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Through the Looking-Glass: Psychoneuroimmunology and the Microbiome-Gut-Brain Axis in the Modern Antiretroviral Therapy Era

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ABSTRACT

Objective: Depression, substance use disorders, and other neuropsychiatric comorbidities are common in people with HIV (PWH), but the underlying mechanisms are not sufficiently understood. HIV-induced damage to the gastrointestinal tract potentiates residual immune dysregulation in PWH receiving effective antiretroviral therapy. However, few studies among PWH have examined the relevance of microbiome-gut-brain axis: bidirectional crosstalk between the gastrointestinal tract, immune system, and central nervous system.

Methods: A narrative review was conducted to integrate findings from 159 articles relevant to psychoneuroimmunology (PNI) and microbiome-gut-brain axis research in PWH.

Results: Early PNI studies demonstrated that neuroendocrine signaling via the hypothalamic-pituitary-adrenal axis and autonomic nervous system could partially account for the associations of psychological factors with clinical HIV progression. This review highlights the need for PNI studies examining the mechanistic relevance of the gut microbiota for residual immune dysregulation, tryptophan catabolism, and oxytocin release as key biological determinants of neuropsychiatric comorbidities in PWH (i.e., body-to-mind pathways). It also underscores the continued relevance of neuroendocrine signaling via the hypothalamic-pituitary-adrenal axis, autonomic nervous system, and oxytocin release in modifying microbiome-gut-brain axis functioning (i.e., mind-to-body pathways).

Conclusions: Advancing our understanding of PNI and microbiome-gut-brain axis pathways relevant to depression, substance use disorders, and other neuropsychiatric comorbidities in PWH can guide the development of novel biobehavioral interventions to optimize health outcomes. Recommendations are provided for biobehavioral and neurobehavioral research investigating bidirectional PNI and microbiome-gut-brain axis pathways among PWH in the modern antiretroviral therapy era.

Key words: cocaine, depression, HIV, methamphetamine, microbiome, tryptophan.

INTRODUCTION

The central nervous system, neuroendocrine signaling, and the immune system dynamically interact in human immunodeficiency virus (HIV) pathogenesis (1). Even before the advent of highly active antiretroviral therapy (HAART), psychoneuroimmunology (PNI) research uncovered neuroendocrine mechanisms whereby psychological factors influence clinical HIV progression (2,3). In the HAART era (i.e., 1997–2006), the associations of psychological factors with HIV disease markers and clinical HIV progression often persisted after adjusting for medication adherence (4–6). Although informative, HAART-era studies mostly examined neuroendocrine mechanisms linking psychological factors with HIV pathogenesis (i.e., mind-to-body pathways whereby mental health and stress influenced HIV disease markers). Relatively few studies characterized the pathways whereby HIV-associated pathophysiologic alterations amplify the risk of depression, substance use disorders, and other neuropsychiatric disorders (i.e., body-to-mind pathways) (7). This unidirectional approach diminished our

ART = antiretroviral therapy, **CRP** = C-reactive protein, **CMV** = cytomegalovirus, **CTRA** = conserved transcriptional response to adversity, **HAART** = highly active antiretroviral therapy, **HPA axis** = hypothalamic-pituitary-adrenal axis, **HIV** = human immunodeficiency virus, **IDO-1** = indoleamine 2,3-dioxygenase 1, **LPS** = lipopolysaccharide, **NE** = norepinephrine, **PGN** = peptidoglycan, **PNI** = psychoneuroimmunology, **PWH** = people with HIV, **SIV** = simian immunodeficiency virus, **Th_{17}** = T-helper 17 cells

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ability to test integrated models to guide the development of biobehavioral treatments for these prevalent comorbidities among people with HIV (PWH) (8,9).

During the past 15 years (2007–present), profound advances in the medical management of HIV ushered in the modern antiretroviral therapy (ART) era where current treatment guidelines recommend ART at any CD4+ T-cell count (10). Modern ART regimens are less burdensome such that many PWH take one pill daily with far fewer adverse effects and can achieve viral suppression (<200 copies/ml) at much lower levels of adherence. Consequently, rates of viral suppression have drastically increased, with 86% of those receiving HIV clinical care at eight sites across the United States were virally suppressed by 2015 (11). Although PWH who have depression and PWH who use stimulants such as methamphetamine may achieve viral suppression more slowly (11,12), these priority populations are displaying unprecedently high rates of viral suppression. This provides new opportunities to examine PNI pathways in PWH who are virally suppressed to mitigate (but not eliminate) the influence of ART adherence (13,14).

Multilevel determinants are implicated in the etiology and maintenance of depressive disorders among PWH (10). Depression is a prevalent comorbidity, affecting as many as one-third of PWH (31%; 95% confidence interval = 28%–34%) (8,9). Greater risk of suicide has also been well characterized among PWH. Although suicide risk decreased somewhat with the advent of HAART (15), the suicide rate remains threefold higher among PWH than the general Swiss population (16). Recent evidence indicates that multiple indicators of suicide risk are elevated among PWH around the globe (17). Advancing our understanding of the complex etiology of depression and suicide risk in PWH will require more comprehensive efforts to understand the relevance of HIV-associated biological alterations in the context of key structural and social determinants.

Substance use disorders are prevalent comorbidities among PWH that increase the risk of HIV seroconversion, complicate HIV disease management, and fuel faster clinical HIV progression (18,19). PWH who use stimulants such as methamphetamine display faster clinical HIV disease progression, even after adjusting for ART adherence and viral load (20,21). PNI studies to characterize the bidirectional, neuroimmune consequences of co-occurring stimulant use disorders and HIV are needed to catalyze the development of novel, biobehavioral treatments (22). Similarly, there may be clinically meaningful neuroimmune predictors and consequences of tobacco, alcohol, and other substance use that warrant further study in PWH (22,23).

The overarching goal of this narrative review is to provide a framework to guide PNI research in the modern ART era with a focus on microbiome-gut-brain axis interactions. There are new opportunities to investigate the potentially bidirectional mechanisms linking depression, substance use disorders, and other neuropsychiatric comorbidities with HIV-associated pathophysiologic alterations that persist despite effective ART (23,24). To accomplish this goal, we first examine seminal PNI studies conducted through the HAART era. Many studies yielded provocative, mechanistic results that can guide PNI research examining the role of neuroendocrine signaling in the reciprocal interactions between gastrointestinal tract (and its resident microorganisms), immune system, and central nervous system, which will be referred to as the microbiome-gut-brain axis. We step "through the looking-glass" to envision a new generation of PNI studies that leverage our conceptual model of the microbiome-gut-brain axis in PWH receiving effective ART. This narrative review concludes with recommendations for a PNI research agenda to investigate the bidirectional pathways linking the microbiome-gut-brain axis and neuropsychiatric comorbidities in PWH.

THAT WAS THEN: PNI STUDIES CONDUCTED THROUGH THE HAART ERA

PNI studies conducted through the HAART era delineated neuroendocrine mechanisms whereby psychological factors are linked to clinical HIV progression. There was convergent evidence from multiple cohort studies that trauma, stress, and depression predict faster clinical HIV progression (6). On the other hand, positive psychological factors such as positive affect, finding meaning, and spirituality predicted slower clinical HIV progression (4). These effects are thought to be partially attributable to alterations in neuroendocrine signaling, with a primary focus on hypothalamic-pituitary-adrenal (HPA) axis function and autonomic nervous system activation.

Clinical studies conducted during the HAART era provided support for the premise that alterations in the HPA axis and the autonomic nervous system mediate the effects of psychological factors on immune function in PWH. Randomized controlled trials indicated that decreases in urinary cortisol and norepinephrine (NE) output partially mediated the effects of a cognitive-behavioral stress management intervention on HIV disease markers such as subsets of naive CD4+ T cells (5,25,26). This was further supported by findings indicating that elevated urinary cortisol and NE predicted higher viral load after adjusting for HAART adherence (27), and greater autonomic nervous system activation at rest predicted poorer CD4+ T-cell recovery and decreased viral suppression in response to HAART (28). There was also evidence that higher urinary cortisol was associated with fewer subsets of naive CD4+ T cells in the HAART era (26), and more diurnal variation in salivary cortisol (thought to be a healthy pattern) was associated with less CD4+ T-cell and CD8+ T-cell activation in PWH who were ART naive (29). The relevance of the autonomic nervous system in HIV pathogenesis is further supported by a reactivity study examining a speech stressor task where PWH (compared with people without HIV) displayed greater stress-induced increases in activated CD8+ CD38+ T cells, smaller increases in natural killer cell number and cytotoxicity, and suppression of the T-cell lymphoproliferative response to phytohemagglutinin mitogen, which are each indicative of immune dysregulation (30). The associations of catecholamines such as epinephrine with these stress-induced immunologic changes varied by HIV status, suggesting functional alterations in the communication of the sympathetic nervous system with the immune system among PWH.

There is compelling evidence that sympathetic nervous system innervation of lymphoid organs (e.g., lymph nodes) modulates HIV replication and potentially the HIV reservoir (i.e., immune cells, organs, and lymphoid tissue where HIV replication persists despite viral suppression). NE released from the sympathetic nervous system nerve terminals that juncture with lymphoid tissue binds with β_2 receptors on the lymphocyte membrane, thereby inducing cellular changes in the lymphocyte via the G protein–linked adenyl cyclase–cAMP–protein kinase A signaling cascade (31). In vitro data have shown that cellular changes of this nature are associated with decrements in interferon-γ and interleukin-10, which in turn, are linked to elevations in HIV viral load (32). Results from other in vitro studies indicate that similar pathways

underlie sympathetic nervous system induced reactivation of human herpesvirus-8 and cytomegalovirus (CMV), two viruses from the herpesvirus family linked to clinical HIV progression (33,34). PNI studies are needed to determine if behavioral and psychological factors can influence the HIV reservoir as well as reactivate herpesvirus coinfections by modulating the autonomic nervous system.

Simian immunodeficiency virus (SIV) studies support stress-related alterations in communication between the sympathetic nervous system and immune system. There is plasticity in the density of sympathetic nervous system catecholaminergic neural fibers that juncture with the lymph nodes, which is modified by social stress in rhesus macaques (35). In fact, SIV replication is increased by 3.9-fold in the vicinity of catecholaminergic varicosities with the lymph nodes (36). Interestingly, there is some indication of specificity for the effect of social stress as related to antiviral responses. Although methamphetamine administration amplified sympathetic nervous system activation, only social instability increased the density of catecholaminergic nerve fibers in lymph nodes while downregulating the expression of genes associated with innate antiviral responses and upregulating inflammatory genes in rhesus macaques (37). Another recent study of acute SIV in pigtailed macaques observed that singly housed (versus socially housed) animals displayed higher viral load in plasma and cerebrospinal fluid, greater CD4+ T-cell count declines, and more CD4+ and CD8+ T-cell activation (25). Taken together, these studies underscore the potentially central importance of social processes in HIV pathogenesis. Although social support was extensively examined in early PNI studies with PWH, findings were generally mixed and varied as a function of disease stage as well as mode of transmission (38).

These well-characterized mechanisms will continue to guide the scientific premise of PNI research, and there are four important opportunities for building upon these seminal PNI studies in the modern ART era. First, substantial advances in our understanding of HIV-associated pathophysiologic alterations can guide efforts to characterize the complex, bidirectional connections between neuroendocrine signaling and the microbiome-gut-brain axis. Second, it is unclear to what extent neuroendocrine signaling will continue to influence HIV pathogenesis in the modern ART era. Third, findings from SIV studies underscore the need for more robust efforts in human studies to characterize the relevance of social adversity, which is only beginning to be examined in PNI research conducted in PWH. Fourth, many PNI studies used stringent inclusion criteria that increased scientific rigor at the expense of generalizability (e.g., conducted mostly in sexual minority men, excluded substance users). Studies are needed to characterize the relevance of PNI mechanisms in more representative samples of PWH in the modern ART era.

THIS IS NOW: MICROBIOME-GUT-BRAIN AXIS ALTERATIONS RELEVANT TO NEUROPSYCHIATRIC COMORBIDITIES

In the sections hereinafter, we review evidence supporting a microbiome-gut-brain axis model relevant to depression, substance use disorders, and other neuropsychiatric disorders in PWH (Figure 1). We begin by providing an overview of what is known about the composition of the gut microbiota in PWH and the relevance of modifiable factors like stimulant use on microbiota composition and function. This section also highlights the importance of *direct* vagal afferent communication between the gut microbiota and the brain in modifying oxytocin release, mood, and behaviors relevant to depression and substance use disorders. Next, we describe the importance of persistent gut-immune dysregulation in PWH with a focus on *indirect*, immune-mediated pathways that could account for microbiome-gut-brain axis interactions. Then, we present findings regarding the relevance of peripheral immune dysregulation for depression in PWH and how this may be amplified by experiences relevant to social adversity. Finally, we briefly review evidence suggesting that neuroendocrine signaling can modify the microbiome-gut-brain axis in the modern ART era.

The Gut Microbiota in PWH

The gut microbiota include trillions of bacteria, eukaryotes, and viruses (39,40). These microorganisms play a vital role in maintaining neuroimmune homeostasis and are associated with health outcomes, including HIV disease progression (39–43). Most research has focused on bacteria, which can influence neural, endocrine, and immune cells in the gut, periphery, and brain through the release of bacterial metabolites or via direct contact of bacteria (or bacterial products) with host cells (40,41,43). This can lead to chronic peripheral and neuroinflammation, dysregulated neurotransmitter synthesis, and altered afferent vagal nerve stimulation. In addition, gut bacteria can influence intestinal permeability, impact blood-brain-barrier integrity, modify nutrient absorption, alter the growth of pathogenic bacteria, and take part in drug metabolism, all of which are relevant to neuroimmune functioning among PWH (40–44). Many of these pathways whereby gut microbiota could potentiate depression, substance use disorders, and other neuropsychiatric comorbidities that compromise HIV disease management remain largely unexamined.

PWH show differences in the composition and function of the gut microbiota compared with people without HIV (42,45). Microbiome alterations are more prominent among untreated PWH, but disruptions persist despite effective ART (45). The gut microbiome generally shows a pattern of decreased community diversity (46–49) as well as enrichment of bacterial taxa linked to inflammation, microbial translocation, and poor CD4+ T-cell restoration. There is also evidence of depletion of bacterial taxa that are inversely associated with these markers (49,50). In addition to the role of HIV infection in altering the gut environment, the gut microbiome can be modified by a variety of behavioral and psychological factors, but studies in PWH are generally lacking or correlative. For example, stimulant use and alcohol use are associated with altered gut microbiota among PWH (51,52). There is also increasing interest in the mechanisms whereby microbiome-related alterations in reward processing influence the maintenance and severity of various neuropsychiatric disorders, including substance use disorders (53). Further research is needed to characterize the bidirectional microbiome-gut-brain axis mechanisms relevant to problematic patterns of alcohol or other substance use among PWH.

Gut Microbiota and Vagal Nerve Stimulation

The vagus nerve innervates the gut, providing bidirectional (80% afferent, 20% efferent) communication with the central nervous system. Vagal tone is essential for decreasing gut permeability so that microbial products like lipopolysaccharide (LPS) do not leak into the periphery to amplify residual immune dysregulation. A recent study of PWH who presented with gastrointestinal symptoms observed that vagal dysfunction was associated with bacterial

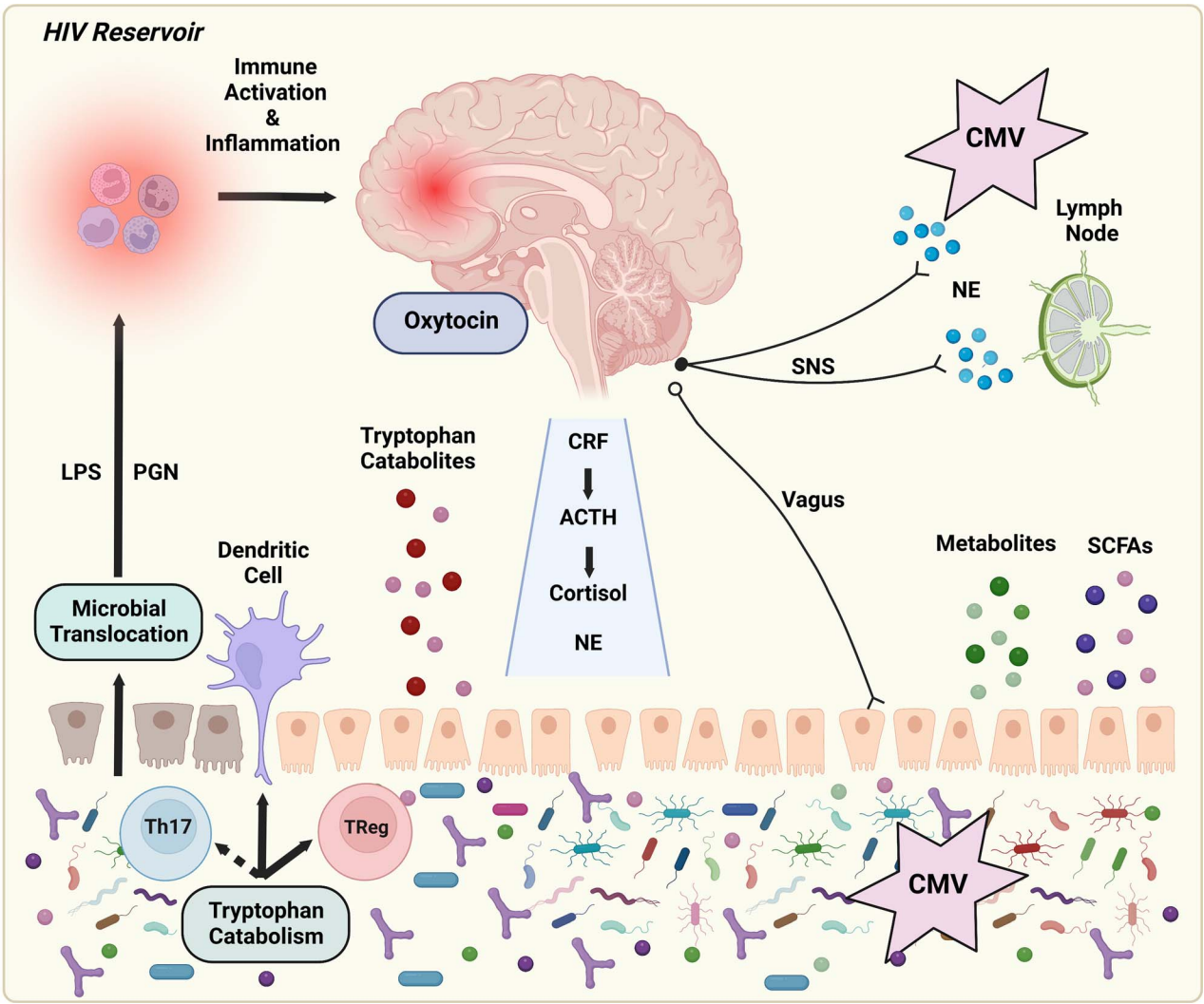

FIGURE 1. A microbiome-gut-brain axis model of neuropsychiatric comorbidities in the modern antiretroviral therapy era. ACTH = adrenocorticotropic hormone; CRF = corticotropin releasing factor; CMV = cytomegalovirus; LPS = lipopolysaccharide; NE = norepinephrine; PGN = peptidoglycan; SCFAs = short-chain fatty acids; SNS = sympathetic nervous system; Th_{17} = T-helper 17 cells; T_{Reg} = regulatory T cells.

outgrowth in the small intestines that was, in turn, linked to greater systemic inflammation (54). Efferent vagal pathways that are modulated by decreases in depressive symptoms have the potential to alter the gut microbiota and decrease microbial translocation, as evidenced by the effects of vagal stimulation (55,56). Prior clinical research in people without HIV observed that increased vagal tone is an important indicator of a favorable response to cognitive-behavioral treatments for depression (57,58). PWH may also experience autonomic neuropathy (59), which is linked to vagal dysfunction and microbiome-gut-brain axis alterations.

Gut microbiota can also modulate mood and behaviors by altering stimulation of the vagal nerve. For example, gut bacteria release metabolites (or induce host cells to release metabolites) that stimulate the vagal nerve afferents that alter hypothalamic function (60) to promote the release of oxytocin (a neuropeptide that influences social behavior, metabolism, and wound healing) in the brain. In fact, *Lactobacillus reuteri* have been shown to activate vagal afferents to potentiate oxytocin release from the paraventricular nucleus of the hypothalamus (61). This process promotes the coordinated activity of oxytocin and serotonin in the nucleus accumbens to increase the experience of social reward (62), which could have important implications for anhedonia, a common symptom of many neuropsychiatric disorders, including substance use disorders and depression (63). Although oxytocin has not been extensively examined among PWH, there is some evidence of nonlinear associations in PNI studies (64). Higher oxytocin levels have been associated with more severe depressive symptoms in PWH (17), potentially reflecting a compensatory response to depressive symptoms. In another cross-sectional study, the association of elevated stress with lower CD4+ T-cell count was observed only at higher levels of oxytocin among low-income ethnic minority women with HIV (65). There is a clear need for microbiome-gut-brain axis studies to understand

the relevance of oxytocin in context of other important neuroimmune pathways among PWH.

The Central Importance of Gut-Immune Dysfunction in HIV Pathogenesis

Damage to the gut during acute HIV is thought to be a primary driver of alterations in gut microbiota (66), expansion of the enteric virome (67), depletion of CD4+ T cells (68), and increased gut permeability (66,68,69). Most notably, there is a preferential depletion of T-helper 17 cells (Th_{17}) cells that are essential for maintaining gut barrier integrity (70), and this is currently irreversible unless ART is initiated early in acute HIV infection (71). Further research is needed to understand how key alterations to microbiome-gut-brain axis pathways could amplify the risk of persistent neuropsychiatric comorbidities during acute HIV infection and after suppressive ART.

HIV-induced damage to the gut results in the translocation of microbial products such as LPS and peptidoglycan (PGN) across the gut barrier. When these microbial products cross the damaged gut barrier and enter the periphery, they chronically stimulate immune cells, which causes ongoing immune activation and inflammation in PWH (24). Despite the prominent focus on microbial translocation of LPS, PGN is also linked to inflammation in the gut and brain (72–74). Fragments of PGN are released into circulation as byproducts of bacterial cell remodeling and are typically recognized by pattern recognition receptors and other PGN-specific recognition proteins on host immune cells (75–77). Although the role of PGN in HIV has not been well established, PGN has been implicated in autoimmune diseases such as Crohn disease (78), rheumatoid arthritis (79), and multiple sclerosis (80). The potential implications for neuroinflammation are supported by observations of high concentrations of PGN in brain lesions in people with multiple sclerosis (80). Given its role in neuroimmune modulation, studies are needed to better understand the relevance of PGN for depression, substance use disorders, and other neuropsychiatric disorders among PWH (76).

There is growing evidence for interactions between stimulant use and microbiome-gut-brain axis pathways via the gut-immune dysregulation. One such pathway is through the impact of stimulant-induced microbial translocation and gut barrier dysfunction. Stimulants such as methamphetamine can decrease parasympathetic tone (81), which could increase intestinal permeability. Stimulants also directly damage gut barrier integrity in self-administering HIV-1 transgenic rats (82) and were associated with depleted tryptophan (an essential amino acid precursor for serotonin) in PWH receiving HAART (83). Tryptophan catabolites could damage gut barrier integrity through several mechanisms described hereinafter (84). Bearing in mind that there are currently no treatments for stimulant use disorders approved by the US Food and Drug Administration, mechanistic studies characterizing these complex microbiome-gut-brain axis pathways could identify novel targets for pharmacologic interventions in PWH who have stimulant use disorders that serve as a key obstacle to sustained viral suppression.

Another mechanism whereby the gut microbiota can alter immune surveillance is inducing the enzyme indoleamine 2,3-dioxygenase 1 (IDO-1) to catabolize tryptophan (85). Tryptophan catabolites influence immune function in the periphery and are neuroactive. PWH display increases in tryptophan catabolism that are linked to depressive symptoms and only partially normalized by ART (7,86). Tryptophan catabolism may also be exacerbated among those with protein-deficient diets, highlighting the importance of food insecurity in the intersection of biological and structural determinants relevant to depression among PWH (87,88). Examining the role of tryptophan catabolism in the microbiome-gut-brain axis in the modern ART era could help address the underlying HIV-associated biological alterations that modify depression and suicide risk to optimize mental health treatment for PWH.

Because PWH have more gut bacterial taxa that produce a metabolite homologous to IDO-1 (89,90), HIV-associated alterations in gut microbiota community composition are accompanied greater tryptophan catabolism. Several gut bacteria produce tryptophan catabolites that exert local effects and translocate to have systemic effects (91). Although there is some evidence that *Lactobacillus* could reduce IDO-1 activity in SIV-infected macaques (92), further research is needed to elucidate the mechanisms whereby changes in the gut microbiota alter tryptophan catabolism in PWH (93). Furthermore, the translocation of microbial products across the gut barrier upregulates IDO-1 via immune activation, which can amplify tryptophan catabolism and its neuropsychiatric consequences.

Dendritic cells are essential for presenting antigens to other immune cells and regulating polarization of T cells into functional subsets. Dendritic cells expressing IDO-1 are thought to promote the development of regulatory T cells that suppress the immune response (94). In untreated HIV, upregulation of IDO-1 in dendritic cells is observed in the lymph nodes and gut lymphoid tissues, and there is concomitant depletion of Th_{17} cells that are essential for maintaining gut barrier integrity (84,95). The mechanistic importance of tryptophan catabolism is supported by in vitro experimental findings that 3-hydroxyanthranilic acid (a catabolite of tryptophan) decreases the ratio of Th_{17} to regulatory T cells in peripheral blood mononuclear cells (84). Because tryptophan catabolites cross the blood-brain barrier (96), there is also biological plausibility for observed associations of tryptophan depletion in plasma with cognitive impairment, depressed mood, anhedonia, and impulsivity in PWH (85,97,98).

The role of the gut microbiota in influencing gut-immune dysregulation may also amplify neuropsychiatric comorbidities beyond substance use and depression, such as cognitive impairment. PWH show a decrease in bacterial production of neuroprotective short-chain fatty acids and other neuroactive metabolites, as well as concomitant increases in tryptophan catabolism, immune activation, and inflammation secondary to microbial translocation as noted previously (42,89,99–102). These mechanisms can potentiate the production of neurotoxic metabolites, increase permeability of the blood-brain barrier, and stimulate immune cells to transport HIV across the blood-brain barrier (43,103,104). In PWH, markers of microbial translocation (e.g., LPS), monocyte activation, changes in gut microbiota composition (e.g., alteration in the ratio of *Firmicutes* to *Bacteroides*), and heightened IDO-1 activity have been associated with cognitive impairment and morphological brain changes (103–107). An extensive review of microbiome-gut-brain axis mechanisms relevant to cognitive impairment among PWH has been published elsewhere (43).

Residual Immune Dysregulation in PWH

Even with long-term effective ART, PWH experience persistent residual immune dysregulation, leading to faster onset and greater severity of age-related diseases (24). Specifically, elevated immune

activation, inflammation, and coagulation in those receiving effective ART are associated with a spectrum of comorbidities that are not related to AIDS, including cardiovascular disease (108,109), cognitive impairment (110,111), metabolic disorders (112), and cancer (24). The clinical relevance of residual immune dysregulation is supported by the fact that HIV-associated non-AIDS conditions occur at younger ages with more severe health implications (109). Residual immune dysregulation could also have important consequences for the development and maintenance of neuropsychiatric disorders such as depression.

Several PNI studies examining the neuropsychiatric consequences of residual immune dysregulation have focused on depression in PWH. Findings from the Multicenter AIDS Cohort study (1984–2010) indicate that elevations in soluble markers of immune activation and inflammation predict greater odds of screening positive for depression in men, and interestingly, this association was more pronounced among those without HIV (113). Specifically, serum C-reactive protein (CRP) levels greater than 3 mg/L were associated with 2.3 times greater odds of screening positive for depression. Another study observed associations between elevated CRP and depressive symptom severity in PWH (114), particularly among men with HIV where elevated CRP levels were associated with 3.7 times greater odds of moderate to severe depressive symptoms. Results from another large cohort study of PWH also indicated that greater depressive symptom severity was associated with an elevated proinflammatory profile consisting of elevated D-dimer, IL-6, and CRP, albeit in only in men (115). Although the inflammatory profile covaries with depression in PWH, many studies conducted to date around the globe have measured different cytokines, focused on depressive symptoms and not clinical diagnoses, enrolled modest sample sizes, and did not adjust for multiple comparisons (116–118). Finally, there is also evidence to support a potentially unique role of innate immune activation. Results from the Veterans Aging Cohort Study (2005–2006) indicate that somatic symptoms of depression were associated with elevated markers of monocyte activation (119). The beneficial associations of selective serotonin reuptake inhibitor use with lower monocyte activation and reduced inflammation in this cohort study underscore the importance of understanding the peripheral mechanisms whereby pharmacological treatment of depression could modify the microbiome-gut-brain axis crosstalk in PWH receiving effective ART, particularly among those who present with elevated inflammation (e.g., CRP >3.0 mg/L).

There is increasing evidence that CMV reactivation is another important driver of residual immune dysregulation in the modern ART era (120–122). CMV infection activates a variety of innate and adaptive cell types including monocytes, macrophages, and CD4+, and CD8+ T cells with high levels of viral replication in select mucosal sites including the gut (120). In the modern ART era, immunologic measures of CMV and Epstein-Barr virus reactivation are independently linked to HIV-associated non-AIDS conditions such as myocardial infarction (123), and CMV-induced immunologic alterations are thought to potentiate accelerated aging in PWH (124). Among PWH receiving effective ART, latently infected T cells maintain the HIV reservoir via several mechanisms including T-cell proliferation (125). Impaired ability to control CMV infection could be a primary driver of cytokine and chemokine overflow that fuel immune activation and immunosenescence of T cells to maintain the HIV reservoir (126). PNI studies conducted in the modern ART era are needed to examine the bidirectional pathways linking asymptomatic CMV reactivation, residual immune dysregulation, and psychological factors.

Elucidating the Effects of Social Adversity

PWH experience social adversity stemming from developmental vulnerabilities as well as intersectional stigma and discrimination that could amplify the risk of neuropsychiatric comorbidities via alterations in the microbiome-gut-brain axis. Many PWH experience early life stress that serves as a risk factor for developmental trajectories that increase vulnerability to HIV and could create fundamentally different set points in neuroendocrine signaling (127). Developmental vulnerabilities (128) as well as intersectional stigma and discrimination related to HIV and other minoritized identities (e.g., racial/ethnic minority, sexual minority, or gender minority) may have important health consequences (129,130).

The field of social genomics provides opportunities to examine the epigenetic mechanisms whereby the HPA axis and the autonomic nervous system could influence residual immune dysregulation in the modern ART era. The conserved transcriptional response to adversity (CTRA) is a validated profile of leukocyte gene expression reflecting upregulated expression of genes involved in inflammation as well as downregulated expression of genes involved with type I interferon (a cytokine involved in antiviral and antitumor responses) and antibody synthesis (131). Psychosocial challenges such as experiences of discrimination have been associated with a higher CTRA, irrespective of HIV status (132). This observation is consistent with findings where homophobic victimization was associated with a higher CTRA among sexual minority men without HIV (133). Interestingly, methamphetamine use and intimate partner violence are associated with upregulation of the inflammatory genes as well as upregulation of the type I interferon and antibody synthesis genes among sexual minority men with HIV (134). The upregulation of type I interferon and antibody synthesis genes may be driven in part by active viremia in this study. These findings are further supported by cross-sectional studies documenting the associations of sexual minority stress and recent stimulant use with alterations in gene expression patterns relevant to immune activation and inflammation in methamphetamine-using sexual minority men with HIV who were virally suppressed (135,136). More comprehensive, longitudinal studies are needed to understand how social adversity and stimulant use alter the transcriptional regulation of leukocytes among PWH.

Neuroendocrine Signaling and the Microbiome-Gut-Brain Axis

Seminal PNI studies provided support for the role of neuroendocrine signaling in altered immune function among PWH. In the modern ART era, PNI studies should expand our understanding of the relevance of the complex, bidirectional interactions of catecholamines, cortisol, and oxytocin with gut microbiota. These neuroendocrine signaling mechanisms for the biologically plausible effects of depression and other neuropsychiatric comorbidities on the microbiome-gut-brain axis in PWH are described briefly hereinafter. Experimental studies are needed to understand whether and how interventions to reduce depression and substance use influence the microbiome-gut-brain axis via alterations in these distinct neuroendocrine signaling pathways.

There is evidence for the impact of neuroendocrine signaling on the gut and inflammation. Catecholamines directly affect the growth and virulence of several species of anaerobes, such as *Enterobacteriaceae*, in the gut (137,138). More recently, this group

demonstrated that higher adrenergic baroreceptor sensitivity, an index of a more hyperadrenergic state, was associated with greater inflammation in PWH (139). Another study with 4000 PWH from the Strategies for Management of Antiretroviral Therapy study revealed cross-sectional inverse associations between heart rate variability with soluble markers of inflammation and coagulation (140). Bearing in mind that stimulants act primarily by altering the function of catecholamines, stimulants and HIV are independently associated with higher NE in cerebrospinal fluid and dysregulated systemic metabolism of tyrosine (an essential amino acid precursor for catecholamines) (141,142). Alterations in catecholamines could partially explain associations of stimulant use with greater immune activation, inflammation, HIV proviral DNA in immune cells, and immune exhaustion in PWH who are virally suppressed or undetectable (142–146). Interestingly, the associations of stimulant use with these outcomes often persist after adjusting for self-reported ART adherence (142–146). A group-based cognitive-behavioral intervention decreased urinary NE output in sexual minority men with HIV, which is consistent with the notion that psychological interventions can influence the autonomic nervous system in PWH (25). Further research is needed to determine if there are distinct effects of vagal tone versus systemic release catecholamines from the HPA axis on the microbiome-gut-brain axis in PWH.

Although changes in HPA axis functioning resulting in elevated cortisol and catecholamines are well characterized, further research is needed with PWH to understand the mechanistic role of the gut microbiota in influencing the neuroendocrine stress responses. There is some evidence that gut microbiota metabolize glucocorticoids with relevance for hypertension and androgen production (147). There are also dynamic, bidirectional interactions where glucocorticoids are thought to influence the composition of gut microbiota (147), which have been shown to modify glucocorticoid receptor expression in mice (148). Translational research with humans is clearly needed to understand the role of the HPA axis in modifying microbiome-gut-brain axis responses, particularly among PWH where adrenal insufficiency secondary to infections such as a CMV is more common (149,150).

There is also increasing evidence that oxytocin release in the brain can modify microbiome-gut-brain axis function (151). For example, one recent experimental study with rats observed that intracisternal injection of oxytocin decreased microbial translocation because of LPS in a dose-dependent manner. Interestingly, these effects of oxytocin on decreased microbial translocation were blocked by vagotomy, which underscores the central importance of efferent vagal communication with the gut (152). There is also experimental evidence in rats that oxytocin could mitigate the effects of stress on gastric emptying and motility (153). Finally, findings from human studies indicate that oxytocin may play an important role in the enteric nervous system of the gut. This is partially supported by findings from biopsies of the gastrointestinal tract where oxytocin was expressed in the myenteric and submucous ganglia and nerve fibers (154). Further research in PWH is needed to determine whether and how increases in oxytocin could modify the microbiome-gut-brain axis.

THROUGH THE LOOKING-GLASS: RECOMMENDATIONS FOR PNI AND MICROBIOME-GUT-BRAIN AXIS STUDIES

Modern PNI studies are needed to determine how several, interrelated HIV-associated pathophysiologic alterations could amplify the risk of neuropsychiatric comorbidities among PWH receiving effective ART. Drawing upon our conceptual model (Figure 1), delineating the mechanisms whereby alterations in gut microbiota influence neural signaling (e.g., the vagus nerve), alter tryptophan catabolism and other neuroactive metabolites, and indirectly impact immune dysregulation in treated HIV is essential to catalyze the development of tailored pharmacologic treatments for depression, substance use disorders, and other neuropsychiatric disorders among PWH. On the other hand, neuropsychiatric disorders such as depression could also potentiate alterations in the microbiome-gut-brain axis via the HPA axis, autonomic nervous system, and oxytocin release. PNI studies are needed to examine how alterations in these neuroendocrine signaling pathways could modify microbiome-gut-brain axis pathways relevant to neuropsychiatric disorders and health outcomes in PWH. More robust efforts are needed to embrace experimental rigor by testing the mechanisms whereby biomedical (e.g., vagal stimulation, probiotics) or behavioral interventions (e.g., cognitive-behavioral therapy) modify microbiome-gut-brain axis pathways relevant to neuropsychiatric disorders. Other experimental, laboratory-based paradigms such as reactivity studies using either pharmacologic (e.g., hydrocortisone, intranasal oxytocin), psychosocial (e.g., Trier Social Stress Test), or physical (e.g., cold pressor task) probes could also yield important mechanistic insights into acute changes in key biological processes relevant to the microbiome-gut-brain axis. Bearing in mind that the experience of social evaluative threat is more closely linked to the HPA axis response (155), further research is needed to advance our understanding of the biobehavioral implications of social adversity across the life course for the microbiome-gut-brain axis among PWH.

Many PWH experience prominent structural vulnerabilities such as housing instability and food insecurity that should receive greater attention in biobehavioral research (87,156). These structural vulnerabilities are often embedded within distinct residential environments, and a burgeoning literature has focused on demonstrating the associations of neighborhood-level factors with health outcomes such as viral suppression (157–159). Advancing our understanding of multilevel determinants of microbiome-gut-brain axis alterations will guide the development of more comprehensive intervention approaches to address prevalent neuropsychiatric comorbidities and optimize health outcomes among PWH.

There is also a clear need for further research examining the relevance of sex and gender in microbiome-gut-brain axis crosstalk. Much of the early PNI research in PWH focused on sexual minority men and the extent to which this will generalize to cisgender women is unknown. There are divergent associations of inflammation with depression as a function of sex at birth across studies. Most notably, studies with cisgender women are needed to understand the distinct mechanisms that may diminish the associations of inflammation with depressive symptoms and poorer quality of life. There is also a clear need for studies with gender minority populations to understand whether and how gender-affirming biobehavioral treatments influence the microbiome-gut-brain axis.

In summary, the modern ART era provides several opportunities to build a robust portfolio of research examining the role of microbiome-gut-brain axis in neuropsychiatric comorbidities. The central importance of HIV-induced damage to the gut and alterations

in gut microbiota have enduring consequences for the mental and physical health of PWH. Interrogating these microbiome-gut-brain axis mechanisms could assist with identifying novel targets for biobehavioral interventions to address prevalent neuropsychiatric comorbidities among PWH such as depressive disorders and stimulant use disorders. This is essential to alleviate human suffering related to neuropsychiatric disorders and optimize the ability of many PWH to derive maximum benefits from ART. In Lewis Carol's *Through the Looking-Glass*, Alice steps once again into a fantastical world, much like the possibilities of PNI and microbiome-gut-brain axis research in the modern ART era.

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