Title
Untreated HIV Infection Is Associated With Higher Blood Alcohol Levels

Permalink
https://escholarship.org/uc/item/0qb1s34m

Journal
JAIDS Journal of Acquired Immune Deficiency Syndromes, 60(3)

ISSN
1525-4135

Authors
McCance-Katz, Elinore F
Lum, Paula J
Beatty, George
et al.

Publication Date
2012-07-01

DOI
10.1097/qai.0b013e318256625f

Peer reviewed

Untreated HIV Infection is Associated with Higher Blood Alcohol Levels

Elinore F. McCance-Katz, MD, PhD[1], **Paula J. Lum, MD, MPH**[2], **George Beatty, MD, MPH**[2], **Valerie A. Gruber, PhD**[1], **Marion Peters, MD**[3], and **Petrie M. Rainey, MD, PhD**[3]

[1]Addiction Medicine Research, Department of Psychiatry University of California San Francisco, San Francisco, CA

[2]Positive Health Program, Department of Medicine University of California San Francisco, San Francisco, CA

[3]Division of Gastroenterology University of California San Francisco, San Francisco, CA

[4]University of Washington, Department of Laboratory Medicine, Seattle WA

Abstract

Alcohol abuse has been associated with HIV/AIDS progression, but the effects of HIV infection and treatment on alcohol exposure have not been explored to date. This pilot study examines the relationship of untreated HIV infection to blood alcohol concentrations (BAC) relative to BAC following initiation of antiretroviral therapy (ART).

Methods—Fifteen volunteers with untreated HIV/AIDS participated in two sets of alcohol or alcohol placebo administration studies prior to and following initiation of ART. Oral alcohol (1 g/kg) or alcohol placebo was administered, participants were followed for pharmacokinetics, subjective responses, and cognitive effects over 8 hours. Following initial alcohol studies, the ART regimen selected by participant clinicians was instituted. Observed ART dosing took place for at least 2 weeks. Participants then returned for a second set of alcohol/placebo administration studies while on ART.

Results—Participants had significantly higher BAC (p<0.001) prior to ART than following ART administration. Alcohol AUC was significantly higher in untreated HIV disease (p=0.011) with significantly higher Cmax (p=0.015) and Cmin (p=0.05). The elimination rate was not different between pre- and post-ART conditions. Despite declines in BAC following ART initiation, no differences in subjective responses were observed with alcohol administration.

Conclusions—Untreated HIV infection is associated with risk for higher BAC than that observed following ART. These findings indicate that patients with untreated HIV disease who ingest alcohol are at greater risk for alcohol associated adverse events and toxicities and

Corresponding Author: Elinore F. McCance-Katz, MD, PhD San Francisco General Hospital Department of Psychiatry 1001 Potrero Ave., Suite 7M Wd 93 San Francisco, CA 94110 Tel: 415-206-4010 Fax: 415-206-5569 elinore.mccance-katz@ucsf.edu.

underscores the need for simultaneous treatment of alcohol use disorders and HIV in patients with co-occurring conditions.

Keywords

alcohol; HIV; drug interactions

Introduction

Alcohol and drug abuse have been strongly linked to the HIV/AIDS epidemic (1). The Centers for Disease Control (CDC) estimates that approximately 36% of HIV/AIDS cases are attributable to high risk behaviors associated with drug and alcohol abuse (2). Intoxication and withdrawal states are associated with poor judgment and impulsive behaviors that often include unprotected sex and trading sex for drugs which may increase risk for HIV transmission.

Recent studies have reported on the association between progression of HIV disease and alcohol abuse (3–5). These studies indicate the need to screen for and treat co-occurring alcohol misuse, abuse, and dependence in HIV-infected individuals. However, the effect of HIV infection on alcohol metabolism and alcohol-associated responses in humans has not been explored. If HIV were to negatively alter effects of alcohol in humans, this could have significant implications for alcohol-associated toxicities, as well as for risk of transmission of the virus and individual responses to HIV disease treatment.

In this study, we undertook a randomized, double-blind, placebo-controlled, within-subjects trial of alcohol or placebo alcohol administration in volunteers with untreated HIV disease, but who were eligible for and willing to start antiretroviral therapy (ART). This study was part of a larger, ongoing study examining drug interactions between alcohol and antiretroviral medications with significant effects on cytochrome P450 (CYP) 3A4. ART included regimens that contained either ritonavir (a CYP3A4 inhibitor) (6) or efavirenz (a CYP 3A4 inducer) (7). Alcohol is known to have a metabolic pathway that includes CYP 3A4 (8); thus the effects of ART on CYP 3A4 could potentially alter the pharmacokinetic profile of alcohol. We report here on findings of the effect of HIV infection prior to and following initiation and stabilization on ART on alcohol pharmacokinetics, subjective and cardiovascular responses.

Methods

Participants

Fifteen volunteers with untreated HIV disease participated in a study which was reviewed and approved by the Institutional Review Board at the University of California, San Francisco (UCSF). The study is registered at ClinicalTrials.gov (NCT00879047). One participant was ART naïve. The remaining fourteen participants had been previously treated with ART, but had discontinued therapy for reasons unrelated to the current study and had been off ART for at least one month prior to enrollment. Participants were referred to the study by their HIV primary care providers or self-referred after seeing IRB-approved flyers in the clinic. Participants gave voluntary, written, informed consent to participate in a study of alcohol or alcohol placebo administration before and after initiation of ART.

All participants were over age 21, had a confirmed diagnosis of HIV disease, 14 of 15 had at least one previous course of ART, a BMI <30, and no current substance use disorder that, in the view of the study team, would interfere with the ability to undertake the study or would require immediate treatment. Further, participants had liver test results that were < 3 times

the upper limit of the normal range, hemoglobin concentration > 10 mg/dL, and no other acute medical illnesses requiring clinical treatment, as determined by medical history and physical examination prior to participation. Subjects could be taking concomitant medications for co-occurring medical disorders if those medications had no known significant effect on CYP 3A4 or 2E1 activity, either as strong inducers or inhibitors.

Study Design

The study design was within-subjects and participants were randomly assigned in a double-blind fashion to receive either alcohol at a dose of 1 g/kg dissolved in a total volume of 16 ounces of an orange-flavored drink or an alcohol placebo where alcohol was sprayed at the surface of the drink, but no other alcohol was contained in the drink. The dose of alcohol administered was one that had been calculated and demonstrated to produce peak blood alcohol concentrations of approximately 100 mg/dL in healthy subjects (9, 10). The study sessions took place at the UCSF Clinical Research Center (CRC) at San Francisco General Hospital. Participants were administered alcohol or placebo in random order and monitored for eight hours using pre-determined study procedures on each of two consecutive days. Upon completion of the first set of study sessions (prior to ART initiation), participants were discharged from the CRC inpatient unit to be followed in the Addiction Medicine Research Clinic where the ART regimen prescribed by their clinician was initiated. Observed ART dosing occurred at the clinic on weekdays. On weekends, participants took their ART at home, but called in each day to report medication ingestion. If they did not call in the morning, they received a reminder call from study staff to assist the participant with medication adherence. Following at least 2 weeks of ART administration in this manner, participants were admitted a second time to the CRC where two study sessions were undertaken that included random assignment to alcohol or placebo alcohol with ART administration. Each study session occurred over 24 hours. Upon completion of the second set of alcohol or placebo administration with ART study sessions, participants were discharged to continue regular care with their HIV primary care providers.

Study Sessions

Participants were oriented to study procedures one day prior to the first set of alcohol administration sessions. On alcohol administration days, they received a standardized breakfast approximately 1.5 hours prior to alcohol or placebo administration. Study sessions began in the morning, with baseline physiological and subjective assessments at −60 and −15 minutes before alcohol administration. For the second set of alcohol or alcohol placebo administration sessions, ART was administered immediately following ingestion of the alcohol drink. Blood sampling (by means of an intravenous catheter placed in an arm vein) occurred at baseline prior to alcohol administration and over the next 8 hours at time points of 15, 30, 60, 90, 120, 180, 240, 300, 360, 420 and 480 minutes. Cardiovascular measurements, including blood pressure and heart rate, were taken at baseline and prior to collection of each blood sample. Electrocardiograms were performed at baseline and at 120 minutes following alcohol administration. A series of measures designed to assess subjective drug responses were administered. Visual analog scales consisted of lines anchored at 0 mm= minimal and 100 mm= maximal and measured for "high/intoxicated", "sleepy/tired", "feel good/happy", "sad/depressed", "nervous/anxious", "paranoid, scared, suspicious", "liking for alcohol", and a visual analog to examine the issue of craving, using the phrase "I want alcohol".

Alcohol Assay

Alcohol concentrations were determined by separation of plasma from heparinized blood samples and measurement of alcohol concentrations in plasma samples using gas

chromatography with flame ionization detection. Isopropanol was used as the internal standard.

Pharmacokinetics Analysis

Alcohol pharmacokinetics were calculated following oral administration alone, and again following stabilization on ART. Area under the 8 hour concentration-time curve (AUC_{0-8}) was calculated using the trapezoidal rule. Maximum plasma concentration (Cmax), time of Cmax (Tmax), and minimum plasma concentration (Cmin), were determined directly by inspection from the concentration-time curve. The elimination rate was determined from the slope of the linear portion of the descending arm of the concentration-time curve. All pharmacokinetic parameters were summarized and displayed by treatment period.

Statistical Analysis

Student's paired t-test was used to test the significance of the differences in pharmacokinetic parameters for alcohol alone and following ART stabilization (within-subject analyses). The Wilcoxon test was used for the within-subject comparison of the values of Tmax. Cardiovascular and subjective responses were compared using repeated measures ANOVA. Comparisons of subject characteristics were made by single factor ANOVA. Because of non-normality of the data for HIV viral load, the non-parametric Wilcoxon signed-rank test, which is not affected by lack of normality, was applied to analyze differences in HIV viral load at baseline and post-study. A difference was considered statistically significant if the p value was 0.05 (two-tailed).

Results

All participants in this study were HIV-infected and 14 of 15 had previous experience with ART, but had previously stopped their prescribed ART regimens. Several participants met diagnostic criteria for substance use disorders, but none met current substance dependence criteria for alcohol or drugs, with the exception of nicotine dependence (n= 1) (Table 1). Although 3 participants had Hepatitis C (HCV) infection confirmed by antibody and RNA testing, no participant had thrombocytopenia or baseline liver test results that exceeded three times the upper limit of normal. Participants with HCV had no more than mild liver fibrosis, as measured by the AST to platelet ratio index (11). An index of < 0.5 was required for participation in this study. Participants were roughly equally divided between those whose HIV clinicians prescribed ritonavir-boosted protease inhibitor-containing regimens or efavirenz-containing regimens (Table 1).

Peak BAC prior to initiation of ART was 131(6.0) mg/dL [mean (SE)], which declined to a peak BAC of 116 (6.2) mg/dL (p=0.015) (Figure 1, Table 2) after 2–3 weeks of observed ART administration. The observed differences in BAC ranged from 10–15% lower once participants were on ART. Pharmacokinetics of alcohol prior to and following ART also showed significant differences in area under the curve (AUC_{0-8}) (p=0.011) and Cmin (p= 0.05). No significant difference was observed in alcohol elimination rate prior to or following stabilization on ART (Table 2). Differences in post-ART BAC were not different by class of antiretroviral medication (either ritonavir- or efavirenz-containing ART) (Figure 2).

Measures of HIV control (viral load and CD4) were collected at baseline and within 15 weeks of study completion with 7 of 15 having follow-up measures collected in 0–7 days after completing the study. Decrease in viral load from baseline to post-study was statistically significant (Table 1). No significant changes in CD4 were observed (Table 1).

Alcohol administration was associated with significant increases in "High/Intoxication" over that of placebo administration both prior to and following ART (p<0.0001) (Figure 3). Although BACs were significantly lower while on ART, no statistically significant changes in perception of alcohol intoxication were reported by study participants. Greater "High/Intoxication" was reported when participants were on ART, particularly at later time points (3–6 h post alcohol administration), but this difference did not reach statistical significance (p=0.23) (Figure 3). Examination of "High/Intoxicated" data by ART regimen is shown in Figure 4. Efavirenz-containing regimens were associated with greater ratings of "High/Intoxicated" as compared to "High/Intoxicated" ratings for those receiving ritonavir-containing regimens, but these differences did not reach statistical significance. No significant differences in any other subjective responses were observed.

Cardiovascular responses were monitored prior to and following alcohol or placebo administration. Significant differences were observed by study condition (p<0.0001) (Figure 5). Relative to placebo alcohol administration, statistically significant increases in heart rate were observed following alcohol administration both prior to (p<0.0001) and following ART (p=0.02), but there was no significant difference in heart rate following alcohol administration with or without ART treatment (Figure 5). No significant changes in systolic or diastolic blood pressure were observed under any of the study conditions. Electrocardiograms were obtained prior to and 2 hours following alcohol administration. All participants were found to have PR, QRS and QTc intervals within normal limits at baseline. There were no significant changes in electrical activity of the heart under these study conditions (data not shown).

Discussion

This is the first study, to our knowledge, that demonstrates a significant difference in BAC in individuals with HIV/AIDS prior to and following initiation and stabilization on ART. We detected a 10–15% decrease in BAC within subjects pre- versus post-ART with significantly higher alcohol AUC, Cmax, and Cmin. There were no significant differences in elimination rate or perception of intoxication. Efavirenz and ritonavir have very different effects on drug metabolic pathways, but had essentially the same effects on alcohol concentrations (Fig. 2), suggesting that these effects were the result of treating the HIV infection, rather than being direct pharmacokinetic drug interactions, although we note that drug-drug interaction studies between alcohol and either ritonavir or efavirenz-containing regimens continue at present. Further, we observed a significant decrease in HIV viral load following participant completion of this study.

Alcohol use in HIV disease occurs commonly (13, 14) with negative consequences to treatment adherence and more rapid HIV progression. Heavy alcohol users (described as alcohol use at least 3–4 times/week) receiving highly active antiretroviral therapy (ART) have been reported to be twice as likely to have CD4 counts less than 500 cells/mm^{3} and 4 times less likely to achieve virologic suppression on ART(15). In a study examining medication adherence in a sample of HIV-infected patients and a history of alcohol abuse, alcohol consumption was the single most significant predictor of adherence, with abstinence from alcohol being associated with better adherence (3). Another study reported similar findings in a sample of 1711 individuals infected with HIV for more than 5 years. In this sample, 45% reported any alcohol use and 10% were hazardous users (described as use exceeding the NIAAA low risk limits of 3 drinks at a sitting/7 drinks weekly for women and 4 drinks at a sitting/14 drinks weekly for men). Hazardous alcohol use was associated with low utilization of ART, decreased adherence, and poor viral response (4). Alcohol consumption in those with HIV disease has also been associated with deleterious effects on the brain (16). Heavy alcohol use and HIV infection appear to have additive adverse effects

on neuropsychological function, which may contribute to poor judgment and high risk behaviors that portend a poor clinical outcome in HIV disease (17). Alcohol abuse has been associated with frontal lobe dysfunction in persons with HIV/AIDS providing additional evidence for the role of alcohol in high risk behaviors associated with HIV disease progression and transmission (18). It is clear that alcohol use has deleterious effects on HIV progression and outcomes. What has not been demonstrated until the present study, is the potential effect of untreated HIV infection on BAC which could possibly exacerbate the development of alcohol toxicities.

Alcohol metabolism and the role of the gut in HIV pathogenesis offer hypotheses to explain the findings in this study. Alcohol is absorbed from GI tract into the bloodstream via simple diffusion. First pass metabolism of alcohol occurs mainly in the stomach and small intestine (19). Alcohol dehydrogenase (ADH) which mediates the first step of alcohol metabolism is present in the mucosa of the stomach and small intestine (20). The majority of alcohol metabolism occurs in the liver via cytosolic alcohol and aldehyde dehydrogenases. In heavy alcohol users, CYP 2E1 metabolizes alcohol and recently CYP 3A4 has been associated with alcohol metabolism (21). In the current study, we observed significantly higher BAC in those with untreated HIV disease relative to BAC with the same alcohol dose once these individuals were treated with either ritonavir- or efavirenz-containing ART. Since ~95% of alcohol elimination is by metabolism (22) the lack of any meaningful change in the alcohol elimination rate (22.4 (0.8) mg/dL-h versus 22.9 (1.0) mg/dL-h, $p = 0.64$; Table 2) suggests that there was no change in hepatic metabolism of alcohol in the systemic circulation.

The mean BAC in untreated patients was approximately 15% greater than in treated patients at all time points during the absorption phase (up to T_{max}), suggesting a consistent difference in absorption rate. However, T_{max} was not significantly different, suggesting that absorption was completed at approximately the same time. In contrast, the mean elimination rate was nearly identical before and after ART treatment, and the time needed for full elimination was longer in the untreated condition. One hypothesis consistent with our observations is decreased bioavailability of alcohol after ART treatment, perhaps resulting from increased first-pass metabolism in the gut wall during absorption. An increase in volume of distribution after ART could also explain the proportional lowering of mean concentrations at each time point, but would also be expected to result in a lower elimination rate, when expressed as mg/dL-h. However, because there was no difference in alcohol elimination rate in this study, the BAC differences detected in the present study are more likely the result of changes in first-pass metabolism in the gut. Recent studies have shown that HIV is associated with depletion of T cells in gut-associated lymphoid tissue (GALT), immune activation and inflammation, damage to the intestinal mucosa, and microbial translocation of gut bacteria that further exacerbates inflammatory responses. These responses appear to play a significant role in progression of HIV disease including co-occurring conditions such as HIV-associated cognitive impairment and dementia (23). HIV infects GALT producing T-cell depletion and immune activation that has been associated with damage to the gut lining from the time of early infection forward (24). Primate studies show that CD4 and regulatory T cells, responsible for suppression of activation and proliferation of effector lymphocytes, are rapidly depleted from the intestinal lamina propria in HIV infection (25). High levels of viral replication in GALT correlate with a decrease in gene expression for regulation of epithelial barrier maintenance, as well as other digestive and metabolic functions. Conversely, these changes have also been correlated with a significant increase in the transcription of immune activation, inflammation, and apoptosis-associated genes (26). This model has been postulated to be responsible for lentiviral disease progression (27). Impairment of the intestinal barrier is readily observed in those with untreated HIV and the intestinal mucosa recovers in those placed on a suppressive ART, as

demonstrated in those with untreated HIV by detection in peripheral blood of ingested sugars that would normally not cross the intestinal epithelium (28).

The present study's findings support other investigations indicating that HIV infection is associated with damage to intestinal epithelium. HIV replication in GALT may cause a decrease in alcohol metabolism in the gastrointestinal tract and, therefore, greater alcohol absorption in those with untreated HIV disease. The best explanation for the results of this study is that damage to the gut lining resulting from HIV infection might result in less alcohol metabolism and greater alcohol absorption both as a result of physical injury to the intestinal epithelium and/or as a result of the loss of intestinal epithelial alcohol and aldehyde dehydrogenases which participate in alcohol metabolism. While the finding of a 10–15% increase in BAC over an 8 hour measurement period may not, in and of itself, be argued to be clinically significant, it is important to note that in this study we gave only one alcohol drink either before or after ART. The goal of this study was not to cause clinically significant events to occur, but only to inform as to whether alcohol exposure varied on or off ART. Those with HIV/AIDS who are hazardous drinkers would likely be at greater risk for alcohol associated toxicities when not receiving ART.

While the findings from this study implicate gut barrier function as important to BAC in HIV; it is also important to consider BAC in those with HIV and HCV as these infections commonly co-occur with an overall prevalence that is related to mode of HIV transmission. For example, in injection drug users with HIV the prevalence of HCV is as high as 89% while those infected with HIV through heterosexual contact have been reported to have lower, but still substantial rates of HCV coinfection at 18% (29). In this study, we enrolled 3 of 15 individuals with both HIV/HCV and all had mild liver disease based on an AST/platelet ratio index (APRI) score of <2.0 which was used as a cutoff for participation. However, the peak BAC for those with HIV/HCV not receiving ART was 147 (10.7) mg/dL and in those with untreated HIV alone was 127 (13.4) mg/dL although this difference did not reach statistical significance. We also observed that in those with comorbid HIV/HCV who started ART peak BAC declined to 132 (19.9) mg/dL. These findings may indicate that combined HIV/HCV presents an even greater risk for higher BAC and alcohol-related toxicities than does untreated HIV infection alone, but as with HIV infection alone, ART appears to be associated with reductions in BAC. We plan to continue to enroll those with HIV/HCV in order to obtain a sample size that will allow further exploration of the effect of combined HIV/HCV infection on alcohol exposure as the project progresses.

A secondary finding of this study was that while BACs were significantly reduced by 10–15% in study participants following treatment with ART, no significant changes in perception of intoxication were reported. There are several possibilities for this finding. First, participants may have experienced a pharmacodynamic drug interaction between alcohol and antiretroviral medications administered. Efavirenz has a substantial rate of neuropsychiatric side effects (30) and many patients report feelings similar to intoxication (dizziness, altered mood) with administration of this medication. Were that to be the case, subjective perception of intoxication due to efavirenz could obscure the effects of reduction in alcohol exposure. We examined this question and found non-significantly greater ratings of "High/Intoxicated" in the efavirenz-treated group relative to the ritonavir-treated group, as shown in Figure 4. This question is currently under study by our research group and will be explored in a larger sample size in which we specifically examine the presence or absence of drug-drug interactions between alcohol and ART. Second, it might be possible that participants, who reported varying levels of alcohol consumption at the time of study entry, might have had some tolerance to alcohol effects such that the observed reductions in BAC with ART, while statistically significant, might not be discernible by alcohol-tolerant study participants. In this study, most participants reported modest alcohol use, although 7

participants reported alcohol use in excess of NIAAA established levels for safe drinking (at-risk drinking) (31), and one participant met diagnostic criteria for alcohol abuse. The presence of alcohol dependence was exclusionary; therefore we believe this possibility less likely. A third possibility is that the overall difference of 10–15% higher BAC in untreated HIV relative to BAC following ART was not sufficient to produce significant differences in "High/Intoxicated" subjective responses.

The results of this study underscore the need to screen for and assess the extent of alcohol use in persons with HIV/AIDS. While the standard of care for HIV-infected patients is ART, the clinical reality is that many patients for whom ART is indicated do not consistently receive it. The findings of this study suggest that patients with untreated HIV infection obtain higher BACs when exposed to alcohol and therefore may be more susceptible to the toxicities of alcohol. Higher BACs and the adverse neurocognitive effects of alcohol on decision making and behavior could in turn contribute to poor initiation of and adherence to effective HIV therapies. These events could lead to HIV disease progression, increased viral transmission, and increased HIV infections in the community.

There are several limitations to this study. The finding of higher BAC in untreated HIV disease was an unexpected finding from a study designed and powered to detect drug interactions between antiretroviral medications and alcohol. As such, larger studies are needed specifically designed to replicate this finding and to test mechanistic hypotheses. We were not able to undertake the studies necessary to determine whether the barrier function of the gut was impaired in study participants with untreated HIV or, if present, whether this was corrected with ART, although we did observe reductions in HIV viral load with ART even in as little as two weeks. However, HIV viral load is only a surrogate marker providing some evidence of rapid response to the HIV infection as a result of effective ART and does not prove the mechanism for the observed differences in BAC. Therefore, the current results should be considered preliminary. Further research is needed to determine whether differences in BAC or responses to alcohol administration might be related to immune function or activation in those with untreated HIV infection as compared to immune function with ART following an adequate period of follow-up (e.g.: 3–6 months) sufficient to have reached viral nadir. In addition, measures of the integrity of intestinal epithelium including markers of microbial translocation, lipopolysaccharide, and markers of intestinal epithelial damage should be followed to try to illuminate aspects of the underlying mechanism of findings from this study.

In summary, we present results from a pilot study showing evidence for significantly higher blood alcohol levels in individuals with untreated HIV/AIDS which can be reduced with ART. While etiology may be multifactorial, these results could be related to inflammatory responses to untreated HIV infection in GALT which might produce injury to the epithelium of the gastrointestinal tract potentially associated with higher BAC, greater likelihood of alcohol-associated toxicities, and a more severe course of HIV disease. These study results support the rationale for the early detection and treatment of hazardous alcohol use and alcohol use disorders, as well as earlier or universal ART in untreated HIV-infected populations (32).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. National Institute on Drug Abuse. HIV/AIDS, *NIH Pub.* No. 06-5760. 2006.

2. Centers for Disease Control and Prevention. Drug-Associated HIV Transmission Continues in the United States. Available at: http://www.cdc.gov/hiv/resources/factsheets/idu.htm

3. Samet JH, Horton NJ, Meli S, et al. Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems. Alcohol Clin Exp Res. 2004; 28:572–577. [PubMed: 15100608]

4. Chander G, Lau B, Moore RD. Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. J Acquir Immune Defic Syndr. 2006; 43:411–417. [PubMed: 17099312]

5. Braithwaite RS, Conigliaro J, Roberts MS, Schecter S, et al. Estimating the impact of alcohol consumption on survival for HIV + individuals. AIDS Care. 2007; 19:459–466. [PubMed: 17453583]

6. Kumar GN, Rodrigues AD, Buko AM, et al. Cytochrome P450-mediated metabolism of the HIV-1 protease inhibitor ritonavir (ABT-538) in human liver microsomes. J Pharm Exp Ther. 1996; 277:423–431.

7. Mouly S, Lown KS, Kornhauser D, et al. Hepatic but not intestinal CYP3A4 displays dose-dependent induction by efavirenz in humans. Clin Pharmacol Ther. 2002; 72:1–9. [PubMed: 12151999]

8. Lieber CS. The discovery of the microsomal ethanol oxidizing system and its physiologic and pathologic role. Drug Metabolism Rev. 2004; 36:511–529.

9. McCance-Katz EF, Price LH, McDougle CJ, et al. Concurrent cocaine-ethanol ingestion in humans: pharmacology, physiology, behavior and the role of cocaethylene. Psychopharmacology. 1993; 111:39–46. [PubMed: 7870932]

10. McCance-Katz EF, Kosten TR, Jatlow P. Concurrent use of cocaine and alcohol is more potent and potentially more toxic than use of either drug alone—a multiple dose study. Biological Psychiatry. 1998; 44:250–259. [PubMed: 9715356]

11. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003; 38(2):518–26. [PubMed: 12883497]

12. US Food and Drug Administration. Draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis and Implications for Dosing and Labeling. 2006.

13. Baum MK, Rafie C, Lai S, et al. Alcohol use accelerates HIV disease progression. AIDS Res Hum Retroviruses. 2010; 26(5):511–8. [PubMed: 20455765]

14. Hahn JA, Samet JH. Alcohol and HIV disease progression: weighing the evidence. Curr HIV/AIDS Rep. 2010; 7(4):226–33. [PubMed: 20814765]

15. Miguez MJ, Shor-Posner G, Morales G, et al. HIV treatment in drug abusers: impact of alcohol use. Addict Biol. 2003; 8:33–37. [PubMed: 12745413]

16. Pfefferbaum A, Rosenbloom M, Sullivan EV. Alcoholism and AIDS: magnetic resonance imaging approaches for detecting interactive neuropathology. Alcohol Clin Exp Res. 2002; 26:1031–1046. [PubMed: 12170114]

17. Rothlind JC, Greenfield TM, Bruce AV, et al. Heavy alcohol consumption in individuals with HIV infection: effects on neuropsychological performance. J Int Neuropsychol Soc. 2005; 11:70–83. [PubMed: 15686610]

18. Fein G, Biggins CA, MacKay S. Alcohol abuse and HIV infection have additive effects on frontal cortex function as measured by auditory evoked potential P3A latency. Biol Psychiatry. 1995; 37:183–195. [PubMed: 7727627]

19. Mezey, E. Effect of ethanol on intestinal morphology, metabolism and function. In: Seitz, HD.; Kommerell, B., editors. Alcohol Related Diseases in Gastroenterology. Springer-Verlag; Berlin: 1985. p. 342-360.

20. Bode C, Bode JC. Alcohol's role in gastrointestinal tract disorders. Alcohol Health and Research World. 1997; 21:76–83. [PubMed: 15706765]

21. Lieber CS. The discovery of the microsomal ethanol oxidizing system and its physiologic and pathologic role. Drug Metabolism Rev. 2004; 36:511–529.

22. Baselt, RC. Disposition of Toxic Drugs and Chemicals in Man. 7th ed.. Biomedical Publications; Foster City, CA: 2004.

23. Ancuta P, Kamat A, Kunstman KJ, et al. Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. PLoS ONE. 2008; 3(6):e2516. http://www.plosone.org/article/info:doi/10.1371/journal.pone.0002516. [PubMed: 18575590]

24. Nilsson J, Kinloch-de-Loes S, Granath A, Sonnerborg A, Goh L, Andersson J. Early immune activation in gut-associated and peripheral lymphoid tissue during acute HIV infection. AIDS. 2007; 21:565–574. [PubMed: 17314518]

25. Chase AJ, Sedaghat AR, German JR, et al. Severe depletion of CD4+ CD25+ regulatory T cells from the intestinal lamina propria but not peripheral blood or lymph nodes during acute simian immunodeficiency virus infection. J Virology. 2007; 8:12748–12757. [PubMed: 17855517]

26. Sankaran S, George MD, Reeay E, et al. Rapid onset of intestinal epithelial barrier dysfunction in primary human immunodeficiency virus infection is driven by an imbalance between immune response and mucosal repair and regeneration. J Virology. 2008; 82:538–545. [PubMed: 17959677]

27. Brenchley JM, Price DA, Douck DC. HIV disease: fallout from a mucosal catastrophe. Nat Immunol. 2006; 7:235–239. [PubMed: 16482171]

28. Epple HJ, Schneider T, Troeger H, et al. Impairment of the intestinal barrier is evident in untreated but absent in suppressively treated HIV-infected patients. Gut. 2009; 58:220–227. [PubMed: 18936106]

29. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. JAMA. 2002; 288(2):199–206. [PubMed: 12095384]

30. Kenedi CA, Goforth HW. A systematic review of the psychiatric side effects of efavirenz. AIDS Behav. 2011; 15(8):1803–1818. [PubMed: 21484283]

31. U.S. Department of Health & Human Services. Helping patients who drink too much: a clinician's guide. National Institute of Health and National Institute on Alcohol Abuse and Alcoholism. 2005. Available at: http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf

32. Dieffenbach CW, Fauci AS. Thirty years of HIV and AIDS: future challenges and opportunities. Ann Int Med. 2011; 154(11):766–771. [PubMed: 21628350]
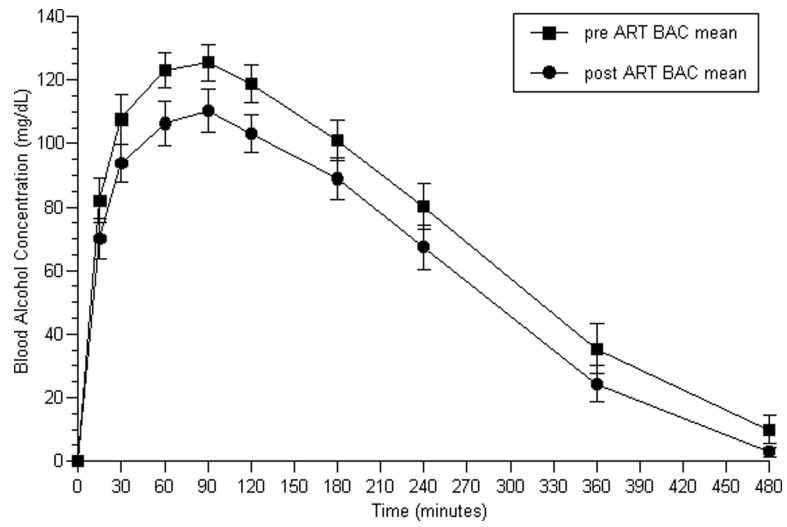
Figure 1.
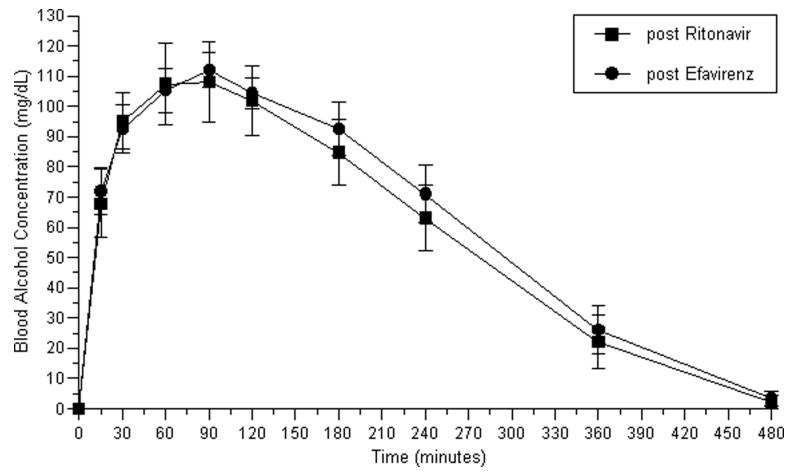Blood Alcohol Concentrations Before and After Initiation of ART

Figure 2.
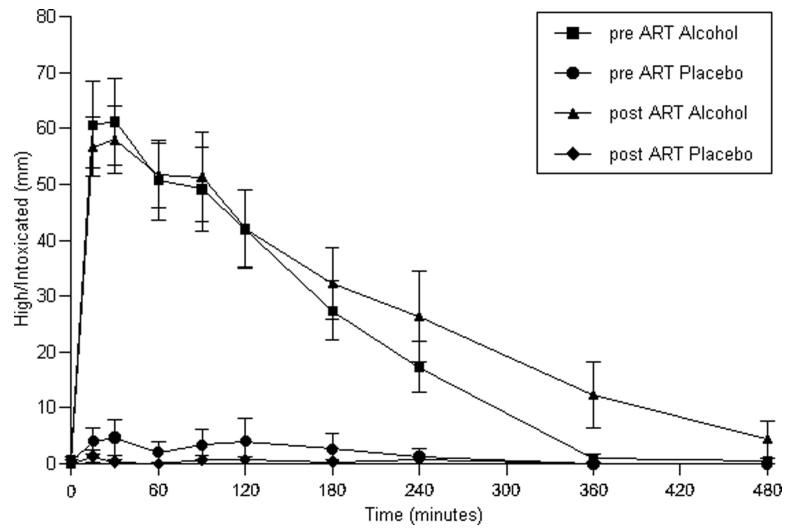Effect of Efavirenz or Ritonavir-Containing ART regimens on BAC

Figure 3.
High/Intoxicated

Table 1

Participant demographics and characteristics

	n=15	
Age (yrs)	44.9 (7.9)[1]	
Female	2 [13.3%][2]	
Race:		
African-American	4 [26.7%]	
Caucasian	8 [53.3%]	
Hispanic	3 [20.0%]	
Current Substance Use Disorders:		
Cocaine Abuse	3 [20.0%]	
Methamphetamine Abuse	1 [6.7%]	
Alcohol Abuse	1 [6.7%]	
Nicotine Dependence	1 [6.7%]	
Current Alcohol Use (drinks/week)	5.7 (6.6)	
Current Nicotine Use (cigarettes/day)	3.15 (1.4)	
Laboratory Values:	Baseline	Post-Study HIV Disease Measures
ALT (U/L) at pre-ARV	38 (30.1)	
AST (U/L) at pre-ARV	39 (22.7)	(0–13 wks)
HIV Viral Load (copies/mL) Mean	57,530 (28,460)	564 (330) p=0.00003
Median	25134	81
Range	<40–394,578	<40–4985
CD4 Count (mm^3) Mean	329 (187)	323 (40)
Median	337	294
Range	119–838	106–622
Efavirenz-containing HAART regimen	8 [53.3%]	
Ritonavir-containing HAART regimen	7 [46.6%]	
Hepatitis B (lifetime)	6 [40.0%]	
Hepatitis C	3 [20.0%]	
Other Diagnoses	Chronic Pain Peripheral Neuropathy Hypertension Hyperlipidemia	

[1] mean (SE)

[2] number [percent of sample]

Table 2

Alcohol pharmacokinetics prior to and following initiation of ART

Pharmaco kinetic Parameter	Pre-ART (n = 15)	With ART (n = 15)	p value
AUC_{0-8} (mg-h/dL)	577 (46)	480 (39)	0.011
C_{max} (ng/ml)	131 (6.0)	116 (6.2)	0.015
T_{max} (h)	1.5 (0.5–2.0)	1.5 (0.25–3.0)	n.s.
C_8	9.9 (4.5)	2.9 (1.6)	0.05
Elimination rate (mg/dL-h)	22.4 (0.8)	22.9 (1.0)	0.64

Note: Values are the mean (standard error of the mean), except that T_{max} is given as median (range). The paired t-test was used to determine p-values for all parameters except T_{max}, where the Wilcoxon test was used.