

# Comparison of T cell clones in the blood and CSF of People Living with HIV: A Single-cell Approach

Mamie Wang  
Program in Computational Biology and Bioinformatics  
Yale University

**Mamie Wang\***, Michael J. Corley†, Jennifer Yoon‡, Jennifer Chiarella‡, Joshua Cyktor§, Serena Spudich¶, Yuval Kluger||, Shelli F. Farhadian‡

\* Program in Computational Biology and Bioinformatics, Yale University, New Haven, CT

† Department of Medicine, Division of Infectious Diseases, Weill Cornell Medicine, New York City, NY

‡ Section of Infectious Diseases, Yale School of Medicine, New Haven, CT

§ Department of Medicine, University of Pittsburgh, Pittsburgh, PA

¶ Department of Neurology, Yale School of Medicine, New Haven, CT

|| Department of Pathology, Yale School of Medicine, New Haven, CT

# Despite suppressive ART, some PLWH continue to show central nervous system (CNS) abnormalities

- Due to multiple factors, such as
  - viral persistence in CNS
  - chronic immune activation in CNS
- We previously showed that
  - HIV enters CNS during acute infection (*Chan JID 2018*)
  - Cerebrospinal fluid (CSF) T cells harbor HIV DNA and RNA, even in PLWH on suppressive ART (*Spudich JCI 2019, Farhadian/Cyktor CROI 2020, Farhadian JCI-insight 2022*)
- However, we **do not know** in PLWH on ART:
  - which CSF T cell types harbor HIV
  - whether HIV-infected T cells in CNS are compartmentalized, or reflect trafficking of infected cells from peripheral blood

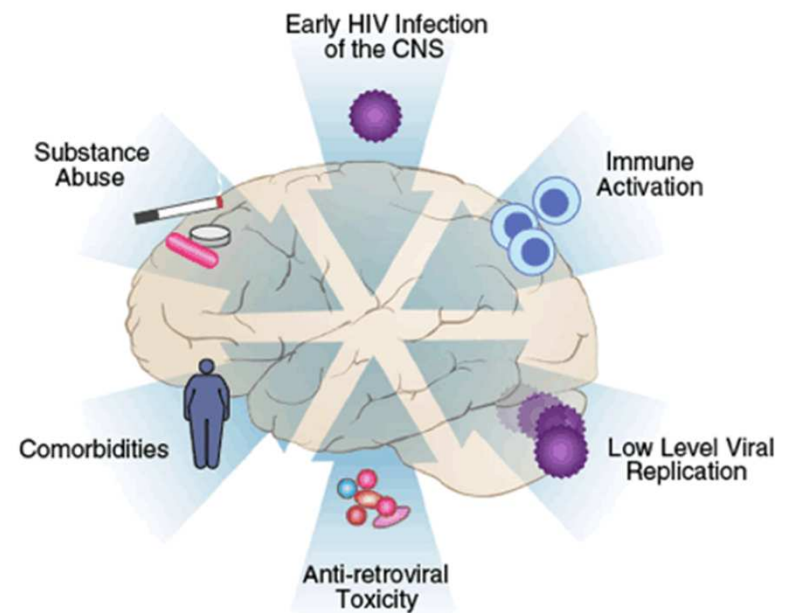
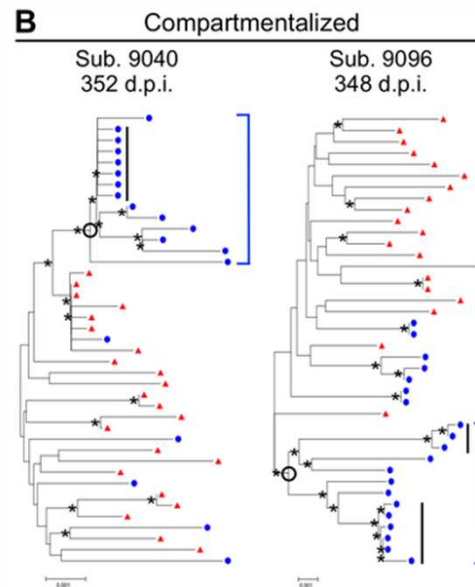


Fig. 1 The pathogenesis of HIV-associated neurocognitive disorder is multifactorial

Farhadian, Patel, Spudich 2017

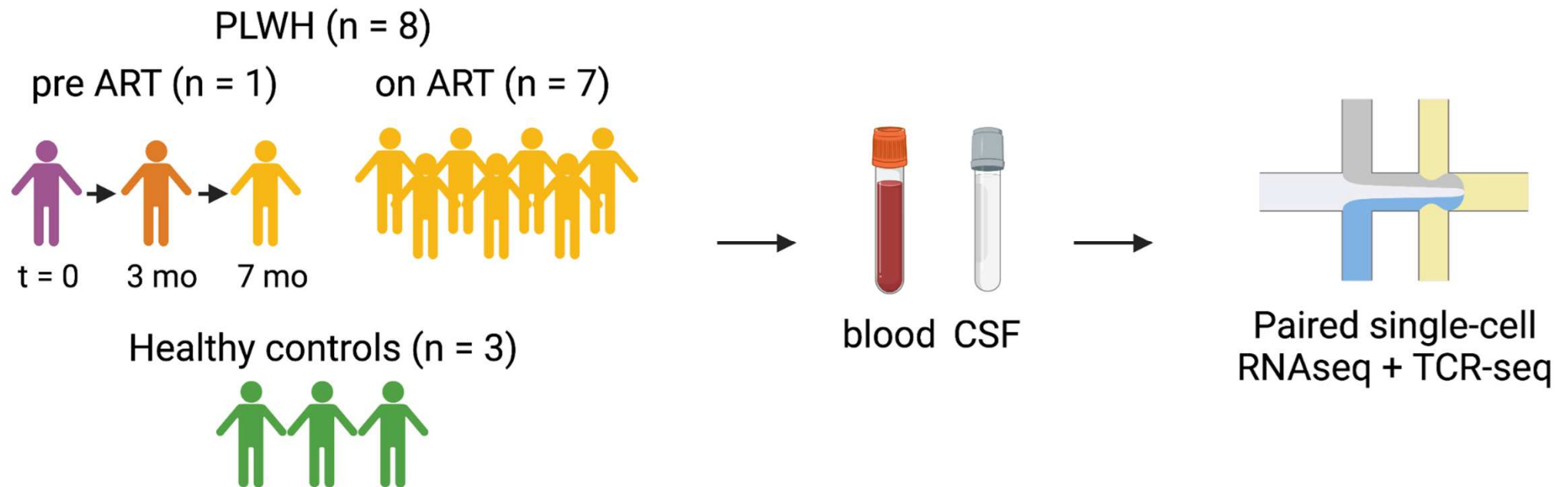
# Research questions

- What type of CSF CD4 T cells contains HIV-1 RNA in PLWH on ART?
- Are HIV-1 RNA producing T cells in the CSF compartmentalized (clonally unique)? Or do they clonally overlap with T cells in the blood?



CSF (blue) and blood (red) derived viral sequences in PLWH not on ART (Sturdevant 2015)

# Single-cell transcriptome and TCR profiling of Blood and CSF of PLWH before and after ART



# Participant characteristics



Participant 1102 (before and after ART)

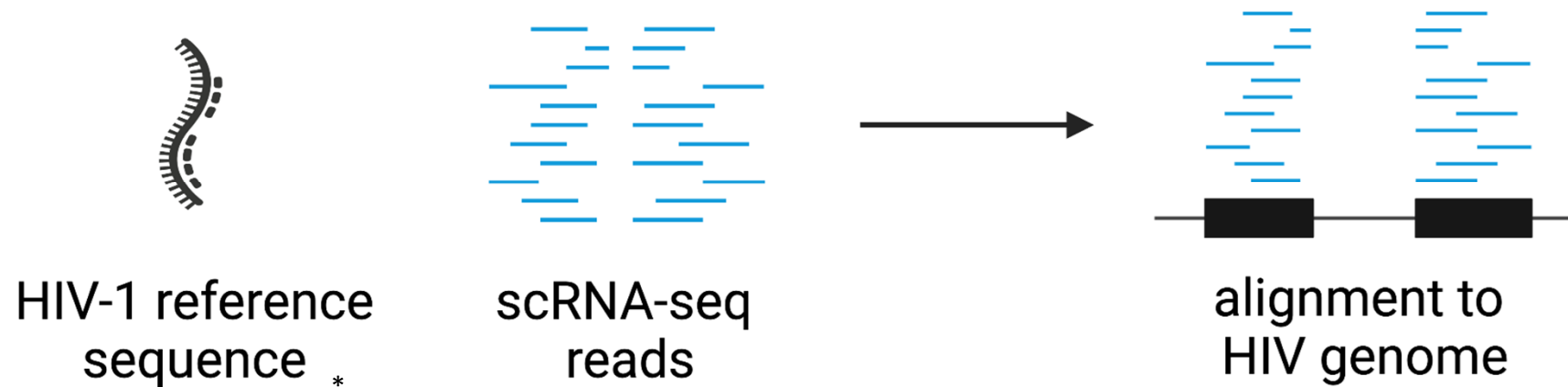
38 year old, Asian, Male



Participants on suppressive ART

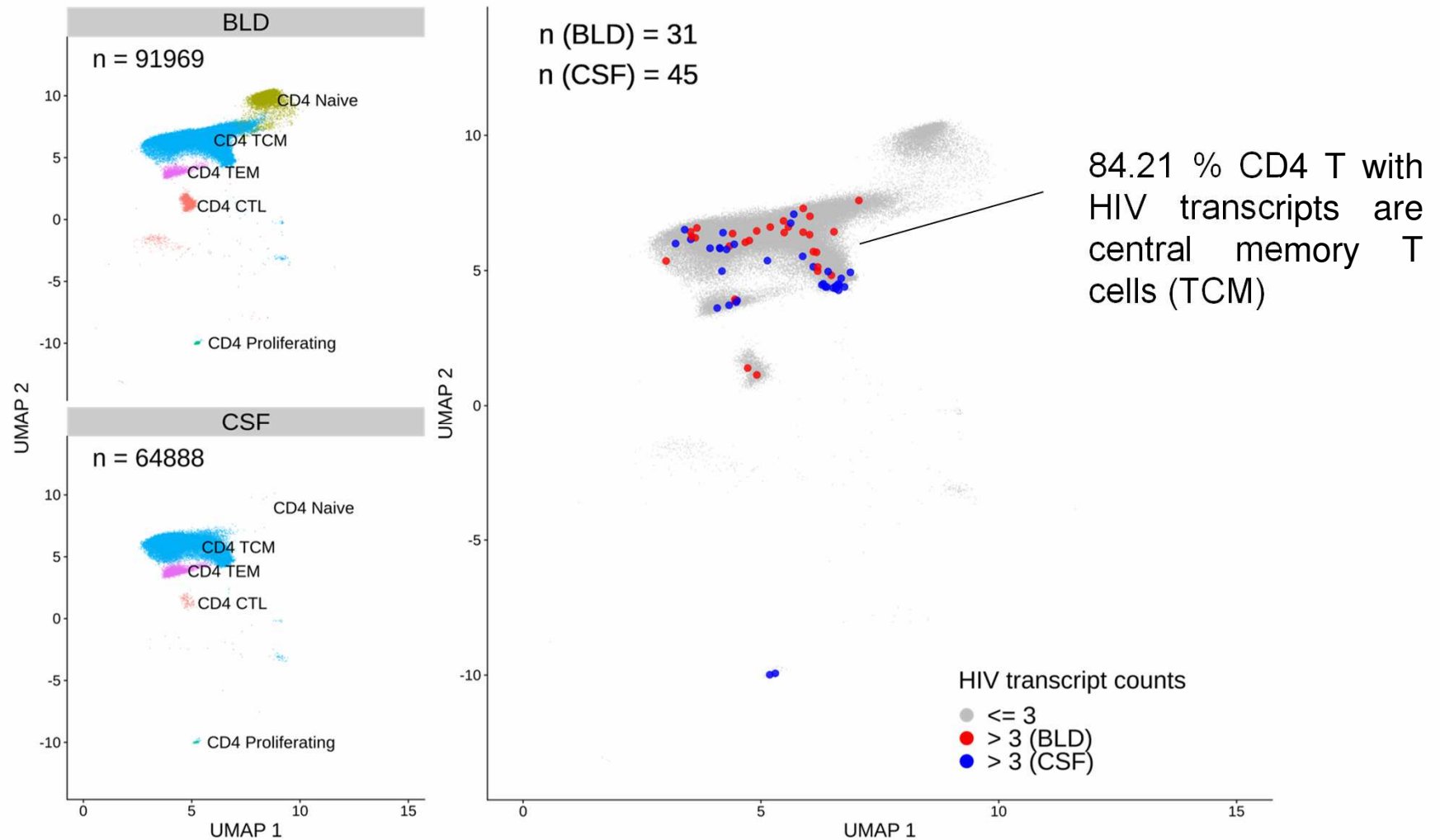
Visit	Time on ART	Plasma HIV Viral Load (copies/mL)	CSF HIV Viral Load (copies/mL)	CD4 Count	ID	Age	Race	Sex	Time on ART	Plasma HIV Viral Load (copies/mL)	CSF HIV Viral Load (copies/mL)	CD4 Count
1	0 month	257,000	49,800	46	1076	47	White	Male	11 years	<20	Not Detected	929
2	3 months	<20	762	104	1037	37	Black or African American	Male	16 years	<20	Not Detected	495
3	7 months	<20	<20	248	1016	56	Black or African American	Male	12 years	Not Detected	Not Detected	359
					1017	62	Black or African American	Male	26 years	Not Detected	Not Detected	503
					1109	61	Black or African American	Female	21 years	Not Detected	Not Detected	740
					1035	59	White	Male	24 years	Not Detected	Not Detected	511
					1111	34	White	Male	14 years	45.1	<20	491

# Identifying cells with HIV transcripts

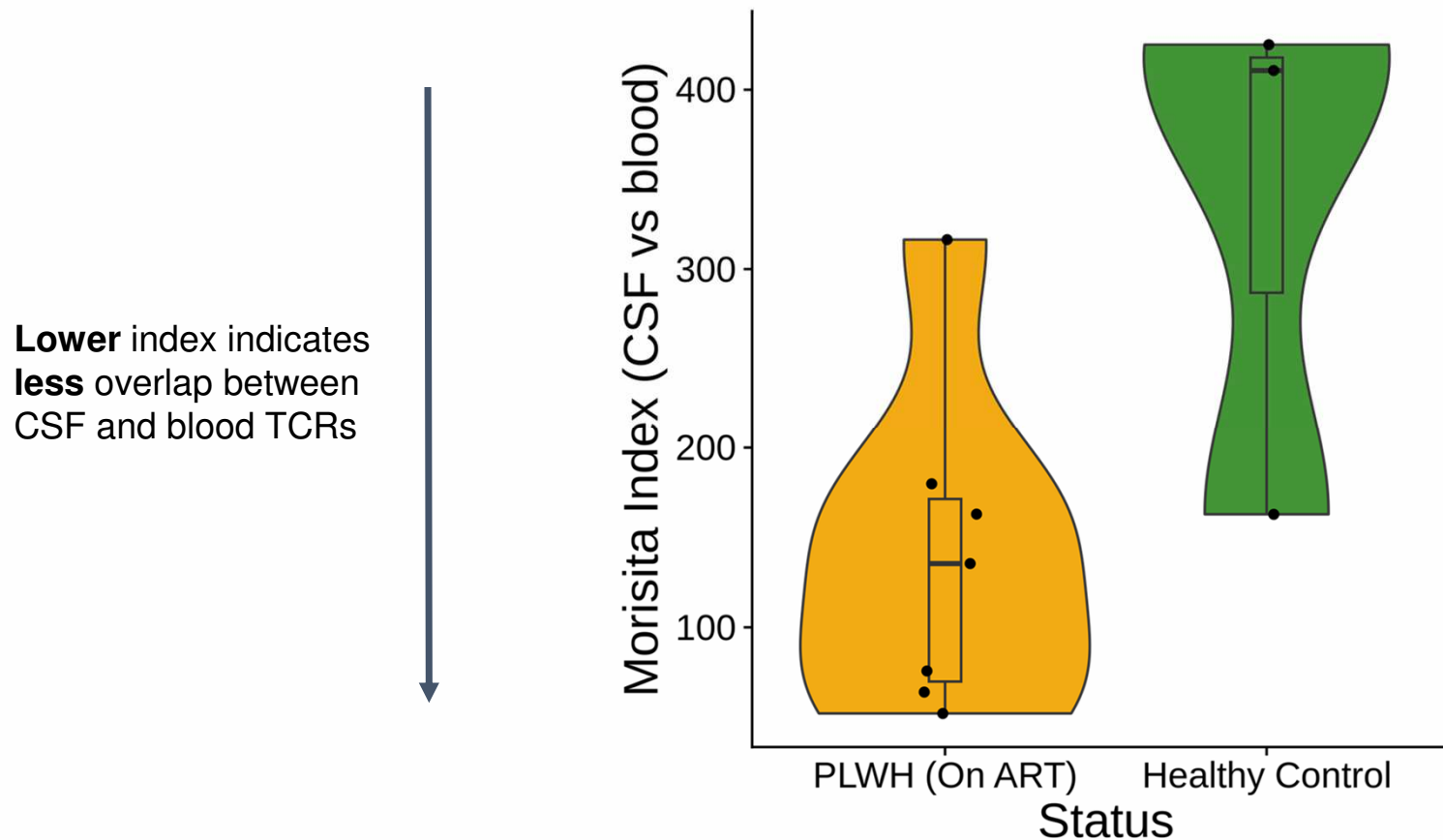


\* HXB2 (GenBank: K03455); plan to use autologous HIV sequences in the future

# HIV transcripts were identified in CD4 T cells in both blood and CSF



# Low clonal overlap of blood and CSF T cells in PLWH on ART compared to healthy controls



Most cells with HIV-1 RNA belong to tissue-specific clones





# Lower frequency of cells in shared clones after ART

**pre ART**

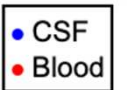
**on ART (v2)**

**on ART (v3)**

Shared clone: present in both BLD and CSF

CSF-specific

BLD-specific



% T cells in shared clones

31

16.3 %

9.9 %

% shared clones

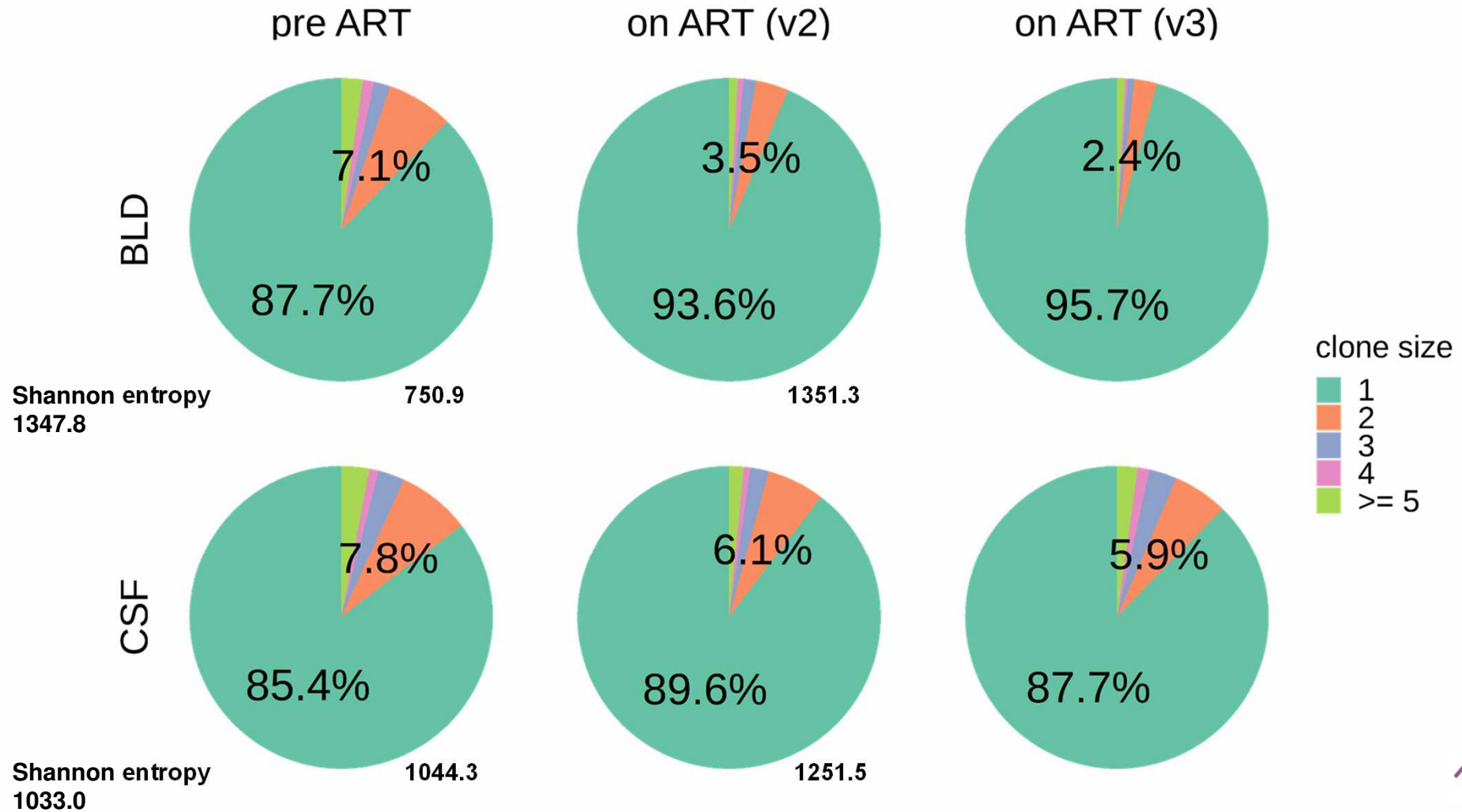
%  
6.4 %

3.9 %

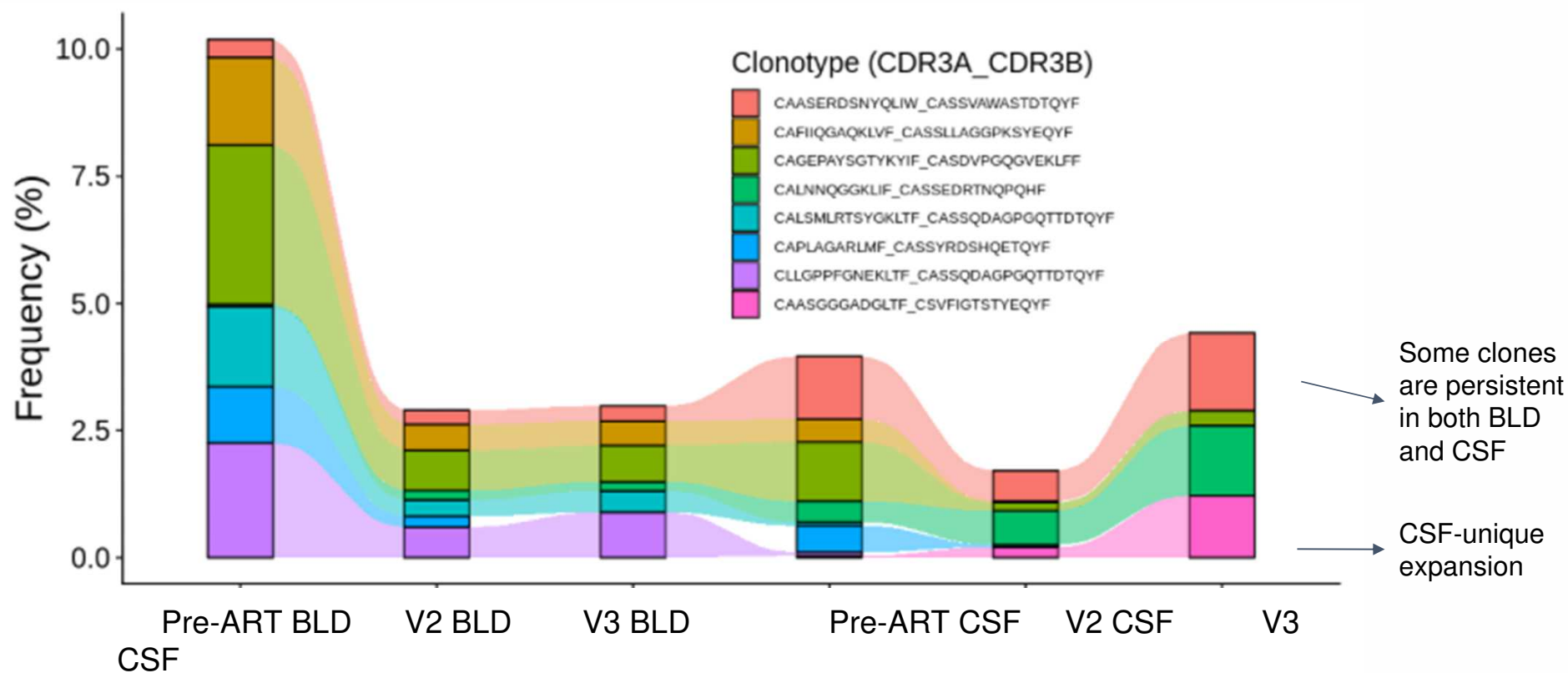
2.3 %



# T cell clones remain expanded in CSF while shrink in blood after ART

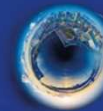


# Expansion of CSF-unique clone after ART



\*None of the above clones contain infected cells





## CONCLUSIONS

### Findings

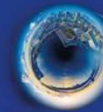
- HIV-1 RNA producing CD4 T detected in CSF and blood of PLWH on ART are primarily central memory T cells
- After initiation of ART in 1 PLWH, there are expanded T cell clones in the CSF, some of which are tissue specific

### Implication

- Preliminary evidence for compartmentalization of T cell clones between CSF and blood in PLWH after ART (persistent viral antigen presence in CNS?)

### Limitations

- No antigen specificity information on the TCR
- 10x platform do not output full-length viral sequence (replication-competent?)



## COMMUNITY SUMMARY

- Question
  - Are HIV infected T cells in central nervous system (CNS) clonally related to T cells in the blood?
- Findings
  - Infected CD4 T cells are present in CSF despite ART
  - Most CSF infected T cells are not clonally related to blood T cells after ART
- Next steps
  - Obtain more data to validate the preliminary findings
  - Understand what attracts some T cells to CNS

**Thank you to the research participants!**

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# Higher frequency of HIV-1 RNA-containing CD4 T cells in CSF than blood in some patients on ART

