Single Housing of Macaques Increases the Immune Impact of SIV Infection

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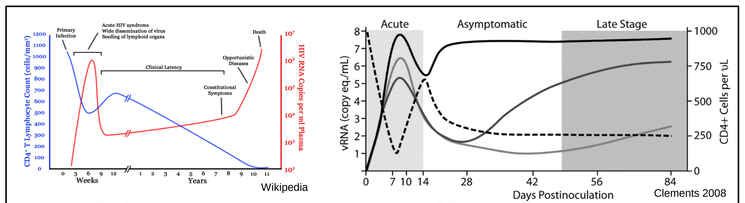
Introduction

ART-treated, SIV-infected macaques are an important model for HIV cure research



HIV in Humans SIV in Macaques

Macaques naturally live in large, complex social groups

- Single housing of uninfected macaques → stress → prolonged changes in immune response[1]
- Social stress in SIV+ macaques → ↓ NK cell & Type I IFN immune response and short survival times[2]
- Stress in HIV+ patients → ↓ CD4+ T cell counts, CD4 & CD8 T cell activation, viral loads & mortality[3-5] ↑

Hypothesis:
Single housing will increase the immune impact of SIV infection compared to social housing in infected macaques.

Methods

Retrospective analysis: Single housing effect on acute SIV

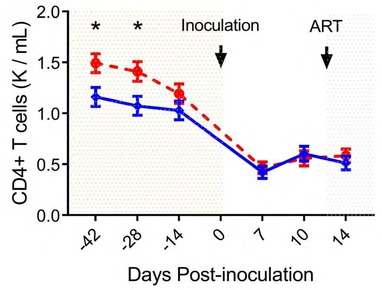
- 36 single (2007-2013) vs 41 social housed (2013-2017)

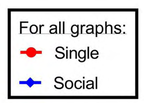
Controlled Variables	Uncontrolled Variables
• Species *(M. nemestrina)* • Age (juvenile) • Sex (male) • MANE-A1*084:01 neg. • Same inoculum stock • Route (IV) • Same room, food, H_2O • Same caretaker & vet • Same research techs • Same PCR assay • Randomized blinded FACS re-analysis	• Year (Pre- & Post-2013) • Origin of macaques • CBC machine (changed 2015) • FACS panel fluorophores • Starting day 12 → different ART/interventions

Retrospective study design:
- Focus on acute infection
- Linear mixed effects regression in SAS

Results

Greater CD4+ T cell decline in with single housing:

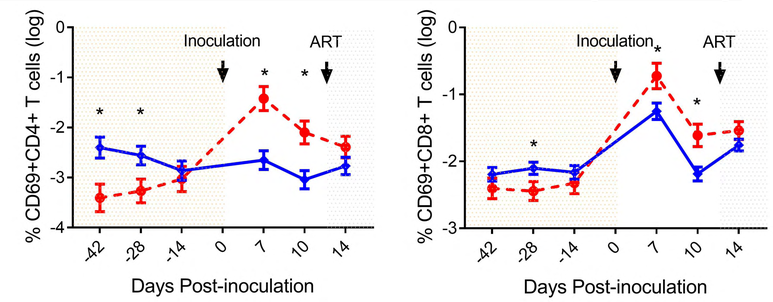




Twofold decline in socially housed animals more analogous to magnitude of decline in HIV infected humans

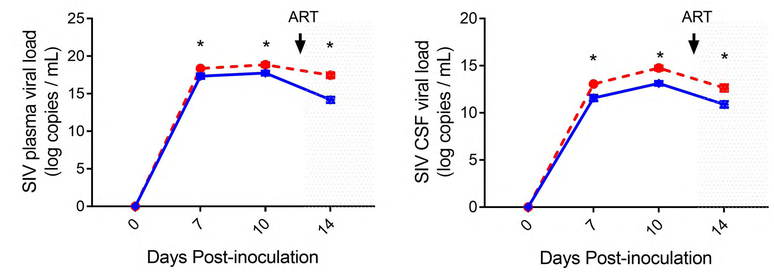
Flow cytometry was used to monitor CD4+ T cell counts throughout infection. Differences between singly and socially housed groups over time (* P = 0.0075) and different magnitude of change between groups pre- and post-inoculation (P = 0.0004).

More CD4+ and CD8+ T cell activation with single housing:



Flow cytometry was used to monitor T cell activation. Differences between singly and socially housed groups over time (* P < 0.0001 for CD4; P = 0.0002 for CD8) and different magnitude of change pre- and post-inoculation (P < 0.0001 for CD4 & CD8).

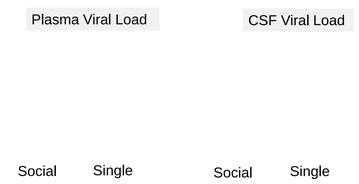
Higher plasma and CNS viral loads with single housing:



qRT-PCR for SIV gag was used to monitor viral loads. Differences between singly and socially housed groups over time (* P < 0.0001 for plasma and CSF).

More variability in viral load data in singly housed cohorts:

Within animal variability in viral loads for days 7 & 10. (Mann-Whitney P < 0.0001 for plasma, P = 0.263 for CSF)



Key Findings

Single housing increases the immune impact of SIV

→ Greater CD4+ T cell decline
→ More CD4+ and CD8+ T cell activation
→ Higher viral loads
→ More data variability

Conclusions

Reducing stress in SIV-infected macaques through social housing could improve the **translational value** and **reproducibility** of data in HIV research

- Similarly, reducing stress in a macaque model of diabetes has improved reproducibility and allowed for successful translation of a bioengineered pancreas into clinical trials[6]

Single housing likely to affect latent viral reservoirs & cure

- SIV disseminated & enters sanctuary sites in acute infection[7] → Need to directly examine effect on reservoir

Further work required to address concerns on social housing & examine effect of additional refinements to improve model

- Work on positive reinforcement training to allow for voluntary acceptance of ART & blood draws in progress

Translational implications for work with HIV+ patients:
Poor outcomes in socially isolated patients likely have pathophysiologic origins that need to be defined in addition to sociobehavioral roots.

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