

Alcohol use and HIV infection in the HAART era

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Although of different etiology, both alcohol abuse and infection with the Human Immunodeficiency Virus (HIV/AIDS) are major public health problems in the United States. As of June 2000, 431924 persons have been reported to be living with HIV/AIDS and 50,000 new additional cases of HIV infection are estimated to occur per year. According to the findings of the National Longitudinal Epidemiology Survey 1 in 2 Americans (44.37%) are active drinkers of alcoholic beverages, with an estimated 14 million Americans suffering from alcohol abuse and dependence. Therefore, it is not surprising, that a significant number of HIV infected individuals may also suffer from alcohol abuse. For instance, more than 60% of the HIV infected participants in the MIDAS (Miami HIV Infected Drug Abuser Study) Cohort, report heavy alcohol use (3-7/week). We found prevalence of alcoholism in HIV infected subjects to be higher among men than women (OR=3.95% CI 1.13-5.9, p=0.013). As the two endemics, alcoholism and HIV infection, converge it is of critical importance to evaluate possible interactions between these two epidemics.

The physiological characteristics of ethanol (EtOH) allow it to interfere intensively with functions of the immune and endocrine systems. Alcohol is completely miscible with water and is fat-soluble. It crosses cell membranes by diffusion and generates excessive amounts of metabolites including NADH, acetaldehyde, and acetate. Elevated levels of NADH lead to hyperlactacidaemia, hypoalbuminaemia and fat infiltration in the liver. The activity of the microsomal-ethanol-oxidizing system causes drug metabolism changes in the liver, and an increased rate of hepatotoxic substances. Whereas acetaldehyde increases lipid peroxidation and immune dysfunction, acetate decreases lipolytic processes in cells¹. In addition, it has been shown that acute administration of alcohol induces dose-related increases in plasma ACTH²⁻³. This response depends on the delivery of the hypothalamic peptides, corticotropin-releasing factor, and vasopressin to the pituitary. On the other hand, exposure to an alcohol diet for 7 to 10 days significantly blunts the hypothalamic-pituitary-adrenal axis in response to immune signals in animal studies³.

The overlap of alcohol abuse and HIV infection in the same individual is especially relevant, since previous findings have demonstrated that chronic and even acute, moderate alcohol use can produce immune impairments and increase host susceptibility to infections caused by both bacterial and viral pathogens⁴. Impaired host defense after alcohol exposure appears to be linked to a combination of decreased inflammatory response, altered cytokine production, and abnormal reactive oxygen intermediate generation. At the most basic cellular level, acute exposure of alcohol reduces both neutrophil migration and antigen recognition. In non-HIV infected subjects chronic exposure to alcohol, induces impairment of the cognitive phase when antigen-presenting cells engage T lymphocytes⁵⁻⁶. Studies in animal models of HIV infection, and reports in human volunteers confirm these changes in cellular function⁶. In addition, alcohol also induces abnormalities of cellular proliferation. Cells exposed to alcohol derived

from HIV infected individuals show, not only a suppressed cellular proliferative response, but also reduced natural killer cell activity and T-cell-dependent immune responses⁷.

Of particular importance for HIV infected individuals, it has been suggested that ingestion of ETOH-containing diets results in a loss of lymphoid cells from the peripheral blood, spleen, and thymus⁴. Some of the cell loss from the thymus is the result of corticosteroid release, but the loss from the spleen and some of the thymocyte loss is independent of corticosteroids, as demonstrated by studies using ADX mice and rats⁴. If the main goal of HIV physicians is to maintain or recuperate the CD4 population, it needs to be understood that alcohol use may affect the thymus-induced immune repletion of HIV infected patients. In support of this proposal, our recent findings have demonstrated that heavy alcohol users on antiretroviral treatment were 2 times less likely to achieve more than 500 CD4 cells than those on antiretrovirals, who were light or non-alcohol users⁸.

The impact of alcohol use on the immune system is not limited to cellular effects. Current research indicates that alcohol use produces an altered cytokine balance⁶⁻⁹⁻¹⁰ leading to new insights on the regulation of the immune system in chronic alcoholism. Animal models have demonstrated that infection with a retrovirus in combination with an EtOH diet significantly decreased interleukin 2 levels. This is of concern, due to the critical role of IL2 in T lymphocyte proliferation. Interleukin 2 has been successfully used in HIV infected patients receiving HAART to further immune recuperation and achieve higher CD4 cell counts. In addition, a preferential induction of Th2 vs. Th1 immune response has been suggested in chronic alcoholics. Animal studies with murine AIDS have confirmed these findings demonstrating an exacerbated elevation of IL6 and TNF with alcohol beverages in amounts that occur during social drinking⁹⁻¹⁰. These results may, at least partially, explain the increased immunodysfunction in HIV infected drinkers. Since both proinflammatory and TH2 interleukins enhance HIV replication, the potential effects of EtOH in replication and disease progression need to be considered.

High levels of HIV transcription are regulated by NF-kappa B, and TAR which is functionally dependent on Tat activation. Cell activities, oxidative stress and certain interleukins have been demonstrated to enhance HIV replication through these pathways¹¹. Alcohol induces proinflammatory and TH2 cytokines, as well as, production of free radicals. The research question is can alcohol influence HIV replication? Conflicting results have been obtained. Bagasra and collaborators¹⁰ reported that alcohol ingestion in HIV seronegative volunteers significantly increased *in-vitro* HIV replication in the isolated and infected peripheral blood and mononuclear cells. The author suggests that increased infectivity and replication of HIV by alcohol use may provide an explanation for the high incidence of HIV infection in alcohol treatment programs. Of interest, our previous studies in Colombia with parenteral use of alcohol suggest an increased risk of HIV infection in these injectors¹². Subsequent investigations have extended these findings and demonstrated that increased HIV replication under the effects of ETOH was associated with increased inhibition of CD8 function¹³. Several studies have demonstrated a critical role of CD8 T lymphocytes in halting HIV viral replication and maintaining HIV specific memory¹⁴⁻¹⁵. Cook and collaborators¹⁶, however, showed individual

variation in response in healthy volunteers, with only a subset of individuals exhibiting an increase of HIV replication with alcohol ingestion.

Antiretrovirals and alcohol

Although HIV is the most complex of the known lentiviruses, several studies have revealed “Achilles heel points” in its life cycle, during which it employs enzymes that may be blocked with the use of chemical compounds. A number of drugs have targeted these vulnerable points to slow disease progression. While earlier research targeted HIV reverse transcriptase inhibitors, recent products involve HIV protease and/or regulatory genes. Combination therapy appears to effectively control HIV viral replication. Adherence to medication, however, is critical in HIV infected patients not only to significantly reduce viral burden but also to prevent the appearance of resistant strains. Low literacy, drug abuse and alcohol use may affect adherence to antiretroviral regimens.

The use of combination therapy poses another potential problem, as many of these drugs can induce or inhibit the same metabolizing enzymes resulting in pharmacokinetic drug interactions. One of the most frequently used metabolic pathways is the P450 enzyme in the liver. Alcohol metabolism also involves this pathway. Both non-nucleoside reverse transcriptases and the HIV protease inhibitors use this pathway. Therefore, one of the possible factors contributing to antiretroviral treatment failure may be alcohol use. Alcohol interference in antiretroviral response has been observed in our most recent study and will be further explored by our group.

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