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The Interaction of HIV With Mental Health in the Modern Antiretroviral Therapy Era

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ABSTRACT

People with HIV (PWH) receiving effective antiretroviral therapy (ART) continue to display residual immune dysregulation that amplifies the risk for neuropsychiatric comorbidities. At the same time, PWH commonly experience intersectional stigma and other psychosocial stressors that are linked to neuroendocrine stress responses, potentiate residual immune dysregulation, and alter other biobehavioral processes relevant to health outcomes. This special issue of *Psychosomatic Medicine* seeks to advance our understanding of the intersection of HIV with mental health in the modern ART era. Several articles cover topics related to the prevalence and treatment of psychiatric comorbidities among PWH such as depression, suicidality, and substance use disorders. Other articles delineate biobehavioral mechanisms relevant to mental health in PWH such as inflammation, immune activation, neuroendocrine signaling, cellular aging, the microbiome-gut-brain axis, and neurobehavioral processes. Collectively, the articles in this special issue highlight the continued importance of biobehavioral and neurobehavioral mental health research in the modern ART era.

Key words: depression, HIV, mental health, methamphetamine, microbiome, psychoneuroimmunology.

The central importance of social, psychological, and neurobehavioral factors has been clear since the beginning of the human immunodeficiency virus (HIV) epidemic. The profound social stigma experienced by people with HIV (PWH) was evident in early terms such as gay-related immune deficiency syndrome or the 4 H's (homosexuals, heroin users, hemophiliacs, and Haitians) that emphasized membership in high-risk groups for what would later be identified as acquired immune deficiency syndrome (AIDS). Stigma related to HIV and other minoritized identities (e.g., racial minority, sexual minority) continues to be an important determinant of prevalent mental health disorders such as depression (1,2), which affects as many as one-third of PWH (3). There was also early evidence that HIV replication in the central nervous system was responsible for neuropsychiatric disorders in PWH. Although HIV-associated neurocognitive disorder was a prominent, debilitating comorbidity in the early days of the HIV epidemic, approximately half of PWH today experience milder forms of neurocognitive impairment (4). It is also increasingly clear that there are synergistic, bidirectional associations of HIV neuropathogenesis with substance use (5–7), which has been consistently identified as a risk factor for difficulties with HIV disease management and onward HIV transmission (8–10). These enduring social, psychological, and neurobehavioral challenges underscore the continued need for this special issue examining the interaction of HIV with mental health.

During the past four decades, biomedical advances have progressively transformed HIV into a chronic medical condition. Although the first AIDS cases were reported in 1981, medical treatment was largely palliative until the authorization of azidothymidine monotherapy by the US Food and Drug administration in 1987 (11). There were several challenges related to the adverse effects from azidothymidine (e.g., anemia) and rapid development of drug resistance that underscored the need for new treatments. In 1996, highly active antiretroviral therapy (HAART) triggered a paradigm shift in the medical management of HIV where combinations of distinct classes of antiretroviral medications substantially improved health outcomes for PWH. At the same time, HAART regimens were burdensome because they comprised multiple pills several times per day, often had debilitating adverse effects, and required high rates of adherence to maximize their clinical benefits (12). In the modern antiretroviral therapy (ART) era (2007–present), regimen burden and adverse effects have decreased dramatically such that PWH can derive meaningful, albeit incomplete, clinical

AIDS = acquired immune deficiency syndrome, **ART** = antiretroviral therapy, **HAART** = highly active anti-retroviral therapy, **HIV** = human immunodeficiency virus, **PWH** = people with HIV, **SIV** = simian immunodeficiency virus

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benefits even at moderate levels of medication adherence (13). There is also evidence that initiating ART at any CD4+ T-cell count optimizes health outcomes while substantially reducing rates of onward HIV transmission to uninfected sexual partners (14,15). Despite these groundbreaking biomedical advances, there is continued evidence for the relevance of social, psychological, and neurobehavioral factors for the interaction of HIV with mental health. Although the biomedical context has changed, addressing the complex, multilevel determinants of mental health in PWH is essential to optimize the benefits of ART as well as alleviate the often-debilitating symptoms of psychiatric and neuropsychiatric disorders.

In July 2019, the National Institute of Mental Health Division of AIDS Research sponsored a conference: "Mood disorders in People Living with HIV," which brought together neuroHIV, social, and behavioral scientists to examine the state-of-the-science around the assessment and treatment of mood disorders among PWH. This National Institute of Mental Health conference highlighted critical gaps in research knowledge, as well as identified a need for integrated research that spans social, psychological, behavioral, and biological processes. The current special issue of *Psychosomatic Medicine* brings together new evidence relevant to the interaction of HIV with mental health. The overarching goal of this special issue is to advance our understanding of biobehavioral and neurobehavioral processes relevant to depression, substance use, and other neuropsychiatric comorbidities, particularly among those receiving effective ART. Hereinafter, we provide an overview of themes from this special issue and highlight directions for future research focusing on the interaction of HIV with mental health in the modern ART era.

Building on an established literature in psychoneuroimmunology that delineated the relevance of the hypothalamic-pituitary-adrenal axis and autonomic nervous system for HIV pathogenesis (16,17), several studies in this special issue examined neurobehavioral and neuroendocrine processes that underlie psychiatric disorders in PWH. Roger McIntosh et al. (18) examined alterations in brain function in relation to depression in postmenopausal women with and without HIV. Greater activity in the anterior insula (potentially reflecting higher interoceptive awareness) during a heartbeat detection task was found to be associated with more severe depressive symptoms regardless of HIV status. The neuroendocrine and immune sequelae of childhood abuse were examined in relation to social processing by Rubin et al (19). This cross-sectional study documented that PWH who experienced early life stress had higher levels of oxytocin and inflammation that paralleled greater difficulties with facial emotion recognition, one important aspect of social processing. Shortell and colleagues (20) also report an association of higher oxytocin with greater depressive symptoms in a sample of predominantly Black/African American PWH. In another study in this issue, Rubin and colleagues (21) examined whether alterations in glucocorticoid receptor gene expression were associated with cognitive function in PWH. Upregulation of a gene relevant to glucocorticoid receptor expression (*FKBP5*) was associated with poorer attention and working memory in older women with HIV. PWH also experience chronic, uncontrollable stressors that have important consequences for neurobehavioral outcomes (22). Findings from Elissa Charney McIntosh and colleagues (23) indicate that greater lifetime chronic stressor exposure was associated with poorer cognitive performance and smaller prefrontal cortex volume. There were no differences in lifetime chronic stressor exposure by HIV status and the associations of lifetime chronic stressor exposure with these neurobehavioral outcomes was not moderated by HIV status. Taken together, these findings underscore the need for longitudinal and experimental studies to examine the neurobehavioral and neuroendocrine processes that underlie depression and other neuropsychiatric comorbidities in PWH.

Randomized controlled trials support the efficacy of psychological interventions for improving medication adherence and viral suppression in those with depression (24), but expanded efforts are needed to test the effectiveness of scalable treatment approaches, particularly in low- and middle-income countries. Nakimuli-Mpungu and colleagues (25) report findings from a cluster randomized controlled trial in Uganda demonstrating the long-term effectiveness of a group support psychotherapy (versus group HIV education) on decreased major depressive episodes and increased ART adherence, which comediate intervention-related improvements in viral suppression over 24 months. Randomized controlled trials conducted in the modern ART era are needed to determine whether effective treatments of depression and substance use disorders can alter biological processes (e.g., inflammation, immune activation) that are linked to non-AIDS morbidity and mortality in PWH who are virally suppressed (26,27).

Psychiatric comorbidities are common in PWH, but their prevalence, etiology, and health-related implications require further study. In this issue, Tsai and colleagues (28) document the global prevalence of suicidality in PWH and identify correlates of suicide risk indicators that will guide more comprehensive assessment and intervention efforts. Substance use disorders are also prevalent comorbidities that increase the risk of HIV acquisition and potentiate faster clinical HIV progression (29,30). Findings reported by Wändell et al. (31) from the Greater Stockholm Cohort Study revealed that substance use disorders were elevated in PWH before the diagnosis of HIV. In addition, the elevated prevalence of substance use disorders persisted in the year after HIV diagnosis, which reflects the chronic and often relapsing nature of problematic substance use. There is also some evidence that the use of stimulants (i.e., methamphetamine, powder cocaine, and crack cocaine) could alter biological processes relevant to HIV pathogenesis in those receiving effective ART (32,33). Findings from Ghanooni and colleagues (34) demonstrate that sexual minority stress processes were associated with measures of accelerated cellular aging (e.g., the extrinsic epigenetic age acceleration clock) derived from measures of DNA methylation in methamphetamine-using sexual minority men with treated HIV. Future longitudinal research is needed to delineate the biobehavioral pathways relevant to cellular aging among PWH. Findings from Derry-Vick and colleagues (35) also underscore the complexities of aging among PWH where the intersection of depression and pain have important implications for poorer physical function. Interestingly, pain and prescription opioid use were independently associated with elevated inflammation in this cross-sectional study. Longitudinal and experimental studies should determine if prescription opioids are merely serving as a proxy for more severe pain or whether prescription opioids are amplifying inflammation in PWH.

Acute HIV infection is a potentially critical period that could serve as a set point for the bidirectional associations between psychological factors and immunologic perturbations. Castell and colleagues (36) report findings that social isolation blunted the number of circulating classical monocytes (CD14+ CD16−) and blocked

platelet activation in pigtailed macaques during acute simian immunodeficiency virus (SIV) infection. These findings build on prior research where social isolation was linked to higher viral load in plasma and cerebrospinal fluid, greater CD4+ T-cell count declines, and more CD4+ and CD8+ T-cell activation in pigtailed macaques during acute SIV infection (37). The translational implications of these experimental SIV studies are supported by results from the study by Paul and colleagues (38) in this issue where poorer mental health and reduced neurocognitive functioning at the time of acute HIV diagnosis independently predicted slower CD4+ T-cell recovery after suppressive ART in the RV254/SEARCH 010 Thai cohort study. These studies highlight the importance of well-characterized acute HIV cohorts to better understand how mental health and substance use in the period surrounding HIV infection could influence set points for immunologic responses to ART.

This special issue concludes with a review article by Carrico and colleagues (39) that places these findings in a broader context, focusing on the bidirectional nature of mind-body relationship in the mental health among people living with HIV. The interrelationships between established psychoneuroimmunologic mechanisms and microbiome-gut-brain axis interactions are highlighted with recommendations for future biobehavioral research to investigate the bidirectional pathways linking the biological and behavioral processes with mental health in PWH.

Although biomedical advances have continued to transform the medical management of HIV, there are enduring social, psychological, and neurobehavioral challenges that fuel depression, substance use disorders, and neuropsychiatric comorbidities. Many of these comorbid mental health and substance use disorders compromise the ability of PWH to maximize the benefits of ART and will require comprehensive, biobehavioral treatments. Expanded efforts are needed to elucidate the biobehavioral mechanisms relevant to the interaction of HIV with mental health to catalyze the development of a new generation of biobehavioral treatments to address these prevalent mental health challenges that disproportionately affect PWH. The articles from this special issue provide important additions to the knowledge base from which to launch a comprehensive effort to reinvigorate biobehavioral and neurobehavioral mental health research in PWH.

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