Challenges and Advances in Identification and Immune Targeting of HIV-Infected Cells: Implications for Cure Studies

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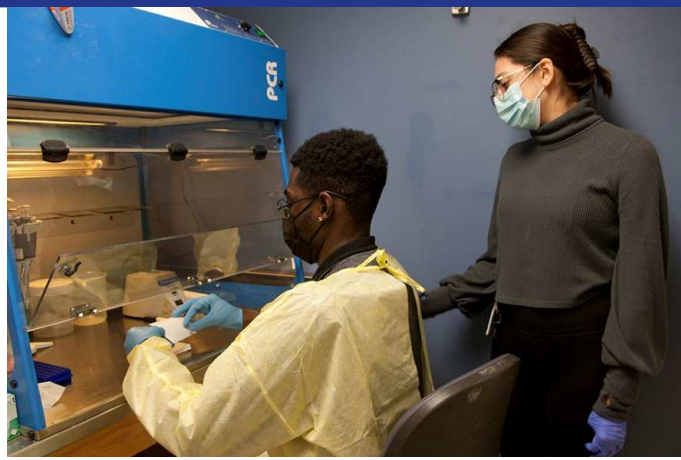
CONFLICTS OF INTEREST

Regeneron
Roche
Grant Support: Merck




Tyler-Marie Deveau


Kofi Asare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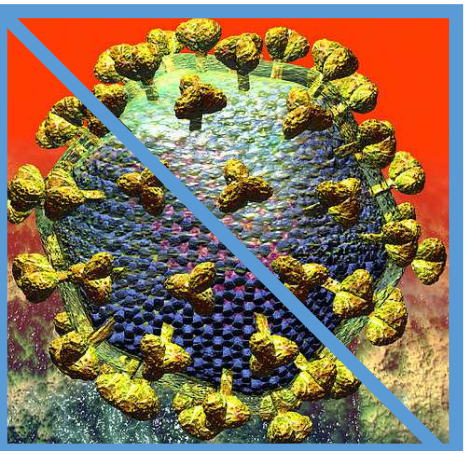
Faculty Mentees

INTRODUCTION

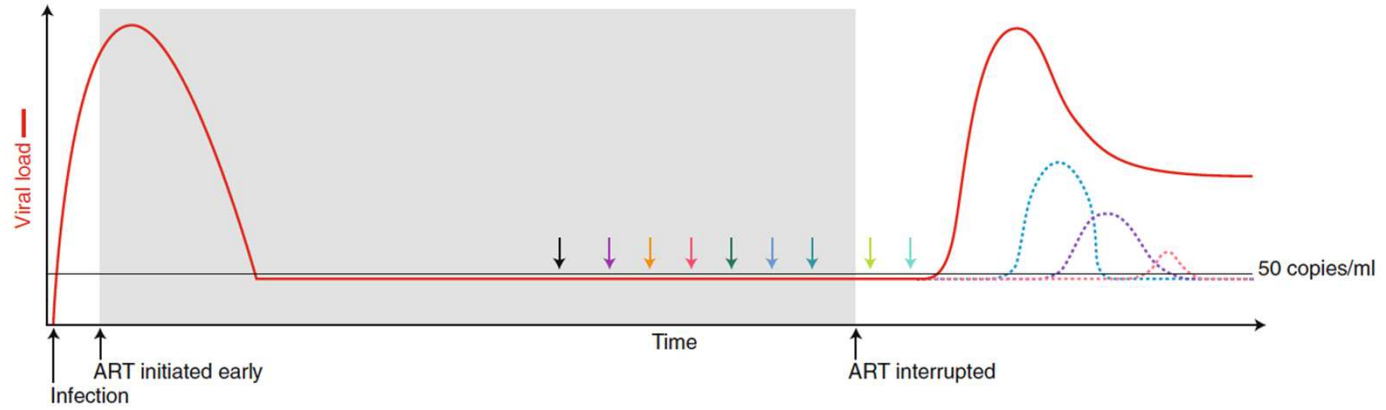
We are making **real**, albeit modest, steps towards controlling HIV off ART

- **Challenge 1:** Measuring response to therapies and predicting outcomes after ATI
- **Challenge 2:** Understanding how various therapeutic strategies recognize and eliminate HIV-infected cells

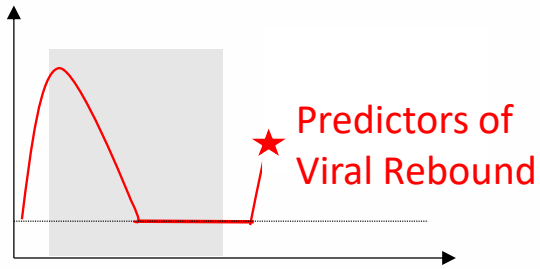


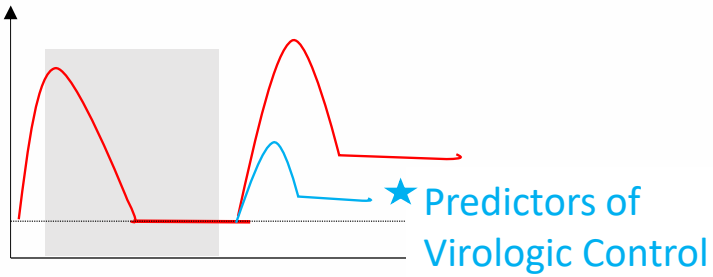
CHALLENGE 1: Cure Interventions - Goals and Biomarkers

➢ ***Goal:*** Sustained ART or intervention-free virologic control
= HIV-1 RNA < 200 copies/ml for an *extended* period of time

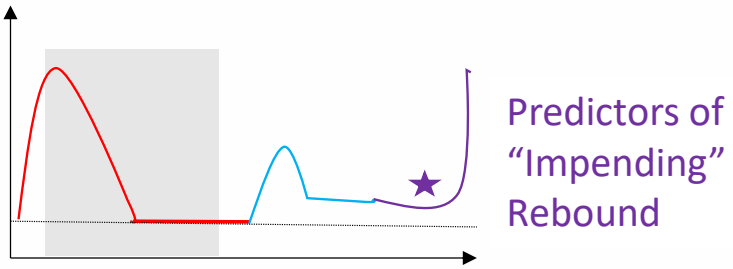


➢ ***Markers to predict success = control:***





➢ ***Markers to predict loss of control:***



Deeks/IAS Nat Med 2022 (Slide curtesy of Drs. Jonathan Li and Marina Caskey)

PREDICTORS OF VIRAL REBOUND TIME & VIRAL SETPOINT

Factors Associated with Time to Rebound (inconsistent across diverse studies):

- Lower CD4+ T cell nadir
- Higher pre-ART viral load
- Earlier timing of ART initiation
- Higher cell-associated (ca)HIV-1 RNA, Total HIV-1 caDNA (early treated)
- Higher intact proviral HIV-1 (chronic treated)
- Lack of detectable HIV-1 RNA, DNA or IUPM in blood or tissues (SCT, hyperacute treated)
- CD4+ and CD8+ T cell responses (proliferative capacity or breadth)

Factors Associated with VL Setpoint after ATI (inconsistent across diverse studies):

- CD4+ and CD8+ T cell responses
- Protective or neutral HLA type
- HLA-associated Gag polymorphisms
- Increased TNFa, IL-6, lower CRP prior to ATI
- Anti-C5/gp41 responses

Factors Associated with Impending Rebound:

- Early immune cell responses (*e.g.* PDCs)
- CD4+ T cell CD30 cell expression

Reviewed by Leal et al. 2020, Prator et al. 2021, Henrich et al. 2020, Mitchell et al. 2020, and Jon Li P.C.

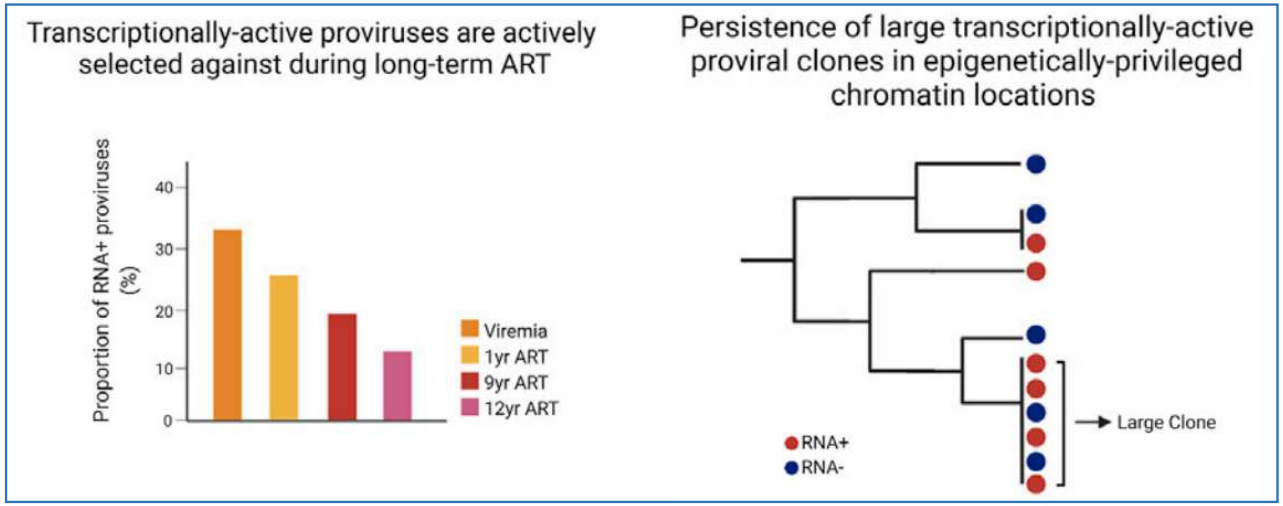
Intuitive, Differences in Rebound Time & Setpoints Modest

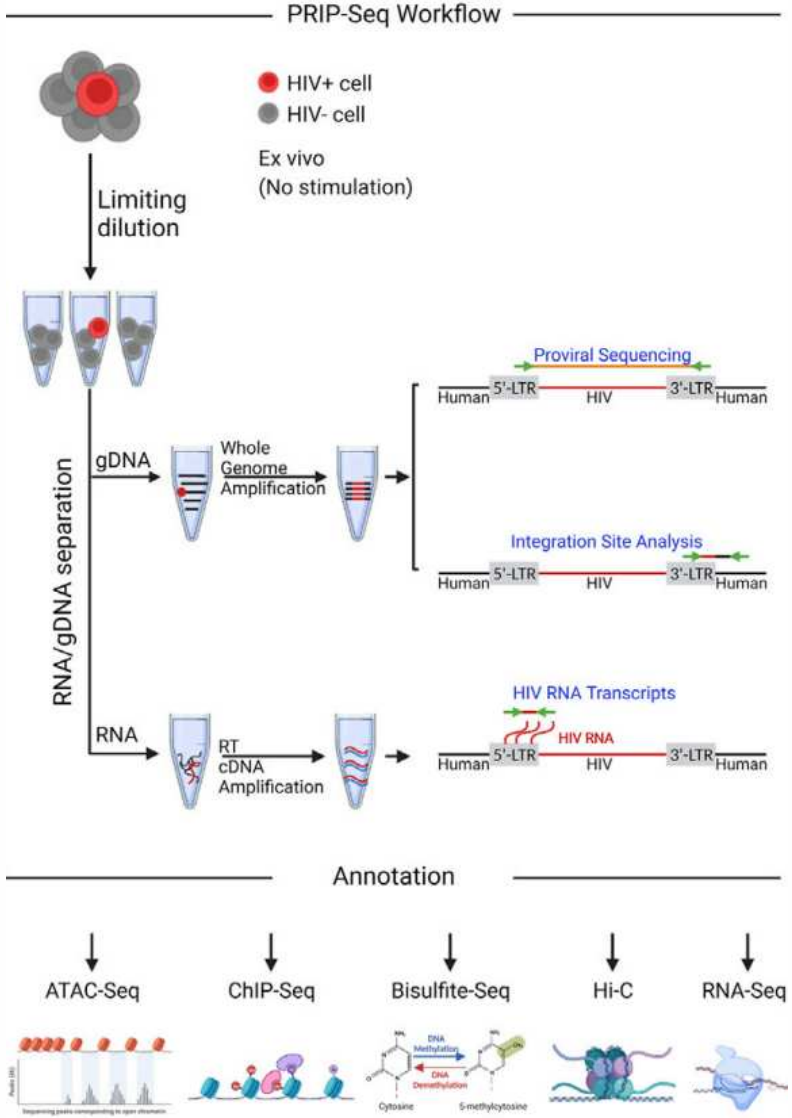
OP 7.3: Pre-treatment Interruption Plasma Metabolites and Glycans Correlate with Time to HIV Rebound and Reservoir Size in ACTG A5345

ASSAYS USED IN HIV CURE TRIALS

Study	CA-DNA	CA-RNA	IPDA	SCA	QVOA	TILDA	EDITS	Other
A5337								
A5366		Primary						p24, integrated DNA
A5386								Sequencing
A5389								
ROADMAP								Sequencing
RIVER	Primary							Integrated DNA
eCLEAR			Primary					FISH-FLOW

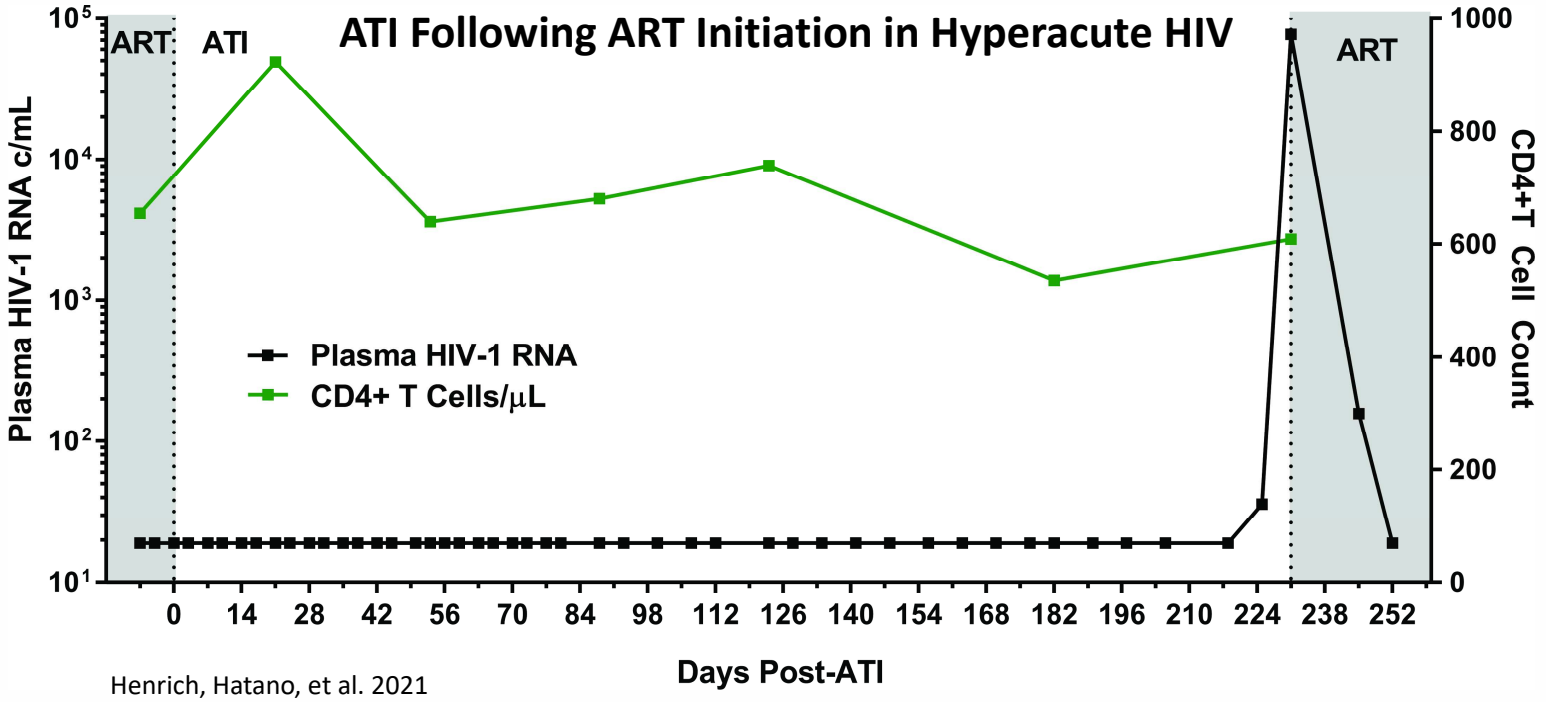
(Courtesy Drs. Li & Caskey)





Einkauf, Osborn, Gao, ..., Rosenberg, Yu, Lichterfeld, Cell 2022

ATI/MAP CHALLENGES – PARTICIPANT CONSIDERATIONS



Henrich, Hatano, et al. 2021

- Point of Care (POC) and at-home testing will be key
  - SAMBA II, M-PIMA™ HIV-1/2 VL, Cepheid GeneXpert (VL QC, Qual)

Tasso+ and M20 Home blood collection devices

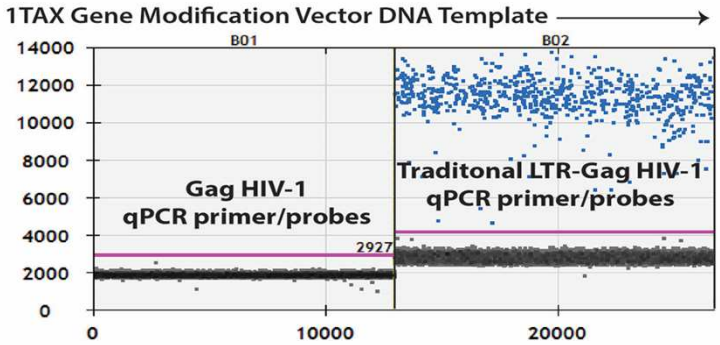
ADDITONAL CHALLENGES

- Need reservoir assays that work with non clade-B HIV

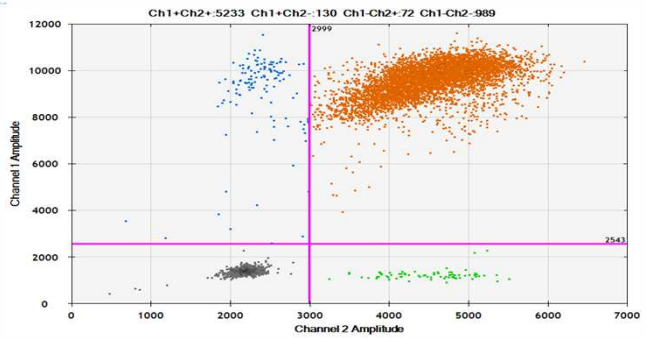
- **Gene therapy** studies involving *lentiviral* delivery vectors pose major challenges:
  - lentivirus vectors used in CAR-T cells, direct gene editing, etc.
  - often based on HTLV and have significant sequence homology to HIV

Poster PP 6.1: Amanda Buck

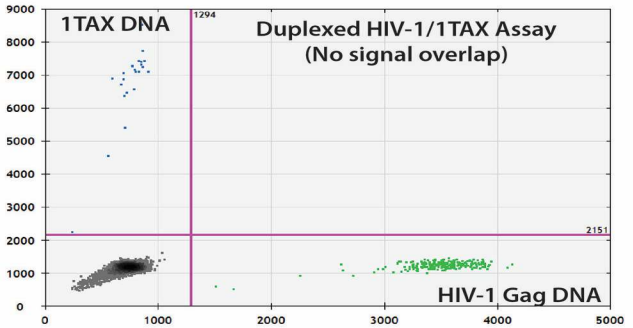
Only 1 of 22 HIV-1 DNA assays screened can be used with lentiviral constructs



IPDA amplifies lentiviral DNA in both 5' and 3' regions



Now able to multiplex vector and HIV quantification (bulk and single cell)



HIV PERSISTS PRIMARILY IN TISSUS – RESERVOIRS ARE DYNAMIC

nature medicine

Defining total-body AIDS-virus burden with implications for curative strategies

Jacob D Estes[1], Cissy Kityo[2], Francis Ssali[2], Louise Swainson[3], Krystelle Nganou Makamdop[4], Gregory Q Del Prete[1], Steven G Deeks[5], Paul A Luciw[6], Jeffrey G Chipman[7], Gregory J Beilman[7], Torfi Hoskuldsson[7], Alexander Khoruts[8], Jodi Anderson[8], Claire Deleage[1], Jacob Jasurda[8], Thomas E Schmidt[8], Michael Hafertepe[8], Samuel P Callisto[8], Hope Pearson[8], Thomas Reimann[8], Jared Schuster[8], Jordan Schoephoerster[8], Peter Southern[9], Katherine Perkey[9], Liang Shang[9], Stephen W Wietgrefe[9], Courtney V Fletcher[10], Jeffrey D Lifson[1], Daniel C Douek[4], Joseph M McCune[3], Ashley T Haase[9] & Timothy W Schacker[8]

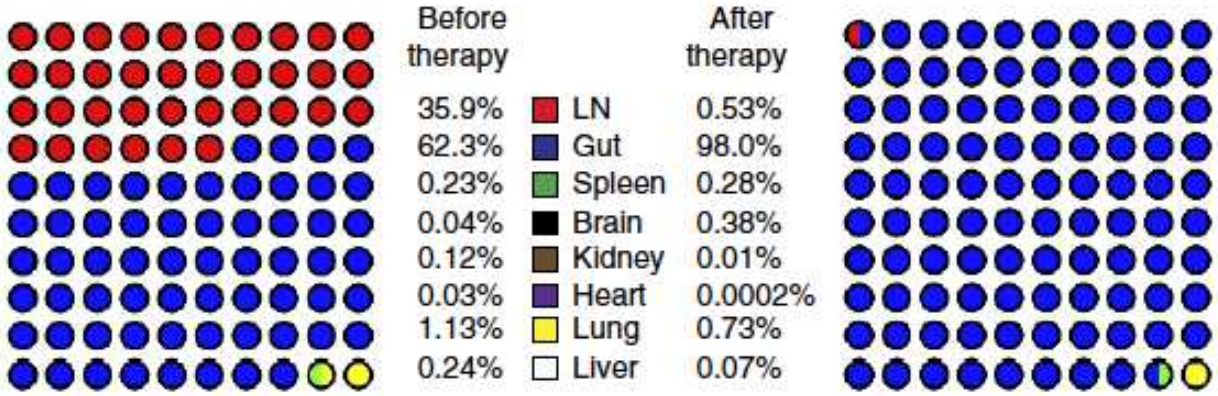
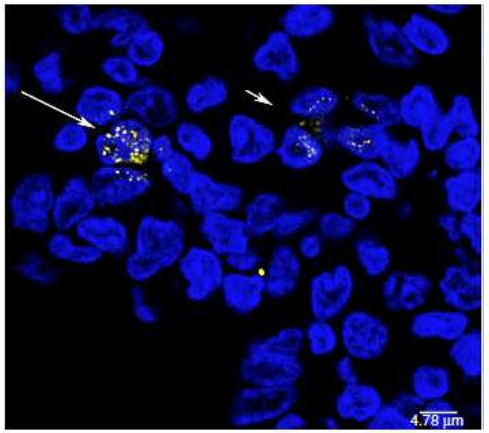
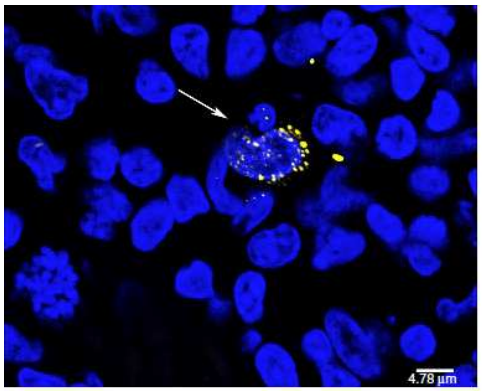


Figure 1 Graphical representation of the proportion of vRNA+ cells in each organ system before and during suppressive ART.

Ongoing viral production (not necessarily replication) in the setting of ART



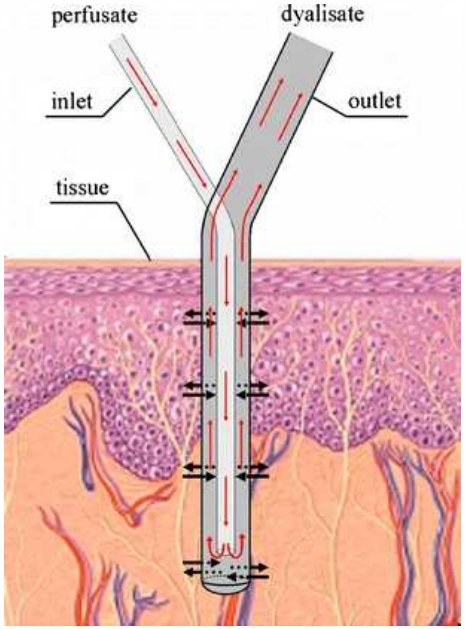


DYNAMIC HIV PERSISTENCE TESTING IN TISSUE

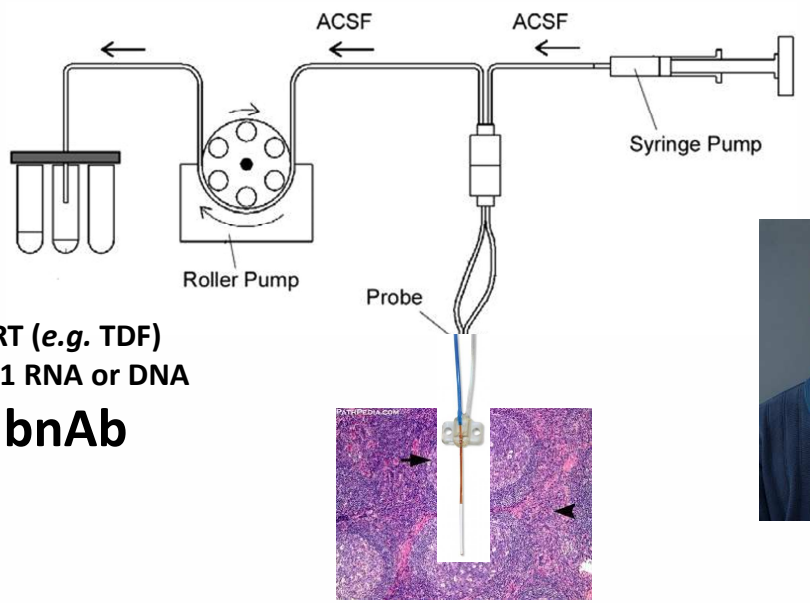
Lymph Node Microdialysis

Amelia Deitchman, PharmD, PhD
Assistant Professor, UCSF

Sophia Miliotis
PharmD-PhD Student, UCSF



Baldini, 2010

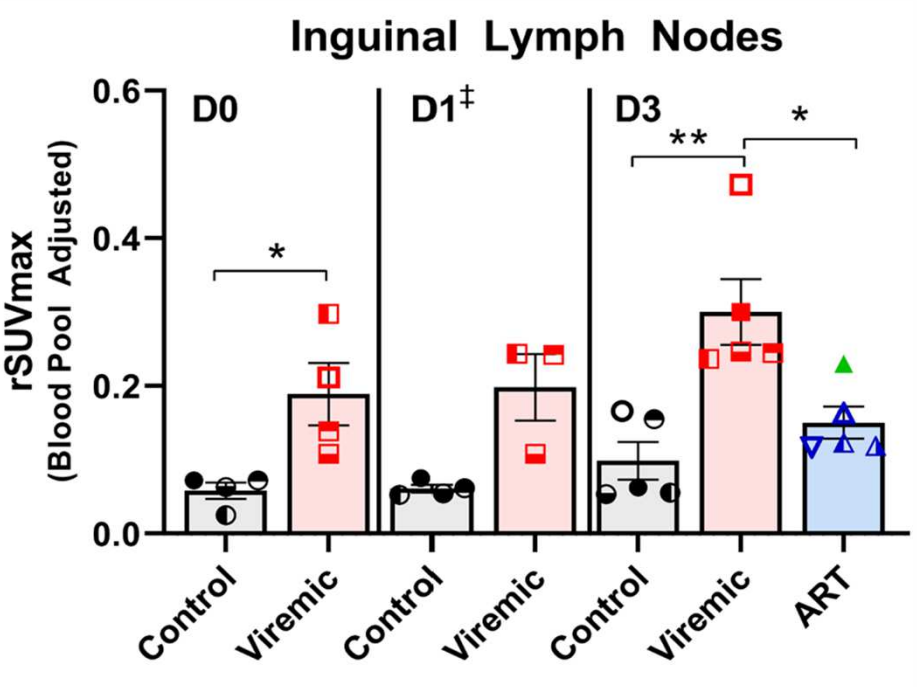


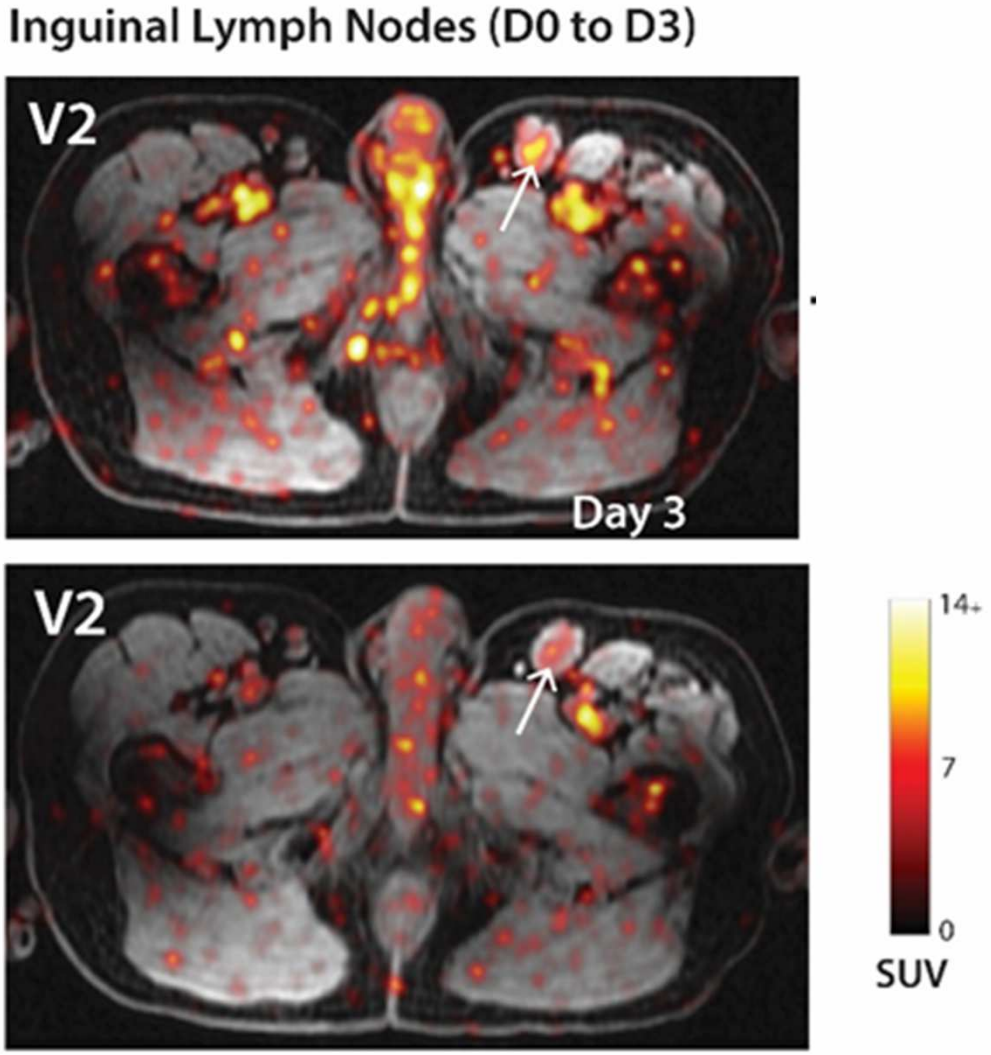
ART (*e.g.* TDF)
HIV-1 RNA or DNA
bnAb

- **Measure tissue response in inguinal LN (daily collections) prior to or during ATI, latency reversal, etc.**
- **Can quantify ART level, HIV-1 RNA/DNA, bnAbs**
- **Can leave in for many days, intermittent collections without need for repeat biopsy**
- **Large pore allows for large molecule dialysis (including mAbs, large proteins, etc.)**

NON-INVASIVE APPROACHES TO CHARACTERIZING HIV PERSISTENCE

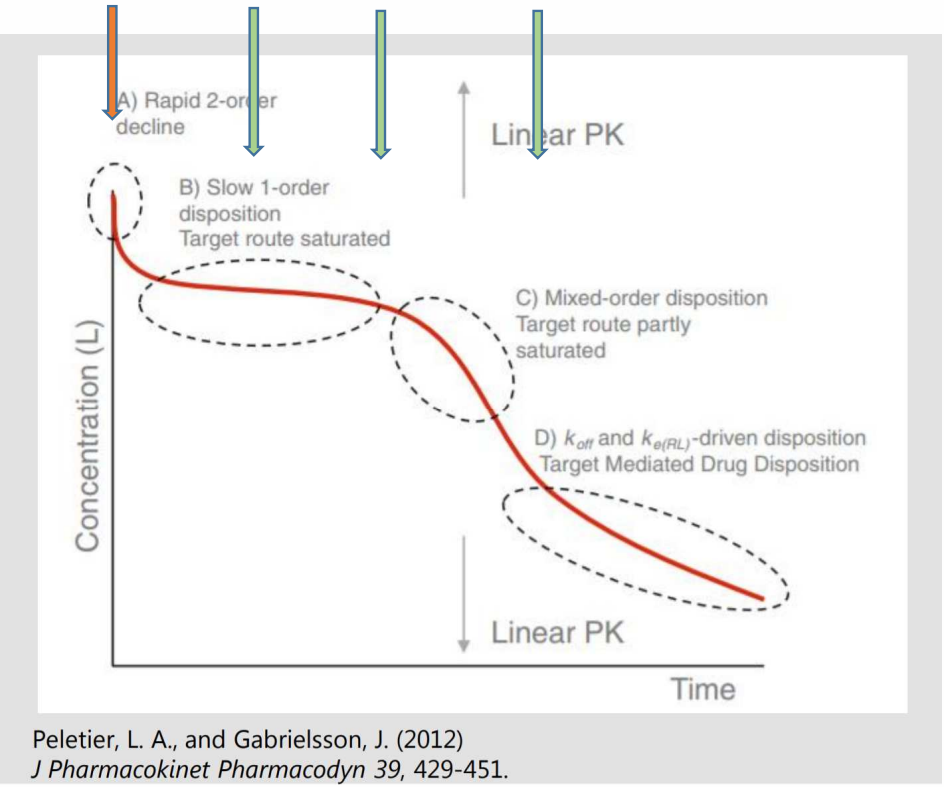
First-in-human immunoPET imaging of HIV-1 infection using ^{89}Zr-labeled VRC01 broadly neutralizing antibody





IMMUNO-PET IMAGING APPLICATIONS

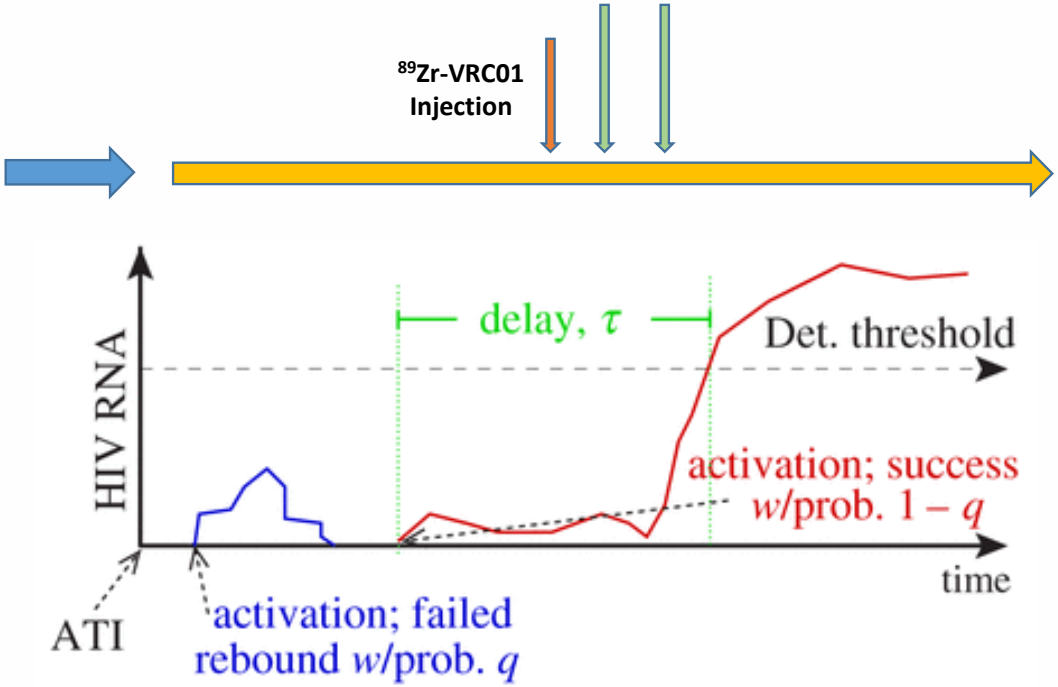
PET EXPLORER Imaging (weeks following dosing)



Peletier, L. A., and Gabrielsson, J. (2012)
J Pharmacokinet Pharmacodyn 39, 429-451.

Determine Whole Body Tissue PK of bnAbs/mAbs

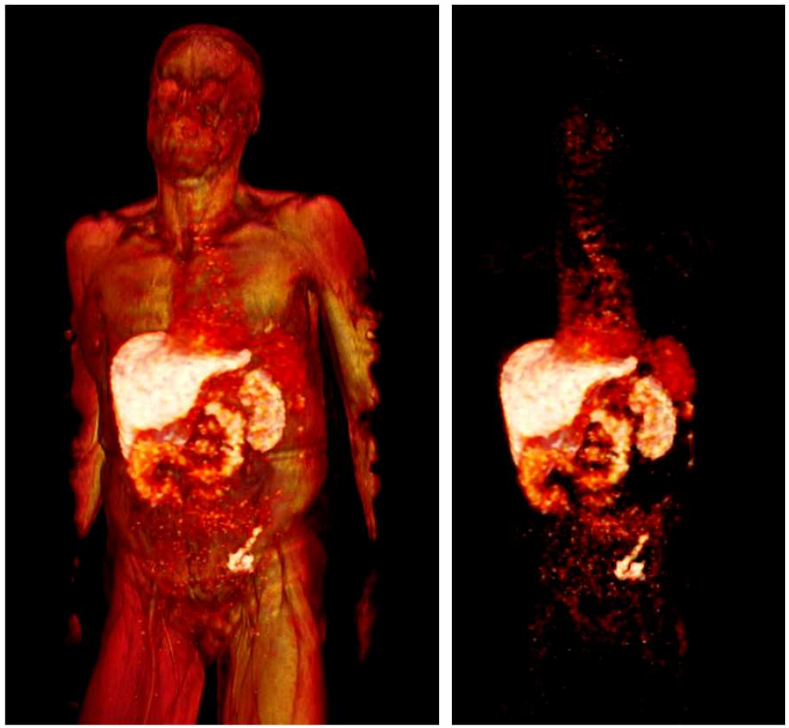
PET MR/EXPLORER Imaging

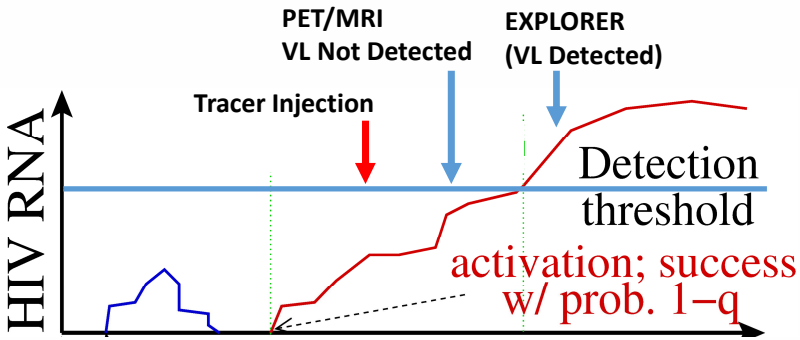


Conway et al. 2019

Understanding Multidimensional HIV Rebound Dynamics

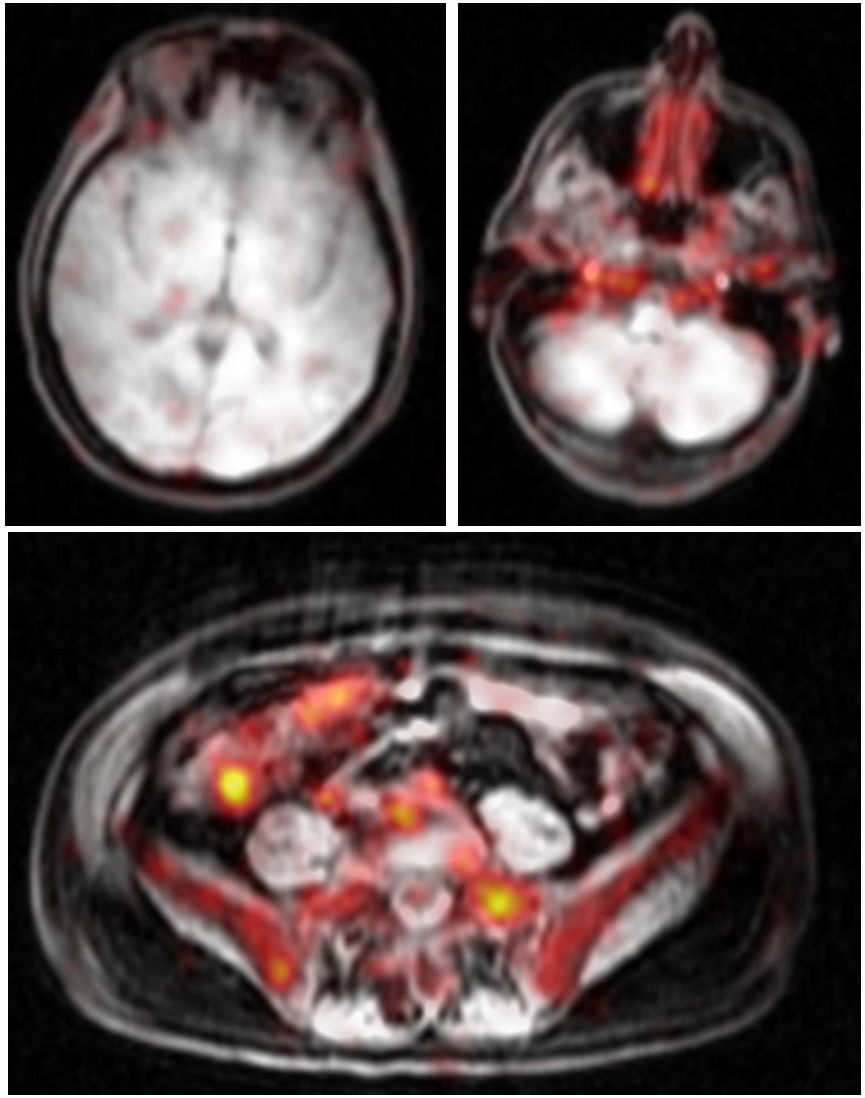
IMMUNO-PET IMAGING DURING ATI





Marked uptake in some tissues (NALT, Gut, LN, spleen, bone marrow, ? CNS) <u>prior to detectable VL</u>

Patchy- unlike more consistently elevated levels throughout tissues in viremic participants

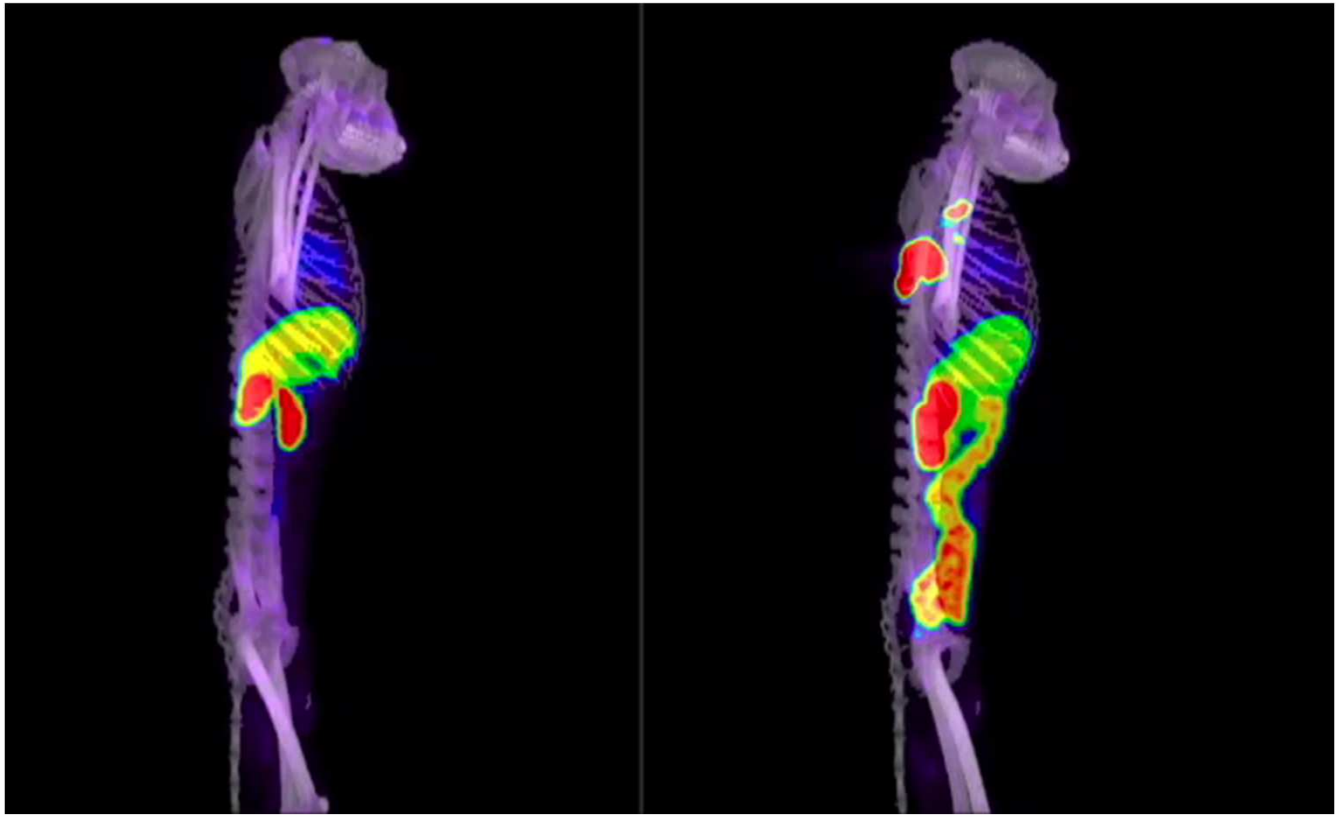


IMMUNO-PET TO DETERMINE THERAPEUTIC RESPONSE

JCI insight

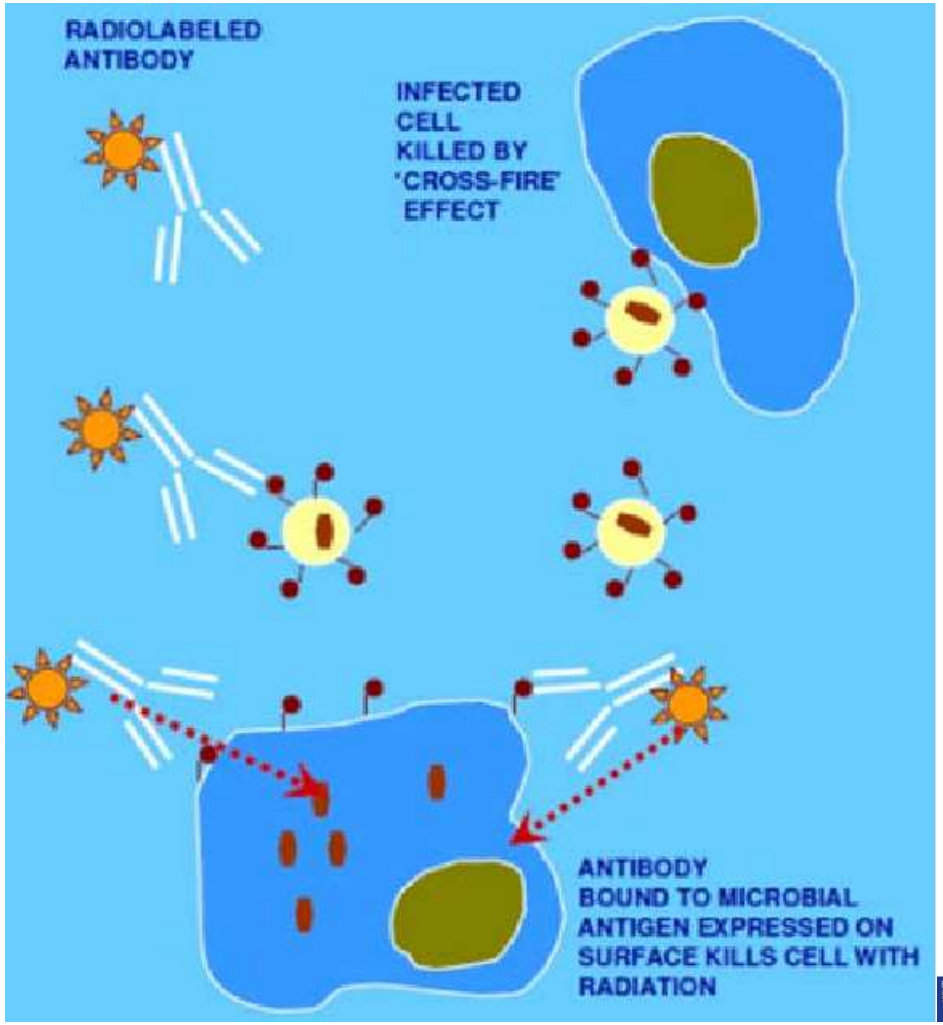
Blockade of TGF-β signaling reactivates HIV-1/SIV reservoirs and immune responses in vivo

Sadia Samer, … , Francois Villinger, Elena Martinelli



THERAPEUTIC APPLICATIONS OF RADIOLABELED MABS

^{213}Bi-Labeled 2556 Antibodies to Directly Kill Target Cells

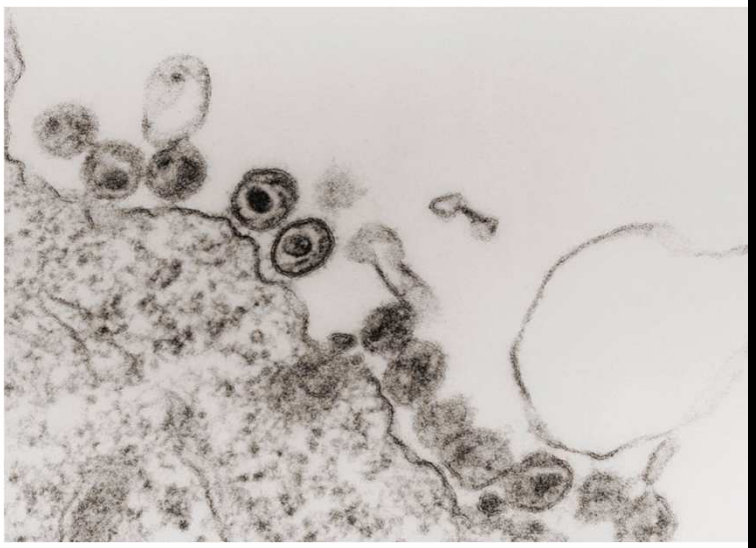


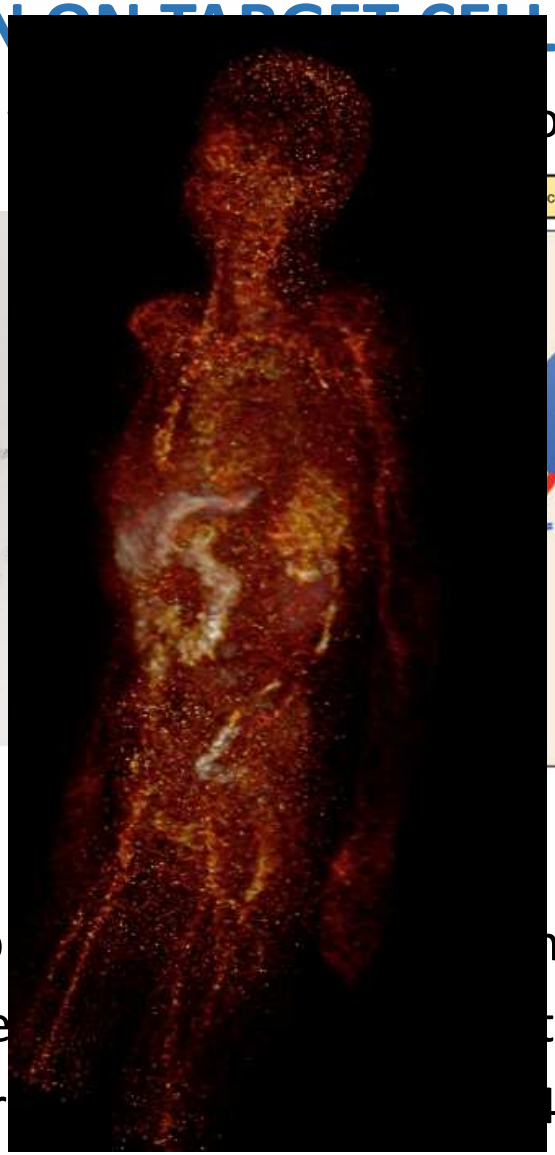
Dadachova et al. 2007
Dadachova et al. 2014

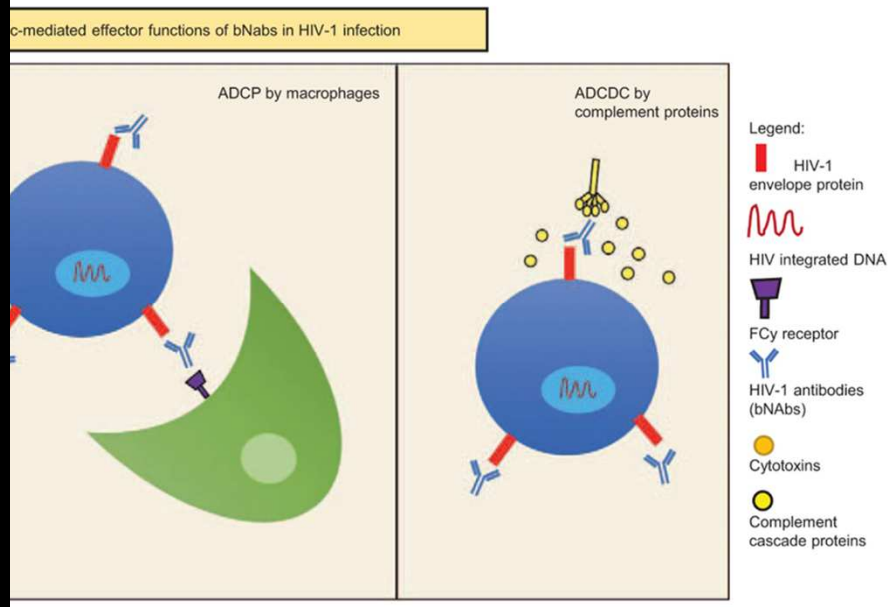
CHALLENGE 2: HOW DO CHARACTERIZE THERAPEUTIC TARGETS?

HIV-1 ENV EXPRESSION ON TARGET CELLS – bnAbs

HIV infected cells can make up ort lifespan (De Boer et al, 2010)







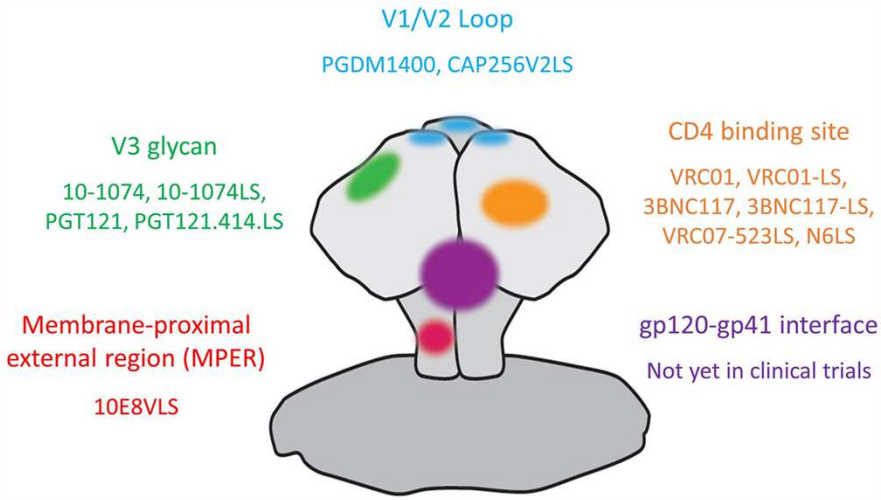
Phagocytosis **Complement**

Is there sufficient HIV-1 Env exp ne cover of ART?

Are viral proteins being produce tomical proximity to infected cells?

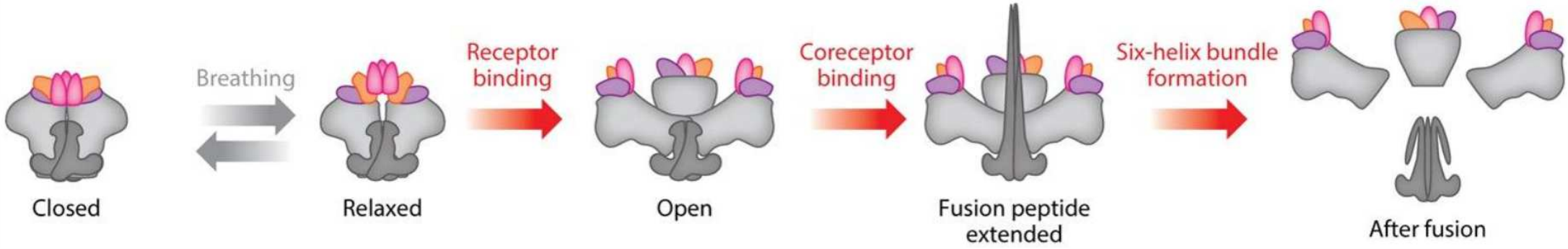
Is HIV-1 Env processed and expr 4+ T or other infected immune cells?

ENV CONFORMATION, bnAb BINDING, & CYTOTOXIC EFFECTS

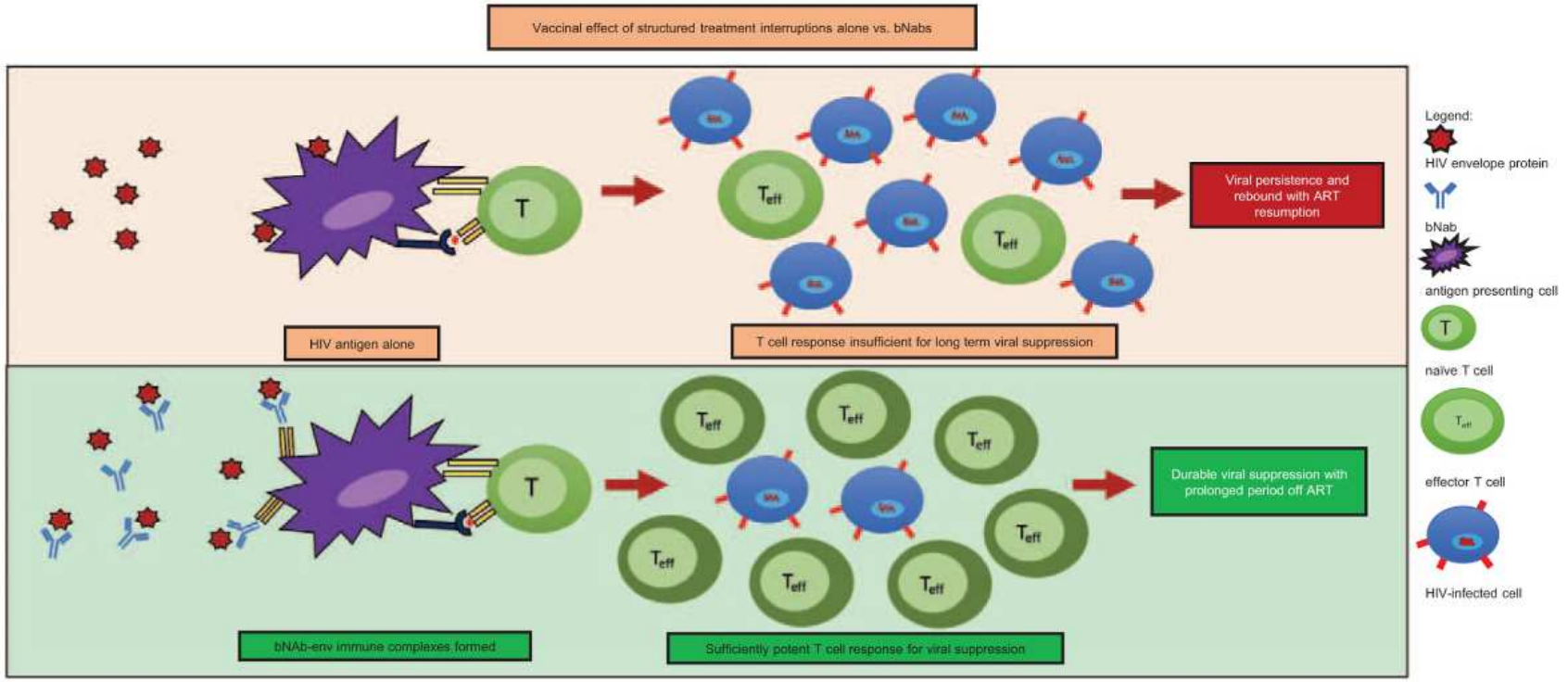


https://www.frontiersin.org/files/Articles/710044/fimmu-12-710044-HTML/image_m/fimmu-12-710044-g001.jpg

Does virus need to be bound to receptor/coreceptor for bnAb-elicited cytotoxic effect?



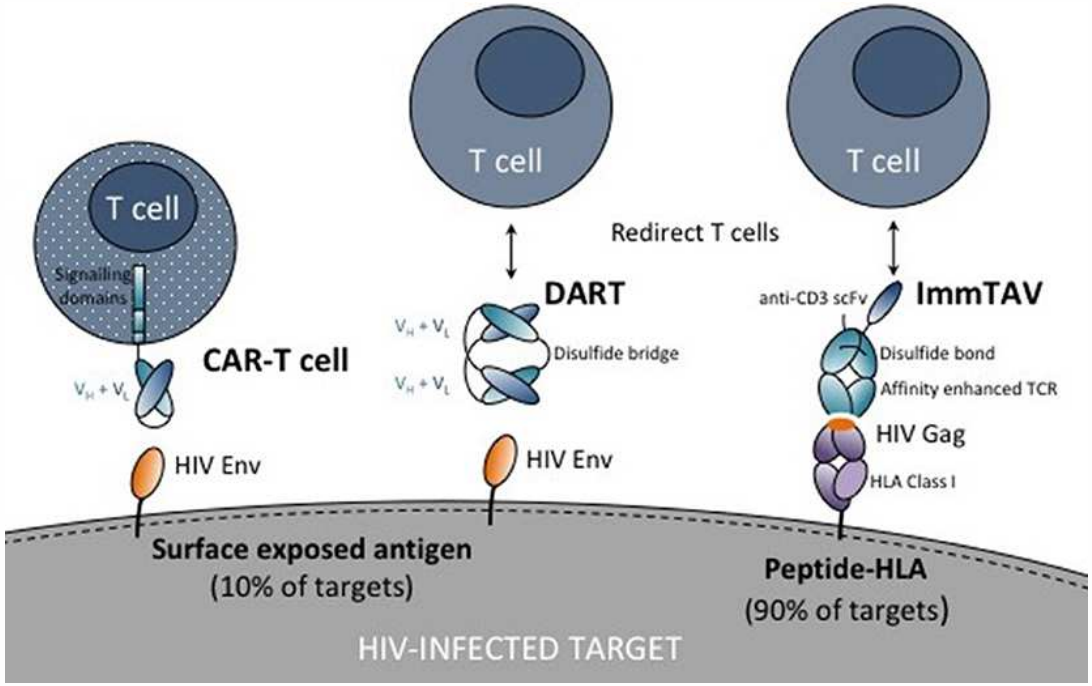
bnAb VACCINAL EFFECT



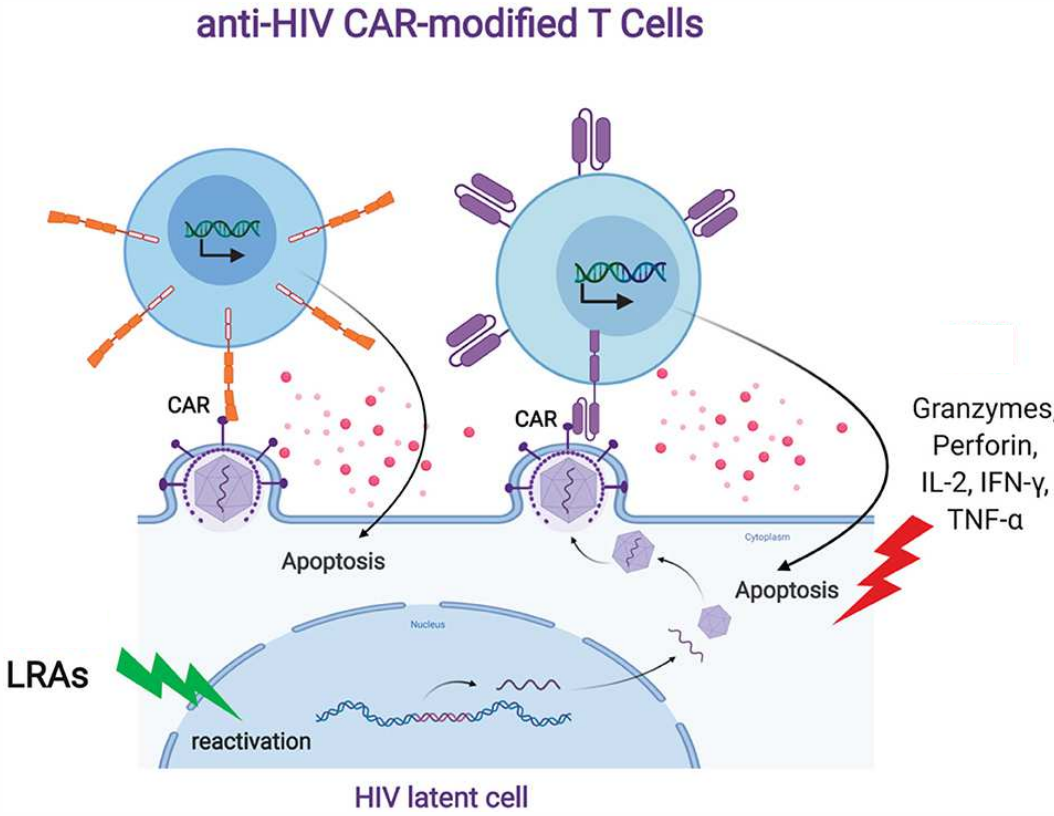
Tipoe et al. 2022

- **To what extent does this happen?**
- **How do we measure/quantify this effect?**

CAR-T & EFFECTOR CELL-MEDIATED CELL KILLING

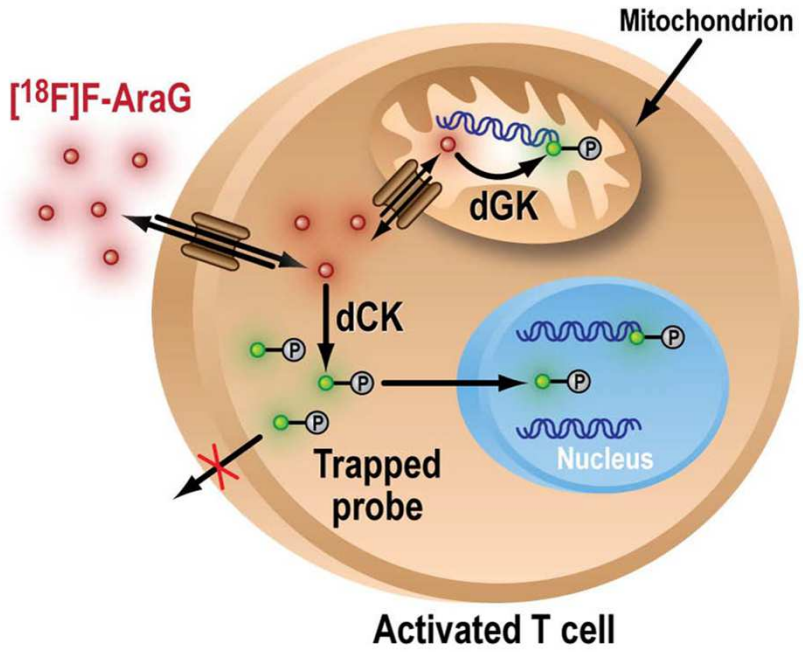


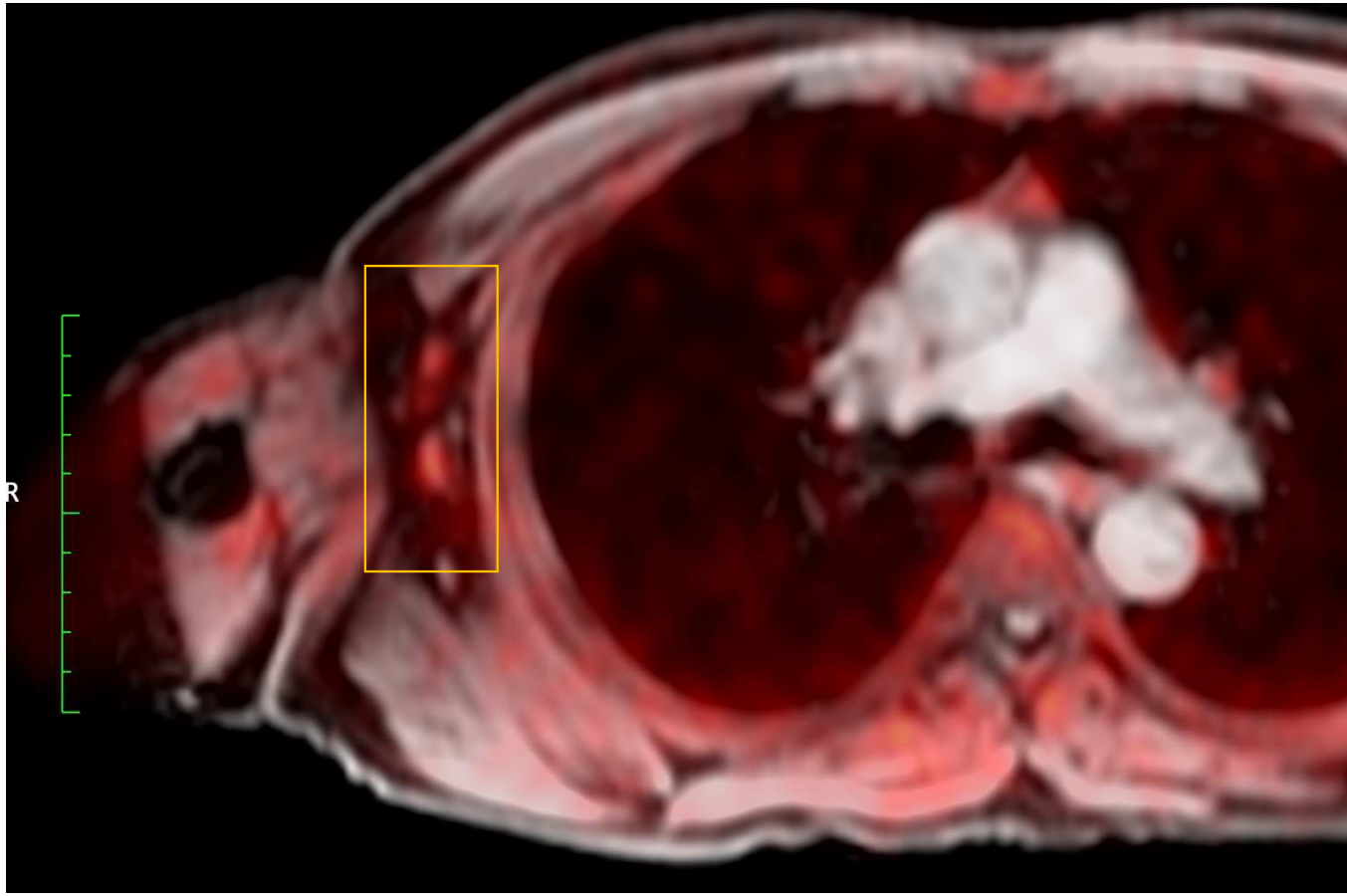
Yang et al. Front. Immunol. 2018



- **In the absence of copious viral production, will CAR-T cells be able to expand or be maintained over time?**
- **Will CAR-T cells have an impact on reservoirs without ATI or latency reversal?**

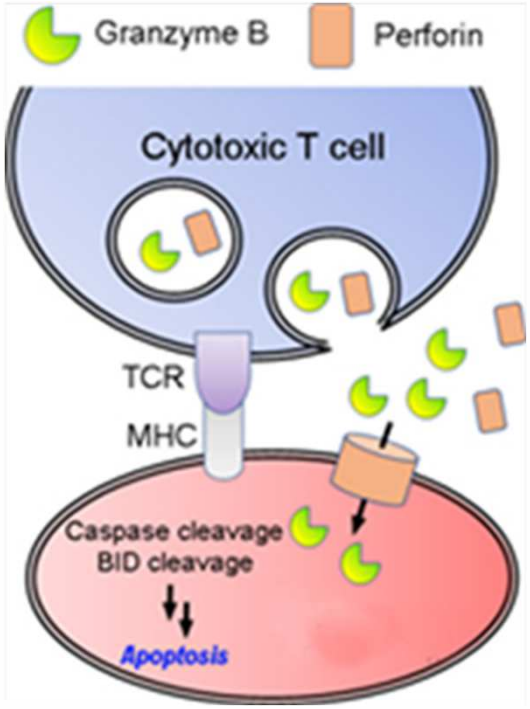
PET IMAGING OF ACTIVATED/CYCLING T CELL RESPONSES

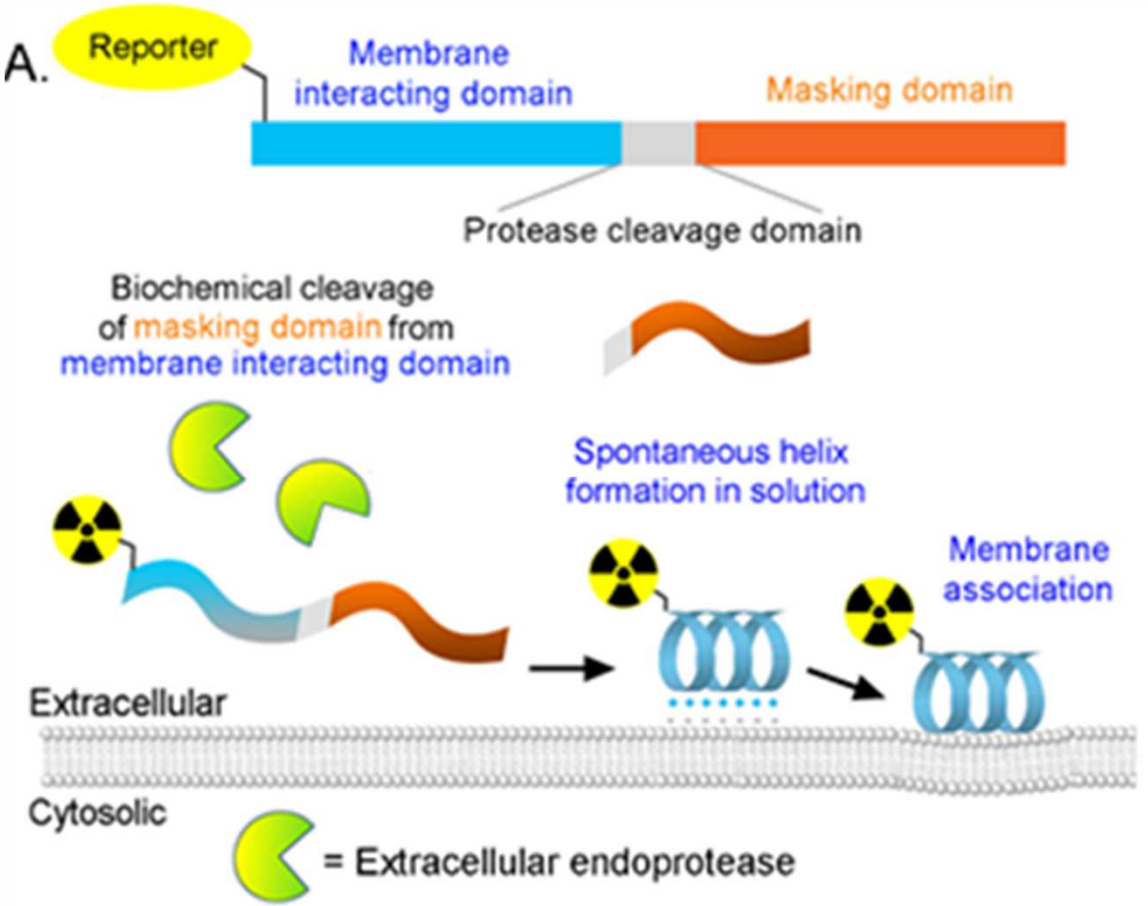




Delaney AIDS Research Enterprise
DARE
to find a cure

PET IMAGING GRANZYME-B PRODUCTION *IN VIVO*





Key questions

- How do we measure response to therapies and predict outcomes with or without ATI?
- How do therapeutic strategies recognize and eliminate infected cells?

Take Home Messages / Next Steps

- Urgent need for rapid turnaround, POC viral load testing in setting of ATI settings
- New approaches to measure and characterize HIV reservoirs are promising but need to be standardized across studies and will need cost effective implementation
- *Less-invasive and non-invasive* assays to measure HIV burden, immune response, and drug PK in tissues are urgently needed but being developed
- Further mechanistic understanding of how therapeutic strategies target reservoirs needed
- **ATI/MAP is still required in order to determine therapeutic efficacy**

Acknowledgements:

Merck & Co.

amfAR Institute
FOR HIV CURE RESEARCH

Vaccine Research Center, NIH

NIH
NIAID

Delaney AIDS Research Enterprise
DARE
to find a cure

UCSF Department of Radiology and Biomedical Imaging

UCSF Radiopharmaceutical Facility

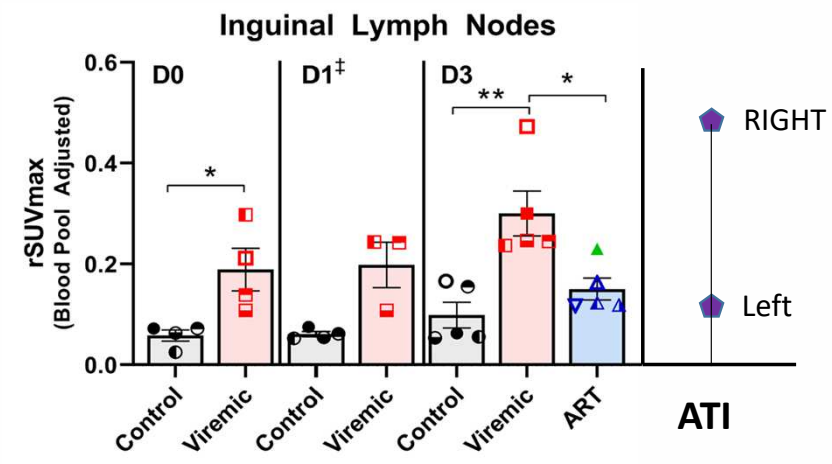
UCSF SCOPE Cohort

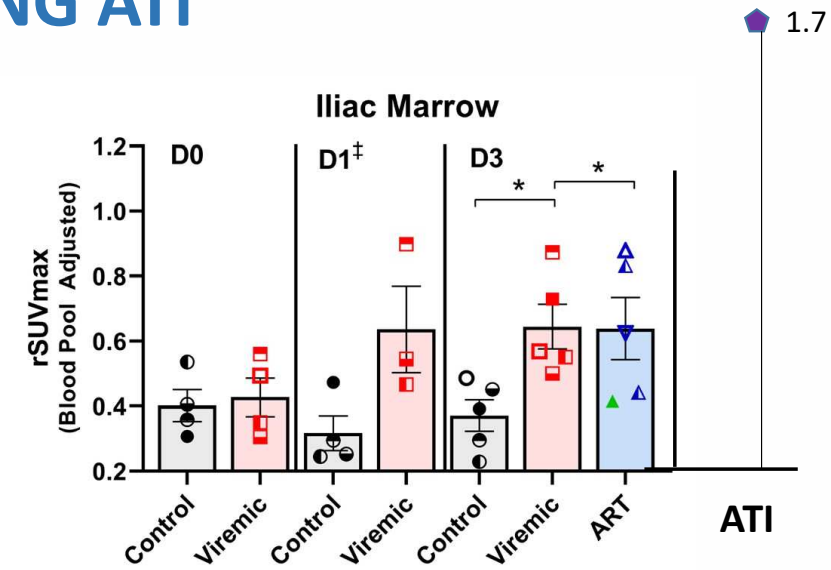
UCSF Center for Functional Molecular Imaging

Henrich Laboratory UCSF

Thank you participants!

IMMUNO-PET IMAGING DURING ATI





Brain
rSUVmax: 1.6