

# Session 5: Persistence

CMV and Inflammaging in People with HIV

**Sara Gianella Weibel, MD (She/Her)**

UCSD, United States



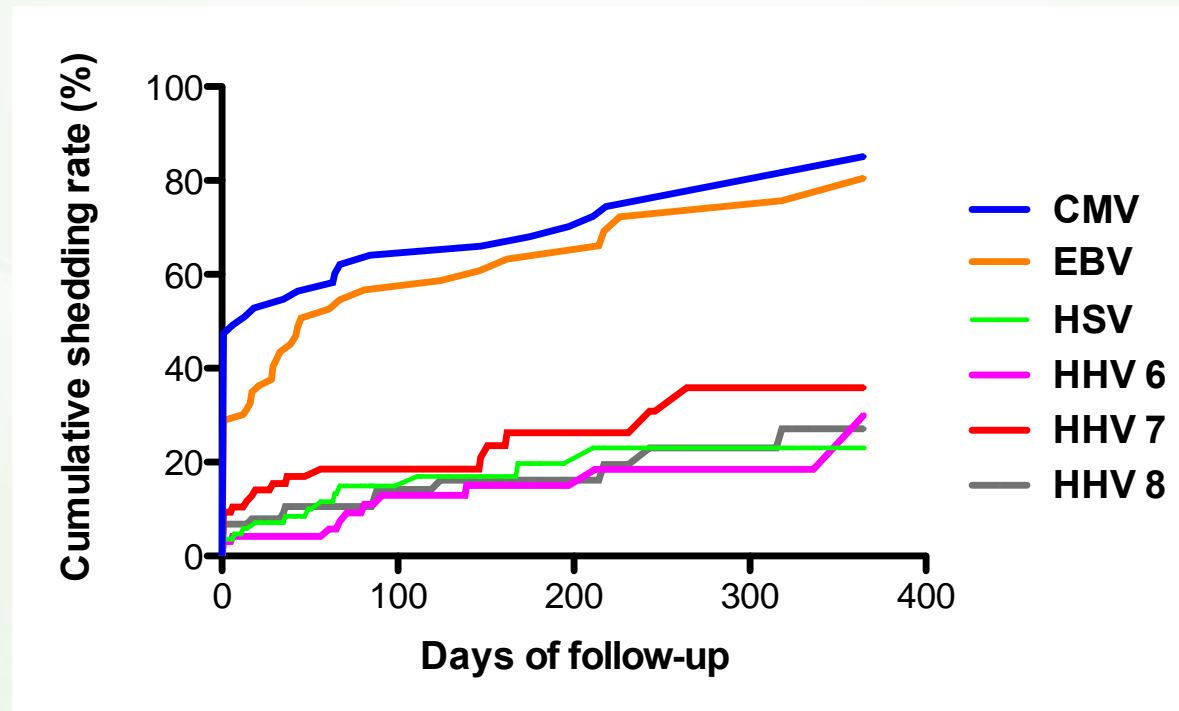
# CMV and Inflammaging in People with HIV

Sara Gianella Weibel, MD (She/Her)  
Associate Professor  
University of California San Diego



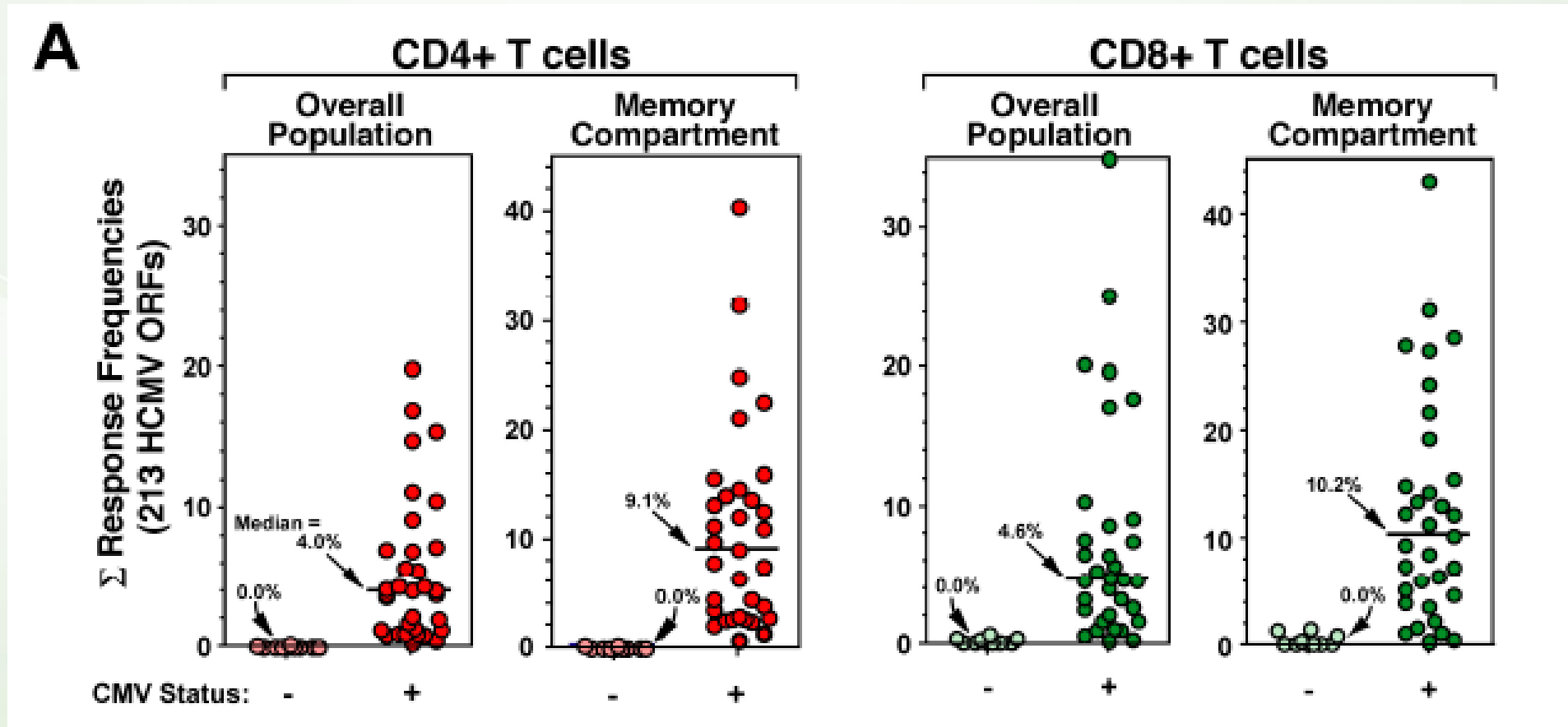
# Background

- Most PLWH are co-infected with CMV.
- Asymptomatic CMV shedding is frequent during ART.



*Morris et al, CID, 2017*

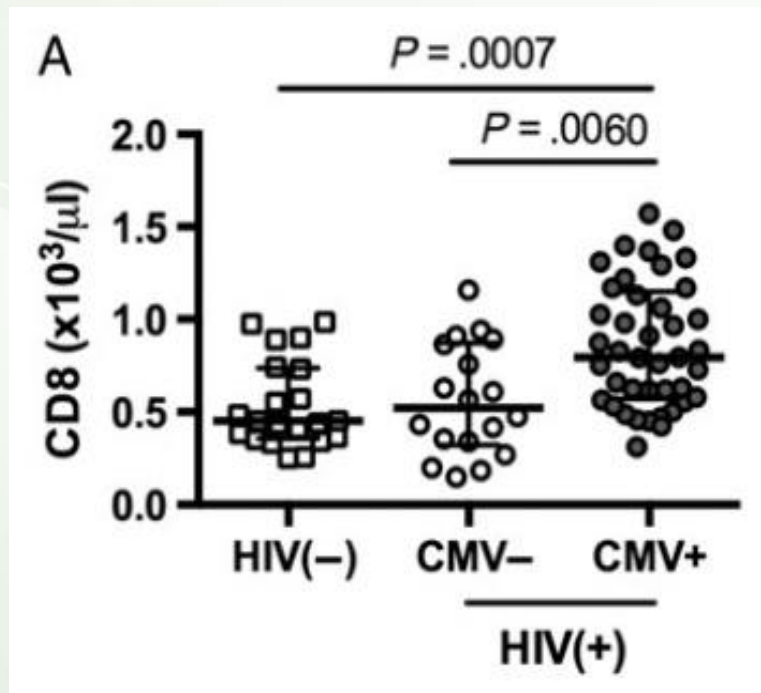
# CMV elicits massive immune responses



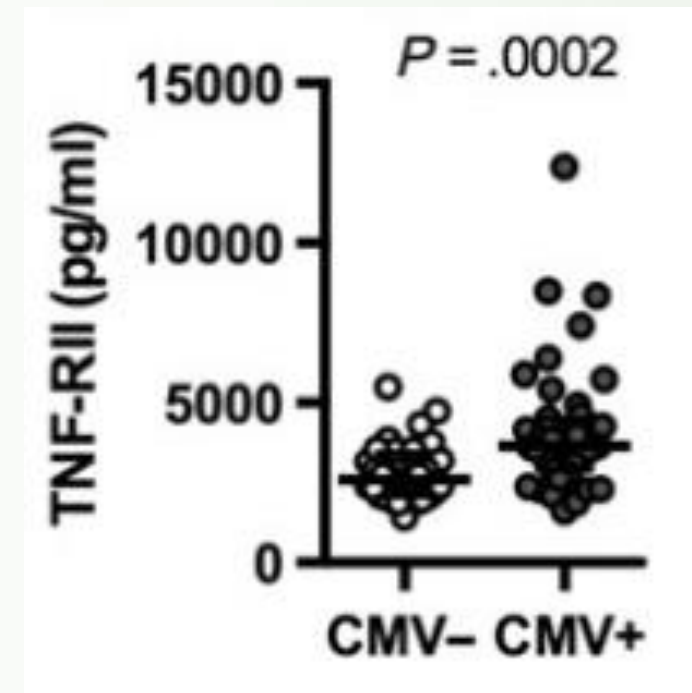
Sylwester/Picker, JEM, 2005

# CMV Associated with CD8 Expansion and Inflammation in HIV Infection

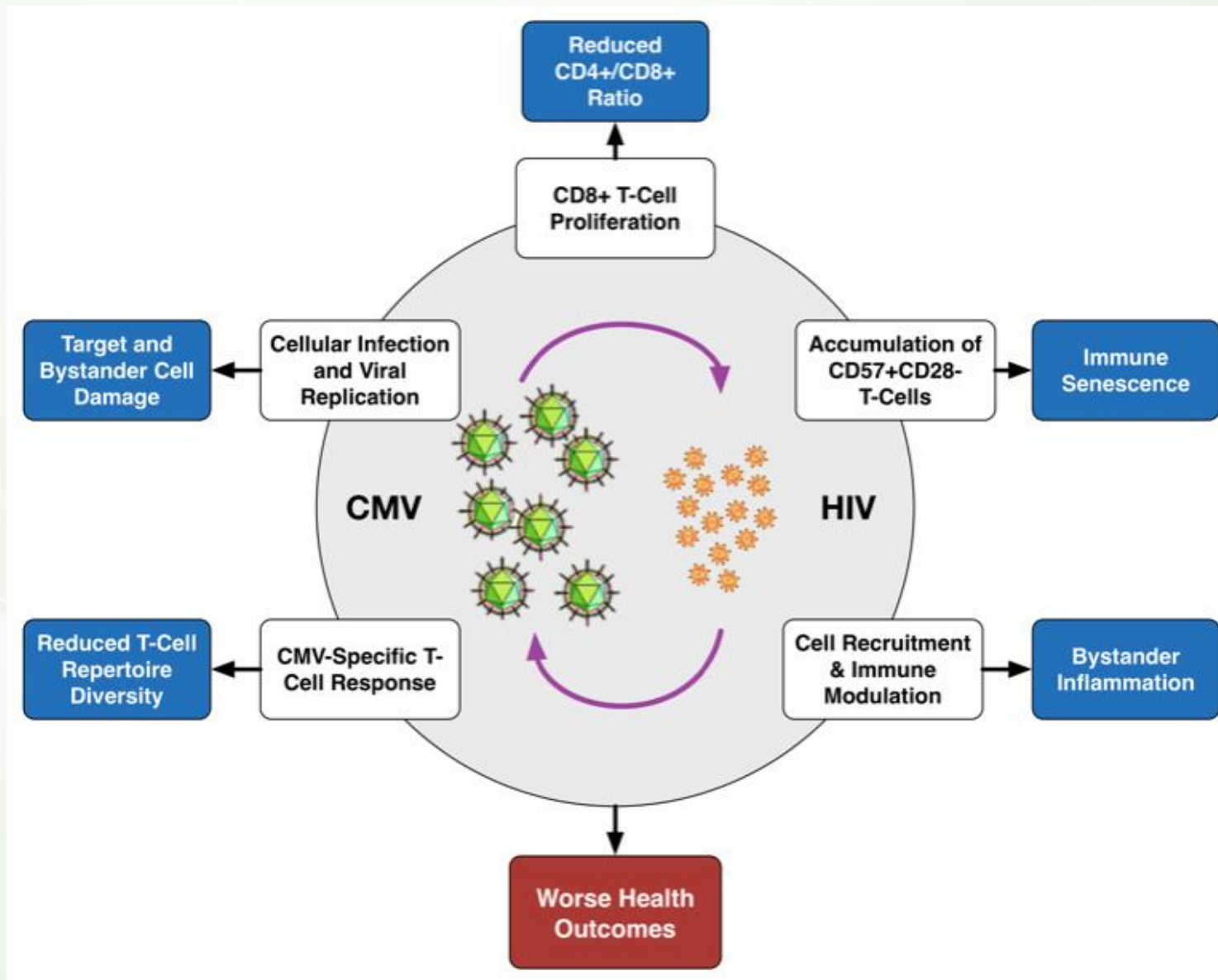
## CD8<sup>+</sup> T Cell Counts



## sTNF-RII



Freeman, *JID*, 2014 (see also: Sacre, *AIDS*, 2011; Mudd, *JID*, 2016; Musselwhite, *AIDS* 2011 and many Gianella papers)



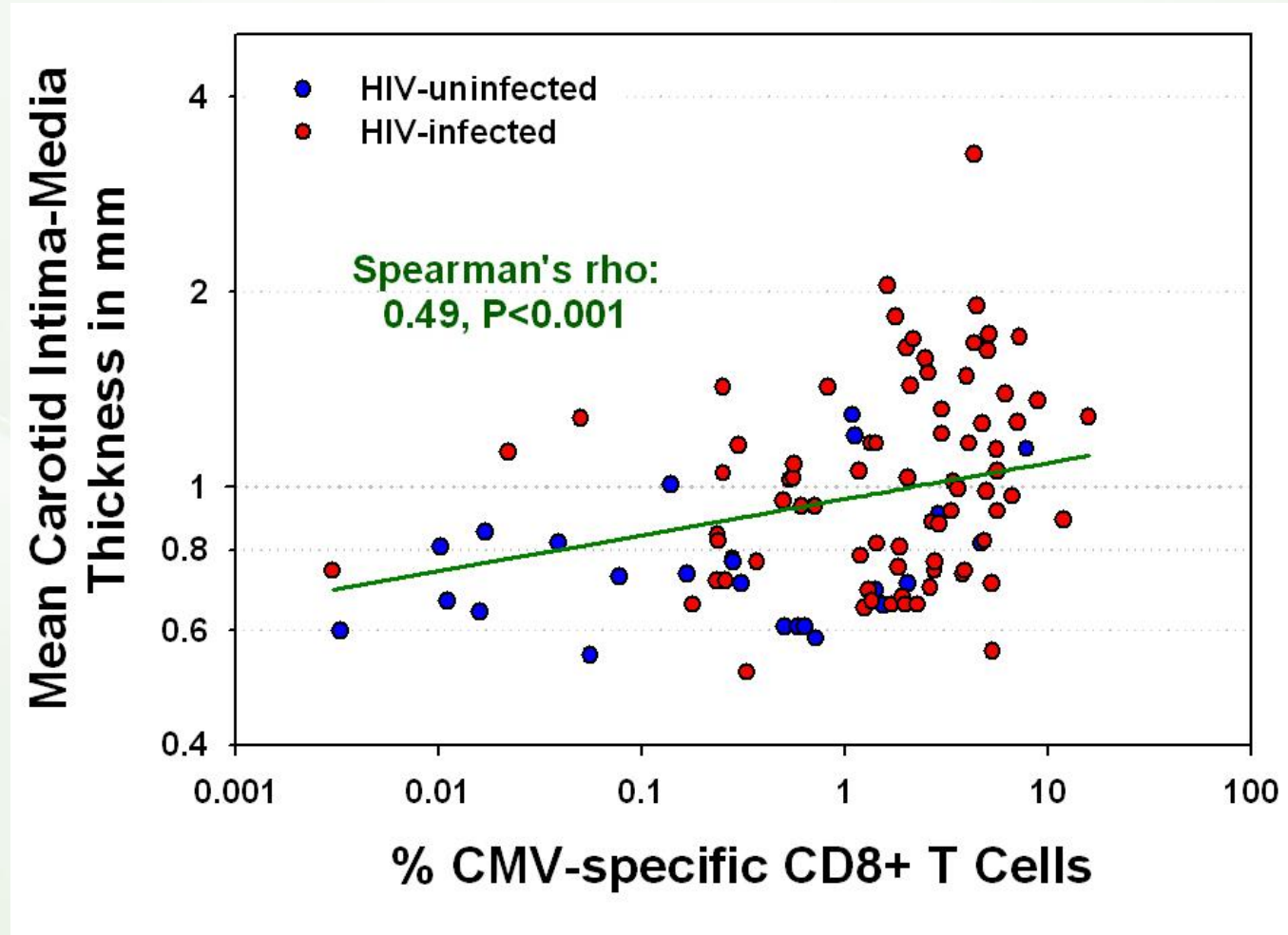
S. Gianella and S. Letendre, 2016

# Ganciclovir Prophylaxis May ↓ Transplant Vasculopathy after Heart Transplant

**TABLE 3. Cox Multivariate Regression Analysis of TxCAD Risk**

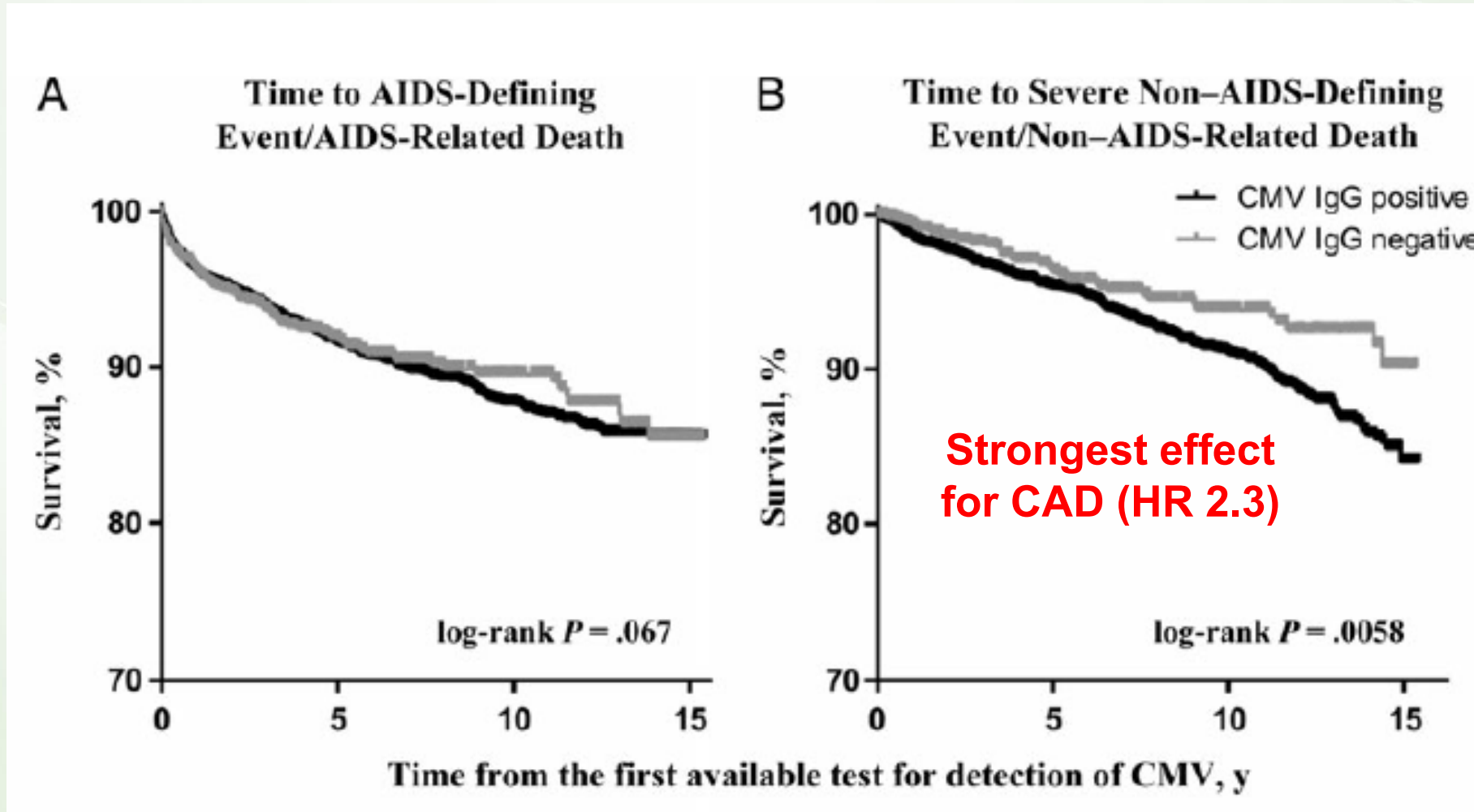
Variable	Relative Risk	95% CI		Significance
		Lower	Upper	
Donor age >40 y	2.7	1.3	5.6	0.01
No ganciclovir	2.9	1.2	7.2	0.01
CMV illness	0.64	0.3	1.2	0.22
Site (Stanford or Utah)	1.3	0.7	2.6	0.36
Calcium blocker	1.51	0.58	3.96	0.39
Rejection episodes (>3)	1.8	0.9	3.5	0.1

# Higher CMV-specific CD8 IFN-g Production Associated with More Atherosclerosis

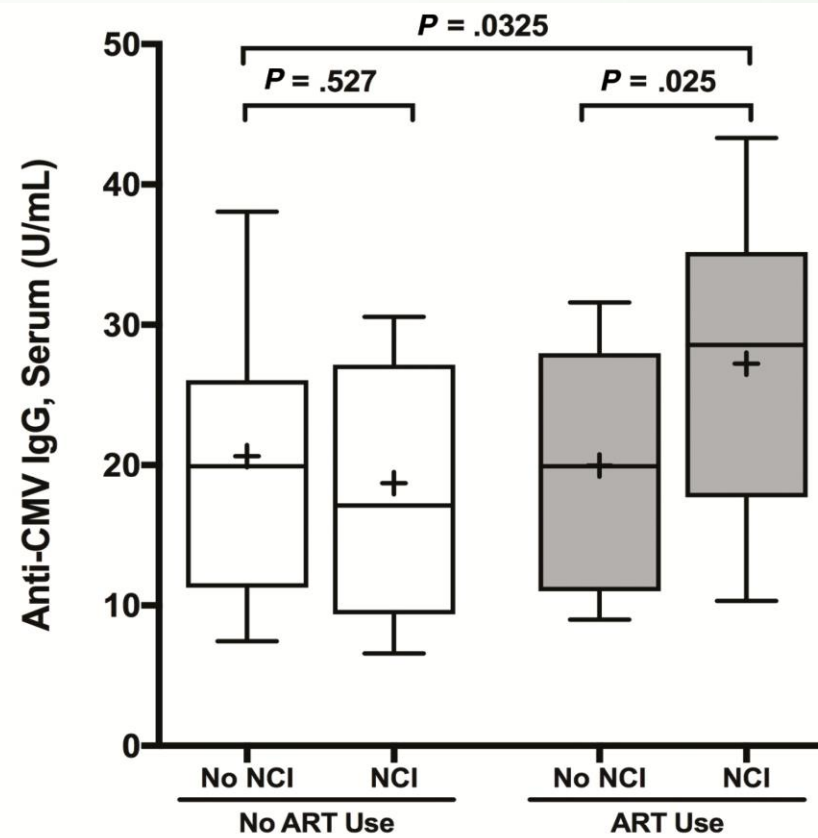
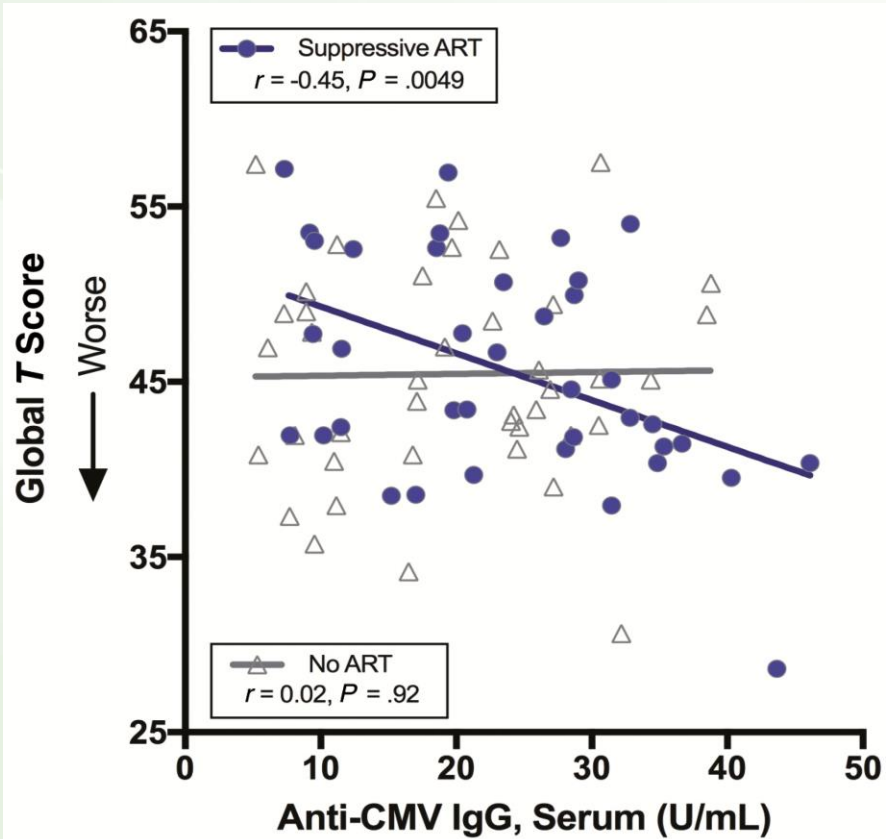




# CMV Serostatus Predicts Non-AIDS Events: ICONA Cohort

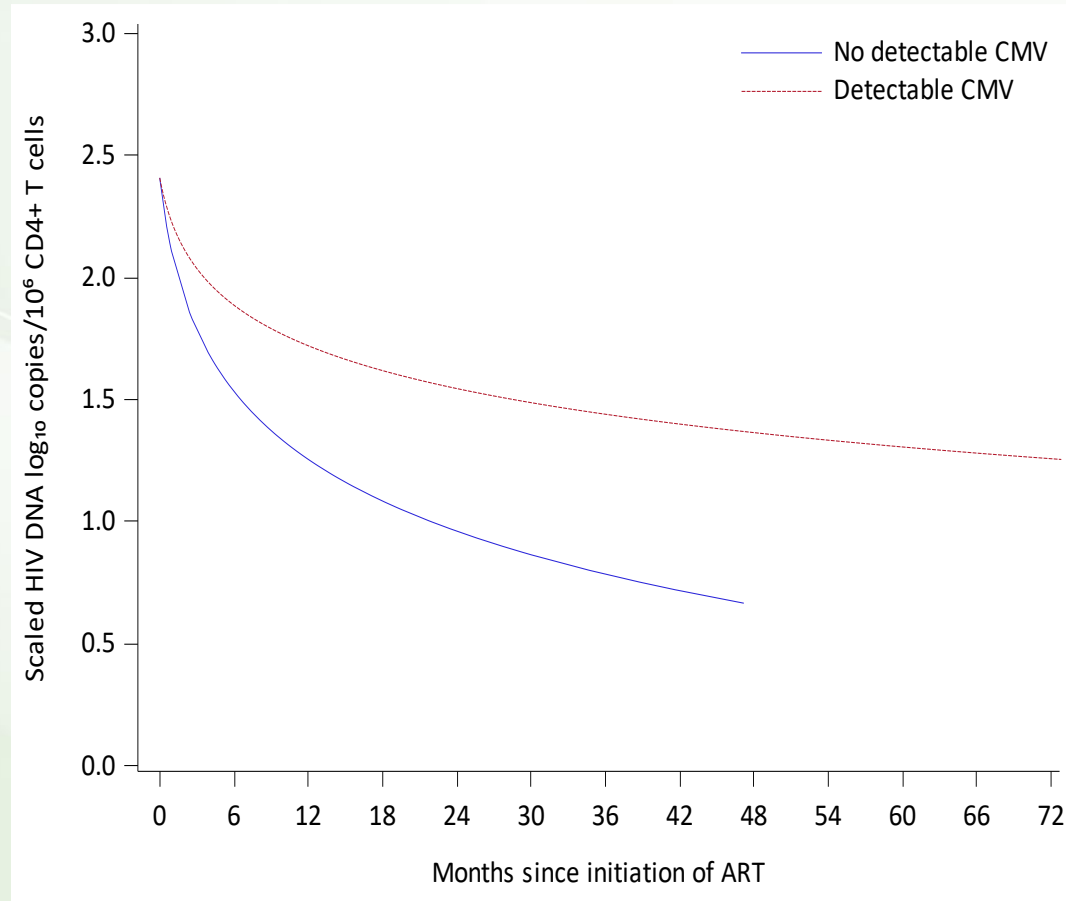


# Associations between anti-CMV IgG levels and neurocognitive functioning

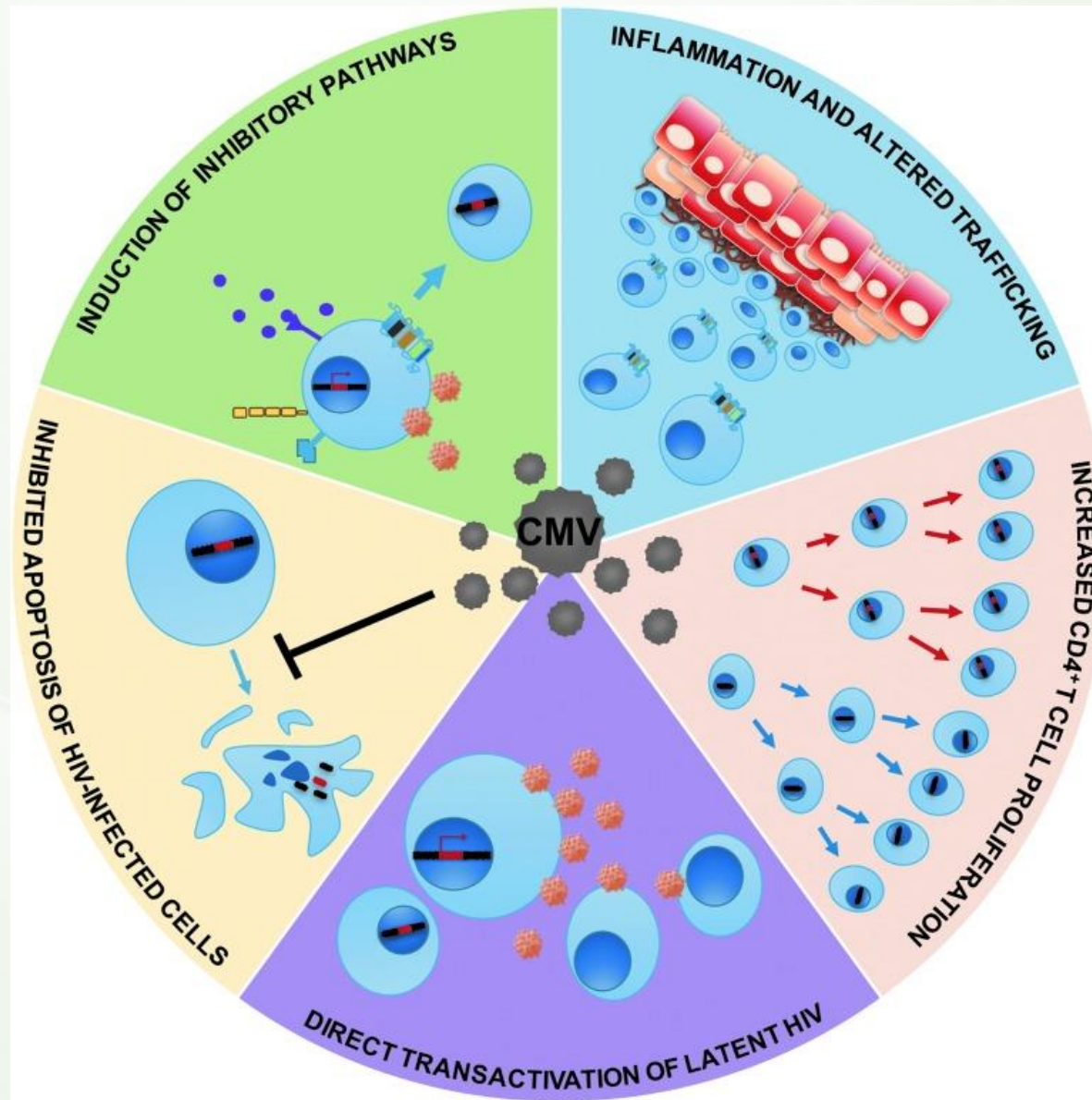


Similar relationship seen in populations of elderly people without HIV (Vescovini, JI, 2010)

# Seminal CMV Shedding Associated with Higher HIV Reservoirs in PBMC



For each doubling of month on ART, HIV DNA declined 0.14 log<sub>10</sub> slower for people with detectable CMV DNA in their PBMC compared to people without detectable CMV



# Antigen-driven clonal selection shapes the persistence of HIV-1-infected CD4<sup>+</sup> T cells in vivo

Francesco R. Simonetti,<sup>1</sup> Hao Zhang,<sup>2</sup> Garshasb P. Soroosh,<sup>1</sup> Jiayi Duan,<sup>1</sup> Kyle Rhodehouse,<sup>1</sup> Alison L. Hill,<sup>3</sup> Subul A. Beg,<sup>1</sup> Kevin McCormick,<sup>4</sup> Hayley E. Raymond,<sup>4</sup> Christopher L. Nobles,<sup>4</sup> John K. Everett,<sup>4</sup> Kyungyoon J. Kwon,<sup>1</sup> Jennifer A. White,<sup>1</sup> Jun Lai,<sup>1</sup> Joseph B. Margolick,<sup>2</sup> Rebecca Hoh,<sup>5</sup> Steven G. Deeks,<sup>5</sup> Frederic D. Bushman,<sup>4</sup> Janet D. Siliciano,<sup>1</sup> and Robert F. Siliciano<sup>1,6</sup>

<sup>1</sup>Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. <sup>2</sup>Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. <sup>3</sup>Institute for Computational Medicine, Johns Hopkins University, Baltimore, Maryland, USA. <sup>4</sup>Department of Microbiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA. <sup>5</sup>Division of HIV, Infectious Diseases, and Global Medicine, UCSF, San Francisco, California, USA. <sup>6</sup>Howard Hughes Medical Institute, Baltimore, Maryland, USA.

> [J Exp Med.](#) 2020 Jul 6;217(7):e20200051. doi: 10.1084/jem.20200051.

## Antigen-responsive CD4<sup>+</sup> T cell clones contribute to the HIV-1 latent reservoir

Pilar Mendoza<sup>1</sup>, Julia R Jackson<sup>2</sup>, Thiago Y Oliveira<sup>1</sup>, Christian Gaebler<sup>1</sup>, Victor Ramos<sup>1</sup>, Marina Caskey<sup>1</sup>, Mila Jankovic<sup>1</sup>, Michel C Nussenzweig<sup>1,3</sup>, Lillian B Cohn<sup>2,4</sup>

Affiliations + expand

PMID: 32311008 PMCID: [PMC7336300](#) DOI: [10.1084/jem.20200051](#)

[Free PMC article](#)

ARTICLE

<https://doi.org/10.1038/s41467-020-17898-8>

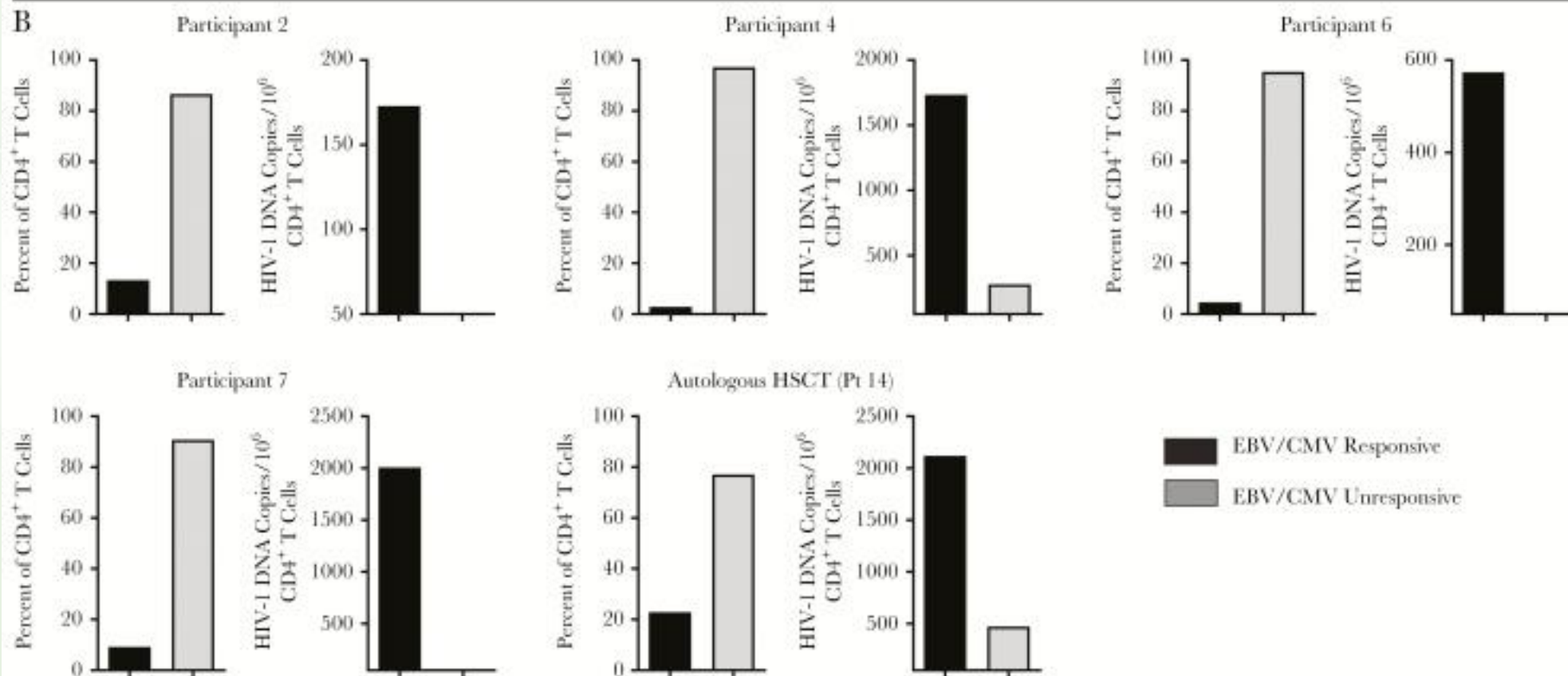
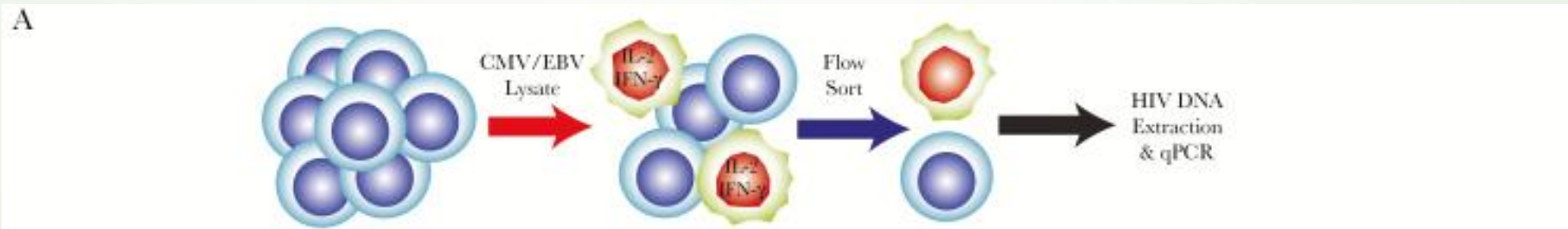
OPEN



## Single-cell TCR sequencing reveals phenotypically diverse clonally expanded cells harboring inducible HIV proviruses during ART

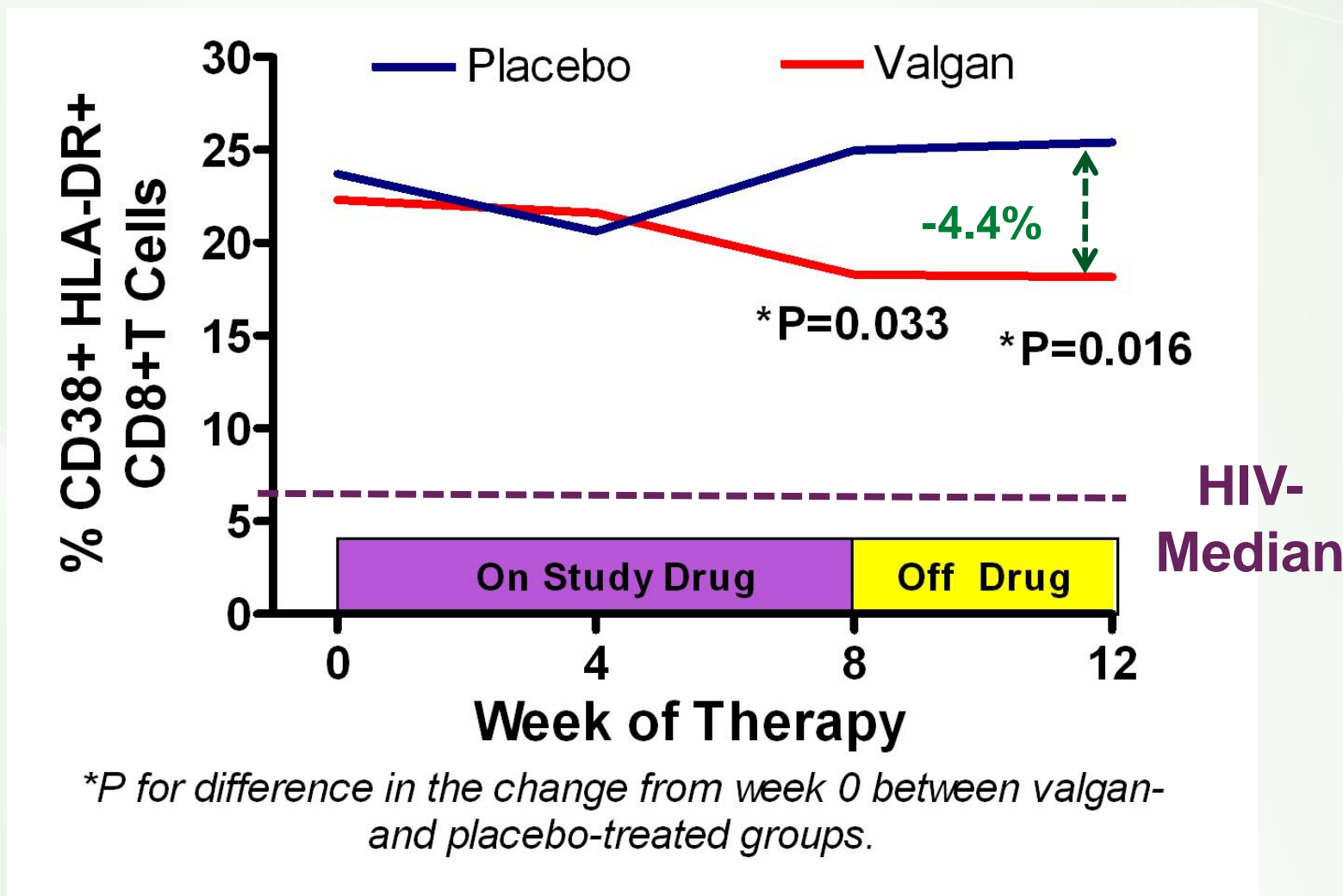
Pierre Gantner<sup>1</sup>, Amélie Pagliuzza<sup>2</sup>, Marion Pardons<sup>1</sup>, Moti Ramgopal<sup>3</sup>, Jean-Pierre Routy<sup>1,4</sup>, Rémi Fromentin<sup>1,2</sup> & Nicolas Chomont<sup>1,2</sup>✉



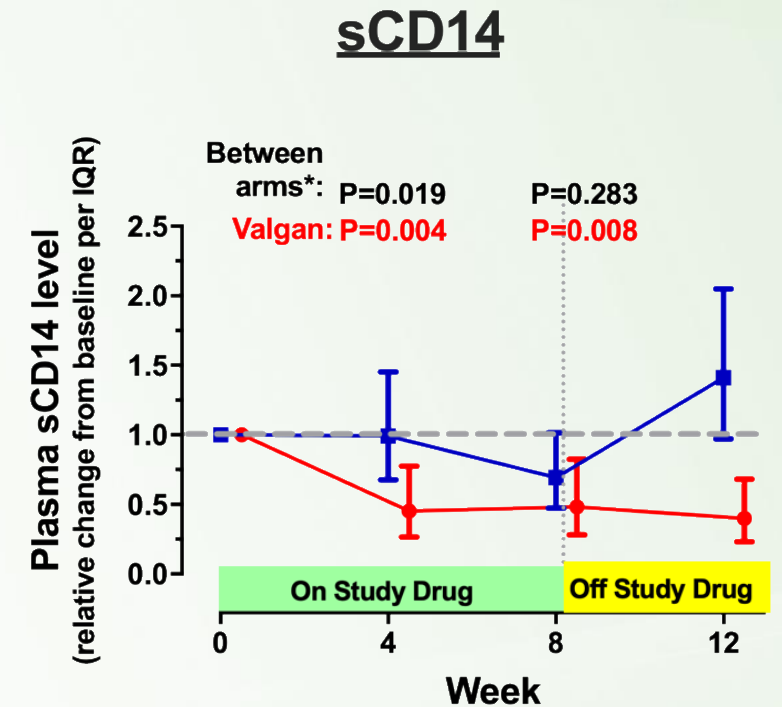
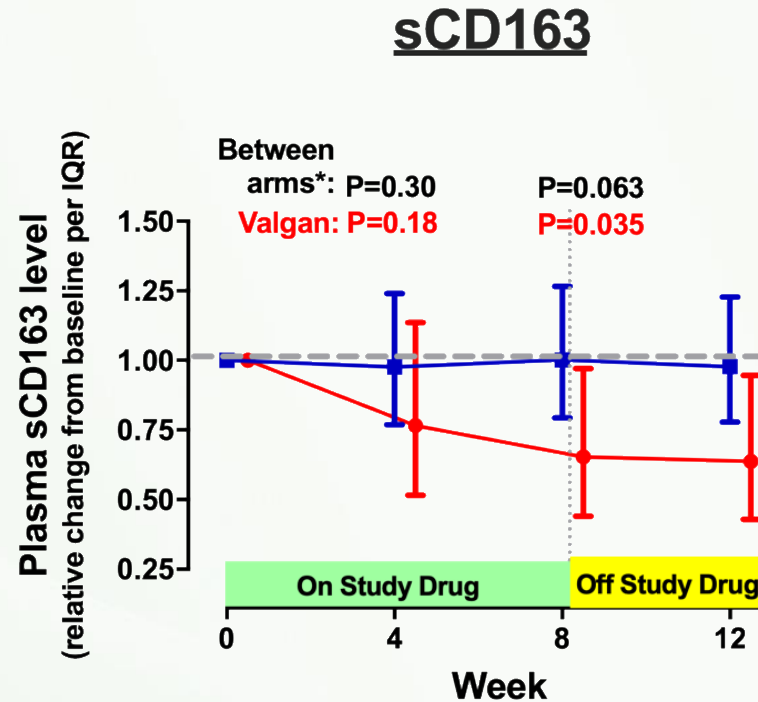
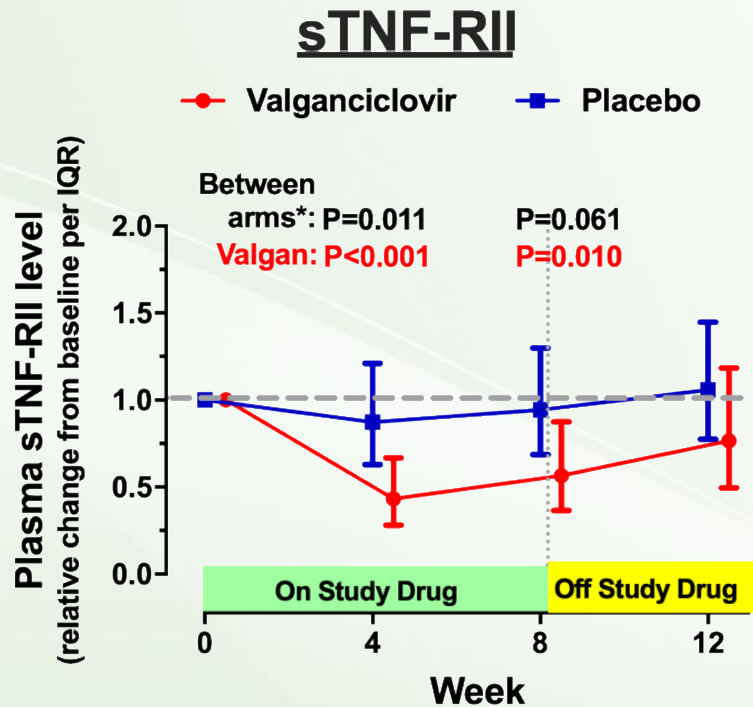


Henrich et al 2017

# Blocking CMV Replication with Valganciclovir ↓ T Cell Activation in PLWH with CD4<350 despite ART



# Valganciclovir Also Caused Major Reductions in Innate Immune Activation (~1 quartile)



\*P values test difference in the change from baseline between treatment arms at each timepoint (linear mixed model).

Correspond to ~22% decrease in MI/Stroke risk;  
~50% decrease in T2DM risk  
(Tenorio, JID, 2014; Brown, Diabetes Care, 2010)



# CMV: Not always the bad guy

## $\gamma$ -Herpesvirus-Induced Protection Against Bacterial Infection Is Transient

Eric J. Yager, Frank M. Szaba, Larry W. Kummer, Kathleen G. Lanzer, Claire E. Burkum, Stephen T. Smiley, and Marcia A. Blackman

## Cytomegalovirus infection enhances the immune response to influenza

David Furman,<sup>1\*</sup> Vladimir Jovic,<sup>2†</sup> Shalini Sharma,<sup>3†</sup> Shai S. Shen-Orr,<sup>4</sup> Cesar J. L. Angel,<sup>1</sup> Suna Onengut-Gumuscu,<sup>5</sup> Brian A. Kidd,<sup>6‡</sup> Holden T. Maecker,<sup>6</sup> Patrick Concannon,<sup>5,7§</sup> Cornelia L. Dekker,<sup>8</sup> Paul G. Thomas,<sup>3</sup> Mark M. Davis<sup>1,6,9\*</sup>

## Herpesvirus latency confers symbiotic protection from bacterial infection

Erik S. Barton<sup>1†</sup>, Douglas W. White<sup>1,5</sup>, Jason S. Cathelyn<sup>2</sup>, Kelly A. Brett-McClellan<sup>1</sup>, Michael Engle<sup>3</sup>, Michael S. Diamond<sup>1,2,3</sup>, Virginia L. Miller<sup>2,4</sup> & Herbert W. Virgin IV<sup>1,2</sup>

## CMV Latent Infection Improves CD8+ T Response to SEB Due to Expansion of Polyfunctional CD57+ Cells in Young Individuals

Alejandra Pera<sup>1\*</sup>, Carmen Campos<sup>1</sup>, Alonso Corona<sup>1</sup>, Beatriz Sanchez-Correa<sup>2</sup>, Raquel Tarazona<sup>2</sup>, Anis Larbi<sup>3</sup>, Rafael Solana<sup>1</sup>

# Ongoing Clinical Trials: A5355



- **Phase II, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of an MVA-based CMV Vaccine (Triplex<sup>®</sup>), in Adults with HIV and CMV Who Are on Potent Combination ART with Conserved Immune Function**
- **Chair: Sara Gianella**



Dr. Don Diamond



1 **Poxvirus Vectored Cytomegalovirus Vaccine to Prevent Cytomegalovirus Viremia in Transplant Recipients: A Phase 2, Randomized Clinical Trial.**

Cite Share Aldoss I, La Rosa C, Baden LR, Longmate J, Ariza-Heredia EJ, Rida WN, Lingaraju CR, Zhou Q, Martinez J, Kaltcheva T, Dagens A, Hardwick N, Issa NC, Farol L, Nademanee A, Al Malki MM, Forman S, Nakamura R, **Diamond DJ**; TRIPLEX VACCINE Study Group.

Ann Intern Med. 2020 Mar 3;172(5):306-316. doi: 10.7326/M19-2511. Epub 2020 Feb 11.

PMID: 32040960

INTERVENTION: Intramuscular injections of **Triplex** or placebo were given on days 28 and 56 after HCT. **Triplex** is a recombinant attenuated poxvirus (modified vaccinia Ankara) expressing immunodominant CMV antigens. ...**Triplex** elicited and amplified CMV-specific ...

2 **MVA vaccine encoding CMV antigens safely induces durable expansion of CMV-specific T cells in healthy adults.**

Cite Share La Rosa C, Longmate J, Martinez J, Zhou Q, Kaltcheva TI, Tsai W, Drake J, Carroll M, Wussow F, Chiuppesi F, Hardwick N, Dadwal S, Aldoss I, Nakamura R, Zaia JA, **Diamond DJ**.

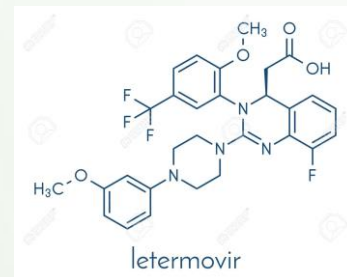
Blood. 2017 Jan 5;129(1):114-125. doi: 10.1182/blood-2016-07-729756. Epub 2016 Oct 19.

PMID: 27760761 **Free PMC article.** Clinical Trial.

Marked and durable CMV-specific T-cell responses were also detected in **Triplex**-vaccinated CMV-seronegatives, and in DryVax-vaccinated subjects. ...Combined safety and immunogenicity results of MVA in allogeneic hematopoietic stem cell transplant (HCT) recipients and **Tri** ...

# Ongoing Clinical Trials: A5383

- **Randomized, Placebo-Controlled Trial to Evaluate the Anti-inflammatory Efficacy of Letermovir (Prevymis) in Adults with HIV and Asymptomatic CMV Who Are on Suppressive ART and Its Effect on Chronic Inflammation, HIV Persistence, and Other Clinical Outcomes**
- **Co-Chairs: Sara Gianella and Peter Hunt**
- **Additional Substudies: Cardiovascular, metabolic, Neuro, Gut**



# Take Home Messages

- CMV is associated with increased inflammation/immune activation
- CMV might be an important cause of morbidity and mortality
- CMV might contribute to HIV persistence
- Clinical trials of anti-CMV interventions are ongoing