Multiomic dynamics of the cellular HIV reservoir after rebound during ATI

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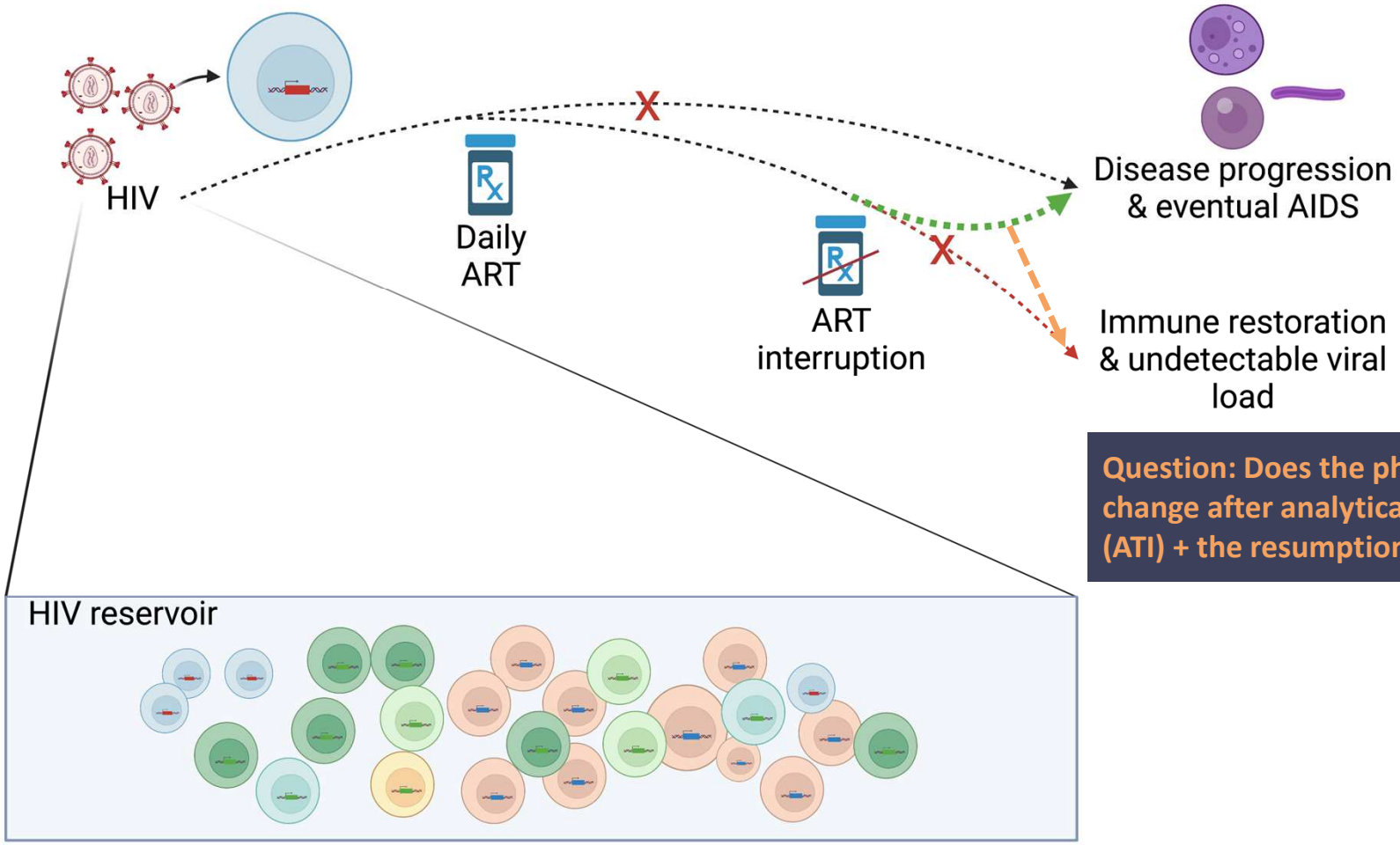
HIV Persistence during Therapy | Reservoirs & Eradication Strategies Workshop
2022.12.14

The HIV reservoir



Question: Does the phenotype of HIV+ cells change after analytical ART interruption (ATI) + the resumption of ART?

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Is cell infected?

scATACseq

genome wide accessible chromatin
can also include provirus

What is the cell?

scATACseq
+
surface protein staining

accessible chromatin + surface antigen markers
high resolution identity

scATACseq
(single-cell **A**ssay for **T**ransposase-**A**ccessible **C**hromatin)
+
scSAPseq
(single-cell **S**elect **A**ntigen **P**rofiling)

scASAPseq
(single-cell **A**TAC with **S**elect **A**ntigen **P**rofiling)
Mimitou et al., *Nature Biotechnology* 2021

viral scASAPseq enables direct *ex vivo* identification and analysis of HIV+ cells in their native and unmanipulated state

Wu et al., *Nature Immunology* 2022 (in press)

Identification of infected cells from ART-treated PLWH pre and post ATI

ORIGINAL ARTICLE

Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption

Katharine J. Bar, M.D., Michael C. Sneller, M.D., Linda J. Harrison, M.Sc., J. Shawn Justement, B.S., Edgar T. Overton, M.D., Mary E. Petrone, B.S., D. Brenda Salantes, B.S., Catherine A. Seamon, R.N., Benjamin Scheinfeld, B.A., Richard W. Kwan, P.A.-C., Gerald H. Learn, Ph.D., Michael A. Proschan, Ph.D., Edward F. Kreider, M.S., Jana Blazkova, Ph.D., Mark Bardsley, B.S.N., Eric W. Refsland, Ph.D., Michael Messer, R.N., Katherine E. Clarridge, M.D., Nancy B. Tustin, B.S., Patrick J. Madden, B.S., KaSaundra Oden, Ph.D., Sijy J. O'Dell, M.Sc., Bernadette Jarocki, B.S., Andrea R. Shiakolas, B.A., Randall L. Tressler, M.D., Nicole A. Doria-Rose, Ph.D., Robert T. Bailer, Ph.D., Julie E. Ledgerwood, D.O., Edmund V. Capparelli, Pharm.D., Rebecca M. Lynch, Ph.D., Barney S. Graham, M.D., Ph.D., Susan Moir, Ph.D., Richard A. Koup, M.D., John R. Mascola, M.D., James A. Hoxie, M.D., Anthony S. Fauci, M.D., Pablo Tebas, M.D., and Tae-Wook Chun, Ph.D.

Article Figures/Media Metrics

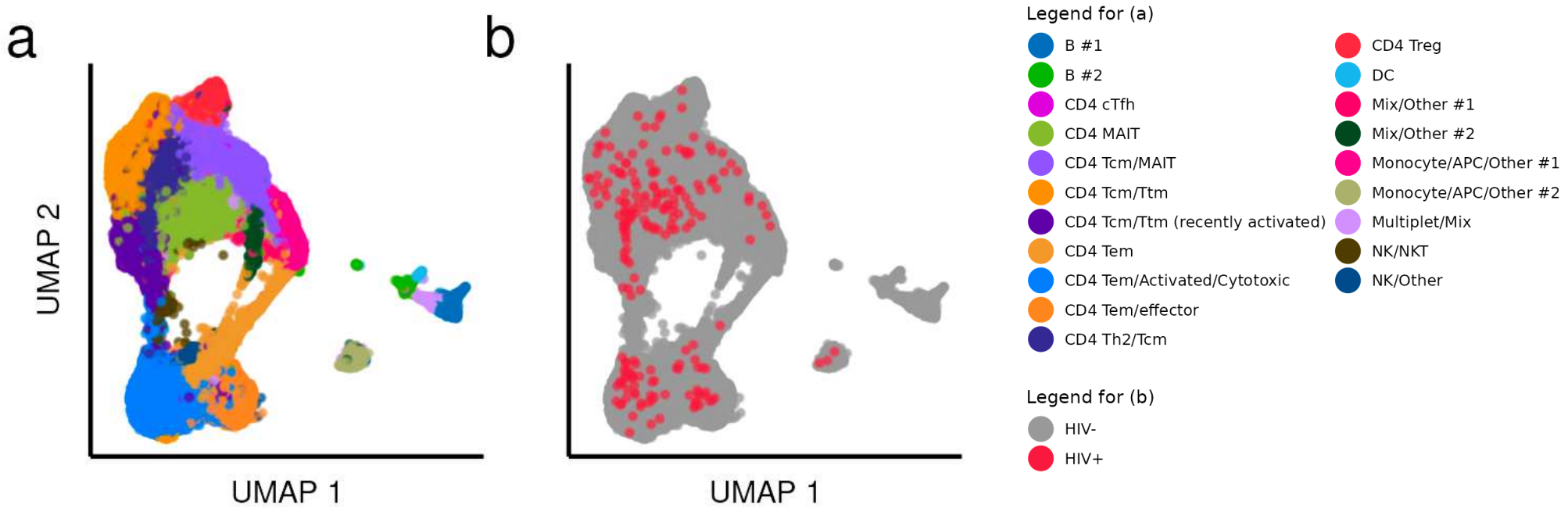
44 References 299 Citing Articles

November 24, 2016
N Engl J Med 2016; 375:2037-2050
DOI: 10.1056/NEJMoa1608243

Individual	Total cells	HIV+ cells (% of total cells)	Total HIV DNA copies per 1e6 CD4+ T cells (%)*
A01	14021 (pre-ATI) 27065 (post-ATI)	9 (0.06%; pre-ATI) 6 (0.02%; post-ATI)	185 (0.019% pre-ATI) 293.8 (0.029% post-ATI)
A08	18427 (pre-ATI) 17461 (post-ATI)	46 (0.25%; pre-ATI) 36 (0.22%; post-ATI)	1791.2 (0.18% pre-ATI) 1564.5 (0.16% post-ATI)
A09	44331 (pre-ATI) 32998 (post-ATI)	67 (0.15%; pre-ATI) 36 (0.11%; post-ATI)	1297.3 (0.13% pre-ATI) 1221.8 (0.12% post-ATI)

Bar et al., *NEJM* 2016
Salantes et al., *JCI* 2018

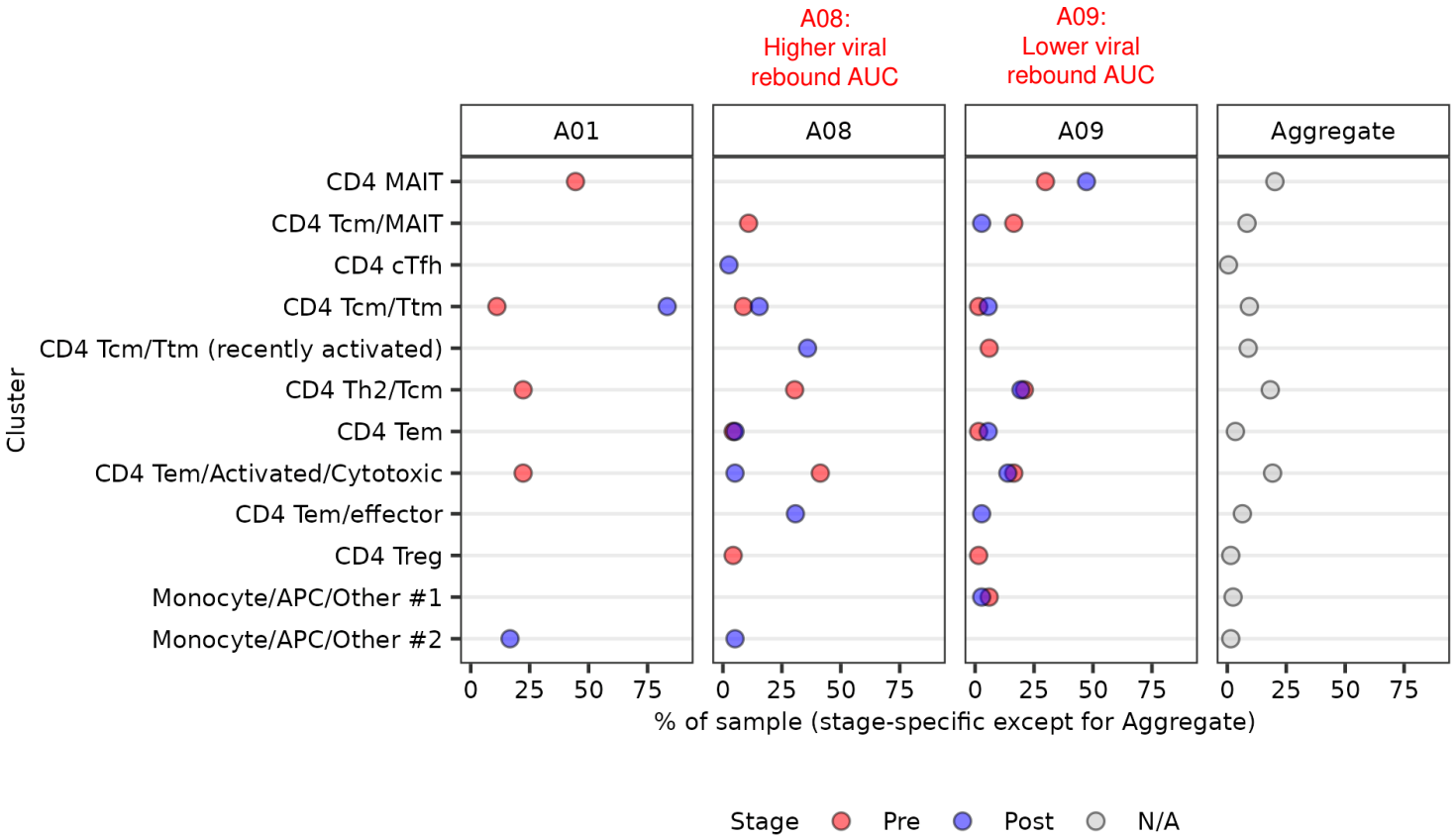
Identification of infected cells from ART-treated PLWH

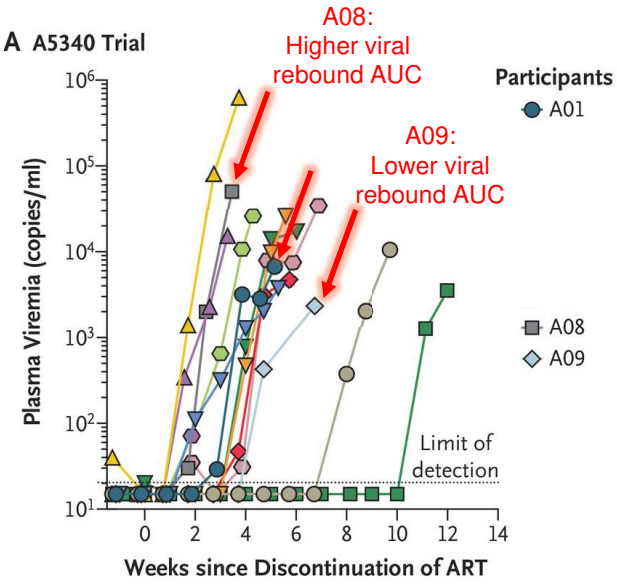


HIV+ cells are found across
many different CD4+ T-cell subsets

Wu et al. *Nature Immunology* 2022 (in press)
* from Salantes et al., *JCI* 2018

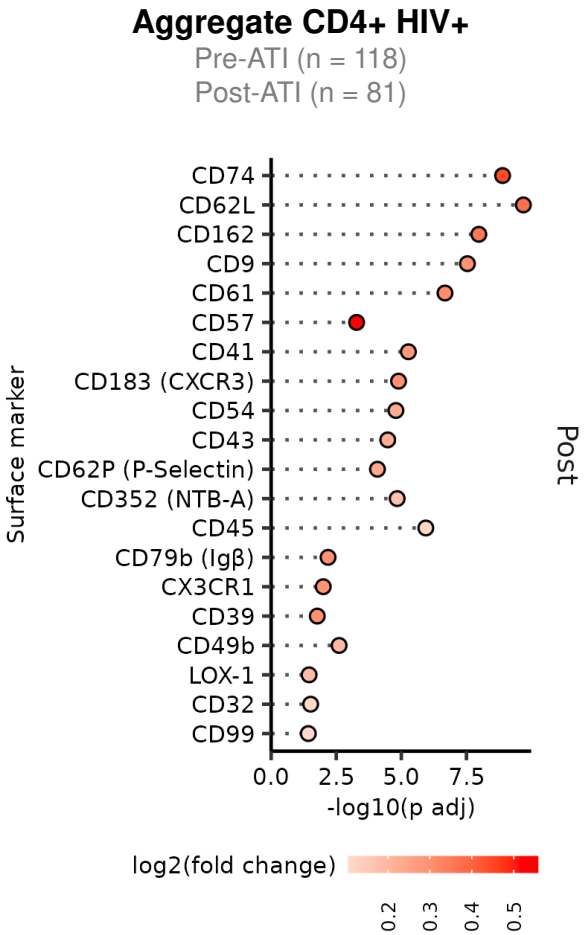
In(stability) of the phenotype of infected cells after ATI, potentially correlating with extent of viral rebound AUC

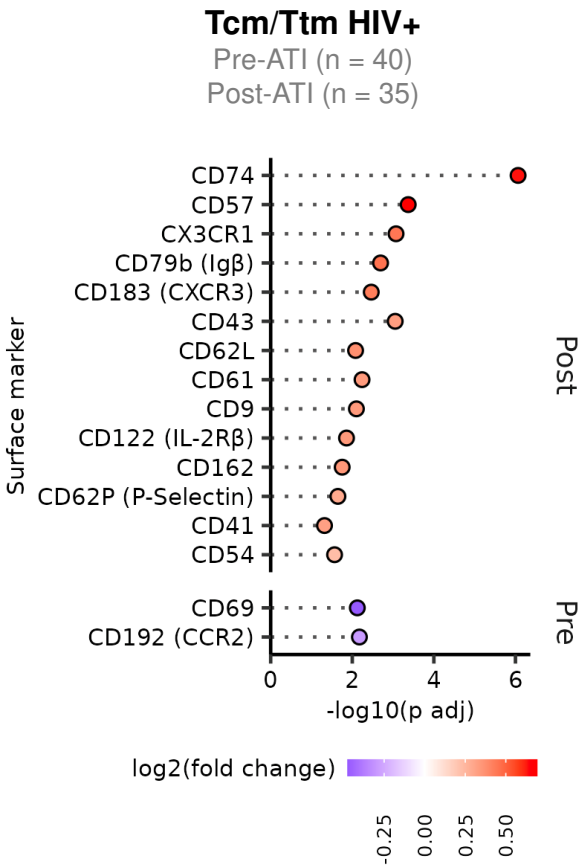


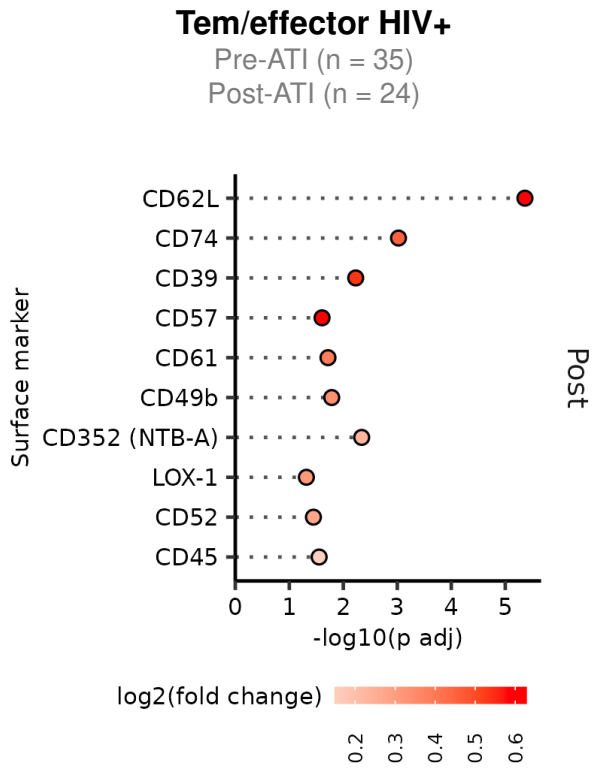


(left): Wu et al. *Nature Immunology* 2022 (in press)
(right): modified from Bar et al., *NEJM* 2016

Differential surface protein expression on HIV+ cells before and after ATI

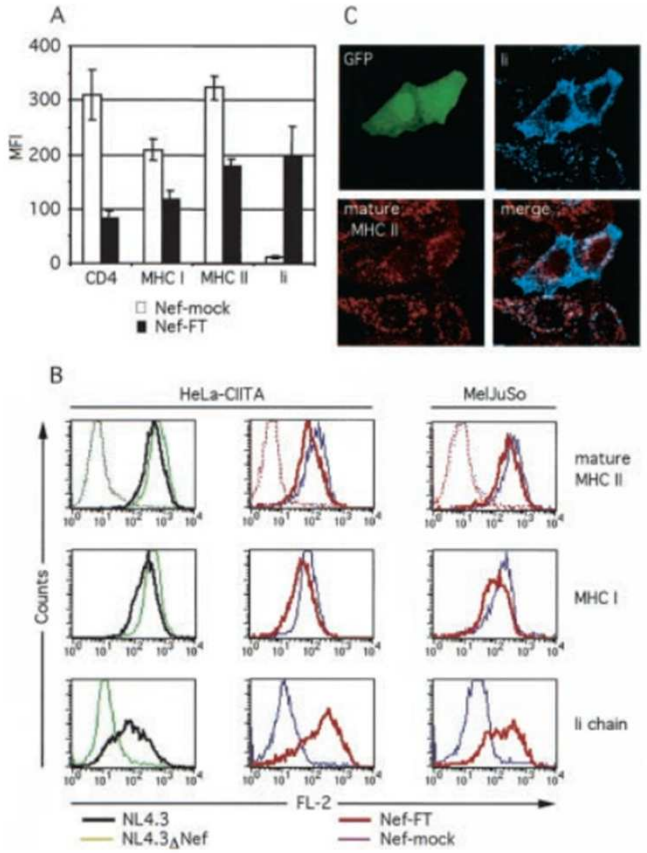


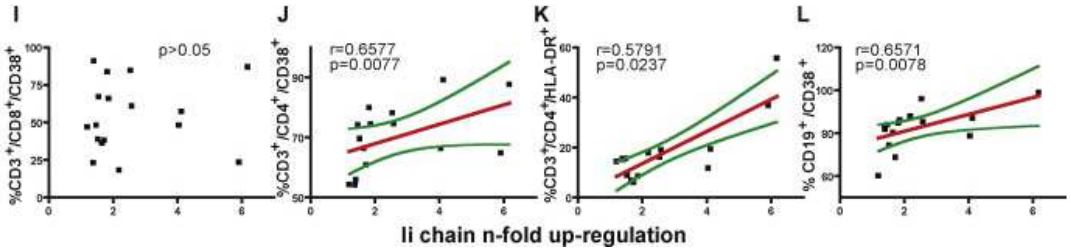




Raw data from Wu et al. *Nature Immunology* 2022 (in press)
Wilcox method in Seurat's FindMarkers() with Bonferroni correction
Showing only HIV+ CD4+ cells & markers with adj p < 0.05

CD74 is known to be a target by HIV-1 Nef (and Vpu) and may be correlated with immune activation



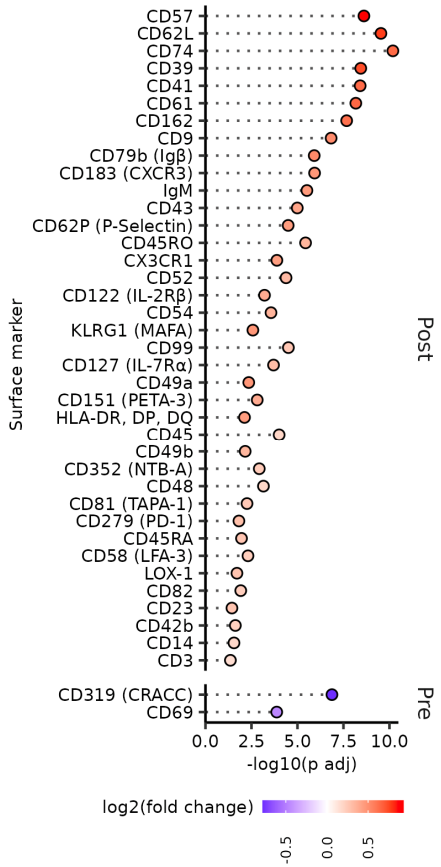


Left: Stumptner-Cuvelette et al. *PNAS* 2001
Right: Ghiglione et al. *Virus Research* 2011

Differential surface protein expression on HIV+ cells is heterogenous between individuals

A08 (higher viral rebound AUC)

Pre-ATI (n = 46)
Post-ATI (n = 37)



A09 (lower viral rebound AUC)

Pre-ATI (n = 63)
Post-ATI (n = 35)

No markers with
adjusted *p* value < 0.05

Raw data from Wu et al. *Nature Immunology* 2022 (in press)
Wilcox method in Seurat's FindMarkers() with Bonferroni correction
Showing only HIV+ CD4+ cells & markers with adj p < 0.05

Community Summary

Key question

- Does the phenotype of HIV+ cells change after ATI + the resumption of ART?

What was accomplished?

- Used our single-cell strategy to phenotypically profile HIV-infected cells at basal (resting) state before and after ATI with VRC01 immunotherapy.

Why is this important?

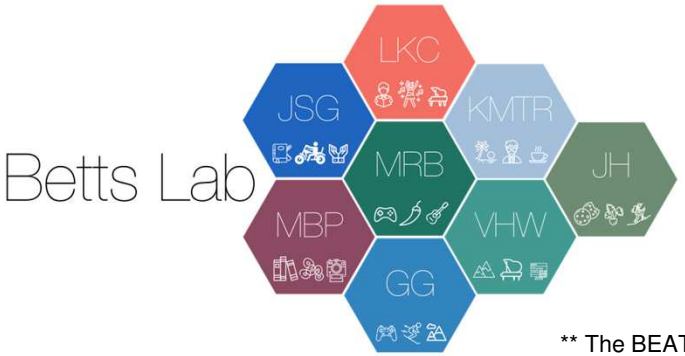
- Provides the highest resolution understanding of the HIV reservoir during ATI-associated perturbations.
- Understanding HIV reservoir dynamics will help with cure efforts.

Future directions

- Validation of various markers as a biomarker of ATI on HIV+ cells.
- Determine if these findings are specific to ATI + VRC01 or if ATI alone is sufficient for the observed differences.

Acknowledgements

- Betts Lab (UPenn)
  - **Son Nguyen, PhD***
  - Betu Pampena, PhD
  - Greg Golden, PhD
  - Kyabeth Torres
  - **Jayme Nordin**
  - Jake Hamilton
  - Ethan Burns
  - Jay Gardner, DD*
  - **Mike Betts, PhD**
- Bar Lab (UPenn)
  - Jaimy Joy, PhD
  - Felicity Mampe*
  - **Katie Bar, MD**
- BEAT-HIV Collaboratory
  - Pablo Tebas, MD
- Vella Lab (UPenn)
  - **Laura Vella, MD PhD**
- Montaner Lab (Wistar)
  - Luis Montaner, VMD PhD
- Sample donors
- Funding sources
  - NIAID P01 AI31338
  - NIAID U19 A1-149680-02 (Riley)
  - NIAID R01 AI118694
  - NIAID R21 AI172629
  - BEAT-HIV Delaney Collaboratory** UM AI164570
  - Penn HIV T32
  - Penn CFAR P30 AI045008



Penn
University of Pennsylvania

* Former

** The BEAT-HIV Delaney Collaboratory is funded by UM AI164570 and co-funded by NHLBI, NINDS, NIDDK, NIDA, NIMH, and NIAID.