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Title:	Acute Neural and Immune Effects of Alcohol in People Living with HIV Infection
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Study Aims:

Aim 1. To investigate acute effects of alcohol on plasma biomarkers of microbial translocation and immune activation in PLWH (people living with HIV) and healthy controls using a controlled alcohol administration paradigm.
Aim 2. To examine acute effects of alcohol on MRI correlates of neuroinflammation in PLWH and controls.
Exploratory Aim 3: In the alcohol condition, PLWH will report higher subjective intoxication and exhibit greater alcohol-induced cognitive deficits than control participants.

Study Design and Procedures:

- **Design and Overview:** This study uses a between-subjects, placebo-controlled 2x2 design to test the acute effects of moderate alcohol consumption on brain, behavior, and immune function in people living with HIV and non-infected control participants. Participants in two groups (HIV seropositive, HIV seronegative) are randomized to receive either alcohol or placebo in this 2x2 study design. The study involves screening, a baseline assessment (Visit 1), and one experimental session (Visit 2). Participants are compensated for their time and effort involved in participation.

- **Screening:** Potential participants will be identified and recruited through collaboration with The Miriam Hospital Immunology Center or through online advertising. Potential participants will provide consent for screening. Those found to be eligible on a preliminary basis will be scheduled to attend Visit 1 at Brown University's School of Public Health.

- **Visit 1:** The research team will obtain informed consent for participation. In-depth assessment will determine eligibility to continue in the experimental portion of the study (Visit 2). Demographic information and social history will be collected. Participants will be interviewed about medical history, mental health, substance use, and other health-related behaviors. Breath alcohol concentration and other non-invasive physiological measures (e.g., blood pressure) will be collected. Urine samples will be collected and tested for drug metabolites and for pregnancy hormones (for women). Participants who meet all study criteria will be randomized to beverage condition and scheduled to return for Visit 2. Within groups formed on HIV status, participants will be randomly assigned to receive alcohol (.60 g/kg) or placebo beverage.

- **Visit 2:** Participants will be instructed to fast overnight prior to Visit 2. Prior to experimental procedures, participants will complete measures of recent substance use, provide a breath alcohol sample and a urine sample for pregnancy testing (for women), and consume a standard snack. Blood samples will be taken prior to beverage administration and hourly for 3 hours afterward, to be used for testing primary biomarker outcomes. Participants will receive a beverage containing alcohol (.60 g/kg) or placebo. The alcohol dose is calculated to produce a peak blood alcohol level of .07 g/dl, which is considered a moderate level. Participants will be blinded to beverage contents. [Single-blinded administration (i.e., participant only) is permissible when double-blinded administration (i.e., participant and researcher) is not feasible due to COVID restrictions on laboratory personnel density.] Following beverage consumption, participants will complete tests of cognitive performance and subjective alcohol effects. When blood sample collection is finished, participants will be given a meal and non-alcoholic beverages. Then participants will complete a 1-hour MRI scan of the brain at Brown's MRI Research Facility. Participants will be released after data collection is complete and breath alcohol concentration is ≤ .039%. Participants will not be permitted to drive to or from Visit 2 and will be provided with transportation or reimbursement for transportation, according to their preferences.

Potential Research Risks and Risk Mitigation:

<u>Potential Risks:</u>

1. General risks of mild-to-moderate alcohol intoxication. According to NIAAA guidelines,[14] the target BAL of .07 g/dL typically is associated with mild-to-moderate impairment in orientation, speech, cognition, and coordination.
2. Risks of alcohol consumption in PLWH.
3. Risks of MRI scan.
4. Psychological discomfort when answering questions about alcohol consumption habits, drug use, or psychiatric symptoms.
5. Breach of confidentiality, including personal information about alcohol/drug use and HIV status.
6. Physical risks associated with blood draw procedures: exposure to blood-borne viruses, infection at sampling site, pain or discomfort, hematoma, excessive bleeding, nerve damage, vasovagal reaction, or fainting.
7. Risk of undue influence from compensation received for participation.
8. Risk to a fetus from maternal alcohol consumption.
9. Risk of distress from experimental manipulation (i.e., placebo-controlled alcohol administration).

Protections against Risks:

1. General risks of mild-to-moderate alcohol intoxication: At the recruitment and screening stage, risks to participants will be minimized through careful screening and selection of individuals who have past-year experience with the study dose and who do not have medical or psychiatric conditions that would increase the likelihood of adverse reactions. During the beverage administration session, participants' breath alcohol concentration will be assessed using a handheld digital sensor at baseline and at half-hour intervals thereafter to ensure that levels follow the expected trajectory. Participants will be seated in a comfortable area where they can be monitored unobtrusively by research staff. To guard against injury, participants will be escorted to the restroom or during any other activity that involves ambulation. Participants will be monitored visually at regular intervals for signs of gross intoxication, including slurred speech, marked cognitive decline, or loss of psychomotor coordination. In the event of medical emergency, defined for the purpose of this study as breath alcohol >.15%, loss of consciousness, difficulty breathing, choking, chest pain, or severe disorientation, researchers will contact emergency medical services by calling 911. The PI or trained RA will be present or on call at all times when alcohol is administered. As part of the informed consent process, participants will be advised in plain language of the subjective and physiological effects that they may experience during the study. Once blood sample collection is complete, participants will be offered a standard meal and non-alcoholic beverages as refreshments. Participants will be instructed not to drive to experimental sessions, and any who do drive will be rescheduled for a later date. Participants will be provided with transportation to and from the experimental session at study expense. If participants choose to withdraw prior to study completion, they will be paid for their participation to that point, accompanied to a comfortable waiting area, and released once breath alcohol concentration ≤.039%. Transportation home will be provided at study expense regardless of study completion. A list of emergency personnel and contact phone numbers will be posted in the laboratory. In summary, participants who receive alcohol are likely to experience some alcohol-related impairment, and study procedures are designed to minimize any negative consequences of this impairment.

2. Risks of alcohol consumption in PLWH: As described above, Dr. Tashima will assess all participants for suitability for study participation. Potential concerns about acute alcohol effects in PLWH and alcohol-antiretroviral (ART) drug interactions are addressed below.

2A. Dose tolerability. Tolerability of the .60 g/kg alcohol dose is supported by several prior studies that have administered higher doses to PLWH without serious adverse events. One study administered an alcohol dose of 1.0 g/kg to 15 PLWH, resulting in peak BAL ≥ .11 g/dL.[15] Another administered 0.70 g/kg of alcohol to 24 PLWH to produce peak BAL around 0.05 g/dL.[16] A placebo-controlled trial with 141 HIV-infected men administered alcohol in a dose to effect peak BAL of .086; Dr. Monti (Mentor) was a collaborator on this study.[17] None of these studies reported serious adverse events in PLWH who were selected using criteria comparable to the current proposal. As specified in Eligibility Criteria, only individuals who report recent alcohol self-administration equal to the study dose will be eligible for participation, reducing the likelihood of adverse events.

2B. Risk of alcohol-antiretroviral drug interactions. Research on ART-alcohol interactions is limited. Current *NIH Guidelines for Antiretroviral Use in HIV-1-Infected Adults and Adolescents* do not state that moderate alcohol use by ART recipients is contraindicated.[5] Rather, research supports advising HIV patients to adhere to their prescribed ART regimens when choosing to drink alcohol.[18,19] One study found no evidence of alcohol-ART pharmacokinetic interaction, and co-administration of alcohol with ART did not significantly increase subjective intoxication or cognitive deficits.[15,20] In a primate model, Molina et al. (2014) found no evidence that chronic binge alcohol increased the toxicity or altered the effectiveness of tenofovir or emtricitabine.[18] Moreover, a prospective cohort study found that PLWH on ART who drank moderately did not exhibit more liver fibrosis than non-drinking PLWH, regardless of ART type. Under no circumstances will an individual's ART regimen be changed to allow participation. The PI will consult Dr. Karen Tashima (Collaborator), research publications, and *NIH Guidelines* on an ongoing basis for newly reported alcohol-ART interactions. In summary, alcohol-antiretroviral drug interactions are considered very unlikely.

3. MRI risks: MRI has no known side effects and does not involve radiation. However, there are several contraindications for MRI scan. The first is metallic materials/implants within the body, such as aneurysm clip, bullet or shrapnel fragment, ear implant, certain prosthetic devices, heart pacemaker, or artificial heart valve. Participants will be thoroughly screened to prevent admission of individuals with these contraindications to the MRI suite. The second contraindication is pregnancy, as risks to the fetus are unknown. Pregnancy tests will be administered to all female participants at the baseline assessment and again on the day of MRI scanning, prior to starting experimental procedures. Third, there is risk of subjective discomfort from being in a small space or from noise emitted by the scanner. Participants will be given a call button to hold during the MRI so that they can communicate distress to the MRI technician and research staff, and procedures can be discontinued if indicated. Participants will be required to wear earplugs to reduce exposure to noise from the scanner. Serious risks of MRI are not likely given these safety precautions, and the subjective discomforts that may occur (e.g., discomfort in an enclosed space) are likely to be small in magnitude and transient in nature.

4. Psychological discomfort associated with assessment: Participants will be advised during the informed consent process that they may choose not to answer any particular question, that their verbal and written responses are confidential, and that they are free to withdraw from the study at any time. Medical screening, questionnaire completion, and laboratory procedures will be performed in private rooms reserved for these purposes. Given these precautions, it is not likely that severe psychological distress will occur.

5. Loss of confidentiality: Several steps will be taken to protect against loss of confidentiality. All data will be collected and stored using technology that employs the industry standard for security. Data will be stored in de-identified, password-protected files on Brown University's secure servers. Participant data and samples will be identified using a unique, randomly generated ID code. Participants' personal identifying information will be kept in a separate location from their response data. At the conclusion of the study, the file that contains links of personal identifiers with unique study IDs will be destroyed by the study PI. The COBRE CLC Data Analyst and Data Systems Management Coordinator will collate and store data on the secure server, using appropriate measures for data protection. All data collected via computer will be stored on Brown University's encrypted, secure servers and accessed through password-protected computers only by primary research staff. Biological samples will be identified with the participant's study ID and will not be associated with personal identifying information or clinical medical records. With these precautions, loss of confidentiality is considered very unlikely; however, participants will be informed of this risk at the time they provide consent.

6. Risks from blood draw procedures: During the informed consent process, participants will be advised of the necessity of obtaining repeated blood samples during the experimental session. Screening will exclude individuals who report psychological discomfort caused by blood draw or the sight of blood, or who report history of adverse reaction to standard blood draw procedures. Collection will utilize an IV catheter set to avoid repeated needle sticks. The total volume of blood to be collected is modest. Blood draw procedures will follow World Health Organization guidelines for safe and well-tolerated procedures to minimize risk of infection or other complications.[8] The CLC Nurse Practitioner will collect the blood samples. Risk reduction strategies are to use sterile, single-use implements; surface disinfectant;

proper hand hygiene; application of 70% isopropyl alcohol to the blood draw site; minimal vein probing; application of pressure after drawing blood; an IV catheter set; and non-latex, vinyl gloves. Blood draw by a licensed professional using these risk reduction methods makes the occurrence of negative outcomes very unlikely.

7. Risk of undue influence from monetary compensation: This risk is low, as the total amount of compensation is modest. The hourly compensation rate for the study sessions translates to approximately $17-25/hour, which is consistent with rates offered by similar studies in the Brown University area. This rate is somewhat higher than the living wage (approximately $11/hr; livingwage.mit.edu) for Providence County, RI, to account for inconvenience and/or discomfort potentially associated with study procedures.

8. Risk to fetus from maternal alcohol consumption: Due to the harmful effects of alcohol on fetal development, all participating women will be required to take a pregnancy test at the beginning of every study session. Females will be excluded if they express unwillingness to use effective birth control throughout the study if sexually active with a male partner. Female subjects who test positive for pregnancy will be informed that they have had a positive test result and are not eligible to participate in the study. They will be informed that it is possible to have a false positive result and will be encouraged to follow up with a medical provider of their choosing. Subjects who are breastfeeding or who intend to become pregnant during the course of the study will be excluded. These precautions make it very unlikely that a fetus will be exposed to alcohol from maternal consumption in the course of this study.

9. Risk of distress from experimental manipulation: All participants will undergo debriefing upon completion of the blinded alcohol administration protocol using the attached Debriefing Form. Participants will be given the opportunity to ask questions about the experiment. Each participant will be reminded that his or her copy of the informed consent document contains contact information for the PI (Dr. Monnig) and Brown University IRB, and will be encouraged to contact these entities if concerns arise in the future.

Statistical Analysis Plan:

Aim 1. To investigate acute effects of alcohol on plasma biomarkers of microbial translocation and immune activation in PLWH and healthy controls using a controlled alcohol administration paradigm.

Aim 1 Analytic Plan: Linear mixed models will be used to analyze the effects of the factors of interest on plasma biomarkers. Models will include random effects for intercept and/or slope where indicated. Different covariance structures to be tested for best fit include unstructured, compound symmetric, and autoregressive.

Aim 2. To examine acute effects of alcohol on MRI correlates of neuroinflammation in PLWH and controls.

Aim 2 Analytic Plan: Analysis of variance (ANOVA) will test the main effect of beverage condition on MRS outcomes (Hypothesis 2A) and DWI (Hypothesis 2C) outcomes. Hypotheses 2B and 2D, predicting differential changes in MRS and DWI outcomes in PLWH in the alcohol condition, will be assessed in the interaction of beverage condition by HIV status.

Exploratory Aim 3: In the alcohol condition, PLWH will report higher subjective intoxication and exhibit greater alcohol-induced cognitive deficits than control participants.

Aim 3 Analytic Plan: ANOVA will be used to test main effects of HIV status, alcohol condition, and their interaction on cognitive performance and subjective intoxication.