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Biomedical Consequences of Alcohol Use Disorders in the HIV-Infected Host Invited Review

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Abstract

Alcohol abuse is the most common and costly form of drug abuse in the United States. It is well known that alcohol abuse contributes to risky behaviors associated with greater incidence of human immunodeficiency virus (HIV) infections. As HIV has become a more chronic disease since the introduction of antiretroviral therapy, it is expected that alcohol use disorders will have an adverse effect on the health of HIV-infected patients. The biomedical consequences of acute and chronic alcohol abuse are multisystemic. Based on what is currently known of the comorbid and pathophysiological conditions resulting from HIV infection in people with alcohol use disorders, chronic alcohol abuse appears to alter the virus infectivity, the immune response of the host, and the progression of disease and tissue injury, with specific impact on disease progression. The combined insult of alcohol abuse and HIV affects organ systems, including the central nervous system, the immune system, the liver, heart, and lungs, and the musculoskeletal system. Here we outline the major pathological consequences of alcohol abuse in the HIV-infected individual, emphasizing its impact on immunomodulation, erosion of lean body mass associated with AIDS wasting, and lipodystrophy. We conclude that interventions focused on reducing or avoiding alcohol abuse are likely to be important in decreasing morbidity and improving outcomes in people living with HIV/AIDS.

Keywords

AIDS; alcohol; cytokines; immune; muscle wasting; SIV

Introduction

While the number of newly diagnosed cases of human immunodeficiency virus (HIV) has decreased during the past decade, the number of people living with HIV/AIDS (PLWHA) has continued to rise. More than 1.1 million people in the U.S. are currently estimated to live with HIV [1]. Chronic alcohol consumption prevails as the most common and costly form of drug abuse, with approximately 7 percent of the adult U.S. population fulfilling the diagnostic criteria for alcohol abuse and/or alcoholism [2, 3]. The use of antiretroviral

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Conflicts of Interest
There are no conflicts of interest.

therapy (ART) has substantially reduced HIV-associated morbidity and mortality, making HIV a chronic disease during which infected individuals are likely to engage in alcohol abuse at a rate comparable to or greater than those of the non-infected population [4,5]. Thus, the social and behavioral patterns of the population at large are also prevalent in HIV+ individuals [6].

Alcohol and HIV Frequently Coexist

Alcohol abuse and HIV frequently coexist in the same individual [4, 7, 8]. Some studies indicate that approximately 50% of HIV+ patients currently in care self-report consuming any alcohol [8, 9]. Moreover, rates of heavy drinking among PLWHA are higher than those in the general population [8, 10]. Reports range from 9% of PLWHA surveyed engaging in regular binge drinking [11] to some reports of problem drinking in as many as 40 to 50% of patients surveyed [12]. Alcohol use disorders (AUD) have long been recognized as a significant behavioral risk factor conducive to increased incidence of HIV infection. Although the potential interaction between alcohol-related biomedical consequences and the progression of HIV infection has received increased attention, there is a dearth of information on the likelihood of changes in the course of disease progression due to alcohol-associated biomedical derangements [13] (Fig. 1).

Alcohol Abuse Contributes to Comorbid Conditions in HIV+

Alcohol abuse has significant multisystemic pathophysiological outcomes including disruption of nutritional, metabolic, oxidative, and neuroendocrine pathways [14]. Due to the chronic nature of the HIV infection and AUD; the heterogeneous patient population; the effects of non-prescription, experimental drugs frequently used by these individuals; and limitations in methodology to investigate the cellular and molecular mechanisms that drive viral kinetics and resulting injury; it is extremely difficult to conduct a controlled study of the alcohol-deranged biological mechanism(s) that can impact the course of HIV infection. Thus, few studies have examined the pathophysiology involved in alcohol-abusing HIV+ patients and even fewer in patients on ART. Most of our knowledge is derived from experimental models, including that of simian immunodeficiency virus (SIV)-infected rhesus macaques, which is known to be the best animal model for studying the pathogenesis of HIV-like infection because of its similarities to HIV/AIDS in humans.

Non-Human Primate Model for the Study of Alcohol Interaction with SIV Disease Progression

The simian immunodeficiency viruses are considered the closest relatives of the human AIDS viruses because of their genetic, antigenic, and biologic properties [15]. Experimental SIV infection of rhesus macaques results in a disease that is remarkably similar to human HIV/AIDS [16]. Inoculation with SIV results in peak viral load between days 14 and 21, and set point viral load is well established after 30 days. This is followed by an asymptomatic infection period and ultimately culminates in a clinical AIDS stage. Immunologically, SIV infection is characterized by a noteable reduction in CD4+ cells and in the CD4+/CD8+ cell ratio, as well as a substantial increase in the rates of lymphocyte turnover [16]. The final

stages of the disease are characterized by diarrhea, weight loss, lymphopenia, thrombocytopenia, and lymphadenopathy/lymphoid hyperplasia, progressing to immunosuppression [17, 18]. The precipitating events that are criteria for euthanasia include enteric disease, diarrhea, weight loss, neurological deficits, and opportunistic infections. Using this clinically relevant model of HIV-like infection, we have provided evidence that chronic alcohol consumption adversely affects the course and progression of the disease, particularly through its effects on the immune and musculoskeletal systems [19, 20, 21]. Our results add to the existing body of knowledge that collectively indicates that alcohol enhances vulnerability to infection and viral replication, discourages adherence to ART, and decreases effectiveness of ART in control of the infection [22] (Fig. 2).

Alcohol-Mediated Immunomodulation and its Impact on HIV Disease

The well-known immunosuppressive effects associated with alcohol consumption have been proposed to increase host susceptibility to HIV infection, impairing the immune mechanisms responsible for control of viral load [23]. However, immune activation seen with chronic alcohol consumption is equally as likely to contribute to the impact of immune dysregulation on disease progression and tissue injury. Alcohol facilitates HIV infection of isolated peripheral blood mononuclear cells [24], and oral epithelial cells [25]. Acute alcohol ingestion has also been shown to increase HIV replication in isolated peripheral blood mononuclear cells and to impair stimulated lymphocyte responses [26]. In addition to these in vitro studies, controlled in vivo studies conducted in SIV-infected (SIVmac251 and SIVB670) rhesus macaques have demonstrated that chronic alcohol administration results in higher viral load and decreases time to end-stage disease [19, 20, 27], suggesting the possibility of an alcohol-induced impairment in immunological control of viral replication. However, this has not been consistently demonstrated in our model. Macaques chronically fed alcohol have been shown to have higher viremia despite greater virus-specific cellular immune responses, compared to a sucrose-treated group [28]. An alternative potential mechanism for the enhanced viral replication may be the changes in the gut mucosal immune system. We have found a higher percentage of SIV target cells (CXCR4+CD4) in the gut, coupled with lower percentages of effector memory (CD95+CD28−) CD8 lymphocytes in animals The ineffective control of viral replication could have serious implications on the risk for enhanced transmission rate among HIV+ alcohol users. Opportunistic infections, such as pneumonia, can increase viral replication thereby accelerating progression to AIDS. Our studies [30] have shown that direct intrapulmonary infection with S. pneumoniae leads to prolonged viral replication in infected lungs of SIV-infected alcohol-fed animals as compared to that of SIV-infected controls. The most likely site of viral replication is the alveolar macrophage [31]. These findings are similar to the enhanced localized viral replication elicited by bleomycin in SIV-infected macaques [32]. These findings suggest that HIV+ alcoholic subjects have greater activation of viral replication, or alternatively, decreased capacity to control viral reactivation during opportunistic infections. Increased localized HIV replication, particularly in alveolar macrophages and $CD4^+$ cells, has been reported to increase viral mutations and promote viral escape from latent reservoirs [33]. Thus, factors that preclude effective prevention or resolution of opportunistic infections are likely to endanger the HIV+ host by reactivating

the virus or facilitating viral mutations. Acute alcohol abuse has been consistently demonstrated to impair some of the principal factors in the control of infection, including the recruitment of neutrophils to the infection site [34], and to attenuate the granulopoietic response [35]. The implications of alcohol-mediated enhancement of local viral replication are of clinical consequence because higher viral loads may facilitate HIV transmission through increased vaginal shedding [36]. The potential for greater transmissibility of HIV in the alcohol-consuming population therefore warrants further investigation.

Alcohol-mediated alterations in immune function may have additional detrimental effects on vulnerable organ compartments. Gut tissue, liver, and brain have been identified as sites where the impact of alcohol consumption most markedly affects immune cell populations during the acute phase of infection [24]. The resulting tissue inflammation has been proposed to favor a milieu with increased susceptibility to infection, but may also participate in accentuated tissue injury. As demonstrated by studies in rodent models of HIV encephalitis, chronic alcohol feeding results in higher microglial reaction, enhanced oxidative stress, increased viremia, and enhanced neuroinflammation [37]. The synergistic detrimental impact of chronic alcohol exposure and HIV infection has also been demonstrated to result in profound and consistent brain volume deficits, including the cortical mantle, insular and anterior cingulate cortices, thalamus, corpus callosum, and frontal sulci [38]. These alterations in brain inflammatory responses and oxidative stress, as well as the reported morphological changes resulting from chronic alcohol abuse in HIV+ subjects, correlate with clinical manifestations of impaired cognitive function. Chronic alcohol abuse has been reported to exacerbate deficits in motor and visuomotor speed and coordination [39, 40], attention and learning [41], and memory [42] in HIV+ patients. Moreover, depression, the most common psychiatric comorbidity in HIV infection [43], is highly prevalent in HIV+ individuals and alcoholics [44, 45]. Studies from our group have observed similar behavioral deficits in learning and memory formation in SIV-infected chronic alcohol-consuming primates [22]. Whether these findings are a consequence of enhanced neuroinflammation or greater viral load remains to be determined and is the focus of current investigations.

Alcohol and the Musculoskeletal System in HIV

While considerable advances have been made in understanding alcohol-induced injury of the liver, pancreas, heart, and the brain; the metabolic consequences of chronic alcohol abuse have not received the same level of investigation. Chronic alcohol consumption and HIV infection both result in notable changes in metabolic regulation that lead to muscle wasting, loss of bone mineral mass, and lipodystrophy. Muscle wasting, frequently associated with weight loss, is one of the most well-known factors affecting survival from HIV and AIDS. Excess alcohol consumption is consistent with ~50% incidence of skeletal muscle myopathy [46] due to decreased muscle protein synthesis [47, 48, 49] and accelerated muscle proteolysis. Previous studies from our laboratory have shown that chronic binge alcohol consumption causes a greater decrease in lean body mass and an increased incidence of SIV-associated AIDS (SAIDS) wasting. Moreover, we have demonstrated a strong association between the development of SAIDS wasting and decreased time to end-stage disease (from ~900 days in sucrose-fed SIV-infected to 390 days in chronic alcohol-fed SIV-infected

macaques) [20]. Similar accentuation of muscle atrophy has been reported in chronic alcohol-fed HIV-1 transgenic rats [50, 51].

Studies suggest that during the initial stage of HIV infection, there is a reduction in lean body mass and preservation of total body fat prior to a decrease in total body weight [52, 53]. Studies in chronic alcohol-fed SIV-infected macaques indicate that rates of skeletal muscle protein synthesis in the fasted and non-intoxicated state are not altered during the asymptomatic or terminal phases of SIV infection [21]. In contrast, reports in the literature indicate that rates of protein synthesis are suppressed following acute and chronic alcohol administration. Moreover, alcohol blunts the muscle anabolic response to the amino acid leucine resulting in “leucine resistance” in the presence of alcohol in the system [54]. The presence of alcohol in the blood at the time of measurement of protein synthesis in our SIV-infected macaques could also unmask alterations in stimulated rates of muscle protein synthesis and contribute to the overall loss in lean body mass has yet to be explored.

The imbalance between increased muscle proteolysis [55] and decreased protein synthesis [56] can be exacerbated by opportunistic infections [57] and attenuated by a reduction of viral load [58]. Thus, decreased lean mass may result from enhanced catabolic processes characteristic of other disease and injury states [59, 60, 61, 62, 63] associated with increased expression of ubiquitin-proteasome pathway elements [64]. This pathway regulates intracellular protein degradation together with lysosomal and non-lysosomal pathways [65] and is modulated by glucocorticoids, catecholamines, and proinflammatory cytokines [66, 67, 68]. Similar increased expression of the genes encoding for the ubiquitin-ATP-dependent proteolytic system has been detected in skeletal muscle of cachectic AIDS patients [69], suggesting that the ubiquitin-proteasome pathway contributes to AIDS-related muscle wasting. We have shown that both alcohol and SIV infection raise levels of ubiquitin-proteasome components as well as proteasomal activity in skeletal muscle mRNA [70]. Moreover, we have found elevated atrogene expression in skeletal muscle of chronic alcohol-fed SIV-infected macaques [71]. Atrogin-1, also known as MAFbx (muscle atrophy F-box protein), has been suggested as a contributing cause of muscle wasting [72, 73].

The increased ubiquitin proteasome pathway activity in skeletal muscle of chronic alcohol-fed SIV-infected (SIVmac251 and SIVB670) animals is associated with marked upregulation of tissue inflammation and oxidative stress and decreased IGF-I expression [70]. Similar derangements in growth factors and proinflammatory cytokine expression have been associated with wasting in AIDS patients [74, 75], as well as in other animal models of chronic alcohol feeding and HIV infection [51, 76, 77]. Proinflammatory cytokines including IL-6 and TNF-α have been determined to exert anti-insulin effects in both skeletal muscle and adipose tissue [78, 79]. Furthermore, it has been shown that myostatin, a negative modulator of skeletal muscle growth [80], is involved in suppression of skeletal muscle growth and in muscle wasting in HIV-infected men [81]. Taken together, our studies and those of others indicate that chronic alcohol consumption promotes an inflammatory and pro-oxidative tissue milieu that precedes upregulation of multiple components of the ubiquitin-proteolytic pathway. In addition to a loss in muscle fiber proteins resulting from activation of the ubiquitin-proteasome system, the autophagy-lysosome pathway may contribute to muscle wasting in chronic disease conditions [82]. Whether this mechanism

contributes to alcoholic myopathy or AIDS wasting remains to be determined, but warrants investigation.

An important factor promoting muscle wasting, particularly in chronic alcohol and SIV/HIV infection, is suppressed anabolic (insulin/IGF-I) signaling that can simultaneously favor proteolysis and inhibit anabolism. We have shown that IGF-I and mTOR mRNA expression and PI3-K activity are significantly decreased, while PTP1B expression is significantly increased in skeletal muscle of chronic alcohol-fed SIV-infected animals at end stage [70, 71]. In addition, we have also shown that skeletal muscle of chronic alcohol-fed SIV-infected animals showed significantly increased atrogin-1 mRNA expression [70]. Thus, our findings coincide with previous clinical and pre-clinical reports indicating that inflammation impacts the responsiveness of muscle tissue to an anabolic stimulus and is associated with marked alterations of protein metabolism [54, 83, 84, 85]. It appears likely that the accentuated loss of muscle mass at SAIDS in chronic alcohol-fed animals is caused by a proinflammatory, pro-oxidative, and anabolic imbalance favoring overall catabolic processes leading to loss of muscle mass associated with impaired muscle growth.

Several reports strongly suggest that chronic alcohol intake disrupts multiple neuroendocrine signaling pathways responsible for control of metabolism [13, 21, 154]. Thus, it is possible that in addition to altering caloric and nutrient intake, alcohol disrupts the neuroendocrine response to feeding, thus further compounding the problem by interfering with the feeding-induced anabolic response. The loss in lean body mass is known to be a comorbidity factor for chronic diseases including cancer and AIDS. Interventions to reduce alcohol consumption or modify nutritional intake should lead to preservation of lean mass. Published studies suggest that even reduction of alcohol drinking without achieving complete abstinence is sufficient to improve muscle strength and decrease myopathy [86].

Alcohol and SIV/HIV Promote Bone Loss

Chronic alcohol consumption is correlated with changes in bone metabolism, decreased bone mineral density, and greater risk of fractures [86, 87, 88] even in the absence of liver failure [89]. Overall, it has been estimated that osteoporosis is prevalent in over 40% of alcoholics [90]. The detrimental effect of chronic alcohol consumption on bone mineral density and bone mineral mass [91, 92] is multifactorial [93]. Impaired bone formation has been proposed as a principal mechanism for increased fracture rates in chronic alcoholics [94, 95], and this has been reported to be restored following relatively short periods of abstinence [96]. Whether the relationship of alcohol consumption with fracture risk, bone mineral density, or osteoporosis is dose-dependent remains unclear and merits further study [97].

High prevalence of osteopenia and osteoporosis is a result of marked alterations in bone metabolism, which is also consistent with HIV infection. [98]. Risk factors for the development of osteopenia include the use of protease inhibitors, duration of HIV infection, high viral load, high lactate levels, low bicarbonate levels, elevated alkaline phosphatase levels, and lower body weight prior to initiation of antiretroviral therapy [99]. Individuals

treated with ART and protease inhibitors have a higher prevalence of reduced bone mineral density and osteoporosis compared to untreated HIV-infected patients [100, 101].

The anabolic hormones, particularly testosterone, are among the most important elements regulating bone, adipose, and skeletal muscle mass. Androgens maintain a critical role in the control of bone remodeling by suppressing osteoclastogenesis and promoting osteoblastogenesis, which results in protection of bone mass and mineral density [102]. In addition, androgen-mediated anabolic effects on bone are also attributed to the inhibitory action on proinflammatory cytokines and the promotion of osteoprotegerin synthesis, reducing the activation and maturation of osteoclasts [103,104]. The contribution of proinflammatory cytokines to bone loss and myopathy has been suggested by several studies [84,105, 106, 107]. Bone resorption is associated with an increased expression of proinflammatory cytokines, particularly in androgen-or IGF-I-deficient states [108, 109, 110]. Studies have reported that HIV infection is associated with decreased circulating levels of testosterone and in addition, some have reported a beneficial effect of treatment with the hormone. Whether alcohol further accentuates deficits in anabolic steroid production and function is not clear. However, studies show that chronic alcohol consumption leads to suppression of the hypothalamic-pituitary-gonadal axis resulting in decreased circulating levels of testosterone [111, 112, 113], suggesting a possible endocrine mechanism for alcohol's effects on bone metabolism.

Alcohol and HIV Dysregulate Adipose Tissue

ART is associated with metabolic dysregulation characterized by dyslipidemia, insulin resistance, and lipodystrophy/lipoatrophy [114], as well as altered adipokine profiles. Adipose tissue and circulating levels of adiponectin are lower in HIV-infected ART patients [115]. Although the pattern of leptin alterations is less clear, recently identified peptides such as visfatin and retinol-binding protein 4 (RBP-4) are altered in HIV-infected individuals. Visfatin expression in adipose tissue correlates with insulin resistance [116]; elevated levels of RBP-4 in obese and diabetic patients correlate with indices of metabolic syndrome, including increased body mass index (BMI), triglycerides, and systolic blood pressure [117]. In addition to changes in circulating markers of metabolic dysregulation, adipose tissue obtained from HIV-infected individuals displays greater proinflammatory cytokine expression, apoptosis, fibrosis, vessel density, and macrophage infiltration, as well as lower adiponectin and leptin mRNA levels than that of control subjects [118]. The elevated expression of proinflammatory cytokines and adipokines, as well as lipodystrophic fat distribution, has been linked to metabolic alterations in HIV+ ART-treated patients [119, 120]. There has been no systematic investigation of the impact of chronic alcohol abuse on adipose tissue mass and phenotype has not been investigated in a systematic way. An association between chronic alcohol consumption and decreased fat mass has been determined [121], and this is considered to be a result of altered neuroendocrine function, resulting in increased cortisol release [122]. In contrast, other studies have determined a tendency of dyslipidemia and increased fat mass in alcoholics, with over 20% of patients fulfilling criteria for metabolic syndrome [123]. However, some new literature suggests that beyond altering fat mass, alcohol may disrupt adipokine profiles such as that of leptin [124] and adiponectin [125] and promote macrophage infiltration into adipose tissue. These

changes in adipose tissue phenotype are thought to be the result of oxidative stress resulting from alcohol metabolism [126] and are associated with hepatic and adipose tissue insulin resistance [127]. It is a likely possibility that excessive chronic alcohol consumption exacerbates the alterations in adipose tissue mass, distribution, and phenotype associated with HIV infection and ART, and this is an area of current investigation.

Potential Mechanisms for Alcohol-Mediated Effects on Body Composition

Results from others as well as those from our studies point to mechanisms involved in erosion of lean body mass and dysregulation of adipose mass phenotype in HIV patients (Fig. 3). Body mass constituted by both lean (muscle and bone) and fat is determined by the net balance between protein synthesis and breakdown in muscle, between mineralization and resorption in bone, and between lipogenesis and lipolysis in adipose tissue. The anabolic and catabolic arms of this balance are regulated by nutritional, endocrine, inflammatory, and oxidative mechanisms. Chronic alcohol consumption disrupts several of the above factors, leading to imbalance between anabolic and catabolic mechanisms [128–132]. Oxidative stress caused by either an excess production of reactive oxygen species or a reduction in antioxidant equivalents in tissue has been consistently shown to be an important mechanism of tissue injury caused by chronic alcohol abuse [133, 134]. Several mechanisms have been identified as contributors to alcohol-induced oxidative stress, including alcohol metabolism, mitochondrial toxicity, tissue inflammation, and glutathione depletion. Although the impact of oxidative stress on hepatic injury has been well established [135], conclusive evidence for its role in alcohol-induced metabolic derangements of muscle is lacking [136]. However, studies aimed at elucidating the mechanisms underlying catabolic and metabolic dysregulation processes in muscle [137, 138], bone [139, 140], and adipose tissue [141] suggest that oxidative stress may be a common mechanism through which alcohol can lead to metabolic dysregulation [142]. Similarly, chronic alcohol administration has been shown to result in enhanced proinflammatory cytokine expression, contributing to injury in several tissues [143, 144, 145, 146]. Upregulation of inflammatory cytokines has been found to aid in catabolic responses in skeletal muscle [147, 148] and bone [149, 150] and to dysregulate adipose tissue metabolism [151]. In addition, chronic alcohol administration is also associated with altered neuroendocrine regulation, in particular with decreased circulating levels of androgens [152, 153] and with impairments in the GH/IGF-I system [154, 155], both of which are critical factors mediating the anabolic and anticatabolic control of bone and muscle mass. HIV/AIDS is associated with dysregulation of these same neuroendocrine, oxidative, and inflammatory factors including the GH/IGF-I system [156, 157], androgens [158], proinflammatory cytokines [159, 160, 161, 162], and oxidative stress [163, 164].

Alcohol Use Disorders Interfere with HIV Disease Management on Multiple Levels

The detrimental role of alcohol abuse in the HIV/AIDS epidemic is further substantiated by its correlation to lack of adherence to ART and decreased effectiveness of ART in control of the infection [165]. In addition to the impact of alcohol consumption on the natural progression of HIV infection [166], alcohol consumption may affect access, adherence, and responsiveness to ART [167, 168]. AUD interferes with disease management in HIV+

patients. AUD is a significant predictor of non-adherence to ART [169, 170, 171, 172]. PLWHA and AUD are consistently found to perform poorly at multiple levels of the HIV treatment cascade, resulting in a higher likelihood of virologic non-suppression [173, 174, 175]. Despite reduced morbidity and mortality from HIV with ART [176], many alcohol-using individuals fail to achieve the minimum 95% adherence and thus do not achieve complete viral suppression and the prevention of the development of a resistant virus [177, 178, 179, 180]. Moreover, alcohol abuse appears to accelerate disease progression, even if medications are taken correctly, by adversely impacting drug absorption and metabolism [167]. Some evidence suggests that lower CD4 counts and higher HIV RNA levels in HIV+ patients undergoing ART and intaking moderate to at-risk levels of alcohol, results in greater disease progression compared to abstainers [166]. Additional factors involved in alcohol's exacerbation of the HIV epidemic are based on the positive correlations between alcohol use and high-risk sexual behaviors in individuals living with HIV/AIDS [181, 182, 183]. Excessive alcohol consumption increases the risk of HIV transmission and sexually-transmitted diseases, "super-/co-infections" (i.e. infection with a new and/or drug-resistant strain of the virus), and also increases resistance to drug treatments [184]. Successful HIV disease management can fail at any of the various aspects of the HIV treatment cascade, including failure to link, engage, and retain patients in care; medication non-adherence; and resistance to antiretroviral medications [185]. Thus, additional comorbid conditions that can potentially impact the risk of infection, transmission, viral control, and disease progression are prevalent in HIV-infected individuals with AUD.

Summary

Alcohol abuse in the HIV-infected population contributes to the burden of the disease, having implications that surpass the original issue of increased risky sexual behavior. The consequences of alcohol abuse alone before or during the course of HIV infection compound the damage inflicted by the virus or the resulting tissue inflammation. Moreover, it has now become increasingly evident that alcohol use disorders diminish adherence to therapy, may potentially aggravate unwanted drug-related side effects, and prevent effectiveness in viral control, further complicating the management of the disease. Additional studies are needed to understand the cellular mechanisms of alcohol-induced pathological effects and their interaction with those produced by the virus, its proteins, or the resulting inflammatory milieu associated with HIV infection. These will lead to improved understanding of potential targets for therapeutic or nutritional interventions aimed at reducing the burden of disease in this population.

The interaction of alcohol with the process of infectivity, viral replication, progression of disease, and mortality is of sufficient magnitude to warrant interventions to decrease or prevent alcohol abuse in HIV-infected individuals. Several measures have been found to be effective at minimizing HIV transmission associated with alcohol use, including early HIV testing and referral to treatment and behavioral interventions aimed at both HIV-infected and HIV-uninfected people with HIV risk behaviors. Moreover, in the alcohol-consuming population, behavioral and pharmacological treatment aimed at reduction of alcohol consumption enhances the effectiveness of HIV treatment [12]. In addition, indirect evidence strongly suggests that several of the comorbid biomedical consequences associated

with alcohol use disorders significantly improve with reduction in alcohol intake. Thus, critical mechanisms that may impact disease progression, including tissue inflammation, loss of muscle and bone mass, and lipodystrophy provide important targets for behavioral or pharmacological interventions. Interventions specifically tailored to decrease alcohol use disorders in the HIV+ population are urgently needed to improve overall outcomes and reduce comorbid conditions in this vulnerable patient population. Clearly a systematic, integrated approach including clinicians, researchers, and public health officials is needed to deal with this ongoing epidemic.

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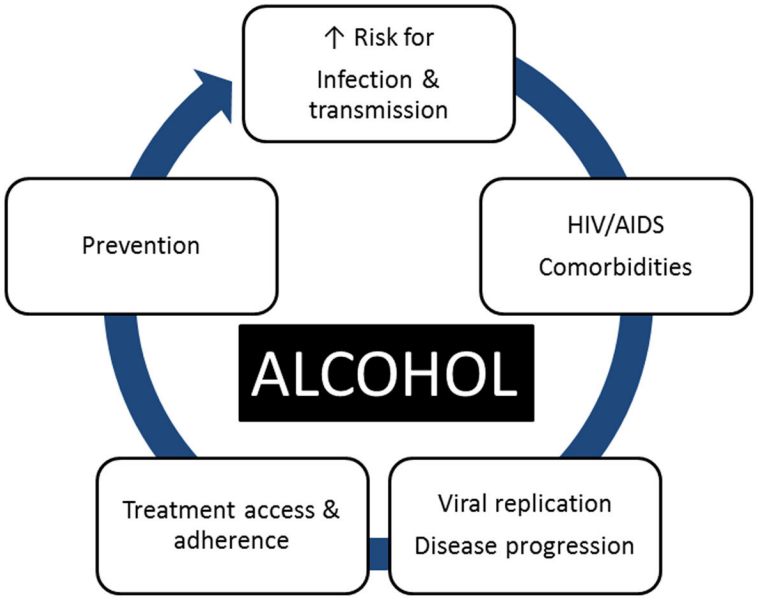

Figure 1.

Alcohol has had significant impact on the HIV epidemic. Risky sexual behavior resulting from impaired cognitive and executive function resulting from alcohol abuse increases risk of infection and impacts on disease transmission. However, alcohol produces multisystemic effects that have been demonstrated to impact biological and biochemical aspects of the HIV disease processes, increasing the risk for comorbid conditions and impacting the disease progression. More recently, the potential interferences with treatment and prevention of infection have been reported, particularly as it pertains to access and availability of antiretroviral therapy and its effectiveness in viral control in this patient population. Issues such as access and adherence to therapy as well as their combined toxicity are the focus of health care provider concern.

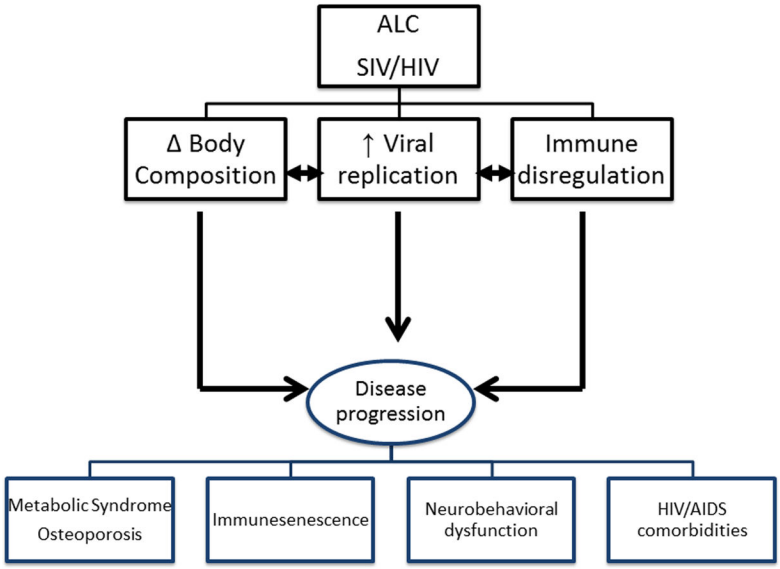

Figure 2.

Key Domains of alcohol abuse interaction with SIV/HIV disease progression. Three salient processes appear to be significantly impacted by chronic alcohol abuse in the SIV-infected macaque: control of body composition, viral replication, and immune responses to infectious challenges. These salient domains are critical in determining disease progression, which in turn is associated with significant loss of functional musculoskeletal mass, immune senescence, neurobehavioral dysfunction and cognitive deficits, and comorbid conditions; all of which are associated with poor outcomes.

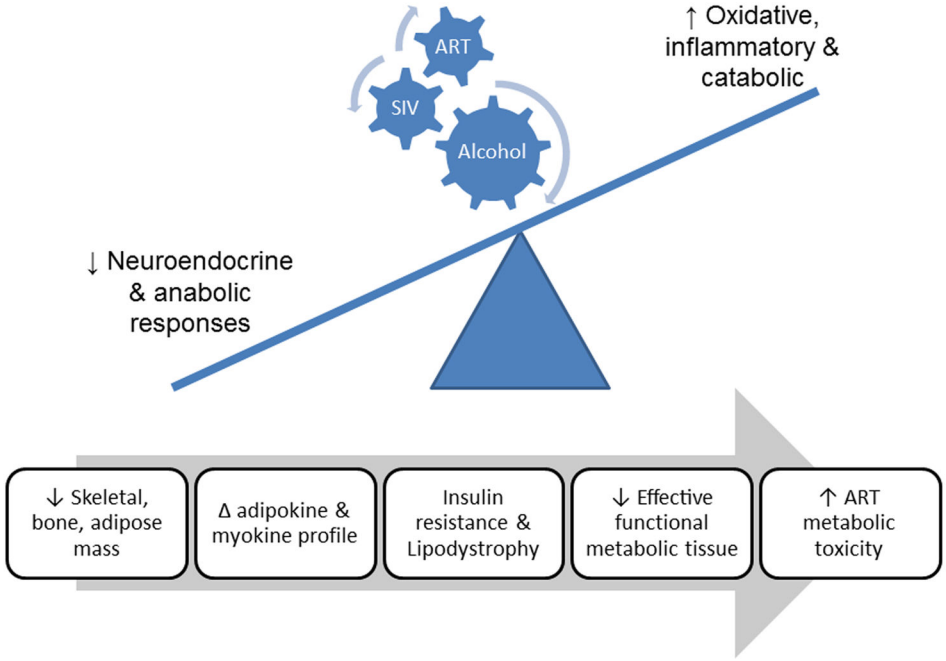

Figure 3.

Chronic alcohol consumption exerts multisystemic effects on SIV-infected macaques that involve neuroendocrine, oxidative, and proinflammatory mechanisms. Chronic alcohol administration decreases musculoskeletal and adipose mass and favors tissue proinflammatory and pro-oxidative milieus that disrupt the balance between the synthetic and catabolic mechanisms leading to erosion of muscle, bone, and adipose tissue mass. The figure reflects the predicted alterations in neuroendocrine and anabolic processes that in the presence of a pro-oxidative, inflammatory, and catabolic milieu lead to decreased functional metabolic mass and possible augmentation of ART-induced metabolic burden and toxicity.