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Review

Review

Impact of Alcohol on HIV Disease Pathogenesis, Comorbidities and Aging: Integrating Preclinical and Clinical Findings

Patricia E. Molina*, Liz Simon, Angela M. Amedee, David A. Welsh, and Tekeda F. Ferguson

Comprehensive Alcohol-HIV/AIDS Research Center and Alcohol and Drug Abuse Center of Excellence, LSUHSC, 1901 Perdido St., New Orleans, LA 70112, USA

*Corresponding author: LSUHSC Physiology, 1901 Perdido St., New Orleans, LA 70112, USA. Tel.: +1-504-568-6187; Fax: +1-504-568-6158; E-mail: pmolin@lsuhsc.edu

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Abstract

Alcohol's multisystemic effects impact HIV disease pathogenesis and increase the risk for comorbidities in persons living with HIV (PLWH). The increased number of aging PLWH increases the potential for alcohol to enhance the risk for comorbidities. Integration of epidemiological, preclinical and translational studies provide an overarching view of the impact of heavy alcohol consumption on HIV risk, pathogenesis, treatment and burden of disease. The combined insult of HIV infection, heavy alcohol consumption and toxic effects of antiretroviral therapy in aging PLWH poses a public health challenge through increased disease burden that also impacts quality of life and increases health care costs. Herein we provide a brief overview of current knowledge on alcohol's impact on HIV disease pathogenesis, with focus on aging PLWH.

Short Summary: Effective combined antiretroviral therapy regimens have extended survival of persons living with HIV (PLWH). Heavy alcohol consumption is common in PLWH. This overview integrates evidence from clinical and preclinical research to identify salient alcohol-related mechanisms and comorbidities contributing to disease pathogenesis and accelerated aging and senescence in PLWH.

INTRODUCTION

Heavy, or 'at-risk', alcohol consumption is defined as consumption of more than 60 and 40 g of ethanol per day (for men and women, respectively) by the World Health Organization (WHO), and by either consumption of more than 14 or 7 drinks per week (for men and women, respectively) or binge drinking (more than 4–5 drinks within a 2-h period) by the National Institute of Alcohol Abuse and Alcoholism (NIAAA). Heavy alcohol consumption is the most common and costly form of substance use disorder in the United States (World Health Organization, 2014; SAMSHA, 2016). Alcohol use is strongly associated with an increased risk of HIV infection (Lefevre *et al.*, 1995) (Fig. 1). Persons living with HIV (PLWH) have a 2–3-fold higher prevalence of alcohol use disorder (AUD) (Conigliaro *et al.*, 2006), and ~8–12% of PLWH are classified as heavy drinkers (Burnam *et al.*, 2001; Galvan *et al.*, 2002). Heavy alcohol consumption can affect disease pathogenesis through direct and indirect interactions with factors including age, stress, sex and access and adherence to antiretroviral therapy (ART) (Fig. 2). In the era of combined ART, HIV infection has become a chronic disease and current estimates indicate that 50% of PLWH in the US are 50 years of age or older (Centers for Disease Control and Prevention, 2016). HIV infection, heavy alcohol consumption and aging independently increase the risk for several comorbidities, including myopathy, cardiovascular disease (CVD), liver cirrhosis, diabetes and pneumonia. Here we provide an overview of salient findings from preclinical and clinical studies and identify areas in need of further investigation.

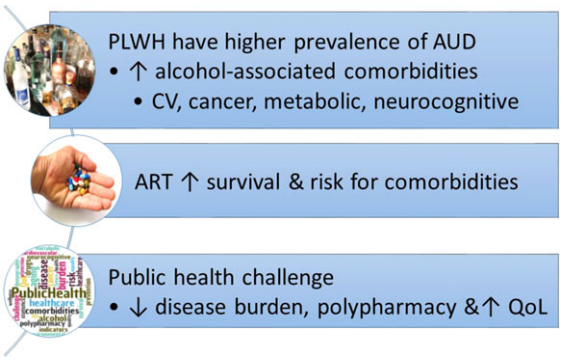

Fig. 1. Key aspects of the interaction of chronic risky alcohol consumption on HIV disease.

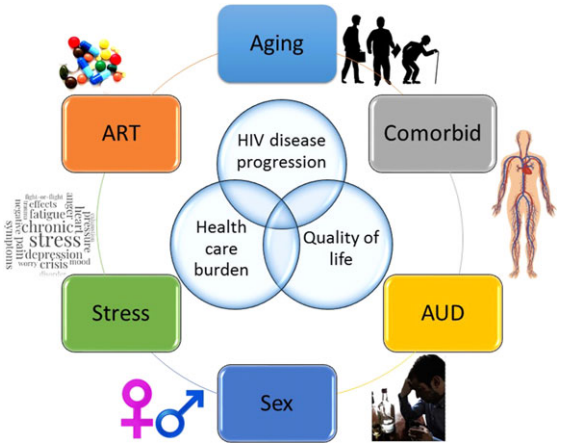

Fig. 2. Chronic heavy alcohol consumption impacts HIV pathogenesis through direct and indirect interactions with factors including age, stress, sex and access and adherence to antiretroviral therapy (ART). As a consequence of chronic heavy alcohol consumption; disease progression, health care burden and quality of life are significantly and detrimentally affected.

IMPACT OF ALCOHOL ON HIV DISEASE

Several clinical studies have evaluated the effects of alcohol use on CD4+ T cell counts and viral load, but consistent associations of these clinical markers with at-risk drinking have not always been observed. One prospective longitudinal study showed greater suppression of CD4+ T cell counts in PLWH with frequent alcohol use (Baum *et al.*, 2010), while another reported that heavy alcohol consumption negatively impacted CD4+ cell counts only in ART-naïve subjects (Samet *et al.*, 2007). Other investigations failed to establish an association between heavy alcohol consumption and CD4+ T cell decline, or have shown an indirect effect of alcohol use on CD4+ T cells due to poor ART adherence (Samet *et al.*, 2007; Hahn and Samet, 2010; Wandera *et al.*, 2017; Hahn *et al.*, 2018). Clinical studies have not found a direct, negative effect of alcohol consumption on viral load, however, heavy alcohol consumption has been identified as a significant contributor to poor ART adherence (Braithwaite and Bryant, 2010). Non-adherence to ART is more likely among PLWH that engage in binge drinking than non-drinkers and, consequently, binge drinkers are less likely to achieve viral suppression, potentially increasing morbidity and mortality.

Due to the multitude of variable behavioral and environmental factors that may modulate disease over the span of HIV infection, it is difficult to accurately assess effects of risky alcohol use on clinical markers of HIV disease in clinical cohorts over short time-spans. Animal model studies using simian immunodeficiency virus (SIV) infected macaques, with well-controlled behavioral and environmental conditions, have provided significant insight on the interaction of HIV and heavy drinking (Amedee *et al.*, 2014). Preclinical studies in the chronic binge alcohol (CBA)-administered SIV macaque have consistently associated increased viral load with alcohol consumption. Additionally, studies using this model (Bagby *et al.*, 2006; Molina *et al.*, 2006, 2008) show a significant temporal acceleration to end-stage disease in the absence of ART, with consistently higher plasma, cerebrospinal fluid and tissue viral loads among CBA-administered animals compared to controls (Poonia *et al.*, 2006; Amedee *et al.*, 2014).

ART leads to a similar reduction in viral load in CBA and control animals, suggesting that, with strict adherence, ART may effectively control viremia (Molina *et al.*, 2014a). However, emerging data suggests that viral expression in reservoirs remains elevated in ART-treated, CBA-administered, SIV-infected macaques (unpublished data), a finding which cannot be explained by decreased adherence and that highlights the possibility that viral reactivation in PLWH may be more common in heavy drinkers than in non-drinkers. In addition, others have shown that SIV continues to replicate in the brain of alcohol-dependent animals, whereas it is undetectable in controls (Kumar *et al.*, 2005). Moreover, recent *in vitro* studies suggest that ethanol may decrease intracellular efficacy of some ART drugs, such as the integrase strand transfer inhibitor, elvitegravir (Midde *et al.*, 2017). Thus, additional *in vivo* studies are needed to determine efficacy of ART in viral reservoirs and the impact of alcohol.

ALCOHOL, HIV AND GERIATRIC COMORBIDITIES

Improvement in survival of PLWH is complicated by comorbidities typically associated with advanced age, including osteoporosis, diabetes, CVD, cancer, renal disease and metabolic alterations (Burgess *et al.*, 2015). All of these HIV-associated metabolic comorbidities can be further exacerbated by heavy alcohol consumption (Wand *et al.*, 2007), particularly in the aging population. A significant proportion of PLWH meet criteria for multimorbidity (Kim *et al.*, 2012), particularly PLWH who are older and obese, and have lower CD4+ cell counts. The high rate of comorbidities in PLWH, due in part to high-risk behaviors (e.g. smoking, heavy alcohol consumption), increases morbidity and mortality (Hawkins *et al.*, 2017). These comorbidities, discussed in the following sections, contribute to the development of a frailty syndrome.

Osteoporosis and bone fractures

PLWH have an increased risk of fracture, associated with risk factors of bone fragility like poor nutrition, smoking, alcohol consumption, liver disease and hypogonadism (Compston, 2016). HIV infection in children and adolescents correlates with reduced bone mineral density (BMD) and quality, suggesting that HIV undermines normal bone formation. Further, ART leads to accelerated BMD loss during the initial treatment period and particularly in those with low CD4+ counts and higher plasma HIV viral loads (both of which are associated with heavy alcohol consumption, as discussed above). Heavy alcohol consumption is an established risk factor for low BMD, fractures and osteoporosis, even in the absence of liver failure (Maurel *et al.*, 2012). The underlying mechanisms are multifactorial and include hormonal (decreased androgens, growth hormone and insulin-like growth factor

1), inflammatory (inflammatory cytokines and chemokines) and nutritional (decreased intake of vitamin D and calcium) factors (Luo *et al.*, 2017). In combination, ART and alcohol likely further diminish aging- and sex-related reductions in bone health in PLWH. Recent reports have found associations between alcohol-related diagnoses and between recent, but not lifetime, drinking and BMD in PLWH (Ventura *et al.*, 2017; Womack *et al.*, 2013). This remains an area in need of further investigation.

Cardiovascular disease

Risk of death from acute myocardial infarction independent of traditional CVD risk factors is 1.5–2 times higher in PLWH than in the general population. Lack of virologic suppression, which most frequently occurs with treatment interruption (Kuller *et al.*, 2008) (as frequently reported in alcoholics), increases the risk for atherosclerosis (Triant *et al.*, 2007). However, progression from atherosclerosis to myocardial infarction is faster in PLWH than in controls, even with controlled viremia (Hsue *et al.*, 2012). The proposed underlying mechanisms include chronic inflammation, microbial translocation and mitochondrial dysfunction, which synergize with traditional risk factors for CVD including tobacco and alcohol use, dyslipidemia and obesity (Triant *et al.*, 2007; Kim *et al.*, 2012). An increased risk of CVD in hazardous and dependent drinkers (compared to infrequent and moderate drinkers) has been observed in PLWH (Freiberg *et al.*, 2010). CVD risk has been attributed to the metabolic toxicities of protease inhibitors. More current ART regimens are associated with improved surrogate markers of atherosclerosis (Torriani *et al.*, 2008). However, there is sparse data examining alcohol as a mediator of the increased risk of CVD among PLWH (Kelso *et al.*, 2015).

Metabolic

The incidence of metabolic comorbidities, such as insulin resistance, is high in PLWH (Falutz, 2011), increasing the risk for glucose intolerance and diabetes (Lombo *et al.*, 2015). Although the mechanisms underlying dysglycemia in PLWH remain poorly understood, chronic subclinical inflammation is emerging as a central mechanism of metabolic derangements (Kolter, 2003). The high prevalence of diabetes among PLWH (Kim *et al.*, 2012) is linked to traditional risk factors such as race/ethnicity, smoking status and obesity (De Wit *et al.*, 2008). Risk factors for metabolic comorbidities also include viral proteins and ART therapy. More recent ART regimens reduce metabolic dysregulation. However, heavy alcohol consumption contributes to the development of insulin resistance (Yki-Jarvinen and Nikkila, 1985), lipodystrophy (Cheng *et al.*, 2009) and altered adipokine profiles, which have all been linked to metabolic alterations in obese (Rasouli and Kern, 2008) and ART-treated (Sevastianova *et al.*, 2008) PLWH. Both heavy alcohol consumption (Molina, 2008) and HIV/AIDS (Rimaniol *et al.*, 1996; Alonso *et al.*, 1997) disrupt endocrine mechanisms (i.e. GH/IGF-I system) (Frost *et al.*, 1996) and gonadal hormones (Poretsky *et al.*, 1995) and increase oxidative stress (Israel and Gougerot-Pocidalo, 1997), which could also contribute to metabolic dysregulation in PLWH.

Neurocognitive impairment

Alcohol and HIV have potentially overlapping and additive, or synergistic, effects on neurocognitive function. In the ART era, the prevalence of HIV-associated dementia (HAD) has declined (Heaton *et al.*, 2010), but neurocognitive impairment in the form of asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) is still prevalent in up to 50% of PLWH (Woods *et al.*, 2009; Heaton *et al.*, 2010; Saylor *et al.*, 2016). Although the severity of cognitive impairments has decreased, incidence of ANI has increased (Heaton *et al.*, 2010) and the domains affected have shifted, resulting in a lower percentage of PLWH with deficits in verbal domains, information processing and motor coordination, but more learning and executive function impairment (Heaton *et al.*, 2011; Sacktor *et al.*, 2016). Theses shifts in cognitive deficits may reflect differential vulnerabilities of brain regions to HIV-associated neuropathology. Site-specific structural changes have been identified at the whole brain level in PLWH, with ventricular enlargement, thinning of the cortex, and decreased volume of the frontal cortex and caudate being associated with cognitive impairment (Rosenbloom *et al.*, 2010). Metabolic dysfunction, CVD and poor ART adherence may aggravate cognitive decline, particularly in aging PLWH (Levine *et al.*, 2016; Canizares *et al.*, 2014). Alcohol-associated alterations in micronutrient deficits, metabolic homeostasis and polydrug use can all increase the risk of neurocognitive impairment (Gongvatana *et al.*, 2014) and remain an understudied area of research.

Geriatric syndromes

Geriatric syndromes are multifactorial health conditions typically occurring with advanced age, and ranging from incontinence to dementia to impaired physical function to polypharmacy. Data suggest that HIV itself leads to precocious aging, geriatric comorbidities and frailty (Freiberg *et al.*, 2013; Womack *et al.*, 2013). These have commonalities with recognized HIV-associated comorbidities including cachexia and sarcopenia, low bone density, neurocognitive impairment, depression and viral (particularly hepatitis) coinfection (Brothers *et al.*, 2014). Hazardous alcohol use in PLWH is associated with an elevated risk of phenotypic frailty (Piggott *et al.*, 2013).

Cellular and immune aging

Early on, it was recognized that HIV infection is associated with immunosenescence resulting from chronic immune activation driven by HIV-1 continuous virion replication, production of pro-inflammatory cytokines, a rise in lymphocyte proliferation and cell death (Meyaard *et al.*, 1992), and an imbalance in Th1/Th2 responses (Romagnani *et al.*, 1994). Our preclinical and clinical studies show significantly increased peripheral blood CD8+ T cell activation and immunosenescence as compared to baseline levels in CBA, non-ART-treated, SIV-infected macaques (Katz *et al.*, 2015). Moreover, the frequency of activated immunosenescent CD8+ T cells positively correlated with alcohol use disorder identification test (AUDIT) scores in PLWH (Katz *et al.*, 2015). Heavy alcohol consumption has also been linked with accelerated cellular aging as reflected by shorter telomere length (Pavanello *et al.*, 2011). Telomeres, DNA–protein protective structures at the ends of each chromosome, undergo continuous loss with each cell division, decreasing in length as cells approach senescence and/or apoptosis. In the MacArthur Health Aging Study, alcohol use predicted loss of telomere length (Epel *et al.*, 2009); and in the Helsinki Businessman Study, lifetime drinking predicted shorter telomeres (Strandberg *et al.*, 2012). Thus, alcohol appears to hasten cellular aging in the general population and this appears to be exacerbated in PLWH. Therefore, biological age and cellular senescence associated with heavy alcohol consumption are likely to synergize to increase the risk for comorbidities and development of geriatric syndromes in PLWH. As the number of aging PLWH continues to rise, diagnosis and management of comorbidities will be of

equal importance to achieving control of viremia, and decreasing alcohol use in this vulnerable population.

MECHANISMS IMPLICATED IN ALCOHOL-HIV PATHOPHYSIOLOGY

Several mechanisms involved in alcohol-induced tissue and organ injury are likely to be responsible for the increased risk of comorbidities, morbidity and mortality in PLWH with AUD. Oxidative stress, mitochondrial injury and epigenetic modifications are among the most salient mechanisms that are potential therapeutic targets.

Chronic inflammation

Chronic inflammatory states correlate with higher viremia, disease progression and clinical sequela of chronic HIV infection (Appay and Kelleher, 2016). Additive or synergistic effects of alcohol and HIV on systemic inflammation promote HIV replication (Bagasra *et al.*, 1996). Although ART can effectively reduce or eliminate plasma HIV levels, low-level viral replication and the expression of viral proteins in discrete tissue reservoir sites may contribute to the inflammatory state and further exacerbate immune dysfunction.

Evidence supporting the link between enhanced viral replication and chronic inflammation and immune dysfunction is derived from preclinical studies in ART-naïve SIV-infected macaques. Those studies showed markedly increased rates of proliferation/activation of gastrointestinal (GI) submucosa CD4+ and CD8+ T cells and decreased total numbers of T cells (Veazey *et al.*, 2015), which correlated with increased SIV expression in CBA-administered animals (Poonia *et al.*, 2006). Similarly, heightened vaginal pro-inflammatory milieu in CBA-administered female SIV-infected macaques coincided with greater viral replication Loganantharaj *et al.* (2014). Relevant to overall disease, chronic intestinal inflammation and the associated immune activation promotes viral replication, compromises the integrity of the gut mucosal barrier, and increases the potential for microbial translocation (Fig. 3).

The GI tract is the primary target for early HIV infection, viral expansion and CD4+ T cell loss (Veazey *et al.*, 1998). The early phase of HIV infection is associated with marked gut inflammation and barrier leak (Gori *et al.*, 2008). Abundant evidence, including

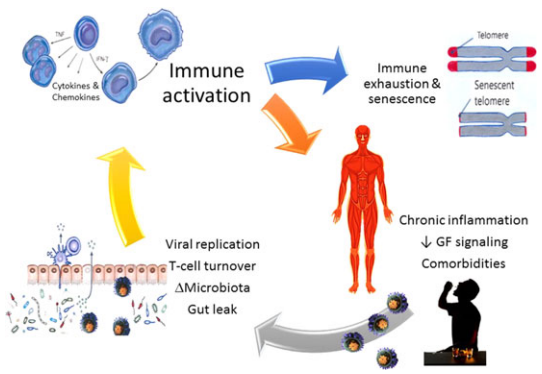

Fig. 3. Integrating findings from clinical and preclinical studies, the current thinking is that chronic heavy alcohol consumption by persons living with HIV (PLWH) promotes increased viral replication, lymphocyte turnover, dysbiosis and gut barrier leak, resulting in translocation of toxins and bacterial products into the systemic circulation. Together, toxins and increased viral replication promote immune activation leading to a state of immune exhaustion and senescence, and chronic systemic inflammation, tissue injury and increased risk for development of comorbidities.

work from our group, now supports a pivotal role for the GI tract microbiota as a regulator of host processes and homeostasis (Samuelson *et al.*, 2017). The microbiota, through production of specific nutrients and biomediators (e.g. short chain fatty acids), maintains epithelial integrity. Preclinical models have clearly demonstrated the essential role of intestinal microorganisms in the development and control of both local and systemic immunity. During HIV infection, the normal microbiota of the alimentary tract is perturbed (Vazquez-Castellanos *et al.*, 2015; Williams *et al.*, 2016). Similarly, alcohol leads to bacterial overgrowth and alters the alimentary tract microbial community composition (Leclercq *et al.*, 2014).

Persistent GI disease/inflammation and loss of mucosal integrity, accompanied by microbial product translocation into the systemic circulation, is associated with HIV disease progression and mortality as supported by clinical and preclinical studies (Dandekar *et al.*, 2010). PLWH have increased biomarkers of microbial translocation, lipopolysaccharide and its receptor (soluble CD14), and bacterial 16 S ribosomal RNA (rRNA) gene, compared with uninfected persons. This increased antigenic burden results in immune activation and chronic inflammation, culminating in immune exhaustion and senescence (Dinh *et al.*, 2015). Alcohol increases intestinal permeability and translocation of bacterial components (Keshavarzian *et al.*, 2009). Collectively, these data indicate that the GI tract is a central point at which HIV, heavy alcohol use and immune activation intersect, and therefore may promote the immune senescence observed as a result of HIV infection (Desai and Landay, 2010; Chou *et al.*, 2013). Preliminary analyses by our group have implicated alcohol-associated dysbiosis as contributory to immune activation in PLWH.

Oxidative stress

Alcohol metabolism is a significant source of reactive oxygen species (ROS) and shifts cellular redox state. Oxidative stress, resulting from either an excess production of ROS or a depletion of tissue reducing antioxidant equivalents, contributes to alcohol- and HIV-mediated tissue injury (Molina *et al.*, 2014b) and promotes HIV-1 replication (Kumar *et al.*, 2012). Oxidative stress activates lymphocytes and accentuates chronic inflammation and lipid peroxidation (Aukrust *et al.*, 2003), producing the cellular damage associated with HIV, heavy alcohol consumption (Fernandez-Sola *et al.*, 2007; Molina *et al.*, 2014a,b) and ART. Moreover, mitochondrial energy generation through oxidative phosphorylation also generates ROS that form adducts with proteins, DNA and lipids, causing cellular damage. Our studies show that CBA administration results in depletion of antioxidant capacity, decreased expression of super oxide dismutase 2 (SOD2) (a potent mitochondrial antioxidant enzyme), and altered gene regulatory networks that regulate oxidative stress. Together, these mechanisms contribute to accentuated skeletal muscle wasting at end-stage disease in SIV-infected macaques (Molina *et al.*, 2008; Lecapitaine *et al.*, 2011; Simon *et al.*, 2015; Duplanty *et al.*, 2017). Whether similar defects in mitochondrial antioxidant capacity occur in other tissues, like the liver, remains to be investigated.

Mitochondrial dysfunction

Excessive ROS production and/or defective antioxidant capacity play a role in mitochondrial dysfunction and mitochondrial DNA (mtDNA) mutations (Calvani *et al.*, 2013). Mitochondrial dysfunction due to heavy alcohol consumption occurs in the liver (Hoek *et al.*, 2002), skeletal muscle (Simon *et al.*, 2017b) and cardiac muscle (Steiner and Lang, 2017) and is characterized by mitochondrial genome degradation in the brain, heart and skeletal muscle and by decreased mitochondrial

biogenesis (mitogenesis). HIV infection also induces mitochondrial damage (Ferri *et al.*, 2000) and long-term ART has been linked to mitochondrial toxicity and impairment of genes responsible for mitogenesis (Barve *et al.*, 2010). Nucleoside reverse-transcriptase inhibitors (NRTIs) in particular have been shown to significantly impair mitochondrial homeostasis (Lewis, 2003) although newer agents, like emtricitabine (FTC) (Venhoff *et al.*, 2007), have less mitochondrial toxicity. Despite known mitochondrial dysfunction with AUD, HIV and ART, few studies have elucidated the interactions between alcohol and ART. Recently, our group demonstrated that CBA impairs expression of genes associated with mitochondrial biogenesis, mitophagy and protection from ROS at end-stage disease in non-ART-administered, SIV-infected macaques (Duplanty *et al.*, 2017). We believe that mitochondrial dysfunction contributes to accelerated HIV disease progression including decreased whole body insulin sensitivity (Ford *et al.*, 2016), decreased myogenic potential (Simon *et al.*, 2017a) and chronic sensory peripheral neuropathy (Bennett *et al.*, 2014).

Altered growth factor signaling

Both alcohol and HIV can alter growth factor expression and signaling, critical mechanisms regulating protein turnover and proliferation in many cell types, including skeletal muscle (Steiner *et al.*, 2015). In PLWH, particularly those with lipodystrophy, significant alterations in the growth hormone (GH)–insulin-like growth factor 1 (IGF-1) axis have been reported (Grinspoon *et al.*, 1998). However, the synergism between AUD and HIV is not well described. Both alcohol and HIV can suppress neurotrophic factors critical for neuronal growth and survival (Bachis *et al.*, 2012; Boyadjieva and Sarkar, 2013; Fields *et al.*, 2014). Brain-derived neurotropic factor (BDNF) is a key growth factor with mechanistic and therapeutic implications in AUD or HIV infection (Davis, 2008) and its expression is lower in the cortex, hippocampus and striatum of PLWH with HAD compared to that of uninfected controls (Bachis *et al.*, 2012). Neuronal apoptosis resulting from HIV infection in experimental models is associated with reduced BDNF expression (Nosheny *et al.*, 2004). Moreover, HIV protein gp120-mediated decreases in neurogenesis can be rescued by BDNF overexpression (Avraham *et al.*, 2014), supporting a role for BDNF in HIV-associated cognitive dysfunction. Similarly, alcoholics have lower plasma BDNF levels than non-alcoholics (Joe *et al.*, 2007) and preclinical models show reduced BDNF expression and phosphorylated TrkB (Raivio *et al.*, 2012) following alcohol administration. Our exploratory microarray analysis shows that CBA administration in SIV-infected macaques upregulates hippocampal genes involved in immune function and dysregulates expression of genes involved in neurogenesis (Maxi *et al.*, 2016), which we believe may result from impaired BDNF signaling cascade. Exploring the potential of targeting BDNF expression in PLWH with cognitive impairment, either pharmacologically or through interventions like aerobic exercise, are promising areas for further research.

Epigenetic alterations

Epigenetic alterations include histone acetylation or deacetylation, DNA methylation, and gene regulation by non-coding RNAs (ncRNAs) and these modifications are achieved by histone acetyl transferases or histone deacetylases (HATs, HDACs), and DNA methyltransferases (DNMTs). Alcohol-mediated gene expression changes are regulated by epigenetic mechanisms in several tissues including liver, brain and immune system (Shukla and Lim, 2013). Products of alcohol metabolism such as acetaldehyde, acetate, acetyl-CoA, ROS, as well as non-oxidative products, such as phosphatidylethanol (PEth) and fatty acid ethyl ester (FAEE) (Molina *et al.*, 2014b), can induce tissue-specific epigenetic changes including histone acetylation (H3AcK9) (Kim and Shukla, 2006) and alterations in non-coding microRNAs (miRNAs).

Epigenetic mechanisms can also impact HIV disease at multiple levels. Histone deacetylation and methylation of the HIV promotor region in cells of gut-associated lymphoid tissue (GALT) and the central nervous system (CNS) (Friedman *et al.*, 2011) are proposed mechanisms of HIV gene silencing (du Chéné *et al.*, 2007), thus facilitating viral persistence. Interestingly, DNA methylation patterns in PLWH mimic those of chronologically older uninfected individuals (Gross *et al.*, 2016; Nelson *et al.*, 2017). miRNA modulation of viral protein expression favoring latency has also been reported (Nair *et al.*, 2004). How alcohol-induced epigenomic modulation of host gene expression contributes to viral persistence remains unexplored. However, CD8 T cells isolated from PLWH display downregulated immunomodulatory miRNA expression in viremic progressors compared to elite controllers and uninfected controls (Egana-Gorrono *et al.*, 2016). Whether alcohol regulates HIV replication or latency via epigenetic mechanisms warrants further investigation and is being pursued by our group.

Circulating miRNAs may serve as biomarkers of disease. Alterations in brain (Yelamanchili *et al.*, 2010) and plasma miR (Witwer *et al.*, 2011) profiles in SIV-infected macaques appear to modulate disease progression. Recent studies from our group identified highly sensitive and specific microRNA signatures distinguishing PLWH with cognitive impairment from those without impairment (Wyczechowska *et al.*, 2017). Altered miR expression profiles in PLWH may impact gene regulatory networks involved in HIV-associated neurocognitive dysfunction (Noorbakhsh *et al.*, 2010; Tatro *et al.*, 2010). Support for epigenetic mechanisms contributing to alcohol-induced pathogenesis is provided by our findings of decreased myoblast differentiation potential associated with a decrease in muscle-specific miR-206 expression, which targets histone deacetylase 4, a known suppressor of myogenic genes (Simon *et al.*, 2017a). Moreover, recent findings suggest decreased anti-HIV miRNAs (miR-27 and miR-181) expression in peripheral blood mononuclear cells (PBMCs) of SIV-infected macaques that could be further modulated by alcohol and require further investigation. Additional mechanisms contributing to persistent CD4 + viral expression in reservoirs should be explored to gain mechanistic insights into disease progression and potential therapeutic targets. Further identification of miRs as potential biomarkers of disease

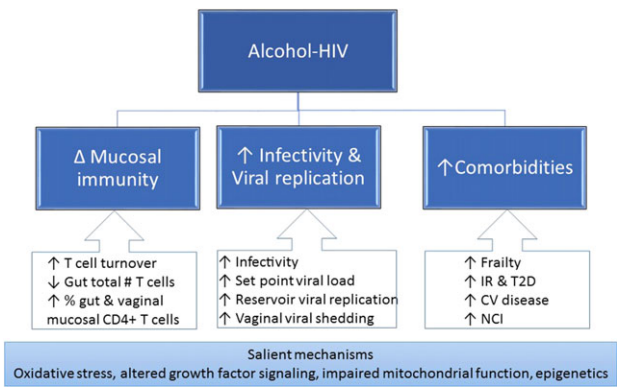

Fig. 4. The alcohol-mediated mechanisms of exacerbated HIV pathogenesis include alterations in mucosal immunity and increased viral infectivity and replication, leading to chronic immune activation and inflammation promoting frailty-related comorbidities. IR, insulin resistance; T2D, type 2 diabetes; CV, cardiovascular; NCI, neurocognitive impairment.

progression and indicators of response to interventions should be a focus of future studies.

SUMMARY

Both preclinical and clinical findings strongly suggest that heavy alcohol consumption can exacerbate HIV pathogenesis through alterations in mucosal immunity, increased viral replication, chronic immune activation and inflammation (Fig. 4). The state of chronic immune activation and inflammation increases the risk of geriatric conditions including frailty, osteoporosis, sarcopenia, insulin resistance and diabetes, CVD and neurocognitive impairment. Additional salient mechanisms include oxidative stress, altered growth factor signaling, impaired mitochondrial homeostasis and epigenetic modifications.

PERSPECTIVES

Alcohol's multifactorial effects on organ systems imposes an additional risk factor for development of comorbidities in PLWH. In an aging PLWH population, heavy alcohol consumption accelerates senescence and the onset of frailty, decreasing quality of life despite the prolonged survival from HIV disease with effective ART. Improved understanding of the pathophysiology of alcohol-associated comorbidities in PLWH will require increased transdisciplinary efforts. We propose that development of biomedical approaches to restore alcohol-induced impaired organ function should be coupled with evidence-based interventions to decrease alcohol use in this vulnerable population.

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CONFLICTS OF INTEREST STATEMENT

None declared.

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