viruses also exhibit selective mechanisms of inducing depressive symptoms based on their unique life cycles. HSV can establish latent infections, which reemerge during periods of stress, increasing viral replication and causing pathological outcomes, including mood disruptions. A similar pattern is observed with EBV infections, which can induce chronic fatigue syndrome.

Some viruses induce more chronic inflammatory responses than others and may directly invade the brain, leading to more direct consequences. For instance, HIV can invade the brain, disrupting dopamine metabolism and affecting neurotransmitter systems like serotonin and glutamate. Antiretroviral drugs, particularly older ones like efavirenz, have neuropsychiatric side effects that exacerbate depressive symptoms.

In the case of influenza virus, alterations in glutamatergic signaling in the brain have been observed, and the influenza protein PB1-F2 has been implicated in disrupting oligodendrocyte development, impairing synaptic plasticity and affecting mood regulation.

For HCV infections, research shows direct effects on en-

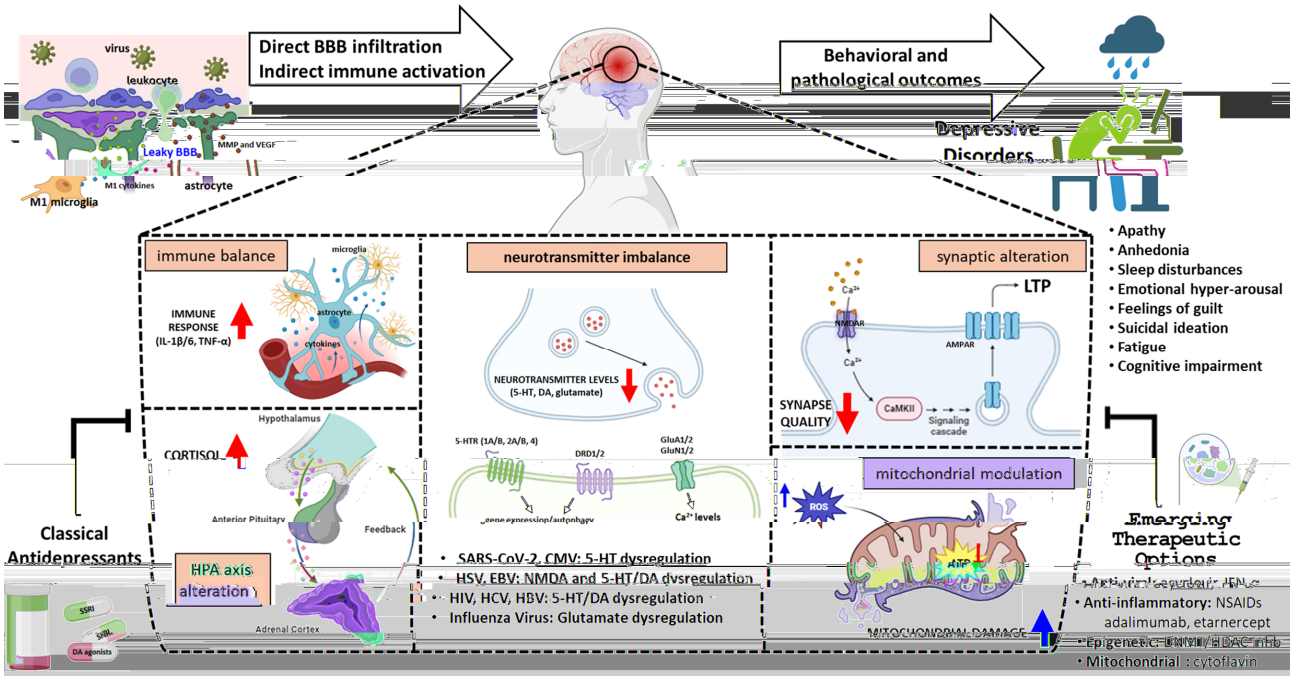

Fig. 2. Proposed mechanisms linking viral infections to depression. Viral infections either directly or indirectly, disrupt the BBB and induce neuroinflammation through microglial activation and cytokine release as well as recruitment of peripheral immune cells into the brain parenchyma, resulting in immune dysregulation. This process leads to neurotransmitter imbalances (5-HT, DA, glutamate), which impair synaptic transmission and reduce synaptic quality. Mitochondrial dysfunction, marked by increased ROS and decreased ATP production, further contributes to neural damage. In addition, dysregulation of the HPA axis elevates cortisol levels, exacerbating inflammation and stress responses. These interconnected mechanisms play a critical role in the pathogenesis of depression, while pharmacological interventions such as SSRIs, SNRIs, and DA agonists are aimed at restoring neurotransmitter balance and mitigating depressive symptoms. Due to the limitation of the efficacy of classical agents used for the control of depressive symptoms, new options are being investigated as a potential therapy against post viral depression, which is described in the right bottom corner. 5-HT, 5-hydroxytryptamine; ATP, Adenosine triphosphate; BBB, blood-brain barrier; Ca^{2+}, calcium cation; DA, dopamine; DNMT inhb, DNA methyltransferases inhibitor; DRD1/2, dopamine receptor 1/2; GluA1/2, AMPA receptor 1/2; GluN1/2, HDAC inhb, histone deacetylases inhibitor; NMDA receptor 1/2; HPA axis, hypothalamic-pituitary-adrenal axis; LTP, long-term potentiation; NSADs, Non-steroidal anti-inflammatory drugs; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors. Figures were created with biorender.com (www.biorender.com).

dothelial cells in the brain, with the liver-brain axis playing a significant role. Evidence suggests dual modulation of serotonin and dopamine neurotransmitter systems following HCV infection.

Considering the emerging role of gut-brain and gut-organ interactions, it can be reasonably hypothesized that viruses that induce chronic infections in organs such as the liver (as seen with HBV) may lead to depressive symptoms over prolonged periods, which is supported by clinical evidence. Viral infections trigger depression through both shared mechanisms and virus-specific pathways, depending on their tropism, ability to persist in the body, and impact on specific neural circuits. Understanding these virus-specific effects can lead to more targeted treatments for virus-induced depression, tailored to the underlying mechanisms of each viral infection (Table 1).

THERAPEUTIC TARGETS AND INTERVENTION

There is ongoing research into potential therapeutic targets for depression related to viral infections, but currently, there are no specific treatments approved specifically for depression caused by viral infections. Treatment for depression related to viral infections typically involves managing the viral infection itself and addressing the depressive symptoms through standard depression treatment approaches, such as psychotherapy, antidepressant medications, and supportive care. In some cases, anti-depressant treatment may show beneficial effects against the viral infection itself as well as viral complication (Ehret and Sobieraj, 2014; Greeson *et al*., 2016; Kalkman and Feuerbach, 2016; Chang *et al*., 2017; Chen *et al*., 2018).

The increase in dopamine concentration during SARS-CoV-2 infection may reduce immunity (innate and adaptive) that promotes viral spread, which could lead to neuronal damage. In addition, dopaminergic signaling in the nervous system may be affected by SARS-CoV-2 infection. COVID -19 can cause various neurological symptoms as it interacts with the immune system. Therefore, one possible treatment strategy for COVID -19 patients could be the use of dopamine antagonists (Rasmi *et al*., 2024). Moreover, SSRI/SNRIs may be effective in reducing mortality in COVID-19 patients, with fluvoxamine showing potential superiority to fluoxetine (Firouzabadi *et al*., 2022). However, SSRIs like escitalopram, sertraline, and fluoxetine only partially reduced depressive/anxiety symptoms in patients with MDD/GAD post-COVID-19, indicating incomplete restoration of affective state after 6 months of therapy (Fedotova and Bereza, 2022).

Despite the potential benefits, medications such as SSRIs produce only limited or, in some cases, adverse therapeutic outcomes, which necessitate combinatorial treatment targeting the viral infection as well or specific therapeutic options relevant to post-viral depression (Elliott *et al*., 1999; de Knegt *et al*., 2011; Denton *et al*., 2021; Mazza *et al*., 2022; Nakhaee *et al*., 2022; Rus *et al*., 2023; Shaheen *et al*., 2023).

In addition to classical candidates such as neurotransmitter receptor/transporter modulators, neurotrophic factors, and neuroprotective molecules, several other approaches as listed below are more relevant for addressing post-viral depression.

Anti-viral medication

While antiviral medications are primarily used to target viral infections and may not directly target depression symptoms, there is evidence suggesting that antiviral medications may improve depressive symptoms in some cases, particularly when the depression is related to viral infections. For example, in people with EBV infection, the immune response against the virus has been associated with MDD risk (Jones-Brando *et al*., 2020). In this study, individuals with MDD had significantly reduced levels of reactivity to EBV Nuclear Antigen-1. Although the quantitative levels of antibodies to EBV virions and Viral Capsid Antigen did not differ between groups, individuals with decreased levels of anti-Nuclear Antigen-1, or elevated levels of anti-virion had increased odds of being in the MDD group. Based on this antibody profile, the authors suggested that eradicating EBV infection could be a plausible target for managing MDD in infected individuals (Jones-Brando *et al*., 2020).

One of the most well-known examples of proactive antiviral treatment affecting depressive symptoms in viral-infected patients is HCV infection. In patients with HCV infection not receiving antiviral therapy, clinically significant emotional distress as well as depression were reported in 35% of CHC patients, which is significantly higher compared with patients with antiviral treatment (Fontana *et al*., 2002). Similarly, achieving a sustained virological response (SVR) with direct anti-viral agents led to a reduction in depressive symptoms over time among HIV-HCV co-infected individuals. The reduction in depressive symptoms was significant and sustained, suggesting improvements in biological pathways and general health due to successful antiviral treatment supporting active treatment for better mental health outcomes (Marathe *et al*., 2023). Likewise, a significant reduction in both depressive and anxious symptoms was reported after treatment with direct-acting antiviral agents. The study noted a decrease in depressive symptoms from 21.11% before treatment to 1.11% after receiving SVR, demonstrating the profound psychological impact of successful antiviral therapy (Danilescu *et al*., 2021).

Similar positive results of anti-retroviral therapy (ART) have been reported in the case of HIV infection (Starace *et al*., 2002; Gutiérrez *et al*., 2014). The incidence of clinically significant depression was lower among HIV-infected patients on ART as well as with anti-protease therapy (Low-Beer *et al*., 2000). The protective effect of ART against depression was also observed with efavirenz-containing regimens, although it is one of the most well-known neuropsycho-toxicant, which may induce schizophrenia-like symptoms in sensitive individuals (Starace *et al*., 2002; Gutiérrez *et al*., 2014).

Acyclovir, an antiviral often used in the treatment of herpes simplex encephalitis, inhibits tryptophan-2,3-dioxygenase activity *in vitro* and *in vivo*, with a concomitant rise in blood and tissue serotonin and 5-hydroxyindole acetic acid levels. It has been reported that acyclovir reduces the turnover of serotonin to 5-hydroxyindole acetic acid, without affecting norepinephrine levels. Acyclovir may have the potential to reduce the clinical symptoms of depression in herpes simplex encephalitis by modulating the level of monoamine, especially serotonin availability (Müller and Daya, 2008).

A double-blind placebo-controlled randomized clinical trial (RCT) explored the effects of the antiviral drug amantadine on patients with depression who were also infected with Borna Disease Virus 1. In this clinical trial, amantadine treatment showed significant improvement in depressive symptoms with safe oral amantadine treatment regimen, paralleling antiviral effects at various infection levels, highlighting the potential for antiviral treatments to impact depressive disorders in the con-

Table 1. Virus-specific mechanisms contributing to depression

Virus	Immune imbalance	Neuroinflammation	Cytokine increase	Neurotransmitter imbalance	HPA axis dysregulation
SARS-CoV-2	Dysregulated immune response leads to chronic inflammation (Leung *et al*., 2022; Premraj *et al*., 2022)	Activation of NLRP3 inflammasome (Kucukkarapinar *et al*., 2022)	Increased IL-6, IL-1β, TNF-α (Kucukkarapinar *et al*., 2022; Peron, 2023)	Disruption of serotonin metabolism via the kynurenine pathway (Khalefah and Khalifah, 2020; Nataf, 2020; Limanaqi *et al*., 2022)	Elevated cortisol levels due to overactive HPA axis (Leung *et al*., 2022; Zürcher *et al*., 2022)
Herpesviruses (HSV, EBV)	Reactivation under stress leads to immune imbalance (Gale *et al*., 2018; Lu *et al*., 2022)	Chronic neuroinflammation, especially in HSV-1 reactivation (Vindegaard *et al*., 2021)	Elevated IL-1β, TNF-α during reactivation (Pender, 2020)	NMDA receptor and serotonin/dopamine dysregulation (Ye *et al*., 2020; Narasimhappa *et al*., 2024)	Reactivation induces HPA axis activation (Kobayashi *et al*., 2020)
Cytomegalovirus (CMV)	Chronic immune activation, especially in older adults (Frye *et al*., 2019; Zheng *et al*., 2023)	Persistent neuroinflammation linked to cognitive decline (Zheng *et al*., 2023)	Elevated IL-1β, IL-6 contributing to depression (Simanek *et al*., 2019)	Serotonin and dopamine metabolism affected by inflammation (Frye *et al*., 2019)	Possible HPA axis dysregulation (Simanek *et al*., 2019)
HIV	Persistent immune activation despite ART (Ayano *et al*., 2021; Fabrazzo *et al*., 2023)	Neuroinflammation linked to HAND (Mudra Rakshasa-Loots *et al*., 2023)	Elevated IL-6, TNF-α linked to mood disorders (Ayano *et al*., 2018)	Disruption in serotonin and dopamine pathways (Berger *et al*., 1994)	Chronic HPA axis dysregulation, elevated cortisol (Shi *et al*., 2020)
Influenza Virus	Acute immune response triggers systemic inflammation (Bornand *et al*., 2016)	Post-viral neuroinflammation causes depressive symptoms (Iosifescu *et al*., 2022)	Increased IL-6, IFN-α contributing to depression (Düsedau *et al*., 2021)	Glutamatergic dysfunction linked to mood disturbances (Wang *et al*., 2024c)	Temporary HPA axis activation during infection (Bornand *et al*., 2016)
Hepatitis B Virus (HBV)	Immune imbalance due to chronic infection (Fabrazzo *et al*., 2023)	Mild neuroinflammation contributing to mood changes (Huang *et al*., 2023)	Elevated TNF-α linked to mood disturbances (Tsai *et al*., 2022)	Serotonin and neurotransmitter dysregulation due to liver inflammation (Fabrazzo *et al*., 2023)	Chronic HPA axis dysfunction from liver disease (Fabrazzo *et al*., 2023)
Hepatitis C Virus (HCV)	Persistent immune activation in chronic infection (Fletcher and McKeating, 2012; Adinolfi *et al*., 2015)	Neuroinflammation linked to cognitive and mood disorders (Adinolfi *et al*., 2015)	Increased IL-1, IL-6, TNF-α levels correlate with depression (Fletcher and McKeating, 2012)	Serotonin and dopamine dysregulation from cytokine imbalance (Cozzi *et al*., 2006)	HPA axis dysregulation common in chronic HCV (Fletcher and McKeating, 2012)

text of viral infections (Dietrich *et al*., 2020).

However, it's important to note that these studies have limitations, including small sample sizes, varying study designs, and potential confounding factors. More research is needed to determine the efficacy and safety of specific modality of antiviral medications as a targeted treatment for depression related to viral infections. For example, up to one-third of patients with HCV develop clinical depressive episodes during interferon-alpha (IFN-alpha) therapy providing the clinical evidence of immune activation theory of depression with gender and genetic liability against the manifestation as well as molecular mechanisms such as dysregulation of ionotropic glutamatergic signaling (Su *et al*., 2019; Cheng *et al*., 2021; Sarkar *et al*., 2021). Similarly, some anti-HIV viral medication has been associated with manifestation of depression symptoms as well as other psychiatric adverse symptoms (Williams *et al*., 2021).

Anti-inflammatory reagents

Although anti-inflammatory medications, specifically nonsteroidal anti-inflammatory drugs (NSAIDs), are effective in reducing inflammation and relieve pain, there is only limited evidence are available to suggest their therapeutic role in depression.

Some studies have shown that anti-inflammatory medications may be effective in reducing depressive symptoms in certain populations. In addition to NSAIDS, a systemic meta-analysis of anti-inflammatory add on medications such as NSAIDs, cytokine inhibitors, statins, minocycline, pioglitazone, and glucocorticoids on top of anti-depressant showed a better therapeutic outcomes, suggesting the need to include longer follow-up, identify optimal doses and subgroups of patients that can benefit best from anti-inflammatory intervention (Köhler *et al*., 2014; Köhler-Forsberg *et al*., 2019; Bai *et al*., 2020; Beurel *et al*., 2020), although standalone treatment in many cases fail to show therapeutic efficacy and even the basal level of inflammation (Raison, 2017; Allison *et al*., 2019). The exact mechanisms through which anti-inflammatory medications may improve depression symptoms are not yet fully understood.

In addition to the classical anti-inflammatory agents as mentioned above including selective COX-2 inhibitors there are several potential targets that have been identified as being involved in the immune modulation pathways implicated in depression as well as more recent development such as NLRP3 inflammasome. First, targeting pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β directly may be a potential approach for immune modulation in depression. In HCV infected patients, interferon alpha can induce proinflammatory status resulting in depressive symptoms, which can be avoided by prophylactic use of anti-depressant (Udina *et al*., 2014; Pinto and Andrade, 2016; Islam *et al*., 2023; Lai *et al*., 2023). Direct inhibitors of cytokines such as infliximab did not show superior efficacy in treating treatment resistant depression. In a meta-analysis of four primary studies with a total of 152 patients, the results did not show a statistically significant effect of Infliximab as an adjuvant treatment for treatment resistant depression (TRD) (Bavaresco *et al*., 2020), although beneficial effects of adalimumab, etanercept, infliximab and tocilizumab has been suggested in another meta-analysis study (Kappelmann *et al*., 2018).

In case of neurotrophic viruses, BBB and endothelial cells serve as a major entry point of viruses. In addition, the pathogen specific array of cytokines and chemokines as well as leukocyte migration profiles could be involved in immunological responses in viral CNS infections, which may serve as identifying new point of intervention and for the development of new diagnostic and treatment strategies (Dahm *et al*., 2016).

In addition to the direct modulation of inflammatory cytokines and inflammatory regulators, players in the modulation of immune activation can be targeted against depression. For example, TLRs are proteins that play a key role in the immune response by recognizing pathogens and initiating immune signaling. They have also been implicated in inflammation and depression. Modulating the activity of TLRs, such as TLR4, may have potential therapeutic implications for depression (Wu *et al*., 2015). On the same rationale, NF-κB is a transcription factor that regulates the expression of genes involved in inflammation. It has been implicated in the pathophysiology of depression and may be a potential target for immune modulation (Adeoluwa *et al*., 2023; Du *et al*., 2024b; Zheng *et al*., 2024).

Considering the central role of microglia in the modulation of CNS inflammation, modulating microglial activity and reducing neuroinflammation may be a potential therapeutic approach for depression (Yirmiya *et al*., 2015). In addition, microglia can serve as CNS reservoir for some neurotropic viruses such as HIV. Inhibiting microglial activation can significantly alleviate depressive symptoms in rodent models by modulating various inflammatory pathways (Lisnasari *et al*., 2022). Moreover, targeting specific components of the microglial inflammasome, such as NLRP3, has been effective in reversing depression-like behaviors in diabetic mice, suggesting a key role of microglial activation in diabetes-associated depression (Su *et al*., 2023). Comprehensive reviews highlight that microglia regulate neural inflammation, synaptic plasticity, and network formation, all crucial for developing novel depression treatments (Wang *et al*., 2022). Furthermore, innovative approaches like a photoresponsive vaccine-like system targeting microglia through the BBB show potential in treating inflammation-related depression, offering a continuous anti-inflammatory effect (Liu *et al*., 2022b). A multiple of molecular targets are available for the modulation of microglial activation, one of which is P2X7 purinergic receptor involved in the microglial inflammasome activation (Bhattacharya and Jones, 2018; Bhattacharya *et al*., 2018; Ribeiro *et al*., 2019; Lee *et al*., 2023; Simões *et al*., 2023).

The inflammasome is involved in the activation of IL-1β and IL-18, two pro-inflammatory cytokines that have been implicated in depression. Activation of the inflammasome leads to the production and release of these cytokines, which can contribute to neuroinflammation and potentially impact mood and behavior. In preclinical studies, inhibiting the inflammasome or its downstream signaling pathways has been shown to reduce inflammation and improve depressive-like behaviors in animal models.

Several experimental approaches to target the inflammasome have been investigated, including pharmacological inhibitors and genetic manipulations in preclinical studies. For example, inhibitors of specific components of the inflammasome, such as NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inhibitors, have shown promise in preclinical models of depression by reducing inflammation and improving depressive-like behaviors (Liu *et al*., 2022a; Lyu *et al*., 2022; Shirayama *et al*., 2023; Han *et al*., 2024). However, these ap-

proaches are still in the early stages of research, and their safety and efficacy in humans with depression have not been fully established.

Epigenetic Modulators

Epigenetic modulators are emerging as a potential therapeutic approach for depression. Targeting epigenetic mechanisms has shown promise in preclinical and some clinical studies for the treatment of depression, including the use of DNA methylation inhibitors and histone deacetylase (HDAC) inhibitors. Some studies have shown that DNA methylation inhibitors can reverse the epigenetic changes associated with depression and improve depressive symptoms in animal models and in some clinical trials (Cheng *et al*., 2023; Maier *et al*., 2024). Similarly, increasing histone acetylation, which can lead to a more relaxed chromatin structure and increased gene expression, has been shown to have antidepressant-like effects in preclinical studies (Misztak *et al*., 2018; Dai *et al*., 2021; Meng *et al*., 2023). For example, the epigenetic downregulation of RAC1, a gene associated with synaptic structure, in the nucleus accumbens has been linked to depression and stress-related behaviors. The repressive chromatin state around RAC1, facilitated by stress, can be reversed by histone deacetylase inhibitors, which not only restores RAC1 expression but also reverses depressive behaviors (Golden *et al*., 2013).

Recently, it has been reported that a small molecule BRD4 modulator, which act as genetic readers of histone acetyl lysine residues to regulate gene transcription, inhibits HIV replication (Alamer *et al*., 2020). Whether this approach may have therapeutic effects on HIV-induced depression remains to be determined.

Non-coding RNAs, such as microRNAs, are small RNA molecules that can bind to messenger RNAs (mRNAs) and regulate their stability or translation, thereby influencing gene expression. Detecting and modulating non-coding RNAs has shown promise in preclinical studies as a potential diagnostic and therapeutic approach for depression (Shi *et al*., 2021). Other epigenetic mechanisms, such as histone methylation, histone phosphorylation, and DNA hydroxymethylation, might also been associated with depression and may represent potential targets for therapeutic intervention.

Targeting mitochondria

Not only neurotopic viruses but also pandemic viruses have been associated with the brain dysfunction and mitochondrial dysregulation. Although the mechanism underlying mitochondrial dysfunction in brain pathology are not completely understood, it has been suggested as a plausible target for the prevention and treatment of virus-induced brain dysfunction (Maurya *et al*., 2022; Righetto *et al*., 2023). A recent small-scale clinical trial on the complex rehabilitation of post-COVID syndrome reported that the intravenous administration of cytoflavin, a combination of succinic acid, riboflavin, nicotinamide and inosine which may have anti-hypoxic and antioxidant properties significantly improves the overall functional state and reduces depression and fatigue levels. This suggests a further need for research specifically targeting mitochondria to modulate post-viral depression and other neurological sequelae (Tereshin *et al*., 2022).

CONCLUSION AND PERSPECTIVES

We provided a comprehensive review of the relationship between viral infections and the manifestation of depression. Various mechanisms through which viruses influence mental health, including direct effects on the brain and indirect effects via immune system interactions, were suggested. Specific viruses linked to an increased risk of depression, such as herpesviruses and influenza, were highlighted, and the biological pathways involved, such as inflammation, neurotransmitter imbalance, and stress responses, were discussed. Understanding these connections could lead to new therapeutic targets for depression, particularly post-viral depression. It's important to focus on integrated treatments that address both the viral infection and its psychological effects. Potential strategies might include using antiviral drugs, managing immune responses, and targeting specific neurotransmitter pathways affected by viral infections. Future research should focus on identifying key biomarkers that predict susceptibility to post-viral depression, allowing for earlier diagnosis and the development of personalized treatment strategies. Immune response markers, such as cytokines, along with genetic and epigenetic factors, could help define at-risk populations. Additionally, longitudinal studies that follow individuals after viral infections will be crucial to understanding long-term mental health outcomes, particularly in the context of pandemics like COVID-19. Animal models that mimic viral-induced depression could further elucidate the molecular mechanisms involved, such as neuroinflammation and neurotransmitter dysregulation, offering insights into novel therapeutic targets. In summary, the contents of this article underscore the complex interplay between viral infections and mental health and point toward a multidisciplinary approach to treatment that combines virology, psychiatry, and neurology to better manage depression associated with viral infections. Future clinical trials should explore combining antiviral treatments, immune modulators, and therapies targeting neurotransmitter imbalances to provide a comprehensive treatment approach that addresses both the biological and psychological dimensions of post-viral depression.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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