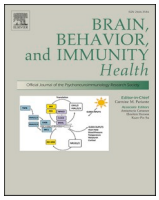
Brain, Behavior, & Immunity - Health 36 (2024) 100737

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



# Accelerated aging in people living with HIV: The neuroimmune feedback model

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A B S T R A C T

People living with HIV (PLWH) experience earlier onset of aging-related comorbidities compared to their counterparts without HIV. This paper lays out a theoretical model to explain why PLWH experience accelerated aging. Briefly, the model is structured as follows. PLWH experience disproportionately heavy burdens of psychosocial stress across the life course. This psychosocial stress increases risks for depressive symptoms and problematic substance use. Depressive symptoms and problematic substance use interfere with long-term adherence to antiretroviral therapy (ART). Lower ART adherence, in turn, exacerbates the elevated systemic inflammation stemming from HIV infection. This inflammation increases risks for aging-related comorbidities. Systemic inflammation also reduces connectivity in the brain's central executive network (CEN), a large-scale brain network that is critical for coping with stressful circumstances. This reduced capacity for coping with stress leads to further increases in depressive symptoms and problematic substance use. Together, these changes form a neuroimmune feedback loop that amplifies the impact of psychosocial stress on aging-related comorbidities. In this paper, I review the existing evidence relevant to this model and highlight directions for future research.

## 1. Introduction

People living with HIV (PLWH) experience earlier onset of aging-related comorbidities such as cardiovascular disease (Hanna et al., 2016; Yang et al., 2019), type 2 diabetes (Guaraldi et al., 2018; Hernandez-Romieu et al., 2017), frailty (Desquilbet et al., 2007), and cognitive impairment (Yang et al., 2019) compared to people without HIV. PLWH also exhibit older biological age as indicated by epigenetic clocks and telomere length (Breen et al., 2022). Combination antiretroviral therapy (ART) has dramatically extended life expectancy in PLWH, but comorbidity-free life expectancies remain substantially shorter in PLWH compared to the general population (Marcus et al., 2020). Despite this overall pattern of accelerated aging, healthy aging is possible for PLWH. A pilot study found that 39% of PLWH exhibited healthy aging as indicated by the multidimensional Rotterdam Healthy Aging Score (Walmsley et al., 2020).

This paper lays out a theoretical model to explain why PLWH experience accelerated aging. This model also helps explain why healthy aging is possible for PLWH, despite a clear population-level pattern of accelerated aging among PLWH.

Briefly, the model is structured as follows. PLWH experience disproportionately heavy burdens of psychosocial stress across the life course. This psychosocial stress increases risks for depressive symptoms and problematic substance use. Depressive symptoms and problematic substance use interfere with long-term adherence to ART. Lower ART adherence, in turn, exacerbates the elevated systemic inflammation stemming from HIV infection. This inflammation increases risks for aging-related comorbidities. Systemic inflammation also reduces connectivity in the brain's central executive network (CEN), a large-scale brain network that is critical for coping with stressful circumstances. This reduced capacity for coping with stress leads to further increases in depressive symptoms and problematic substance use. Together, these changes form a neuroimmune feedback loop that amplifies the impact of psychosocial stress on aging-related comorbidities (Fig. 1).

Repeated cycling of this feedback loop leads to increases in systemic inflammation over time. These increases in systemic inflammation accelerate the pathogenesis of aging-related comorbidities such as cardiovascular disease, type 2 diabetes, frailty, and neurocognitive impairment.

PLWH who experience lower burdens of psychosocial stress may be less vulnerable to accelerated aging driven by this neuroimmune feedback loop. Resilience factors that disrupt the feedback loop (e.g., strong social support, retention in medical care, robust mental health) may protect against accelerated aging.

The components of this theoretical model can be divided into six causal hypotheses: 1) Greater psychosocial stress increases the severity of depressive symptoms and problematic substance use, 2) Depressive symptoms and problematic substance use reduce ART adherence, and 3) Lower ART adherence increases systemic inflammation, 4) Greater systemic inflammation reduces connectivity in the CEN, 5) Lower

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https://doi.org/10.1016/j.bbih.2024.100737
Received 18 August 2023; Received in revised form 2 January 2024; Accepted 4 February 2024
Available online 5 February 2024

connectivity in the CEN increases depressive symptoms and problematic substance use, and 6) Greater systemic inflammation increases risks for aging-related comorbidities. In the sections below, I briefly review and evaluate the current empirical evidence that bears on each hypothesis.

**Hypothesis 1. Greater psychosocial stress increases the severity of depressive symptoms and problematic substance use.**

PLWH experience unique stressors, including HIV stigma and the stress of managing a chronic condition (Dale et al., 2022; Orban et al., 2010). PLWH are also more likely to belong to marginalized groups in terms of sexual orientation (Bosh et al., 2021), gender modality (Baral et al., 2013), race/ethnicity (Bosh et al., 2021), socioeconomic status (Centers for Disease Control Prevention, 2011). PLWH experience higher rates of lifetime traumatic events and intimate partner violence compared to the general population (LeGrand et al., 2015). Together, these factors expose PLWH to a disproportionately heavy burden of psychosocial stress across the life course.

Existing evidence shows that psychosocial stressors and structural marginalization in multiple domains is associated with depressive symptoms and problematic substance use among PLWH (Earnshaw et al., 2020; Glynn et al., 2019; Liu et al., 2023; Burke et al., 2005). For example, one study found that lower education was associated with trajectories of worsening or persistently severe depressive symptoms among PLWH (Gunzler et al., 2020). A study of sexual minority men living with HIV and at high risk for HIV found that experiences of victimization were associated with higher levels of alcohol use, marijuana use, and illicit drug use (Swann et al., 2018). A study of Black women living with HIV found that gendered racial microaggressions were associated with increased depressive symptoms and greater odds of depression diagnosis (Dale and Safren, 2020). There is a small but growing body of longitudinal studies that provide evidence of directionality. For example, a study of women living with HIV found that internalized HIV stigma at baseline predicted depressive symptoms 18 months later (Turan et al., 2019). A longitudinal study of women living with or at risk for HIV found that those who reported being food insecure were more likely to report illicit substance use at the following visit (Whittle et al., 2019). Another study reported that unemployment was a longitudinal predictor of depression among men living with HIV (Ware et al., 2020). This paper is focused on depression and problematic substance use, but psychosocial stress may also contribute to other mental health conditions in PLWH, including anxiety and posttraumatic stress disorder (Olagunju et al., 2012; Andu et al., 2018). Further longitudinal work is needed to clarify the combined effects of psychosocial stress in multiple domains on depressive symptoms, problematic substance, and other mental health outcomes in PLWH.

**Hypothesis 2. Depressive symptoms and problematic substance use reduce antiretroviral therapy (ART) adherence.**

Depressive symptoms and problematic substance use can interfere with everyday life activities, such as attending medical appointments or remembering to take a prescribed medication (Grenard et al., 2011; Socias and Milloy, 2018).

Among PLWH, depressive symptoms and problematic substance use are associated with lower ART adherence. For example, one study found that PLWH who exhibited harmful alcohol use had nearly 7-fold higher odds of non-adherence and PLWH with depression had nearly 6-fold higher odds of non-adherence compared to PLWH who did not have these conditions (Parro-Torres et al., 2022). A study among women living with HIV found that greater internalized HIV stigma predicted lower ART adherence and this effect was longitudinally mediated by depressive symptoms (Turan et al., 2019). A meta-analysis found that receiving treatment for depression led to improvements in ART adherence (Sin and DiMatteo, 2014).

A multisite study examining a range of substances found that alcohol use, cocaine use, other stimulant use, and heroin use were associated with lower ART adherence, but marijuana use was not (Rosen et al., 2013). Another study found that PLWH who exhibit dependence on marijuana use exhibit reduced ART adherence, but those who exhibit non-dependent marijuana use do not (Bonn-Miller et al., 2014). A third study found that problematic cannabis use predicted consistently detectable HIV viral load (Xavier Hall et al., 2021). A meta-analysis found that among PLWH with opioid use disorder, those who were receiving medications to treat opioid use disorder exhibited higher ART adherence and were more likely to exhibit HIV viral suppression (McNamara et al., 2021).

Neurocognitive impairment, which is frequently comorbid with depression and problematic substance use, may also play a role in ART non-adherence (Nyundo, 2022; Rubin and Maki, 2019; Thaler et al., 2015). Along these lines, one study reported that PLWH with HIV-associated neurocognitive disorder had lower resting state functional connectivity in the CEN compared to healthy control participants (Chaganti et al., 2017).

Depressive symptoms and problematic substance use frequently co-occur (Bryant et al., 2015), and both have been linked to ART

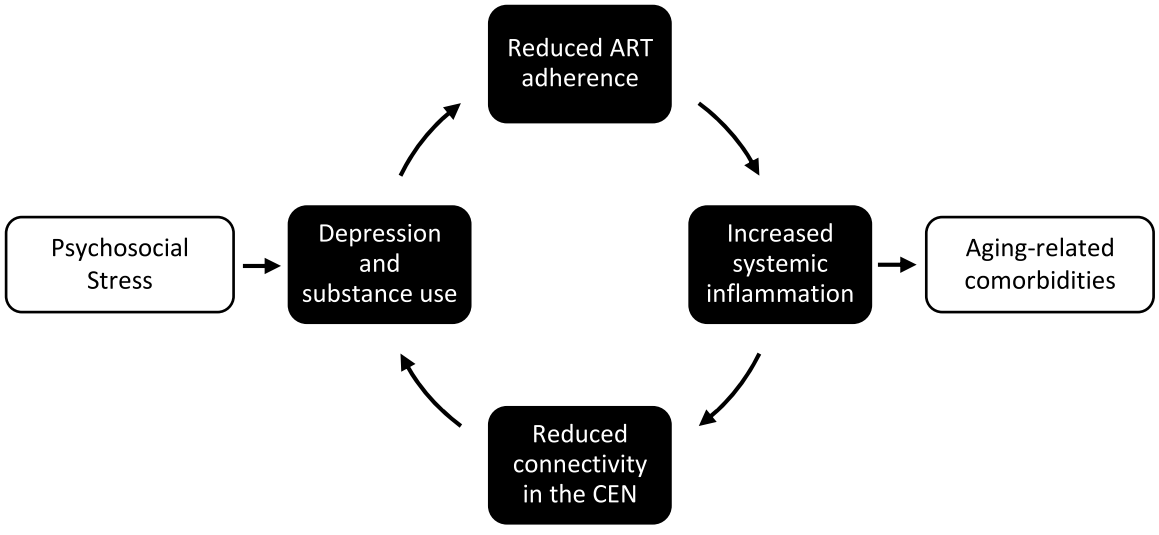


**Fig. 1. The neuroimmune feedback model.** Repeated cycling of this feedback loop drives increasing risks for aging-related comorbidities in people living with HIV. ART = antiretroviral therapy; CEN = central executive network.

adherence. The temporal sequence linking depressive symptoms, substance use, and ART adherence is unclear. One possibility is that depressive symptoms lead to problematic substance use, and problematic substance use interferes with ART adherence. Alternatively, problematic substance use could interfere with ART adherence, which in turn could exacerbate depressive symptoms via neuroinflammatory pathways. Longitudinal studies are needed to clarify the timescales and temporal sequences linking depressive symptoms, substance use, and ART adherence (Hammond et al., 2016).

**Hypothesis 3. Lower antiretroviral therapy (ART) adherence increases systemic inflammation.**

PLWH exhibit elevated markers of immune activation and systemic inflammation compared to their counterparts without HIV (Subramanya et al., 2019; Kiefer et al., 2018; Temu et al., 2021). Successful viral suppression of HIV through ART partially reverses the systemic inflammation associated with HIV, but residual excess systemic inflammation is detectable even in PLWH who achieve sustained viral suppression (Wada et al., 2015; Masyuko et al., 2021; Castillo-Mancilla et al., 2020). Multiple inflammatory markers remain elevated even when ART adherence is good and the virus is suppressed (Castillo--Mancilla et al., 2020).

A growing body of evidence suggests that a patient's level of adherence to ART (e.g., proportion of doses missed) is an important determinant of systemic inflammation among PLWH. For example, one study used electronic monitoring of pill caps to assess ART adherence among PLWH who were virally suppressed. That study reported that longer interruptions of ART adherence were associated with higher plasma levels of multiple inflammatory markers (Musinguzi et al., 2019). Another study found that every 10% increase in ART adherence was associated with a 15% decrease in circulating concentrations of the pro-inflammatory cytokine interleukin-6 (Castillo-Mancilla et al., 2018). A third study found that the effect of ART adherence on circulating interleukin-6 was stronger among PLWH who initiated ART during early infection (Castillo-Mancilla et al., 2022), which suggests that early detection and treatment does not negate the need for high levels of ART adherence to limit systemic inflammation. Intermittent nonadherence to ART can lead to blips of increased viral replication – these blips are a likely cause of peripheral inflammation and neuroinflammation in PLWH (Yukl et al., 2010; Calvo-Cidoncha et al., 2015; Fleming et al., 2019). It is also worth noting that psychosocial stress may also exert direct pro-inflammatory effects, even in the absence of depressive symptoms, problematic substance use, and ART non-adherence (Chow et al., 2023; Stadtler et al., 2021).

It is important to note that reverse causality is a potential alternative explanation for the observed associations between ART adherence and systemic inflammation. For example, increased systemic inflammation could increase depressive symptoms, and depressive symptoms could interfere with ART adherence. Alternatively, a third variable could cause both low ART adherence and high systemic inflammation, resulting in spurious correlations. Rigorous modeling approaches (e.g., random intercept cross-lagged panel models) could be used to establish the directionality of the relationship between ART adherence and systemic inflammation.

**Hypothesis 4. Greater inflammation reduces connectivity in the Central Executive Network (CEN).**

The CEN is a large-scale brain network that subserves several key functions in the pursuit of goal-directed behavior, including problem-solving, decision-making, and manipulation of information in working memory (Borders, 2020). The CEN plays a key role in exerting self-control, reappraising stressful stimuli, and inhibiting impulses initiated by other brain systems (Turner et al., 2019; Gagnepain et al., 2017). These functions are important for successfully coping with stressful life circumstances (Menon, 2011).

Brain activity exhibits a reliable network architecture that can be observed at rest via functional magnetic resonance imaging (fMRI) (Raichle, 2015). Certain networks (e.g., the CEN) are consistently observed across subjects, but the degree of resting-state functional connectivity (rsFC) in these networks varies between individuals (Bressler and Menon, 2010).

Existing evidence suggests that PLWH exhibit lower resting-state functional connectivity (rsFC) in multiple large-scale networks, including the CEN, compared to healthy controls (Thomas et al., 2013). Recent research suggests that aging and HIV are associated with similar organizational patterns in the brain's network architecture (Lew et al., 2023). Given the role of systemic inflammation in the pathophysiology of both aging- and HIV-related comorbidities (Ferrucci and Fabbri, 2018), it is plausible that systemic inflammation is one of the mechanisms driving lower CEN rsFC in PLWH.

Experiments with animal models suggest that inflammation contributes to deficits in executive function (Culley et al., 2014). A study of PLWH found that peripheral inflammatory markers were associated with executive function (Swanta et al., 2020). Another study found that greater variability in C-reactive protein, perhaps reflecting intermittent waves of inflammation, is associated with lower executive function in PLWH (Rubin et al., 2018). These observations inspire the hypothesis for this section – that greater systemic inflammation reduces CEN rsFC. A growing body of observational and experimental evidence shows that peripheral inflammation leads to alterations in rsFC (Lekander et al., 2016; Labrenz et al., 2016; Walker et al., 2020), but existing studies vary widely in which networks and regions of interest they investigate.

To date, few studies have directly assessed associations between systemic inflammation and CEN rsFC. Inflammatory markers are associated with executive function in PLWH (Swanta et al., 2020; Rubin et al., 2018), but I am unaware of any studies directly assessing the association between CEN rsFC and inflammation in PLWH. A study of people with heart disease reported that cardiac surgery led to alterations in resting-state functional connectivity (rsFC) of the dorsolateral prefrontal cortex, a key anchoring region of the CEN (Zhu et al., 2023). These changes in connectivity were proportional to measures of executive function and plasma levels of tumor necrosis factor-a. These findings suggest that peripheral inflammation may play a role in altering brain networks underlying executive function.

Another study investigated peripheral inflammation and CEN rsFC in two separate age groups (Nusslock et al., 2019). In a sample of African American youth, ages 13–14, higher scores on a composite index of multiple inflammatory markers were associated with lower CEN rsFC. in a sample of African American young adults (age 25), the association between the inflammatory composite score and CEN rsFC was in the same direction as it was in the younger sample but not statistically significant. In this young adult sample, higher classical monocyte counts exhibited a statistically significant association with lower CEN rsFC, highlighting a potential role for monocyte trafficking in driving CEN rsFC.

Notably, monocyte chemoattractant protein-1 (MCP-1 or CCL2), a marker of increased monocyte trafficking, is associated with structural markers of brain tissue damage in PLWH (Ragin et al., 2006). Experimental work has shown that MCP-1 mediates enhanced transmigration of HIV-infected leukocytes across the blood-brain barrier (Eugenin et al., 2006). Reduced integrity of the blood-brain barrier has also been linked to brain tissue damage in HIV (Ellis et al., 2021a). Taken together, these findings suggest that monocyte trafficking from the periphery to the brain may play a key mechanistic role in connecting peripheral inflammatory immune activation to brain alterations in HIV.

A study using fluorodeoxyglucose positron emission tomography found that interferon alpha therapy reduced metabolic activity in the prefrontal cortex (Juengling et al., 2000). Notably these reductions in metabolism covaried with depressive symptoms. This suggests that inflammation-related decreases in CEN rsFC may be mediated by altered patterns of brain metabolism.

A considerable body of evidence demonstrates that systemic

inflammation contributes to dopamine depletion (Miller et al., 2009, 2013; Felger et al., 2013; Capuron et al., 2012; Kamata et al., 2000; Mauriño et al., 2010; Harrison et al., 2015; Saloner et al., 2020; Labandeira-Garcia et al., 2012; Goodkin et al., 2023). Dopamine plays a key role in modulating functions of the prefrontal cortex (Ott and Nieder, 2019; Sotoyama et al., 2022). Thus, dopamine depletion is a potential mechanism linking HIV-related inflammation to alterations in CEN rsFC.

It is important to note that inflammation and affective symptoms may be associated with lower rcFC in some parts of the brain but higher rsFC in other parts of the brain. As an example of the latter, one study found that greater rsFC between the subgenual anterior cingulate cortex and the bilateral amygdala was associated with greater intensity of depressive symptoms, and greater amplitude of low-frequency fluctuations in the orbitomedial frontal cortex was associated with higher plasma levels of inflammatory proteins among PLWH (McIntosh et al., 2018).

Longitudinal research among PLWH is needed to test whether peripheral inflammation predicts subsequent reductions in CEN rsFC and to identify the specific mechanistic pathways linking peripheral inflammation to CEN rsFC.

**Hypothesis 5. Lower connectivity in the Central Executive Network (CEN) increases depressive symptoms and problematic substance use.**

Existing evidence suggests that lower CEN rsFC is associated with an increased risk for depression and problematic substance use (Kaiser et al., 2015; Wilcox et al., 2019). A meta-analysis reported that patients with major depressive disorder exhibit lower rsFC in the CEN compared to healthy controls (Kaiser et al., 2015). Along the same lines, lower rsFC in the CEN is associated with reduced cognitive control in patients with alcohol use disorder (Camchong et al., 2013), nicotine use disorder (Cole et al., 2010), stimulant use disorder (McHugh et al., 2017), and opioid use disorder (Zhai et al., 2015). Further research is needed to investigate whether these patterns persist in PLWH who also have depressive and/or substance use disorders.

Apathy, a general lack of motivation, is an especially common symptom in PLWH (Bryant et al., 2015). Apathy exhibits considerable overlap with the depressive symptom of anhedonia (a loss of interest in activities that are usually rewarding) (Husain and Roiser, 2018). Apathy and anhedonia share a set of underlying neural mechanisms (Husain and Roiser, 2018). Notably, a study of older adults (without HIV) with mild neurocognitive impairment found that lower CEN rsFC was associated with greater severity of affective symptoms, particularly apathy (Munro et al., 2015).

Sickness behavior is a set of behavior changes whose evolved function is to reduce active energy expenditure and prioritize immune function during infection (Shattuck and Muehlenbein, 2015). Depressive symptoms (including apathy and anhedonia) play a prominent role in sickness behavior (Schrock et al., 2019), and some cases of depression may be a chronic form of sickness behavior (Maes et al., 2012). Experimental studies have demonstrated that inflammatory immune activation plays a key mechanistic role in triggering sickness behavior (Lasselin et al., 2020). While depressive symptoms during acute infection are thought to be adaptive, chronic depressive symptoms in the context of chronic inflammation may become maladaptive and increase the risk of acquiring additional chronic comorbidities (Schrock et al., 2022). Clarifying the mechanistic links between sickness behavior and depressive symptoms may advance our understanding of how depressive disorders develop in PLWH.

A growing body of evidence suggests that peripheral inflammation and neuroinflammation may play a mechanistic role in linking HIV to elevated depressive symptoms. For example, a study reported that the association between HIV status and depressive symptoms is mediated by inflammatory markers in plasma and cerebrospinal fluid (Mudra Rakshasa-Loots et al., 2023). Astrocyte activation may play a role in linking inflammation to depressive symptoms – a study of PLWH found that an increased concentration of glial fibrillary acidic protein in cerebrospinal fluid (a marker of astrocyte activation) is associated with elevated depressive symptoms and apathy (Ellis et al., 2022). Social isolation, which can be both a cause and a consequence of depressive symptoms, has been linked to elevated inflammatory markers in plasma and cerebrospinal fluid in PLWH (Ellis et al., 2021b).

Prospective studies are needed to test whether CEN rsFC predicts subsequent severity of depressive symptoms and problematic substance use in PLWH. Studies should also investigate CEN rsFC as a predictor of specific symptoms, particularly apathy and anhedonia. Neuroimaging components could be added to clinical trials to test whether CEN rsFC mediates the effect of treatment on reduced severity of depressive symptoms and problematic substance use.

It is important to note that the causal relations between CEN rsFC, depressive symptoms, and substance use may be multidirectional. For example, lower CEN rsFC may increase susceptibility to problematic cannabis use, and problematic cannabis use may lead to further alterations in CEN rsFC (Ertl et al., 2023). Thus, CEN rsFC, depressive symptoms, and substance use may form their own feedback loop nested within the broader neuroimmune feedback loop. Longitudinal research is needed to clarify how CEN rsFC, depressive symptoms, and substance use interact over time.

CEN function exhibits considerable plasticity and is amenable to improvement through interventions (Tang et al., 2015). For example, a study among older adults (without HIV) found that a multi-domain cognitive training intervention increased CEN rsFC (Cao et al., 2016). Another study of adults with elevated levels of psychological distress (without HIV) found that three days of intensive mindfulness meditation training increased CEN rsFC (Taren et al., 2017). Repetitive transcranial magnetic stimulation over the left dorsolateral prefrontal cortex, a key anchoring region of the CEN, is an effective, non-invasive treatment for depression (Teng et al., 2017). The dorsolateral prefrontal cortex is a highly accessible target for neuromodulation, which makes it an ideal region for interventions aimed at improving CEN rsFC (Tang et al., 2015). These interventions enable experimental enhancement of CEN rsFC, which could be leveraged to strengthen causal inferences about the effects of CEN rsFC on depressive symptoms and problematic substance use.

**Hypothesis 6. Greater systemic inflammation increases risks for aging-related comorbidities.**

A large body of evidence highlights the role of inflammation in the pathogenesis of aging-related comorbidities (Chung et al., 2009; Liberale et al., 2020). In PLWH, markers of systemic inflammation are longitudinal predictors of coronary artery disease events (Avery et al., 2023) and all-cause mortality (Piggott et al., 2015). Markers of systemic inflammation are cross-sectionally associated with diabetes incidence (Brown et al., 2010) and frailty (Fukui et al., 2018) in PLWH, but longitudinal studies are needed. Other infectious diseases (e.g., Hepatitis B and C) are common comorbidities of HIV, and these coinfections may further exacerbate systemic inflammation (Shmagel et al., 2016; Crane et al., 2014). Associations between inflammation and aging-related outcomes among PLWH are reviewed in detail elsewhere (Deeks, 2011; Leng and Margolick, 2015; Sieg et al., 2021).

A longitudinal study of women living with HIV found that greater variability in the inflammatory marker C-reactive protein over time was associated with greater cognitive impairment (Rubin et al., 2018). This highlights the possibility that repeated waves of systemic inflammation may play a role in driving neurocognitive decline among PLWH. Another longitudinal study of PLWH reported that higher C-reactive protein was associated with poorer neurocognition, but only among those with moderate to severe depressive symptoms (Saloner et al., 2021). This suggests that inflammation and depressive symptoms may interact over time to accelerate neurocognitive aging. This pattern is broadly consistent with the neuroimmune feedback model outlined in this paper.

A growing body of evidence suggests that HIV and consequent systemic inflammation may be associated with biomarkers of accelerated aging among PLWH. One study reported that polymorphisms for genes that express inflammatory proteins were associated with biological age indexed by a methylation clock in among PLWH (Sundermann et al., 2019). Another study reported that PLWH exhibited older sleep-based brain age compared to their counterparts without HIV (Leone et al., 2021). A third study found that HIV, elevated inflammatory markers, methamphetamine use, and comorbid disease risk were each associated with shorter leukocyte telomere length, a marker of older biological age (Mehta et al., 2021). Taken together, these findings suggest that systemic inflammation plays a role in driving accelerated aging and disproportionately high burdens of aging-related comorbidities in PLWH.

## 2. Conclusion

In this paper, I outline a novel theoretical model to explain why PLWH experience accelerated aging relative to their counterparts without HIV. This model also helps explain the wide range of variability in aging-related health among PLWH.

In this model, depressive symptoms, problematic substance use, low antiretroviral therapy adherence, elevated systemic inflammation, and low connectivity in the brain's central executive network form a self-perpetuating feedback loop. For people facing heavier burdens of psychosocial stress, this feedback loop cycles faster and with greater intensity. Repeated cycling of this feedback loop increases systemic inflammation over time, which accelerates the onset of aging-related comorbidities. Protective factors that interrupt this feedback loop include social support, non-stigmatizing medical care, and interventions that improve mental health and reduce systemic inflammation.

A limitation of this model is that it does not include all causal relations between the variables of interest, nor does it discuss all the potential mechanisms that may link these variables of interest. For example, psychosocial stress may exert a direct effect on ART adherence that is not mediated by depressive symptoms or problematic substance use. I chose to focus this model on a specific set of hypothesized effects that have an important emergent property, the neuroimmune feedback loop, which is the focus of this paper.

This framework could be generalized by replacing ART adherence with other health behaviors, such as diet or physical activity. Adapting the model in this manner could yield useful frameworks for explaining varying health trajectories in PLWH who are highly adherent to ART. It could also provide a useful status-neutral framework for understanding health trajectories in both PLWH and people at elevated risk for HIV seroconversion.

Existing evidence is consistent with the model outlined in this paper, but many of the relevant clinical studies are observational and cross-sectional. Clinical trials and longitudinal studies are needed to identify the specific mechanisms that sustain this feedback loop and the temporal trajectories over which these mechanisms operate. The field of psychoneuroimmunology is uniquely equipped to offer novel insights on mechanisms that drive accelerated aging among PLWH.

## Funding

NIH/NIDA K01DA057143.

## CRediT authorship contribution statement

**Joshua M. Schrock:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

none

## Data availability

No data was used for the research described in the article.

## References

Andu, E., Wagenaar, B.H., Kemp, C.G., Nevin, P.E., Simoni, J.M., Andrasik, M., et al., 2018. Risk and protective factors of posttraumatic stress disorder among African American women living with HIV. AIDS Care 30 (11), 1393–1399.

Avery, E.F., Kleynhans, J.N., Ledergerber, B., Schoepf, I.C., Thorball, C.W., Kootstra, N. A., et al., 2023. Leukocyte count and coronary artery disease events in people with human immunodeficiency virus: a longitudinal study. Clin. Infect. Dis. 76 (11), 1969–1979.

Baral, S.D., Poteat, T., Stromdahl, S., Wirtz, A.L., Guadamuz, T.E., Beyrer, C., 2013. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. Lancet Infect. Dis. 13 (3), 214–222.

Bonn-Miller, M.O., Oser, M.L., Bucossi, M.M., Trafton, J.A., 2014. Cannabis use and HIV antiretroviral therapy adherence and HIV-related symptoms. J. Behav. Med. 37, 1–10.

Borders, A., 2020. Rumination and Related Constructs: Causes, Consequences, and Treatment of Thinking Too Much. Academic Press.

Bosh, K.A., Hall, H.I., Eastham, L., Daskalakis, D.C., Mermin, J.H., 2021. Estimated annual number of HIV infections— United States, 1981–2019. Morb Mortal Weekly Rep 70 (22), 801.

Breen, E.C., Sehl, M.E., Shih, R., Langfelder, P., Wang, R., Horvath, S., et al., 2022. Accelerated aging with HIV begins at the time of initial HIV infection. iScience 25 (7), 104488.

Bressler, S.L., Menon, V., 2010. Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn Sci 14 (6), 277–290.

Brown, T.T., Tassiopoulos, K., Bosch, R.J., Shikuma, C., McComsey, G.A., 2010. Association between systemic inflammation and incident diabetes in HIV-infected patients after initiation of antiretroviral therapy. Diabetes Care 33 (10), 2244–2249.

Bryant, V.E., Whitehead, N.E., Burrell, L.E., Dotson, V.M., Cook, R.L., Malloy, P., et al., 2015. Depression and apathy among people living with HIV: implications for treatment of HIV associated neurocognitive disorders. AIDS Behav. 19, 1430–1437.

Burke, J.G., Thieman, L.K., Gielen, A.C., O'Campo, P., McDonnell, K.A., 2005. Intimate partner violence, substance use, and HIV among low-income women: Taking a closer look. Voilence Against Women 11 (9), 1140–1161.

Calvo-Cidoncha, E., González-Bueno, J., Almeida-González, C.V., Morillo-Verdugo, R., 2015. Influence of treatment complexity on adherence and incidence of blips in HIV/HCV coinfected patients. J Manag Care Spec Pharm 21 (2), 153–157.

Camchong, J., Stenger, V.A., Fein, G., 2013. Resting-state synchrony in short-term versus long-term abstinent alcoholics. Alcohol Clin. Exp. Res. 37 (5), 794–803.

Cao, W., Cao, X., Hou, C., Li, T., Cheng, Y., Jiang, L., et al., 2016. Effects of cognitive training on resting-state functional connectivity of default mode, salience, and central executive networks. Front. Aging Neurosci. 8.

Capuron, L., Pagnoni, G., Drake, D.F., Woolwine, B.J., Spivey, J.R., Crowe, R.J., et al., 2012. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. Arch Gen Psychiatry 69 (10), 1044–1053.

Castillo-Mancilla, J.R., Morrow, M., Boum, Y., Byakwaga, H., Haberer, J.E., Martin, J.N., et al., 2018. Higher ART adherence is associated with lower systemic inflammation in treatment-naive Ugandans who achieve virologic suppression. J. Acquir. Immune Defic. Syndr. 77 (5), 507–513.

Castillo-Mancilla, J.R., Brown, T.T., Palella Jr., F.J., Macatangay, B.J.C., Breen, E.C., Jacobson, L.P., et al., 2020. Partial normalization of biomarkers of inflammation and immune activation among virally suppressed men with HIV infection and high ART adherence. Open Forum Infect. Dis. 7 (4).

Castillo-Mancilla, J.R., Musinguzi, N., Asiimwe, S., Siedner, M.J., Orrell, C., Bangsberg, D.R., et al., 2022. High residual inflammation despite HIV viral suppression: Lessons learned from real-time adherence monitoring among people with HIV in Africa. HIV Med. 23 (5), 465–473.

Centers for Disease Control Prevention, 2011. Characteristics associated with HIV infection among heterosexuals in urban areas with high AIDS prevalence—24 cities, United States, 2006-2007. MMWR Morbidity and mortality weekly report 60 (31), 1045–1049.

Chaganti, J.R., Heinecke, A., Gates, T.M., Moffat, K.J., Brew, B.J., 2017. Functional connectivity in virally suppressed patients with HIV-associated neurocognitive disorder: a resting-state analysis. Am. J. Neuroradiol. 38 (8), 1623–1629.

Chow, F.C., Mundada, N.S., Abohashem, S., La Joie, R., Iaccarino, L., Arechiga, V.M., et al., 2023. Psychological stress is associated with arterial inflammation in people living with treated HIV infection. Brain Behav. Immun. 113, 21–28.

Chung, H.Y., Cesari, M., Anton, S., Marzetti, E., Giovannini, S., Seo, A.Y., et al., 2009. Molecular inflammation: underpinnings of aging and age-related diseases. Ageing Res. Rev. 8 (1), 18–30.

Cole, D.M., Beckmann, C.F., Long, C.J., Matthews, P.M., Durcan, M.J., Beaver, J.D., 2010. Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics. Neuroimage 52 (2), 590–599.

Crane, M., Avihingsanon, A., Rajasuriar, R., Velayudham, P., Iser, D., Solomon, A., et al., 2014. Lipopolysaccharide, immune activation, and liver abnormalities in HIV/hepatitis B virus (HBV)–coinfected individuals receiving HBV-active combination antiretroviral therapy. J. Infect. Dis. 210 (5), 745–751.
Culley, D.J., Snayd, M., Baxter, M.G., Xie, Z., Lee, I.H., Rudolph, J., et al., 2014. Systemic inflammation impairs attention and cognitive flexibility but not associative learning in aged rats: possible implications for delirium. Front. Aging Neurosci. 6, 107.
Dale, S.K., Safren, S.A., 2020. Gendered racial microaggressions associated with depression diagnosis among Black women living with HIV. J. Urban Health 97 (3), 377–386.
Dale, S.K., Ayala, G., Logie, C.H., Bowleg, L., 2022. Addressing HIV-related intersectional stigma and discrimination to improve public health outcomes: an *AJPH* supplement. Am J Public Health 112 (S4), S335–S337.
Deeks, S.G., 2011. HIV infection, inflammation, immunosenescence, and aging. Annu. Rev. Med. 62, 141–155.
Desquilbet, L., Jacobson, L.P., Fried, L.P., Phair, J.P., Jamieson, B.D., Holloway, M., et al., 2007. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. J Gerontol A Biol Sci Med Sci 62 (11), 1279–1286.
Earnshaw, V.A., Eaton, L.A., Collier, Z.K., Watson, R.J., Maksut, J.L., Rucinski, K.B., et al., 2020. HIV stigma, depressive symptoms, and substance use. AIDS patient care and STDs 34 (6), 275–280.
Ellis, R.J., Peterson, S., Cherner, M., Morgan, E., Schrier, R., Tang, B., et al., 2021a. Beneficial effects of cannabis on blood–brain barrier function in human immunodeficiency virus. Clin. Infect. Dis. 73 (1), 124–129.
Ellis, R.J., Iudicello, J., Sun-Suslow, N., Grelotti, D., Cherner, M., Morgan, E., et al., 2021b. Social isolation is linked to inflammation in aging people with HIV and uninfected individuals. J. Acquir. Immune Defic. Syndr. 86 (5), 600–606.
Ellis, R.J., Fan, Y., Grelotti, D., Tang, B., Letendre, S., He, J.J., 2022. Astrocyte activation is a potential mechanism underlying depressed mood and apathy in people with HIV. J. Neurol. Psychol. 9 (1).
Ertl, N., Lawn, W., Mokrysz, C., Freeman, T.P., Alnagger, N., Borissova, A., et al., 2023. Associations between regular cannabis use and brain resting-state functional connectivity in adolescents and adults. J Psychopharm 37 (9), 904–919.
Eugenin, E.A., Osiecki, K., Lopez, L., Goldstein, H., Calderon, T.M., Berman, J.W., 2006. CCL2/monocyte chemoattractant protein-1 mediates enhanced transmigration of human immunodeficiency virus (HIV)-infected leukocytes across the blood–brain barrier: a potential mechanism of HIV–CNS invasion and NeuroAIDS. J. Neurosci. 26 (4), 1098–1106.
Felger, J.C., Li, L., Marvar, P.J., Woolwine, B.J., Harrison, D.G., Raison, C.L., et al., 2013. Tyrosine metabolism during interferon-alpha administration: association with fatigue and CSF dopamine concentrations. Brain Behav. Immun. 31, 153–160.
Ferrucci, L., Fabbri, E., 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat. Rev. Cardiol. 15 (9), 505–522.
Fleming, J., Mathews, W.C., Rutstein, R.M., Aberg, J., Somboonwit, C., Cheever, L.W., et al., 2019. Low-level viremia and virologic failure in persons with HIV infection treated with antiretroviral therapy. AIDS 33 (13), 2005–2012.
Fukui, S.M., Piggott, D.A., Erlandson, K.M., 2018. Inflammation strikes again: frailty and HIV. Curr. HIV AIDS Rep. 15 (1), 20–29.
Gagnepain, P., Hulbert, J., Anderson, M.C., 2017. Parallel regulation of memory and emotion supports the suppression of intrusive memories. J. Neurosci. 37 (27).
Glynn, T.R., Llabre, M.M., Lee, J.S., Bedoya, C.A., Pinkston, M.M., O'Cleirigh, C., et al., 2019. Pathways to health: an examination of HIV-related stigma, life stressors, depression, and substance use. Int. J. Behav. Med. 26 (3), 286–296.
Goodkin, K., Evering, T.H., Anderson, A.M., Ragin, A., Monaco, C.L., Gavegnano, C., et al., 2023. The comorbidity of depression and neurocognitive disorder in persons with HIV infection: call for investigation and treatment. Front. Cell. Neurosci. 17, 1130938.
Grenard, J.L., Munjas, B.A., Adams, J.L., Suttorp, M., Maglione, M., McGlynn, E.A., et al., 2011. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. J. Gen. Intern. Med. 26, 1175–1182.
Guaraldi, G., Malagoli, A., Calcagno, A., Mussi, C., Celesia, B.M., Carli, F., et al., 2018. The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: a cross sectional study of people aged 65–74 years and more than 75 years. BMC Geriatr. 18, 1–10.
Gunzler, D., Lewis, S., Webel, A., Lavakumar, M., Gurley, D., Kulp, K., et al., 2020. Depressive symptom trajectories among people living with HIV in a collaborative care program. AIDS Behav. 24 (6), 1765–1775.
Hammond, E.R., Crum, R.M., Treisman, G.J., Mehta, S.H., Clifford, D.B., Ellis, R.J., et al., 2016. Persistent CSF but not plasma HIV RNA is associated with increased risk of new-onset moderate-to-severe depressive symptoms; a prospective cohort study. J. Neurovirol. 22 (4), 479–487.
Hanna, D.B., Ramaswamy, C., Kaplan, R.C., Kizer, J.R., Anastos, K., Daskalakis, D., et al., 2016. Trends in cardiovascular disease mortality among persons with HIV in New York City, 2001–2012. Clin. Infect. Dis. 63 (8), 1122–1129.
Harrison, N.A., Cercignani, M., Voon, V., Critchley, H.D., 2015. Effects of inflammation on hippocampus and substantia nigra responses to novelty in healthy human participants. Neuropsychopharmacology 40 (4), 831–838.
Hernandez-Romieu, A.C., Garg, S., Rosenberg, E.S., Thompson-Paul, A.M., Skarbinski, J., 2017. Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009–2010. BMJ Open Diabetes Research and Care 5 (1), e000304.
Husain, M., Roiser, J.P., 2018. Neuroscience of apathy and anhedonia: a transdiagnostic approach. Nat. Rev. Neurosci. 19 (8), 470–484.
Juengling, F.D., Ebert, D., Gut, O., Engelbrecht, M.A., Rasenack, J., Nitzsche, E.U., et al., 2000. Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. Psychopharmacology (Berl) 152 (4), 383–389.
Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatr. 72 (6), 603–611.
Kamata, M., Higuchi, H., Yoshimoto, M., Yoshida, K., Shimizu, T., 2000. Effect of single intracerebroventricular injection of alpha-interferon on monoamine concentrations in the rat brain. Eur. Neuropsychopharmacol 10 (2), 129–132.
Kiefer, E.M., Hoover, D.R., Shi, Q., Dusingize, J.C., Sinayobye, J.D., Anastos, K., 2018. Longitudinal evaluation of markers of inflammation in HIV-positive and HIV-negative Rwandan women. HIV Med. 19 (10), 734–744.
Labandeira-Garcia, J.L., Rodriguez-Pallares, J., Rodríguez-Perez, A.I., Garrido-Gil, P., Villar-Cheda, B., Valenzuela, R., et al., 2012. Brain angiotensin and dopaminergic degeneration: relevance to Parkinson's disease. Am J Neurodegener Dis 1 (3), 226–244.
Labrenz, F., Wrede, K., Forsting, M., Engler, H., Schedlowski, M., Elsenbruch, S., et al., 2016. Alterations in functional connectivity of resting state networks during experimental endotoxemia–an exploratory study in healthy men. Brain Behav. Immun. 54, 17–26.
Lasselin, J., Schedlowski, M., Karshikoff, B., Engler, H., Lekander, M., Konsman, J.P., 2020. Comparison of bacterial lipopolysaccharide-induced sickness behavior in rodents and humans: relevance for symptoms of anxiety and depression. Neurosci. Biobehav. Rev. 115.
LeGrand, S., Reif, S., Sullivan, K., Murray, K., Barlow, M.L., Whetten, K., 2015. A review of recent literature on trauma among individuals living with HIV. Curr. HIV AIDS Rep. 12 (4), 397–405.
Lekander, M., Karshikoff, B., Johansson, E., Soop, A., Fransson, P., Lundström, J.N., et al., 2016. Intrinsic functional connectivity of insular cortex and symptoms of sickness during acute experimental inflammation. Brain Behav. Immun. 56, 34–41.
Leng, S.X., Margolick, J.B., 2015. Understanding frailty, aging, and inflammation in HIV infection. Curr. HIV AIDS Rep. 12 (1), 25–32.
Leone, M.J., Sun, H., Boutros, C.L., Liu, L., Ye, E., Sullivan, L., et al., 2021. HIV increases sleep-based brain age despite antiretroviral therapy. Sleep 44 (8).
Lew, B.J., McCusker, M.C., O'Neill, J., Bares, S.H., Wilson, T.W., Doucet, G.E., 2023. Resting state network connectivity alterations in HIV: parallels with aging. Hum. Brain Mapp. 44 (13), 4679–4691.
Liberale, L., Montecucco, F., Tardif, J.-C., Libby, P., Camici, G.G., 2020. Inflamm-ageing: the role of inflammation in age-dependent cardiovascular disease. Eur. Heart J. 41 (31), 2974–2982.
Liu, Z., Chen, X., Li, J., Xie, Z., Huang, Y., Luo, D., 2023. HIV-related stress predicts depression over five years among people living with HIV. Front. Public Health 11, 1163604.
Maes, M., Berk, M., Goehler, L., Song, C., Anderson, G., Galecki, P., et al., 2012. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. BMC Med. 10, 66.
Marcus, J.L., Leyden, W.A., Alexeeff, S.E., Anderson, A.N., Hechter, R.C., Hu, H., et al., 2020. Comparison of overall and comorbidity-free life expectancy between insured adults with and without HIV infection. JAMA Netw. Open 3 (6), e207954, 2000-2016.
Masyuko, S.J., Page, S.T., Polyak, S.J., Kinuthia, J., Osoti, A.O., Otieno, F.C., et al., 2021. Human immunodeficiency virus is associated with higher levels of systemic inflammation among Kenyan adults despite viral suppression. Clin. Infect. Dis. 73 (7), e2034–e2042.
Mauriño, R., Machado, A., Santiago, M., 2010. Effect of in vivo striatal perfusion of lipopolysaccharide on dopamine metabolites. Neurosci. Lett. 475 (3), 121–123.
McHugh, M.J., Gu, H., Yang, Y., Adinoff, B., Stein, E.A., 2017. Executive control network connectivity strength protects against relapse to cocaine use. Addict Biol 22 (6), 1790–1801.
McIntosh, R.C., Paul, R., Ndhlovu, L.C., Hidalgo, M., Lobo, J.D., Walker, M., et al., 2018. Resting-state connectivity and spontaneous activity of ventromedial prefrontal cortex predict depressive symptomology and peripheral inflammation in HIV. J. Neurovirol. 24 (5), 616–628.
McNamara, K.F., Biondi, B.E., Hernández-Ramírez, R.U., Taweh, N., Grimshaw, A.A., Springer, S.A., 2021. A systematic review and meta-analysis of studies evaluating the effect of medication treatment for opioid use disorder on infectious disease outcomes. Open Forum Infect. Dis. 8 (8), ofab289.
Mehta, S.R., Iudicello, J.E., Lin, J., Ellis, R.J., Morgan, E., Okwuegbuna, O., et al., 2021. Telomere length is associated with HIV infection, methamphetamine use, inflammation, and comorbid disease risk. Drug Alcohol Depend. 221, 108639.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 15 (10), 483–506.
Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 65 (9), 732–741.
Miller, A.H., Haroon, E., Raison, C.L., Felger, J.C., 2013. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress. Anxiety 30 (4), 297–306.
Mudra Rakshasa-Loots, A., Bakewell, N., Sharp, D.J., Gisslén, M., Zetterberg, H., Alagaratnam, J., et al., 2023. Biomarkers of central and peripheral inflammation mediate the association between HIV and depressive symptoms. Transl. Psychiatry 13 (1), 190.
Munro, C.E., Donovan, N.J., Guercio, B.J., Wigman, S.E., Schultz, A.P., Amariglio, R.E., et al., 2015. Neuropsychiatric symptoms and functional connectivity in mild cognitive impairment. J Alzheimers Dis 46 (3), 727–735.
Musinguzi, N., Castillo-Mancilla, J., Morrow, M., Byakwaga, H., Mawhinney, S., Burdo, T.H., et al., 2019. Antiretroviral therapy adherence interruptions are associated with systemic inflammation among Ugandans who achieved viral suppression. J. Acquir. Immune Defic. Syndr. 82 (4), 386–391.

Nusslock, R., Brody, G.H., Armstrong, C.C., Carroll, A.L., Sweet, L.H., Yu, T., et al., 2019. Higher peripheral inflammatory signaling associated with lower resting-state functional brain connectivity in emotion regulation and central executive networks. Biol Psychiatry 86 (2).
Nyundo, A.A., 2022. Neurocognitive decline as a major predictor of nonadherence to antiretroviral therapy among adults living with HIV in Dodoma region, central Tanzania. Health Sci Rep 5 (4), e669.
Olagunju, A.T., Adeyemi, J.D., Ogbolu, R.E., Campbell, E.A., 2012. A study on epidemiological profile of anxiety disorders among people living with HIV/AIDS in a Sub-Saharan Africa HIV clinic. AIDS Behav. 16 (8), 2192–2197.
Orban, L.A., Stein, R., Koenig, L.J., Conner, L.C., Rexhouse, E.L., Lewis, J.V., et al., 2010. Coping strategies of adolescents living with HIV: disease-specific stressors and responses. AIDS Care 22 (4), 420–430.
Ott, T., Nieder, A., 2019. Dopamine and cognitive control in prefrontal cortex. Trends Cogn Sci 23 (3), 213–234.
Parro-Torres, C., Hernández-Huerta, D., Ochoa-Mangado, E., Pérez-Elías, M.J., Baca-García, E., Madoz-Gúrpide, A., 2022. Antiretroviral treatment adherence and mental disorders: observational case-control study in people living with HIV in Spain. AIDS Care 34 (8), 1064–1072.
Piggott, D.A., Varadhan, R., Mehta, S.H., Brown, T.T., Li, H., Walston, J.D., et al., 2015. Frailty, inflammation, and mortality among persons aging with HIV infection and injection drug use. J Gerontol A Biol Sci Med Sci 70 (12), 1542–1547.
Ragin, A.B., Wu, Y., Storey, P., Cohen, B.A., Edelman, R.R., Epstein, L.G., 2006. Monocyte chemoattractant protein-1 correlates with subcortical brain injury in HIV infection. Neurology 66 (8), 1255–1257.
Raichle, M.E., 2015. The Restless Brain: How Intrinsic Activity Organizes Brain Function. Proc. Royal Soc. B 370 (1668), 20140172.
Rosen, M.I., Black, A.C., Arnsten, J.H., Goggin, K., Remien, R.H., Simoni, J.M., et al., 2013. Association between use of specific drugs and antiretroviral adherence: findings from MACH 14. AIDS Behav. 17 (1), 142–147.
Rubin, L.H., Maki, P.M., 2019. HIV, depression, and cognitive impairment in the era of effective antiretroviral therapy. Curr. HIV AIDS Rep. 16 (1), 82–95.
Rubin, L.H., Benning, L., Keating, S.M., Norris, P.J., Burke-Miller, J., Savarese, A., et al., 2018. Variability in C-reactive protein is associated with cognitive impairment in women living with and without HIV: a longitudinal study. J. Neurovirol. 24 (1), 41–51.
Saloner, R., Cherner, M., Grelotti, D.J., Paolillo, E.W., Moore, D.J., Heaton, R.K., et al., 2020. Lower CSF homovanillic acid relates to higher burden of neuroinflammation and depression in people with HIV disease. Brain Behav. Immun. 90, 353–363.
Saloner, R., Paolillo, E.W., Heaton, R.K., Grelotti, D.J., Stein, M.B., Miller, A.H., et al., 2021. Chronically elevated depressive symptoms interact with acute increases in inflammation to predict worse neurocognition among people with HIV. J. Neurovirol. 27 (1), 160–167.
Schrock, J.M., Snodgrass, J.J., Sugiyama, L.S., 2019. Lassitude: the emotion of being sick. Evol. Hum. Behav.
Schrock, J.M., Sugiyama, L.S., Naidoo, N., Kowal, P., Snodgrass, J.J., 2022. Greater chronic morbidity is associated with greater fatigue in six countries: a case of evolutionary mismatch? Evol Med Public Health 10 (1), 156–169.
Shattuck, E.C., Muehlenbein, M.P., 2015. Human sickness behavior: ultimate and proximate explanations. Am. J. Phys. Anthropol. 157 (1), 1–18.
Shmagel, K.V., Saidakova, E.V., Shmagel, N.G., Korolevskaya, L.B., Chereshnev, V.A., Robinson, J., et al., 2016. Systemic inflammation and liver damage in HIV/hepatitis C virus coinfection. HIV Med. 17 (8), 581–589.
Sieg, S.F., Shive, C.L., Panigrahi, S., Freeman, M.L., 2021. Probing the interface of HIV and inflammaging. Curr. HIV AIDS Rep. 18 (3), 198–210.
Sin, N.L., DiMatteo, M.R., 2014. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. Ann. Behav. Med. 47 (3), 259–269.
Socias, M.E., Milloy, M.J., 2018. Substance use and adherence to antiretroviral therapy: what is known and what is unknown. Curr. Infect. Dis. Rep. 20, 1–6.
Sotoyama, H., Inaba, H., Iwakura, Y., Namba, H., Takei, N., Sasaoka, T., et al., 2022. The dual role of dopamine in the modulation of information processing in the prefrontal cortex underlying social behavior. Faseb. J. 36 (2), e22160.
Stadtler, H., Shaw, G., Neigh, G.N., 2021. Mini-review: elucidating the psychological, physical, and sex-based interactions between HIV infection and stress. Neurosci. Lett. 747, 135698.
Subramanya, V., McKay, H.S., Brusca, R.M., Palella, F.J., Kingsley, L.A., Witt, M.D., et al., 2019. Inflammatory biomarkers and subclinical carotid atherosclerosis in HIV-infected and HIV-uninfected men in the Multicenter AIDS Cohort Study. PLoS ONE [Electronic Resource] 14 (4), e0214735.
Sundermann, E.E., Hussain, M.A., Moore, D.J., Horvath, S., Lin, D.T.S., Kobor, M.S., et al., 2019. Inflammation-related genes are associated with epigenetic aging in HIV. J. Neurovirol. 25 (6), 853–865.
Swann, G., Forscher, E., Bettin, E., Newcomb, M.E., Mustanski, B., 2018. Effects of victimization on mental health and substance use trajectories in young sexual minority men. Dev. Psychopathol. 1–15.
Swanta, N., Aryal, S., Nejtek, V., Shenoy, S., Ghorpade, A., Borgmann, K., 2020. Blood-based inflammation biomarkers of neurocognitive impairment in people living with HIV. J. Neurovirol. 26 (3), 358–370.
Tang, Y.Y., Posner, M.I., Rothbart, M.K., Volkow, N.D., 2015. Circuitry of self-control and its role in reducing addiction. Trends Cogn Sci 19 (8), 439–444.
Taren, A.A., Gianaros, P.J., Greco, C.M., Lindsay, E.K., Fairgrieve, A., Brown, K.W., et al., 2017. Mindfulness meditation training and executive control network resting state functional connectivity: a randomized controlled trial. Psychosom. Med. 79 (6), 674–683.
Temu, T.M., Zifodya, J.S., Polyak, S.J., Wagoner, J., Wanjalla, C.N., Masyuko, S., et al., 2021. Antiretroviral therapy reduces but does not normalize immune and vascular inflammatory markers in adults with chronic HIV infection in Kenya. AIDS 35 (1), 45–51.
Teng, S., Guo, Z., Peng, H., Xing, G., Chen, H., He, B., et al., 2017. High-frequency repetitive transcranial magnetic stimulation over the left DLPFC for major depression: session-dependent efficacy: a meta-analysis. Eur Psychiatry 41 (1), 75–84.
Thaler, N.S., Sayegh, P., Kim, M.S., Castellon, S.A., Hinkin, C.H., 2015. Interactive effects of neurocognitive impairment and substance use on antiretroviral non-adherence in HIV disease. Arch. Clin. Neuropsychol. 30 (2), 114–121.
Thomas, J.B., Brier, M.R., Snyder, A.Z., Vaida, F.F., Ances, B.M., 2013. Pathways to neurodegeneration: effects of HIV and aging on resting-state functional connectivity. Neurology 80 (13).
Turan, B., Rice, W.S., Crockett, K.B., Johnson, M., Neilands, T.B., Ross, S.N., et al., 2019. Longitudinal association between internalized HIV stigma and antiretroviral therapy adherence for women living with HIV: the mediating role of depression. AIDS (London, England) 33 (3), 571.
Turner, B.M., Rodriguez, C.A., Liu, Q., Molloy, M.F., Hoogendijk, M., McClure, S.M., 2019. On the neural and mechanistic bases of self-control. Cerebr. Cortex 29 (2).
Wada, N.I., Jacobson, L.P., Margolick, J.B., Breen, E.C., Macatangay, B., Penugonda, S., et al., 2015. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS 29 (4), 463–471.
Walker, K.A., Gross, A.L., Moghekar, A.R., Soldan, A., Pettigrew, C., Hou, X., et al., 2020. Association of peripheral inflammatory markers with connectivity in large-scale functional brain networks of non-demented older adults. Brain Behav. Immun. 87, 388–396.
Walmsley, S.L., Ren, M., Simon, C., Clarke, R., Szadkowski, L., 2020. Pilot study assessing the Rotterdam healthy aging score in a cohort of HIV-positive adults in Toronto, Canada. AIDS 34 (6), 859–867.
Ware, D., Rueda, S., Plankey, M., Surkan, P., Okafor, C.N., Teplin, L., et al., 2020. The longitudinal impact of employment, retirement and disability status on depressive symptoms among men living with HIV in the Multicenter AIDS Cohort Study. PLoS One 15 (10), e0239291.
Whittle, H.J., Sheira, L.A., Frongillo, E.A., Palar, K., Cohen, J., Merenstein, D., et al., 2019. Longitudinal associations between food insecurity and substance use in a cohort of women with or at risk for HIV in the United States. Addiction 114 (1), 127–136.
Wilcox, C.E., Abbott, C.C., Calhoun, V.D., 2019. Alterations in resting-state functional connectivity in substance use disorders and treatment implications. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 91, 79–93.
Xavier Hall, C.D., Morgan, E., Bundy, C., Foran, J.E., Janulis, P., Newcomb, M.E., et al., 2021. Substance use predicts sustained viral suppression in a community cohort of sexual and gender minority youth living with HIV. AIDS Behav. 25 (10), 3303–3315.
Yang, H.-Y., Beymer, M.R., Suen, S-c, 2019. Chronic disease onset among people living with HIV and AIDS in a large private insurance claims dataset. Sci. Rep. 9 (1), 18514.
Yukl, S.A., Gianella, S., Sinclair, E., Epling, L., Li, Q., Duan, L., et al., 2010. Differences in HIV burden and immune activation within the gut of HIV-positive patients receiving suppressive antiretroviral therapy. J. Infect. Dis. 202 (10), 1553–1561.
Zhai, T., Shao, Y., Chen, G., Ye, E., Ma, L., Wang, L., et al., 2015. Nature of functional links in valuation networks differentiates impulsive behaviors between abstinent heroin-dependent subjects and nondrug-using subjects. Neuroimage 115, 76–84.
Zhu, Y., Zhou, M., Jia, X., Zhang, W., Shi, Y., Bai, S., et al., 2023. Inflammation disrupts the brain network of executive function after cardiac surgery. Ann. Surg. 277 (3), e689.