

# Enlisting Effector Cells to Clear HIV Infection



CARE | Collaboratory of AIDS  
Researchers for Eradication

David Margolis MD  
*UNC HIV Cure Center*

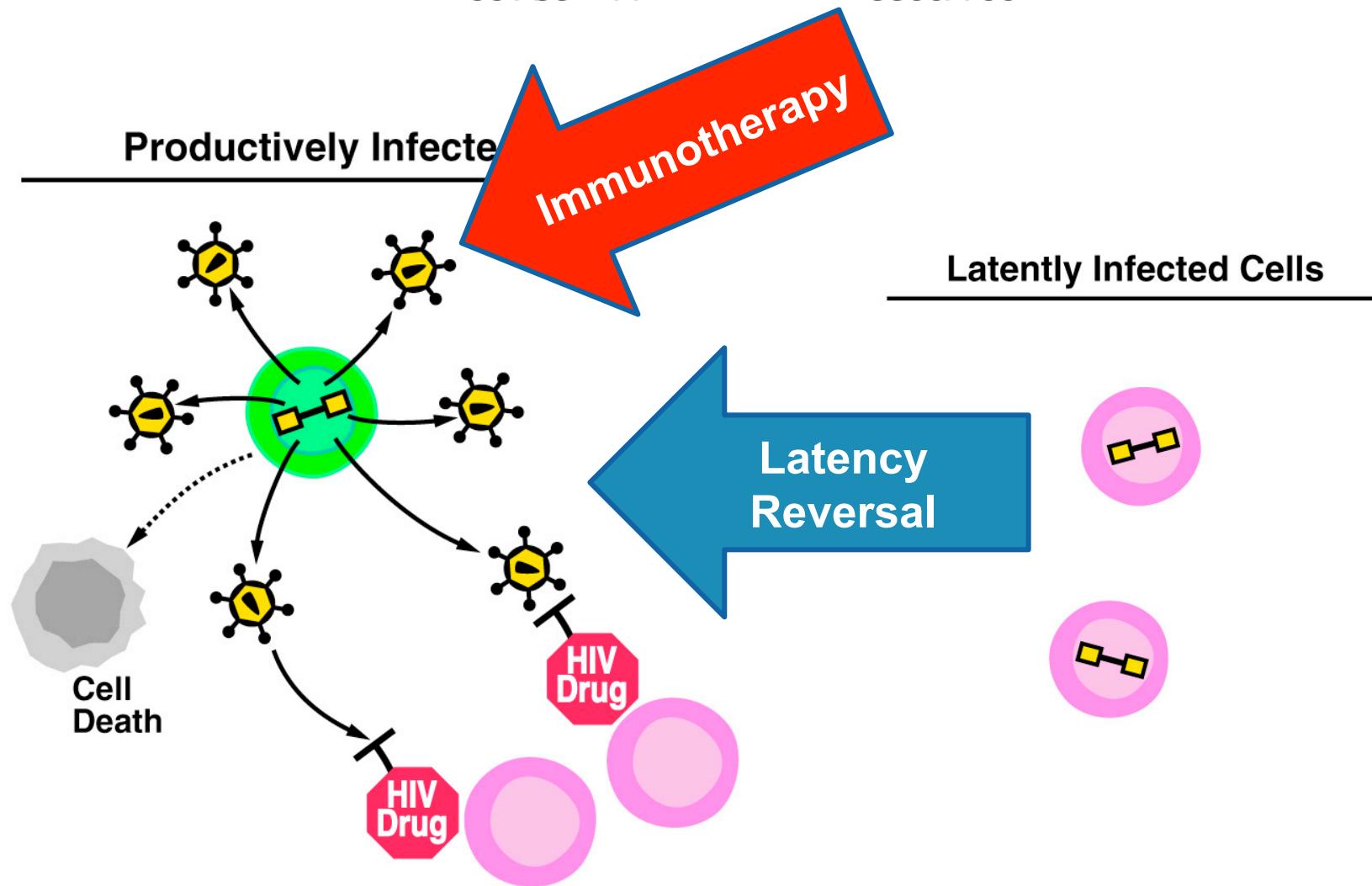


THE UNIVERSITY  
*of NORTH CAROLINA*  
**at CHAPEL HILL**

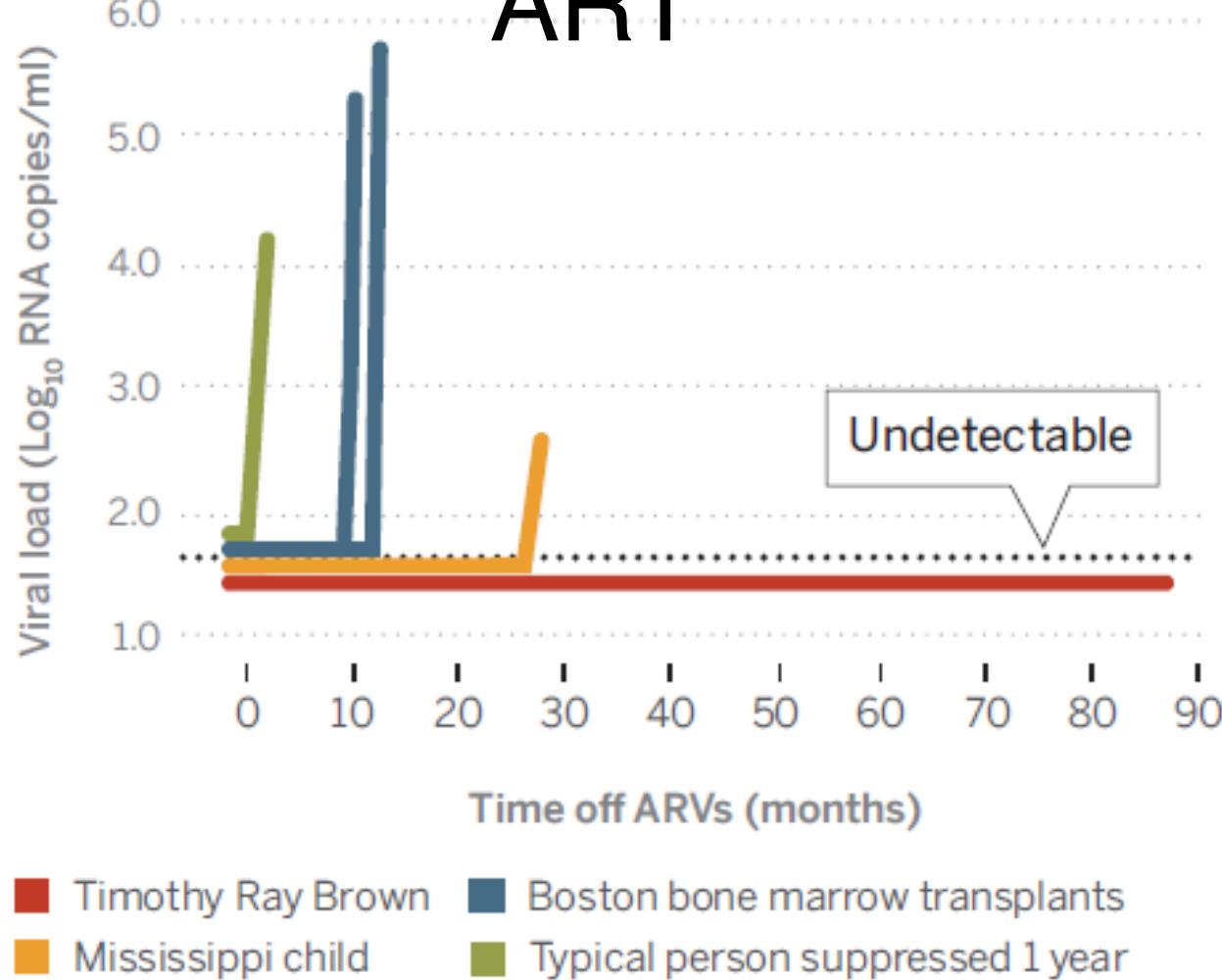
# Disclosures

- Gilead: common stock
- Merck: consulting
- Will discuss the experimental use of licensed drugs, but no treatment recommendations are made

# A first step to eliminate latent HIV infection



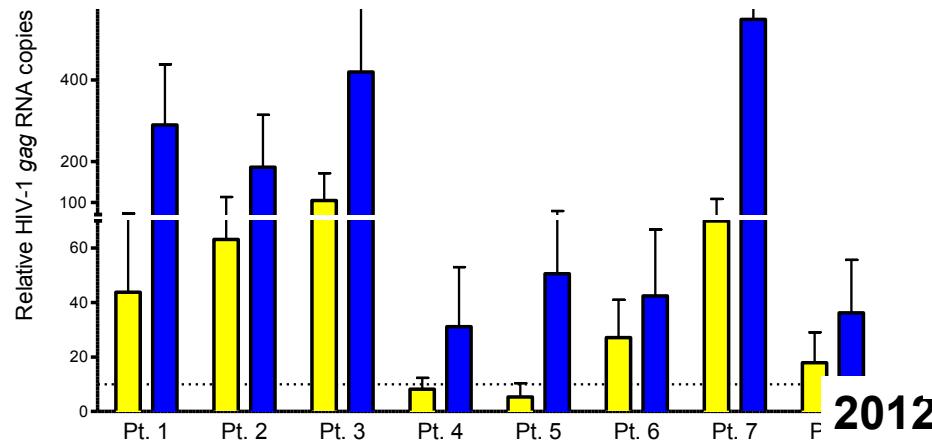
# Aiming for sustained “remission” off ART



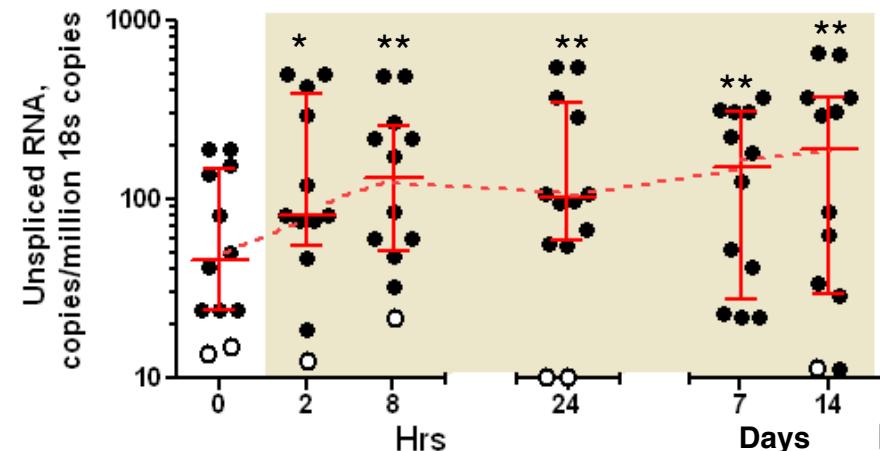
Cohen J. *Science* 2014

## Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy

N. M. Archin<sup>1</sup>, A. L. Liberty<sup>1</sup>, A. D. Kashuba<sup>1</sup>, S. K. Choudhary<sup>1</sup>, J. D. Kuruc<sup>1</sup>, A. M. Crooks<sup>1</sup>, D. C. Parker<sup>1</sup>, E. M. Anderson<sup>1</sup>, M. F. Kearney<sup>2</sup>, M. C. Strain<sup>3</sup>, D. D. Richman<sup>3</sup>, M. G. Hudgens<sup>1</sup>, R. J. Bosch<sup>4</sup>, J. M. Coffin<sup>2</sup>, J. J. Eron<sup>1</sup>, D. J. Hazuda<sup>5</sup> & D. M. M.

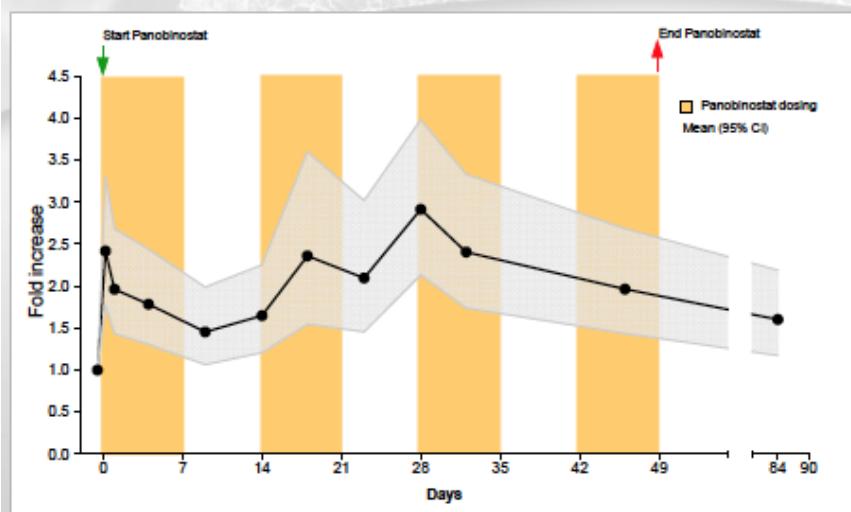


14 daily doses of vorinostat Elliot PLoS Path 2014



## Thrice weekly cycles of Panobinostat

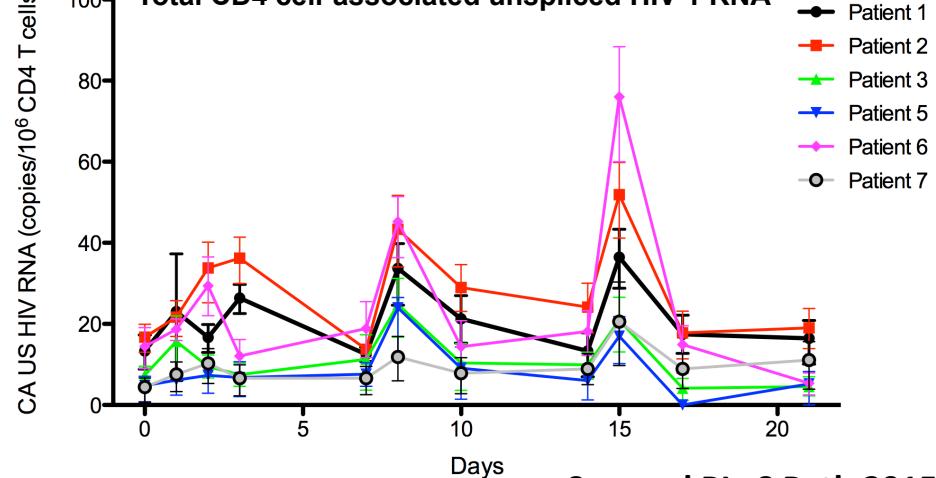
Measured in total CD4+ T cells using semi-nested qPCR (quadruplicates)



Rasmussen Lancet ID 2014

## Weekly Romidepsin

Total CD4 cell-associated unspliced HIV-1 RNA

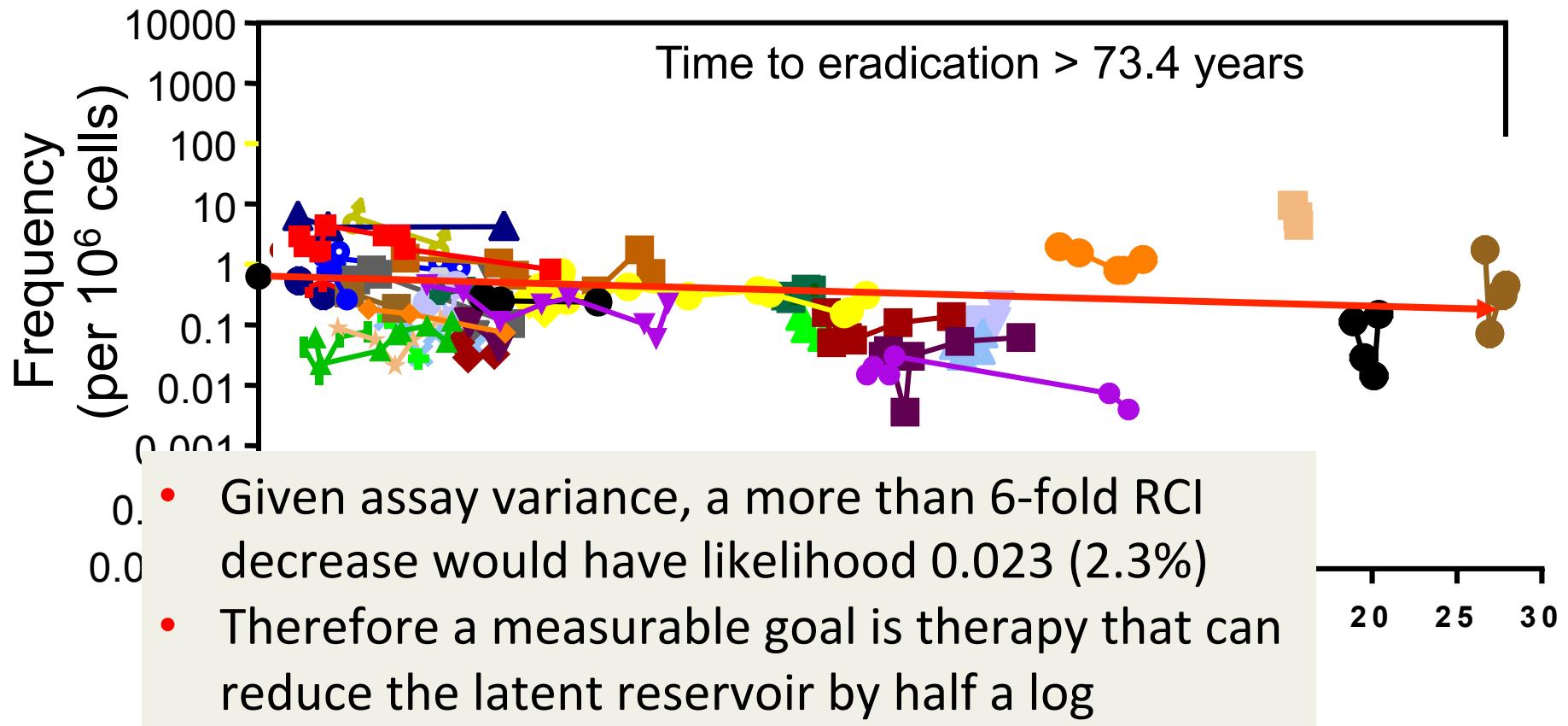


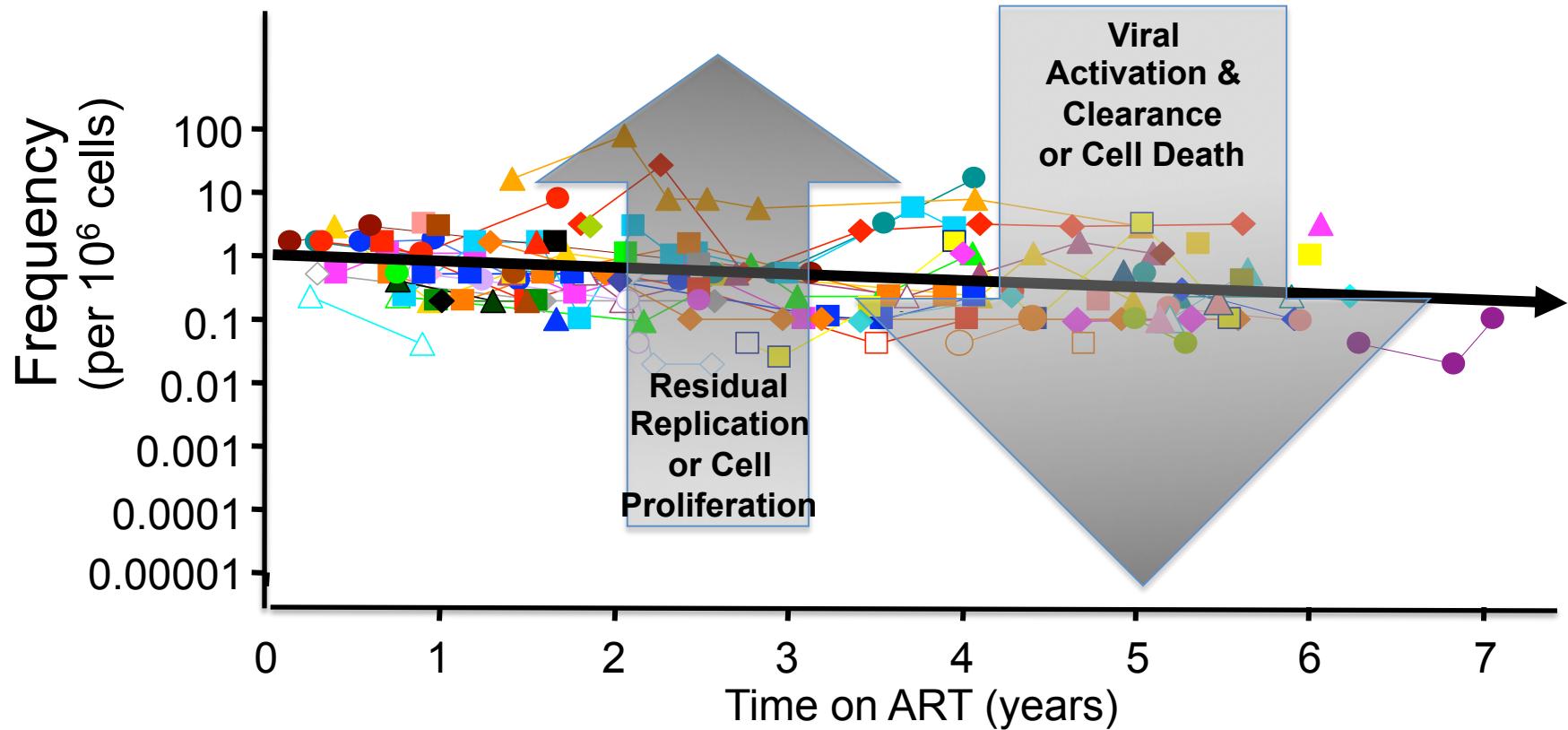
Sogaard PLoS Path 2015

# Challenges to clearing persistent infection after latency reversal

- Recent absence of antigen – low frequency of HIV-specific antiviral responses
- Immune dysfunction, deletion, or exhaustion
- Archived viral diversity, including immune escape
- Viral antigen is rare, dispersed, compartmentalized, and may be transient
- Latency Reversing Agents (LRAs) are host-targeted, and alone or in combination may alter antiviral immune response

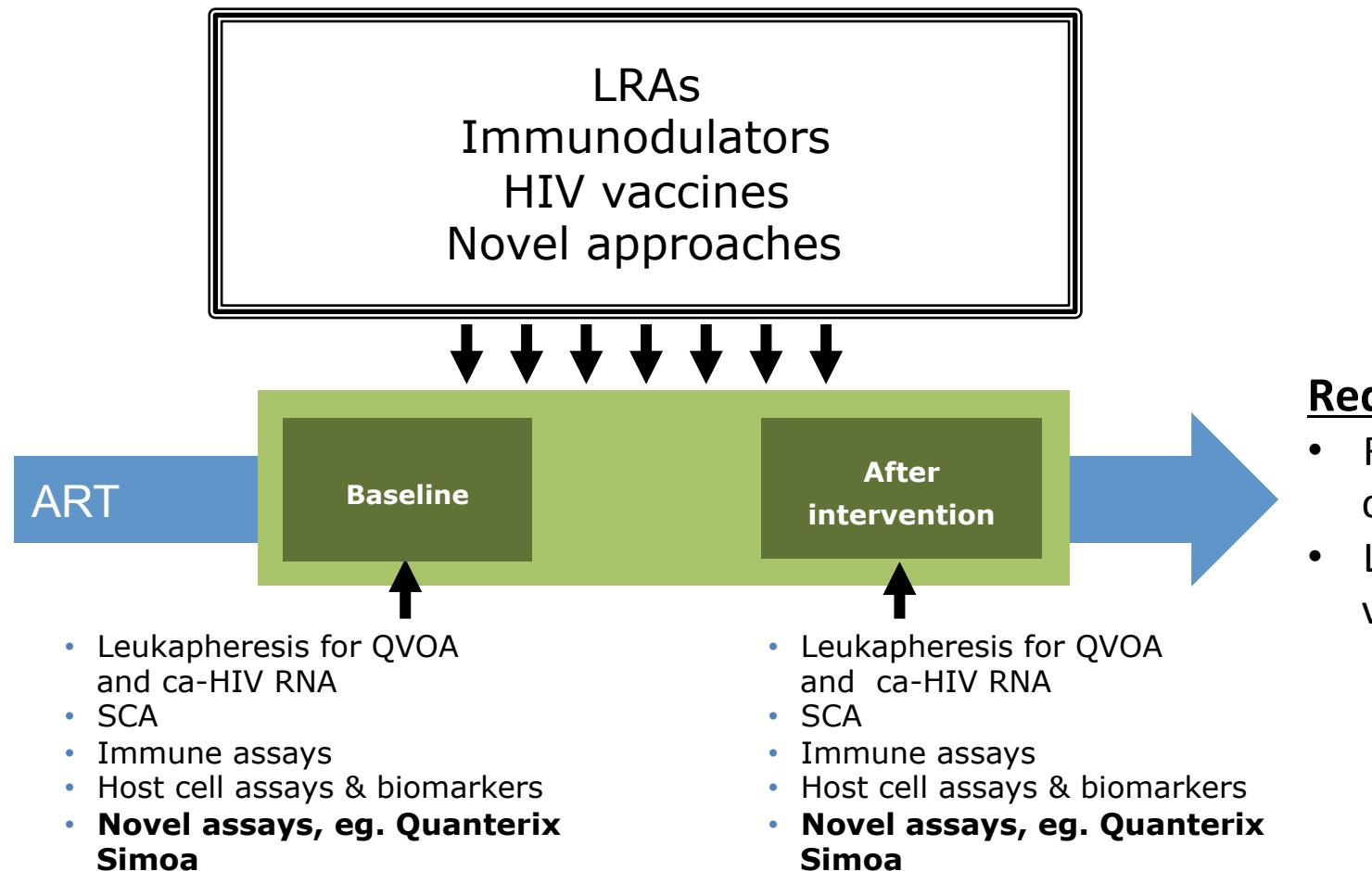
Two step problem:  
*Persistent HIV infection despite ART*





From Siliciano Nature Med. 2003

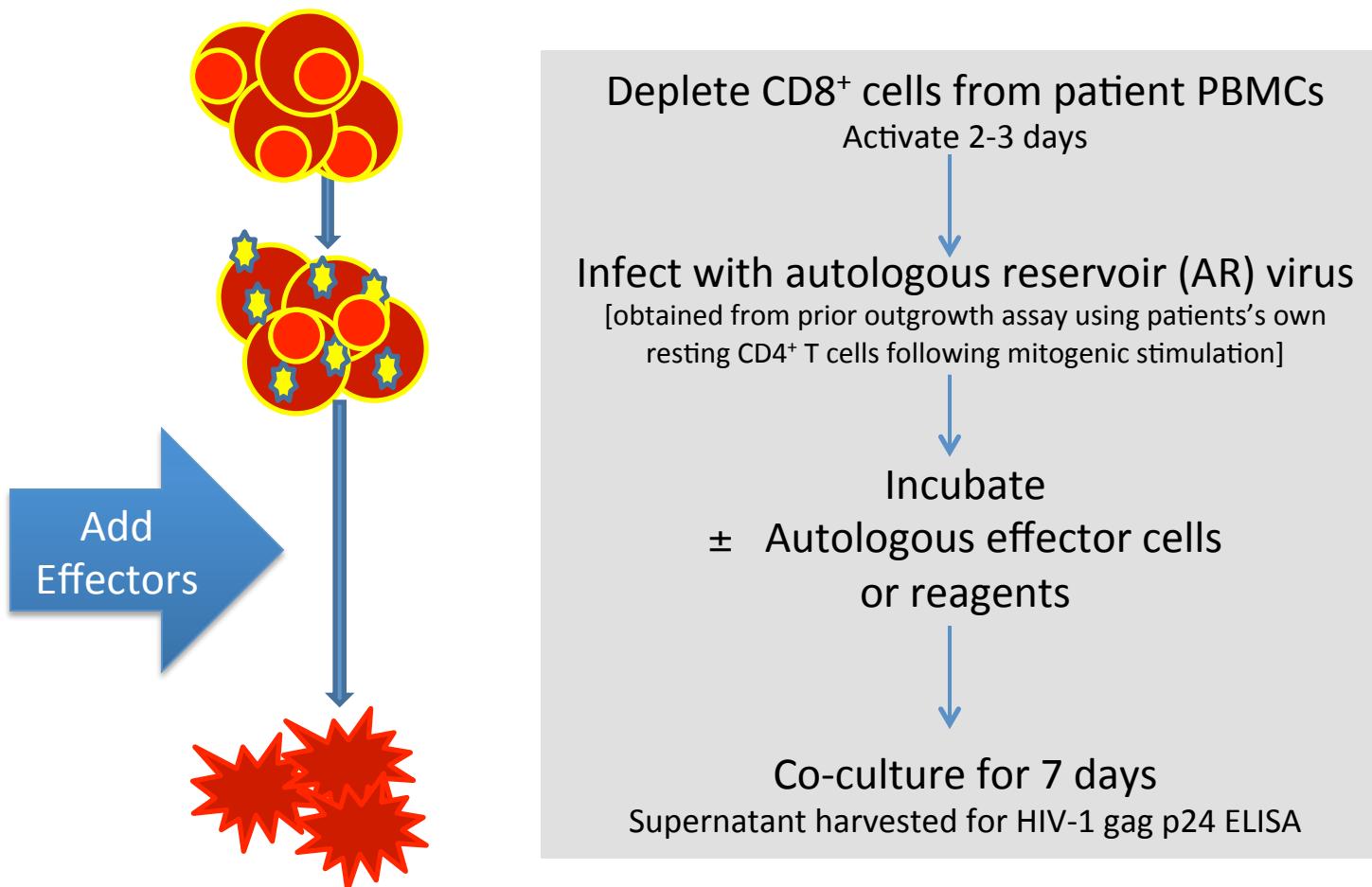
# Testing interventions in vivo



## Reduction in:

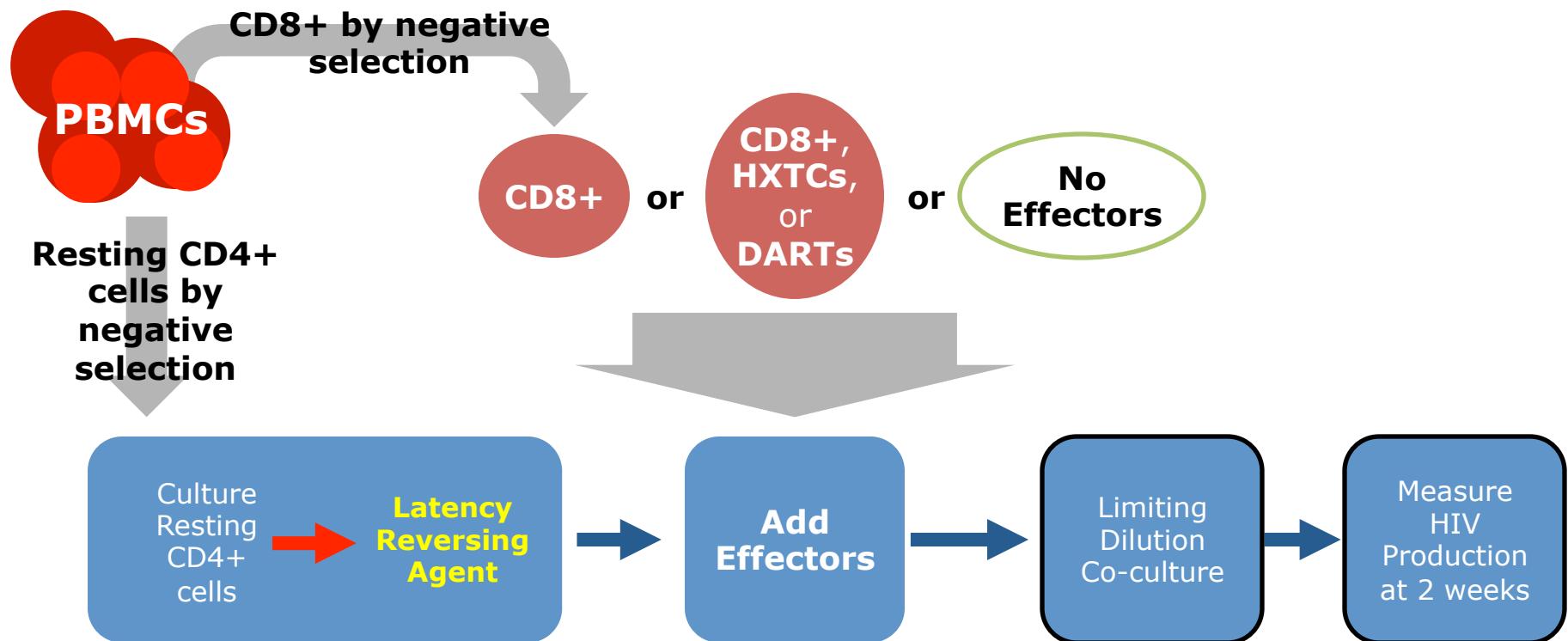
- Resting CD4 cell infection
- Low-level viremia

# Viral Inhibition Assay to Assess Effector Clearance Using Lymphocytes from HIV-Infected ART-Suppressed Patients



# Ex-Vivo Latency Clearance Assay:

*A modified quantitative viral outgrowth assay*

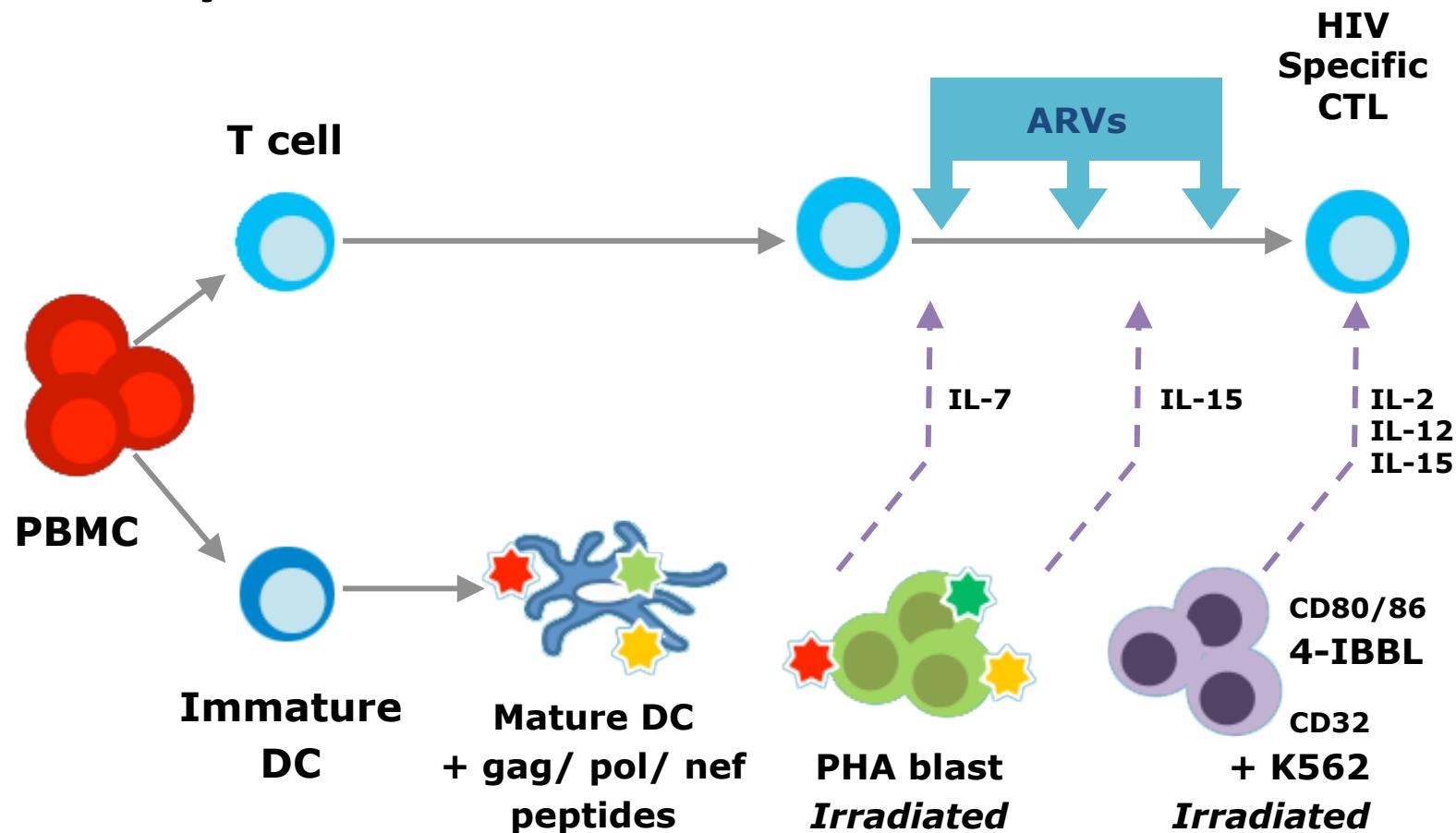


# HIV specific Ex-vivo Expanded T cells (HXTCs)

Cath Bolland

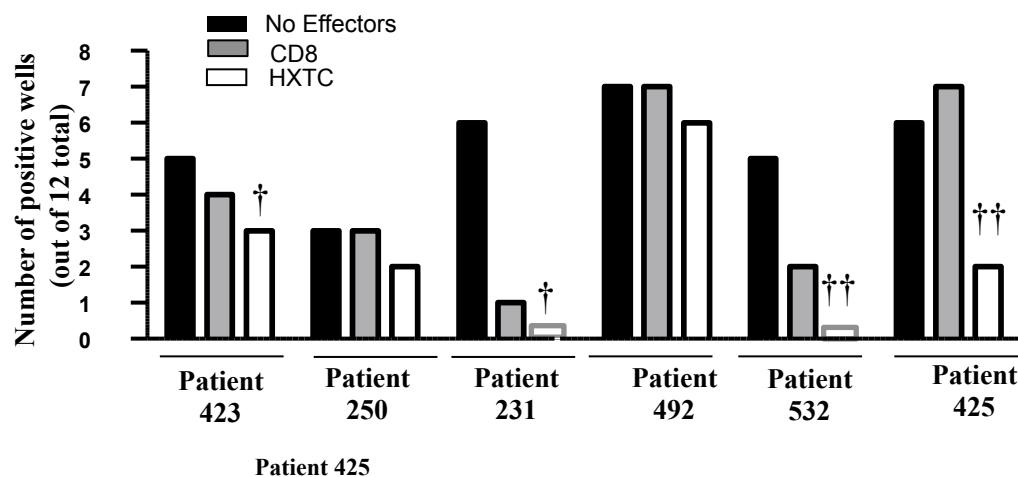


Clio Rooney

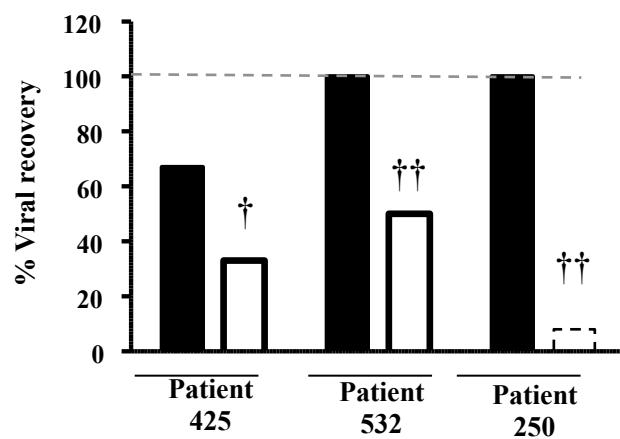


# HXTCs Reduce Recovery of Virus from autologous resting CD4+ T cells stimulated with:

**PHA**



**VOR**

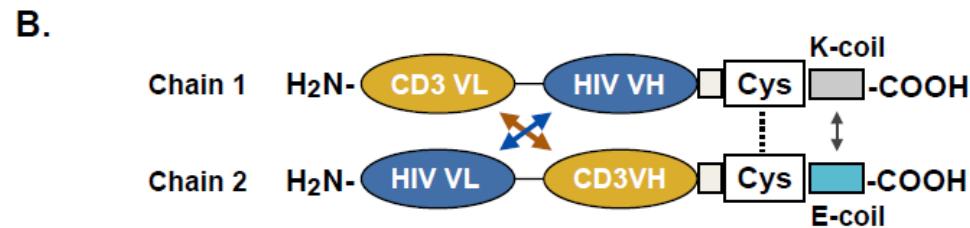
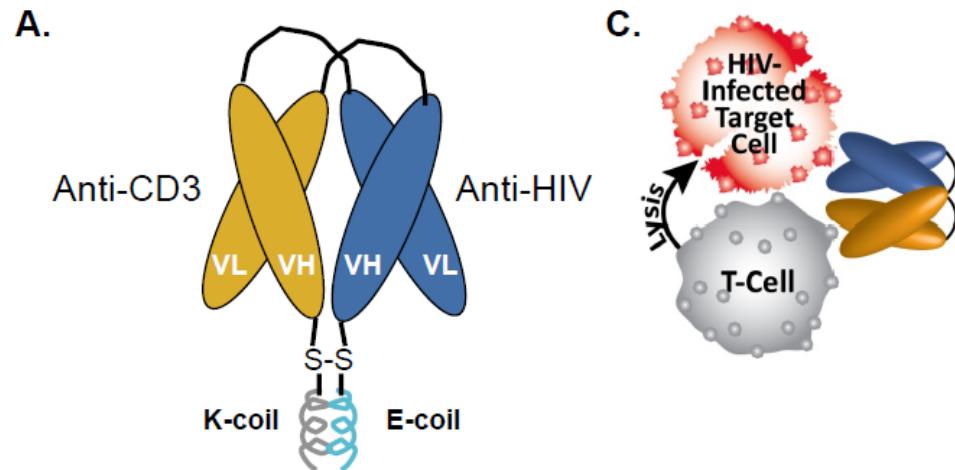


†p<0.05 compared to No Effector

††p<0.05 compared to BOTH

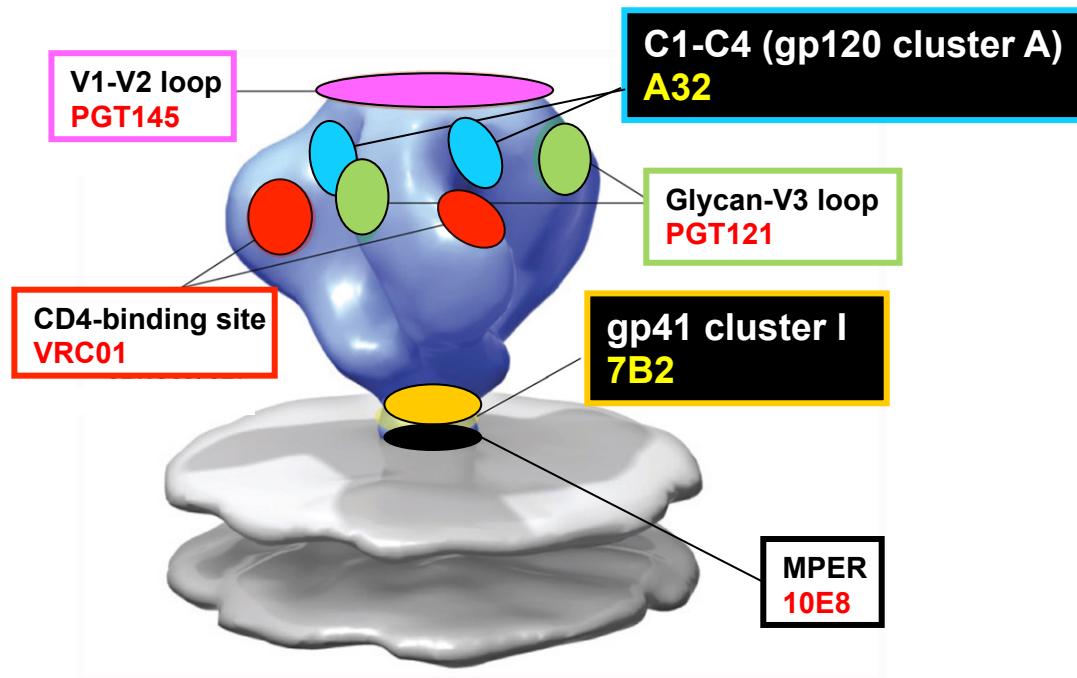
Sung et al. JID 2015

# Dual Affinity ReTargeting (DARTs) Molecules for HIV



- Do not require pre-existing HIV specificity
  - Not impacted by archived CTL escape variants
- Anti-Env arm based on well characterized mAbs with
  - Breadth in binding to CD4 inducible epitopes and ADCC activity
  - Little to no binding to free virions

# Targeting Conserved Env Epitopes on HIV-Infected Cells with non-neutralizing ADCC-mediating mAbs

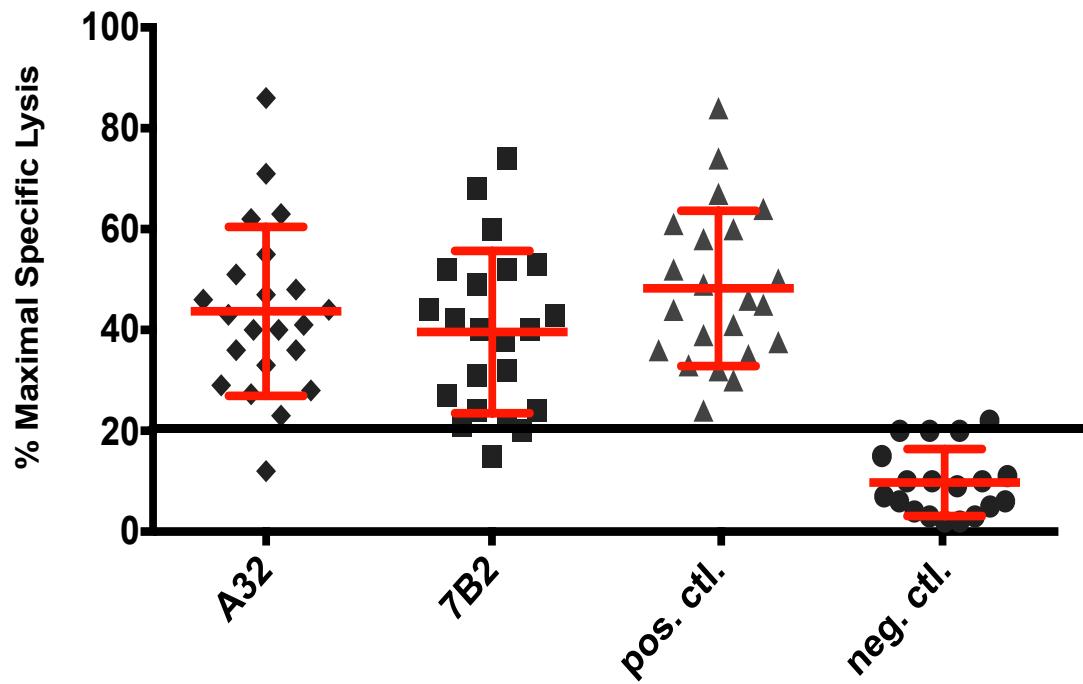


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at CHAPEL HILL

 **CHAVI-ID**  
Duke Center for HIV/AIDS Vaccine Immunology  
and Immunogen Discovery

 **MACROGENICS**

# A32 and 7B2 mAbs: Broad and Potent mediators of ADCC

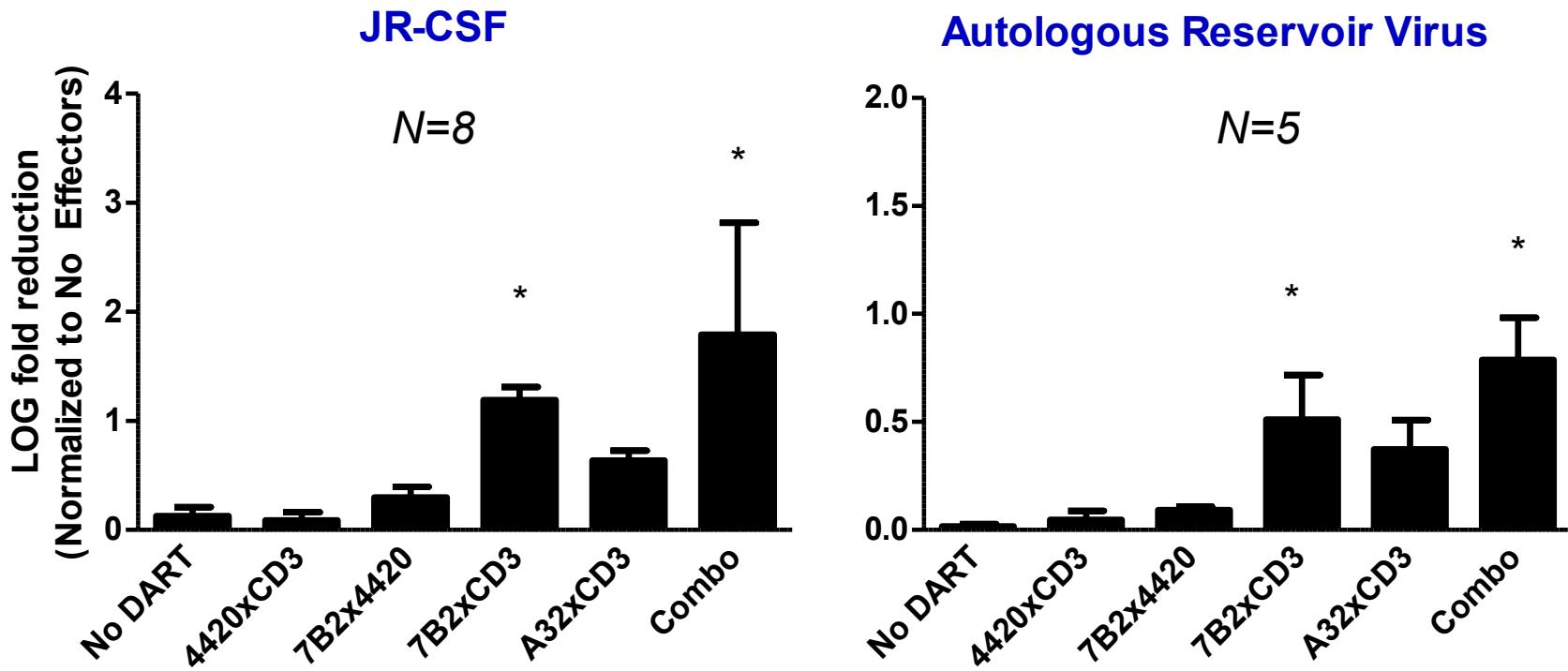


- 25 mAbs tested for Antibody Dependent Cellular Cytotoxicity activity against 22 IMCs
- 7B2 (gp41) and A32 (gp120) chosen based on potency and breadth of specificity

IMC Recognized	21	20	22	1
Percentage	95	91	100	5
Mean Max %SL	43.69	39.58	48.25	9.73
Range %SL	12-86	15-74	24-84	2-22

Sung, et al. JCI 2015

# HIVxCD3 DART-Mediated Killing Activity Using Lymphocytes from HIV-Infected ART-Suppressed Patients



**HIVxCD3 DARTs are specifically active against autologous reservoir virus infected patient cells**

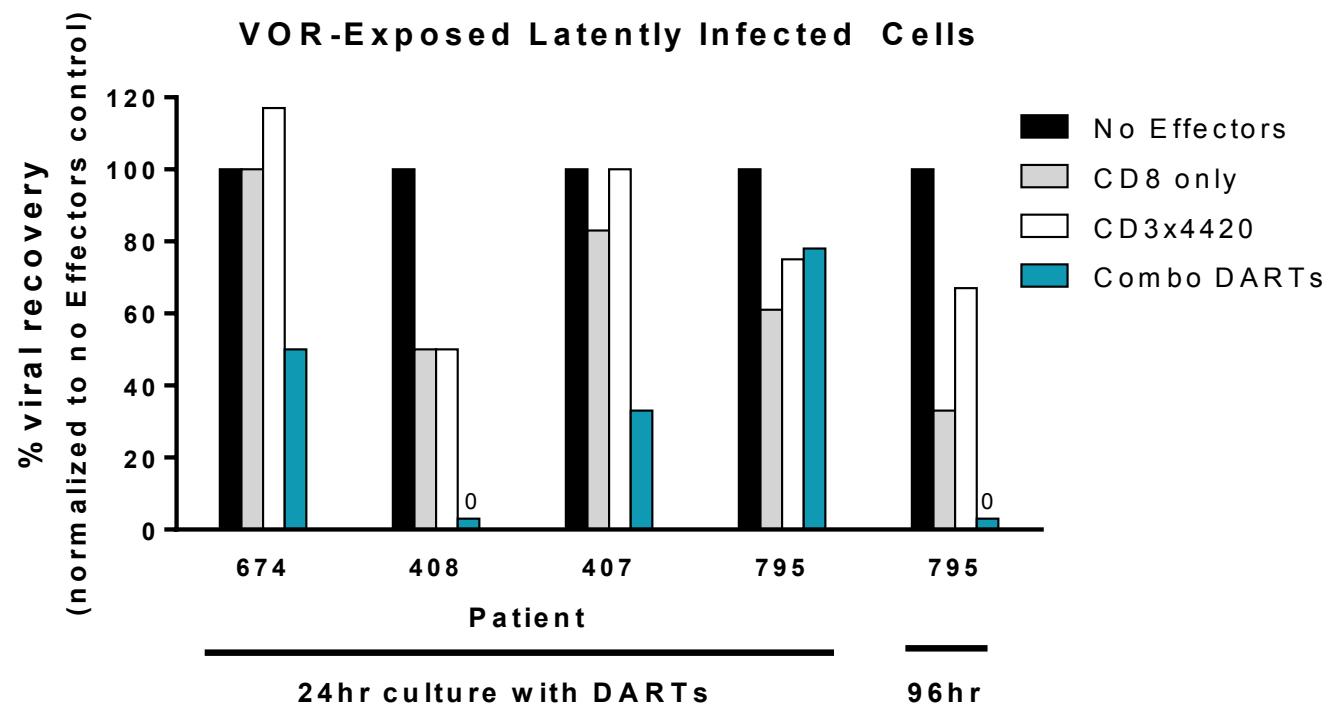
N= 8 (left panel), N=5 (right panel)

\*indicates p<0.05 by Dunnett's test for multiple comparisons

Combo (1:1 mix of A32xCD3 and 7B2xCD3)

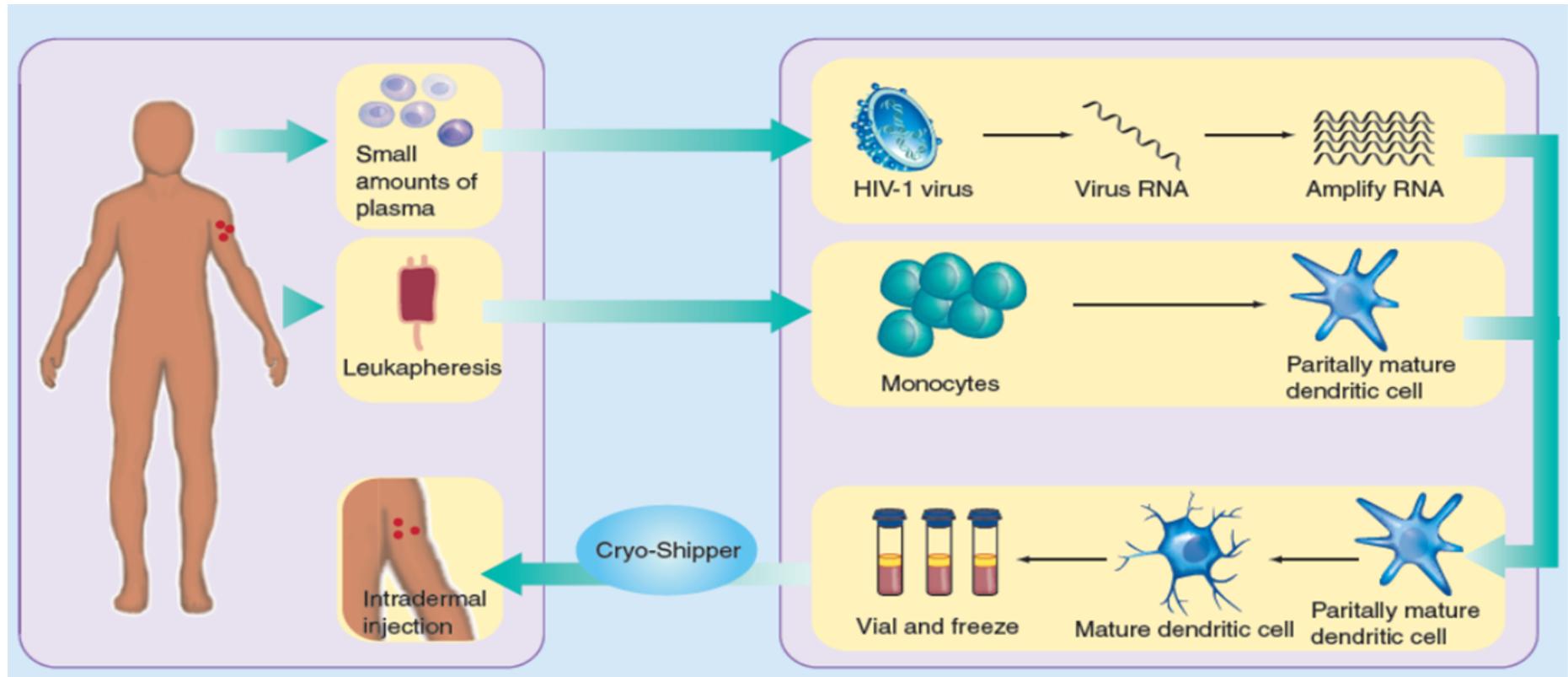
Sung, et al. JCI. 2015

# HIVxCD3 DART Mediated Clearance of Resting Patient CD4 Cells Exposed to Vorinostat



HIVxCD3 DART-mediated virus clearance in 4 of 4 patients (longer time needed for Pt 795)

## Enhancing HIV-specific immunity

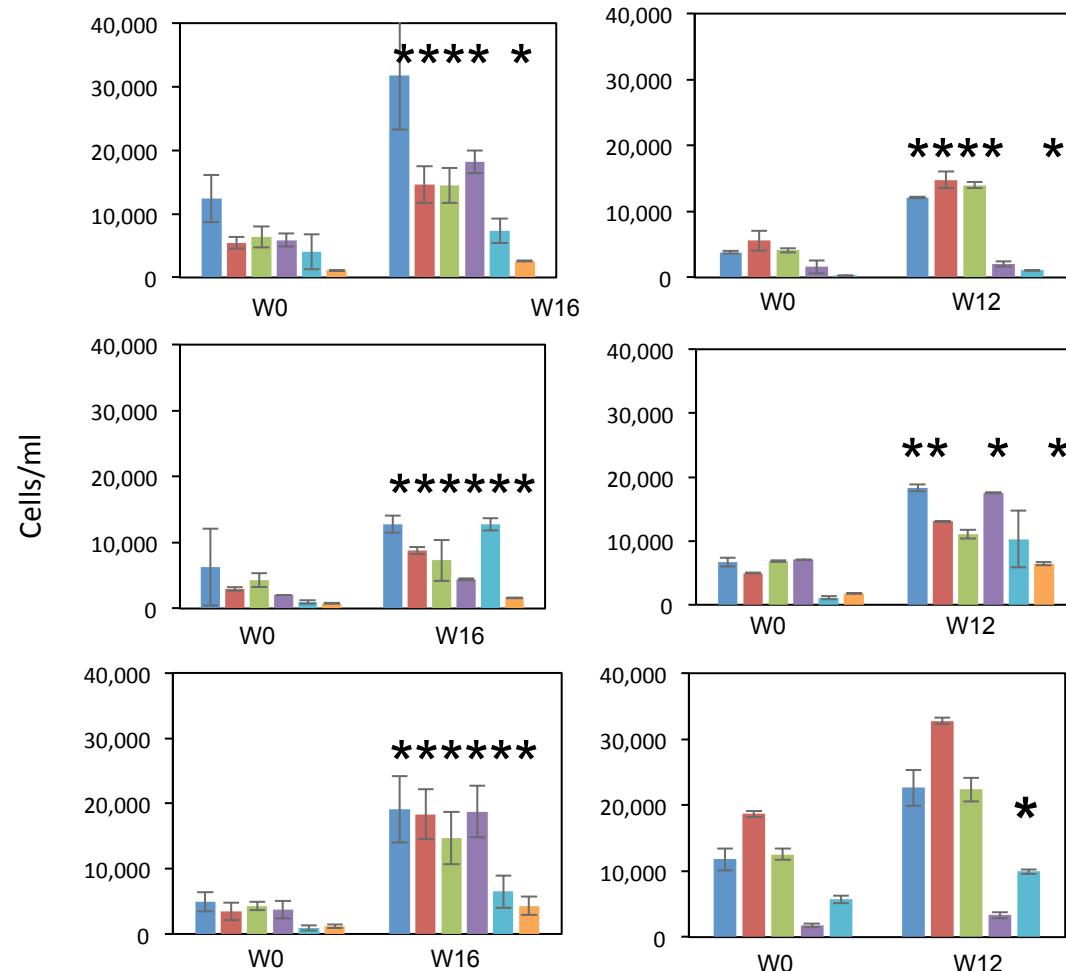


- Provides all 3 signals required for adaptive immune response (TCR, CD28, IL 12) in context of patient's own Gag, Rev, Nef, Vpr
- Produces memory T cells for a durable response
- Does not require CD4+ T cell help

# Multi-functional immune responses to the total antigen RNA payload in participants treated with 4 doses of AGS-004

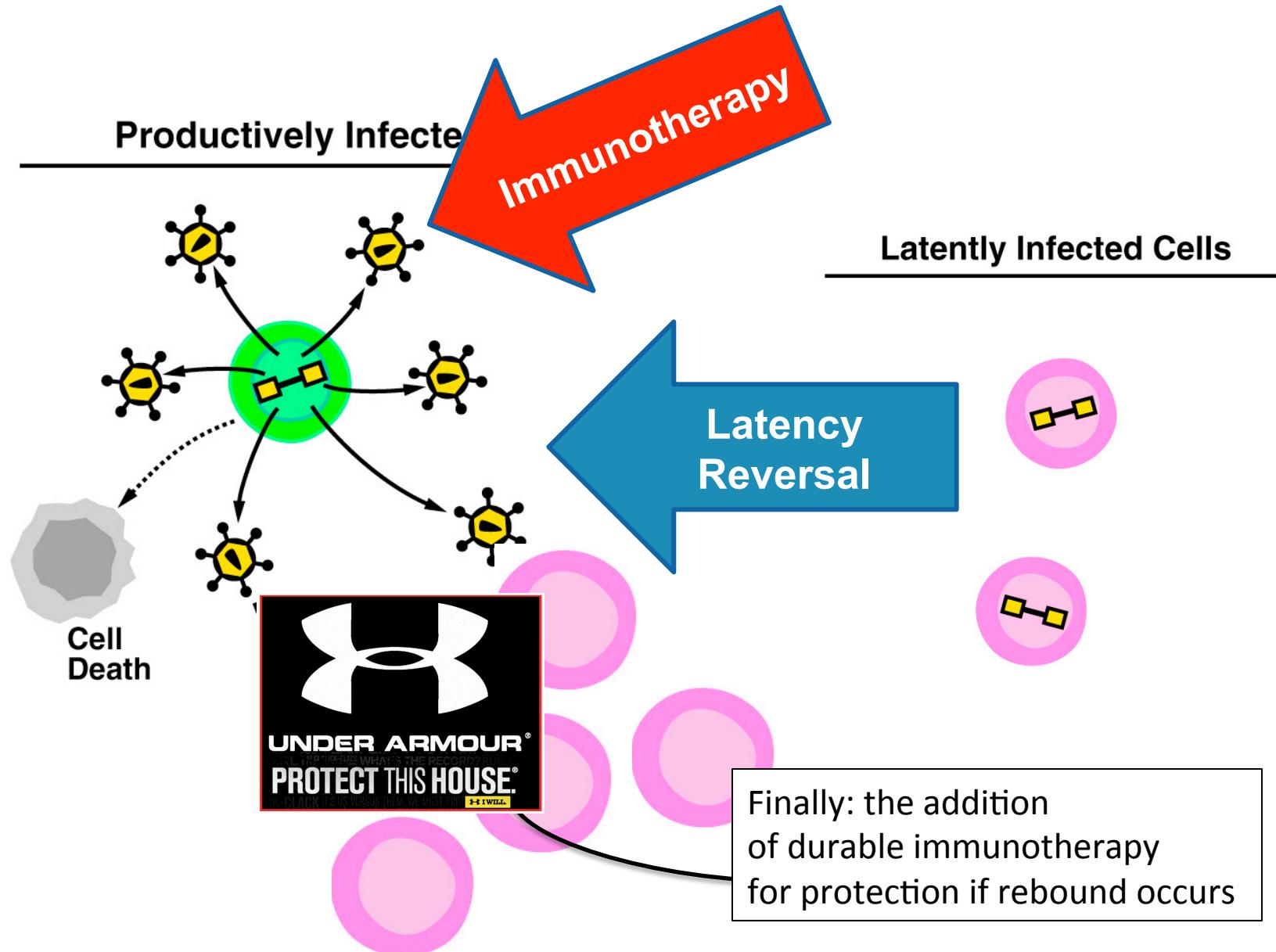
Memory CD28+ CD45RA- CTL recall responses ex vivo to AGS-004 at baseline and week 16 in 6 participants treated during AHI and aviremic for more than 6 months

- BrdU+
- CD107a+
- GrnB+
- IFN  $\gamma$ +
- IL2+
- TNF $\alpha$ +



\*p<0.005

# Steps to eliminate HIV infection



Julia Sung, Carolina Garrido, Anne Marie Turner

Nancie Archin and Jenn Kirchher PhD, Brigitte Allard, Katherine Sholtis, Erin Stuelke

Natalia Soriano

Victor Garcia-Martinez & lab

Nilu Goonetilleke & lab

Cynthia Gay, JoAnn Kuruc & trials team

Joe Eron & ACTU

Angela Kashuba & lab

Yara Park & UNC Blood Bank

Ron Swanstrom & CFAR

Daria Hazuda, Richard Barnard, Bonnie Howell & Merck scientists

David Farve, Shari Gordon, Rick Dunham & GSK scientists

