Published in final edited form as:

J Acquir Immune Defic Syndr. 2012 December 1; 61(4): 455–461. doi:10.1097/QAI.0b013e3182712d39.

Alcohol Consumption and CD4 T-cell count response among persons initiating antiretroviral therapy

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Abstract

Background—We evaluated the longitudinal association of alcohol use with immunological response to combination antiretroviral therapy (ART) among HIV infected individuals.

Methods—This was a prospective cohort study of individuals initiating ART. Participants underwent an Audio Computer-Assisted Self Interview querying drug and alcohol use within 6 months of treatment. Immunological response to ART was defined by CD4 T-cell count (CD4). Primary independent variables were self-reported number of drinks consumed per drinking day (quantity) and days of alcohol consumption in a typical week (frequency). We used linear mixed effects models to quantify the association between CD4 T-cell count and alcohol quantity and frequency and Cox proportional hazards models to estimate the relative hazard of an increase 100, 150 and 200 CD4 cells/mm³ per additional drink per drinking day. Analyses were stratified by gender. Viral suppression was examined as a time-varying covariate.

Results—Between 2000-2008, 1107 individuals were eligible for inclusion in this study. There was no statistically significant difference in CD4 T-cell count by average drinks per drinking day at any frequency of alcohol use irrespective of gender or viral suppression. Similarly, we found no difference in the hazard ratio for drinks per drinking day within the categories of drinking frequency for time to CD4 T-cell count increase of 100, 150 and 200 cells/mm³, respectively.

Conclusions—Among individuals initiating antiretroviral therapy (ART) the benefits of therapy and viral suppression on the immune system outweigh detrimental effects of alcohol, reinforcing the importance of initiating ART and ensuring adequate adherence to therapy.

Keywords

HIV; alcohol; Immune Response; CD4 T-CELL COUNT; antiretroviral therapy

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Introduction

Alcohol use is prevalent among HIV infected individuals^{1,2} and is associated with decreased adherence to combination antiretroviral therapy (ART)^{3,4}, decreased viral suppression on ART⁵ and increased mortality.⁶ In addition, chronic alcohol use and HIV infection are both associated with immune suppression.⁷ HIV infection results in CD4 T-lymphocyte depletion, while heavy alcohol use is associated with defects in both cell-mediated and humoral immunity.^{7,8}

Given that both alcohol use and HIV suppress the immune system, investigators have sought to determine if alcohol use furthers hastens HIV disease progression through its effect on CD4 T-cell count (CD4). Samet and colleagues investigated the association of alcohol use and CD4 T-cell count among 595 individuals with a history of alcohol problems.⁹ Among persons not on ART, heavy alcohol use, defined as >14 drinks per week or >4 drinks per occasion in men and >7 drinks per week or >3 drinks per occasion in women, was associated with a lower CD4 T-cell count, compared to no alcohol use. Limiting the analysis to only those on ART, heavy alcohol use was not associated with a lower CD4 T-cell count after adjusting for medication adherence. In a study of 130 individuals with HIV and a history of alcohol and drug use who had a CD4 T-cell count > 200 cells/mm³, Baum et al found that two or more drinks per day was associated with a 2-3 times increased risk in decline of CD4 200 cells/mm³ compared to 1 or fewer drinks per day or no alcohol use.¹⁰ When they limited their analysis to persons not on ART, 2 or more drinks daily was associated with 7 times increased risk in decline of CD4 to < 200 cells/mm³ compared to those with 1 or fewer daily drinks. Neither study stratified their analyses by gender to assess if alcohol's effect on immune response to therapy differed between men and women.

While it appears that there is a relationship between alcohol use and lower CD4 T-cell count among persons not receiving ART, it is less clear if 1) this association persists among persons on ART; 2) the effect of alcohol use on CD4 T-cell count response to therapy varies by whether or not viral suppression is achieved; 3) the effect of alcohol on immune response varies by gender—potentially important as women experience the adverse consequences of alcohol use at lower levels compared to men¹¹; and 4) immunological response to ART varies by patterning of alcohol use. Thus, we examined the effects of the quantity and frequency of alcohol use on immunological response to ART, whether alcohol use differentially affects CD4 T-cell count response in people who achieve viral suppression compared to those who do not, and finally, the effect of alcohol on immune response stratified by gender.

Methods

Study Design

This is a prospective cohort study of individuals enrolled in the Johns Hopkins HIV Clinical Cohort (JHHCC). The JHHCC is a longitudinal cohort of approximately 6000 HIV-infected adults receiving care in the Johns Hopkins HIV Clinic. All patients receiving care are eligible to participate. Data collected on enrollees include demographic, clinical, diagnostic, laboratory, and pharmacy data. Information from the clinical record is abstracted by trained staff. Laboratory data are obtained electronically. A description of the data collection methods for the Johns Hopkins HIV cohort has been published elsewhere.¹²

Survey

In July 2000 an Audio Computer-Assisted Self-Interview (ACASI) collecting patient reported outcomes was added to the data collection procedures of JHHCC. The survey takes about 15 minutes to complete and collects patient reported outcomes including alcohol use,

illicit drug use, depressive symptoms, ART use and ART adherence over the prior six months. A description of the ACASI methods has been published elsewhere.¹³ Written informed consent is obtained from participants. This study has been approved by the Johns Hopkins University School of Medicine Institutional Review Board.

Study Inclusion

We included HIV infected individuals who participated in an ACASI within six months of ART initiation, who had a CD4 T-cell count measured prior to or on the start of ART and who were not virologically suppressed at the time from a prior regimen. ART was defined as any regimen that included a combination of the following medications: nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase strand transfer inhibitor, or a CD4 T-cell entry inhibitor.

Outcome description

Our outcome was immunological response to ART, defined in two ways: 1) CD4 T-cell count after ART initiation, and 2) time from ART initiation to an increase of 100, 150 and 200 CD4 cells/mm³. Different levels of CD4 cell count response to therapy were selected to determine if there was a threshold for the effect of alcohol use on immune response.

Independent variables

Our primary independent variables were the self-reported average number of alcoholic drinks consumed per typical drinking day (quantity of drinking, continuous), and number of days of alcohol consumption in a typical week (frequency of drinking, categorized as less than 1, 1 to 3 and greater than 3 days) over the past 6 months. Alcohol use may vary over time. We assessed the variation in alcohol use over time within a subject by calculating the standard deviation of reported drinks per week across the subjects' available ACASIs (all ACASI 6 months prior to initiation of ART to end of follow-up). We found that the majority of patients did not change their reported drinks per week over time (mean of SD: 1.87; median 0) which lead to our decision to use alcohol use reported from the ACASI closest to ART initiation, within a 6 month window, as our main exposure variable

Additional independent variables were chosen a priori and were either demonstrated to be associated with immunological response to ART in previous literature or thought to be clinically important. These included age, race, HIV transmission risk factor, baseline CD4 T-cell count as a marker of disease severity, baseline HIV-1 RNA, PI use, NNRTI use, cocaine use, and depressive symptoms. HIV transmission risk was obtained from patient self-report; patients were able to report multiple risk factors. Cocaine use was ascertained using the ACASI, and defined as any self-reported cocaine use in the 6 months prior to the interview. We categorized depressive symptoms using the 5-item Centers for Epidemiological Studies Depression Scale (CESD-5, low symptoms: score of 0-3, moderate symptoms: score 4-7 or high symptoms: 8-14).¹⁴ Collection of the CESD-5 did not begin until 2004; therefore, we assessed sensitivity of our finding to this variable in the subset of individuals who initiated ART after 2004. Analyses were stratified by gender as women experience biological effects of alcohol at lower levels of use compared to men.¹¹ A time-varying indicator variable was created for HIV-RNA suppression and was used as a biomarker for adherence. Viral suppression was defined as an HIV-RNA < 1000 copies/ml. CD4 T-cell count and HIV-1 RNA measurements were not necessarily captured at concurrent time points. The HIV-1 RNA at the closest time to CD4 measurement was used to determine whether individuals had viral suppression. The median time lag in absolute value between CD4 T-cell count and HIV-1 RNA measurements after ART initiation was 0 days with a mean of 3.7 days (range: 0-180). We performed a sensitivity analysis limiting

the range between CD4 T-cell count and HIV-1 RNA measurements to 90 days and found no difference between a maximum of a 90-day time lag and 180-day time lag.

Statistical Methods

Descriptive statistics were calculated for the outcome variables and independent variables for the entire cohort and separately by gender. Graphical displays of the outcome variables included scatter plots of CD4 T-cell count as a function of time and Kaplan-Meier curves for time from ART initiation to an increase of 100, 150 and 200 CD4 T-cells/mm³.

Linear mixed effects models were used to quantify the association between CD4 T-cell count and alcohol drinking frequency (days per week, categorical) and consumption (drinks per drinking day) after adjusting for time from initiation of ART (linear spline with 4 degrees of freedom) and the a priori identified potential confounding variables. The models included a random intercept for subject to account for the within subject correlation over time in CD4 T-cell count as well as a random slope for time. Gender, viral suppression and alcohol drinking frequency were treated as effect modifiers so that the models estimated the adjusted linear association between CD4 T-cell count and alcohol consumption separately for men and women, viral suppression and alcohol drinking frequency. Interaction between this variable and the drinking exposure variables was examined in order to estimate a separate drinking dose effect with and without HIV-RNA suppression. Likelihood ratio tests were used to test if alcohol-drinking frequency modified the CD4 T-cell count and alcohol consumption association. Standard linear regression diagnostic procedures including residual plots and normal probability plots were used to confirm the validity of linearity and residual distribution assumptions.

Cox proportional hazards regression models were used to estimate the relative hazard of an increase in the CD4 T-cell count of 100, 150 and 200 CD4 cells/mm³ per additional alcoholic drink per drinking day. The relative hazards were estimated separately by gender and alcohol drinking frequency after adjusting for the potential confounding variables. Separate baseline hazard functions were estimated for days with and without viral suppression. An interaction between alcohol related covariates and viral suppression strata was assessed but found to be non-significant ($p > 0.05$) and thus not included in the final model. Likelihood-ratio tests were used to determine if alcohol drinking frequency modified the relationship between an increase in the CD4 T-cell count of 100, 150 or 200 CD4 cells/mm³ and alcohol consumption. Martingale and Schoenfeld residual plots were used to visually inspect the linearity and proportional hazards assumptions within the model. Models were adjusted for potential confounders, including age, race, HIV transmission risk factor, baseline CD4 T-cell count, baseline HIV-1 RNA, PI use, NNRTI use, cocaine use, and depressive symptoms.

Because we were interested in determining whether the effect of alcohol on CD4 T-cell response was driven by daily quantity, weekly frequency or a combination of both we did not initially create a summary measure of alcohol use. However, to allow us to compare our results to prior studies examining alcohol use and CD4 T-cell count, we created a summary measure for alcohol use using the same categories used by Samet and colleagues⁹, following guidelines provided by the National Institute on Alcohol Abuse and Alcoholism: Heavy alcohol use was defined as >14 drinks per week or >4 drinks per occasion in men and >7 drinks per week in women and >3 drinks per occasion in women; moderate alcohol use was any use below these levels.¹⁵ We then ran the same analyses outlined above.

Missing Data—The drinks per drinking day and frequency variables were incomplete for 4 percent ($n = 67$) of the subjects. The missing values were imputed by examining the two closest ACASI (on either side of the regimen start date) and averaging the values for the

variable(s) with missing data. If the two closest ACASI contained only a single non-missing value for the missing variable, that value was used to impute the missing value. If both values were missing for the missing variable, the patient was removed from the study ($n = 11$, $<1\%$).

Results

The initial population included 1695 subjects with ACASI interviews from the JHHCC who initiated ART between January 16, 2000 and July 15, 2008. Twenty three individuals were excluded due to a lack of initial CD4 T-cell count ($n = 12$) or consumption/frequency of alcohol use ($n = 11$), and 22 individuals were excluded due to a lack of CD4 T-cell counts and HIV-1 RNA measurements after ART initiation. An additional 543 patients with suppressed viral loads at the time of ART initiation were excluded, leaving 1107 subjects in the study population.

Table 1 provides descriptive statistics for the study population. The median age was 42 years (range: 20-77), 61% were male, and 85% were African American. Sixty percent had an initial CD4T-cell count less than 200 cells/mm³. Sixty percent of the subjects reported no alcohol use and 17, 13 and 10 percent of the subjects reported less than 1, 1-3 and greater than 3 days of alcohol use on average per week, respectively. Among subjects who reported consuming alcohol, the median number of drinks consumed per drinking day was 2 (interquartile range [IQR]: 1 to 4), with the median number of drinks per drinking day increasing with increasing frequency of use.

Sixty two percent of viral loads over time were <1000 , 94% of which were <400 . Overall, patients with suppressed viral loads had higher average CD4 T-cell count compared to non-suppressed subjects. The mean CD4 T-cell count changed very little over time for subjects without viral load suppression.

Tables 2 and 3 summarize the linear mixed effects model for males and females respectively. In neither men nor women was there a statistically significant difference in CD4 T-cell count by average drinks per drinking day at any frequency of use, irrespective of virological suppression. Among the potential confounding variables, the estimated mean CD4 T-cell count increased/decreased as a function of the baseline CD4 T-cell count ($p < 0.05$) for both males and females. Wider CIs for the estimates among the females were likely driven by their smaller sample size compared to men. In addition, within models that estimated the effect of drinks per drinking day stratified only by gender and viral load suppression but adjusted for drinking frequency, we found no difference in the estimated effects of drinks per drinking day ($p = 0.54$ and 0.58 among males; $p = 0.75$ and 0.48 among females), for suppressed and non-suppressed, respectively).

Table 4 summarizes the Cox proportional hazards model estimating the relative hazard of achieving a CD4 T-cell count increase of 100, 150 and 200 cells/mm³ for each additional drink per drinking day, stratified by weekly drinking frequency and gender. For example, we estimate that the hazard of an increase of 100 cells/mm³ increases by roughly 1% per additional drink per drinking day among males who report less than 1 day of drinking per week (HR: 1.01, 95% CI: 0.96 to 1.07). Overall, we found no difference in the HR for drinks per drinking day within the categories of drinking frequency (Likelihood-ratio test for drinks per drinking day and drinking frequency interaction: $p = 0.53$, 0.81 and 0.27 among males; $p = 0.33$, 0.86 and 0.45 among females for time to CD4 T-cell count increase of 100, 150 and 200 cells/mm³, respectively).

We performed a sensitivity analysis limiting our sample to only those individuals initiating ART after 2004 who also completed the CESD-5. CESD-5 score was not significant in the models, and the results similar to results in the overall models.

We then examined the relationship between alcohol use and CD4 T-cell response to therapy using categories for weekly consumption: heavy, moderate and none. Using linear mixed effects models and combining both men and women, there was no significant difference in CD4 cell count between heavy drinkers and abstainers (difference: 1.45, 95% CI: -26.89 to 27.97) and moderate drinkers and abstainers (3.93, -15.63 to 23.48) among those with viral suppression and those without viral suppression (heavy versus abstinent: 0.76, -27.16 to 26.68; moderate vs. abstinent -1.65, -21.13 to 17.83). Similarly, there was no difference in time to CD4 T-cell increase of 100 (Adjusted Hazard Ratio Heavy vs. No Alcohol Use: 0.94, 95% CI: 0.74 to 1.20) (For increase of 150 cells/mm³: 0.90, 0.69 to 1.17; for increase of 200 cells/mm³: 0.95, 0.72 to 1.25).

Discussion

In this cohort of HIV infected individuals, level of alcohol use at the time of ART initiation was not associated with CD4 cell count response to therapy irrespective of whether or not viral suppression was achieved and irrespective of gender. Among those who suppressed their viral load, immunological response to therapy was robust, and associated significantly with CD4 cell count and viral load at the time of ART initiation. Similarly, among those who did not suppress their viral load, there was no differential increase or decline in CD4 cell count by either daily quantity or weekly frequency of alcohol use. These results demonstrate that the benefit of viral suppression on ART outweighs the potential detrimental effects of alcohol use on immunological response to therapy in both men and women.

Our results support and extend findings from two earlier studies in the ART era examining associations between alcohol use and immunological response to therapy.^{9,16} Samet and colleagues, prospectively assessed CD4 T-cell count among 595 HIV-infected individuals, of whom 354 were on ART. Using linear mixed models, they found that among persons on ART heavy alcohol use was not associated with CD4 cell count. Similarly, in a longitudinal study of 516 HIV infected women using data from the HIV Epidemiologic Study (HERS) cohort, alcohol use was not statistically associated with CD4 T-cell count, irrespective of ART use.¹⁶ Our results add to the evidence that alcohol use does not have a significant impact on CD4 T-cell count among persons receiving ART, and extends this finding to individuals initiating ART who achieve viral suppression and those who do not.

Our results are in contrast to a recent study by Baum and colleagues who prospectively followed HIV infected individuals with alcohol and/or illicit drug use.¹⁰ Among 130 individuals with a baseline CD4 >200 cells/ml, they examined the association of alcohol use and time to decline of CD4 >200. Defining frequent alcohol use as ≥2 alcoholic drinks daily, and adjusting for ART use as a time-varying covariate, they found that frequent alcohol use was associated with an increased risk in decline of CD4 cell count. When they combined alcohol and cocaine use, they found the risk of CD4 cell count decline persisted, though it was not greater than frequent alcohol use alone. There are number of potential explanations for the difference in findings between our study and those of Baum and colleagues. Our sample was limited to individuals initiating ART, whereas Baum included both individuals on and off of ART. Though they adjusted for use of ART, it may be that the increased risk in decline of CD4 cell count in their sample was driven by those not on ART. A second possible explanation is that concurrent cocaine use may be responsible for the association between alcohol use and CD4 cell count in their study. In a previous study by Baum et al, using the same cohort of drug users, crack cocaine use was associated with a

decline of CD4 cell count to less than 200 cells/mm³ independent of ART use and controlling for any alcohol use, suggesting a direct link between crack cocaine and HIV disease progression.¹⁷ In the Women's Interagency HIV Study (WIHS), both intermittent and persistent crack use was associated with greater CD4 cell count decline, controlling for ART use and adherence. Alcohol use was not significantly associated with lower CD4 cell count in WIHS study, though it was associated with increased HIV viral load.¹⁸

We did not find a difference in CD4 cell count response to ART by gender. We hypothesized that women consuming alcohol would experience decreased immune response to ART at lower levels of alcohol use compared to men; however, neither men nor women showed an effect of level of alcohol use on CD4 cell count. This is likely explained by the generally equal potency of antiretroviral therapy between men and women.¹⁹

Though we did not find a blunted CD4 cell count response after ART initiation among persons with alcohol use, alcohol consumption does negatively affect HIV disease progression and transmission through other mechanisms: decreased medication adherence^{4;20-22}, and increased transmission risk behaviors.^{23;24} Hendershot and colleagues synthesized literature on the association between alcohol use and antiretroviral adherence.²¹ Across 40 studies, with 25,000 participants, any alcohol use was associated with a 40% decreased odds of adherence, and at-risk drinking or an alcohol use disorder was associated with 53% lower odds of antiretroviral adherence. Alcohol use is also associated with risky sexual behaviors.²⁴ In a meta-analysis of 27 studies, any alcohol use, problem drinking, and alcohol use in sexual contexts were all significantly associated with unprotected sex among HIV infected individuals.²⁴ With alcohol's negative effect on HIV medication adherence and viral suppression and its association with increased transmission behaviors, screening for alcohol use and brief interventions encouraging reduction or abstinence in alcohol use is essential to optimize the management of HIV.

Given that individuals with alcohol use can have a robust immunological response to ART, and that prior studies have demonstrated lower CD4 cell count among persons not on ART who consume alcohol, early initiation of ART is essential to achieve optimal CD4 cell count. With more durable ART regimens, that are more forgiving to medication non-adherence, initiation of ART should be considered irrespective of alcohol use.

Our study has potential limitations. The median drinks per drinking day among the highest frequency drinkers was 4 (interquartile range 2, 6). Thus our sample may not have included the heaviest drinkers. As a result, we cannot generalize our findings to the subset of individuals who drink outside of the range of what was reported in this study. Our generalizability is also limited to populations similar to our study sample, which includes largely urban, African-American HIV infected individuals. Also, this is a longitudinal cohort study, and though we adjusted for potential confounders, there was likely residual confounding. In addition, alcohol use was measured by self-report, which may have led to under-reporting of alcohol use. Finally, the CESD-5 was used as our measure of depressive symptoms, chosen specifically in this cohort for its brevity. However, this 5-question measure is not used routinely in research, and may not have adequately identified individuals with depression.

In conclusion, among persons initiating ART, alcohol use is not associated with decreased immunological response to ART, irrespective of viral suppression. People who drink alcohol and achieve viral suppression can reap the same immunologic benefits of those who do not drink alcohol. Although there are a number of other important medical and behavioral reasons that a patient's alcohol consumption should be addressed, an immunological effect on the CD4 cell count response to ART at levels of alcohol use in this study is not among

them. Aggressive treatment for HIV, coupled with adherence interventions to ensure viral suppression should be considered for people who consume alcohol within the range of use studied in this cohort.

Acknowledgments

Conflicts and Sources of Funding: This research is funded by the National Institute of Alcohol Abuse and Alcoholism (R01 AA016893, to Moore, K23 AA015313, to Chander; R01 AA014500, to McCaul, Hutton, Chander, U24AA020801 to McCaul, Moore, Chander, Hutton, Lau) and The National Institute of Drug Abuse (R01 DA11602, to Moore and Lau, and K24 DA00432, to Moore) NIAID K01-AI071754 (Lau)

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Table 1

Demographic and HIV clinical characteristics of 1107 persons initiating antiretroviral therapy, overall and by gender.

Variable	Overall Sample (n = 1107)	Males (n = 678)	Females (n = 429)
Age (years): Median (range)	42 (20-77)	42 (21-76)	41 (20-77)
Race			
African American	943 (85%)	555 (82%)	388 (90%)
Caucasian	149 (13%)	110 (16%)	39 (9%)
Hispanic	8 (<1%)	8 (1%)	0 (0%)
Other/Unknown	7 (<1%)	5 (<1%)	2 (<1%)
Baseline HIV-1 RNA (copies/ml)			
<10,000	474 (43%)	298 (44%)	176 (41%)
10,000-99,999	460 (42%)	277 (41%)	183 (43%)
>99,999	173 (15%)	103 (15%)	70 (16%)
Baseline CD4 (cells/mm ³)			
200	659 (60%)	406 (60%)	253 (59%)
201-350	306 (28%)	176 (26%)	130 (30%)
351-500	94 (8%)	65 (10%)	29 (7%)
>500	48 (4%)	31 (5%)	17 (4%)
Alcohol Frequency (days per week)			
0	667 (60%)	378 (56%)	289 (67%)
<1	189 (17%)	128 (19%)	61 (14%)
Drinks Per Day: Median (IQR)	2 (1-2)	1.5 (1-2)	2 (1-3)
1-3	144 (13%)	97 (14%)	47 (11%)
Drinks Per Day: Median (IQR)	3 (2-3.6)	3 (2-3.5)	3 (2-4)
>3	107 (10%)	75 (11%)	32 (7%)
Drinks Per Day: Median (IQR)	4 (2-6)	4 (2-5.8)	4.5 (2-6)
NNRTI Use *	465 (42%)	298 (44%)	167 (39%)
PI Use *	701 (63%)	432 (64%)	269 (63%)
Cocaine Use	202 (18%)	119 (18%)	83 (19%)
Transmission Risk Factor **			
Injection	510 (46%)	319 (47%)	191 (45%)
Men Having Sex with Men	244 (22%)	244 (36%)	n/a
Heterosexual Transmission	594 (54%)	267 (39%)	327 (76%)
Transfusion	46 (4%)	21 (3%)	25 (6%)
CESD Depressive Symptoms ***			
Low (0-3)	28%	30%	25%
Moderate (4-7)	61%	61%	59%
High (8-14)	11%	8%	14%
NA	1%	1%	1%
Suppression Percent ****	62%	62%	60%

* These variables are defined in the methods section

** Categories not mutually exclusive

*** Values obtained from the 638 patients with CESD data after 2004

**** Suppression percent is taken out of all 18865 data points included in the longitudinal analysis

Table 2

Linear mixed effects model among males, examining alcohol consumption and CD4 response to therapy*.

Variable	Estimate**	95% CI	P-Value
Age	0.19	(-1.10, 1.48)	0.774
NNRTI	16.40	(-5.39, 38.18)	0.140
Cocaine	-18.13	(-47.55, 11.29)	0.227
Race			
White	Reference	NA	NA
African American	-36.27	(-66.06, -6.48)	0.017
Hispanic	-60.50	(-164.03, 43.03)	0.252
Other/Unknown	-32.48	(-160.07, 95.11)	0.618
Drinks Per Day (suppressed viral load)***			
Days per Week			
<1	-0.06	(-7.08, 6.95)	0.986
1-3	-0.51	(-9.75, 8.73)	0.913
>3	-2.74	(-9.35, 3.88)	0.418
Overall	-1.32	(-5.51, 2.87)	0.536
Drinks Per Day (non-suppressed viral load)			
Days per Week			
<1	-1.22	(-7.92, 5.49)	0.722
1-3	0.05	(-8.30, 8.20)	0.991
>3	-1.45	(-8.07, 5.18)	0.669
Overall	-1.14	(-5.23, 2.94)	0.583
Baseline CD4 (cells/mm ³)			
200	Reference	NA	NA
201-350	188.24	(162.76, 213.73)	<0.001
351-500	319.02	(280.60, 357.45)	<0.001
>500	434.12	(380.75, 487.48)	<0.001
Baseline HIV-1 RNA (copies/ml)			
<10,000	Reference	NA	NA
10,000-99,999	17.80	(-14.97, 50.58)	0.287
>99,999	10.13	(-23.25, 43.51)	0.552

* Time from ART initiation included in the model as a natural spline with four degrees of freedom

** Estimate reflects CD4 cell count compared to referent.

*** Relationship between each additional drink per drinking day and CD4 cell count post ART initiation, overall and stratified by weekly frequency of alcohol use.

Table 3

Linear mixed effects model among females * examining alcohol consumption and CD4 response to therapy.

Variable	Estimate **	95% CI	P-Value
Age	1.55	(0.14, 2.97)	0.032
NNRTI	27.34	(2.74, 51.94)	0.029
Cocaine	6.56	(−26.12, 39.23)	0.694
Race **			
White	Reference	NA	NA
African American	−4.75	(−46.34, 36.84)	0.823
Hispanic	NA	NA	NA
Other/Unknown	76.02	(−98.14, 250.17)	0.392
Drinks Per Day (suppressed viral load) ***			
Days per Week			
<1	4.10	(−7.28, 15.49)	0.480
1-3	1.55	(−7.37, 10.47)	0.734
>3	2.69	(−10.28, 15.66)	0.685
Overall	0.97	(−4.90, 6.83)	0.747
Drinks Per Day (non-suppressed viral load)			
Days per Week			
<1	−7.70	(−18.25, 2.86)	0.153
1-3	−3.65	(−12.37, 5.07)	0.412
>3	2.05	(−8.43, 12.53)	0.701
Overall	−2.01	(−7.66, 3.64)	0.485
Baseline CD4 (cells/mm ³)			
200	Reference	NA	NA
201-350	188.90	(160.51, 217.29)	<0.001
351-500	289.54	(240.58, 338.50)	<0.001
>500	441.05	(377.63, 504.48)	<0.001
Baseline HIV-1 RNA (copies/ml)			
<10,000	Reference	NA	NA
10,000-99,999	50.38	(14.54, 86.21)	0.006
>99,999	47.28	(9.75, 84.81)	0.014

* Time from ART initiation included in the model as a natural spline with four degrees of freedom

** Estimate reflects CD4 cell count compared to referent.

*** Relationship between each additional drink per drinking day and CD4 cell count post ART initiation, overall and stratified by weekly frequency of alcohol use.

Table 4

Cox proportional hazards model estimating the relative hazard of achieving a CD4 cell increase of 100 cells/mm³, 150 cells/mm³ and 200 cells/mm³ for each additional drink per drinking day, stratified by weekly frequency of consumption and gender.

CD4 cell increase	Males		Females	
	HR	95% CI	HR	95% CI
Increase of 100 CD4 cells/mm ³				
< 1 day per week	1.01	(0.96, 1.07)	0.98	(0.87, 1.10)
1-3 days per week	0.98	(0.90, 1.07)	1.05	(0.96, 1.14)
> 3 days per week	0.96	(0.90, 1.03)	0.93	(0.81, 1.08)
Increase of 150 CD4 cells/mm ³				
< 1 day per week	1.00	(0.94, 1.07)	0.98	(0.87, 1.11)
1-3 days per week	1.00	(0.91, 1.09)	1.01	(0.93, 1.09)
> 3 days per week	0.97	(0.90, 1.04)	0.97	(0.87, 1.09)
Increase of 200 CD4 cells/mm ³				
< 1 day per week	1.03	(0.96, 1.10)	0.94	(0.81, 1.08)
1-3 days per week	1.02	(0.92, 1.13)	1.03	(0.96, 1.11)
> 3 days per week	0.95	(0.86, 1.04)	1.02	(0.91, 1.14)