Impact of Chronic Binge Alcohol on Hepatic Immune Cell Infiltration in SIV-Infected Rhesus Macaques

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Introduction

- Liver disease is a major cause of death in people with HIV, especially those who heavily consume alcohol.

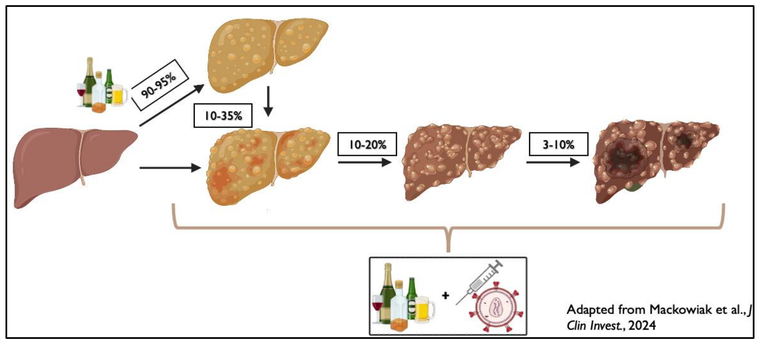

Figure 1. Cofactors contribute to alcohol-associated liver disease progression.

- The liver plays a key role in immune regulation and is highly sensitive to HIV and alcohol .
- ART reduces viral replication but does not eliminate liver inflammation or fibrosis.
- Chronic HIV/SIV and alcohol exposure increase harmful immune responses (e.g., proinflammatory $CD4^+$ T cells, IFN-γ, TNF-α) and reduce anti-inflammatory signaling (e.g., IL-10), leading to liver damage.
- Cell markers like CD25, CD28, CD38, MCP-1 (immune activation), and Caspase-3 and MLKL (cell death/stress) reveal immune dysfunction.
- Imbalances in cytokines and immune signaling contribute to chronic liver inflammation.
- **Hypothesis**: Chronic binge alcohol will increase liver immune cell infiltration and inflammation in a model of SIV infected rhesus macaques.

Objective and Significance

Objective: To determine how chronic alcohol exposure contributes to immune cell infiltration and inflammation in the livers of SIV-infected macaques

Significance: This study will clarify how alcohol-driven immune dysregulation promotes liver inflammation in HIV/SIV infection, advancing understanding of ALD in people living with HIV.

Materials & Methods

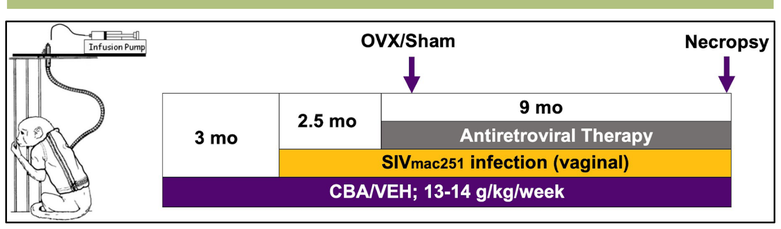

Figure 2. Non-human primate model and treatment timeline.

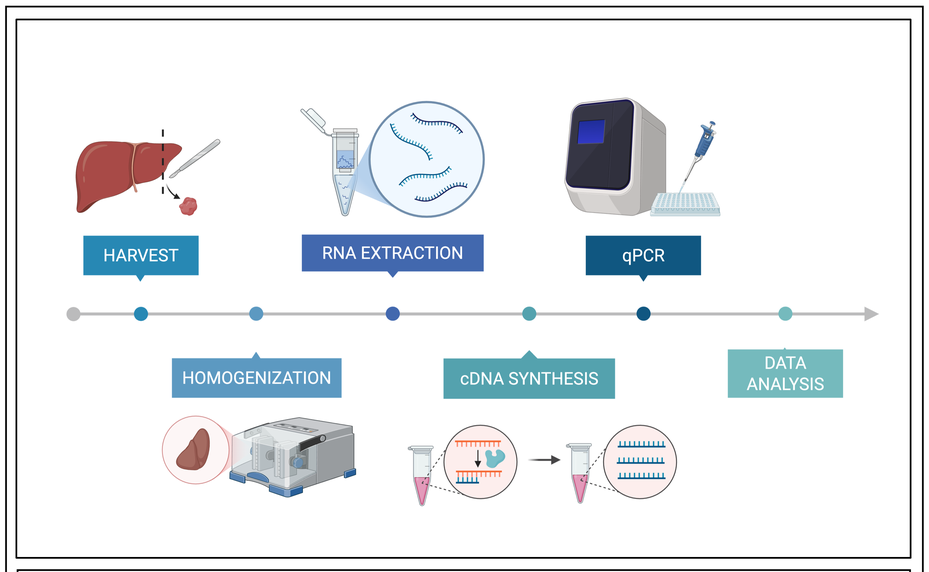

Figure 3. qPCR workflow used to assess immune-related gene expression in liver tissue from SIV-infected macaques exposed to chronic alcohol.

Results

Hepatic Cytokine Expression

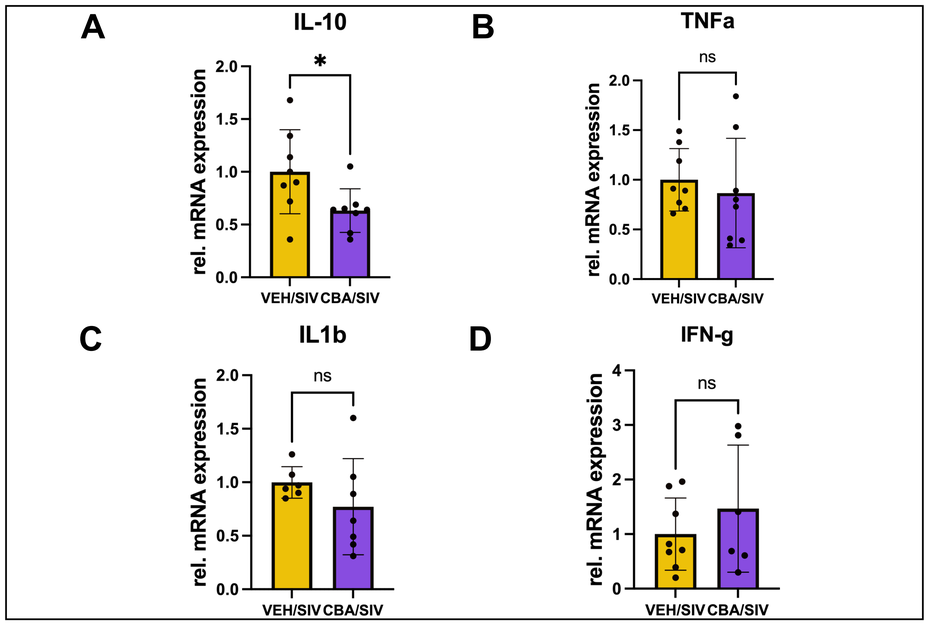

Figure 4: Cytokine gene expression in liver tissue from SIV-infected macaques with or without chronic alcohol exposure. *(A)* IL-10 expression was significantly decreased in the alcohol-treated group compared to controls. *(B–D)* No significant differences were observed in the expression of TNF-α, IFN-γ, or IL-1β between the alcohol-treated and control groups. *p<0.05, unpaired t-test.

Hepatic Cell Death Expression

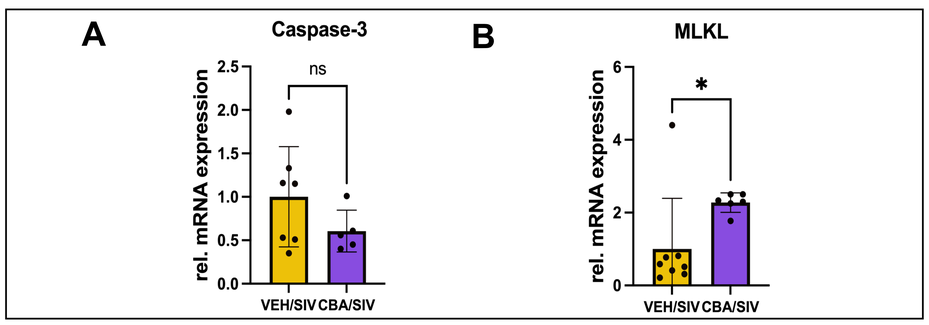

Figure 6: Cell death–related gene expression in liver tissue from SIV-infected macaques with or without chronic alcohol exposure. *(A)* Caspase-3 expression showed no significant difference between groups. *(B)* MLKL expression was significantly increased in the alcohol-treated group compared to controls. *p<0.05, unpaired t-test.

Hepatic Chemokine Expression

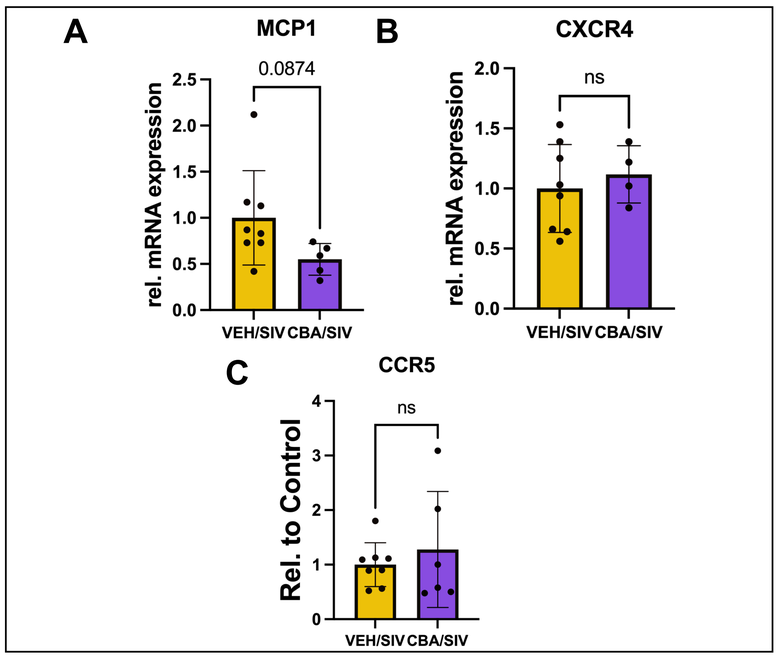

Figure 5: Chemokine gene expression in liver tissue from SIV-infected macaques with or without chronic alcohol exposure. *(A)* MCP-1 expression trended lower in the alcohol-treated group, though the difference was not statistically significant. *(B, C)* Expression levels of CXCR4 and CCR5 showed no significant differences between groups. *p<0.05, unpaired t-test.

Conclusion

- Alcohol contributes to hepatic injury in SIV infection
  - IL-10 expression was significantly reduced, potentially indicating suppression of anti-inflammatory signaling and impaired immune regulation.
  - MCP-1 showed a trending decrease, which may reflect reduced monocyte/macrophage recruitment to the liver or an early dampening of inflammatory response.
  - MLKL expression was increased, suggesting activation of necroptosis, a pro-inflammatory cell death pathway.
- Together, these findings potentially indicate alcohol-induced anti-inflammatory immune dysregulation and increased cell death activity.

Future Directions:

- Investigate the effects of a high-fat diet on the ALD phenotype in the SIV macaque model.
- Investigate alcohol's impact on hepatocyte cell death pathways using a 3D spheroid in vitro model established in the lab.

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