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A REVIEW OF THE EFFECTS OF ALCOHOL AND ITS INTERACTION WITH HIV ON THE IMMUNE SYSTEM

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ABSTRACT

Objective: **Alcohol and HIV seem to augment each other in their negative effect on various aspects of the body. In fact, people with alcohol abuse disorders are more likely than the general population to contract HIV while on the other hand, people with HIV are more likely to abuse alcohol at some time during their lives. Among other effects, alcohol induces immune dysregulation which exacerbates HIV pathogenesis, eventually leading to HIV disease progression and death. This review is a comprehensive analysis of the findings of various studies that have over the years looked at how alcohol induces immune dysregulation in HIV infection. It brings about the need for better addressing the issue of alcohol consumption among those either at risk of infection or those living with the infection, thus helping in the fight against HIV infection.**

Data sources: **The data used in this review was sourced from peer reviewed papers from various studies conducted by various HIV researchers.**

Study Selection: **The studies used in this review were selected from the various HIV studies where HIV's interactions with alcohol especially looking at their effect on the immune system were studied.**

Data synthesis: **The data used in this review was analyzed looking at the various case studies and the significant findings from each study.**

Conclusion: **Alcohol consumption has a definite effect on HIV infection: transmission, progression of disease or treatment. Thus, addressing alcohol use in HIV-infected patients may have a substantial impact on HIV disease progression.**

INTRODUCTION

Both alcohol and HIV negatively affect the body's immune system as demonstrated in various studies. It has been shown that people with alcohol abuse disorders are more likely than the general population to contract HIV while those infected with HIV are more likely to abuse alcohol (1). Alcohol increases the risk of and susceptibility to infection by comorbidities like pneumonia in HIV infected individuals (2). Similarly, chronic alcohol use by HIV-infected patients has been associated with immunosuppression. As a result, alcoholics are prone to bacterial and viral infections; increased severity of diseases (e.g. viral hepatitis), show higher incidence of cardiovascular ailments such as cardiomyopathy and high blood pressure, oesophageal and pharyngeal cancers all which accelerate progression of HIV disease and death. Despite antiretroviral therapy, alcohol is associated with significantly increased mortality in people living with HIV compared with uninfected individuals (3). On the immune front, alcohol consumption affects both innate and adaptive immunity affecting the structural, cellular, and humoral components of the immune system which exacerbates HIV pathogenesis through alterations in mucosal immunity, increased viral replication, chronic immune activation and inflammation. This review looks at how alcohol affects HIV infected people in various aspects: nutrition, transmission, disease progression, microbial translocation, neurological effects and effects on various immune cells. Studies on Simian immunodeficiency virus (SIV) are also quoted since this infection mirrors HIV infection.

Nutritional deficiency

Nutritional deficiency is seen in alcohol abusers and this might increase a person's susceptibility to infection by HIV/SIV and accelerate disease progression to AIDS. The link between alcohol use, decreased nutrition, and immune markers has also been demonstrated experimentally in the SIV model. The nutritional deficiencies are due to a high percentage of caloric intake from alcohol (affected persons don't eat well), decreased absorption of nutrients due to alcohol's damage to the gut, and interference with the metabolism of nutrients (4).

Effect of Alcohol on HIV Transmission and disease progression

Alcohol increases susceptibility to other infections as complications of AIDS (e.g. tuberculosis, bacterial pneumonia, hepatitis C) which increase viral replication leading to further disease progression. Alcohol increases viral replication in HIV-infected patients, thus increasing the virus concentration in the semen and in the vagina which increases the chances of HIV transmission (5). Women who consumed alcohol were less likely to have lactobacillus species present in their vaginal flora, leading to a flora consistent with that of bacterial vaginosis which has been associated with increased risk of HIV acquisition (6).

Studies have also shown that increased alcohol decreases medication compliance, leading to poorer response to HIV therapy, delays in seeking treatment and higher HIV transmission rates (7). Thus, prevention programs targeting reduction in alcohol consumption can be considered primary HIV prevention strategies.

HIV patients treated with ART who are frequent alcohol users are more likely to show a decline in $CD4^+$ cell counts and higher HIV RNA levels just like HIV patients not on ART (8; 9). These higher viral loads, in turn, make patients more infectious during unprotected sex with uninfected partners, which become more likely when patients drink alcohol (10).

Exposure to alcohol shows increased levels of monocytes expressing the viral co

receptor CCR5 cells thus increasing susceptibility to SIV infection in primates (11) while in human beings it increases the risk of infection with HIV (12) resulting in more rapid progression of disease to AIDS or death. Viral set point (plasma viral load after infection) is predictive of disease progression in HIV infection. In alcohol-consuming macaques, viral set points are significantly higher than in control animals indicating that alcohol consumption is associated with accelerated disease progression (13). Figure 1 below shows the general effects of alcohol on HIV.

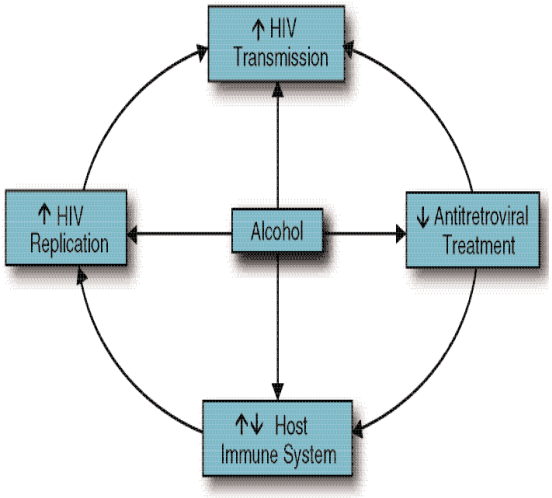

Figure 1: *The general effects of alcohol on HIV*

Neurological effects of alcohol HIV infected persons:

Alcohol can act directly on the brain to reduce inhibitions and diminish risk perception. Neurological effects are seen in HIV patients who abuse alcohol as they are more likely to engage in risky behaviours (e.g. injection drug use and high-risk sex) that place them at risk of contracting HIV (14). Alcohol also destroys brain cells thus enabling HIV to cross the blood-brain barrier into the brain resulting in the development of neurotoxins that damage the neurons in the brain hence the neurological symptoms, dementia or death. By disrupting the blood–brain barrier, alcohol also increases infiltration of HIV-1-infected monocytes/macrophages into the brain, where they can serve as a viral reservoir that spreads viral infection to resident cells (i.e. perivascular macrophages, microglia, and astrocytes) and thus exacerbate neuroinflammation and neuropsychological impairment (15).

Microbial Translocation:

Both HIV and SIV infections by themselves cause intestinal permeability which results in translocation of microbes and microbial products (e.g. LPS) into the circulatory system causing chronic activation of the immune system and this activation leads to the generation of more target cells (CD4+) for the virus (16). These microbial products then activate immune cells to secrete cytokines such as TNFα, IL-1, IL-6, and chemokines which result in increased mucosal and systemic immune activation leading to chronic inflammation, thus rendering patients more vulnerable to HIV transmission and increased HIV disease progression (17). Eventually, the body's capacity to replenish the CD4+ T-cells is exhausted resulting in disease progression to AIDS. On its own, alcohol consumption also disrupts the intestinal lining, disrupts intestinal barrier function, and leads to microbial translocation (18); as well as reduce Th17 cells which enhance maintenance mucosal barriers as well as help recruiting neutrophils and macrophages to infected tissues thus contributing to pathogen clearance at mucosal surfaces (19).This effect might exacerbate the gut leak associated with HIV/SIV infection in case the HIV infected persons also use alcohol, thereby further accelerating disease progression. In fact, heavy or moderate alcohol has been associated with elevations in macrophage activation (sCD163) and monocyte activation (sCD14) in HIV infected individuals (20).

There are various mechanisms by which alcohol or its breakdown products lead to

microbial translocation. One is direct damage to epithelial cells through generation of reactive oxygen species (ROS) and disruption of the expression of tight junction proteins such as zona occludens (ZO)-1 and occluding. Alcohol dramatically increases the expression of microRNA (miR) 212 (a small, regulatory molecule in the colon tissue) which binds to the messenger RNA from which the ZO-1 protein is produced; thus preventing ZO-1 production, leading to increased permeability of the intestinal epithelium (21) thus allowing bacteria and toxins to reach the bloodstream. The second mechanism is by promoting both dysbiosis (decreased diversity or an imbalance in the types of microbes) and bacterial overgrowth in the gut that decreases the presence of beneficial bacteria (e.g. *Lactobacillus* and *Bifidobacterium)*, and increasing pathogenic bacteria such as Proteobacteria and Bacilli (22). This together with increased gut permeability leads to continuous entry of bacterial toxins into the systemic circulation resulting in chronic and sustained activation of immune responses that, in turn, could lead to immune exhaustion and dysfunction. The third mechanism is by alcohol increasing turnover of viral target cells (memory $CD4^+$ T cells) in intestinal tissues which results in significantly higher plasma viral copies in alcohol consumers compared with controls as shown in SIV infection (23).

Alcohol has been linked with accelerated cellular aging as reflected by shorter telomere length in people who have heavy alcohol consumption (24). Alcohol significantly increases peripheral blood CD8+ T cell activation and immune senescence as compared to baseline levels in non-ART-treated, SIV-infected macaques (25). Telomeres are DNA–protein protective structures at the ends of each chromosome which undergo continuous loss with each cell division, decreasing in length as cells approach senescence. Thus, alcohol hastens cellular aging in the general population and this appears to be exacerbated in people living with HIV.

Effects on Cytokines and Chemokines:

Chronic alcohol consumption causes perturbations in the expression of cytokines which contributes to HIV disease progression. Alcohol interferes with the actions of granulocyte/macrophage colony–stimulating factor (GM–CSF) which exposes the body to lung infections since GM-CSF normally induces macrophage maturation and promotes epithelial barrier maintenance important for protecting the body against lung infections (26). Acute alcohol intoxication suppresses the production of certain chemokines (e.g. MIP-2) during infection and inflammation, thereby markedly impairing the recruitment of neutrophils to the site of infection which contributes to increased susceptibility to infection (27). Acute alcohol exposure also suppresses the production of proinflammatory cytokines such as TNF-α, IL-1 and IL-6 in immune cells like macrophages and monocytes; and increases expression of anti-inflammatory cytokines which impairs host defence against HIV infection (28). Simian studies show that chronic alcohol intake results in increased expression of TNF-α and atrogin-1 which leads to a higher viral set point and thus more rapid progression to end-stage disease (13).

Effect of alcohol on Cell-Mediated Host Defence Mechanisms:

Alcohol impairs innate immune responses (polymorphonuclear and mononuclear cells) while also causing impaired acquired immune responses such as impaired B lymphocyte function, altered cytokine balance, and chronic T-cell activation.

Alcohol suppresses tissue recruitment of polymorphonuclear (PMN) cells during infection leading to increased susceptibility to bacterial infections. It also interferes with overall bactericidal activity of the PMN by interfering with various molecules (e.g.,

superoxide or elastase) and those processes necessary to deliver neutrophils to the site of an infection; and significantly inhibits PMN phagocytic activity whether the cells are from uninfected as well as SIV-infected rhesus macaques (29). Alcohol abuse also profoundly affects the production of new granulocytes (i.e., granulopoiesis), particularly in response to infection and often leading to granulocytopenia, which is associated with increased mortality (30).

In HIV-1 infected individuals, alcohol inhibits both IFN-gamma-induced proteasomes and immunoproteasomes in macrophages thus impairing protein processing required for antigen presentation by macrophages thereby affecting disease progression (31). Chronic alcohol ingestion significantly up-regulates CCR5 receptor expression and inhibits endogenous production of beta-chemokines by macrophages which could thus enhance HIV R5 strain infection of macrophages (2). Chronic alcohol ingestion also decreases the number of dendritic cells, interferes with their differentiation, and impairs their functions, such as their ability to stimulate other cells, ability to absorb and ingest particles from outside the cell, and ability to express co-stimulatory receptors (32). This dysfunction prevents the organism from generating antigen presentation and thus virus-specific adaptive immune responses involving CD4+ and CD8+ lymphocytes.

NK cells which are involved in the elimination of tumour cells and pathogen infected cells are quantitatively and qualitatively altered by alcohol abuse. Qualitatively, alcohol inhibits the expression of several NK cell proteins (e.g. IFN- γ, perforin and granzymes A and B), which leads decreases NK cells' cytotoxicity ability to destroy their target cells resulting in alcohol-associated tumour development and viral infection (33).

On T cell responses, alcohol suppresses Th1 immune responses such as IFN-γ responses and favours Th2 responses (Increased IL-10 and IL-13) which may result in impaired antiviral and antitumor immunity after moderate acute alcohol use (34). Alcohol decreases the absolute numbers of T cells (CD4+, CD8+) but increases their rates of turnover (attempt to stabilize T cell numbers) resulting to increased level of proliferating CD4+ T cells (target cells) that support the higher levels of HIV replication observed (35). Alcohol also promotes apoptosis of CD4+ T cells by (i)enhancing activation of TNF-α-inducible NF kappa B, the transcriptional regulator of Fas promoter and ii) increased susceptibility to Fas-and activation-induced apoptotic death via augmentation of caspase 3 activity thus enhancing HIV disease progression (36). In vitro experiments had shown that alcohol reduced CD4+ T cell functions (reduced IL-2) and reduced T suppressor (CD8) cell function increasing an individual's risk of acquiring HIV infection (37). There is also increased number of T cells expressing CXCR4 coreceptor in alcohol consumers resulting in enhanced early replication of viral subtypes that use this coreceptor (38) and this is associated with HIV disease progression.

The number of B-cells in the blood and their capacity to generate protective antibodies are reduced in chronic alcohol consumption (39) and this also inhibits antigen presentation because B-cells also function as antigen-presenting cells. B-cell differentiation is also suppressed in chronic alcoholics thus explaining why these persons have reduced antibody responses to vaccines (40).

CONCLUSION

Alcohol consumption, be it either moderate or binge, acute or chronic has a definite negative effect on HIV infection transmission, progression of disease or treatment. Thus addressing alcohol use in

HIV-infected patients or those at risk of infection may have a substantial impact in reducing HIV transmission, progression of disease and ensuring better treatment outcome s in people living with the infection.

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