HHS Public Access

Author manuscript

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Am J Drug Alcohol Abuse. 2017 January ; 43(1): 7–23. doi:10.1080/00952990.2016.1211667.

Immune Activation and Neuroinflammation in Alcohol Use and HIV Infection: Evidence for Shared Mechanisms

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Abstract

Background—Emerging research points to innate immune mechanisms in the neuropathological and behavioral consequences of heavy alcohol use. Alcohol use is common among people living with HIV infection (PLWH), a chronic condition that carries its own set of long-term effects on brain and behavior. Notably, neurobiological and cognitive profiles associated with heavy alcohol use and HIV infection share several prominent features. This observation raises questions about interacting biological mechanisms as well as compounded impairment when HIV infection and heavy drinking co-occur.

Objective and Method—This narrative overview discusses peer-reviewed research on specific immune mechanisms of alcohol that exhibit apparent potential to compound the neurobiological and psychiatric sequelae of HIV infection. These include microbial translocation, systemic immune activation, blood-brain barrier compromise, microglial activation, and neuroinflammation.

Results—Clinical and preclinical evidence supports overlapping mechanistic actions of HIV and alcohol use on peripheral and neural immune systems. In preclinical studies, innate immune signaling mediates many of the detrimental neurocognitive and behavioral effects of alcohol use. Neuropsychopharmacological research suggests potential for a feed-forward cycle in which heavy drinking induces innate immune signaling, which in turn stimulates subsequent alcohol use behavior.

Conclusion—Alcohol-induced immune activation and neuroinflammation are a serious health concern for PLWH. Future research to investigate specific immune effects of alcohol in the context of HIV infection has potential to identify novel targets for therapeutic intervention.

1. Introduction

Alcohol is the most commonly used drug among people living with HIV infection (PLWH) in the United States: 51% consumed alcohol and 15% reported binge drinking in the past 30 days (1). Alcohol use is linked to outcomes with serious consequences for the individual and for public health, including medication non-adherence (2), high-risk sexual behaviors (3, 4), HIV progression (5), and increased mortality (6, 7). Strikingly, even moderate drinking (30

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Declaration of Interest: The author has no relevant financial disclosures or conflicts of interest.

drinks per month, or an average of one drink per day) was associated with significantly greater risk of mortality in men living with HIV (8). This level of consumption is below the current threshold for high-risk drinking, defined by the National Institute on Alcohol Abuse and Alcoholism as >14 drinks for men and >7 drinks for women per week, or >5 drinks for men and >4 drinks for women on any single occasion (9). Therefore, it is imperative to examine interactions of HIV and alcohol use that may place PLWH at greater risk of harm.

Immune interactions of alcohol and HIV are complex and not well understood, particularly with regard to effects on brain, behavior, and cognition. Over the past 30 years, evolving treatment approaches to HIV have complicated systematic research on its neural effects and possible interactions with alcohol. A significant shift occurred with the advent of "combination" (or "highly active") antiretroviral therapy (ART) in 1996. Although rates of HIV-associated dementia have declined in the combination ART era, milder HIV-associated neurocognitive disorders persist, affecting 44% of PLWH without severe comorbidities (10). The observation that rates and patterns of cognitive impairment have changed following the introduction of combination ART (11) suggests that these drugs modulate central nervous system (CNS) effects of HIV, yet CNS profiles of various drug regimens are not well characterized. Lack of clarity also arises from inconsistency in alcohol research methodology, including definitions of heavy drinking and assessment timeframes (12). Heterogeneity across study samples in HIV clinical status (e.g., comorbidities, viral load, history of severe immunosuppression) and alcohol use characteristics (e.g., current vs. remote heavy drinking) is another source of variability. Going forward, greater specificity of neural targets and consistency in research methodology will help to clarify HIV-alcohol interactions.

This review focuses on specific immune mechanisms of alcohol that have apparent potential to compound the neurobiological and psychiatric sequelae of HIV infection. Recently, immune effects of alcohol have emerged as a major contributor to systemic and neurobiological damage associated with chronic heavy drinking (13). Notably, several immune pathways implicated in heavy alcohol use overlap with those affected by HIV infection. Mounting evidence indicates that HIV infection and heavy drinking are likely to produce compounded damage to brain and cognition when they co-occur (14, 15). Independently, alcohol use disorder (AUD) and HIV infection are associated with abnormality in the brain's frontal lobes, limbic system, and subcortical structures, which are substrates of higher-order cognition and reward processing (16–20). Both AUD and HIV infection are associated with deficits in executive function, learning, memory, and processing speed (11, 21, 22). Not surprisingly, chronic heavy alcohol use exacerbates information processing and psychomotor speed impairment in PLWH (23–26). Therefore, it is of utmost importance to understand how alcohol may potentiate HIV consequences at systemic and neural levels. Alcohol-HIV interactions with respect to HIV transmission, acute infection, viral replication, adaptive immunity, and disease progression have been reviewed in detail elsewhere (5, 12, 27). This conceptual overview focuses on specific immune mechanisms with potential for additive or synergistic consequences in co-occurring heavy drinking and HIV infection.

2. Systemic immune activation

Mechanisms through which alcohol and HIV may affect the brain via indirect effects on other organ systems, particularly the gastrointestinal tract, are a rapidly growing area of interest. Independently, HIV and alcohol use induce translocation of microbial products from the gastrointestinal tract into systemic circulation (28), leading to immune activation and inflammation. Figure 1 illustrates this model, and Table 1 provides a summary of key terms and biomarkers. Briefly, lipopolysaccharide (LPS) in plasma is used as a marker of microbial translocation, and immune activation is indexed by plasma levels of lipopolysaccharide binding protein (LBP), soluble cluster of differentiation 14 (sCD14), and endotoxin immunoglobulin core antibody IgM (EndoCAb). As an aid to interpretation, acute LPS challenge typically results in increased plasma levels of LBP and sCD14 and depletion of EndoCAb (29–31). HIV and alcohol first will be addressed separately, followed by evidence on co-occurring HIV and alcohol use.

2A. Microbial translocation and immune activation in HIV infection

Following a landmark study that identified microbial translocation as a source of chronic immune activation in HIV infection (32), numerous studies have documented elevated LPS, LBP, and sCD14 and lower EndoCAb in PLWH relative to healthy control groups (32–37). Chronic immune activation is a hallmark of HIV that persists despite virologic suppression and appears to stoke disease progression independent of viral replication [e.g., (38, 39); see (40, 41) for reviews]. Basic research has uncovered pathophysiological mechanisms of microbial translocation and evidence of its independent contribution to chronic immune activation in HIV infection. HIV exposure causes intestinal epithelial barrier compromise via disruption of tight junctions proteins, such as occludin and zona occludens-1 (ZO-1), and increased production of proinflammatory cytokine tumor necrosis factor alpha (TNF-α) (42). At all stages of infection, HIV profoundly depletes CD4+ T cells in the gut, particularly the Th17 CD4+ type critical to multiple gut immune functions (43, 44). Perturbed composition of the gut microbiome, characterized by decreased diversity and/or enrichment of pathogenic bacteria, also is a factor in microbial translocation (33, 45–47). In a simian immunodeficiency virus (SIV) model, researchers directly linked gut barrier compromise to microbial translocation and immune activation independent of viral activity (48). Furthermore, experimentally induced microbial translocation in uninfected non-human primates caused immune activation and systemic inflammation of a magnitude comparable to SIV infection (49). Finally, SIV-infected non-human primate species that do not progress to AIDS have robust viral replication yet lack microbial translocation and other key pathogenic processes (50).

Immune activation is a powerful predictor of clinical outcomes in HIV infection. sCD14, a marker of monocyte activation, consistently and uniquely predicts cognitive impairment, virologic failure (i.e., failure of ART to suppress viral load), disease progression, and mortality in PLWH (36, 51–57). One study found that PLWH in the highest quartile for sCD14 had a 6-fold increased risk of mortality compared to those in the lowest quartile (37). In a large veteran cohort, sCD14 in combination with other biomarkers accounted for a modest proportion of mortality risk in PLWH with HIV RNA ≥10,000 copies/ml (58).

Microbial translocation and systemic immune activation also interact with cardiovascular risk factors in PLWH, who are at significantly greater risk of cardiovascular disease (59). Decreased or dysfunctional high density lipoprotein (HDL) in serum is an important risk factor that disproportionately affects PLWH (60–62). Under certain conditions, sCD14 and LBP transfer LPS to non-immunoreactive lipoproteins, particularly HDL (63, 64), as an alternative to monocyte activation via TLR4 binding (63, 65). One possibility is that low or dysfunctional HDL characteristic of HIV infection limits access to this inhibitory pathway, thereby impeding the natural "sink" that removes LPS from circulation and promoting chronic immune activation.

2B. Microbial translocation and immune activation in heavy drinking

Alcohol is a potent immunomodulator, with effects contingent on dose and chronicity of exposure. Acute alcohol produces an initial pro-inflammatory phase followed by an anti-inflammatory or immune-inhibitory phase [e.g., (66–68); see (69) for review]. In contrast, chronic alcohol upregulates pro-inflammatory innate immune response, e.g., by sensitizing monocyte response to LPS (70, 71). Alcohol inhibits adaptive immunity by suppressing T-cell proliferation, inducing T cell dysfunction, and disrupting homeostasis among T cell subtypes (72–74). Similar to HIV infection, alcohol disrupts gut immune function via dysbiosis, structural barrier damage, and perturbation of lymphocyte populations. Rodent models have shown that acute or chronic alcohol feeding increases intestinal permeability and alters composition of the gut microbiome (75–78). Intestinal epithelial compromise results from upregulation of oxidative stress and disruption of tight junctions via acetaldehyde-mediated redistribution of tight junction proteins such as ZO-1 (78–81). Chronic alcohol further disrupts gut immune function by diminishing colonic CD4+ T cells, specifically the Th17 subtype depleted in HIV infection (82).

Perhaps due to shared pathophysiological processes, immune biomarker perturbations seen in heavy drinking are similar to those observed in HIV infection, i.e., elevated LPS, LBP, and sCD14 and decreased EndoCAb. Observational studies have reported higher LPS, LBP, and sCD14 levels in individuals with alcoholic liver disease compared to healthy controls (83–85). Even in the absence of liver disease, individuals in early abstinence from alcohol dependence have shown higher plasma LPS, LBP, and sCD14 than healthy controls (86, 87). Moreover, intestinal permeability and plasma LPS levels decreased significantly after 19 days of abstinence, suggesting remediation of gut function with cessation of drinking (86). EndoCAb, which typically is suppressed in chronic HIV infection, also is significantly lower in community heavy drinkers compared to light drinkers (88). In animal models, chronic alcohol treatment impairs synthesis of this LPS-clearing antibody in mesenteric lymph nodes (89).

To date, two experimental studies have assessed acute changes in LPS, LBP, and/or sCD14 from moderate-to-heavy alcohol consumption by healthy individuals. A peak blood alcohol level (BAL) of approximately .085 g/dL increased markers of microbial translocation and immune activation in healthy participants (90). Specifically, serum LPS, LBP, and sCD14 increased within 30 minutes of alcohol consumption; both LBP and sCD14 remained significantly elevated at 24 hours post-consumption (90). Another study that administered a

comparable alcohol dose (1 g/kg; median peak BAL of .070 g/dL) to healthy men reported an increase in a marker of intestinal epithelial cell damage (91). sCD14 also increased in the alcohol condition, but the effect was difficult to interpret as it was similar to the water control condition (91).

2C. Experimental alcohol-induced microbial translocation in HIV

Although controlled studies of alcohol-induced microbial translocation in PLWH have not been reported, an animal model using HIV-transgenic rats indicated a synergistic effect of alcohol and HIV on this specific outcome (92). HIV-transgenic rats model chronic virus effects in the absence of active viral replication, analogous to virologic suppression in PLWH (93). Binge alcohol exposure caused significantly greater microbial translocation in the HIV-transgenic animals, compared to alcohol-only or HIV-only conditions, and was linked to increased TLR4 expression, pro-inflammatory cytokines, and liver damage (92).

2D. Clinical research on co-occurring HIV infection and heavy drinking

As noted previously, a biomarker profile indicative of microbial translocation and immune activation has emerged independently in HIV infection and heavy drinking. However, empirical evidence on the *combined* effects of HIV infection and heavy drinking is sparse, as HIV clinical research studies typically have excluded individuals with AUD or heavy drinking. A review of the current literature identified four observational studies to date examining associations of LPS, LBP, or sCD14 with alcohol use in PLWH. One study of PLWH with an AIDS diagnosis (87% on ART) compared participants with AUD to participants without substance use disorder. The AUD group had higher LPS and LBP, but there were no group differences in sCD14 or EndoCAb (36). Carrico et al. (2015) analyzed sCD14 levels as a function of alcohol use in a sample of PLWH who were not receiving ART (90% with CD4 cell count ≥350 cells/mm^3; 83% with viral load ≥1000 copies/ml). Individuals who screened positive for heavy drinking in the past three months had significantly higher sCD14 than non-drinkers in analyses adjusted for demographics, smoking status, and HIV clinical characteristics (94). Our lab recently reported a pilot study of immune biomarkers and alcohol use in men living with HIV infection who met NIAAA criteria for heavy drinking in the past month. All participants were receiving ART and had achieved virologic suppression (95). Alcohol use quantity and frequency positively predicted sCD14 even after controlling for demographic and clinical variables. In addition, participants who reduced their drinking over a three-month period showed a significant decrease in sCD14 (95). Although alcohol use was not associated with either LPS or EndoCAb, power was limited by the small sample size. In contrast to those positive findings, a cohort study of PLWH (77% on ART; 73% with virologic suppression) reported that having >5 drinks per day at least once in the past 30 days was not associated with sCD14 (96). Notably, studies differed in operational definitions of heavy drinking and in sample characteristics such as ART usage and clinical status. Taken together, however, they offer preliminary support for connections among heavy drinking, microbial translocation, and innate immune activation in PLWH.

2E. Peripheral immune activation as contributor to neuroinflammation

Although the blood brain barrier (BBB) protects the privileged immune status of the CNS, the BBB is selectively permeable to immune cells and often is altered in neuropathology (97). Several known mechanisms propagate peripheral pro-inflammatory signals across the BBB, potentially contributing to neuroinflammation. Some cytokines, including interleukin-6 (IL-6) and TNF-α, cross the BBB via cytokine-specific transporters (97). Both alcohol and HIV increase permeability of the BBB via pro-inflammatory mechanisms that resemble processes observed at the level of the intestinal epithelial barrier (98). Specifically, alcohol and HIV induce oxidative stress in endothelial cells of the BBB, leading to barrier compromise via disruption and redistribution of tight junction proteins, including ZO-1 and occludin (98–103). LPS is not thought to cross the intact BBB, but LPS in peripheral circulation increases the permeability of the BBB to cell-free virus (104). At the same time, HIV sensitizes the BBB to LPS insult, and HIV-infected monocytes exhibit an enhanced capacity to migrate into the brain (103, 104). Alcohol facilitates migration of monocytes across the BBB via oxidative stress mechanisms (99). Systemic administration of alcohol to rodents increased levels of proinflammatory cytokines TNF-α and monocyte chemoattractant protein-1 (MCP-1; also called CCL2) in the brain, and alcohol prior to LPS administration potentiated and temporally extended this response (105). In short, HIV, alcohol, and LPS exposure interact to compromise the BBB and promote influx of pro-inflammatory cytokines and HIV-infected monocytes to the CNS.

3. Neuroimmune mechanisms of alcohol use and HIV infection

3A. Brief overview of HIV-related neuroinflammation

Viral proteins, infected monocytes, and cytokines are significant contributors to neuronal damage. Neuroinflammation is mediated to a large extent by glial cells (i.e., microglia, astrocytes, oligodendrocytes), which populate the human brain in quantities similar to neurons and are a major constituent of white matter (106). Microglia, the brain's resident immune defense cells, are activated by pathogens such as bacteria or viruses to secrete cytokines, both pro- and anti-inflammatory (107). Even with virologic suppression, the CNS serves as a viral reservoir for HIV [see (108) for review]. Microglia are uniquely susceptible to HIV infection, whereas neurons and astrocytes do not appear to harbor productive infection [see (109) for review]. Infected microglia emit neurotoxic viral proteins such as Tat and gp120, contributing to neuronal apoptosis and drawing additional cytokines and infected monocytes across the BBB (109). Although somewhat counterintuitive, the largely non-productive nature of HIV infection in astrocytes also contributes to HIV persistence in the CNS (110). Because antiretroviral drugs only are able to target cells with active viral replication, astrocytes serve as a latent viral reservoir. Thus, viral reservoirs throughout the body are a major obstacle to HIV eradication and a focus of current research. For example, a recent preclinical study reported that HIV replication in astrocytes could be turned "on" by inhibiting a specific host restriction factor (110).

Neuroinflammation marked by glial activation is evident in postmortem brain tissue from PLWH and is associated with neurocognitive impairment (111, 112). There is strong evidence that neurodegenerative processes in HIV infection persist despite effective ART. A

longitudinal imaging study reported that, compared to a healthy control group, PLWH with virologic suppression showed progressive white matter atrophy over a 2-year period (113). Although virologic suppression typically is associated with better cognitive function, ART does not fully eradicate the virus from the CNS, and findings are mixed with regard to possible neuroprotective or neurotoxic effects of ART (114). Ongoing CNS insult despite appropriate ART may contribute to the high prevalence of HIV-associated neurocognitive disorders, which are estimated to affect 44% of PLWH without confounding comorbidities (10).

3B. Neuroimmune mechanisms of alcohol use

As in HIV, glial activation is central to alcohol-induced neuroinflammation and neurodegeneration (115–118). It is well known that alcohol readily crosses the BBB and affects a host of neurotransmitter systems, including dopaminergic, opioid, and serotonergic systems (119). Emerging research indicates that some neurotoxic and behavioral consequences of alcohol use are mediated by innate immune receptors, particularly the TLR4 complex. TLR4, the receptor that recognizes gut-derived LPS, is expressed not only on monocytes in systemic circulation but also on the brain's microglia and astrocytes (120, 121). A remarkable series of *in vitro* and *in vivo* murine models demonstrated that TLR4 signaling is the primary pathway through which chronic or binge alcohol induces glial activation (116, 118). The mechanistic role of TLR4 in alcohol neurotoxicity has been established in experiments with mice that are genetically deficient in TLR4 (i.e., TLR4-knockouts). TLR4 signaling following alcohol treatment causes glia to produce and secrete cytokines (e.g., MCP-1, TNF-α, IL-6), reactive oxygen species, and other inflammatory mediators (115, 122, 123). These proinflammatory cascades promote neuronal apoptosis and inhibit neurogenesis (118, 123, 124). In addition, alcohol-induced TLR4 signaling led to white matter degeneration through downregulation of myelin proteins and death of oligodendrocytes, the cells that produce myelin (125). Increased expression of microglial TLR4 was observed after 10 minutes of alcohol exposure, suggesting a feed-forward mechanism of neuroinflammation (123). Postmortem studies corroborate the presence of increased pro-inflammatory cytokines MCP-1 and interleukin-1beta (IL-1β), microglial markers, and TLR4 expression in brain tissue of individuals with a history of heavy drinking (124, 126, 127). Intriguingly, alcohol-preferring ("P") rats had higher levels of TLR4 in the ventral tegmental area and central amygdala predating alcohol exposure, suggesting a genetic role of TLR4 in vulnerability to excessive drinking (128).

Although the exact mechanisms through which alcohol activates TLR4 are a focus of ongoing research, it appears that alcohol mimics actions of endogenous TLR4 ligands such as LPS and IL-1β (123, 129, 130). Essentially, alcohol is an exogenous substance that replicates some effects of endogenous bacterial antigens like LPS on glial cells. This parallel is significant in light of the fact that LPS normally does not infiltrate the brain. Alcohol may not be unique among addictive drugs in this capacity, as other researchers have shown that some opioid effects are mediated by TLR4 signaling (131). Indeed, the full significance of overlapping neural mechanisms responding to bacterial ligands and addictive drugs has yet to be explored.

In summary, chronic and binge models of alcohol exposure have identified neuronal death, myelin damage, and inhibited neurogenesis as major contributors to alcohol-related neurodegeneration. Alcohol neurotoxicity is mediated to a great extent by innate immune mechanisms, specifically, glial activation, cytokine production, oxidative stress, and innate immune gene induction. Upregulation of innate immune gene transcription amplifies proinflammatory signaling and, in the context of repeated neurotoxic insults, can stoke a self-perpetuating or “feed-forward” cycle (132).

3C. Neurodegenerative interactions of HIV infection and alcohol

Complete discussion of possible interactions of HIV and alcohol in the CNS is outside the scope of this review [see (15) for further discussion]. However, recent research has highlighted several mechanisms with potential for converging neurodegenerative effects in co-occurring HIV infection and heavy drinking. These include epigenetic changes, regulation of synaptic plasticity, and generation of oxidative stress. HIV infection of cultured astrocytes resulted in downregulation of genes involved in synaptic plasticity and dendritic spine density, as well as induction of apoptosis (133). Effects of alcohol on synaptic plasticity are complex and vary according to many factors, including the specific brain region, developmental stage, neurotransmitter system, and alcohol concentration [see (134) for review]. Although acute alcohol transiently increases synaptic plasticity, chronic exposure or withdrawal inhibits plasticity through decrease in dendritic spine density (135). These effects of alcohol use or HIV infection on dendritic architecture are paralleled by epigenetic changes that influence synaptic plasticity, specifically through expression of histone deacetylase 2 (HDAC2) (135). The HIV viral protein Tat induced epigenetic changes in neurons by upregulating HDAC2, which in turn decreased expression of genes that facilitate synaptic plasticity via long-term potentiation (136). Although initial alcohol exposure reduced HDAC2 in rodent models, chronic binge exposure led to increased HDAC2 in blood and amygdala (137). Similarly, individuals presenting with acute alcohol intoxication in a healthcare setting had elevated HDAC2 levels (137). In neuronal cell culture, alcohol produced a dose-dependent increase in HDAC2 expression (138). Important to note, upregulation of HDACs appears to mediate neuronal dysfunction and cognitive impairment across a diverse array of neurodegenerative conditions (139). In preclinical trials, HDAC inhibiting agents have shown potential to ameliorate cognitive and affective symptoms in both HIV infection and AUD, e.g., (140, 141).

Closely tied to neuroinflammation and a known contributor to alcohol neurotoxicity (142), oxidative stress is thought to play a role in epigenetic alterations associated with alcohol use and HIV. In neuronal culture, alcohol-induced HDAC2 upregulation was linked to levels of oxidative stress and was blocked by antioxidant administration (138). In an animal model of co-occurring HIV infection and heavy drinking, alcohol increased plasma viremia, reduced clearance of infected macrophages from the brain, and increased microglial activation and oxidative stress markers (143). It is important to note that, although some animal models and *in vitro* studies [e.g., (144, 145)] have demonstrated that alcohol increases levels of HIV viral proteins and rates of cellular infection, *in vivo* evidence in humans is inconclusive (27). At the same time, mounting evidence suggests that alcohol and other drugs of abuse may mechanistically accelerate HIV-related neurodegeneration through oxidative stress

mechanisms. For example, treating mice with the HIV viral protein Tat plus alcohol potentiated increases in oxidative stress markers and pro-inflammatory cytokines IL-1β and MCP-1 in brain tissue, compared to Tat or alcohol alone (146). Elevated MCP-1 is significant because MCP-1 enhances migration of infected monocytes across the BBB (147) and predicts HIV-related neurocognitive dysfunction and neurodegeneration (56, 148, 149). In another study, combined treatment with alcohol and HIV viral protein gp120 synergistically augmented free radical production and suppressed antioxidant activity in rat brain (150). Indeed, oxidative stress signaling may be an important common pathway by which alcohol and other drugs exacerbate HIV-related neurodegeneration. For example, exposing microglia to HIV plus morphine amplified markers of oxidative stress and cellular DNA damage more than either HIV or morphine alone (151). In summary, research provides strong evidence that HIV infection and heavy drinking share mechanisms of neuroinflammation and neurodegeneration, but preclinical findings require confirmation in human clinical research.

3D. Preliminary clinical evidence linking immune activation, inflammation, and brain abnormality

Clinical research has begun to link systemic immune activation and inflammation to brain abnormality and cognitive impairment in PLWH. First, immune biomarkers have shown considerable potential to serve as indicators of risk for HIV-related neurodegeneration and/or cognitive decline. Most studies have found positive associations of cognitive impairment with plasma LPS and/or sCD14 levels in PLWH [(36, 53, 152); but see also (153)]. In a study comparing predictive validity of several biomarkers, sCD14 and MCP-1 were the strongest predictors of cognitive impairment in PLWH (56). Second, peripheral levels of cytokines were correlated with several domains of cognitive functioning in PLWH and tended to be better predictors of cognition than HIV clinical characteristics (154, 155). Associations between plasma cytokines and cognition support a relationship between peripheral and CNS inflammation, with further studies needed to establish directionality. Third, non-invasive magnetic resonance imaging (MRI) measures of neurometabolism and white matter microstructure give evidence of CNS pathology in HIV infection [see brief review (156)]. Specifically, elevated myo-inositol, elevated choline, decreased N-acetyl-aspartate, and abnormal white matter microstructure in PLWH are consistent with neuroinflammatory processes (156). Large neuroimaging studies of PLWH have reported that immune activation markers (e.g., MCP-1, sCD14) in plasma and cerebrospinal fluid are associated with elevated choline, elevated myo-inositol, and decreased N-acetyl-aspartate (149, 157–159). Neuroimaging studies also support a link between peripheral and CNS immune activation. When comparing healthy controls to PWLH with various degrees of cognitive impairment, markers of inflammation (myo-inositol & choline) were elevated in PLWH, regardless of cognitive status; and a marker of neuronal integrity (N-acetyl-aspartate) was decreased only in HIV-positive participants with marked cognitive impairment (160). The researchers noted that results were consistent with a progressive model of primary neuroinflammation leading to neuronal injury. Another study reported that peripheral cytokines involved in monocyte activation were overexpressed in PLWH and were negatively correlated with N-acetyl-aspartate in frontal white matter and anterior cingulate

cortex (159). As a caveat, abnormalities detected by currently available clinical imaging techniques are not specific to neuroinflammatory states (161).

Neuroimaging research on effects of heavy drinking in HIV infection is limited, as previous neuroimaging studies of PLWH generally have excluded individuals with AUD. A handful of MRI studies of comorbid AUD and HIV have found significantly greater ventricular expansion (typical of brain atrophy), neurometabolic abnormality, and white matter damage in comorbid AUD and HIV compared to either condition alone (16, 162–164). These findings point to neurodegeneration yet do not identify neuroinflammation as a causal factor per se, given the limitations of current clinical MRI methods. Further research is needed to determine the neural correlates of peripheral inflammation and to characterize patterns of neuroinflammation in heavy drinking and HIV, separately and concomitantly.

4. Behavioral consequences of HIV- and alcohol-related neuroinflammation

4A. Affective and behavioral dysregulation

Peripheral levels of LPS and cytokines have distinct relevance for affective and behavioral symptom presentations in both AUD and HIV infection. Pro-inflammatory cytokines used in clinical practice, e.g., interferon-α treatment for chronic hepatitis, have long been recognized for their ability to induce or exacerbate dysphoric mood and somatic symptoms (165). As previously noted, it is not necessary for LPS to cross the BBB to exert deleterious neuroinflammatory effects. In fact, peripheral injection of LPS, standard vaccine, or cytokines is used as an experimental model of low-grade inflammation with rapid onset (i.e., 2–4 hours) (166). Experimental studies confirm the ability of these agents to cause “sickness behaviors” in otherwise healthy humans and animals [see review (167)]. Sickness behaviors include fatigue, decreased motor activity, and reduced pursuit of natural reinforcers, e.g., food, novelty, and socialization. For example, LPS injection in mice caused reductions in food intake, novel object exploration, and social interaction, even at relatively low doses (168). In humans, responses to pro-inflammatory challenge can manifest as neuropsychiatric symptoms of anhedonia, social withdrawal, and depressed mood (167, 169, 170).

Recent neuroimaging studies offer insight into the neural bases of these symptoms. On functional MRI (fMRI), researchers detected suppressed activity in the striatum, a neural substrate of reward, in healthy participants who received a low-dose LPS injection (171). An fMRI study of individuals receiving interferon-α treatment for hepatitis C found a similar reduction of striatal activity in the treatment group compared to wait-list control, in conjunction with perturbations in dopaminergic activity on positron emission tomography (PET) (172). In healthy participants, induction of low-grade inflammation produced significant metabolic changes in the insula, a brain region key to interoception (i.e., internal representation of physiological states) (173). Across studies, ratings of depressed mood, decreased motivation, and fatigue closely corresponded to neural changes.

There is reason to posit that PLWH may be especially susceptible to affective and behavioral changes caused by elevated LPS. In response to acute LPS challenge, PLWH had significantly greater pro-inflammatory (TNF-α, IL-6, and IL-8) and lower anti-inflammatory (IL-10) cytokine response than HIV-negative individuals (174). An observational study

found that IL-6, TNF-α, and monocyte counts were higher in PLWH who endorsed predominantly somatic depressive symptoms, particularly fatigue (175). Another study found higher levels of several pro-inflammatory cytokines and oxidative stress markers in PLWH who endorsed depressive symptoms, compared to PLWH without depressive symptoms (176). As a large proportion of PLWH receiving ART continue to experience burdensome but nonspecific symptoms such as fatigue and anxiety (177), controlled, prospective studies to identify root causes of these symptoms is essential to improving quality of life.

The centrality of innate immune signaling, especially involving TLR4, to alcohol-related neuropathology extends to cognitive and behavioral consequences. Chronic or binge alcohol treatment caused long-term memory impairment and anxiety behaviors in wild type mice, but not TLR4-knockouts (178, 179). Persistent glial activation and epigenetic alterations accompanied these behavioral changes in wild-type mice but were absent in TLR4-knockout mice (178, 179). Importantly, behavioral effects were not attributable to differences in voluntary alcohol intake for the mouse strains (178).

4B. Increased voluntary alcohol intake

Preclinical and clinical evidence suggests that heavy alcohol exposure may interact with innate immune mechanisms to increase subsequent alcohol consumption. Again, TLR4-mediated immune signaling appears to play a critical role. LPS exposure in rodents either a week or month prior to alcohol availability caused a significant and durable increase in voluntary alcohol consumption (180). Because the LPS-induced increase in drinking was abolished in mice lacking CD14, the TLR4 co-receptor, the researchers inferred that TLR4 signaling mediated the effect of LPS on drinking behavior (180). In another study, LPS or cytokine treatment prior to alcohol feeding sensitized rodents to social interaction anxiety during alcohol withdrawal (181). Immune activation also may contribute to effects of adolescent alcohol exposure on adult substance use. Adolescent wild-type mice receiving intermittent heavy alcohol treatment showed greater alcohol preference and conditioned cocaine reward later in development, but these effects were abrogated in TLR4-knockouts (179). Alcohol-preferring (“P”) rats have innately higher levels of TLR4 expression in behaviorally relevant brain regions prior to alcohol exposure, and inhibiting gene expression of either TLR4 or MCP-1 reduced their voluntary alcohol intake (128). Although translational significance for human behavior remains to be determined, observational studies are consistent with animal models. Individuals in early abstinence from alcohol showed positive correlations of intestinal permeability and plasma cytokines with depression, anxiety, and alcohol craving (86, 182).

5. Conclusion and future directions

With access to combination ART, life expectancy of PLWH approaches that of uninfected individuals (183). However, increased mortality was observed at a considerably lower level of drinking for men living with HIV (≥30 drinks per month) than for HIV-negative men (≥70 drinks per month) (8). Understanding the mechanisms by which even moderate alcohol intake may contribute to mortality and morbidity in PLWH is a pressing public health

concern. The absence of evidence-based guidelines for alcohol consumption in PLWH underscores the import of this issue. Research reviewed here strongly suggests that heavy alcohol use may exacerbate specific inflammatory processes already present in HIV infection, including microbial translocation, immune activation, BBB compromise, microglial activation, and neuroinflammation.

Currently, long-term effects of alcohol use on the clinical course of HIV infection are not well understood. Research linking systemic immune activation to neuroinflammatory processes remains in early stages. Because most previous neuroimaging studies of PLWH have excluded individuals with heavy drinking, integrated and multidisciplinary research on this complex comorbidity is imperative. Animal models permit hypothesis-driven studies of additive or synergistic effects of alcohol and HIV on key inflammatory processes. As animal models have certain limitations in the study of HIV, however, clinical neuroimaging research in cohorts of PLWH with varied alcohol use patterns will be critical to understanding these relationships. Development of advanced neuroimaging methods with specificity for neuroinflammation and microglial activation will aid in diagnosis and targeted treatment of HIV- and alcohol-related neuropathology. Moreover, peripheral markers of immune activation warrant further investigation as proxy biomarkers of neuroinflammation [e.g., (56)]. In clinical settings without ready access to neuroimaging tools, such biomarkers would be highly useful for identifying individuals in need of more intensive assessment and treatment.

Microglial activation, particularly the TLR4-mediated cascade, is a novel and promising target for neuropharmacological interventions (184, 185). In addition, prebiotic and/or probiotic supplements are receiving attention as an adjunctive therapy in HIV infection and AUD. Prebiotic and/or probiotic supplements have shown initial promise to mitigate inflammation in small randomized, controlled trials with PLWH (186–188) and in rodent models of alcoholic liver disease (189, 190). An important question for such trials is whether therapeutic interventions that reduce systemic inflammation by way of the gut microbiome also have benefits for neural health and psychological functioning.

In conclusion, basic and clinical findings on immune mechanisms of alcohol have critical implications in the setting of HIV infection. Up to this point, alcohol and HIV research agendas have proceeded largely independent of each other. The possibility for heavy drinking to compound systemic, neurobiological, and cognitive complications in HIV infection presents a serous cause for concern, as well as a compelling rationale to integrate these lines of research. Studies on specific immune mechanisms shared by heavy drinking and HIV infection will help to identify critical targets for behavioral and biomedical interventions in this complex comorbidity.

Acknowledgments

Funding: This work was supported by National Institute on Alcohol Abuse and Alcoholism grants T32AA007459 (PI: Monti) and K23AA024704-01A1 (PI: Monnig).

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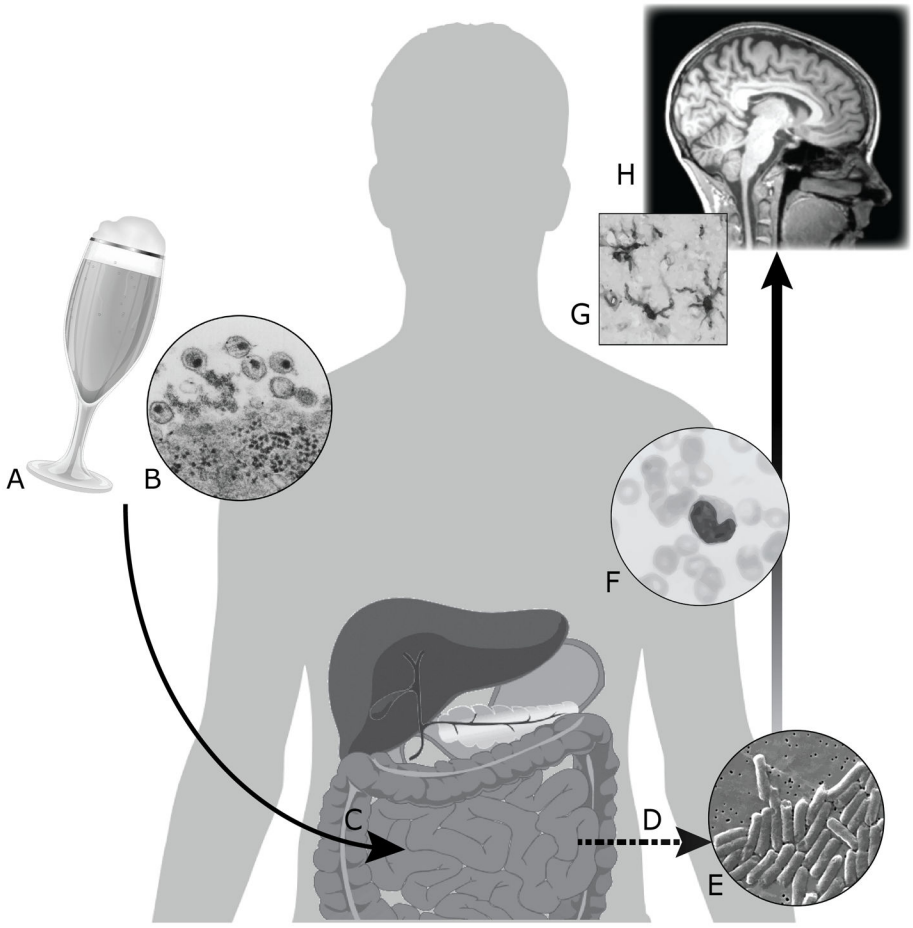

Figure 1.

Alcohol (**A**) and HIV (**B**) are associated with deleterious effects on the gastrointestinal tract (**C**), including intestinal hyperpermeability, dysbiosis of the gut microbiota, and epithelial cell damage (33, 42, 76, 78, 182, 191). Research suggests potential for additive effects in co-occurring HIV infection and heavy drinking. These mechanisms contribute to microbial translocation (**D**), the unphysiological movement of microbial components into systemic circulation. LPS, a component of cell walls of Gram-negative bacteria (**E**), stimulates pro-inflammatory signaling by monocytes in circulation (**F**). Systemic inflammation may be propagated to the central nervous system via infiltration of infected monocytes, free virus, and cytokines. Neuroinflammation mediated by microglia (**G**) is thought to underlie many of the changes observed on MRI (**H**) in alcohol use disorders or HIV infection and to contribute to cognitive and behavioral dysfunction.

Table 1

Key terms in microbial translocation and immune activation

Key Term	Description
Endotoxin core antibody immunoglobulin M (EndoCAb)	Antibody against the LPS core antigen that binds to and neutralizes LPS
Innate immune activation	Rapid, nonspecific immune response to infectious agents initiated by pathogen recognition and exercised through pro-inflammatory signaling pathways
Lipopolysaccharide (LPS; also referred to as endotoxin)	Component of cell walls of Gram-negative bacteria and a major ligand for TLR4; LPS in plasma is used as a measure of microbial translocation
Lipopolysaccharide binding protein (LBP)	Acute phase protein in plasma that binds to and presents LPS to sCD14 or the membrane-bound CD14/TLR4 receptor complex
Microglial activation	Response of the brain's resident innate immune cells (i.e., microglia) to pathogens, viral proteins, and toxins that involves production and secretion of pro-inflammatory mediators (e.g., cytokines, reactive oxygen species); chronic and/or excessive microglial activation is a recognized factor in neurodegeneration
Microbial translocation	Movement of microbial components normally confined to the gut into systemic circulation, as a result of structural and/or functional compromise of the intestinal barrier
Neuroinflammation	Central nervous system condition marked by elevated pro-inflammatory cytokines and oxidative stress signals that create a neurotoxic milieu, leading to neurodegeneration when chronic
Proinflammatory cytokines	Broad class of proteins that are critical to immune response to contain infection but are harmful with prolonged or extreme elevations; types include interleukins (e.g., IL-6), interferons (e.g., interferon-α), and tumor necrosis factor (e.g., TNF-α)
Soluble cluster of differentiation 14 (sCD14)	CD14 is the co-receptor for TLR4 and is expressed on monocytes and macrophages; the soluble form, sCD14, is a plasma marker of monocyte activation and presents LPS to the TLR4 receptor complex
Toll-like receptor 4 (TLR4)	Innate immune receptor dedicated to recognition of pathogens such as LPS; binding of LPS to TLR4 initiates a pro-inflammatory response that involves production and secretion of cytokines