Effect of HIV-1 infection, virion production, and proviral integration site on CD4+ T cell proliferation

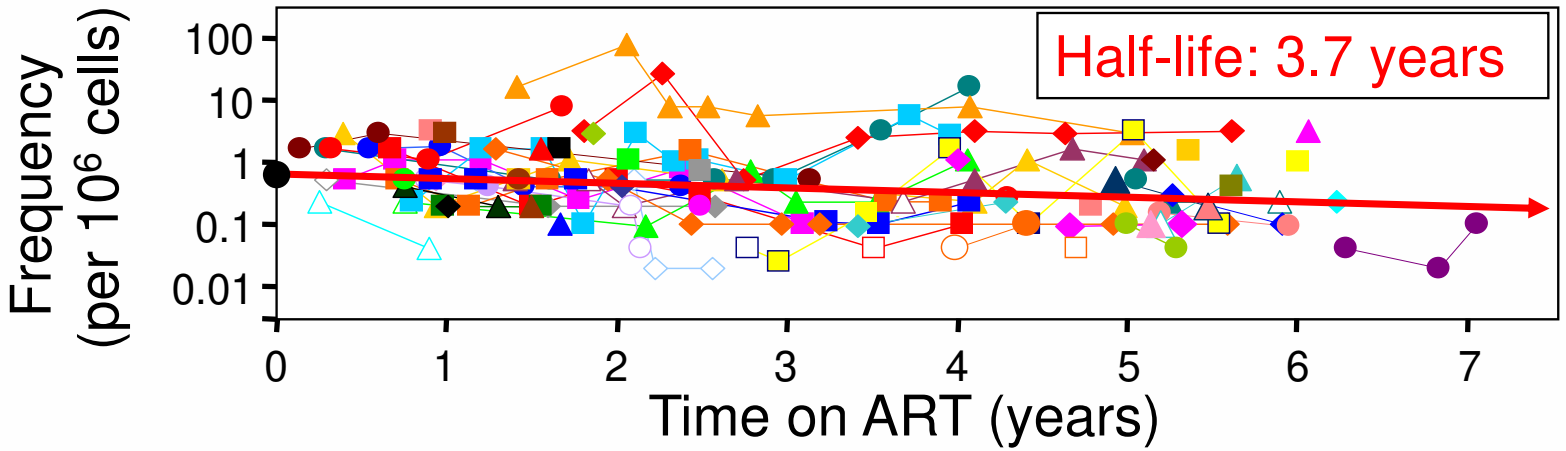
Josh Kufera, PhD

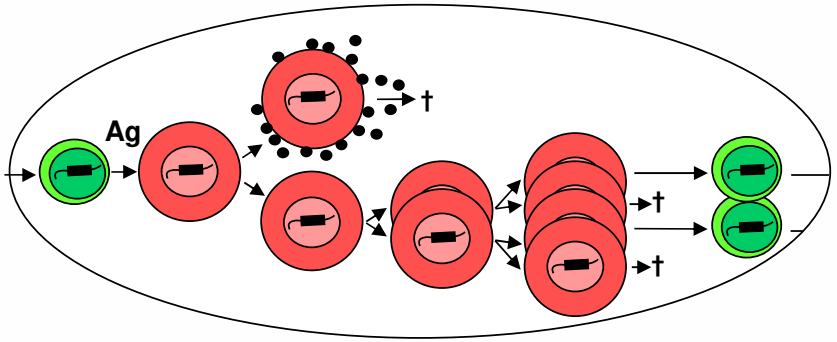
Johns Hopkins University School of Medicine

Department of Medicine

Disclosures: None

Slow decay of the reservoir reflects a balance between infected cell clearance and proliferation

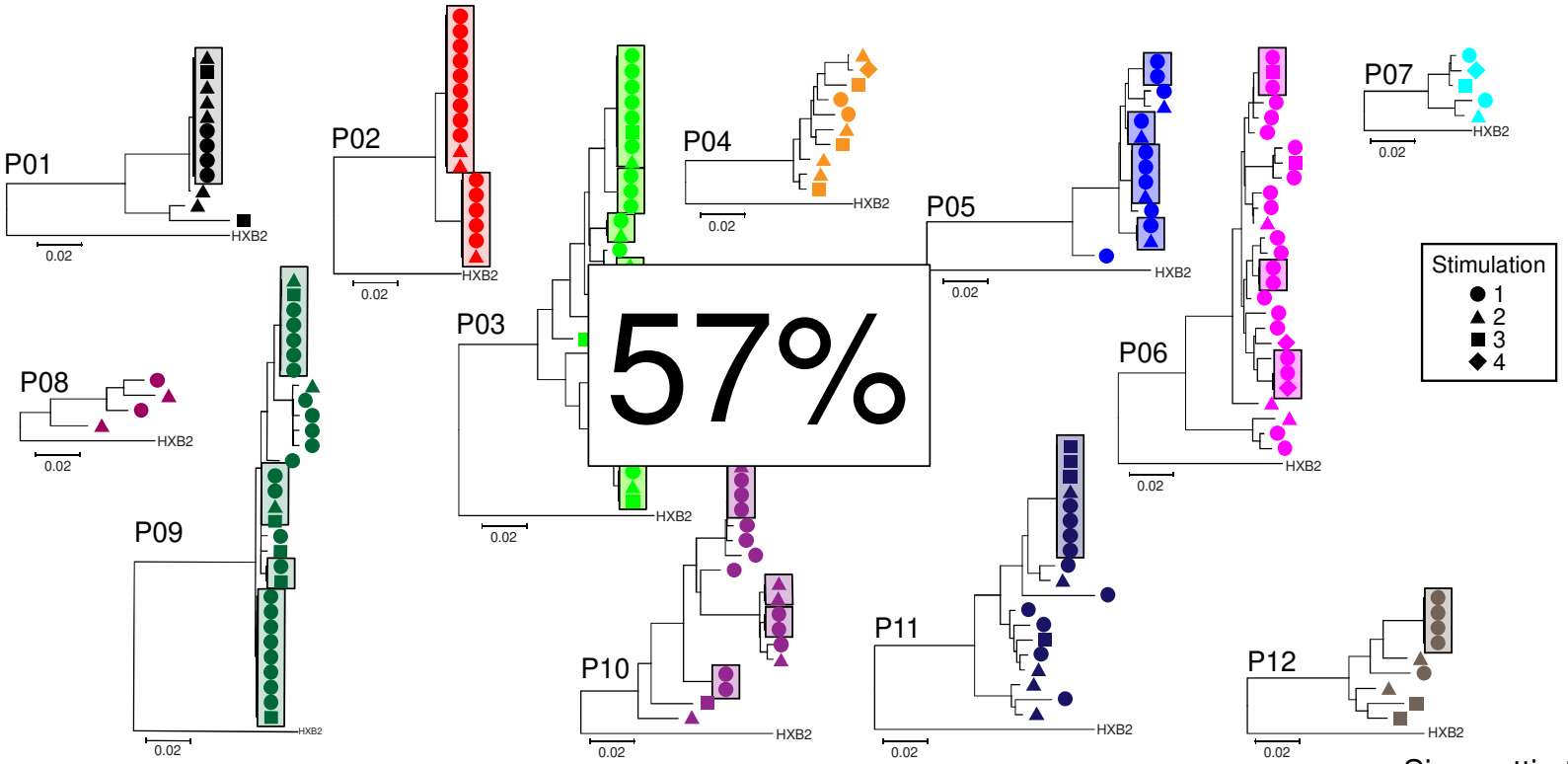




>50% of the latent reservoir has arisen from proliferation

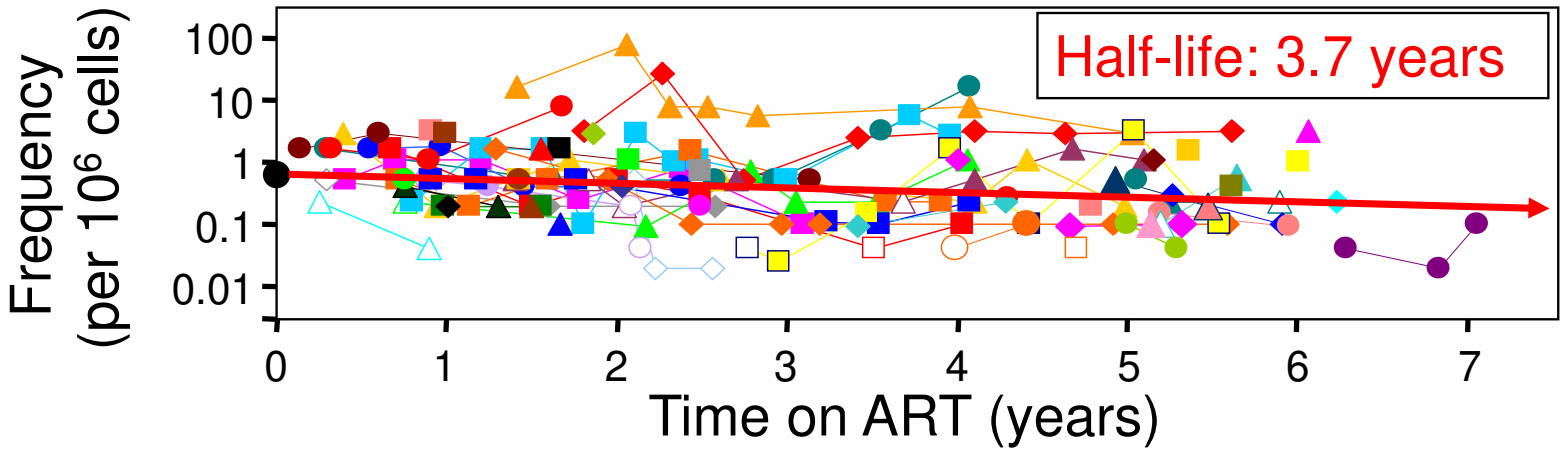
J Siliciano et al, **Nature Med** 2003
Hosmane et al, **JEM** 2017

Independent isolates of replication-competent HIV with identical sequence



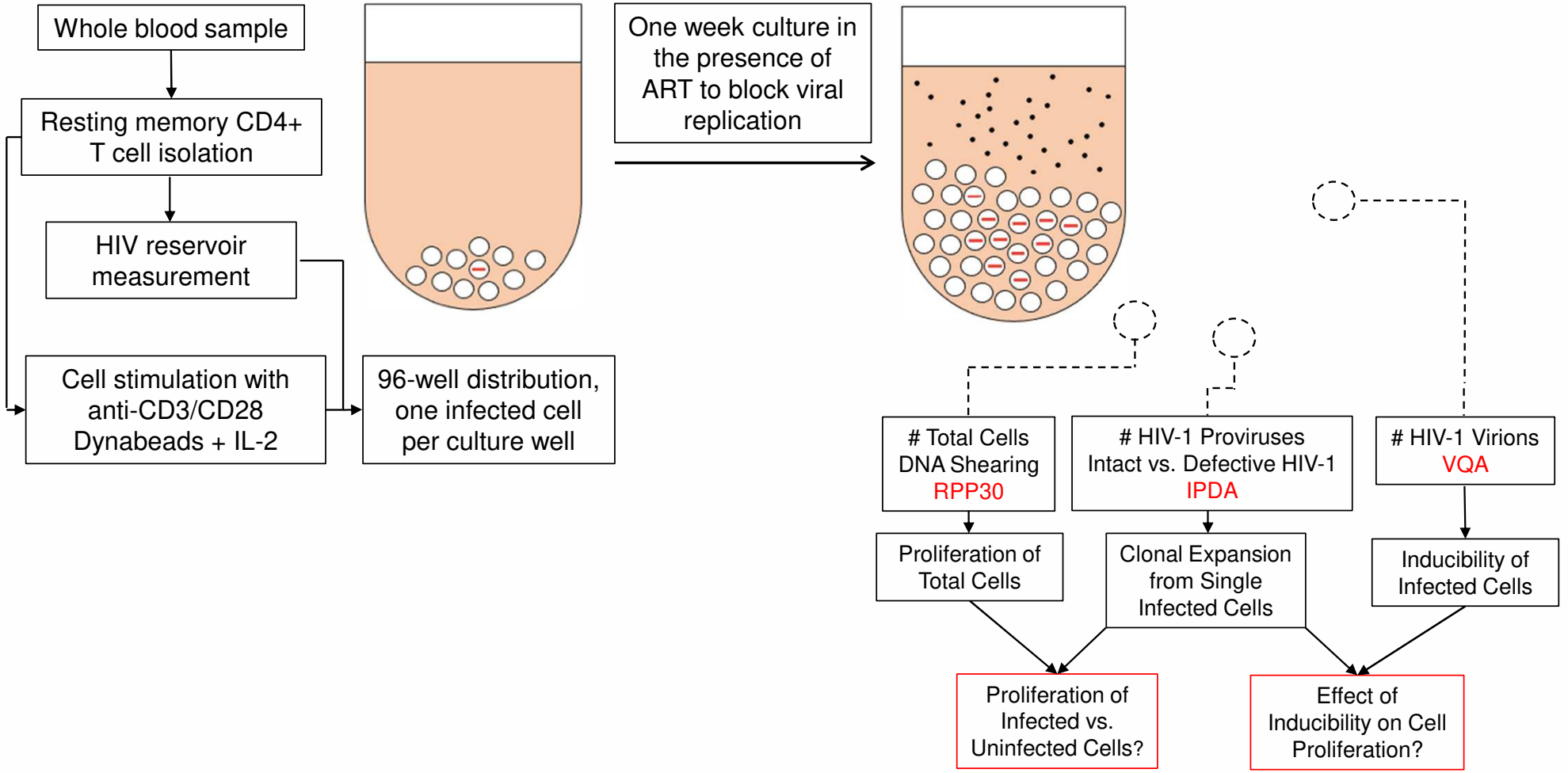
Simonetti et al, PNAS 2016
Lorenzi et al, PNAS 2016
Hosmane et al, J Exp Med 2017
Bui et al, PloS Path 2017

Slow decay of latently infected CD4+ T cells

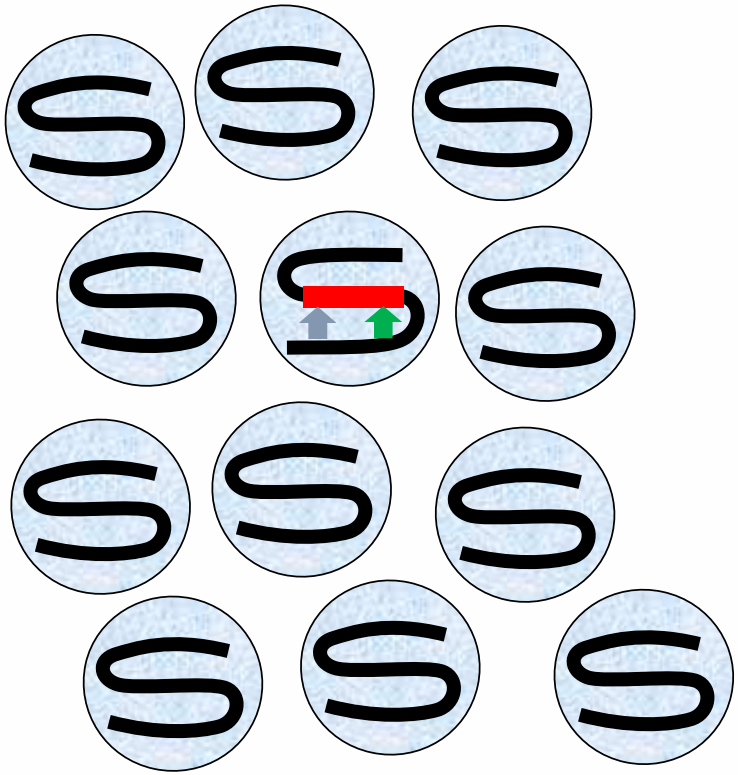


- Is each cell in the reservoir capable of enormous clonal expansion?
- What stimuli drive the expansion?
- Do the same stimuli induce viral gene expression?

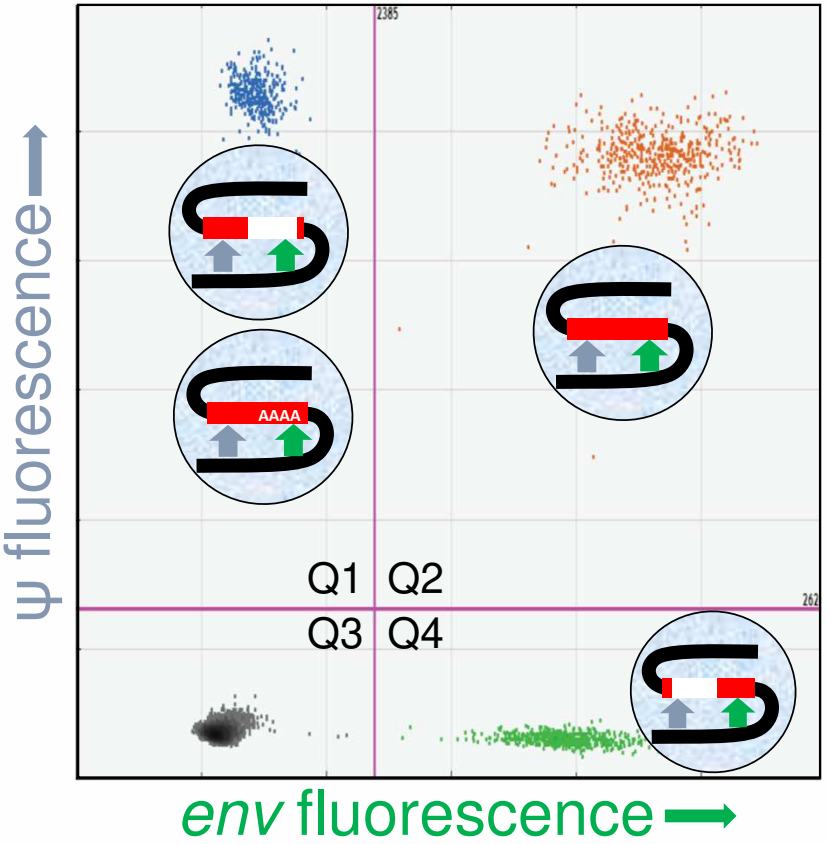
Microculture Scheme



Intact proviral DNA assay (IPDA)

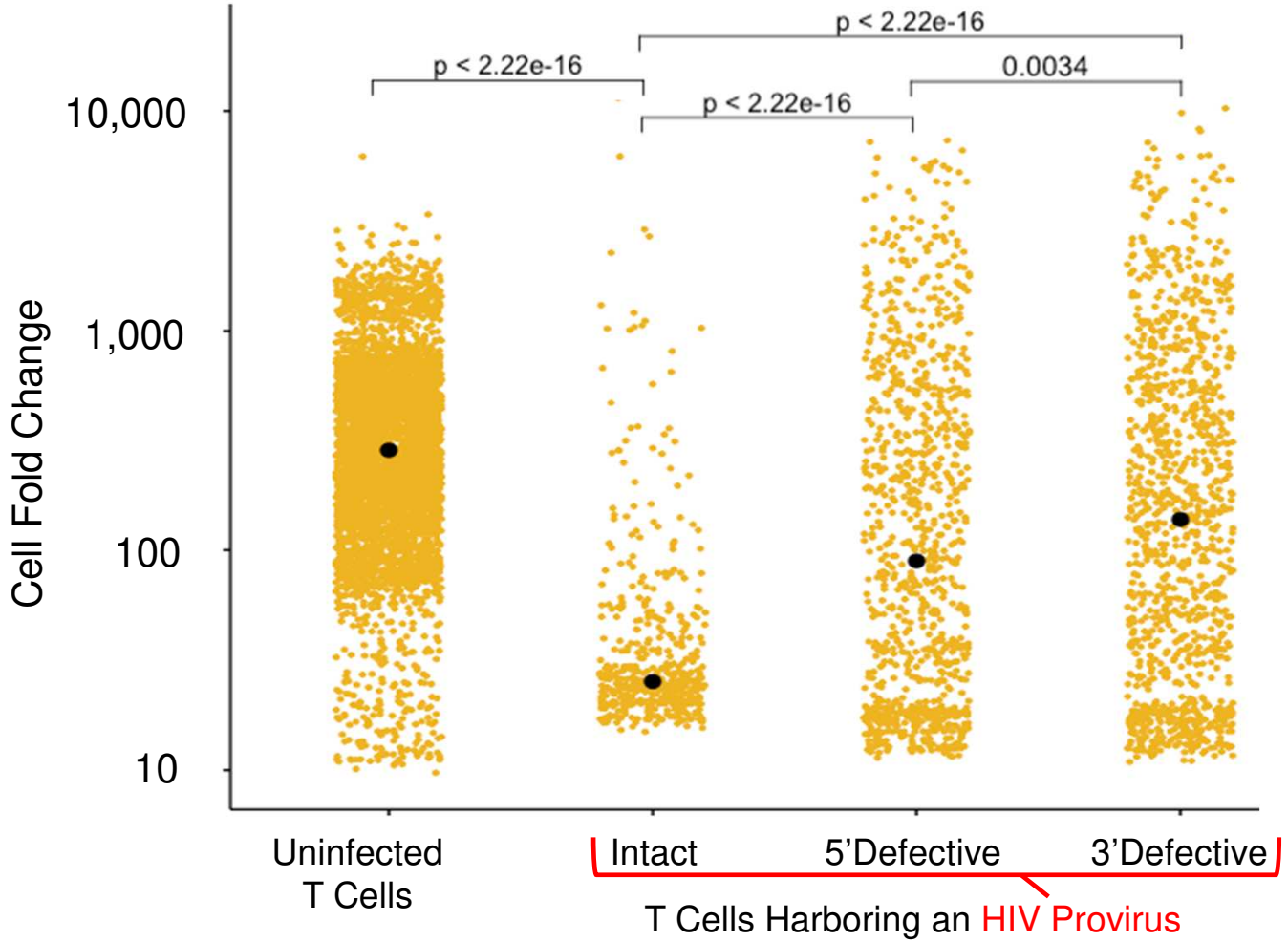


Nano-liter sized droplets

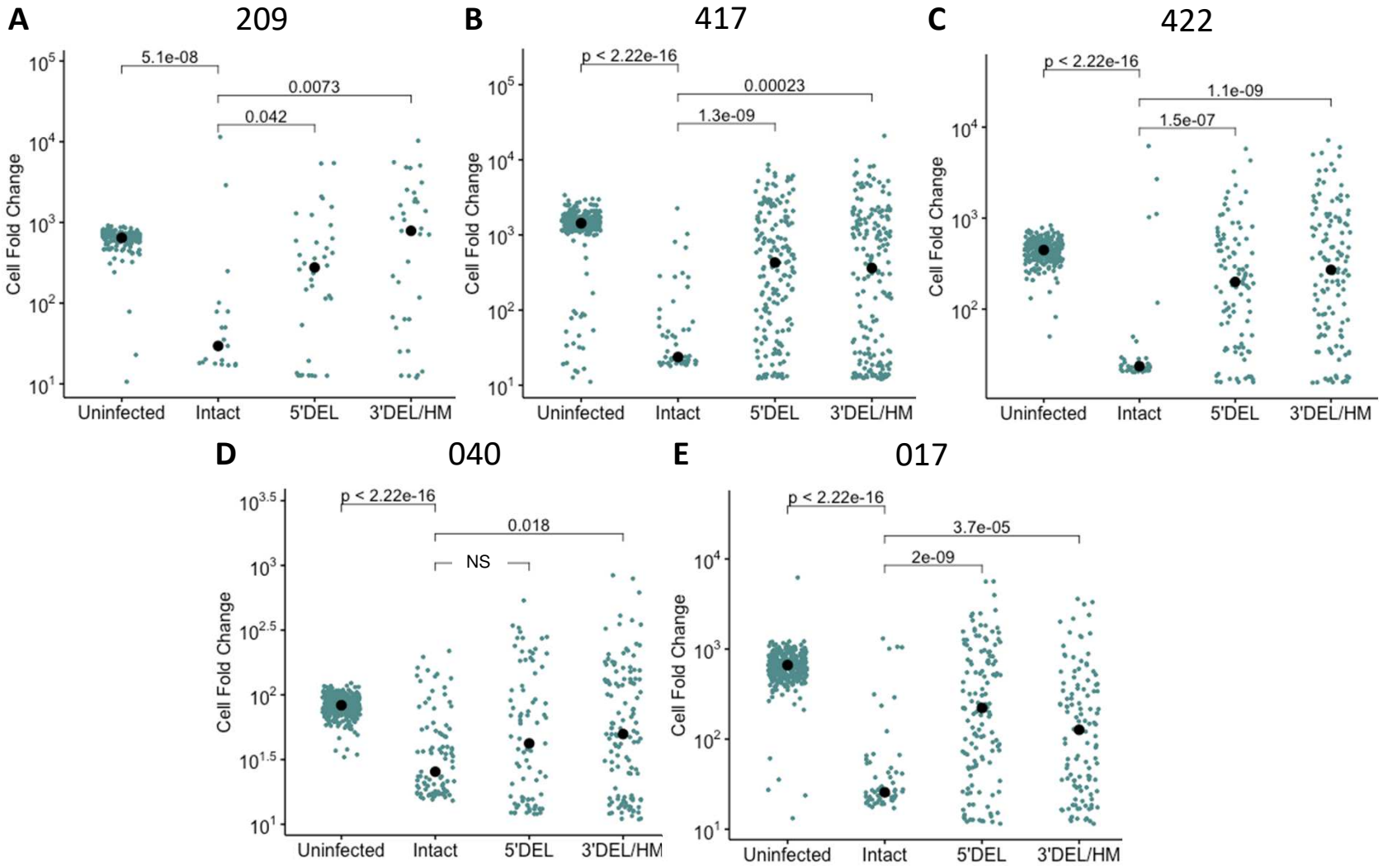


Bruner et al, **Nature** 2019

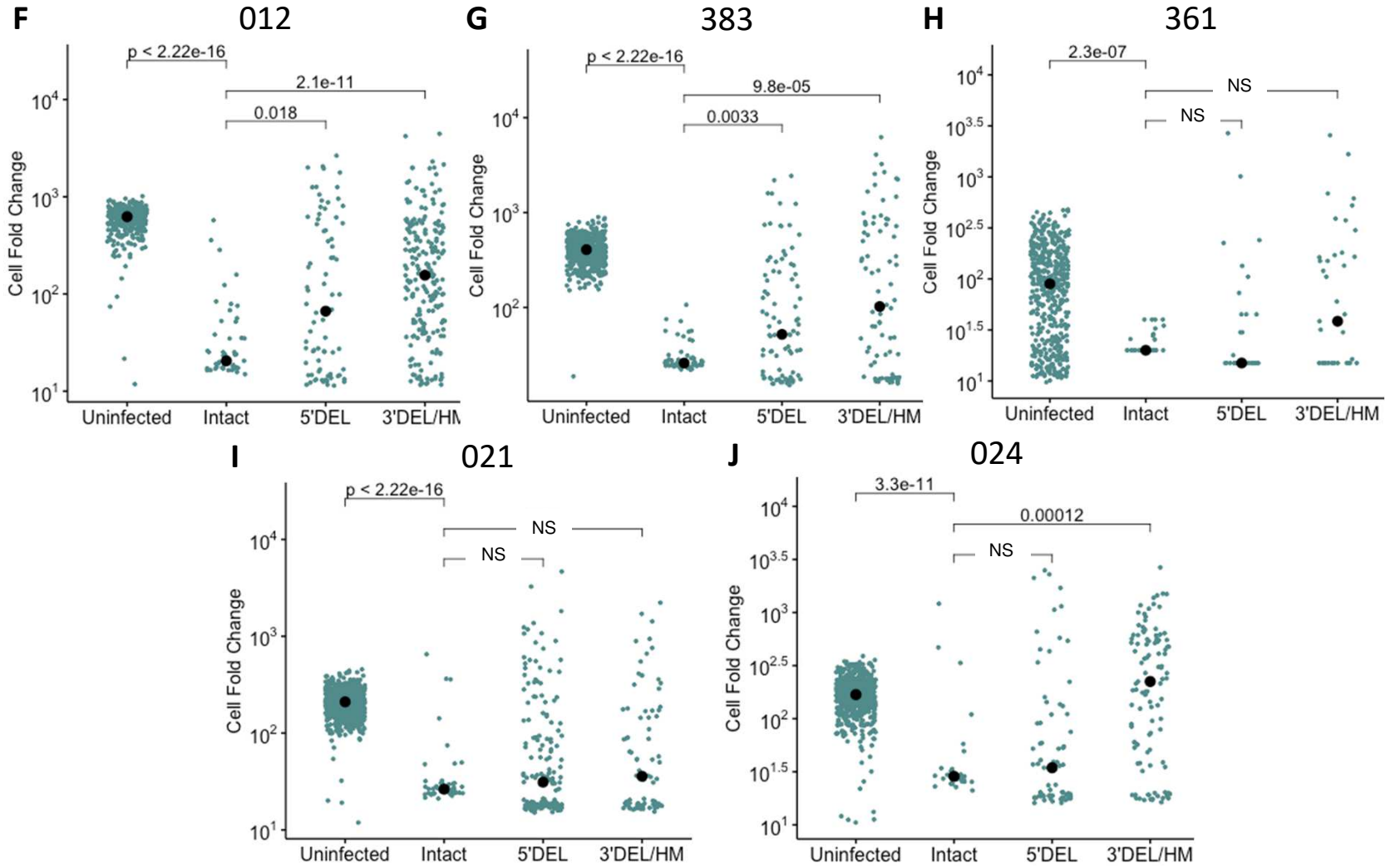
Infected T cells with an intact HIV provirus demonstrated attenuated proliferation



Trend is consistent across 10 study participants



Trend is consistent across 10 study participants



The effect of virus production on infected CD4+ T cell proliferation

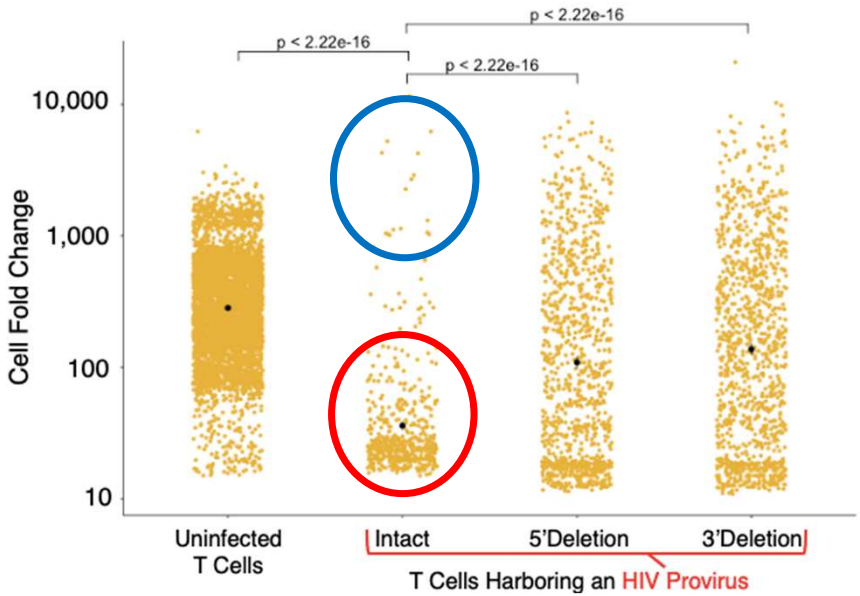
Proliferation of uninfected cells

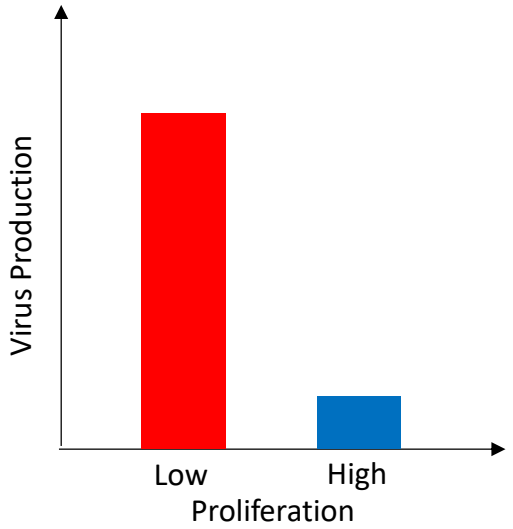
Proliferation of single infected cell

HIV Production by infected cell or its progeny

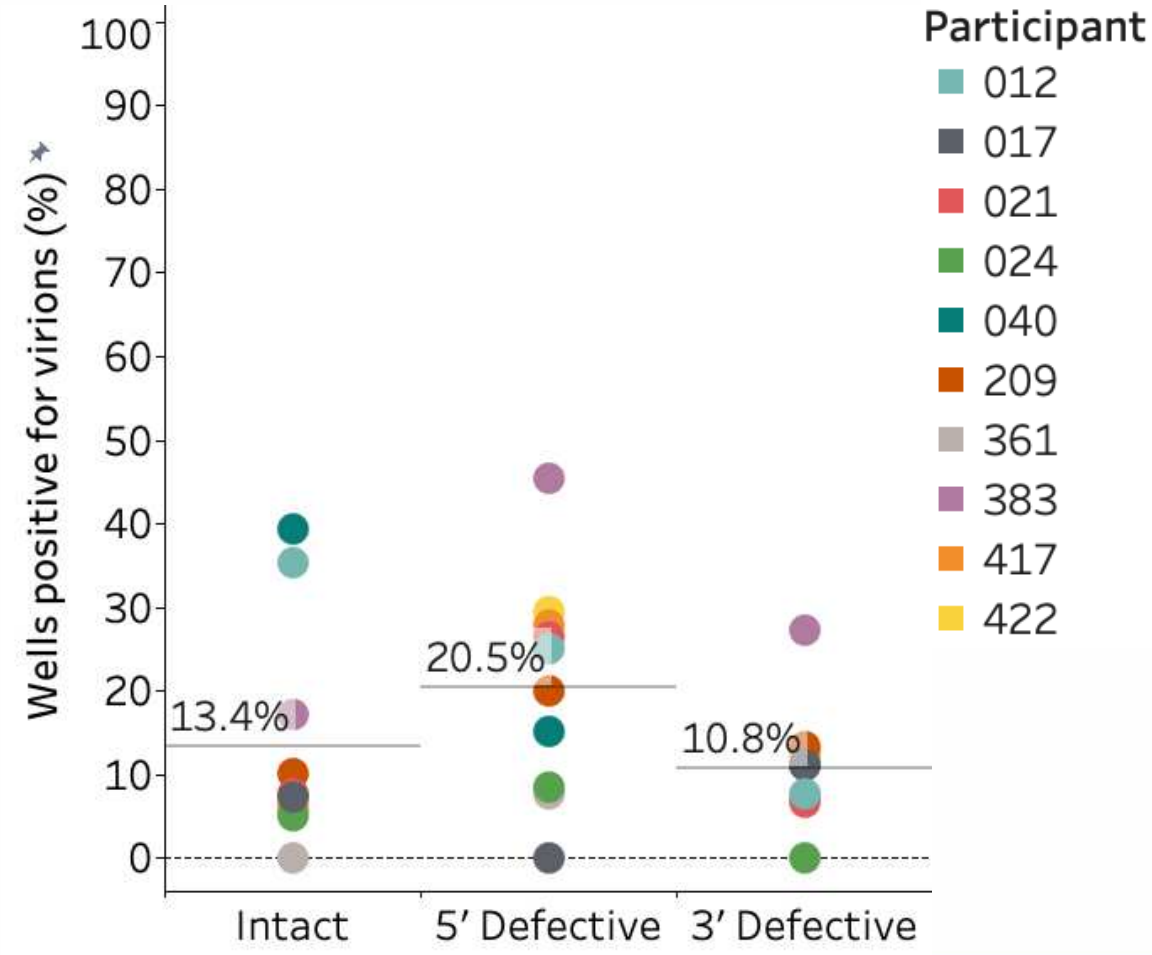
1. Proliferation of infected vs. uninfected cells?

2. Does virus production restrict infected cell proliferation?

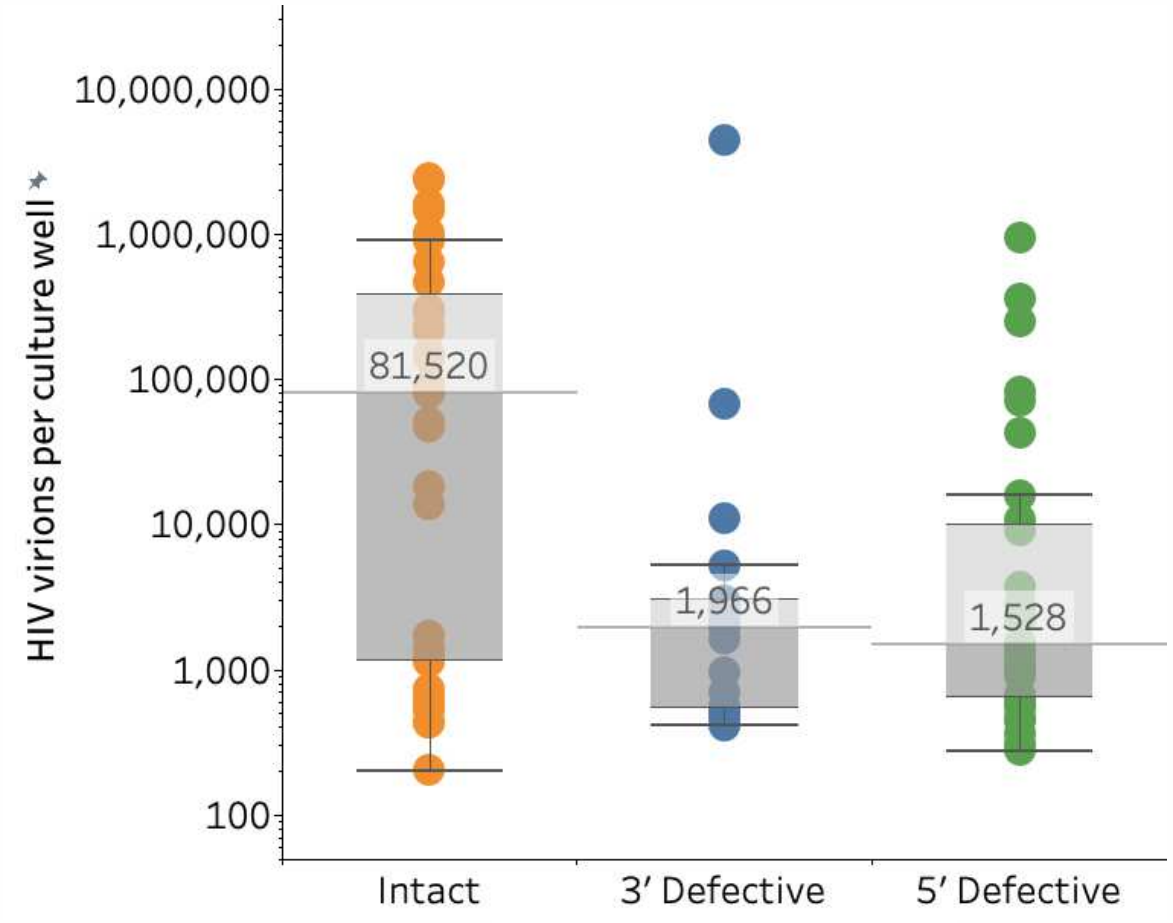




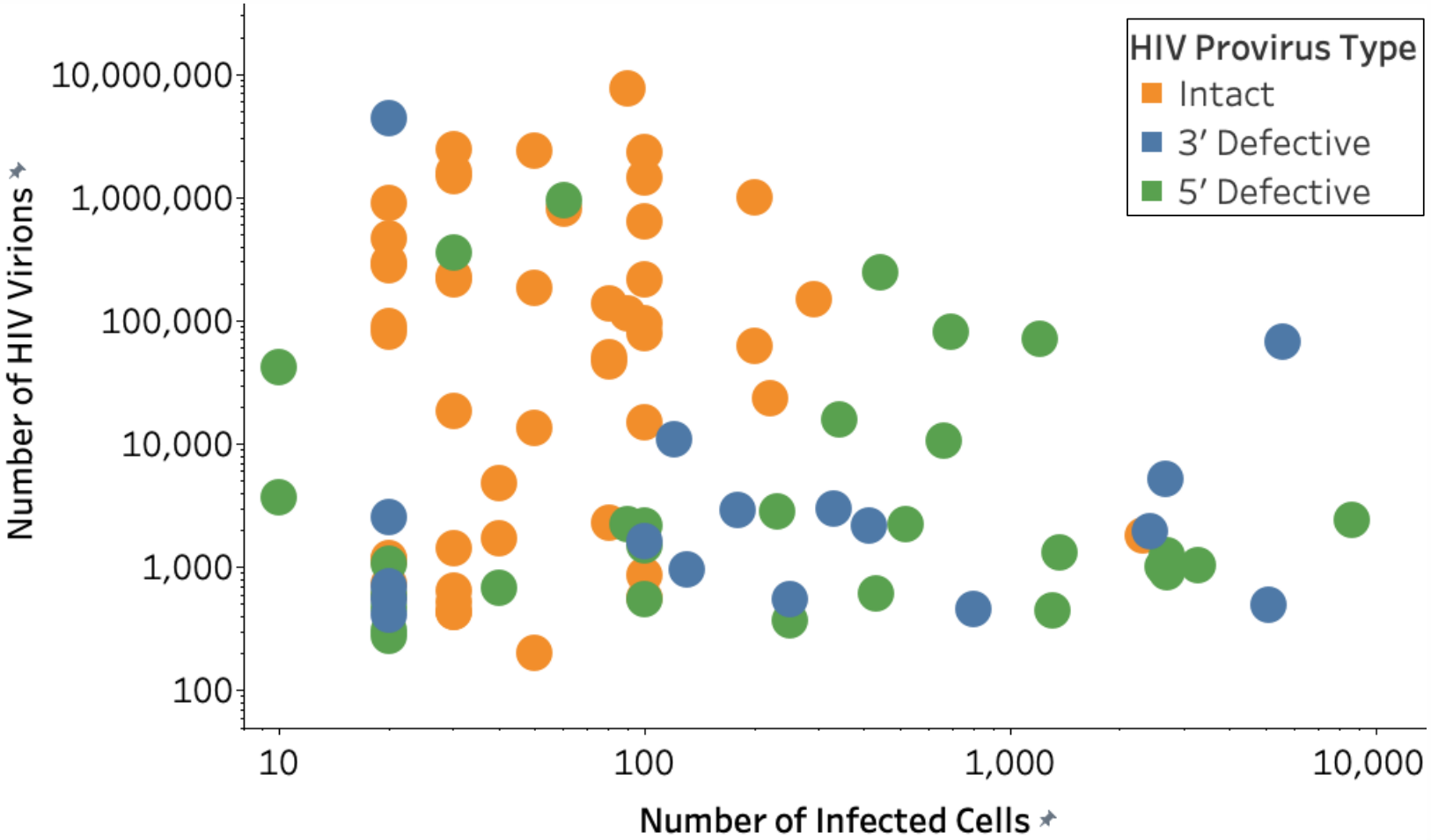
A low fraction of infected cells produced virus



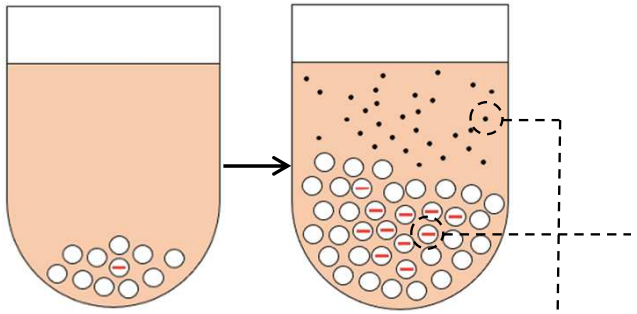
Median viral burst >1 log greater for clones with intact PV



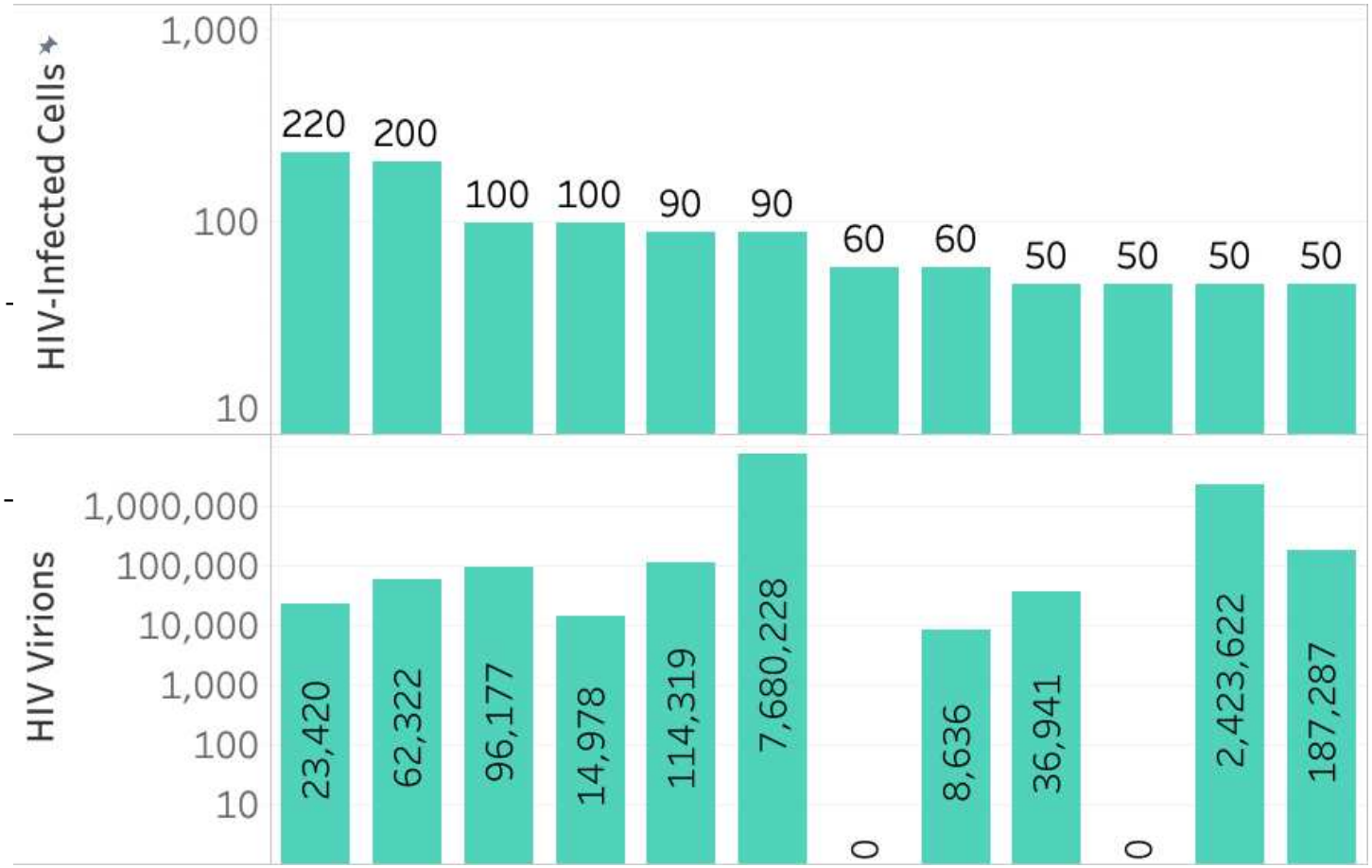
Largest clones produced fewer virions



Cell fate can vary among members of the same *in vivo* clone



Integration site:
ZNF850, Chr 19



Conclusions

- Latently-infected T cells expanded suboptimally *ex vivo.*
- A low fraction of all proviruses produced virions.
- Virion production was associated with but did not fully explain restricted infected cell proliferation.

Implications

- Clinical implication -> anti-proliferative agents
- *In vivo*, intact proviruses initially decay faster than defective proviruses -> could be due to impaired proliferation
- Viral protein expression -> Transient, targetable?

Acknowledgements

Siliciano Lab
Robert Siliciano, MD, PhD
Janet Siliciano, PhD
Ciara Armstrong
Fengting Wu
Anushka Singhal
Jun Lai
Hao Zhang
Hannah Wilkins
Subul Beg
Zheng Wang, PhD

Scientific Advisors
Francesco Simonetti, MD, PhD
Stuart Ray, MD
Andrea Cox, MD, PhD
Justin Bailey, MD, PhD

Study Participants

Martin Delaney
Collaboratories

Howard Hughes Medical Institute
Pharmacology & Molecular Sciences Department,
Johns Hopkins University School of Medicine