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Alcohol Abuse and HIV Infection: Role of DRD2

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Abstract

According to a survey from the HIV Cost and Services Utilization Study (HCSUS), approximately 53% of HIV-infected patients reported drinking alcohol and 8% were classified as heavy drinkers. The role of alcohol as a risk factor for HIV infection has been widely studied and recent research has found a significant association between heavy alcohol consumption and lower levels of CD4 T cells among HIV-infected alcoholics. Although there is evidence on the role of alcohol as a risk factor for HIV transmission and disease progression, there is a need for population studies to determine the genetic mechanisms that affect alcohol's role in HIV disease progression. One of the mechanisms of interest is the dopaminergic system. To date, the effects of dopamine on HIV neuroimmune pathogenesis are not well understood; however, dopaminergic neural degeneration due to HIV is known to occur by viral invasion into the brain *via* immune cells, and modulation of dopamine in the CNS may be a common mechanism by which different types of substances of abuse impact HIV disease progression. Although previous studies have shown an association of D(2) dopamine receptor (DRD2) polymorphisms with severity of alcohol dependence, the expression of this allele risk on HIV patients with alcohol dependence has not been systematically explored. In the current study, DRD2 Taq1A and C957T SNP genotyping analyses were performed in 165 HIV-infected alcohol abusers and the results were examined with immune status and CD4 counts.

Keywords

Alcohol; dopamine; DRD2; genotyping; HIV; polymorphisms

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

INTRODUCTION

Out of the 34 million people living with Human Immunodeficiency Virus (HIV) globally, approximately 1.2 million people are in the United States [1, 2]. According to the *Centers for Disease Control* and Prevention (CDC), approximately 51% of adults in the US are regular drinkers [3]; and based on a review of research literature and empirical studies in eight countries, the World Health Organization (WHO) report that alcohol use and sexual behavior are risk factors for sexually transmitted diseases such as HIV infection [4]. Among HIV-infected patients, there is more likelihood of abuse of alcohol than other substances, and alcohol use is highly prevalent, with reports of approximately 53% of HIV patients drinking alcohol and 8% classified as heavy drinkers [5]. Antiretroviral therapy (ART) drug to drug interactions and substance abuse can interfere with ART metabolism and adherence [6]. In particular, alcohol has been reported to interact with medications altering therapeutic drug metabolism and inducing toxicity [7]. More recently, alcohol has been reported to interact with several antiretroviral protease inhibitors [8, 9]. Therefore, alcohol and therapeutic drug interactions are becoming an increasing problem since alcohol has been reported the most commonly abused substance in the United States [10].

Overall, the role of alcohol consumption as a risk factor for HIV infection has been widely studied and reported [4]. Recent research has found a significant association between heavy alcohol consumption and lower levels of CD4 T cells among HIV-infected alcoholic patients [11]. Although there is substantial evidence on the role of alcohol as a risk factor for HIV transmission, there is a need for population studies to determine the genetic mechanisms that may affect the relationship between alcohol intake and the rate of HIV transmission and disease progression. One of the mechanisms of interest in this area is the dopaminergic system. Despite different mechanisms of action, it is known that all substances of abuse modulate dopamine levels in the CNS [12]. To date, the effects of dopamine on HIV neuropathogenesis are not well understood; however, dopaminergic neural degeneration due to HIV is known to occur by its invasion into the brain *via* immune cells, and modulation of dopamine in the CNS may be a common mechanism by which different types of substances of abuse impact the development of HIV associated neurocognitive disorders (HAND) [13].

Dopamine (DA) is a catecholamine neurotransmitter in the brain known to control locomotor activity, cognition, emotion, positive reinforcement, food intake, and endocrine regulation [14]. Dopamine receptors (DR) are G-protein coupled receptors (GPCR) divided into two subclasses, the D1-like DR, D1 and D5, and the D2-like DR, D2, D3 and D4 [12].

Although previous studies have shown an association between D2 dopamine receptor (DRD2) gene polymorphisms and alcohol dependence [15–17], the link between these gene polymorphisms in HIV patients and alcohol dependence has not been explored. Therefore, in the current report, we will be addressing the influential role of the dopamine system and DRD2 gene polymorphisms on the impact of alcohol on HIV disease progression, with an emphasis on host immune activation. First, we will briefly discuss the role of alcohol abuse in HIV disease progression, then focus centrally on the independent and concomitant effects of alcohol abuse and HIV on the dopaminergic system, followed by a discussion of DRD2 gene polymorphisms and their role on immune status of HIV infected alcohol users. We will

concentrate on literature reported from human studies and highlight novel findings from our current study, in which DRD2 Taq1A and C957T SNP genotyping analyses were performed in 165 HIV infected alcohol abusers and the results were correlated with immune status and CD4 counts.

ALCOHOL ABUSE AND HIV DISEASE PROGRESSION

Before discussing the role of the dopaminergic system and DRD2 gene polymorphisms on the impact of alcohol on HIV disease progression, we will give a summary of the literature highlighting a link between alcohol abuse and HIV disease progression since it is crucial to understand the independent and interactive effects of alcohol and HIV as underscored in a recent review [18].

Extensive studies have demonstrated that chronic alcohol use, much like HIV infection, is associated with increased gut permeability and inflammatory responses, resulting in activation of proinflammatory cytokines and antigen presenting cells [19, 20]. Alcohol abuse has also been associated with lowering the production and compromising the function of granulocytes and lymphocytes, which further reduces the capacity to resist bacterial and viral infections [21]. Overall, it is known and extensively reviewed that alcohol abuse suppresses immune responses, leading to an increased risk of infections and also impairing the ability of the immune system to fight infections in alcohol-abusing patients [22]. Findings in a recent publication considering alcohol binge drinking adolescents, reported binge drinkers had greater risk for lymphopenia with significantly lower circulating CD4+ and CD8+ T-cells than controls; which consequently may increase susceptibility to infections by compromising their immune systems [23]. In summary, these studies demonstrate that alcohol alters the quantity and function of immune cells that play a key role in HIV pathogenesis; therefore, the immune-compromise effect mentioned above may be exacerbated in people who are HIV-positive.

While several reports in the early 1990's indicated no correlation between alcohol abuse and HIV disease progression [24–26], Westerberg pointed out that the use of variable measures of alcohol abuse may have influenced the conclusions regarding the role of alcohol in HIV [24]. It was not until 1994, when a Canadian study reported an alcoholic patient whose condition progressed to acquired immunodeficiency syndrome (AIDS) three months after HIV-1 seroconversion, that researchers began to speculate that the patient's accelerated disease progression was due to alcohol abuse and caused by the suppression of T cell function and stimulation of HIV replication [27]. Although this isolated study reported a correlation, at that time, studies with large cohorts were not able to find any association between alcohol intake and progression to AIDS [26, 28–30].

Subsequent years brought substantial evidence of the influence of alcohol not only on the acquisition of HIV, but on the severity of HIV disease progression [31–36]. Below, we will highlight the most relevant literature reported from *in vitro* human studies and population studies linking alcohol abuse with HIV disease progression. For instance, several *in vitro* studies have reported alcohol's important role as a cofactor in the progression of HIV disease as shown by the ability of alcohol to enhance HIV R5 strain infection of human

blood mononuclear phagocytes [37]; and the concomitant effect of alcohol and HIV to decrease macrophage function [38]. Overall, alcohol has been shown to have a negative impact on immune cells resulting in increased susceptibility to diseases caused by bacterial and viral infections, such as tuberculosis, pneumonia, and AIDS as mentioned above [19, 22, 39]. Further, effects of alcohol on HIV disease progression during HIV monoinfection and HIV/HCV coinfections have also been recently reviewed [20].

Recent clinical studies have emphasized the effects of alcohol drinking on declining immune status and acceleration of HIV disease progression as assessed by lower CD4+ T-cell counts and rising HIV viral load irrespective of highly active antiretroviral therapy [33, 34, 40]. For example, a particular study analyzing the correlation between alcohol and HIV disease progression using longitudinal regression models and assessing CD4 cell counts, HIV RNA levels, and alcohol consumption has demonstrated that heavy alcohol drinking has a negative effect on the CD4 count in HIV-infected individuals not receiving ART [11]. A more recent study investigating how substance abuse, including alcohol abuse, impacts the health of South African patients attending HIV clinics concluded that substance abuse was significantly related to severe health problems, in which patients were more likely to have tuberculosis, less likely to be on antiretroviral drugs, and had lower CD4 counts [41]. Interestingly, there is a study that has shown improvement of CD4 cell count after alcohol withdrawal; specifically, HIV-positive alcoholics abstaining from alcohol consumption showed a 41% significant increase in CD4+ T-cells [42].

Overall, the immune function of individuals who abuse alcohol has been reported to be compromised due to immunotoxicities and nutritional deficiencies [30, 43], which can put HIV-infected individuals at higher risk to develop AIDS and other AIDS associated disorders [44, 45]. Despite the evidence supporting detrimental effects of alcohol on the immune system and immune cell subsets involved in HIV disease progression, there are reports emphasizing that the severity of HIV disease progression is due mainly to poor medication adherence and modification of drug metabolism, which in turn can lead to the emergence of drug-resistant virus [32]. In particular, alcohol has been reported to interact with medications altering therapeutic drug metabolism and inducing toxicity [7]. More recently alcohol has been shown to interact with several antiretroviral protease inhibitors [8, 9].

In summary, the reviewed literature illustrates that alcohol not only affects the immune system, but also drug metabolism; furthermore, alcohol can have a negative impact behaviorally on accessing medical care, support seeking, and medication adherence. These effects may combine or contribute to the severity of HIV infection and disease progression.

ALCOHOL ABUSE AND THE DOPAMINERGIC SYSTEM

The link between alcoholism and regulation of the dopaminergic system dates back to the 1980's when scientists in the alcohol field demonstrated alterations in neurotransmitter function resulting in tolerance and dependence [46]. These alterations were deemed responsible for changes in neuronal membrane structure and function of dopaminergic receptors [46, 47]. Further, changes in human brain dopamine (DA) levels in response to

alcohol intake are currently being considered as possible neurobiological markers of vulnerability to AUDs [48]. According to the current literature, striatal DA is increased by all drugs of abuse, including alcohol; and even alcohol-conditioned flavor cues can induce striatal DA release, and this response has been shown to be strongest in subjects with a greater genetic risk for alcoholism. Consequently, striatal DA responses to alcohol cues may also be considered an inherited risk factor for alcoholism [49].

Moreover, dopaminergic degeneration can be manifested as Reward Deficiency Syndrome (RDS), which occurs due to dopaminergic dysfunction in the nucleus accumbens and ventral tegmental areas of the brain. These are the centers of natural rewards like food, and unnatural rewards like alcohol and other drugs of abuse [50–52]. Therefore, defects in neurotransmitter genes, including the dopamine D2 receptor, result in RDS and may lead to individuals seeking substances of abuse as rewards [52, 53].

The literature reviewed above focuses on the CNS since this is the area where most of the dopaminergic effects and dysfunctions have been observed; however, there is substantial evidence indicating that perturbations in the CNS result in modulation of immune function. Thus, these two separate systems, neurological and immune, are tightly linked in conceptualizing neuroimmunomodulation [54]. Although this interaction is well established, the mechanisms that control brain-immune interactions remain to be elucidated.

HIV AND THE DOPAMINERGIC SYSTEM

In vitro, dopamine has been shown to promote HIV replication by increasing the expression of dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) [55] and chemokine receptor type 5 (CCR5) [56] *via* dopamine D1 and D2 receptors respectively, and by stimulating HIV transcription in cells of the immune system [57]. In terms of HIV-1-associated neurodegenerative disorders, the causes of HIV-associated neurodegeneration are similar to those mediating alcohol-induced neuronal injury as recently reviewed [58]. HIV infiltration of the brain *via* immune cells such as monocytes and macrophages has been shown to be crucial in the neuropathogenesis of AIDS [59] and HIV encephalitis [60] by crossing the blood-brain barrier [61]. And this infiltration, in turn, may also have some implication in the dopaminergic potentiation of HIV-associated neurocognitive disorders.

SUBSTANCE ABUSE, HIV, AND THE DOPAMINERGIC SYSTEM

Further, HIV neuropathogenesis through direct effects of dopamine on HIV-infected macrophages has been known to be intensified by drugs of abuse [13]. And these increases in CNS dopamine may in turn dysregulate the function of not only monocytes, macrophages, but also T cells [12]. Thus, increased CNS dopamine levels due to drug abuse may accelerate HIV-associated neurological disorders [62]. Other reports from HIV-infected postmortem brains suggest a widespread deficit in dopamine in different brain regions which may be due to HIV-induced neurodegeneration [63]. Furthermore, HIV and drugs of abuse in the CNS both target subcortical brain structures and the dopaminergic system in particular [64]. Overall, it seems that the modulation of dopamine by HIV can vary widely depending

on the immune cells and the brain area affected, where several dopaminergic interactions are key components in the mechanisms of neurotoxicity.

ALCOHOL ABUSE, HIV, AND THE DOPAMINERGIC SYSTEM

As highlighted above and recently reviewed by Purohit and colleagues, most of the literature points to a major effect of other substances of abuse such as methamphetamines and cocaine on the dopaminergic exacerbation of HIV disease progression and in particular HIV-associated neurocognitive disorders [65]. In the context of alcohol abuse and HIV, a recent report in HIV-1 transgenic rats demonstrated a significant increase in splenic levels of several dopamine neurotransmitter receptor genes (DRD1a, DRD2, and DRD3) during acute binge drinking and these effects were ethanol concentration-dependent [66]. In addition, ethanol has also been shown to cause a concentration-dependent increase in Tat expression in the spleen of HIV-1 transgenic rats [67]. In humans, HIV-1 viral protein, Tat, has been shown to induce secretion of several neurotransmitters including dopamine [68]. Therefore, there could be a synergistic effect of HIV-1 viral proteins and ethanol that may result in the induction of dopamine neurotransmitter receptor expression and in turn alter dopaminergic pathway functions. However, there is still a lack of significant human studies connecting alcohol abuse, HIV, and the dopaminergic system. Therefore, in the next part of this report we will provide evidence of an association of DRD2 gene polymorphisms not only with alcohol abuse as shown by the literature, but also, for the first time, with HIV disease progression in alcoholics as shown by CD4 T cell counts from HIV-infected alcoholics.

ROLE OF DRD2 IN ALCOHOL ABUSE

In alcoholism, associations have been found with genetic variants in the DRD2 gene, which is the most extensively investigated psychiatric gene in molecular genetic studies, especially the gene on chromosome 11 (q22-q23), also called Taq1A (rs1800497) C>T/Glu713Lys substitution [69]. It is located in exon 8 of ANKK1 (ankyrin repeat and kinase domain1) gene, which is the coding region of the ANKK1 gene, and 10kb downstream of the DRD2 gene, from where is known to control the synthesis of dopamine in the brain [70]. This single nucleotide polymorphism (SNP) of Taq1A may result in reduced DRD2 expression and density [71–73] and altered substrate binding specificity [70]. This polymorphism and its differential expression of DRD2 receptors suggest a link between the dopaminergic system and susceptibility to alcoholism [74]. Moreover, a meta-analysis performed in 1993, based on the results from 8 studies, supported a statistically significant association between the A1 allele of DRD2 and alcoholism, with an increase in relative risk associated with increased severity of alcoholism [15].

Overall, the DRD2 ANKK1 gene SNP has been found to be associated with multiple disorders including obesity [75, 76], diabetes [76, 77] alcohol addiction [15, 74, 78, 79]; and alcohol withdrawal syndrome [80]. Prevalence of the A1 allele, 43.0% and 56.3%, has been found among a mixed group of less and more severe alcoholics and in a group of severe alcoholics, respectively [81]. Other recent studies examining the differences in genotype and allele frequencies between alcohol dependent (AD) patients in Korea showed a significant difference in DRD2 -141C and ANKK1 Taq1A polymorphisms between the AD patients and

the controls, suggesting that DRD2 -141C and TaqIA A1 alleles can be a predisposing factor for alcohol dependence [82]. Gender differences have also been reported in relation to the TaqIA SNP, indicating that male alcoholics have higher proportions of A1 allele or genotypes than their control and female counterparts [79, 83].

Another DRD2 polymorphism of interest is the C957T SNP (rs6277) C>T/Pro319Pro on exon 7, which has been found to be related to decreased receptor expression and altered mRNA folding and stability, which is in turn reflected as a decrease in dopaminergic functions [84]. In terms of an association between alcohol dependence and the C957T SNP, contradictory results have been published, with some studies finding an association with the C-allele [85, 86] and one study with the T-allele [87]. Overall, haplotypes composed of polymorphisms, which are supposed to induce a low DRD2 expression, have been associated with alcohol dependence [88].

Although previous studies have shown an association of D2 dopamine receptor (DRD2) polymorphisms with severity of alcohol dependence [15, 69, 86, 87], the expression of this allele risk on the severity of drinking behavior in HIV patients with alcohol dependence has not been explored. Therefore, based on the reviewed literature on the effects of alcohol and HIV on the immune system and evidence of the role of the dopaminergic system and DRD2 gene polymorphisms, we hypothesize that immune status in terms of CD4 count <500> among HIV positive alcoholics could indicate the effect of alcohol on immune function and susceptibility to alcoholism assessed by the prevalence of A1 allele.

MATERIALS AND METHODS

Participants

Consents from participants were obtained consistent with the policies of Florida International University (FIU) and the National Institutes of Health (NIH). The protocol was approved by the Institutional Review Board (IRB) of FIU. HIV positive alcohol abusers (n=165) with an average age of 45 (SD=6.88) years were recruited for the study. African Americans comprised 80% of the participants; 64% males and 36% females; and 85% were receiving ART. The mean total CD4 count was 454 (SD=300).

Standard Assessments of Alcoholism

The Alcohol Use Disorders Identification Test (AUDIT) developed by the World Health Organization is used to identify persons with hazardous and harmful patterns of alcohol consumption [89]. Total AUDIT scores of 8 or more indicate hazardous alcohol use and alcohol dependence. An abbreviated version of AUDIT known as AUDIT-Consumption (AUDIT-C) is frequently used because of its advantages of brevity and sensitivity to the alcohol drinking frequency. AUDIT-C positive is considered if the total AUDIT-C score for men is ≥ 4 and for women is ≥ 3 [90, 91]. According to the National Institute on Drug Abuse and Alcoholism (NIAAA) guidelines, at-risk drinking is >14 drinks/week (>4 drinks/day) for men and >7 drinks/week (>3 drinks/day) for women [92].

In our study, the mean total AUDIT scores and AUDIT-C scores were 14.34 (SD=9.13) and 6.31 (SD= 3.26) respectively. To segregate less severe alcoholics from more severe

alcoholics, we considered the total AUDIT scores <16> and age of drinking onset <25> years. Almost all participants had been admitted to an alcohol treatment facility at least twice on average. The average time of drinking onset was 21.5 (SD=10.2) years with an average consumption of 24 drinks per week.

DRD2 Taq1A and C957T SNP Genotyping Analyses

To investigate the role of DRD2 gene polymorphisms in alcohol induced HIV disease progression, we conducted DRD2 Taq1A and C957T SNP genotyping analyses in a baseline cross-sectional study of HIV positive alcohol abusers (n=165). Peripheral blood was drawn from consented participants and genomic DNA was extracted as per manufacturer's instructions using the QIAmp DNA blood mini kit (catalog # 51104) from QIAGEN (Valencia, CA). Genomic analyses of DRD2 SNPs Taq1A (rs1800497) and C957T (rs6277) were conducted using the TaqMan® Universal PCR Master Mix, No AmpErase® UNG (catalog #: 4324018) from Applied Biosystem (Foster City, CA). The experiments were performed and analyzed in a 7300 Real Time PCR System ((Applied Biosystems). 7300 & 7500 Real Time PCR Systems TaqMan(R)RNase P Instrument Verification Plate (catalog # 4350584) and the 7300 Real Time PCR Systems Spectral Calibration Kits (catalog # 4349182) were used as per manufacture's protocol (Applied Biosystems).

Statistical Analyses

Data analyses were done using chi-squared test and statistical analysis tools from Applied Biosystems. The allele and genotype frequencies were analyzed for compliance with the Hardy Weinberg equilibrium. The mean was calculated for the AUDIT scores, AUDIT-C scores and CD4 counts. Averages were calculated for age of participants, age of drinking onset, and alcohol consumption per week. No statistically significant age, gender, and ethnic differences were found between the groups.

RESULTS

Genotyping analyses were performed in a cohort of 165 HIV-positive alcohol abusers recruited for the study. A summary of the participants' demographic data is presented in Table 1 below.

Alcohol Abuse and DRD2 Polymorphisms

The genotype frequencies of DRD2 Taq1A SNP (rs1800497) wild type A1+, heterozygous A1A2 and mutant type A2+ were 39, 50, and 76 respectively and were in Hardy-Weinberg equilibrium. Unexpectedly, DRD2 Taq1A SNP, which has been previously found to be strongly associated with alcoholism [15, 78, 79, 81, 82], did not have any significant association with alcohol drinking behavior in our study sample as assessed by AUDIT and AUDIT-C. Given that the average time of drinking onset was 21.5 years (SD=10.2) with a mean 24 drinks/week, our sample reflected a more severe genetic type of alcoholic as explained earlier [93–96]. According to a meta-analytic review, the calculated prevalence of A1 allele associated with more severe alcoholics has been reported to be 47.2% [97]. The overall A1 allele prevalence in our study sample was 54%. In our more severe alcoholics, the A1 allele prevalence was 52.5%, although no statistically significant difference between

the more severe and less severe alcoholic groups was found ($\chi^2=2.37$, $df=2$, $p=0.30$). The total frequency of A1 allele in our study was 38.8%, and in the more severe alcoholics it was 36%. The genotype frequencies of DRD2 C957T SNP (rs6277) wild type CC, heterozygous CT and mutant type TT were 10, 58, and 97 respectively but did not comply with Hardy Weinberg equilibrium. No statistically significant age, gender and ethnic differences were found between the groups.

Alcohol Abuse, HIV, and DRD2 Polymorphisms

According to our results shown in Table 2, the Taq1A genotypes differed significantly between the immune-compromised and immune-competent groups in our HIV-positive alcoholic population ($\chi^2=9.73$, $df=2$, $p=0.008$). The mean (SD) CD4 counts in the immune-compromised and the immune-competent groups were 263(SD=137) and 740(SD=245), respectively. We did not find any significant age and gender differences in the prevalence of A1 allele in the immunocompromised and the immunocompetent groups respectively.

For the DRD2 C957T SNP, we found a greater prevalence of TT genotype (~60%) in our study sample of HIV positive alcohol abusers, but it had no significant association with heavy alcohol consumption or CD4 counts $<500>$ ($\chi^2=0.48$, $df=2$, $p=0.78$).

CONCLUSION

It is known that alcohol influences immunity through various mechanisms, and is also considered to be a HIV disease progression factor in addition to its association to the susceptible A1 allele of ANKK1 gene. We hypothesized that immune status in terms of CD4 count $<500>$ among HIV positive alcoholics could indicate effect of alcohol on immune function and susceptibility to alcoholism assessed by the prevalence of A1 allele. We found that the Taq1A genotypes differed significantly between the immune-compromised and immune-competent groups in our HIV-positive alcoholic samples as shown by significant differences in mean (SD) CD4 counts in the immune-compromised (263(SD=137)) and the immune-competent (740(SD=245)) groups (Table 2).

Analyses of the other genotype frequencies of DRD2 C957T SNP wild type CC, heterozygous CT and mutant type TT did not comply with Hardy Weinberg equilibrium. Although we found a greater prevalence of TT genotype (~60%) in the HIV positive alcohol abusers, there was no significant association with heavy alcohol consumption or CD4 counts.

Current studies from different populations, have reported a significant association of alcohol and substance abuse with ART adherence [98–100]. We failed to find similar findings in our study sample. It is difficult to conclude if alcohol played a role in ART adherence in our study sample since 85% of the participants were on ART and we did not have a control sample of HIV positive non-alcoholics to make proper comparisons. However, we found a significant association of the Taq1A genotype and lower CD4 counts, from which a correlation between alcohol and poor immune function can be inferred and increased susceptibility to alcoholism, with indirect adverse effects on ART adherence. The literature reviewed above and our own study, lead us to conclude that alcohol abuse is an influential

factor in HIV disease progression, associated with detrimental outcomes such as weakened immune system, greater susceptibility to opportunistic infections, and lower compliance to medications. Moreover, the influence of alcohol on immune regulation, as measured by CD4 count, in HIV positive alcoholics may be attributable to the effects of DRD2 gene polymorphisms, and this is supported by our research study, where we report for the first time that the Taq1A genotype differs significantly between the immune-compromised and immune-competent groups in our HIV-positive alcoholic samples. Alcohol abuse and HIV independently and concomitantly may further affect neurotransmitters' transporters and receptors like DRD2, having an impact on neuro-cognitive functions, exacerbating risky behaviors such as alcoholism and resulting in poor disease outcomes and HIV disease progression.

In summary, our research provides support for a DRD2 polymorphism as a moderator of CD4 clinical outcome in an HIV-positive population of alcoholics receiving ART. Our findings also suggest that HIV prevention researchers may find value in considering such genetic factors in designing more supportive and personalized interventions for this specific HIV-positive alcoholic population who carry this type of genetic polymorphism.

LIMITATIONS OF THE STUDY AND FUTURE DIRECTIONS

It is important to note that our findings should be interpreted carefully since our study was conducted on a small cohort of HIV-positive alcoholics and without control populations. The data provided is intended to supplement an extensive review of the current literature and to highlight the role of DRD2 in HIV-positive alcoholics. Our future work will enable the inclusion of HIV positive non-alcoholic/drug abusing, HIV negative non-alcoholic, and alcoholic groups, permitting fuller investigation of genotype differences. However, our results illustrate a significant association of the Taq1A genotype and lower CD4 counts within the studied population of HIV-positive alcoholics, which is a new significant observation supporting the role of DRD2 polymorphisms in HIV-positive alcoholics. Our intent is that this finding and the compilation of literature, delineating the role of DRD2 in alcohol abuse and HIV infection, will serve as the basis for future studies in which more in depth analysis into other populations may be pursued.

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Table 1

Demographic data from HIV-positive alcohol abusers. 165 HIV-positive alcohol abusers with a mean total CD4 count of 454 (SD=300) were recruited for the study. Participants were classified as immune-compromised, CD4 count of 263 (SD=137), or immune-competent, CD4 count of 740 (SD=245), using their baseline CD4 counts <500>.

Gender (%)	Race/Ethnicity (%)	Age (Years) (Mean ± SD)	Total CD4 Count (Mean ± SD)	CD4 Count within Groups Below (Mean ± SD)	
Males (64%) Females (36%)	African Americans (80%) Hispanics (20%)	45 ± 6.88	454 ±300	Immune-Compromised (CD4<500) n=99	Immune-Competent (CD4>500) n=66
				263±137	740±245

Table 2

Genotype frequencies of DRD2 SNPs (Taq1A and C957T) in HIV-positive alcohol abusers. Peripheral blood was drawn from consented participants, HIV positive alcohol abusers (n=165), and genomic DNA was extracted. Genomic analyses of DRD2 SNPs Taq1A (rs1800497) and C957T (rs6277) were performed. Participants were classified as immune-compromised or immune-competent using their baseline CD4 counts <500>.

	Immunocompromised (<500)	Immunocompetent (>500)
	(n=99)	(n=66)
DRD2 Taq1A[*] genotypes (n)		
A1+	27	12
A1A2	21	29
A2+	51	25
DRD2 C957T[†] genotypes (n)		
TT	57	40
CT	35	23
CC	7	3

* Between the immunocompromised and immunocompetent groups, Taq1A genotypes differed significantly ($\chi^2 = 9.73$, $df=2$, $p=0.008$).

† Between the immunocompromised and immunocompetent groups, C957T genotypes did not differ significantly ($\chi^2 = 0.48$, $df=2$, $p=0.78$).