Effects of Alcohol on SIV Levels within the CNS of Rhesus Macaques

Harrison Daste, James Prusak, Nedra Lacour, Angela M. Amedee

Department of Microbiology, Immunology and Parasitology, and the Comprehensive Alcohol Research Center, LSUHSC New Orleans

Introduction

- Human Immunodeficiency Virus (HIV) presents patients with clinical challenges. Combination antiretroviral therapy (cART) has increased the length of life in people living with HIV (PLWH); however, comorbidities still affect the quality of life in these patients.
- Despite treatment of the virus with cART, HIV persists in many tissue reservoirs, including the Central Nervous System (CNS). Approximately half of PLWH develop neurocognitive disorders.
- Alcohol use disorders (AUD) have been associated with failure to control viremia, neurocognitive impairment, and worse disease outcomes in PLWH.
- The rhesus macaque model used within this pilot study allows us to model the course of HIV infection, AUD, and use of cART, giving us insight into mechanisms that exacerbate co-morbidities and HIV disease progression.

Objectives

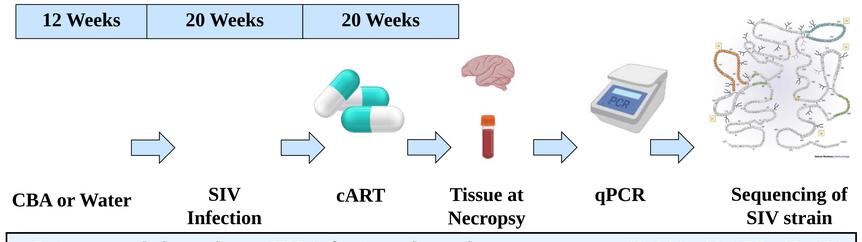
Hypothesis

- We hypothesize that AUD will exacerbate the adverse neurocognitive deficits observed in PLWH by increasing viral levels within CNS tissues.

Experimental Objective

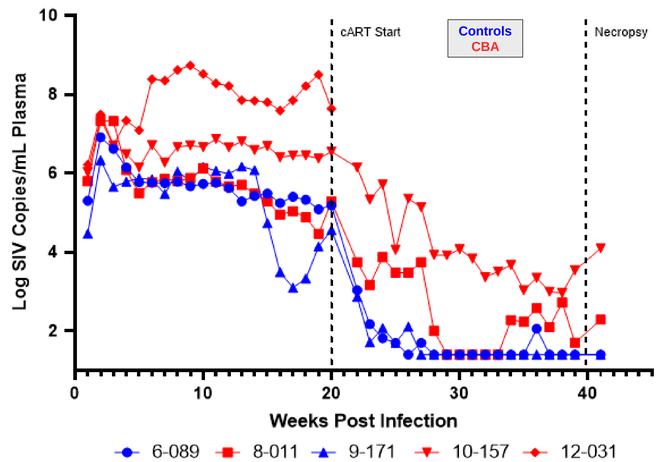
- Utilizing samples from a 5-animal pilot study, virus levels were analyzed in the plasma and CNS to assess the study-design modifications in a well-established rhesus macaque model of HIV and provide preliminary data for the overall hypothesis.

Methods



- Prior to and throughout SIV infection, three rhesus macaques (8-011, 10-157, 12-031; depicted in red) were administered CBA via a gastric catheter to achieve 50mM blood alcohol for five days per week. Two control animals (6-089 and 9-171, depicted in blue) were administered water. All five rhesus macaques were fed a high fat or Western diet.
- All animals were infected intravenously with an SIV quasispecies (SIVmac251 and SIV17e), which contained a neurotropic SIV genotype (SIV17e).
- Animal 12-031 was euthanized early in the study protocol, due to high viral loads and end-stage disease manifestations.
- Beginning 20 weeks post-SIV, four animals were treated with a 3-drug cART regimen, Biktarvy, containing 2 reverse-transcriptase inhibitors and an integrase inhibitor.
- Using quantitative PCR (qPCR), viral loads were measured in plasma and cerebrospinal fluid (CSF) obtained during the study course and in CNS tissues taken at necropsy.
- The SIV envelope gene was amplified by PCR from CSF and tissue samples, cloned, and sequenced to identify the specific SIV strain present.

Plasma Viral Loads



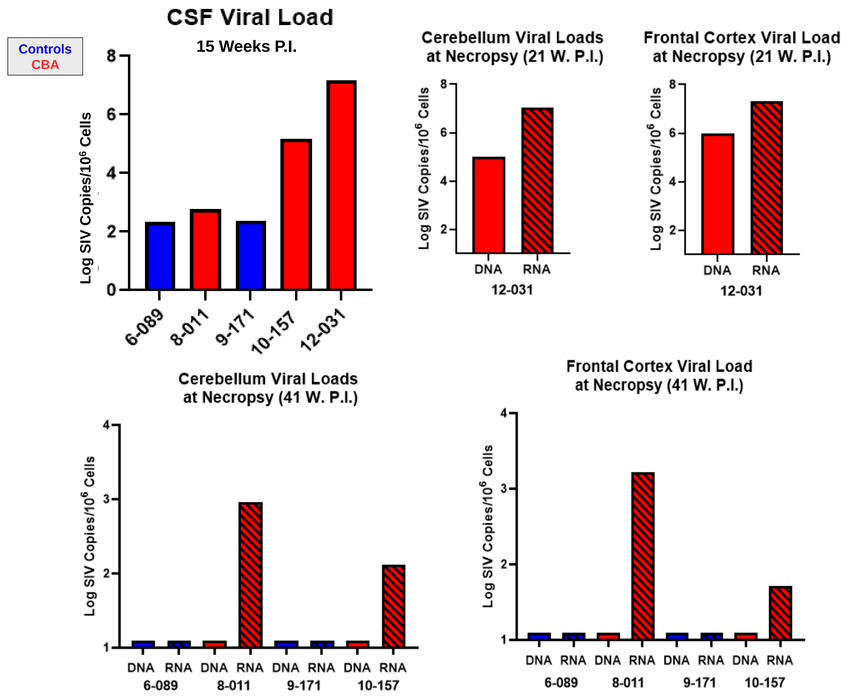
- Prior to cART, plasma viral levels were slightly higher in the three CBA animals compared to controls.
- In animals receiving cART, all showed decreased plasma viral levels. However, over the course of treatment, plasma viremia remained detectable in the two CBA animals while plasma viremia was undetectable in the two controls.

Viral Genotypes

Animal #	Tissue	% 17E Genotype	% 251 Genotype
8-011	CSF - 15wks	0	100%
9-171	CSF - 15wks	0	100%
10-157	CSF - 15wks	0	100%
12-031	CSF - 15wks	100%	0
12-031	Frontal Cortex	100%	0
12-031	Cerebellum	100%	0
8-011	Cerebellum	100%	0

This research project was supported through the National Institutes of Health (NIAA P60 AA009803), LSU Health Sciences Center School of Medicine, & LSUHSC-CARC.

CNS Viral Loads



- At 15 weeks post-infection, SIV levels in the CSF were highest in CBA animals 10-157 and 12-031, but were similar in animals 6-089, 8-011, and 9-171.
- At the time of necropsy, animal 12-031 had high levels of proviral DNA and SIV RNA in both the cerebellum and frontal cortex.
- In the 4 cART animals, proviral DNA reservoirs were undetectable (<25 copies/10^6 cells) in the cerebellum and frontal cortex, while detectable levels of viral RNA were found in both the cerebellum and frontal cortex of the two CBA animals.

Summary & Conclusions

- Higher levels of virus were found in the plasma and CNS of animals administered CBA, as compared to controls. Despite a three-drug cART, viral levels in plasma remained detectable in the CBA animals.
- The SIV17e strain was the only genotype identified in the CNS tissues of CBA animals 8-011 and 12-031.
- The findings of this pilot study support the hypothesis that CBA increases viral levels in the brain.
- The observations also demonstrate the efficacy of using this animal model to decipher the mechanisms of neurocognitive deficits seen in PLWH and those with AUD.
- Future studies will look at viral levels within other discrete regions of the CNS and evaluate if they harbor drug resistant mutations.