

19ª edición

POSTCROI

Una actualización de la “29th Conference on Retroviruses and Opportunistic Infections”

Curación del VIH

Javier Martinez-Picado, PhD



LIVE RECONFERENCES

POST **CROI** 2022

SATURDAY, FEBRUARY 12, 2022

Workshop-1 SCOTT M. HAMMER WORKSHOP FOR NEW
INVESTIGATORS AND TRAINEES

CME

8:30 AM MT - 12:30 PM MT

ADVANCES IN MOLECULAR VIROLOGY OF HIV AND SARS-CoV-2

*Theodora Hatziloannou, Rockefeller University,
New York, NY, USA*



ADVANCES IN HIV AND SARS-CoV-2 IMMUNOLOGY

*Penny Moore, University of the Witwatersrand,
Johannesburg, South Africa*



BREAK

ADVANCES IN HIV CURE WITH CLINICAL PERSPECTIVES

*Peter W. Hunt, University of California San Francisco,
San Francisco, CA, USA*



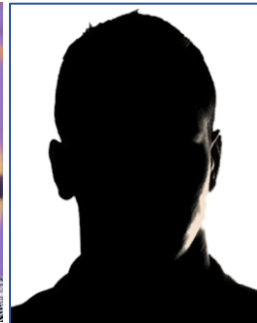
4th case of HIV cure



Timothy Brown
Berlin Patient
13 years



Adam Castillejo
London Patient
4.5 years



Düsseldorf Patient
3 years



CCR5 Δ 32
Donor

HIV
patient

cured
HIV patient



HIV^{resistant}



HIV⁺



HIV^{resistant}

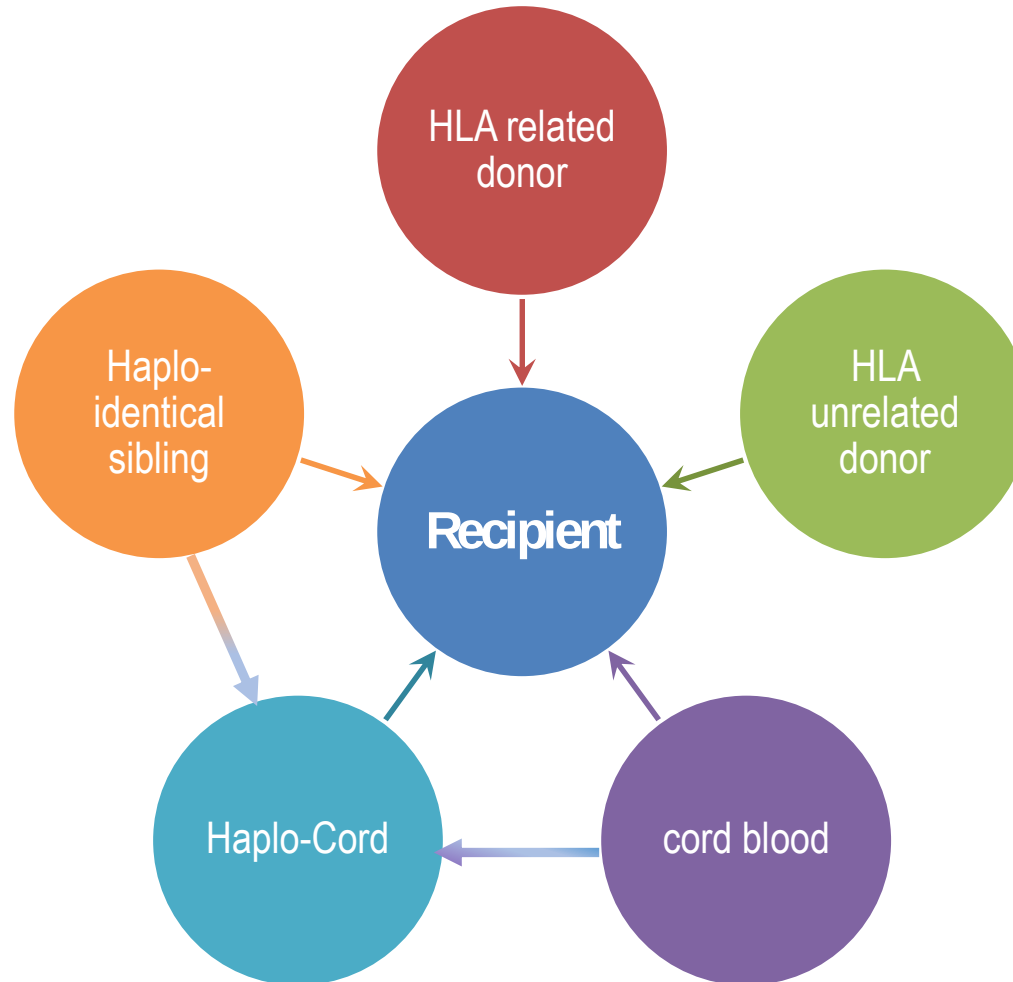
HIV-1 REMISSION WITH CCR5 Δ 32 Δ 32 HAPLO-CORD TRANSPLANT IN A US WOMAN: IMPAACT P1107

Yvonne Bryson

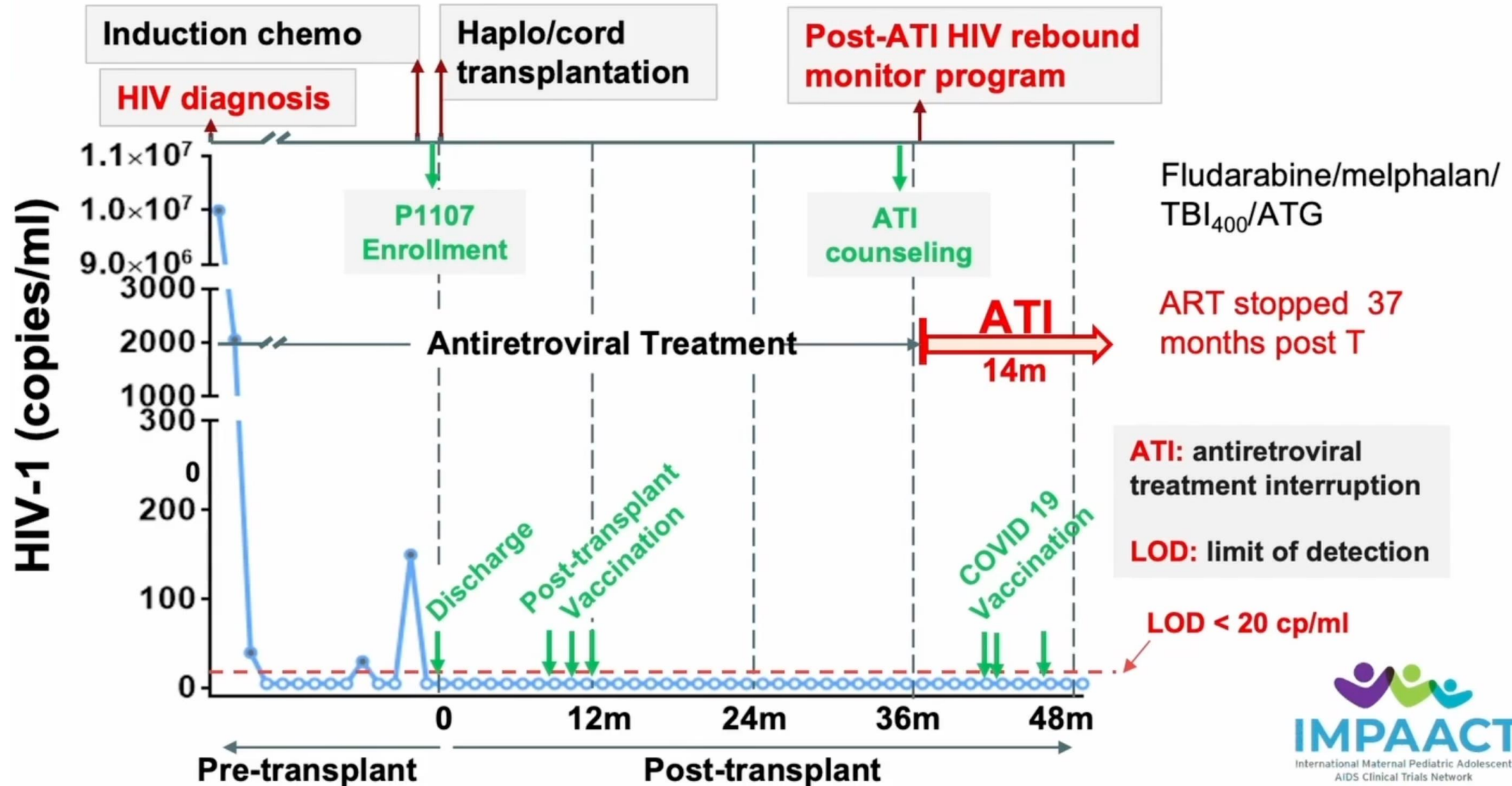
- Female; mid age; mixed race
- Dx acute HIV-1 in 2013
- High-risk AML monosomy 7 in 2017
- Partially matched CCR5 Δ 32/32 cord units
- Haplo-cord transplant: 5/8 match CBU + relative PBMCs in 2017

4th case of HIV cure

- Haplo-cord transplant: 5/8 match CBU + relative PBMCs in 2017



HIV-1 and AML Treatment Course



4th case of HIV cure

- Durable remission of AML 4.5 years post-Stem Cell Transplant
- 14 months off art; no viral rebound
- No Graft vs Host Disease
- Negative-(transient trace) HIV DNA by ddPCR
- No detectable replication-competent latent reservoir in 74.5 million CD4+
- Undetectable HIV-1-specific cellular immune responses
- HIV antibodies negative
- *In vitro* resistant to lab and autologous virus

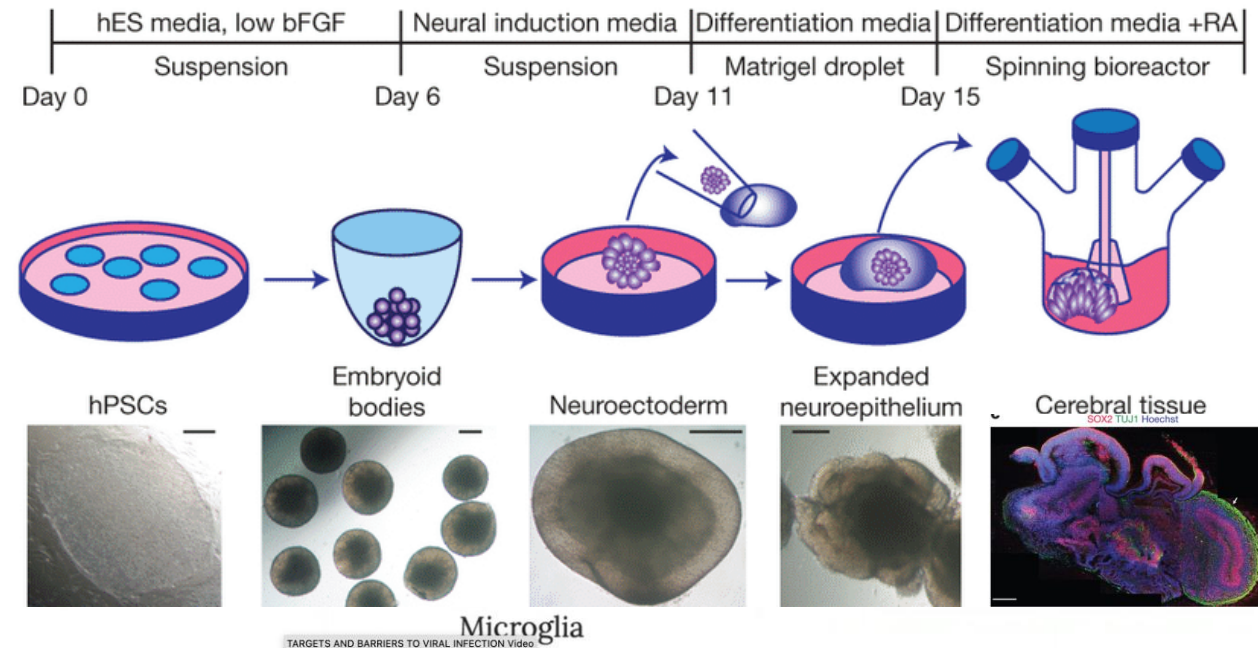
Anatomical reservoirs: BRAIN !

HIV INFECTION OF BRAIN ORGANOID MICROGLIA INDUCES INFLAMMATION AND NEURONAL DEATH

Weili Kong

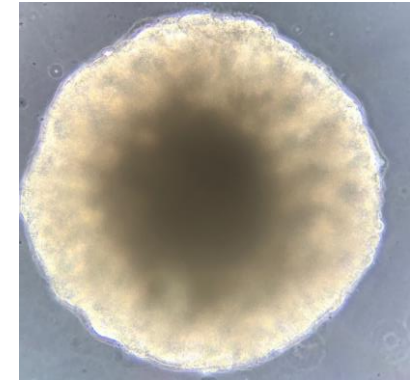
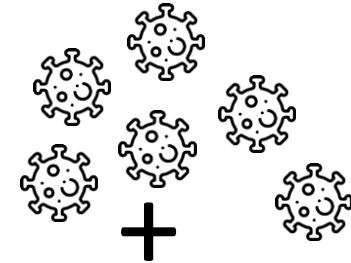
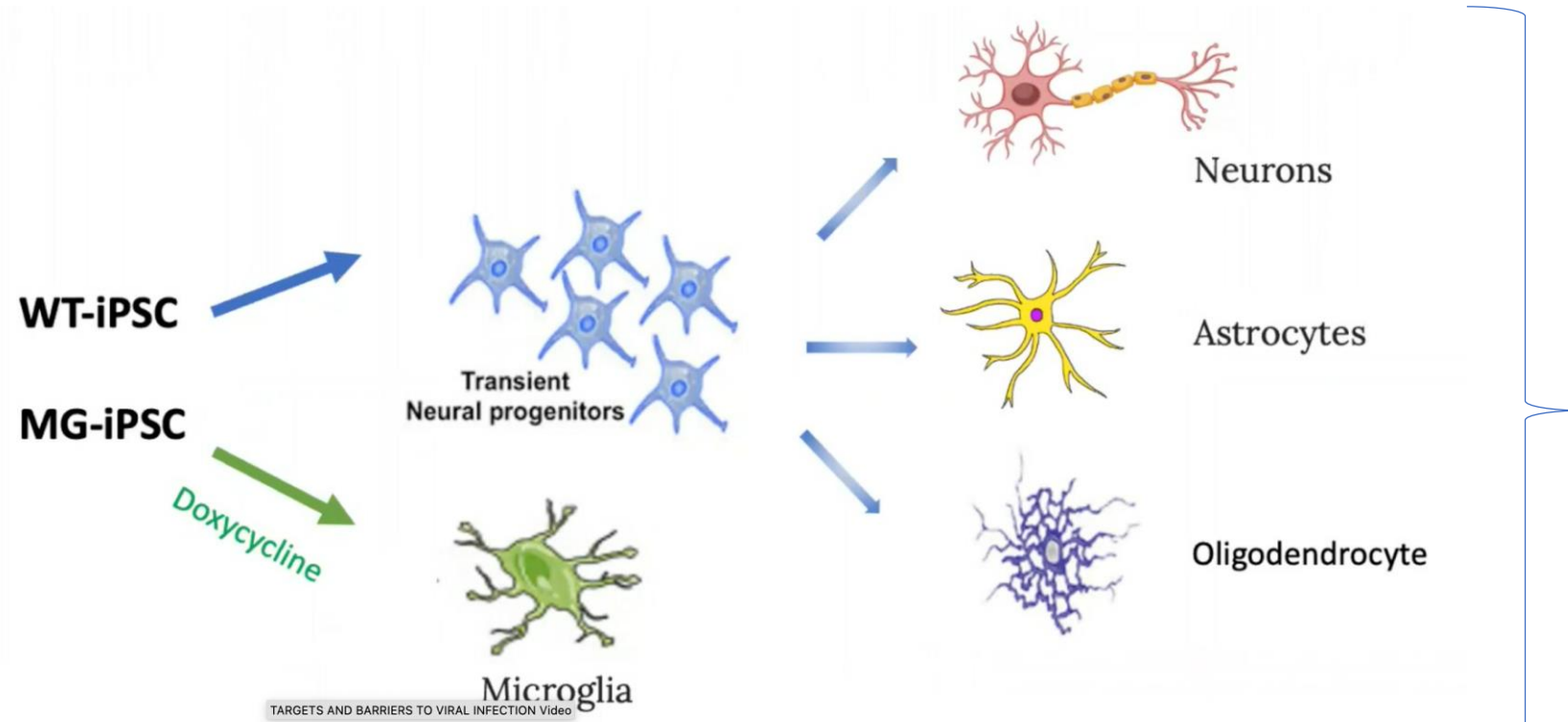


The Extraction of the Stone of Madness
Hieronymus Bosch (c. 1488–1516)

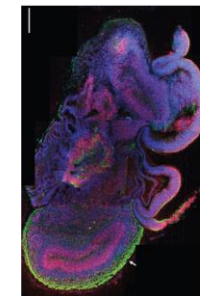


Tissue Engineering Brain Organoids
Lancaster *et al.* Nature

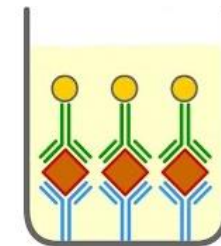
Brain Organoids



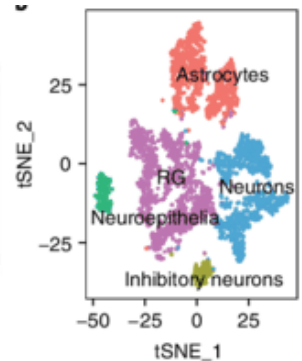
Immuno
staining



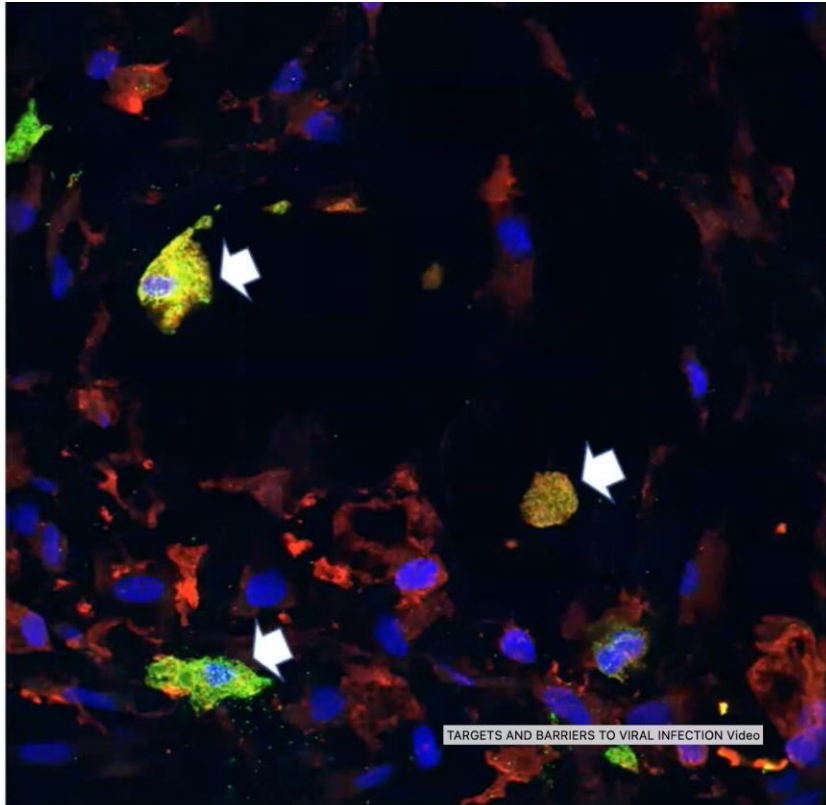
ELISA



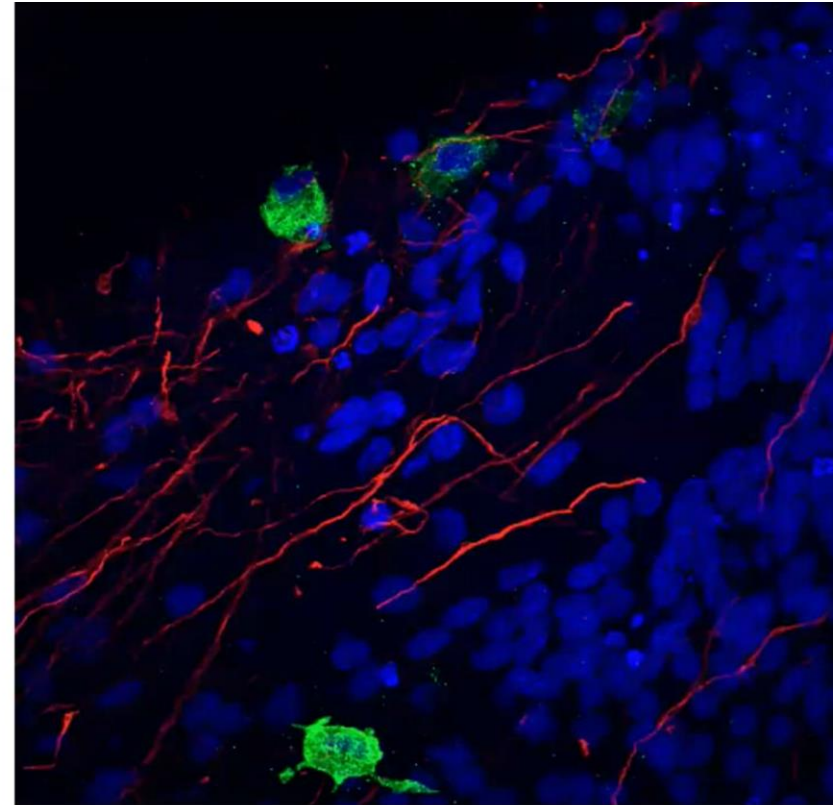
scRNAseq



HIV preferentially infected microglia



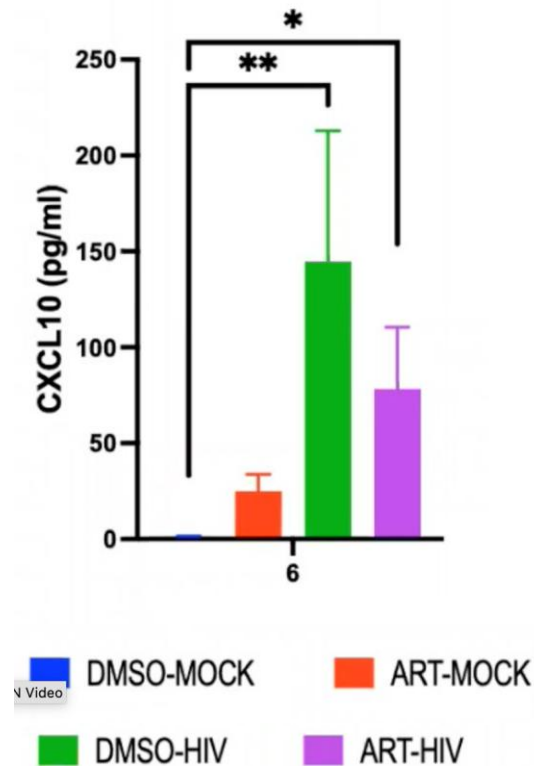
DAPI/IBA1/Gag
microglia HIV



DAPI/GFAP/Gag
astrocytes HIV

HIV infection increases inflammation

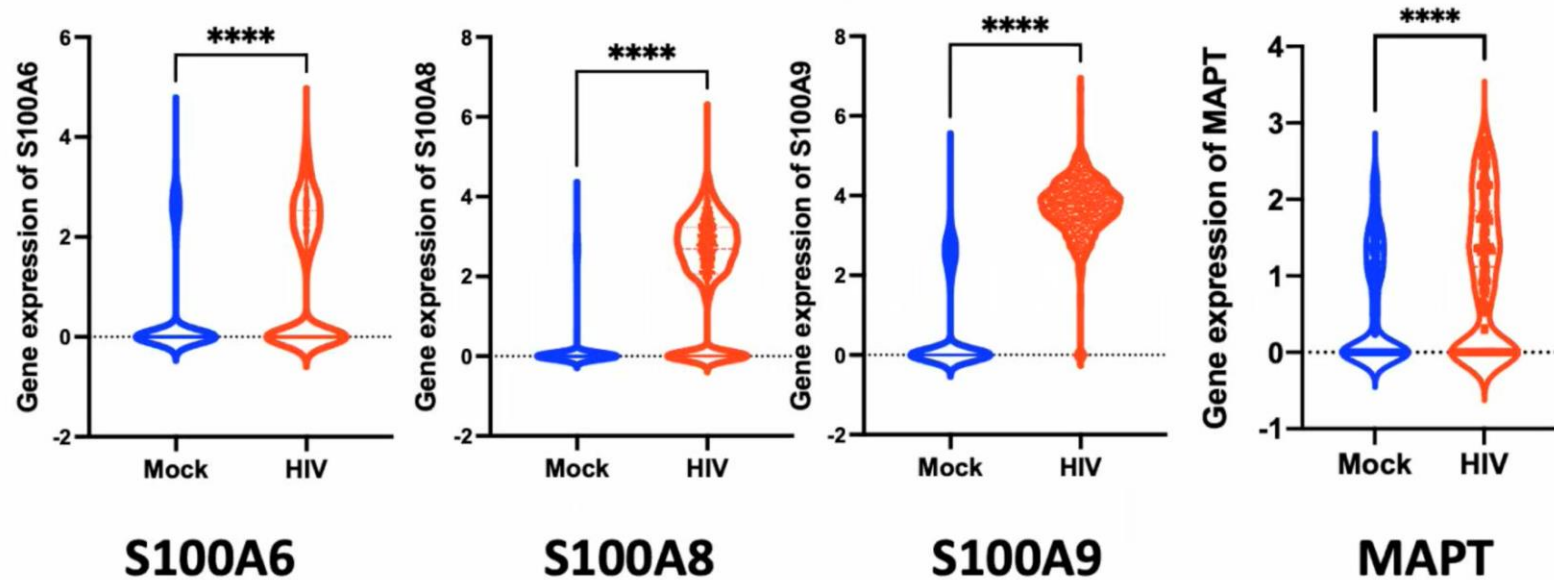
- Infection → CCL2 and CXCL10, which promote recruitment of T cells and monocytes to cross the BBB (contributing to development of HAND)



HIV infection of microglia leads to S100 protein-inflammation and tau accumulation in uninfected neurons

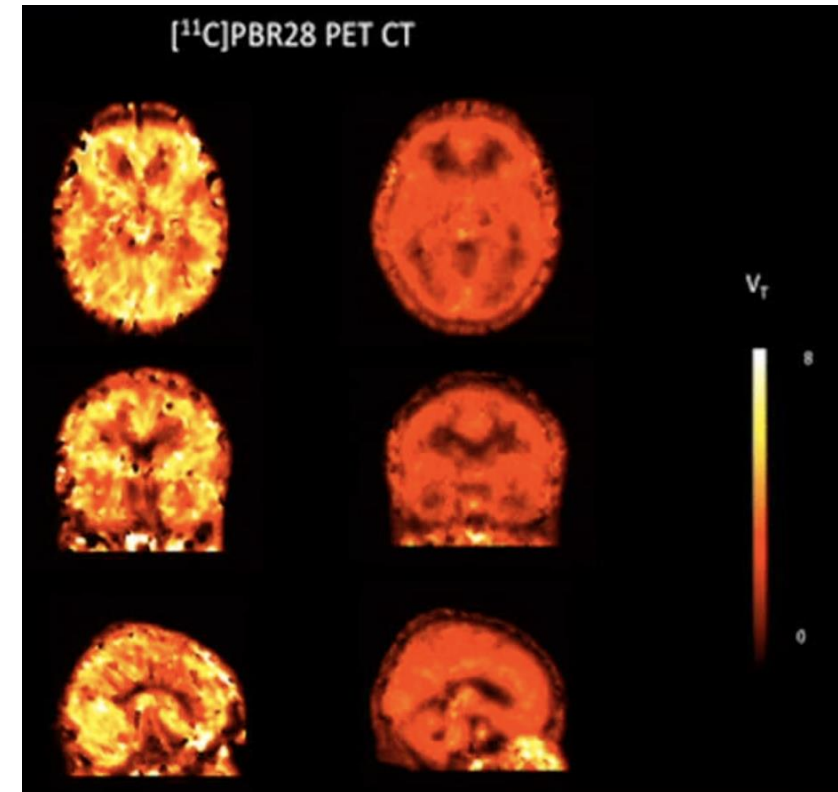
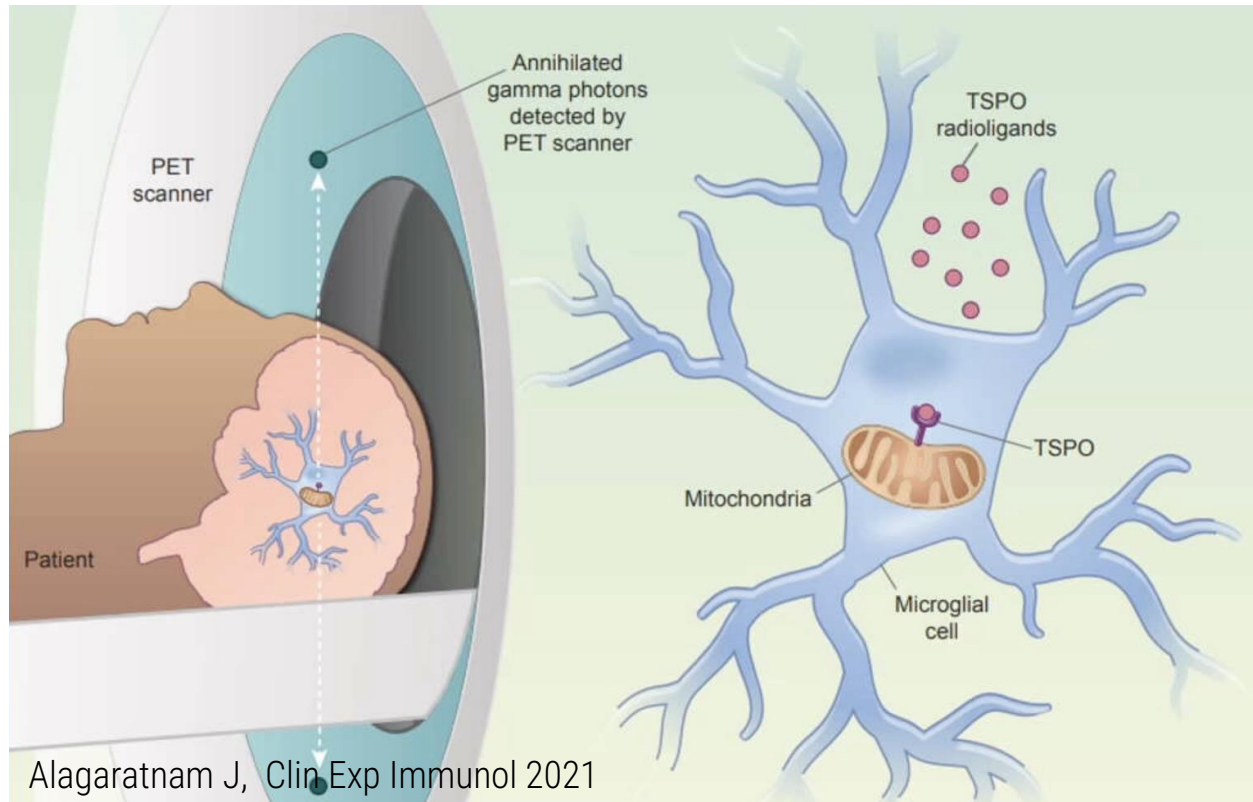
↑ S100 family of genes that regulate diverse cellular processes including inflammation, proliferation, migration, apoptosis, energy metabolism

↑ neuro-inflammatory responses in bystander neurons leading to decreased mitochondrial energy generation, diminished neurotransmitter transport, and increased neuronal cell death



Assessing neuro-inflammation *in vivo*

- Translocator protein (TSPO) expressed in Microglial Mitochondria

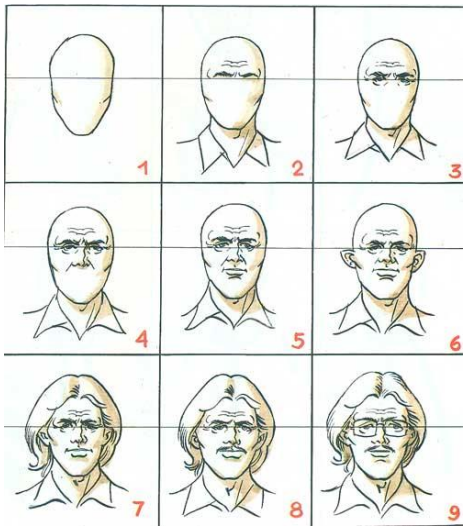


- More neuroinflammation in people with chronic ART vs. acute ART (and HIV–)

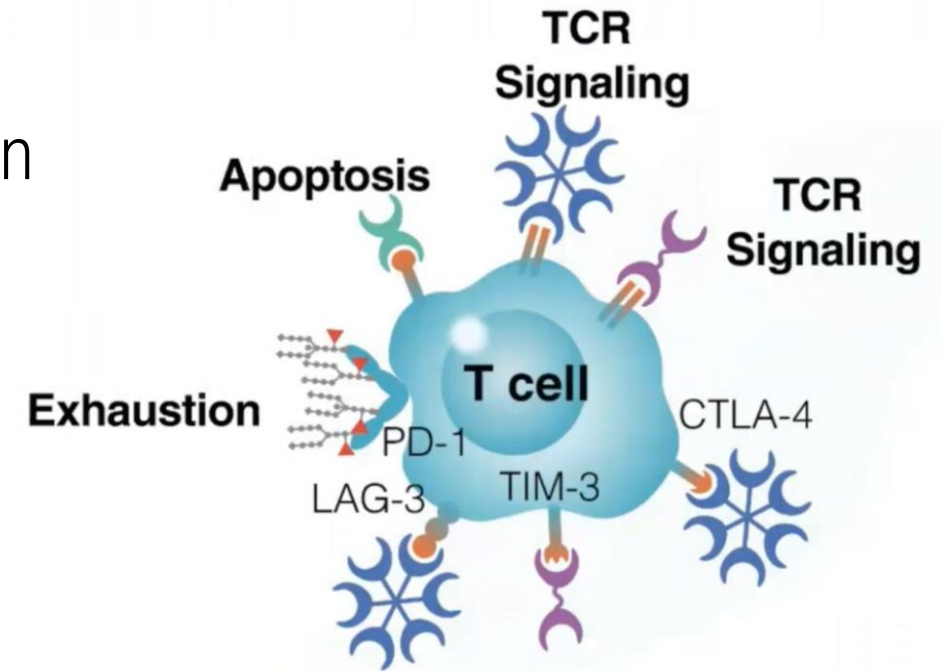
Identification of cells susceptible to HIV infection

CyTOF-Lec REVEALS GLYCAN FEATURES DEFINING CELLS DIFFERENTIALLY SUSCEPTIBLE TO HIV

Tongcui Ma



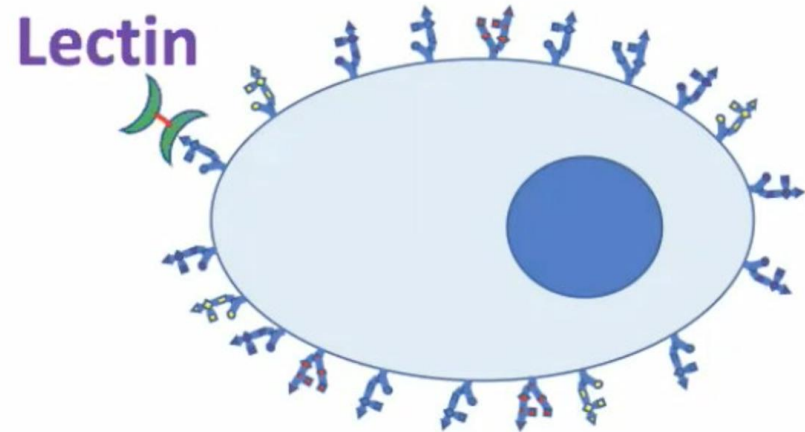
- Glycans play an important role in T cell function and signaling
- Can glycans help distinguish those cells that are more susceptible to HIV infection?



Colomb F et al. Curr HIV/AIDS Rep, 2019

CyTOF-Lec

- Combining CyTOF with glycan single-cell analysis



WGA, binding total sialic acid
 MAL-1, binding branched sialic acid
 CLA, binding to fucose and/or sialic acid
 AOL, binding total fucose
 UEA-1, binding branched fucose
 ABA, binding to TF antigen

Sialic acid binding

Fucose binding

Lineage Markers

T Cells:
 CD3
 CD4
 CD8

B Cells:
 CD19

Phenotyping Markers

Differentiation

State:

CD45RO
 CD45RA
 CD62L
 CD127
 CD27
 ROR γ t
 Tbet
 CRTH2

Activation

State:

CD69
 CD25
 CD28
 CD30
 HLADR
 CD38
 ICOS
 OX40

Exhaustion/Activation

markers:

PD1
 TIGIT
 CTLA4

Adhesion

and

integrins:

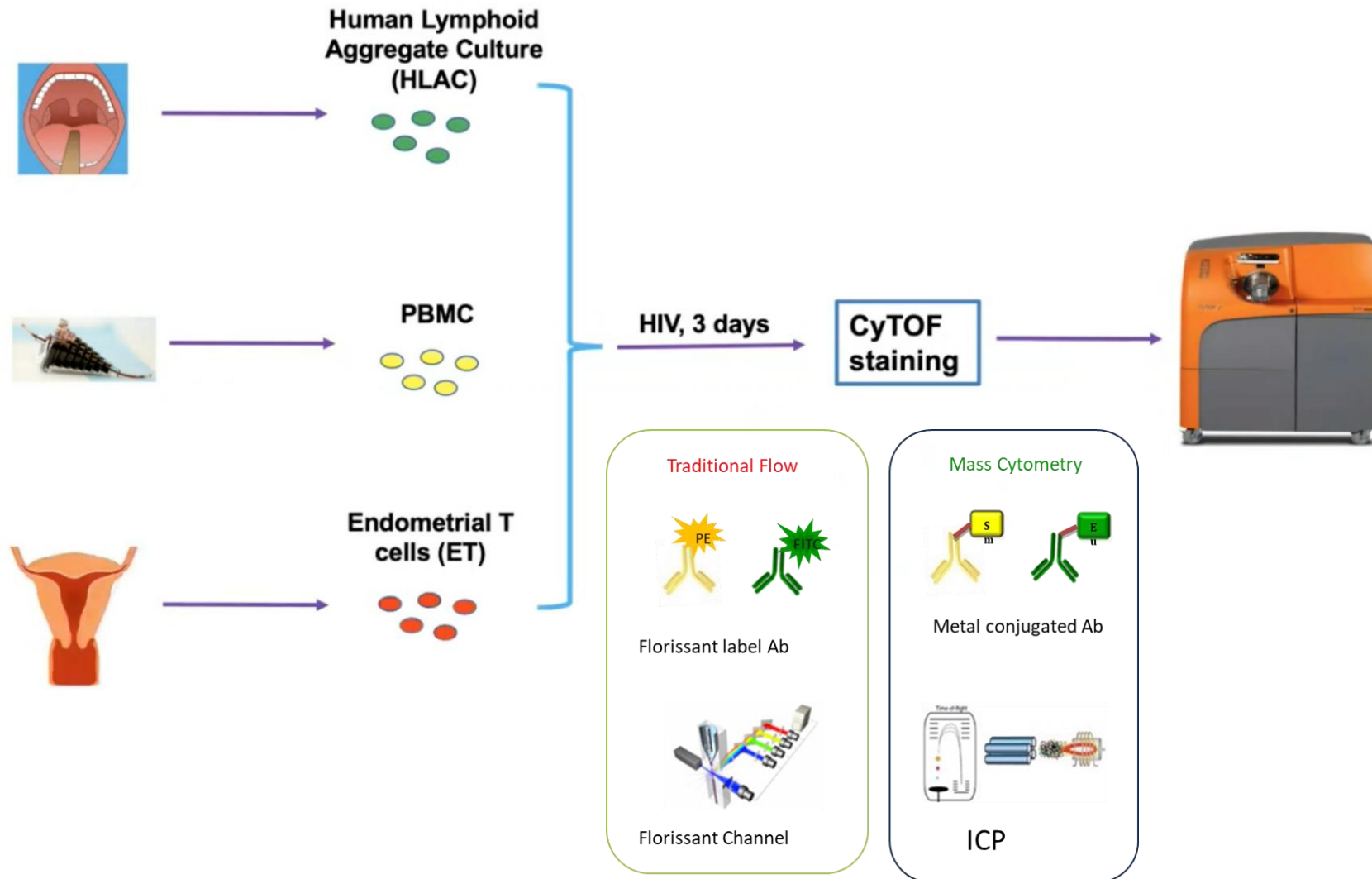
CD7
 α 4 β 7

Homing

Receptors:

CCR5
 CCR6
 CCR7
 CXCR4
 CXCR5

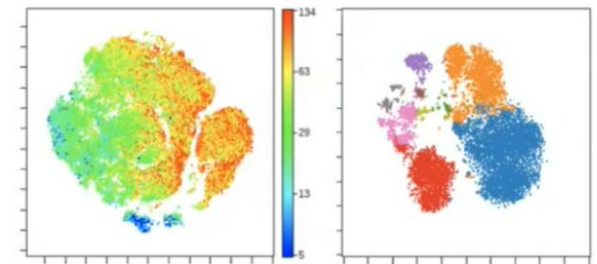
CyTOF-Lec



Clustering approaches

Heat map

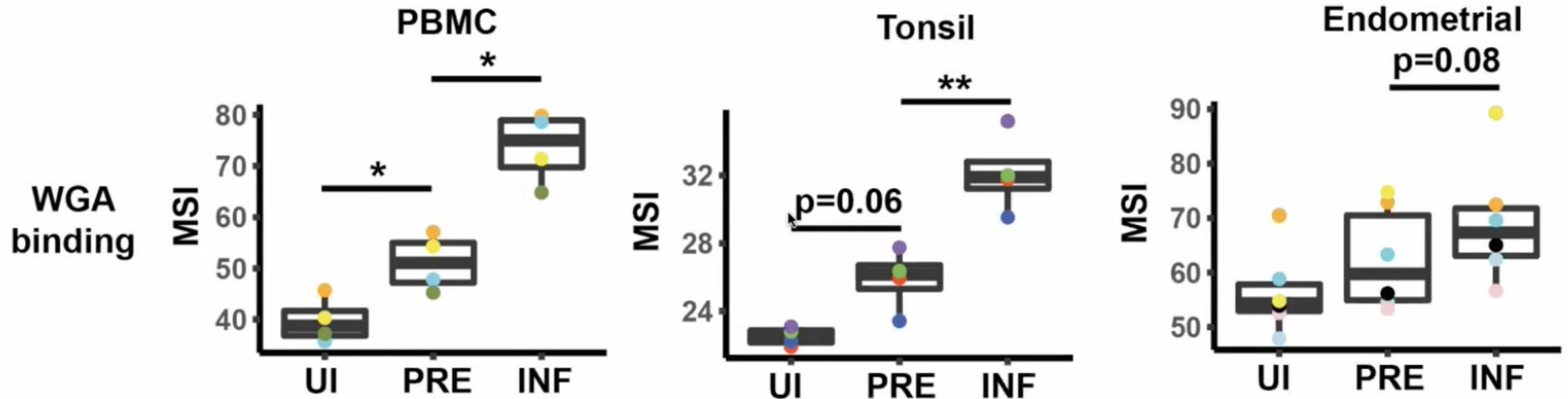
FlowSOM



HIV preferentially infects cells with high sialic acid, and further unregulates it



Memory CD4⁺ T cells with high levels of sialic acid express high levels of **HIV receptor/co-receptor**, are **T_{EM}⁻** like, and express markers of **activation** and **cell survival**



UI: Uninfected; PRE: Predicted Precursor of infection; INF: Infected

HIV cure in babies: after the Mississippi baby

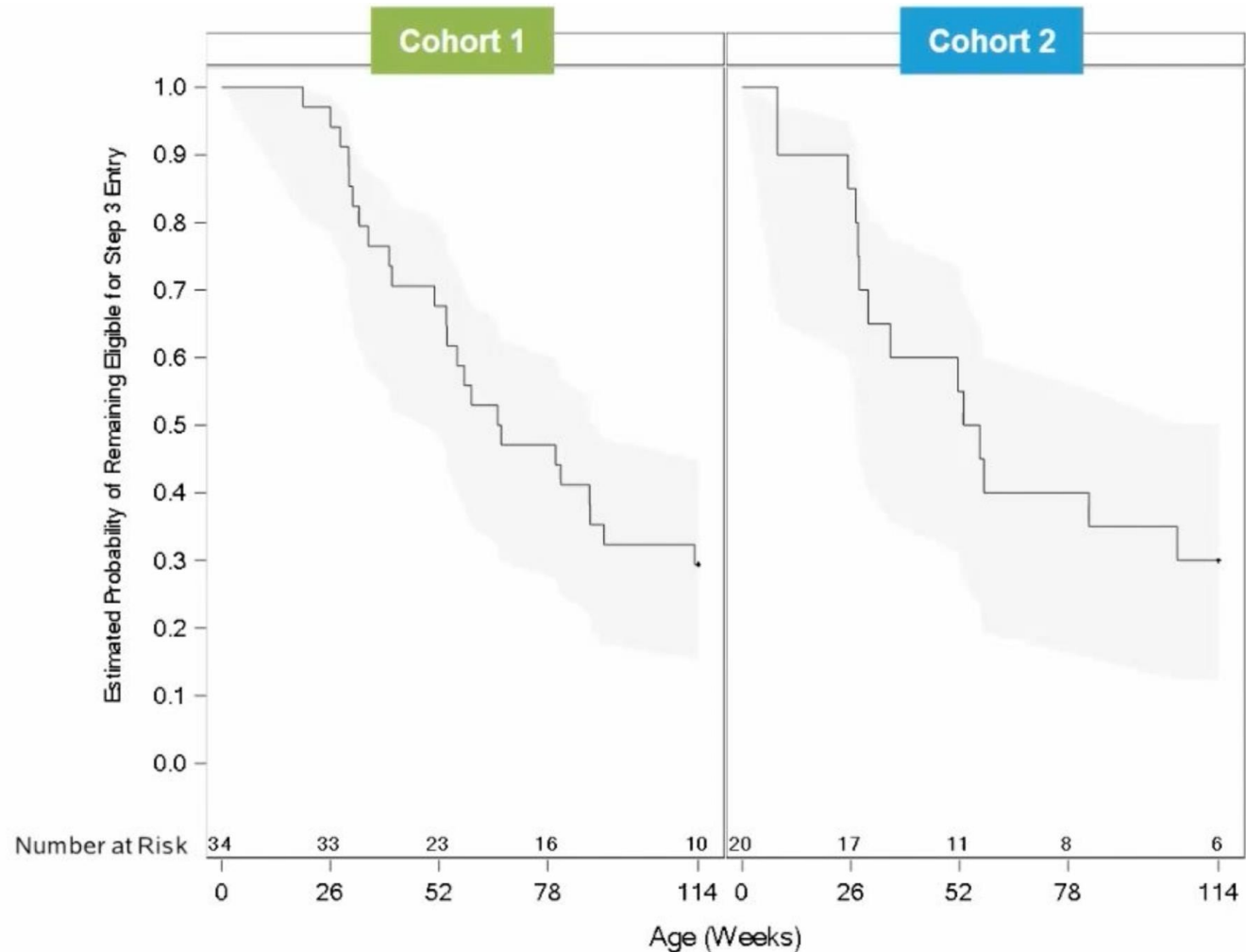
31. TWO-YEAR VIROLOGIC OUTCOMES OF VERY EARLY ART FOR INFANTS IN THE IMPAACT P1115 STUDY

Deborah Persaud

- 2 cohorts, 30 sites, 11 countries, 2015-2017
- 54 infants infected in utero
- ART <10 days
- Potential ART interruption after 2 years if:
 - Plasma viremia < LOD
 - HIV-1 cell-associated DNA (proviral) < LOD
 - Negative HIV-1 Abs



Potential Eligibility for ART interruption through 2 years of age



Estimated Probability of Remaining Potentially Eligible at two years of age:

Overall:
30% (95% CI 18%-42%)

Cohort 1:
29% (95% CI 15%-45%)

Cohort 2:
30% (95% CI 12%-50%)

HIV cure in babies, with some help from bNAb

32. TREATMENT WITH BROADLY NEUTRALIZING ANTIBODIES IN CHILDREN WITH HIV IN BOTSWANA

Roger L. Shapiro

- Let's get some help from broadly neutralizing Abs (VRC01-LS + 10-1074)
- ART < 7 days
- Eligible if:
 - > 2 years
 - Plasma viremia < 40 cps/ml last 24 weeks before study entry
- Design:
 - 8-32 weeks ART + Abs
 - up to 24 weeks Abs
 - Back to ART without Abs

HIV cure in babies with some help from bNAb

- 11 (44%): 24 weeks < 40 cps/ml
in longer ART/bNAbs overlaps
- 14 (56%): median failure : 4 weeks
- Future:
 - Longer ART/bNAbs overlap
 - Newer nNAb combinations with greater breadth and potency

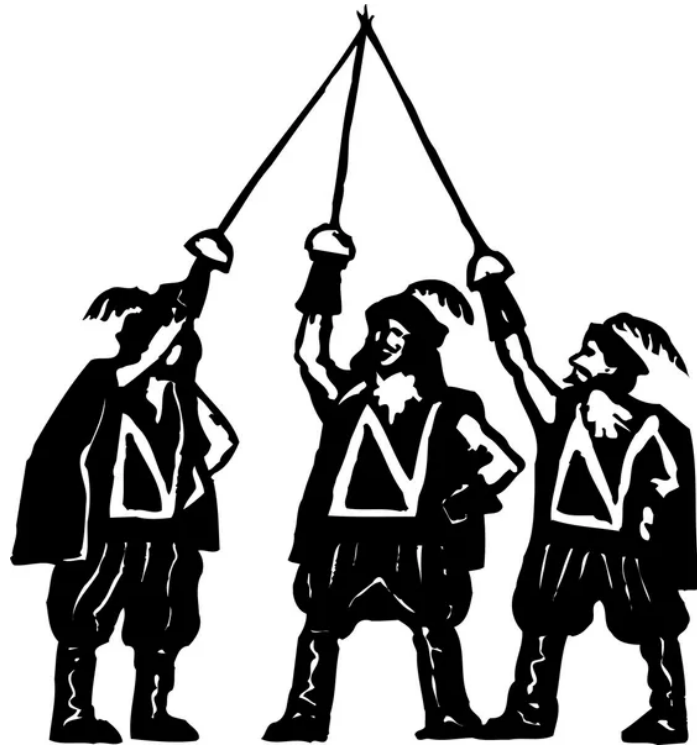
Enrolled	Visit Week on bNAbs Alone																
	0	1	2	3	4	6	7*	8	10	12	14	15*	16	18	20	22	24
1	--	--	--	--	--	--		--	--	--	--		--	--	--	--	--
2	--	--	--	--	--	--							--	--	--	--	--
3	--	--	--	--	--	--		--	890								
4	--	--	--	--	--	--		--	--	--	--		--	--	--	--	--
5	--	--	--	--	--	--		--	--	--	--			--	--	--	--
6	--	--	--	--	--	--		--	--	--	--		234	--	--	--	--
7	--	--	--	--	--	--		--	--	--	--		--	--	--	--	--
8	--	--	--	43K									--				
9	--	--	--	--	--	--		--	--	--	--		--	--	--	--	--
10	--	--	--	58	37K								--	--	--	--	--
11	--	--	--	--	--	--		--	--	--	--		--	--	--	--	--
12	--	--	--	--	--	--		--	--	--	--		--	--	--	--	--
13	--	--	--	225	23K								--	--	--	--	--
14	--	--	--	--	--	--		--	--	--	--		--	--	--	--	--
15	--	--	--	--	--	--		--	--	--	--		--	--	--	--	--
16	--	--	--	--	--	--		--	--	--	--		--	--	1K		
17	--	--	--	742													
18	--	--	--	119	31K												
19	--	--	--	--	--	--		--	--	--	--		--	42	6K		
20	--	--	6K														
21	--	246	85K														
22	--	--	--	--	--	293	438										
23	--	--	--	--	--	--		7K									
24	--	--	--	--	--	--		--	--	--	369	3K					
25	--	1K															

-- indicates HIV RNA < 40 copies/mL

*additional visit scheduled if prior HIV RNA 40-399 copies/mL

ART + bNAb + Latency Reactivation Agent

Open Label
Research Clinical Trial
eCLEAR



ART

3BNC117
(bNAb)Romidepsin
(LRA)

ART

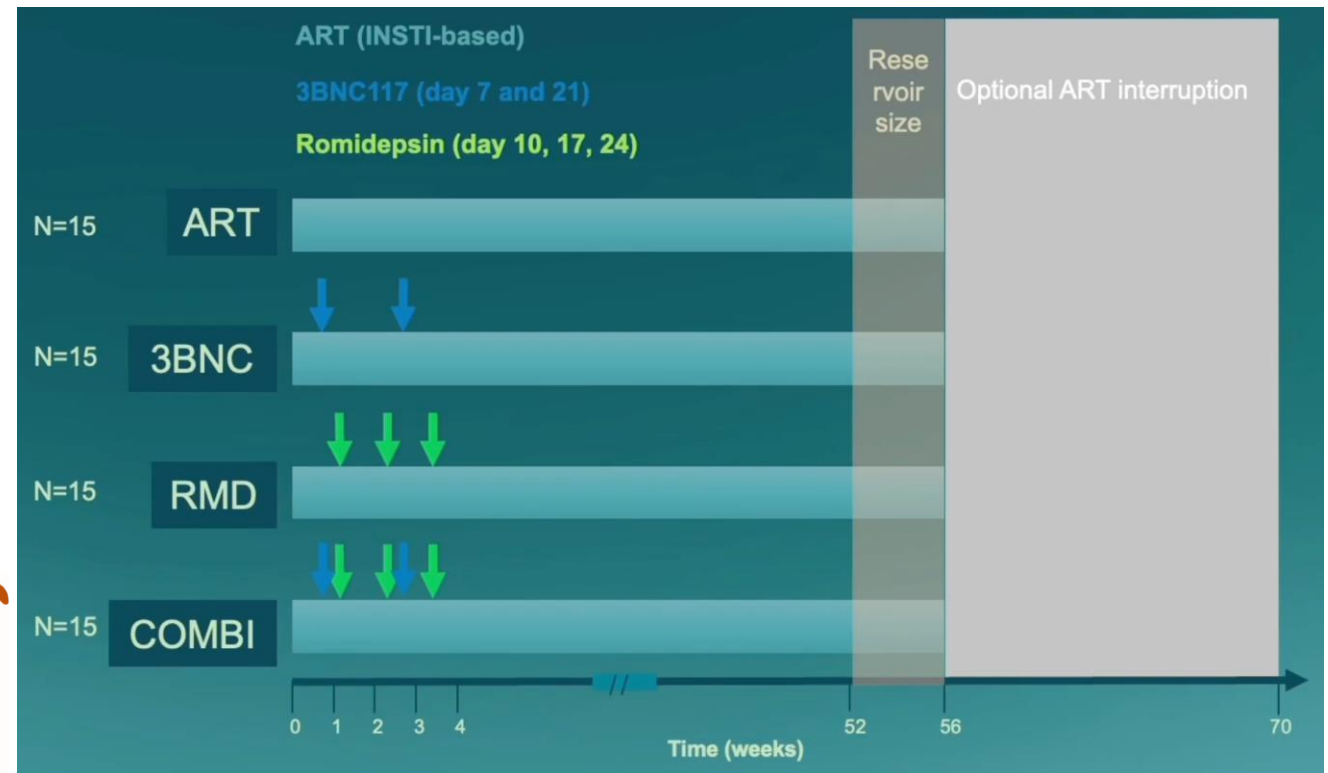
RhmAbs

AZD5582
(Smac mimetic)

A64

THE IMPACT OF 3BNC117 AND ROMIDEPSIN TREATMENT AT ART INITIATION ON HIV-1 PERSISTENCE

Ole Søgaaard



5 sites Denmark + 2 sites in UK

Pre-ART sensitivity to 3BNC117

ART+3BNC117: 8/15 (53%) sensitive

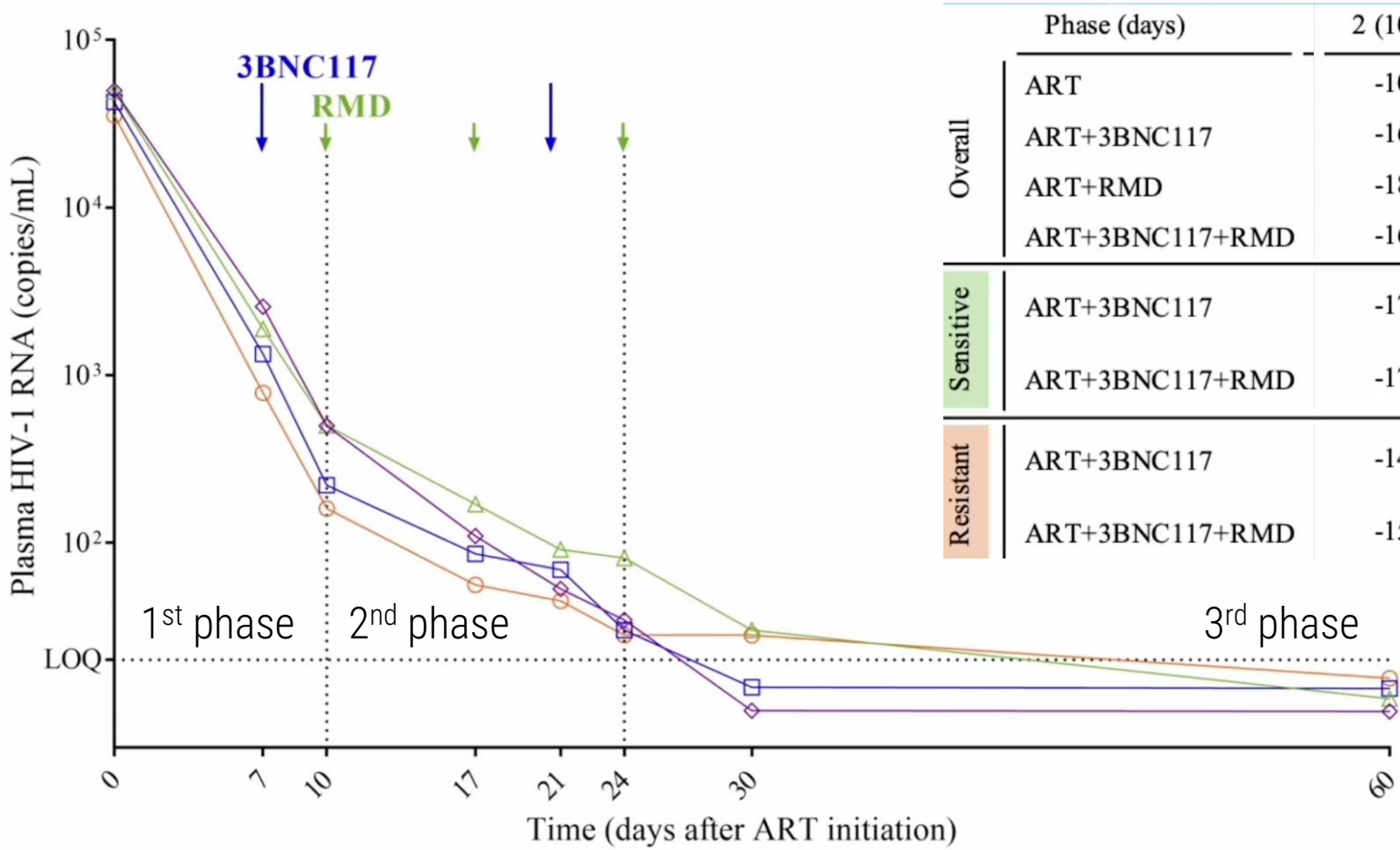
	Participant ID	Monogram PhenoSense		<i>env</i> sequencing	Assessment
		IC90	MPI	Sensitive/total	
ART+3BNC117 (n=15)	109	-	-	33/33	Sensitive
	135	-	-	31/31	Sensitive
	210	0.62	98.0	-	Sensitive
	211	-	-	30/31	Sensitive
	302	0.66	99.8	-	Sensitive
	412	0.18	99.5	-	Sensitive
	701	0.92	99.7	-	Sensitive
	703	0.30	99.9	-	Sensitive
	106	2.48	99.1	-	Resistant
	125	1.63	97.2	-	Resistant
	126	2.10	97.8	-	Resistant
	205	3.41	97.0	-	Resistant
	401	4.15	98.2	-	Resistant
	404	1.88	99.0	-	Resistant
	704	>50	44.2	-	Resistant

ART+3BNC117+RMD: 10/16 (63%) sensitive

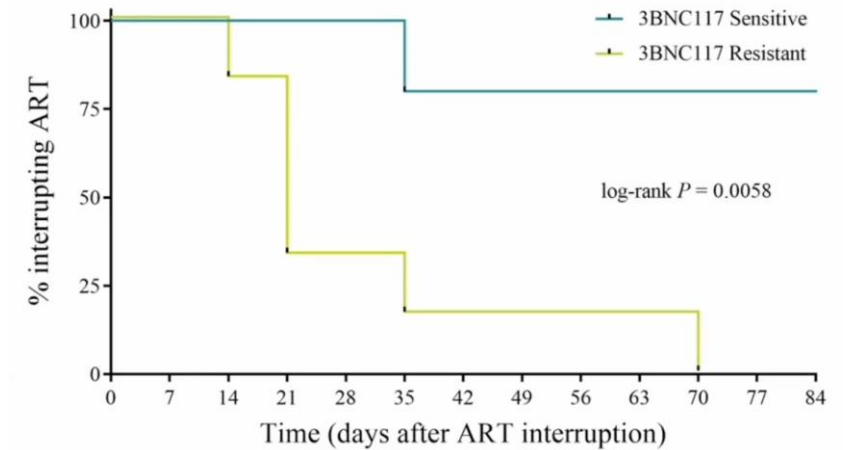
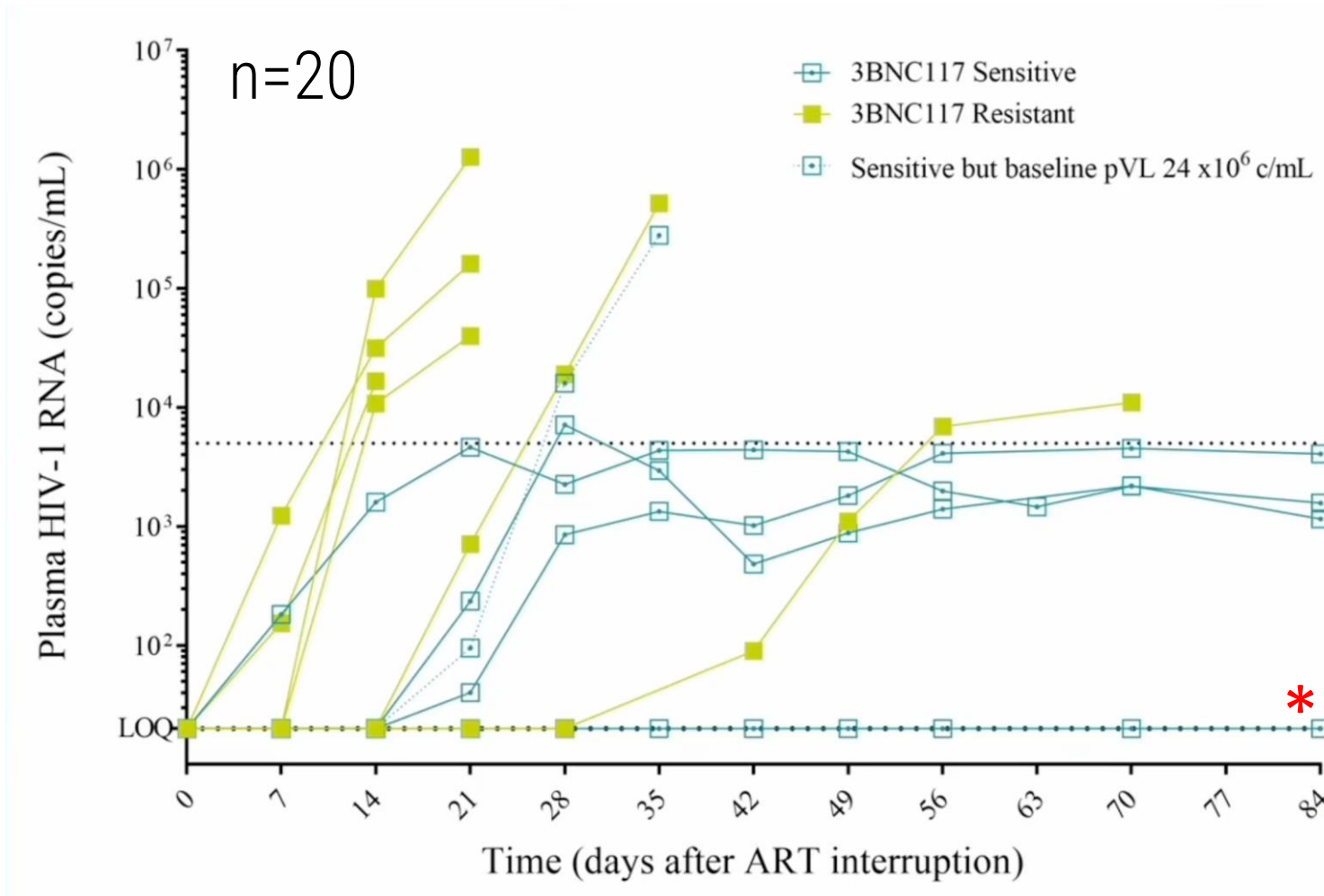
	Participant ID	Monogram PhenoSense		<i>env</i> sequencing	Assessment
		IC90	MPI	Sensitive/total	
ART+3BNC117+RMD (n=16)	103	0.96	99.2	-	Sensitive
	107	0.25	99.9	-	Sensitive
	116	0.34	99.9	-	Sensitive
	130	-	-	33/33	Sensitive
	203	1.22	99.6	-	Sensitive
	212	0.67	99.9	-	Sensitive
	303	0.20	99.6	-	Sensitive
	304	0.74	99.9	-	Sensitive
	408	0.15	99.5	-	Sensitive
	706	0.80	99.7	-	Sensitive
	112	>50	08.6	-	Resistant
	301	4.51	98.8	-	Resistant
	308	3.09	94.6	-	Resistant
	402	-	-	7/35	Resistant
	411	3.22	99.3	-	Resistant
	709	7.44	96.3	-	Resistant

Plasma HIV RNA kinetics

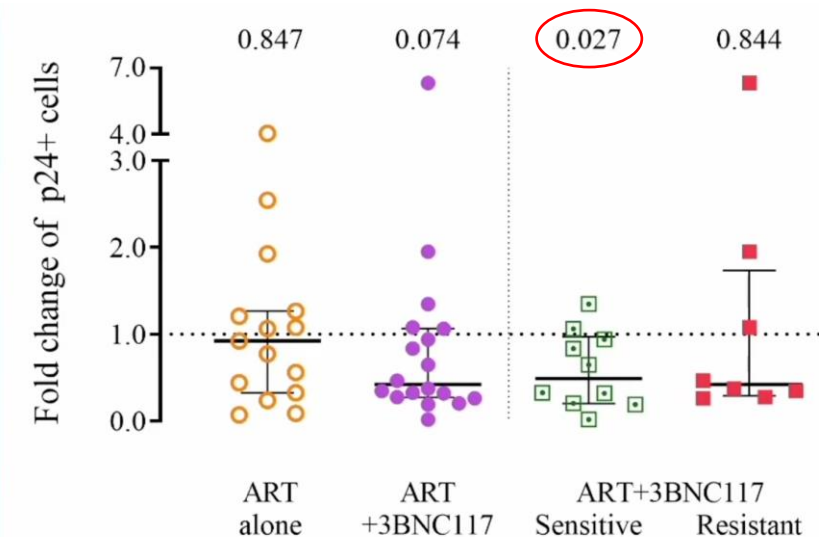
3 phase decay pVL mixed-effect model



	Phase (days)	2 (10-24)	95%-CI	P
Overall	ART	-10.0	(-14.9;-4.86)	ref
	ART+3BNC117	-16.4	(-27.0;-4.29)	0.070
	ART+RMD	-18.5	(-29.0;-6.51)	0.017
	ART+3BNC117+RMD	-16.9	(-27.3;-4.93)	0.048
Sensitive	ART+3BNC117	-17.9	(-28.8;-5.16)	0.045
	ART+3BNC117+RMD	-17.9	(-28.8;-5.28)	0.042
Resistant	ART+3BNC117	-14.7	(-26.0;-1.58)	0.247
	ART+3BNC117+RMD	-15.1	(-26.2;-2.28)	0.198

ATI: only in 3BNC117 treated ($\pm$ RMD)

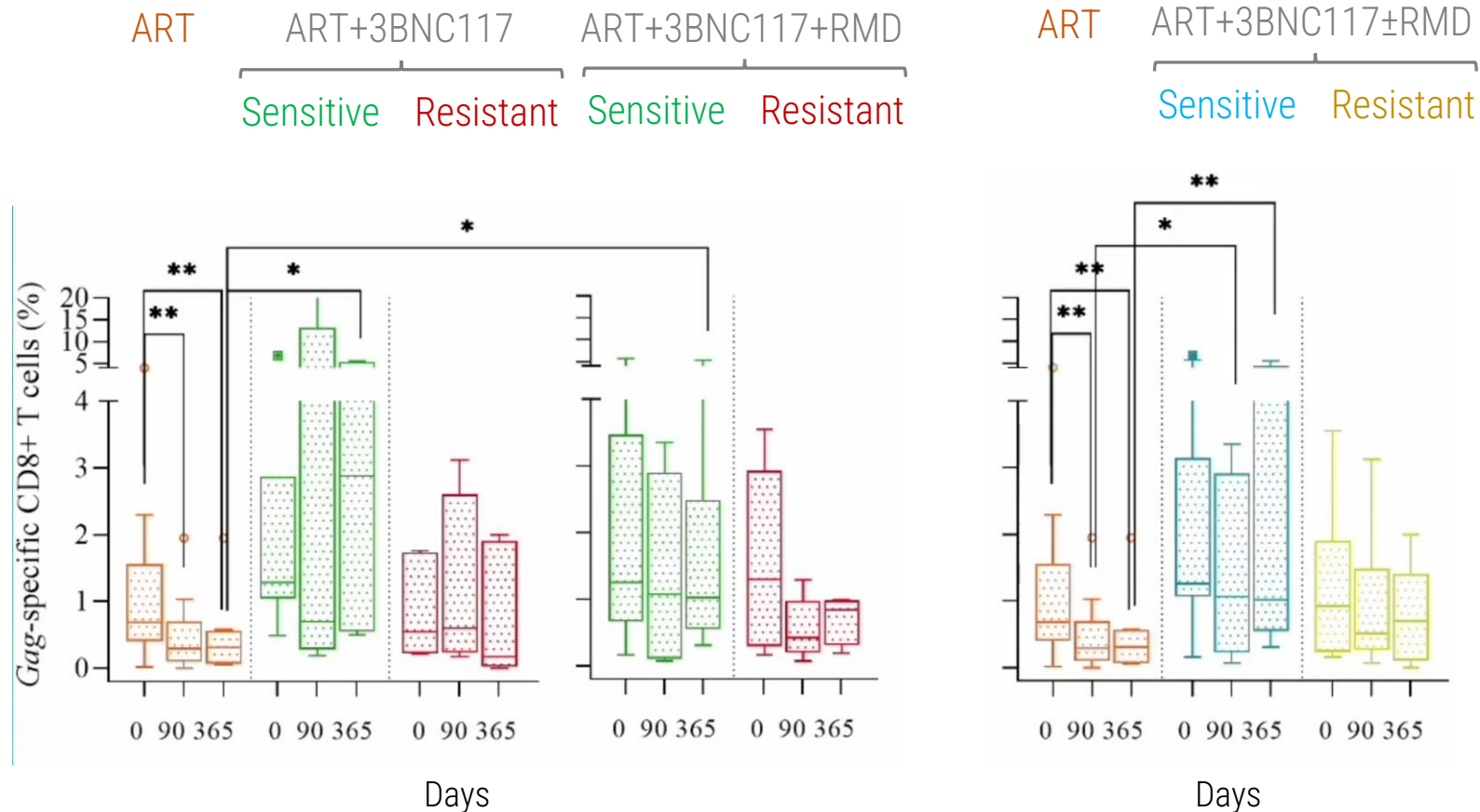
FISH flow assay for HIV mRNA and p24 @ day 10



3BNC117 induces long-term HIV CD8 T-cell immunity

≠ vaccinal effect of bNAbs

Enhanced HIV gag-specific CD8 T cell responses in 3BCN117 treated/sensitive individuals



- 4th case of HIV (+AML) cure through HSCT
 - *With CBU + 3rd party donor; 14 months undetectable*
- Reservoir in brain: microglia!
 - *Organoids and TSPO-PET*
- CyTOF to identify cells that are susceptible of HIV infection
 - *Role of glycans, specially sialic acids in memory, activated T_{EM} cells*
- HIV cure in early-treated infants (*looking for a new "Mississippi baby"*)
 - *30% without signs of infection after 2 years of ART*
 - *44% with some help of bNAbs*
- Combination strategies: ART+bNAbs+LRA
 - *Works only in bNAbs-sensitive cases*
 - *Potential vaccinal effect of the bNAbs*



4th case of HIV cure

- Haplo-cord transplant match CBU + relative PBMCs in 2017

