CMV, Inflammation, and Aging in Treated HIV

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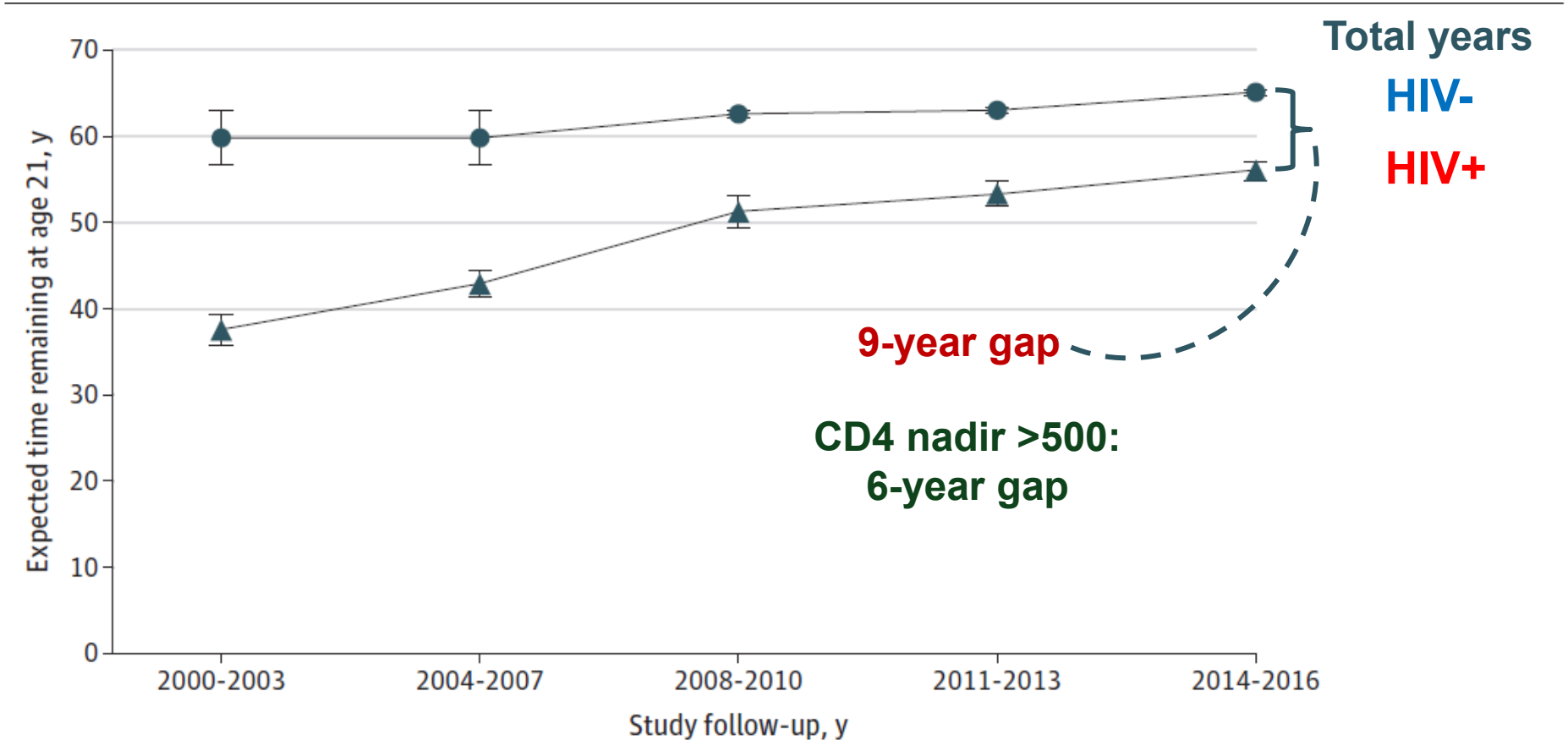
Disclosures

- Drug donation for trial: Merck
- Research grant: Gilead
- Consulting: Merck and Viiv
- Honoraria: Gilead and Viiv

Life Expectancy Gap Is Narrowing for People with HIV

Particularly Those Who Start ART at High CD4 Counts



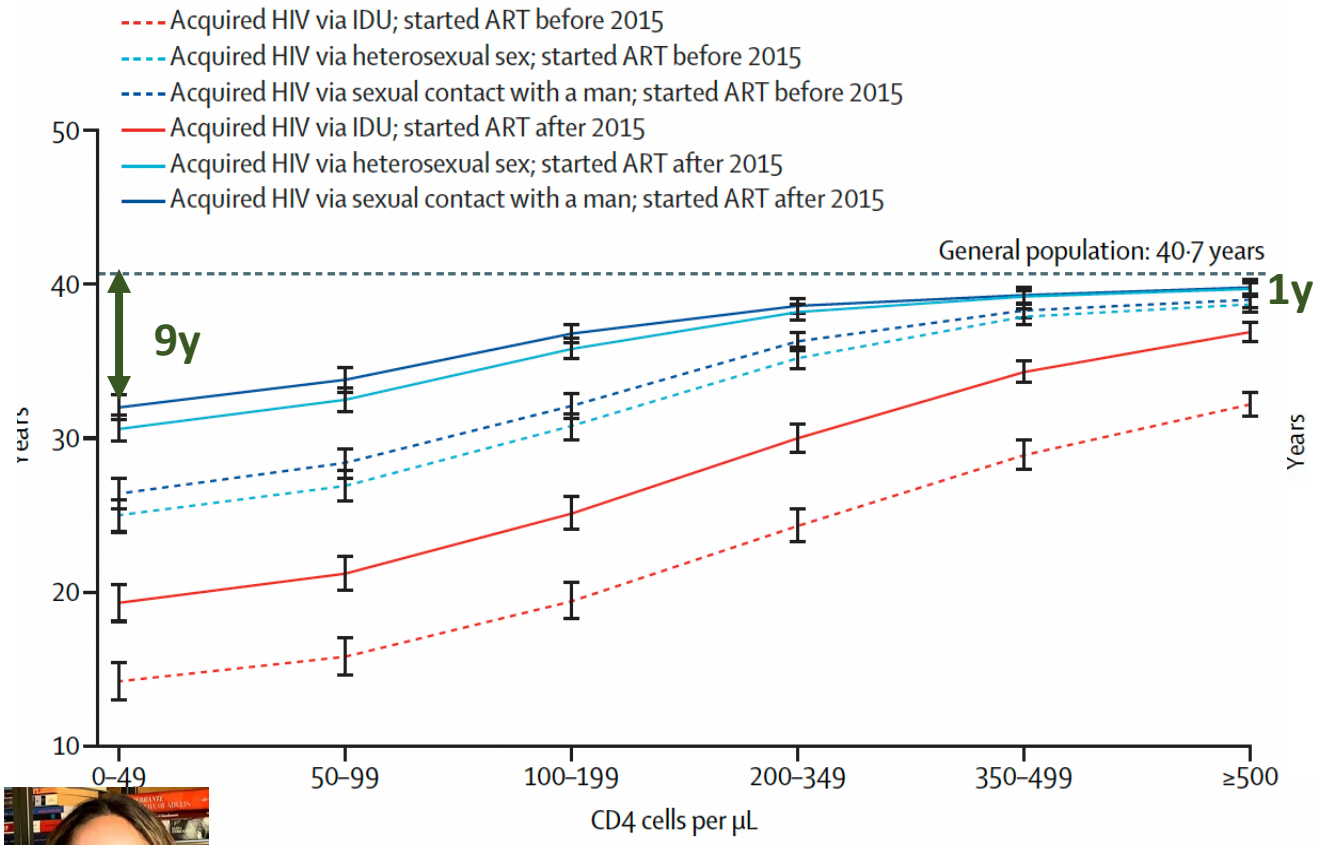
Marcus et al, JAMA Network Open 2020

**Samji, PLoS One, 2013*

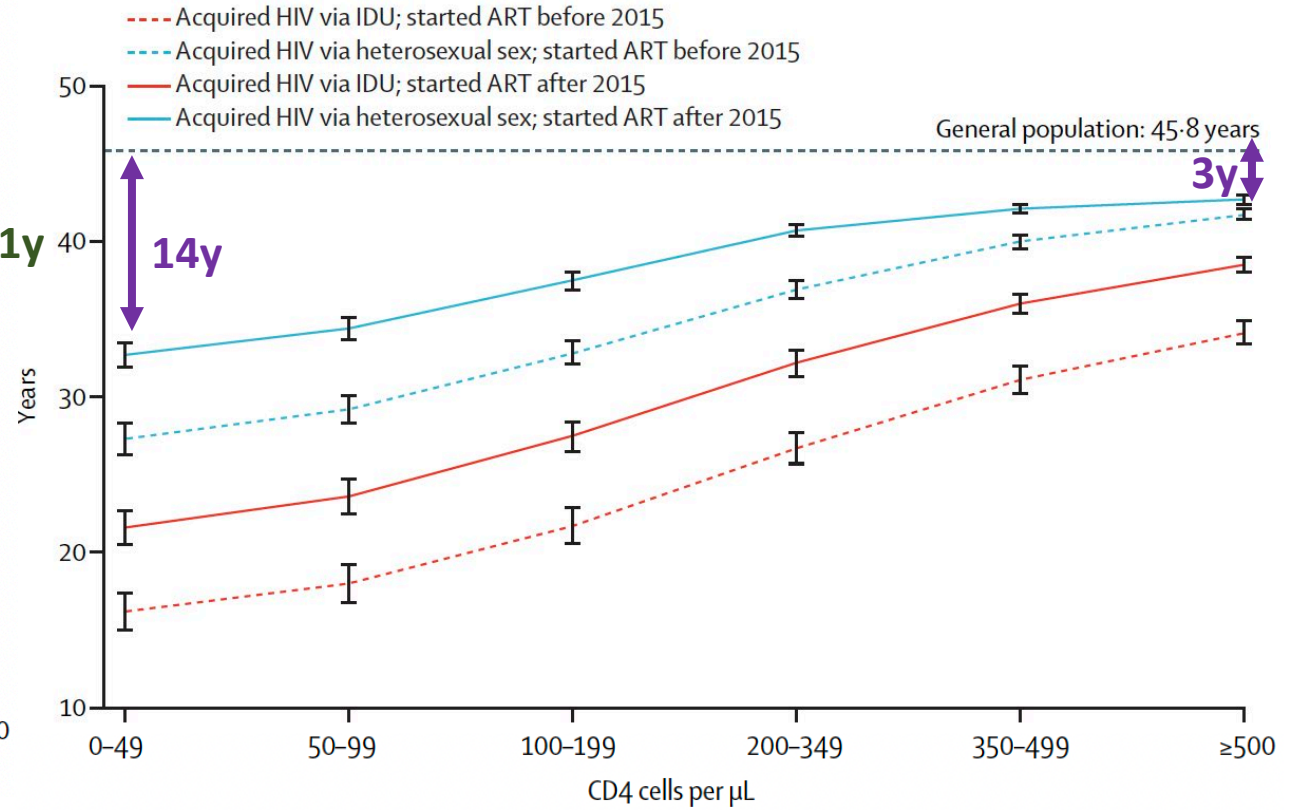
Life Expectancy Gap Greater for Women than Men in People with HIV Suppressed on ART for >1y

ART-CC & UK CHCS (>200,000 PWH)

Men



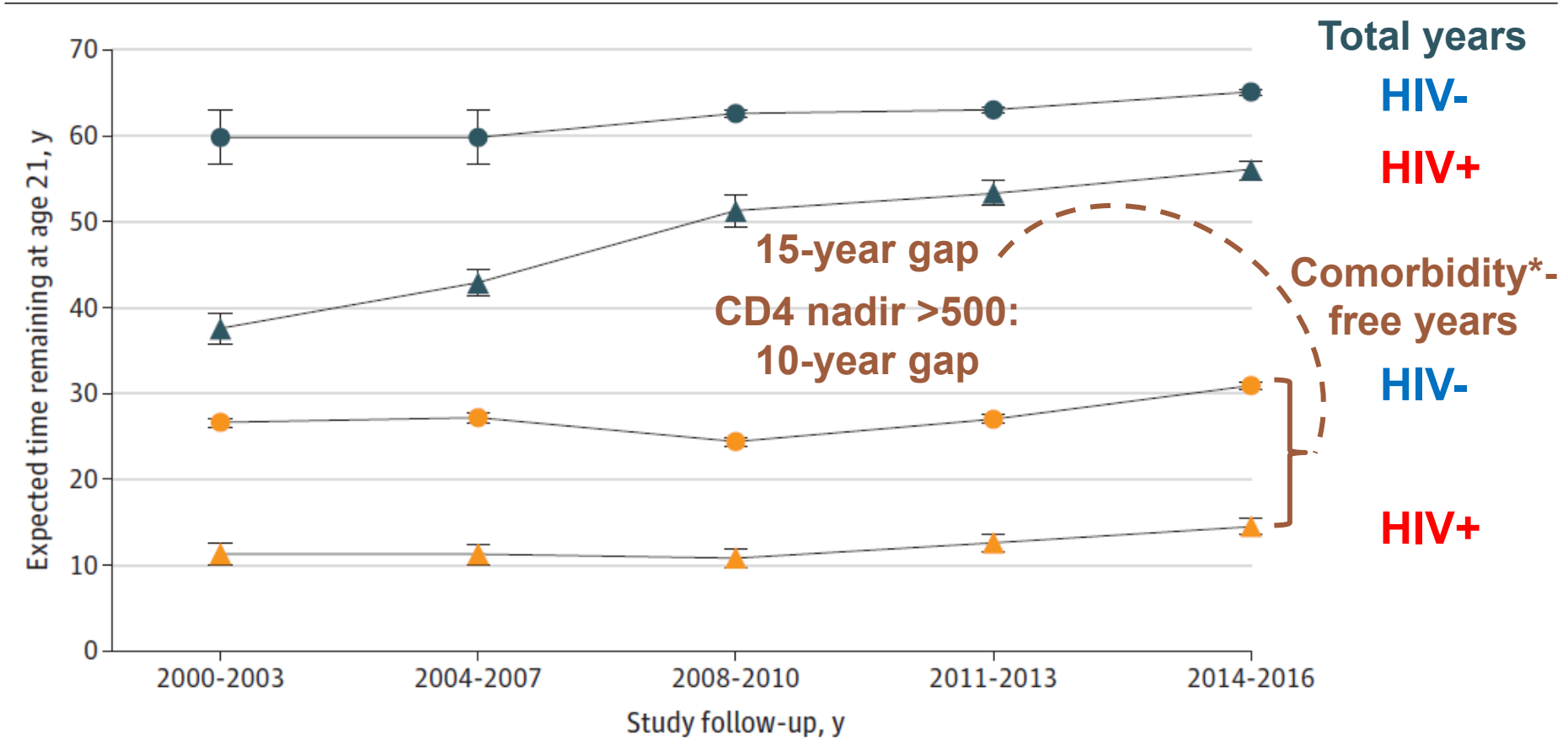
Women



See Abelman et al, *J Clin Invest*, in press

Trickey, Lancet HIV, 2023

People with HIV Are Accumulating Comorbidities 10-15 Years Earlier than the General Population



*Chronic liver, kidney, or lung disease; diabetes; cancer; CVD

Marcus et al, JAMA Network Open 2020

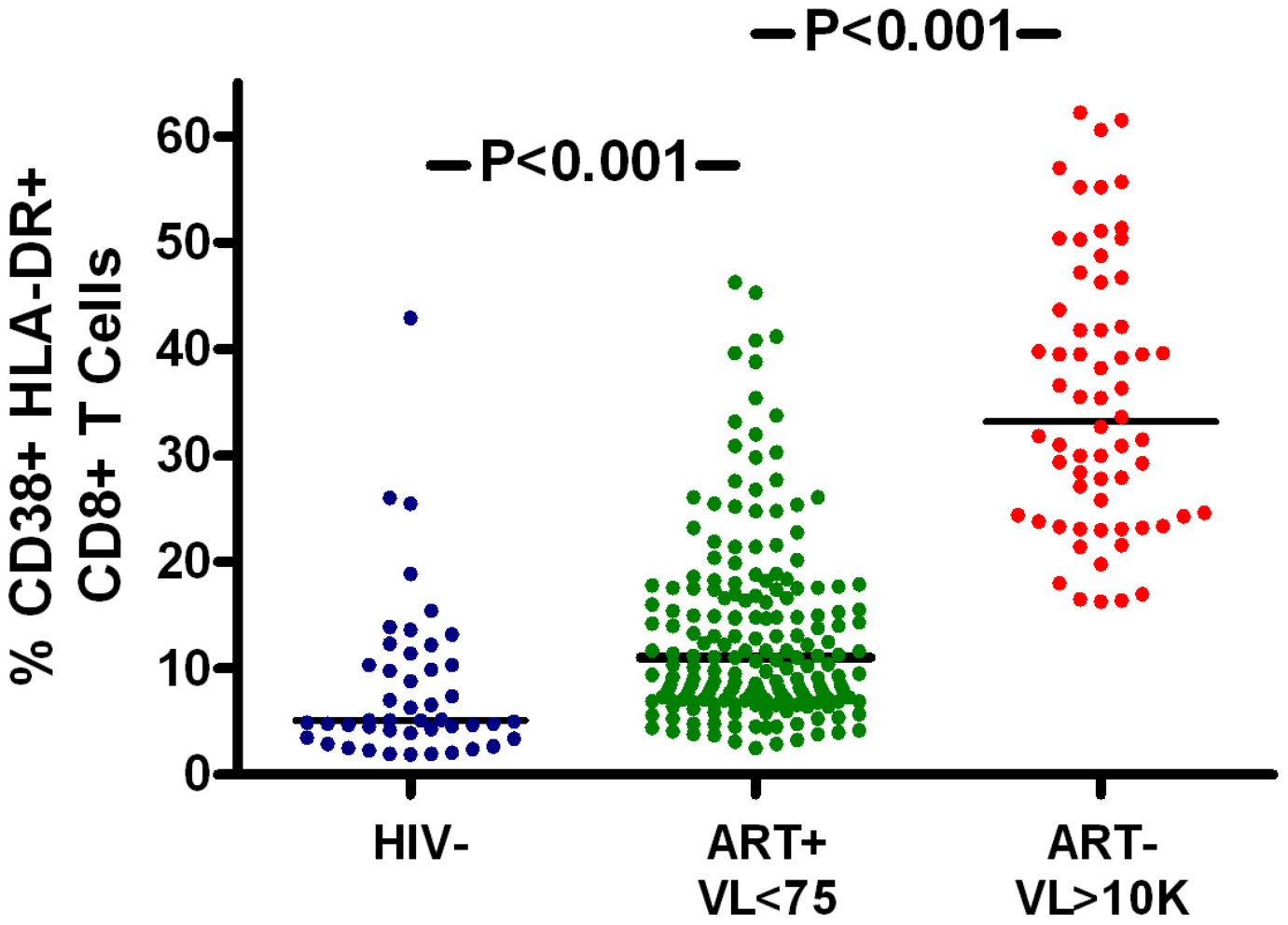
Many Aging-associated Comorbidities Are Increased in People with Treated HIV

- Cardiovascular disease [1-3]
- Cancer (infection-related, lung) [4]
- Bone fractures/osteoporosis [5,6]
- COPD [12]
- Liver disease [7]
- Type 2 Diabetes [8]
- Cognitive decline [9]
- Non-AIDS infections [10]
- (Early) Macular Degeneration[13]
- Frailty [11]

1. Freiberg M, et al. JAMA Int Med. 2013;173(8):614-22. 2; Tseng Z, et al. JACC. 2012;59(21):1891-6. 3. Grinspoon SK, et al. Circulation. 2008;118:198-210. 4. Silverberg, M, et al. AIDS, 2009;23(17):2337-45. 5. Triant V, et al. J Clin Endocrinol Metab. 2008;93:3499-3504. 6. Arnsten JH, et al. AIDS. 2007;21:617-623. 7. Odden MC, et al. Arch Intern Med. 2007;167:2213-2219. 8. Hernandez-Romieu, BMC Open Diab Res Care, 2016. 9. McCutchan JA, et al. AIDS. 2007;21:1109-1117. 10. Sogaard, CID, 2008;47(10):1345-53. 11. Desquilbet L, et al. J Gerontol A Biol Sci Med Sci. 2007;62:1279-1286; [12] Attia, Chest,2014; [13] Jabs, Am J Opthal, 2015

Time Magazine, February 23, 2004

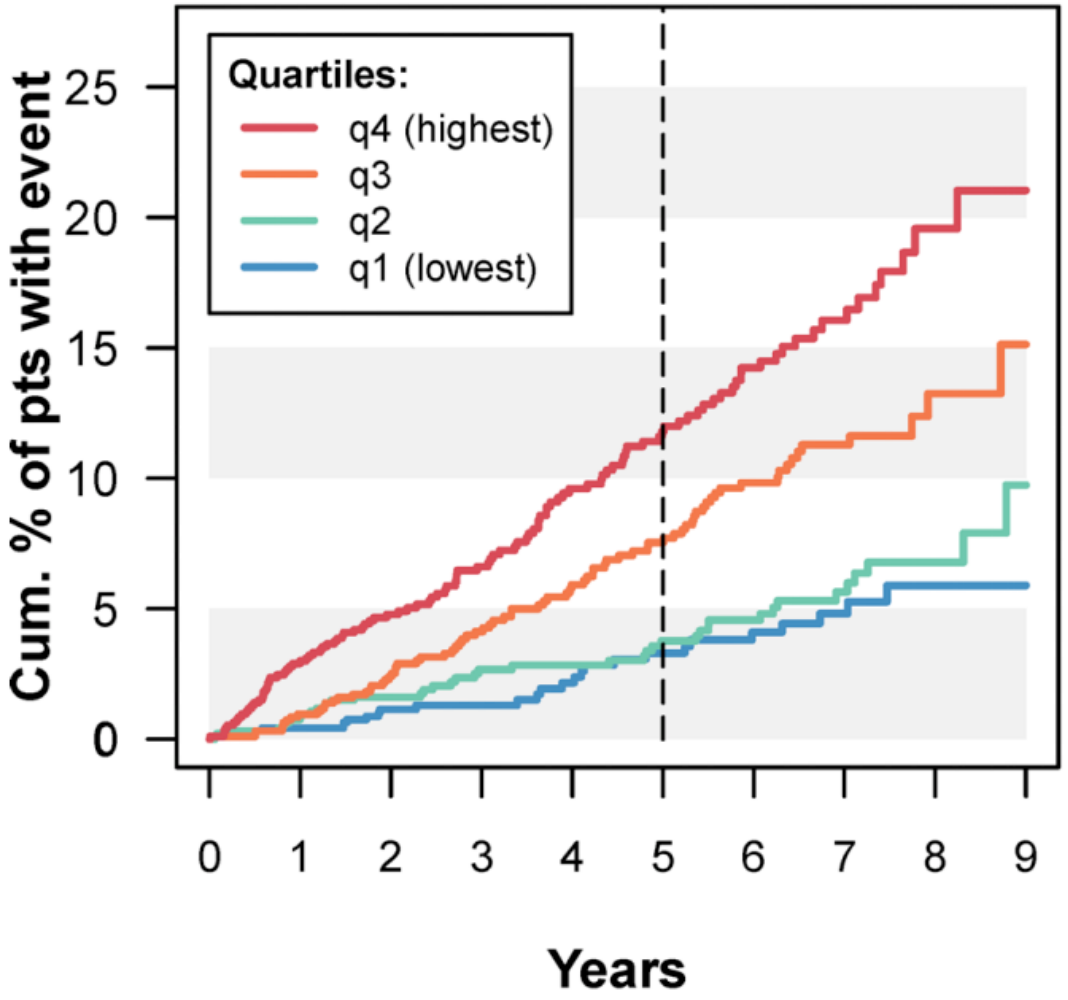
T Cell Activation Remains Abnormally High During ART-mediated Viral Suppression



Hunt, et al, JID, 2003; PLoS One, 2011

Inflammation Strongly and Durably Predicts Morbidity and Mortality in Treated HIV Infection
(IL-6 Levels)

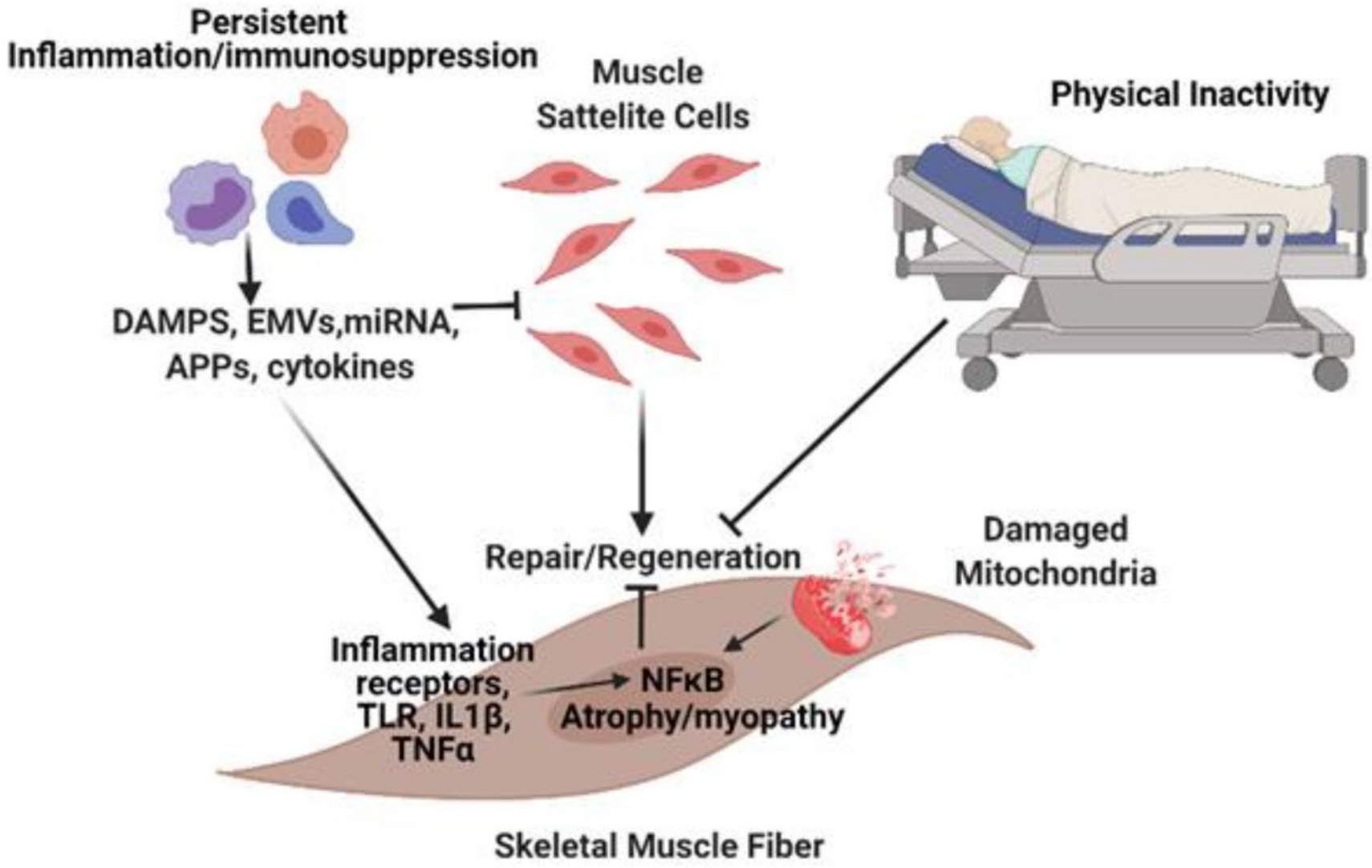
Clinical events:
Cardiovascular event
Cancer
Cirrhosis
Renal failure
Death



Our Field's Goal:
Safely **move people from top 2 quartiles into the bottom 2 quartiles…**

Grund et al, PLoS One, 2016

Inflammation May Cause Muscle Wasting and Impaired Regeneration

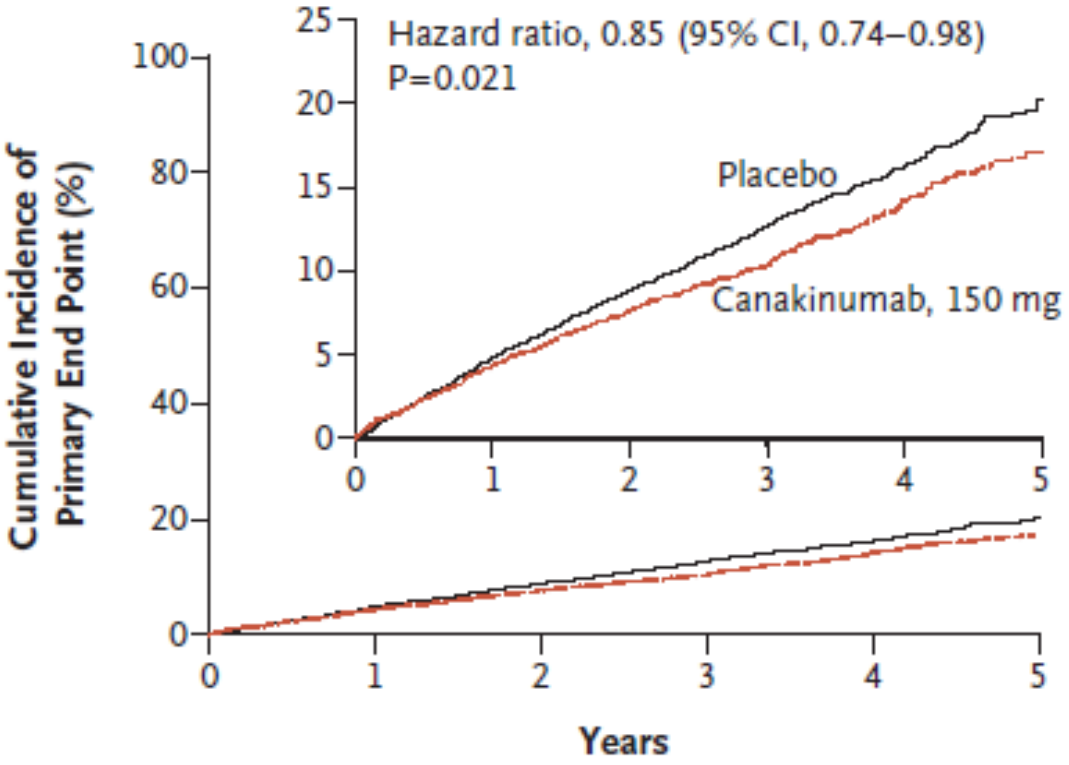


Mankowski, JCM, 2021

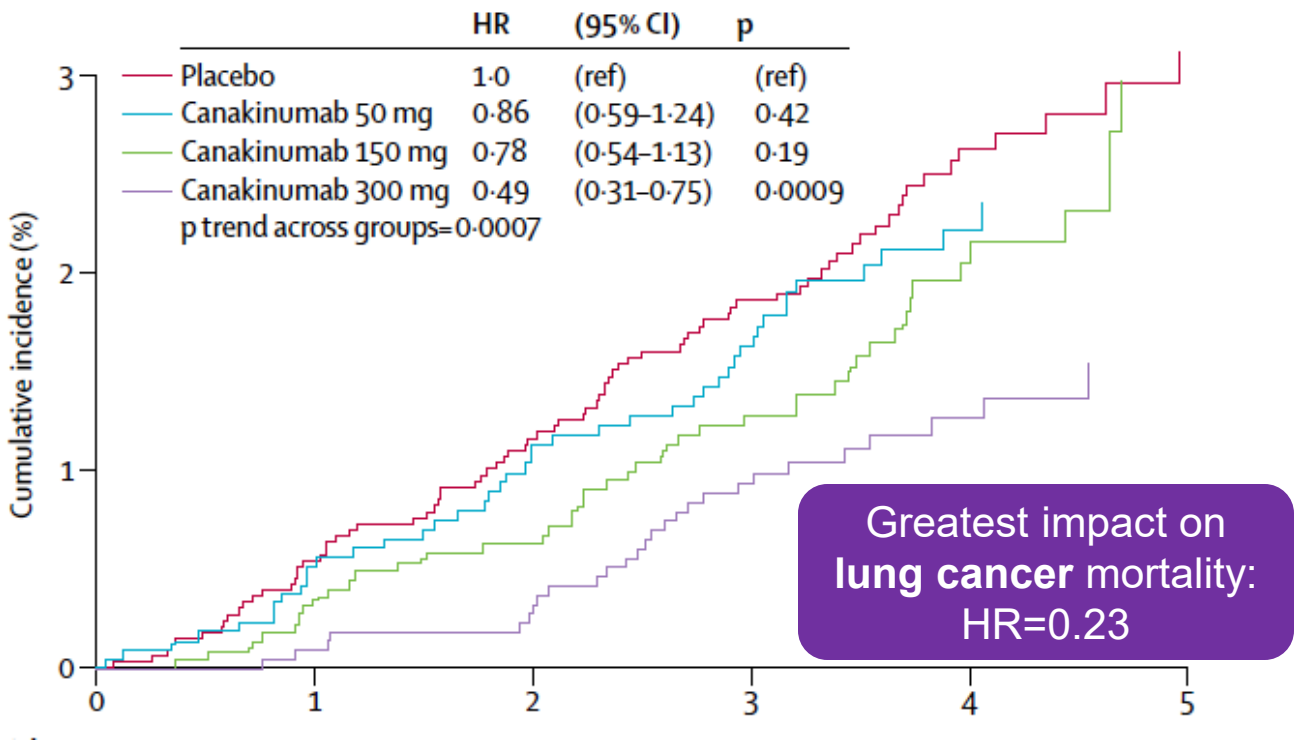
Treating Inflammation (IL-1β pathway) Decreases Heart Disease and Cancer

in People with Cardiovascular Disease (and without HIV)

IL-1β Blockade Decreases CAD Events



IL-1β Blockade Decreases Cancer Mortality



Greatest impact on **lung cancer** mortality: HR=0.23

Proof that inflammation causes disease risk (cancer>CVD)

↑ Death from Sepsis – <u>not</u> FDA approved

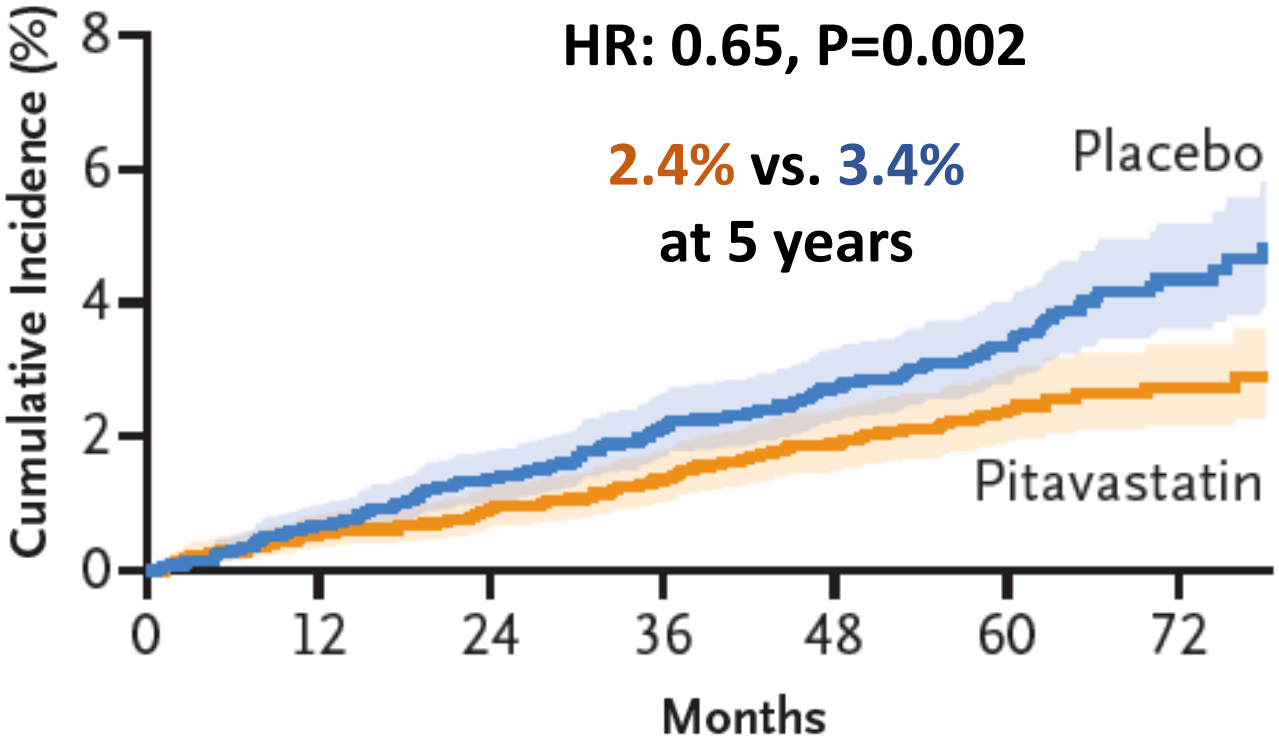
Ridker Circ Res, 2016
Ridker, NEJM, 2017
Ridker, Lancet, 2017

Reducing Immune Activation in Treated HIV v1.0:

Test commonly used / safe medications with anti-inflammatory properties

Statins Now Proven to Reduce Cardiovascular Disease in Treated HIV, but…

Cardiovascular Event Rate



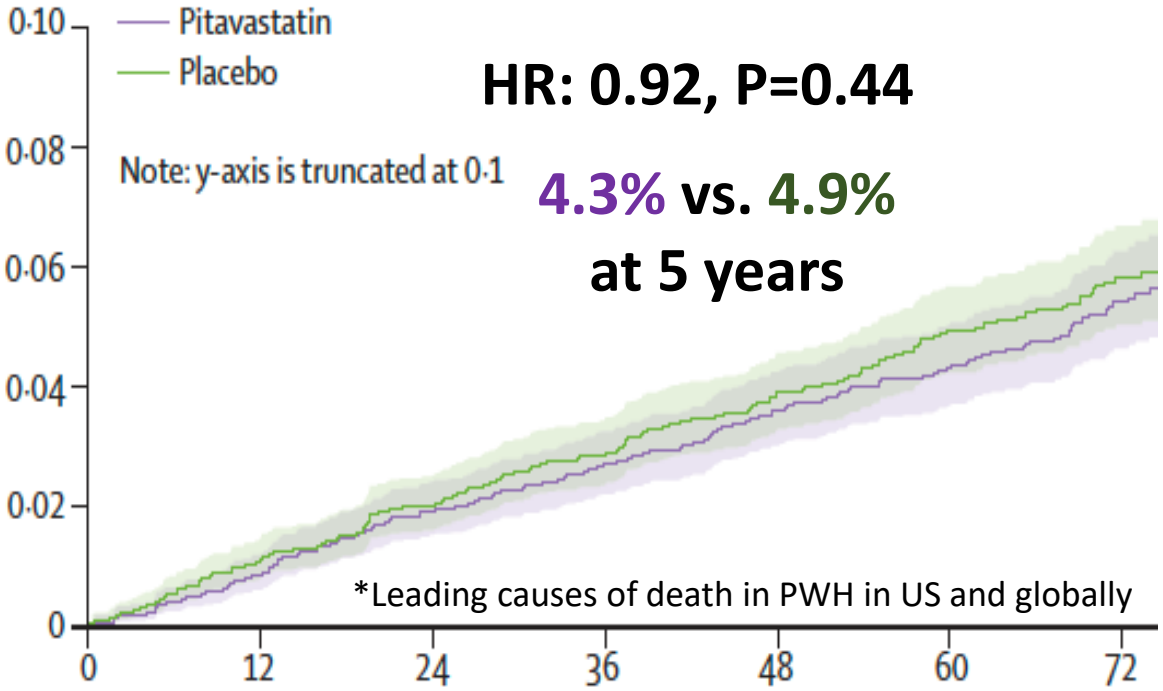
HR: 0.65, P=0.002

2.4% vs. 3.4%
at 5 years

Grinspoon, REPRIEVE Trial, NEJM, 2023

Major Non-CVD Events

(*Cancer 3%, *TB 1% in both arms)



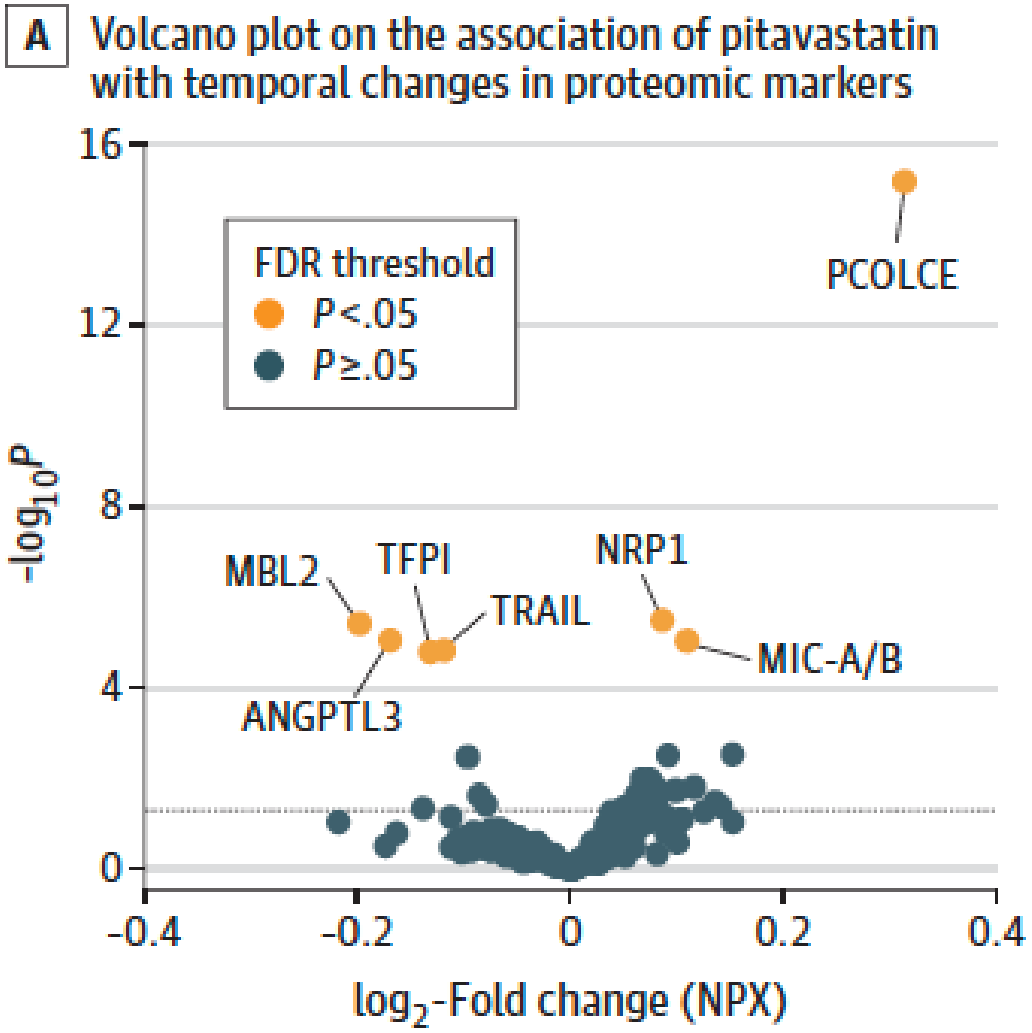
HR: 0.92, P=0.44

4.3% vs. 4.9%
at 5 years

Also no effect on CHF, Frailty or Cognitive Function
(Erlandson, AIDS and JACC, 2025)

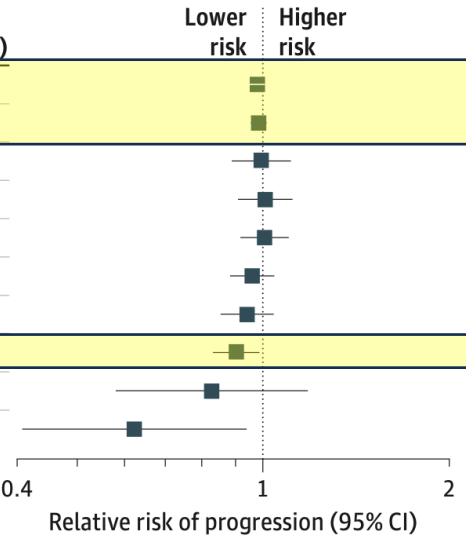
Pitavastatin not so pleiotropic in people with HIV?
Diggs, Lancet HIV, 2025; Reiss, Hunt, Lancet HIV, 2025

Statins Improved Plaque Stabilization Markers and LDL, But Not Key Inflammation Markers



- **Only *non-significant trends* toward reduced IL-6 and CRP in pitavastatin arm despite n=699.**
- **Reductions in non-calcified coronary plaque more closely linked to LDL than CRP reduction:**

Measure	No.	Estimated difference (95% CI)	P value
Change in hsCRP at month 4	499	0.98 (0.95-1.01)	.16
Change in hsCRP at month 24	524	0.99 (0.96-1.01)	.32
Change in LpPLA-2 at month 4	505	0.99 (0.89-1.11)	.92
Change in LpPLA-2 at month 24	515	1.01 (0.91-1.12)	.86
Change in oxidized LDL at month 4	505	1.01 (0.92-1.10)	.88
Change in oxidized LDL at month 24	515	0.96 (0.89-1.04)	.35
Change in LDL cholesterol at month 4	501	0.94 (0.85-1.04)	.25
Change in LDL cholesterol at month 24	519	0.91 (0.83-0.99)	.03
LDL cholesterol <70 at month 4	501	0.83 (0.58-1.18)	.30
LDL cholesterol <70 at month 24	519	0.62 (0.41-0.94)	.03



Kolossvary, REPRIEVE Trial, JAMA Cardiology, 2025

Lu, REPRIEVE Trial, JAMA Cardiology, 2024

Reducing Immune Activation in Treated HIV v2.0:

Directly block the inflammatory pathways that are abnormal in HIV (and predict disease)

The “Whack-a-Mole” Problem for Immune-based Interventions in HIV

- Might interfere with immune defenses, increasing infection risk
- Might not block all important inflammatory pathways
- Blocking one pathway might make others worse

Examples: Hydroxycholorquine[1], MTX[2-3], IL-1b inhibition[4], IL-6R inhibition[5], mTOR inhibition[6], Jak 1/2 inhibition[7]

[1]Paton, JAMA, 2012; [2]Hsue, CID, 2019; [3]Freeman, Frontiers Immunol, 2022; [4]Hsue, JACC, 2018; [5]Funderburg, CID, 2023; [6]Henrich, CROI 2019, #131; Marconi, CID, 2022

Safely reducing inflammation in treated HIV v3.0

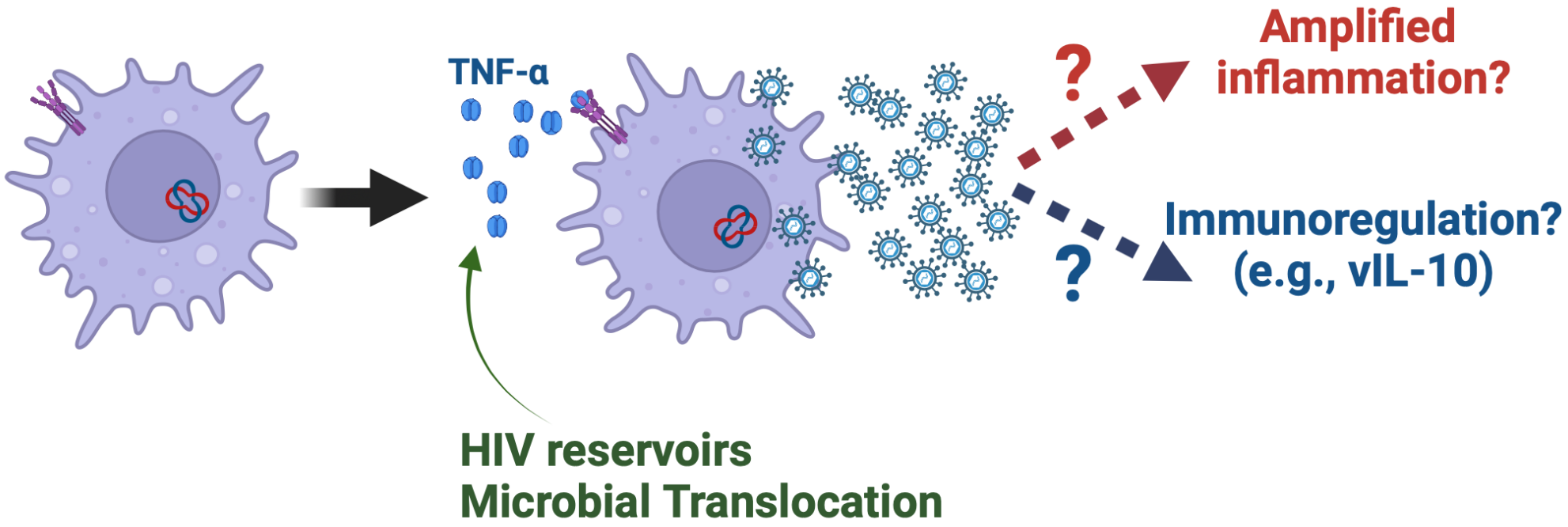
Address the root drivers (HIV, Microbial Translocation, CMV)

Inflammation Induces Lytic CMV Replication,
which may amplify and/or regulate inflammation in tissues

Latently CMV-infected Macrophage

Lytic CMV replication induced by TNF-α

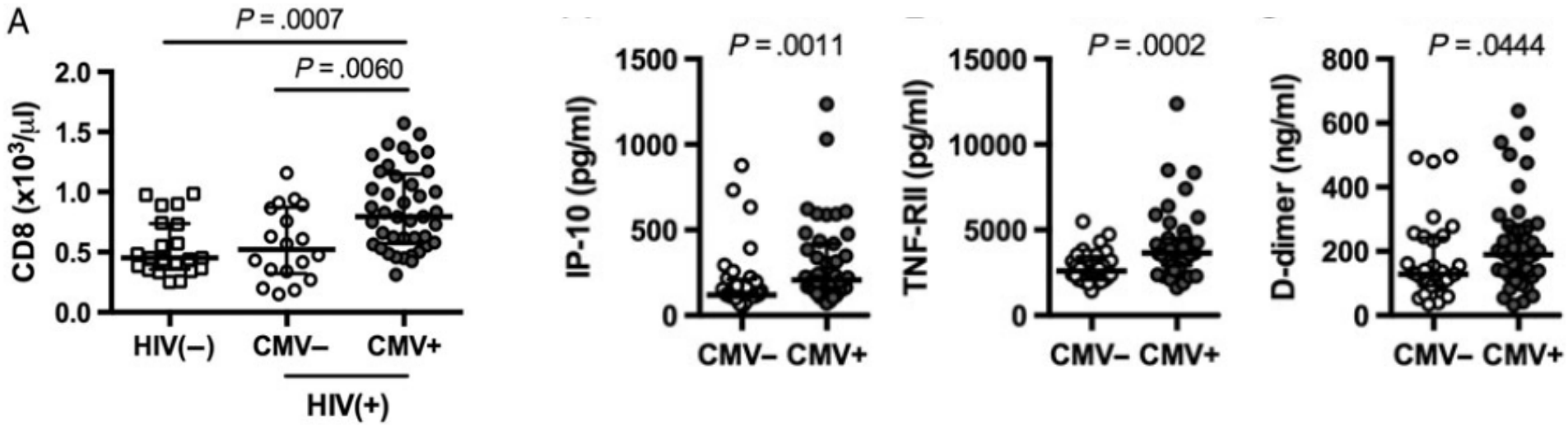
CMV *Reshapes* the Local Immune Environment



Forte et al, mBio 2018

CMV Associated with CD8 Expansion and Inflammation in HIV Infection

CD8+ T Cell Counts | **IP-10** | **sTNF-R2** | **D-Dimer**

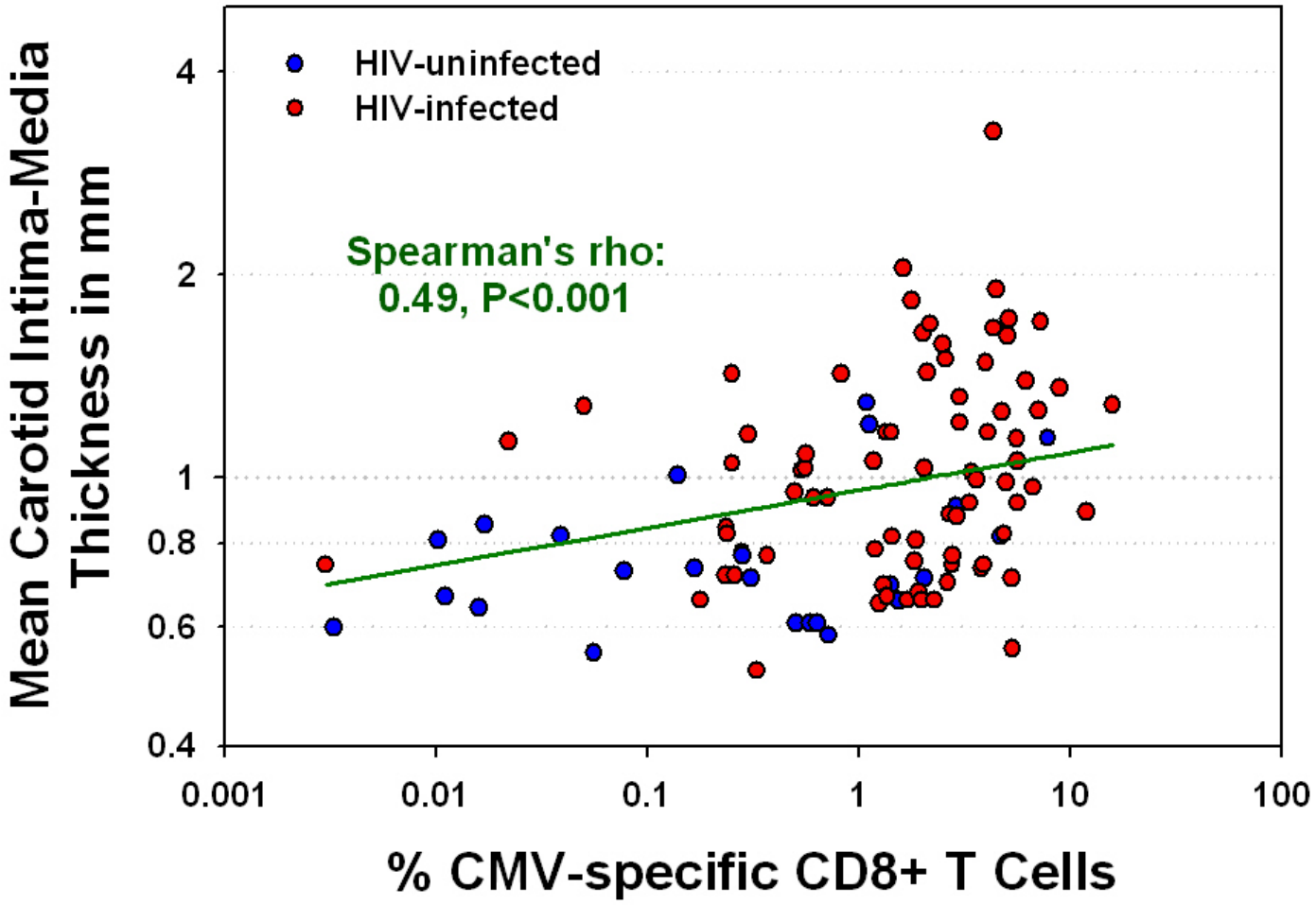


- CMV causes ↑CX3CR1 expression on T cells/monos to vascular tissue
- CX3CR1+ CD8s also express PAR-1, which can activate coagulation cascade
- CMV viremia (or prior end organ dz) predicts venous thromboembolism in HIV

Mike Freeman, PhD
CWRU

Freeman, CID, 2016 (see also: Sacre, AIDS, 2011;
Mudd, JID, 2016; Musselwhite, AIDS 2011; Chen J Immunol, 2020)

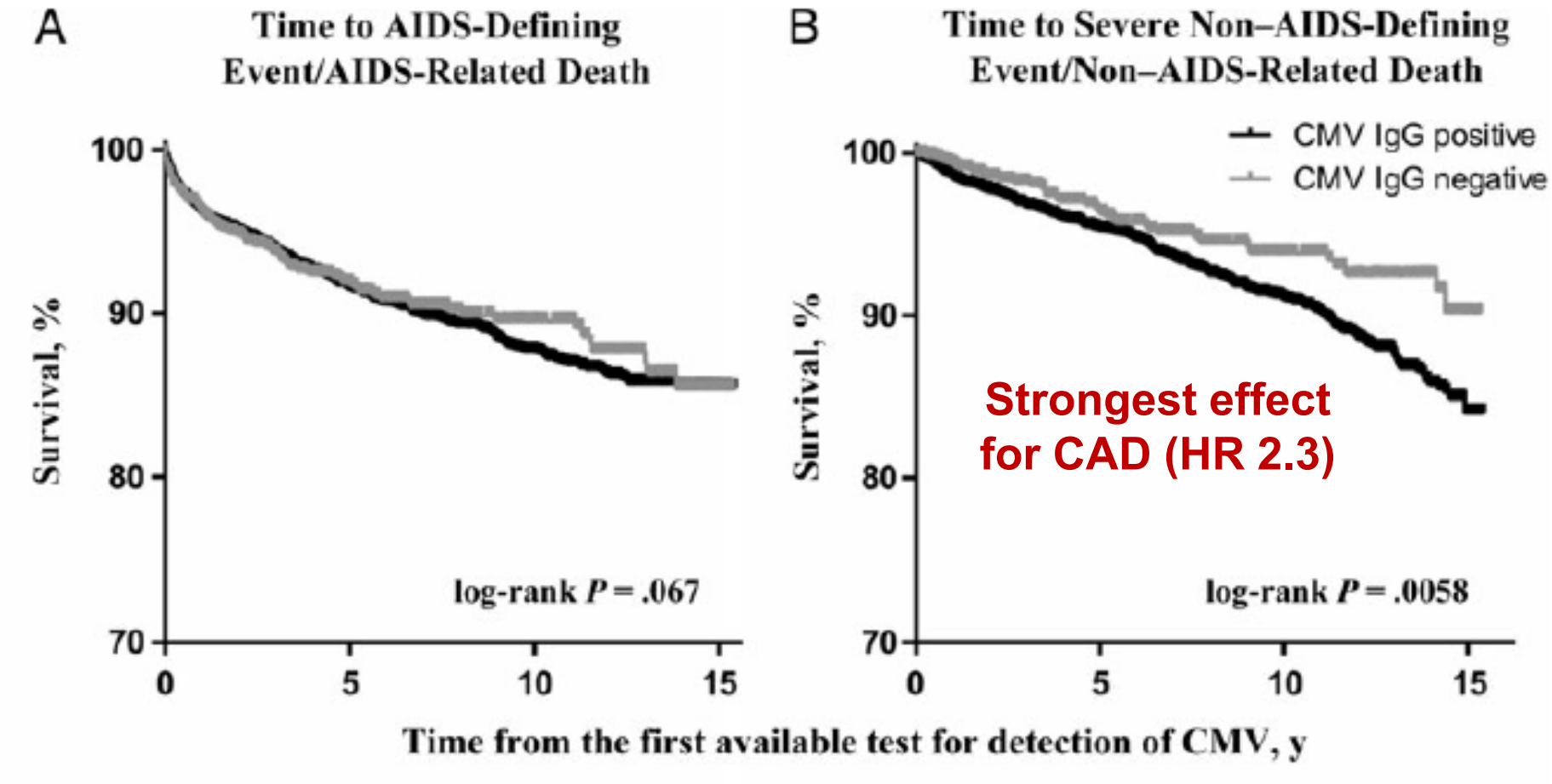
Higher CMV-specific CD8 IFN-γ Production Associated with More Atherosclerosis



Priscilla Hsue, now at UCLA

Hsue et al, AIDS, 2006 (see also: Parrinello, JID, 2012; Lo, AIDS, 2010)

CMV IgG+ Predicts Non-AIDS Events in Treated HIV: ICONA Cohort

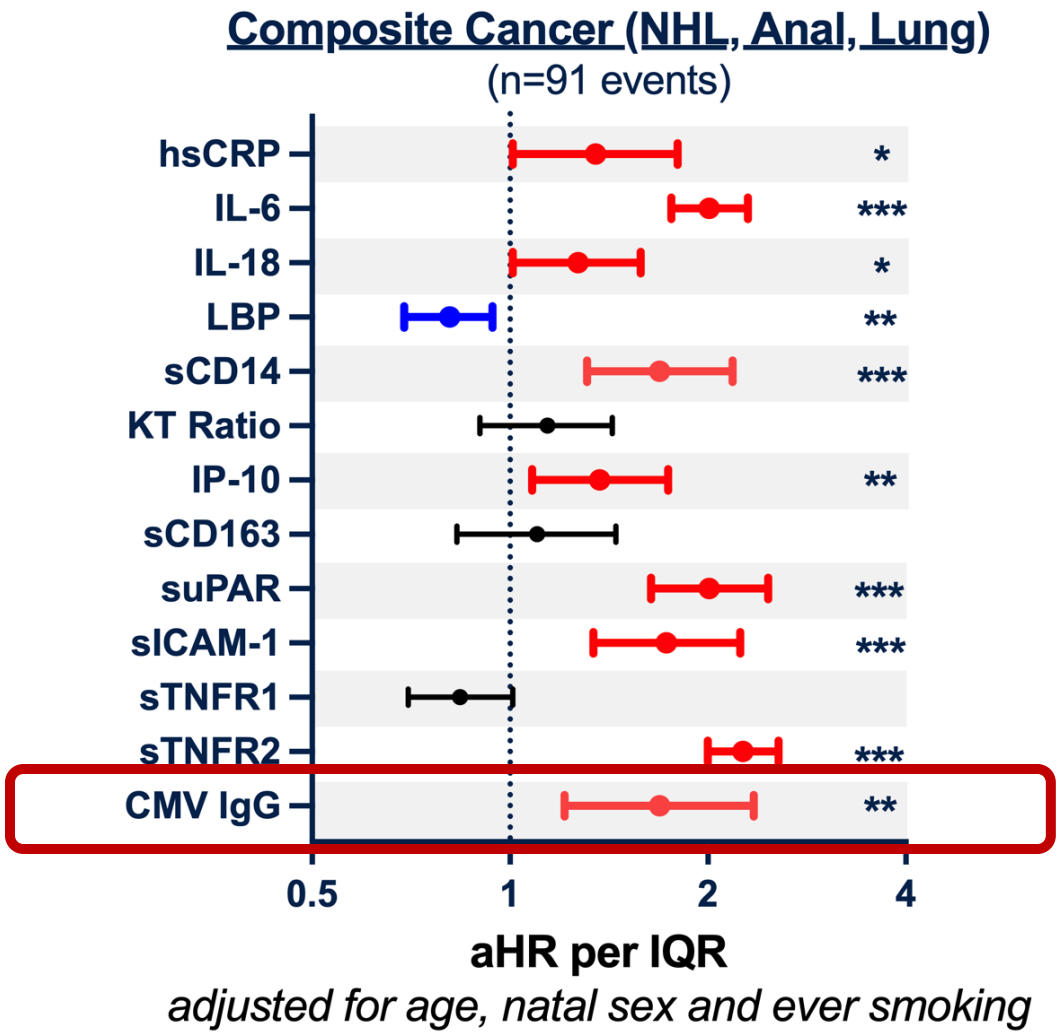


Lichtner et al, JID, 2015

CMV-specific IgG Titers Also Associated with Cancer Risk in Treated HIV

CNICS Case-Cohort Study (n=977)

Sam Schnittman



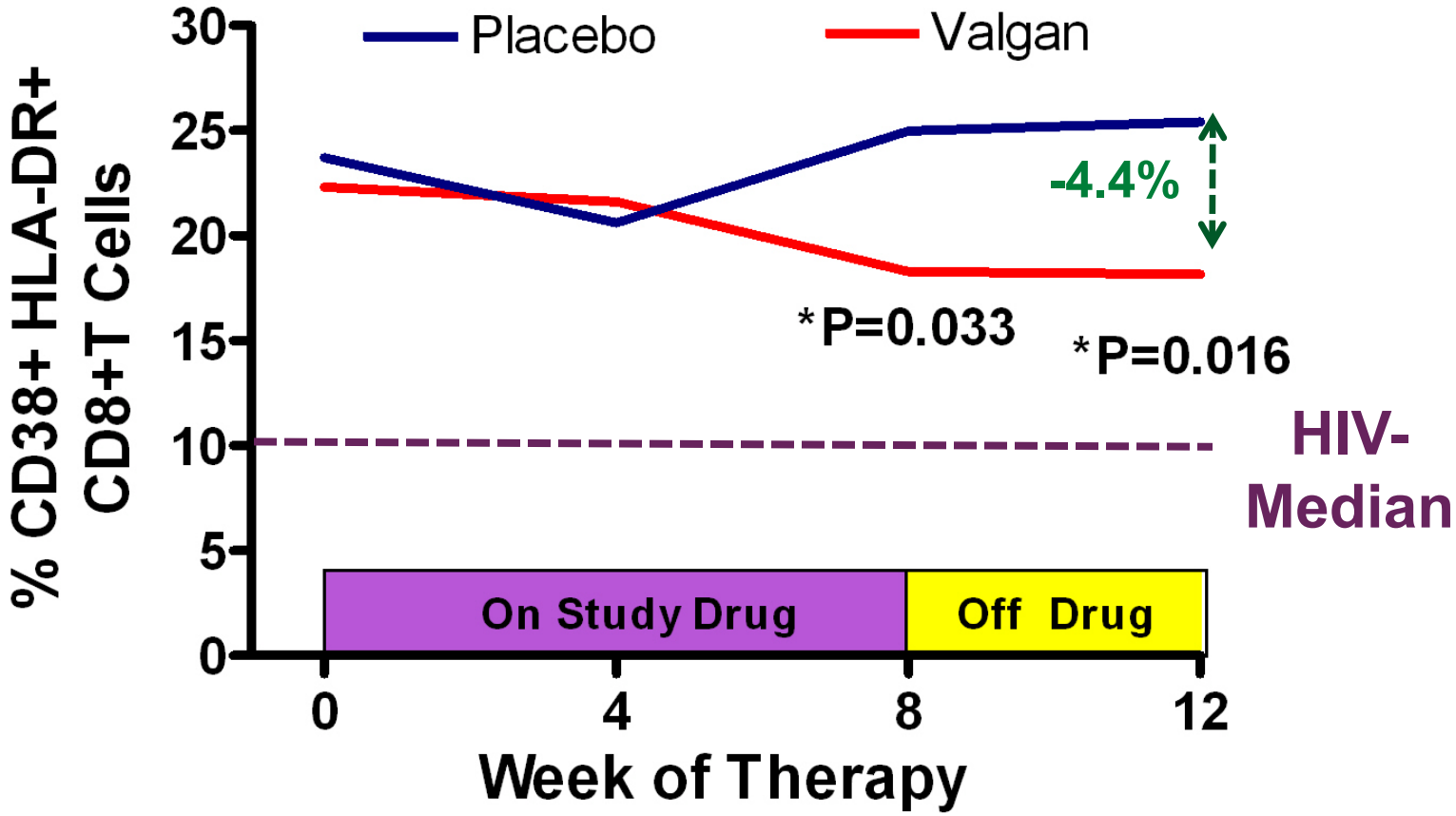
Gaby Beck-Engeser

Gabby Ambayec

Presented in part: Schnittman et al, CROI 2022, Abstract #552 (see also: Hodowanec, Path Imm, 2019)

Blocking Asymptomatic CMV Replication with Valganciclovir ↓ Immune Activation

in People with HIV and CD4<350 despite ART



*P for difference in the change from week 0 between valgan- and placebo-treated groups.

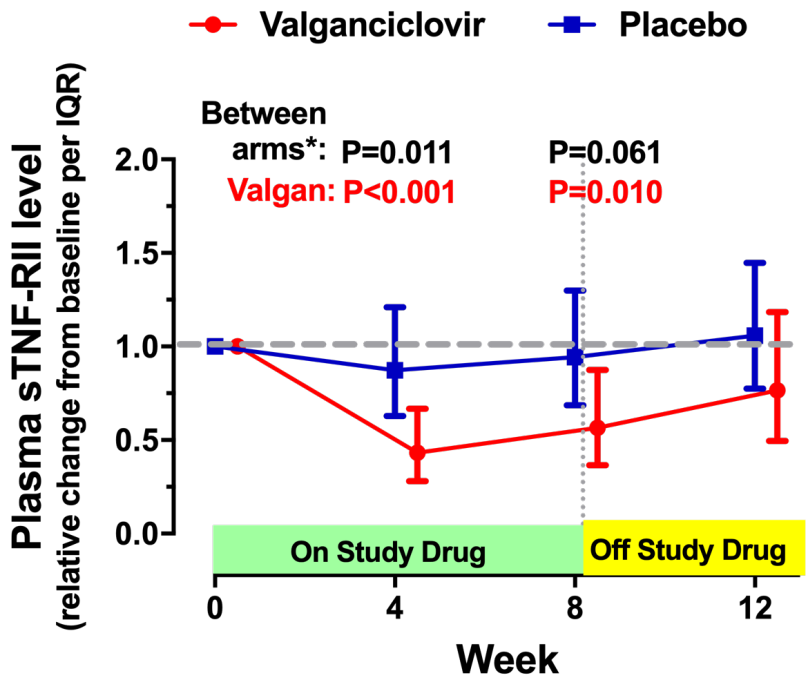
Hunt et al, JID, 2011

Valganciclovir toxicities (cytopenias) made a longer term trial unattractive.

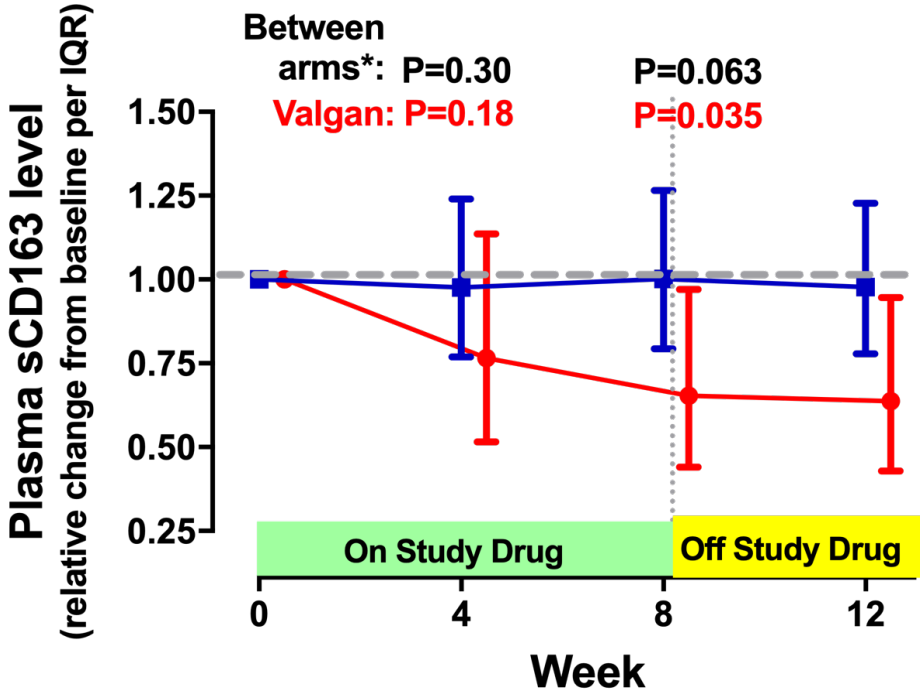
Becky Hoh
Steve Deeks
SCOPE Cohort
HIV-ID-Global Medicine

Valganciclovir Broadly Decreased Immune Activation in Treated HIV

sTNF-R2



sCD163



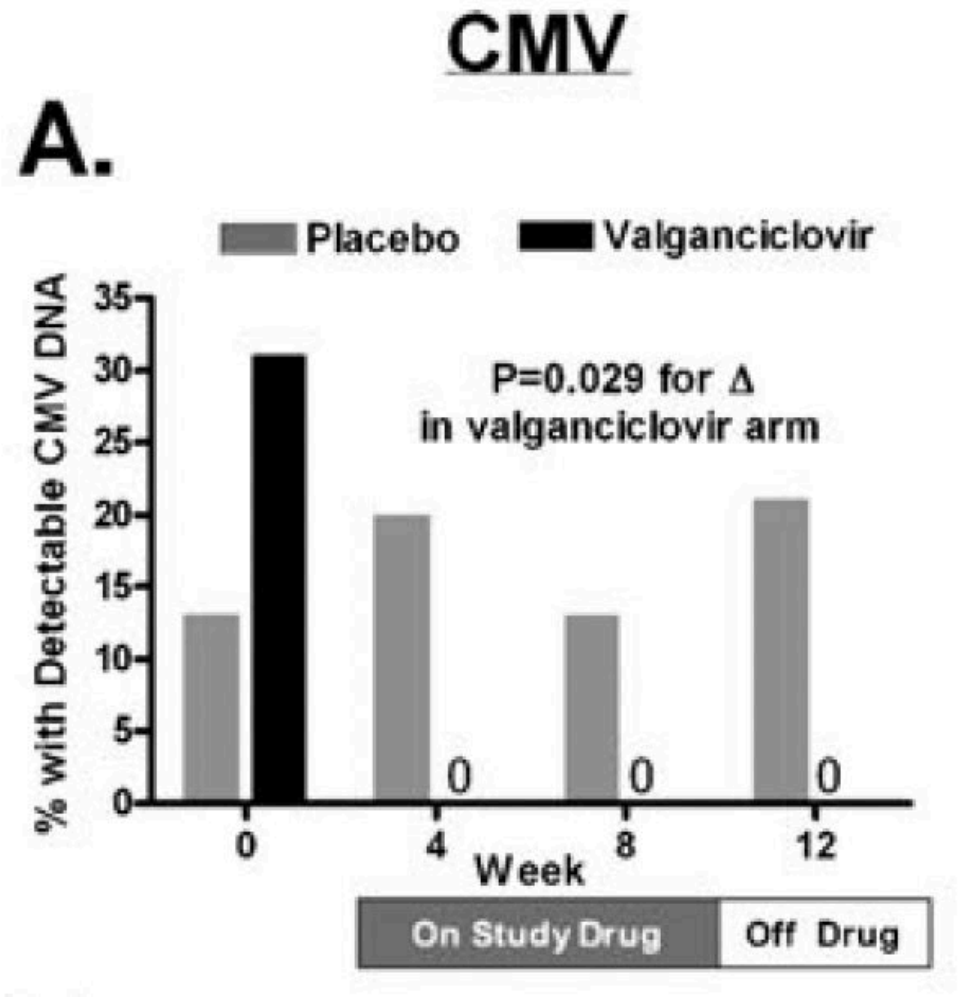
Unclear if effect mediated by CMV suppression or other herpesviruses (i.e., EBV, HHV-6, KSHV, etc).

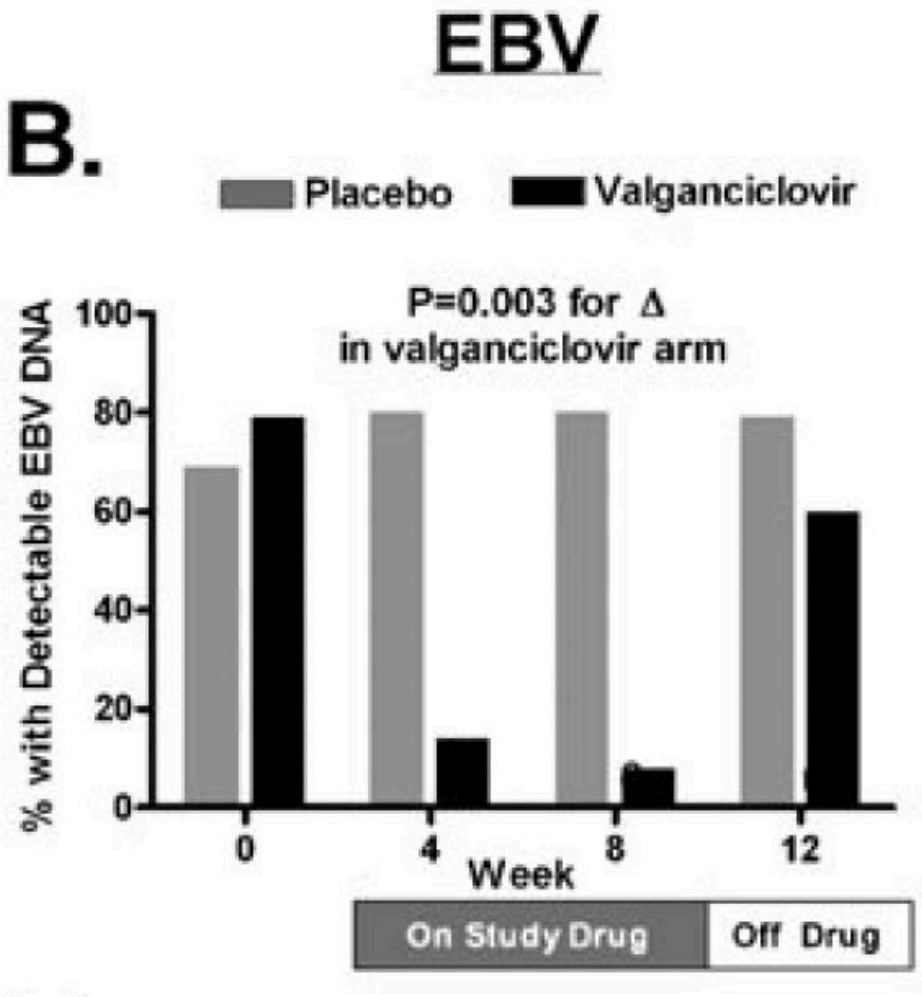
Gaby Beck-Engeser

Sabrina Ann Sevilla

Beck-Engeser, CROI 2019, #643; Sevilla, CROI 2020, #236; Hunt, JID, 2011

Valganciclovir Suppressed CMV - *and EBV* - Shedding

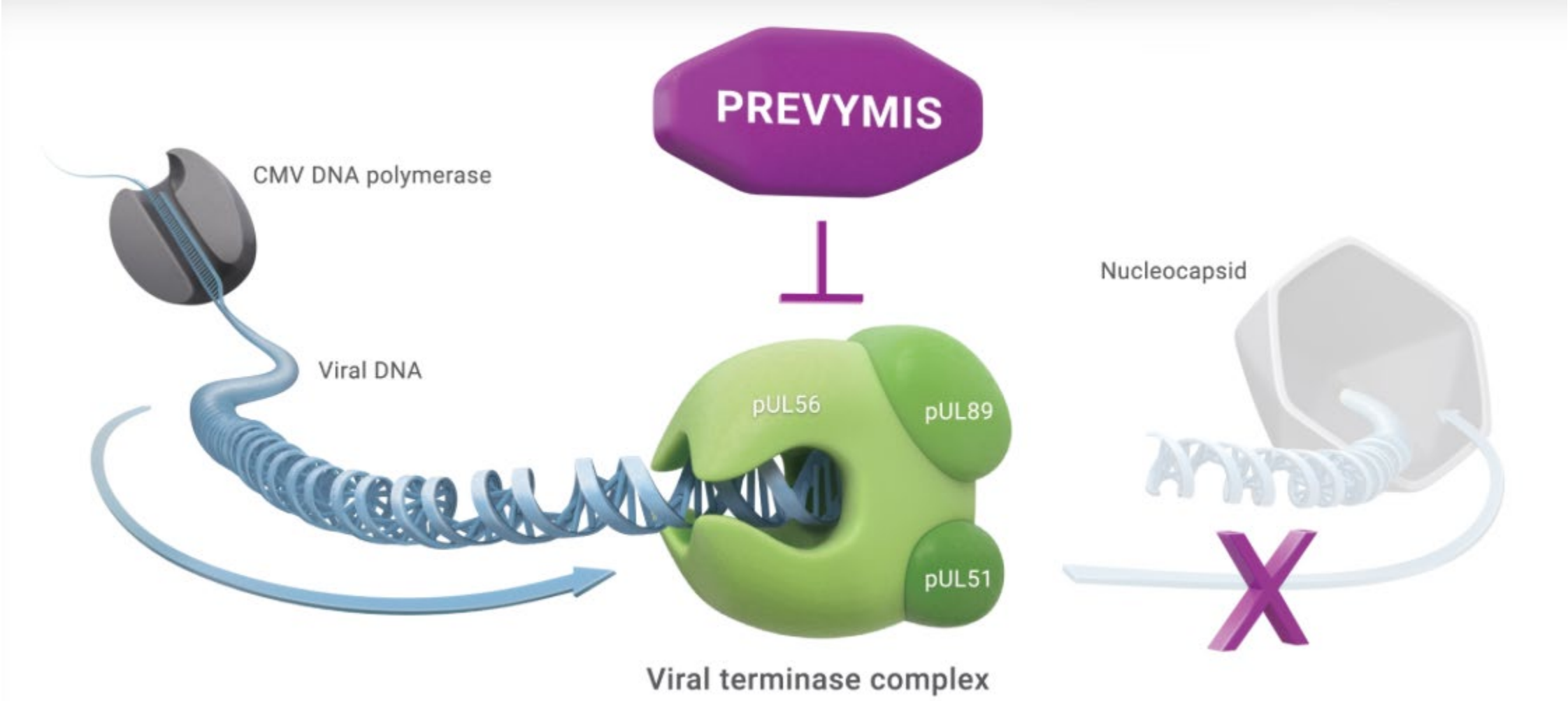




Hunt et al, JID, 2011

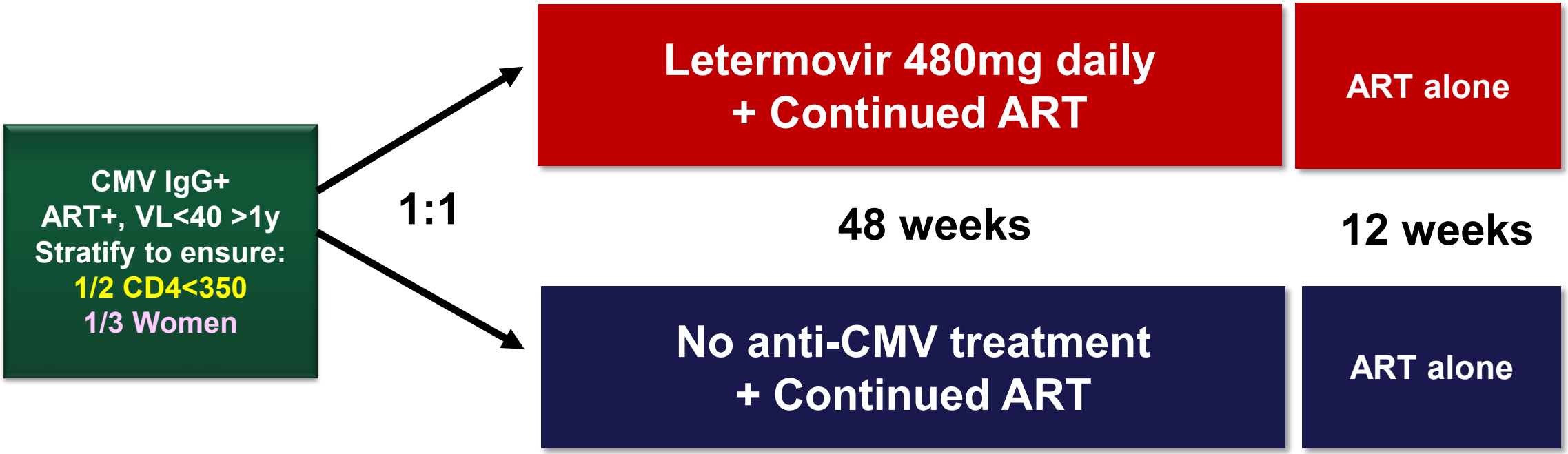
Letermovir (Prevymis) Mechanism of Action

CMV Terminase Complex Inhibitor



No direct activity against <u>ANY</u> other herpesviruses

A5383: Letermovir (CMV terminase inhibitor) to Reduce Immune Activation in Treated HIV (n=180)



A futility analysis was required after the first 40 participants reached week 8 (sTNFR2 primary endpoint)

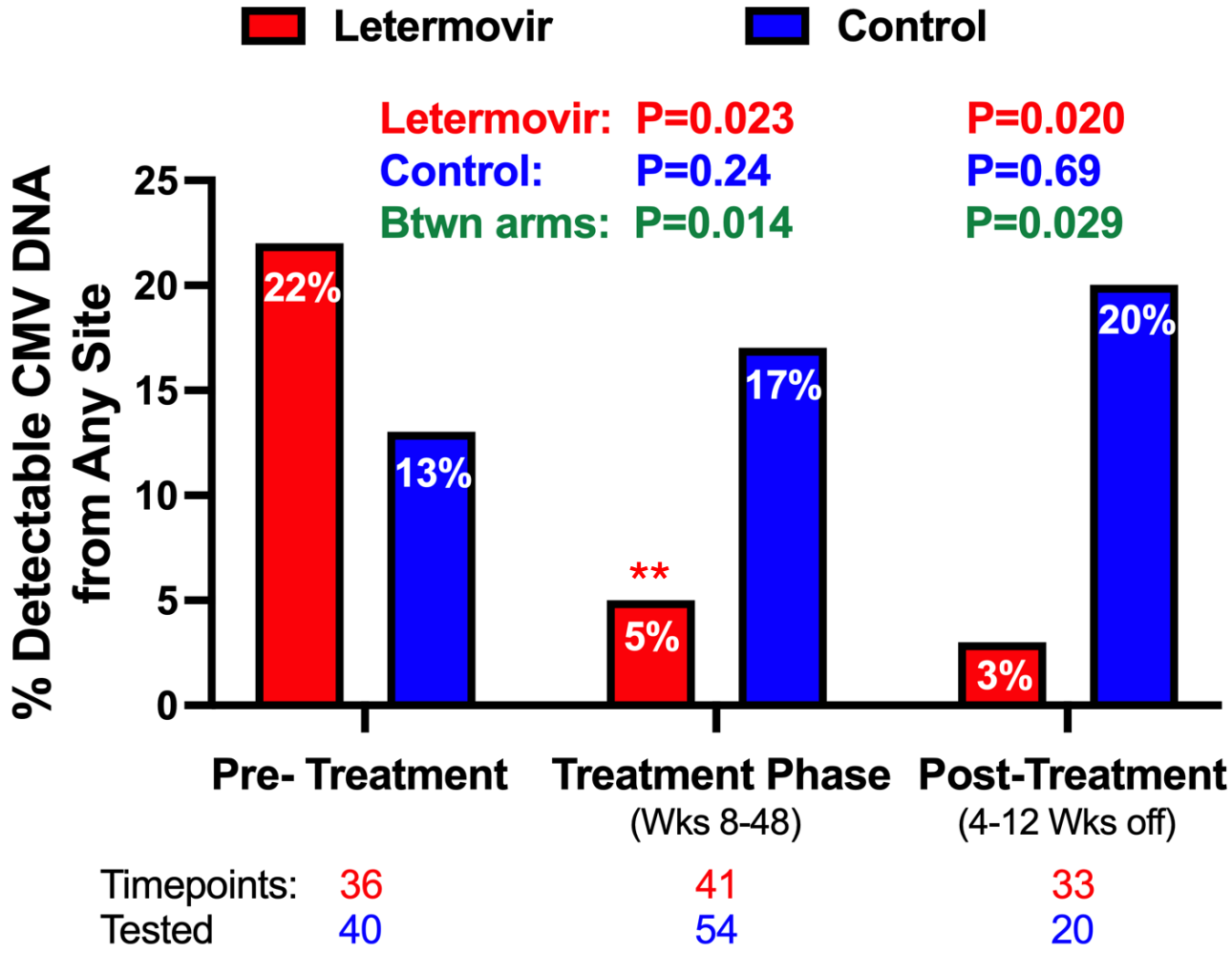
https://clinicaltrials.gov/ct2/show/NCT04840199

Table 1. Baseline Characteristics

Characteristics	Letermovir	No CMV Treatment
N	18	21
Sex at birth (female)	4 (22%)	7 (33%)
Age	59 (55, 60)	57 (52, 62)
Race		
Native American	0 (0%)	1 (5%)
Black	8 (44%)	7 (33%)
White	9 (50%)	13 (62%)
Other	1 (6%)	0 (0%)
Ethnicity		
Not Hispanics or Latino	17 (100%)	22 (100%)
CD4 T Cell < 350 cells/mm^3	8 (44%)	9 (43%)
*CD4 T Cell count (cells/mm^3)	389 (268, 809)	384 (299, 655)

Of 42 participants enrolled, 39 contributed to the per-protocol analysis, stratified by CD4 count (44% <350 cells/mm^3) and sex at birth (28% female).

Letermovir Suppresses Mucosal* CMV Shedding



*Includes **throat washes, semen, rectal and cerivovaginal swabs**

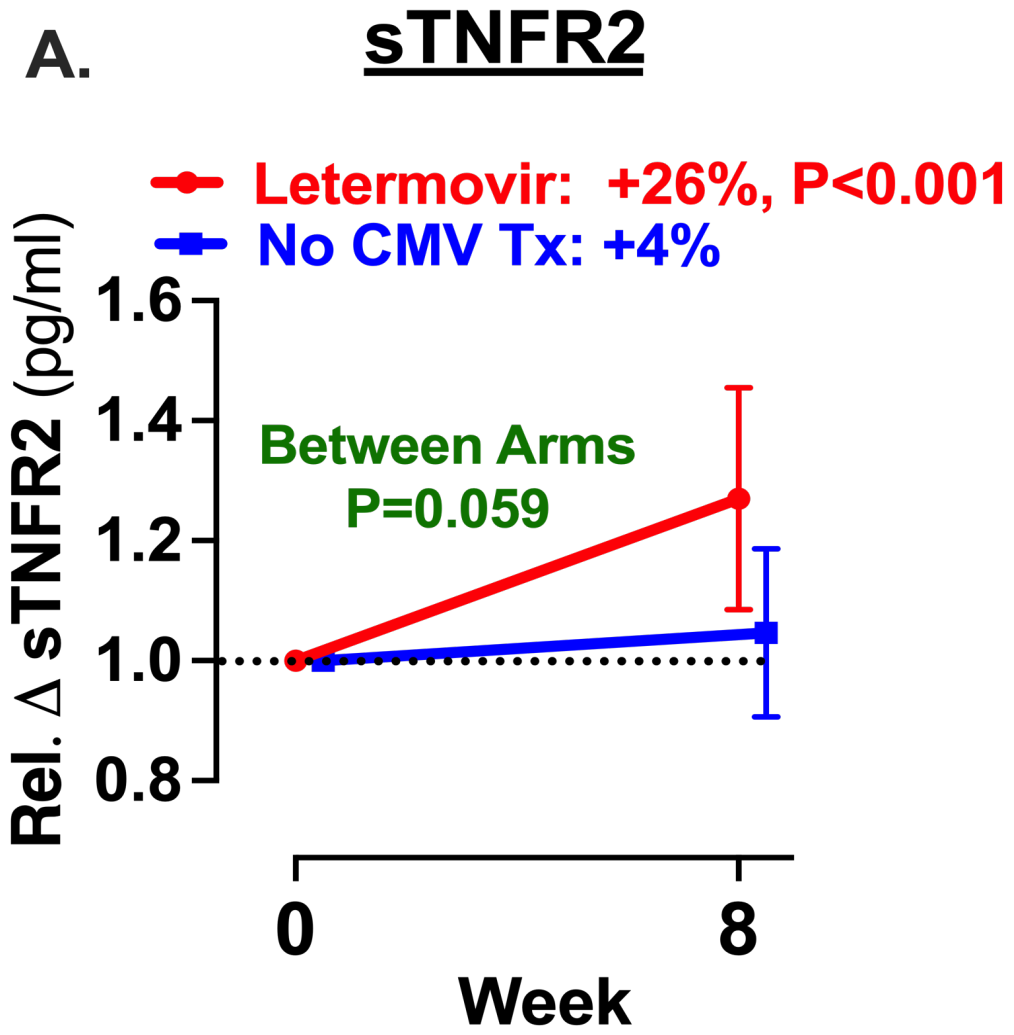
P values test change from baseline using repeated measures logistic regression modeling

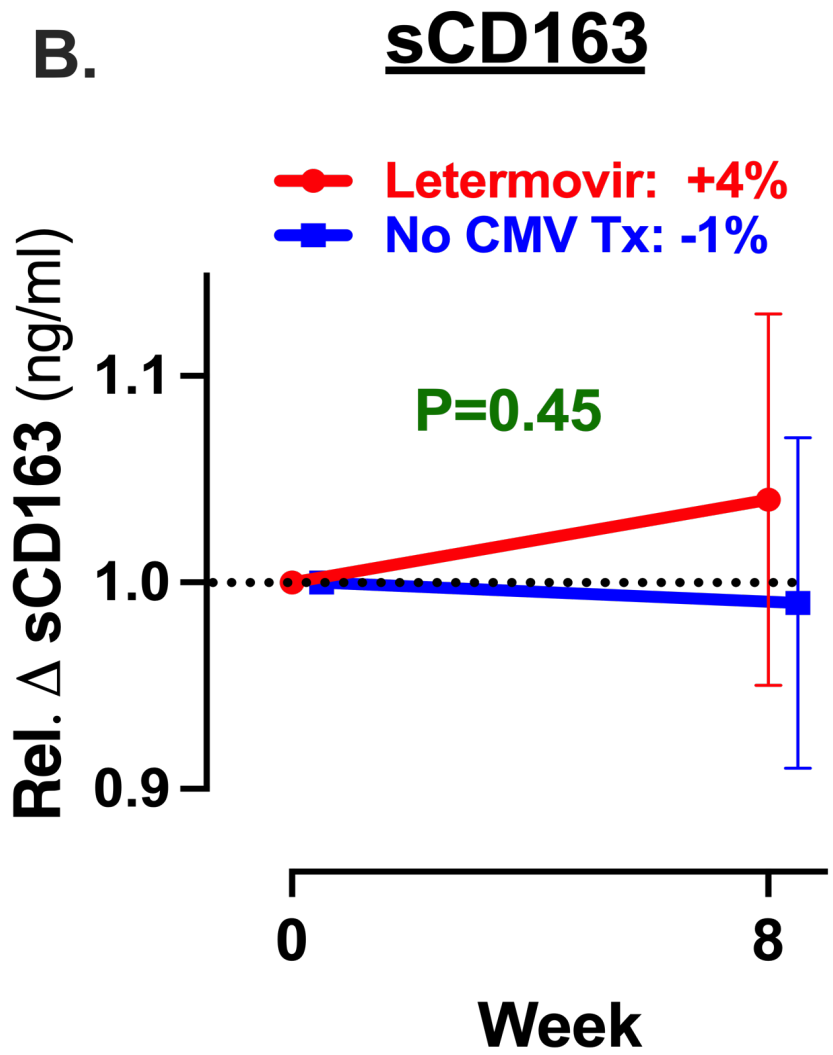
***During treatment, there were only 2 detectable CMV DNA levels in the letermovir arm (both in semen and at week 8), and both had declined from baseline:*
10,645 c/ml->51 c/ml
1,805 c/ml-> 460 c/ml

All plasma CMV DNA levels tested in the study were undetectable

Letermovir Trial Futility Analysis Results

(August 18, 2023)

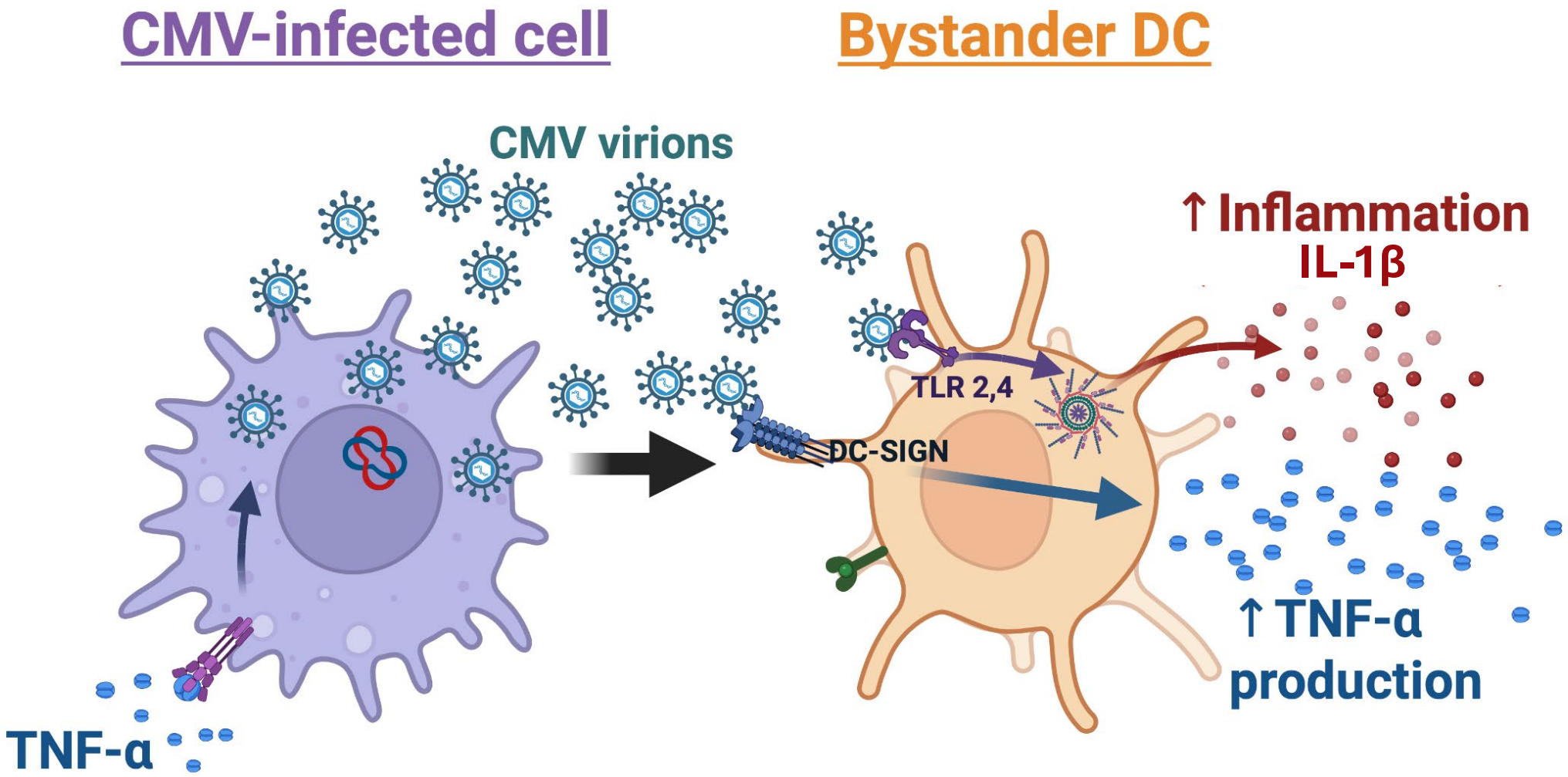




In retrospect, the declines in sTNFR2 and sCD163 with valganciclovir reflected effects on *other* herpesviruses, not CMV (we suspect EBV).

Gianella et al, Poster 354 LB, CROI 2024

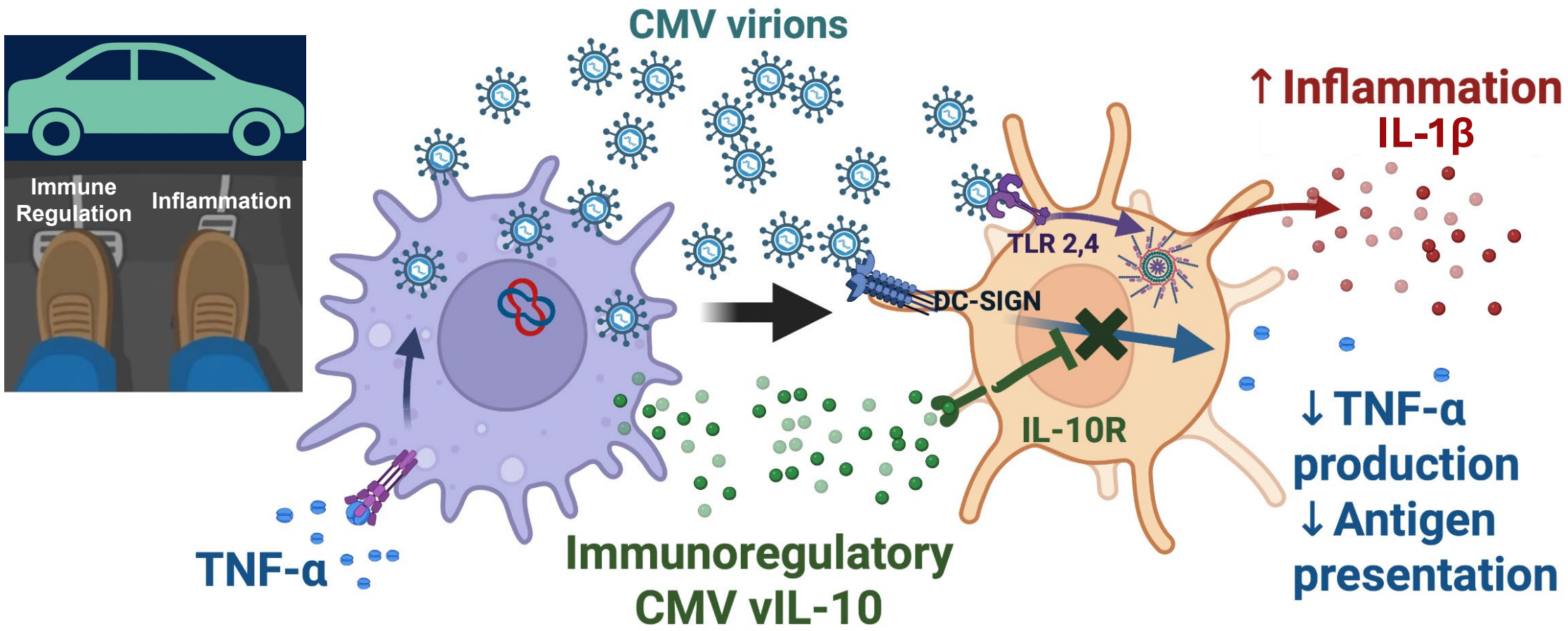
CMV May Amplify Inflammation…



Gianella et al, #182 LB, CROI 2025

…But CMV Also Dampens Inflammation via vIL-10

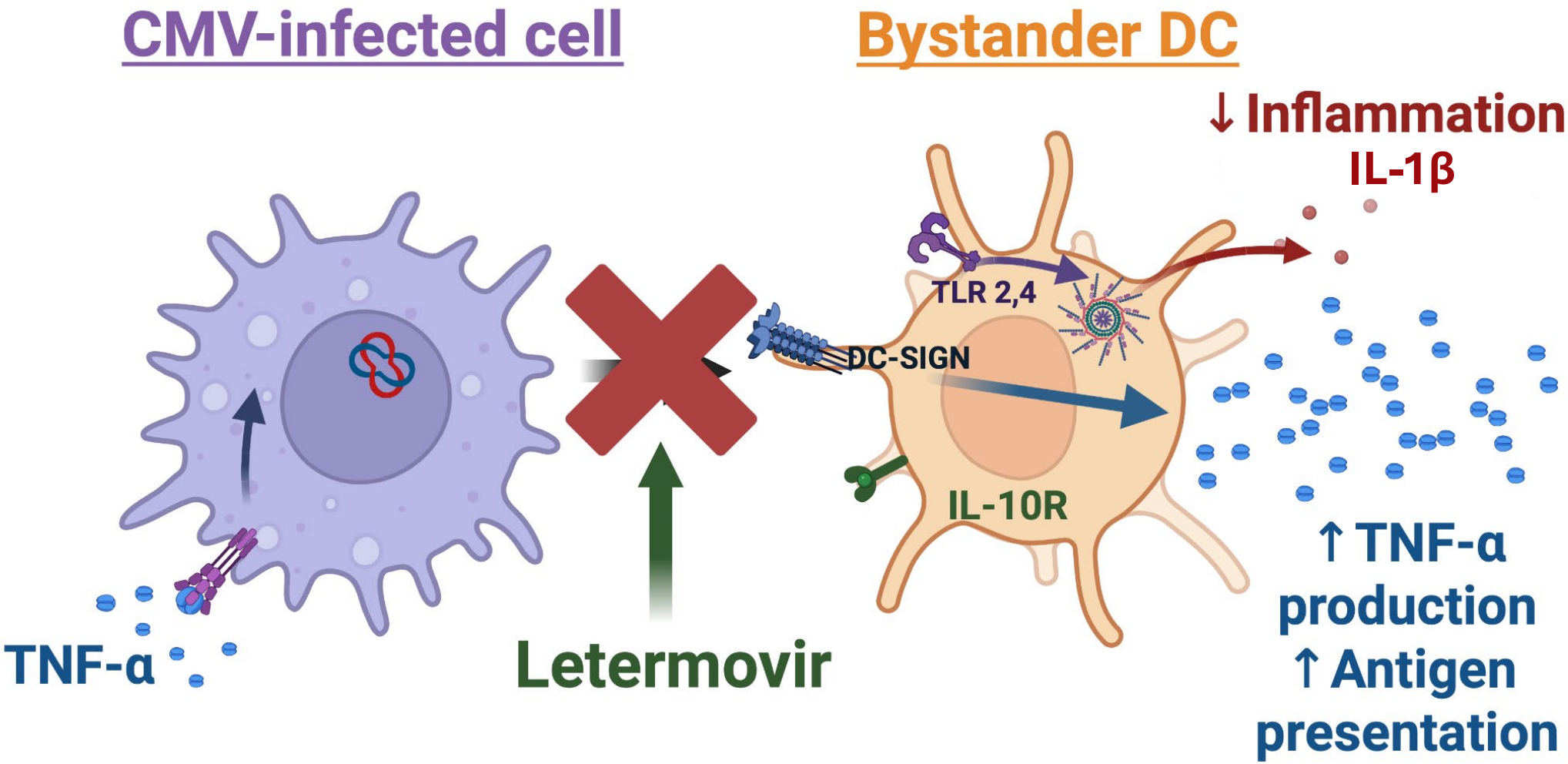
Strategy for Evading Host Immune Response



CMV has its foot on the accelerator and the brake at the same time!

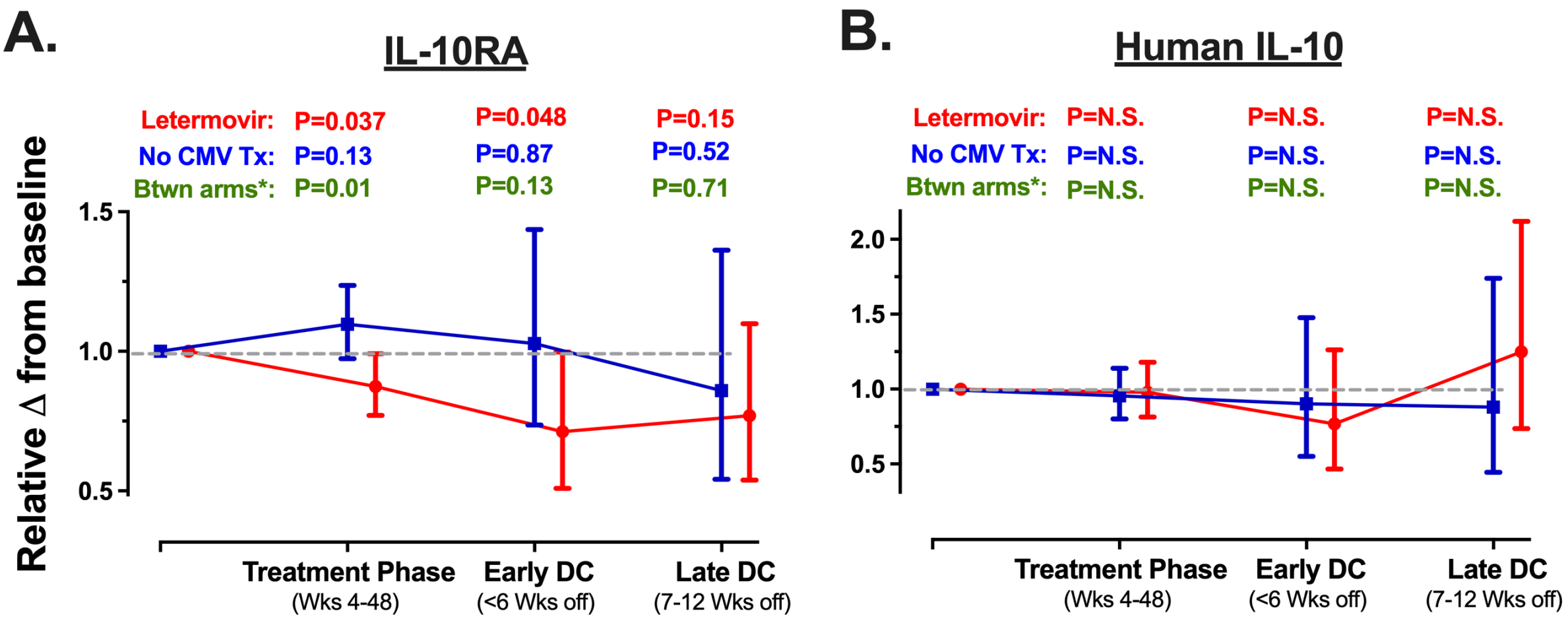
Gianella et al, Poster 182 LB, CROI 2025

Letermovir Takes the Foot Off BOTH the Accelerator AND the Brake at the Same Time!



Gianella et al, #182 LB, CROI 2025

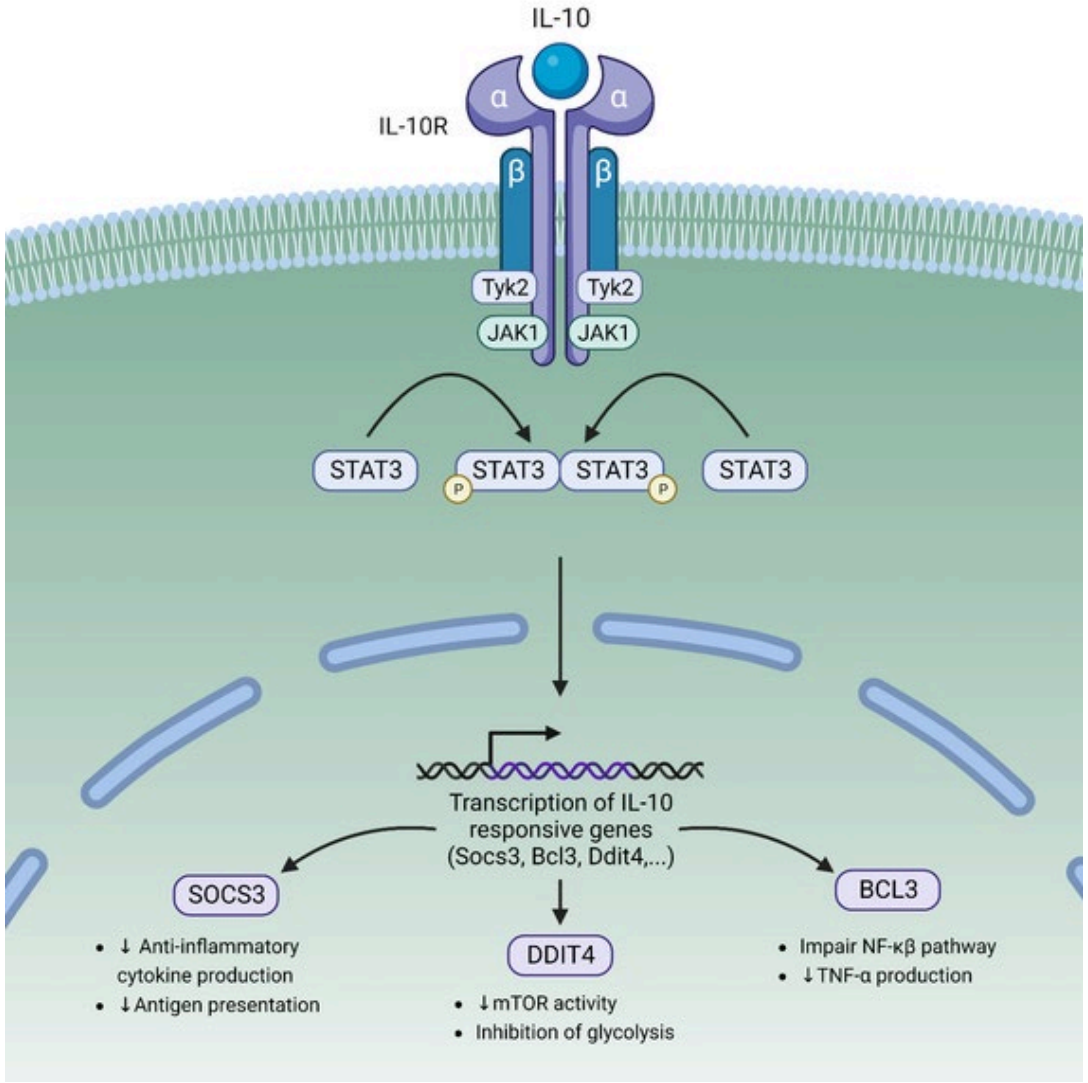
Letermovir Decreases Marker of IL-10R Activity

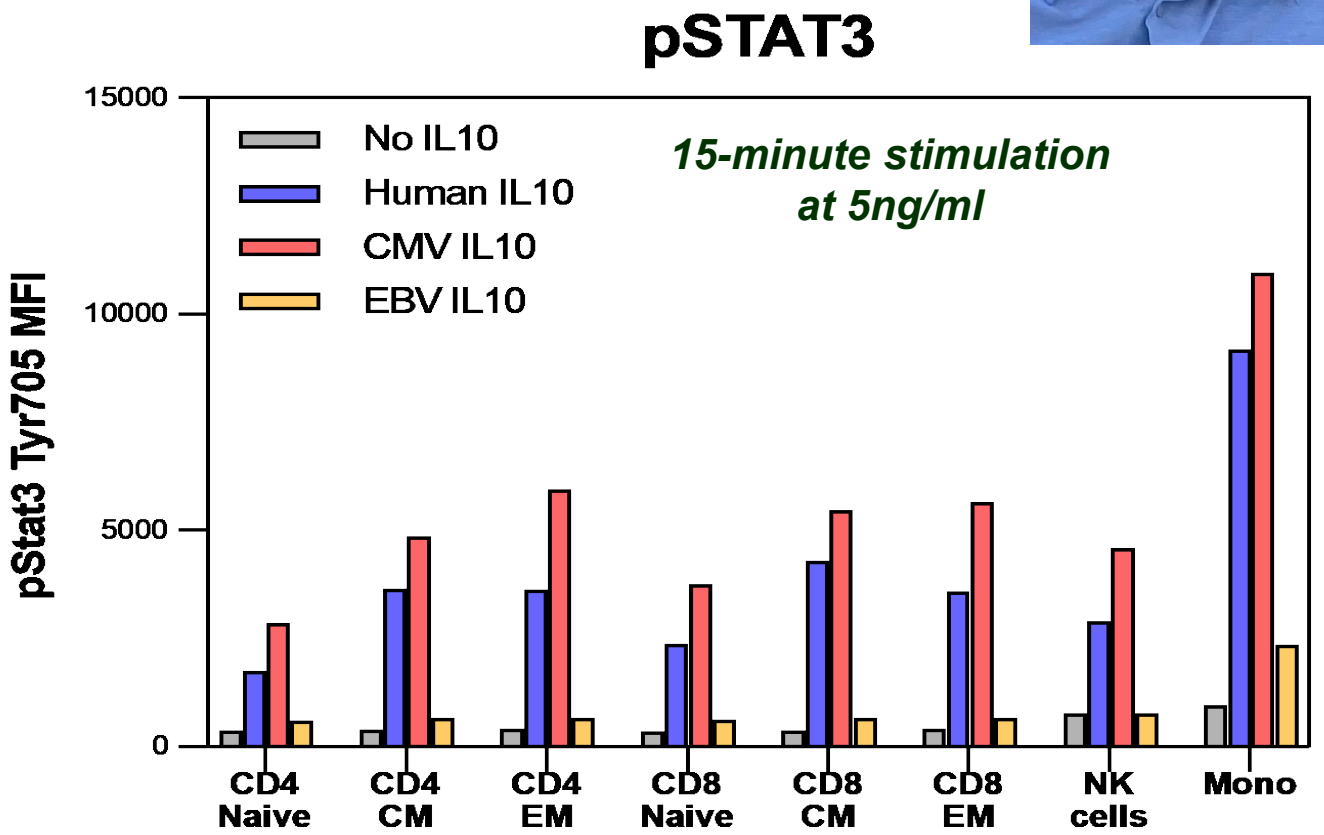


No evidence of a decline in IL10RA in the valganciclovir trial (-4%, P=0.65)

Gianella et al, Poster 354 LB, CROI 2024

CMV vIL-10 is *Super*-agonist while EBV vIL-10 is a *Partial* Agonist





Bugbee, Frontiers in Immunol, 2023

Yoshinori Fukazawa, PhD

Could CMV Be *Immunoregulatory* and EBV Be *Pro-inflammatory*?

- EBV's vIL-10 is a "partial agonist," displacing human IL-10, "taking foot off the brake" of inflammatory response (Jog et al, Front Immunol, 2018)
- CMV's vIL-10 is a "super-agonist," more potent than human IL-10, enhancing the "brake" on inflammation (Poole et al, Front Immunol, 2020)
- Polymporphisms associated with increased IL-10R signaling associated with risk of CMV retinitis in people with AIDS (Sezgin, JID, 2010)
- Polymorphisms associated with decreased IL-10 expression are associated with increased risk of Multiple Sclerosis (Myhr, J Neurol Sci, 2002)
- Why did valganciclovir not change IL-10R activity?
  - We removed a superagonist and a partial agonist at the same time!

CMV and EBV Also Have Qualitatively Different Effects on Multiple Sclerosis Risk

RESEARCH

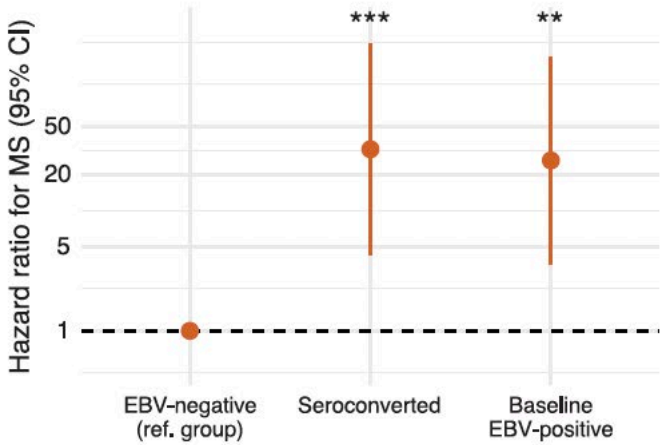
REPORT

MULTIPLE SCLEROSIS

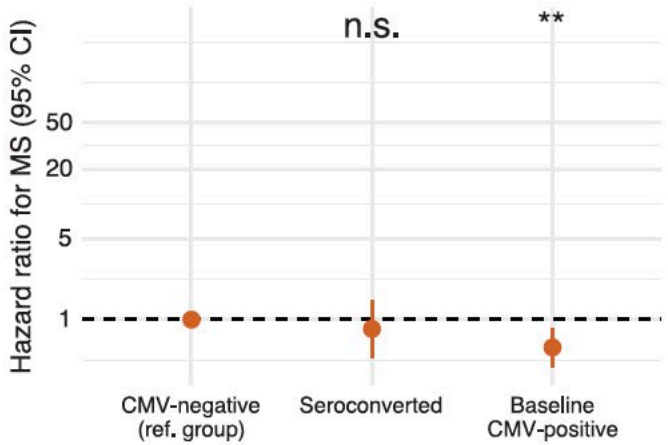
Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1]†, Marianna Cortese[1]†, Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[6], Stephen J. Elledge[6], David W. Niebuhr[9], Ann I. Scher[9], Kassandra L. Munger[1]‡, Alberto Ascherio[1,10,11]*‡

EBV

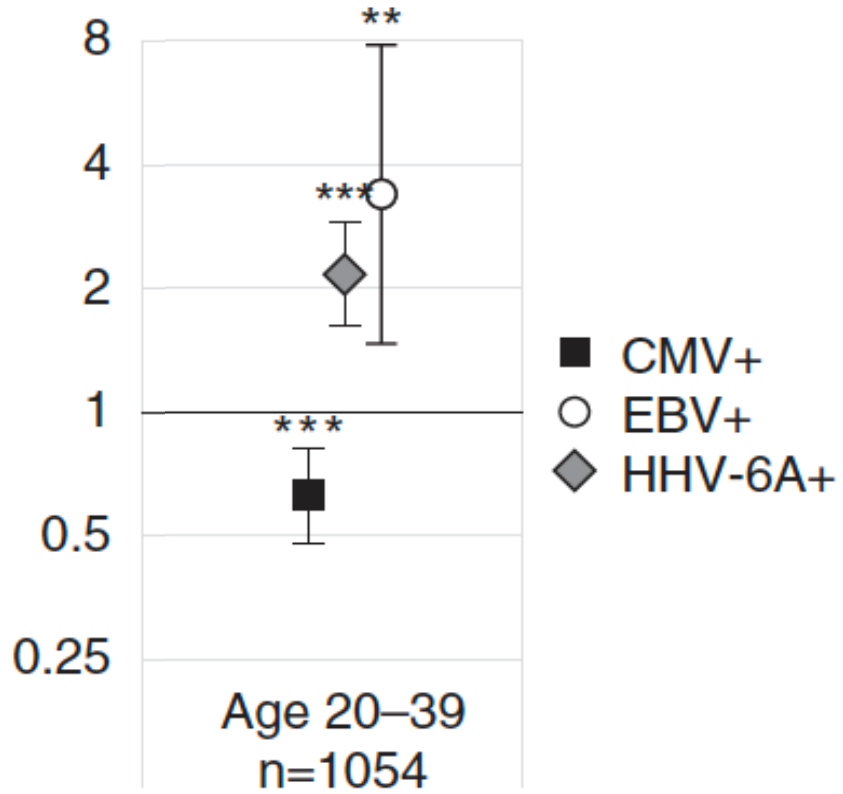


CMV



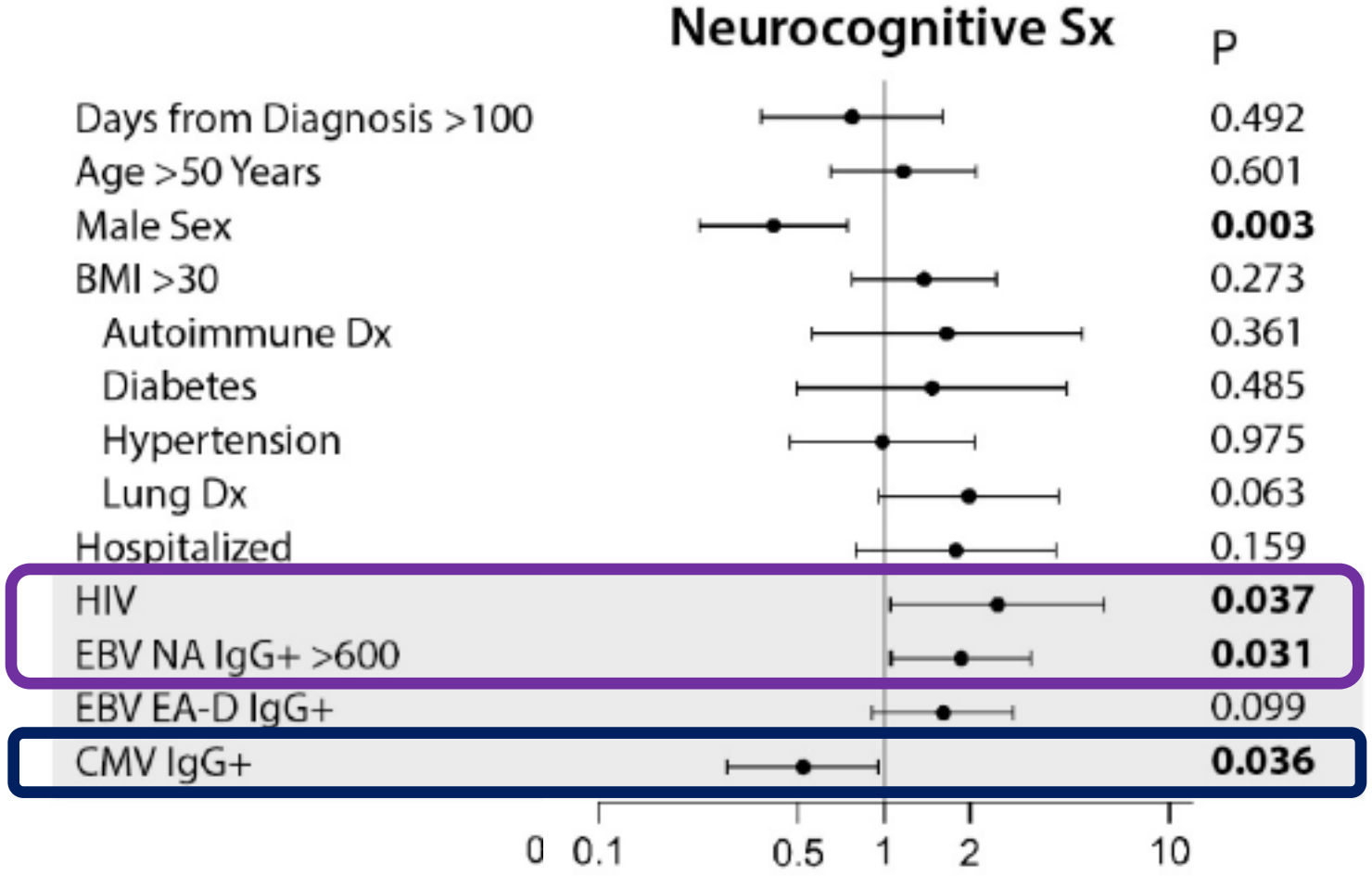
Bjornevik et al, Science, 2022

CMV associated with a 30% decreased odds of MS



Grut et al, Eur J Neurol, 2021

CMV and EBV Have Qualitatively Different Effects on Neurologic Long COVID Risk



EBV reactivation and HIV associated with an increased risk

CMV seropositivity associated with a 50% decreased risk of neurologic "Long COVID" (e.g., "brain fog")

Peluso et al, JCI, 2023

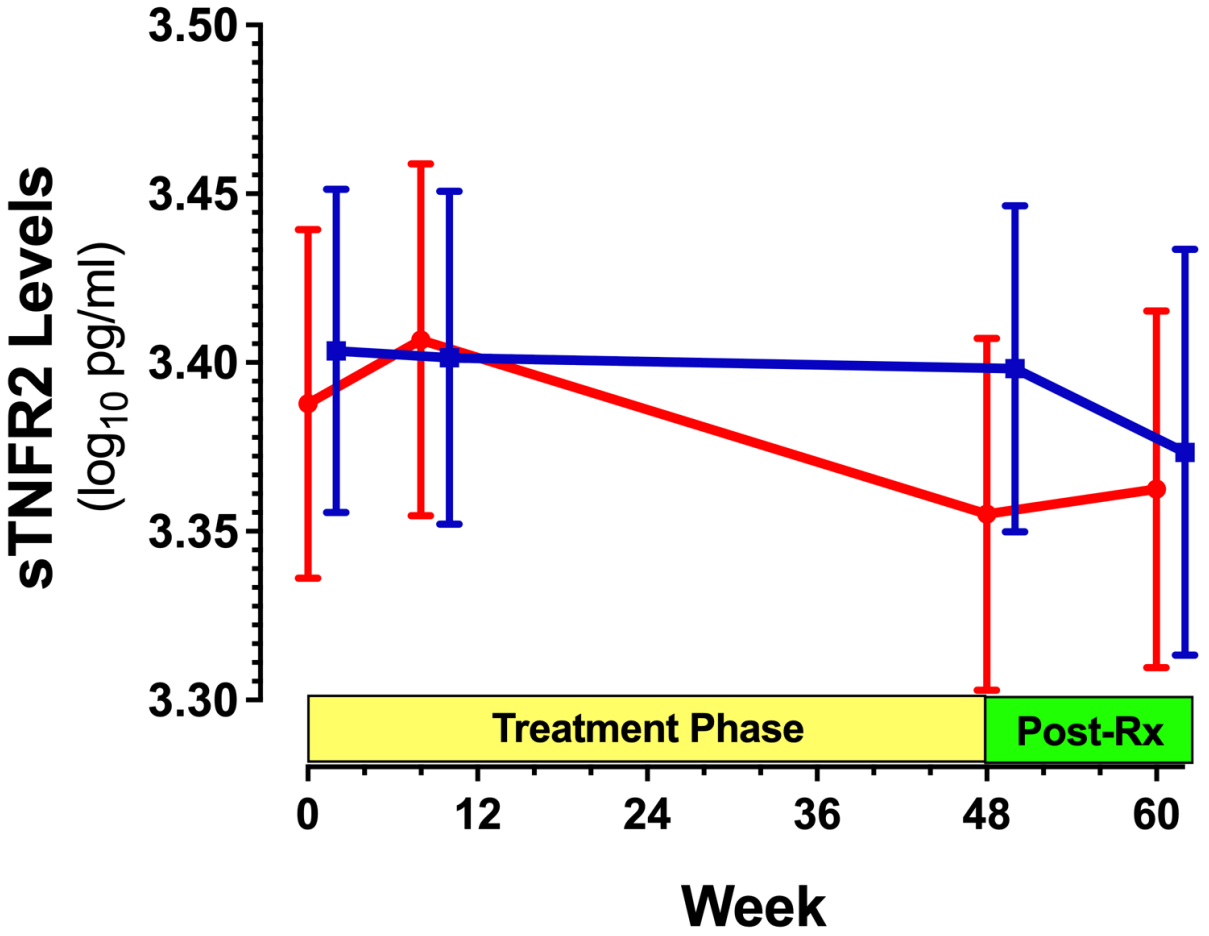
Letermovir-mediated early increases in inflammation may have been due to loss of the immunoregulatory CMV vIL-10.

But what happened with longer-term letermovir treatment?

sTNFR2 Increase was Transient Followed by a Significant Reduction

P values for slope during segment:

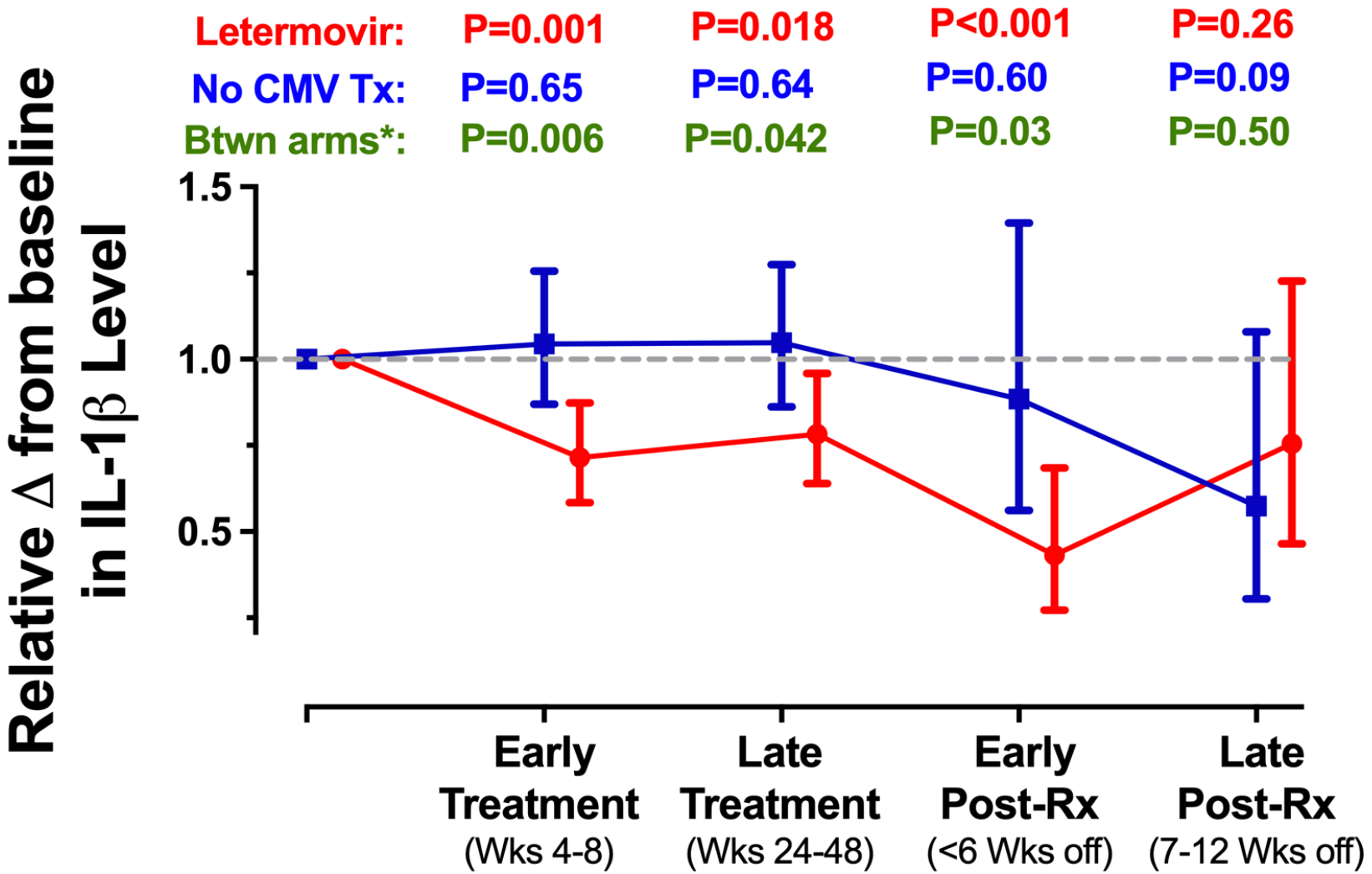
Letermovir:	P=0.12	P<0.001	P<0.43
No CMV Tx:	P=0.88	P=0.82	P=0.28
Btwn arms*:	P=0.24	P=0.018	P=0.19



Similar patterns for CRP, IL-6, and D-dimer

Gianella et al, #182 LB, CROI 2025

Letermovir Caused Early and Sustained Reductions in Plasma IL-1β Levels



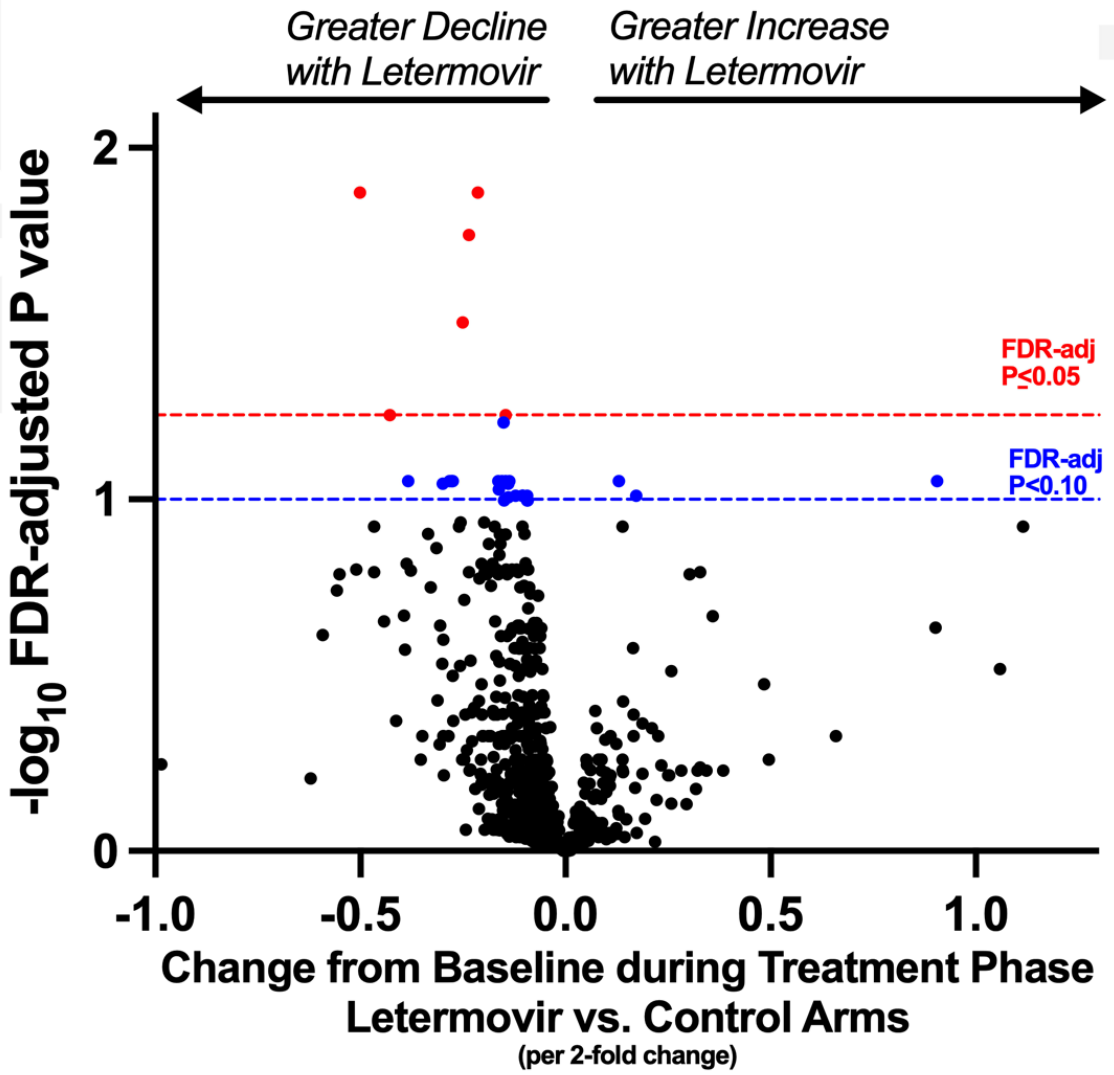
IL-1β is causally associated with CVD and cancer mortality in the general population (CANTOS trial)

*P values test change from baseline using linear mixed models

Gianella et al, #182 LB, CROI 2025

Letermovir Broadly Reshapes the Plasma Inflammatory and Cardiometabolic Proteome in Treated HIV

↓with Letermovir	
Inflammation-Chemotaxis	CEACAM8
	CXCL12 (SDF-1)
	CXCL17
	IL-6R
	QPCT
	TNFSF13 (APRIL)
NK cell marker	NCAM-1/CD56
Immunoregulatory	FCGR3B
Gut-EC Adhesion	EPCAM
Complement	CD46
	CD55
	CD59
	CD93
Endothelial Dysfunction, Atherosclerosis, Angiogenesis	CDH5
	CTSB
	EDIL3
	ESM1
	ITGβ1
	ITGβ2
	NOTCH1
	NRP-1
	OLR1 (oxLDL-R)
	SEMA7A
	VEGF-D
Adipokine-T2DM risk	FABP-4
	IGFBP7
Other	ENPP5
	CDON

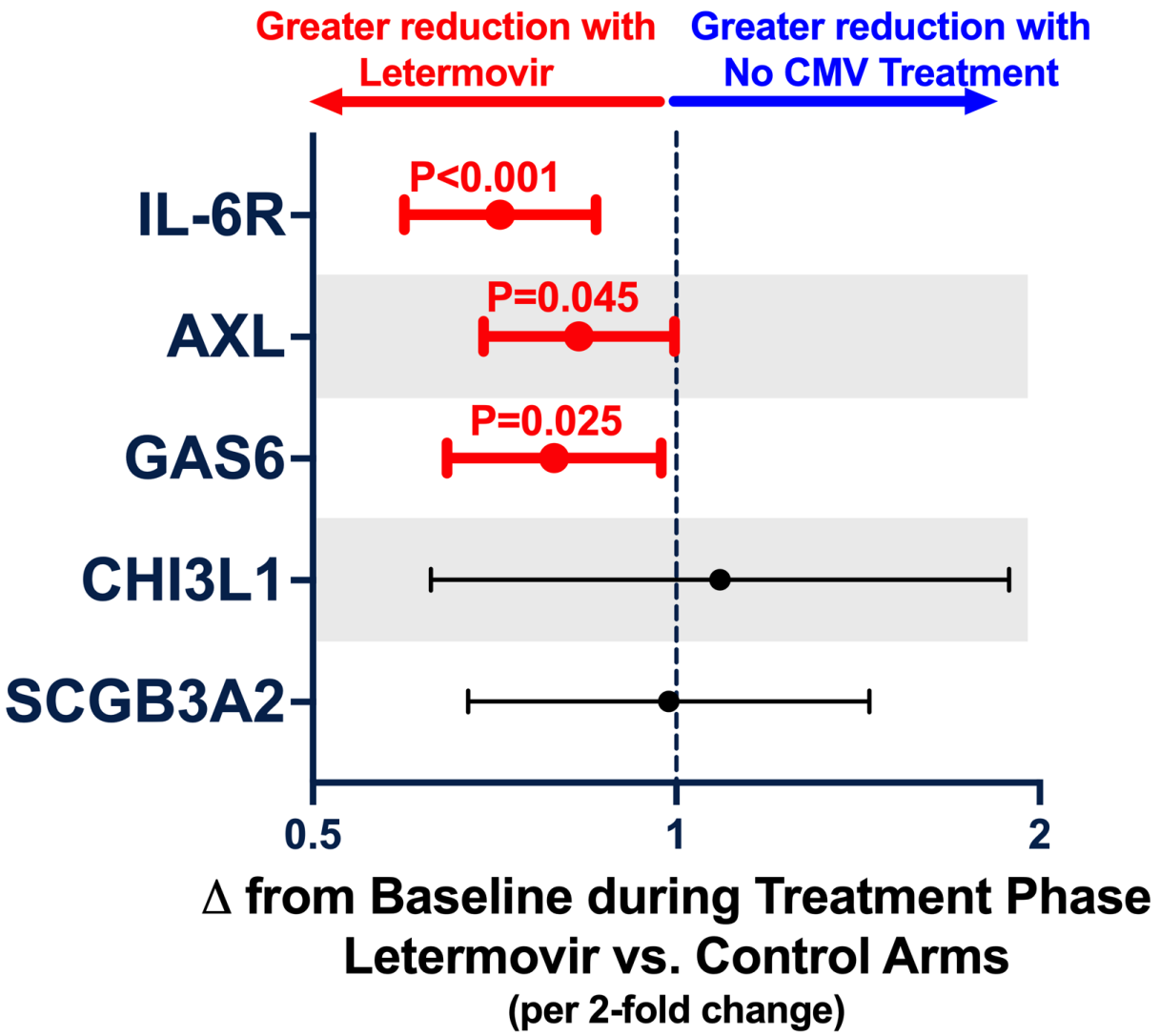


↑with Letermovir	
Fetuin-B	Insulin GF Regulation
TFF3	Gut-EC Healing
TCL1B	Other

Letermovir reduced many proteins associated with CVD and cancer risk.

Gianella et al, Poster 354 LB, CROI 2024

Treating asymptomatic CMV with letermovir reduces most of the proteins *causally linked* to CVD in treated HIV*

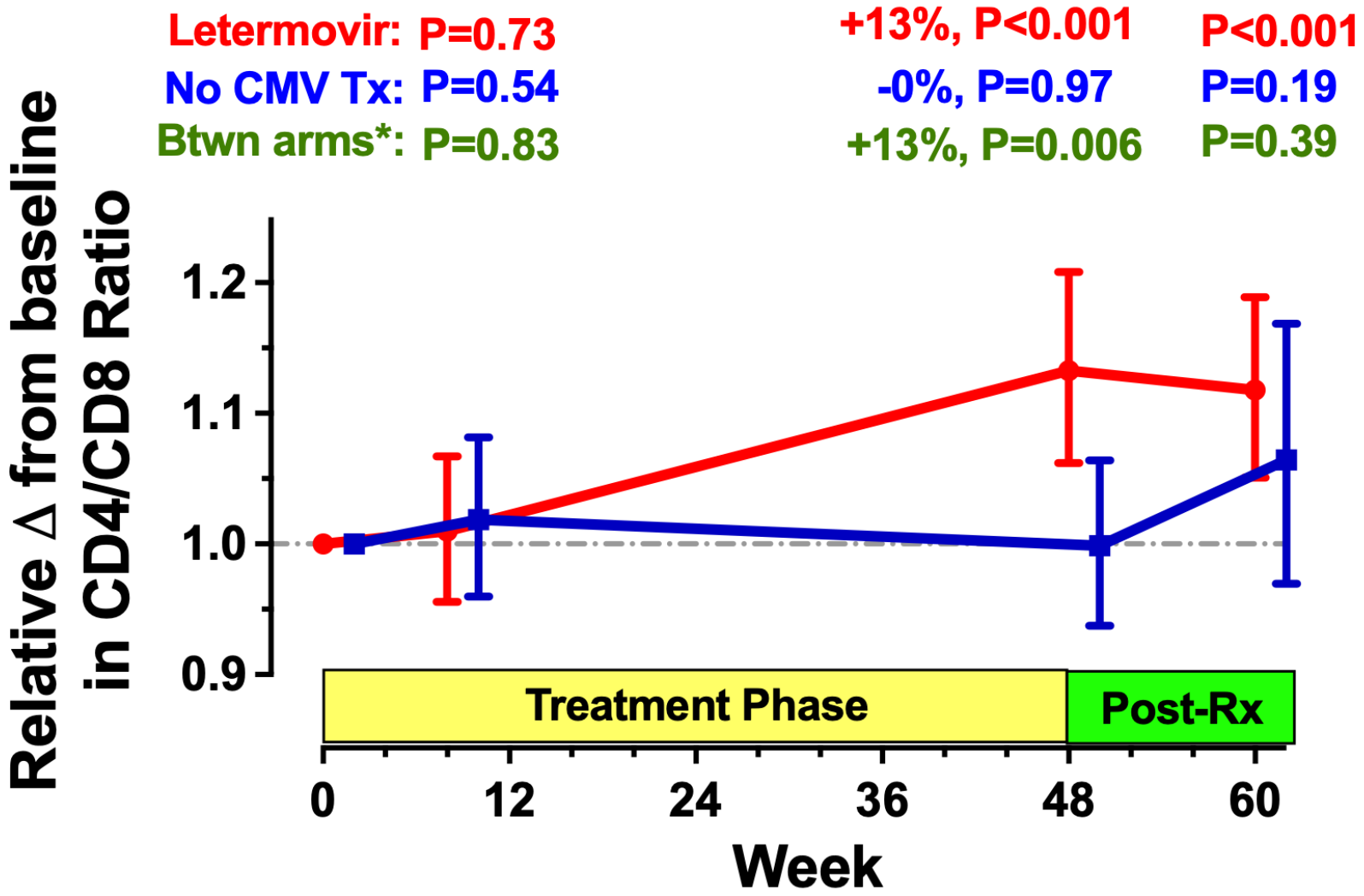


- IL-6R, AXL, and GAS6 linked to CVD and cancer in general population
- AXL/GAS6 also linked to transplant vasculopathy.
  (Glinton, J Heart Lung Transpl, 2021)
- CMV also previously linked to transplant vasculopathy.
  (Valantne, Circulation, 1999)

No evidence for causality for sTNFR2 or IL-10*

*Gianella et al, Poster 354 LB, CROI 2024 (*Reilly, JID, 2023)*

CD4/CD8 Ratio Increased with Letermovir

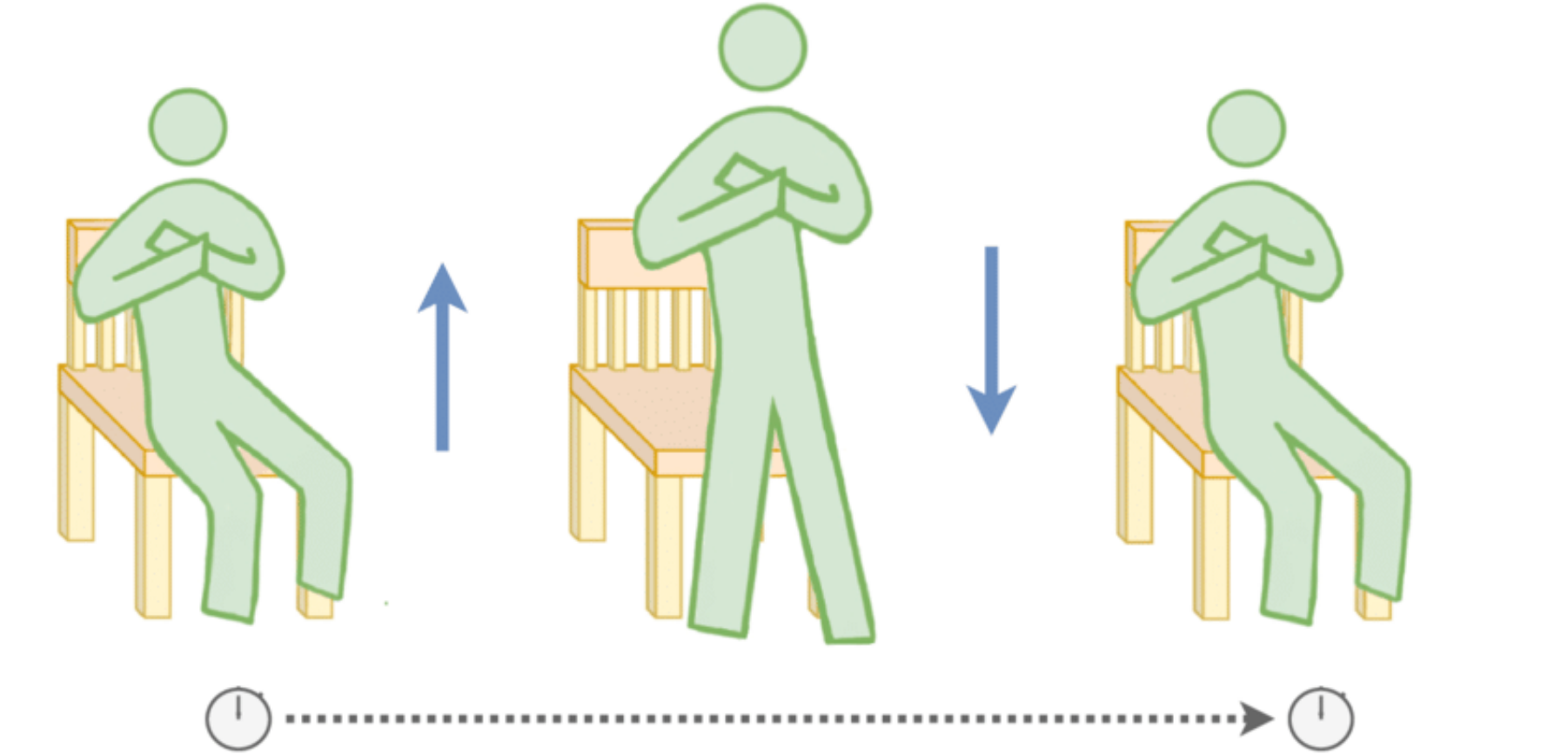


This effect size corresponds to a ~14% reduction in NHL and Anal Cancer, and a 7% reduction in lung cancer risk (Castilho for NA-ACCORD, JNCI, 2022)

P values reflect change from baseline at each timepoint

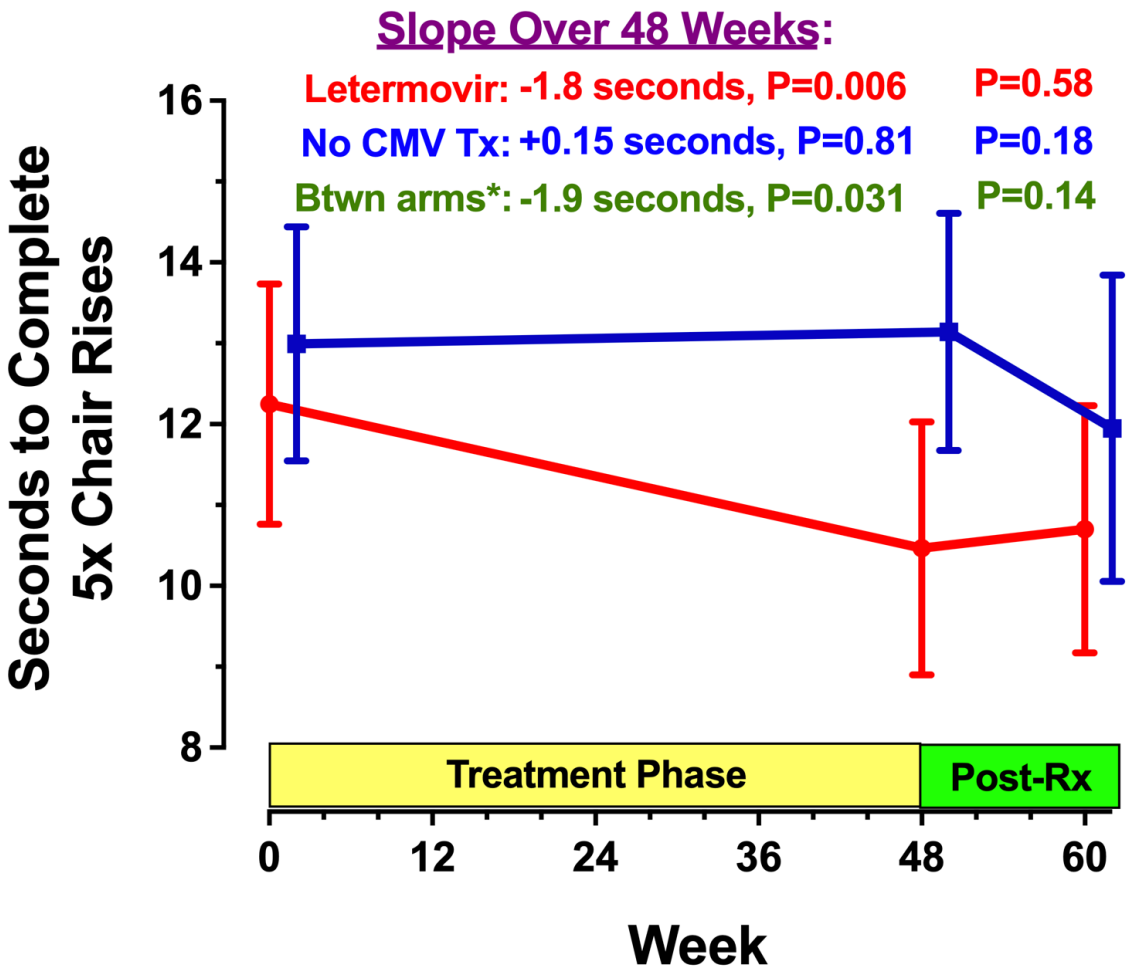
Gianella et al, #182 LB, CROI 2025

5x Chair Rise Test – Measure of Physical Function and Leg Strength

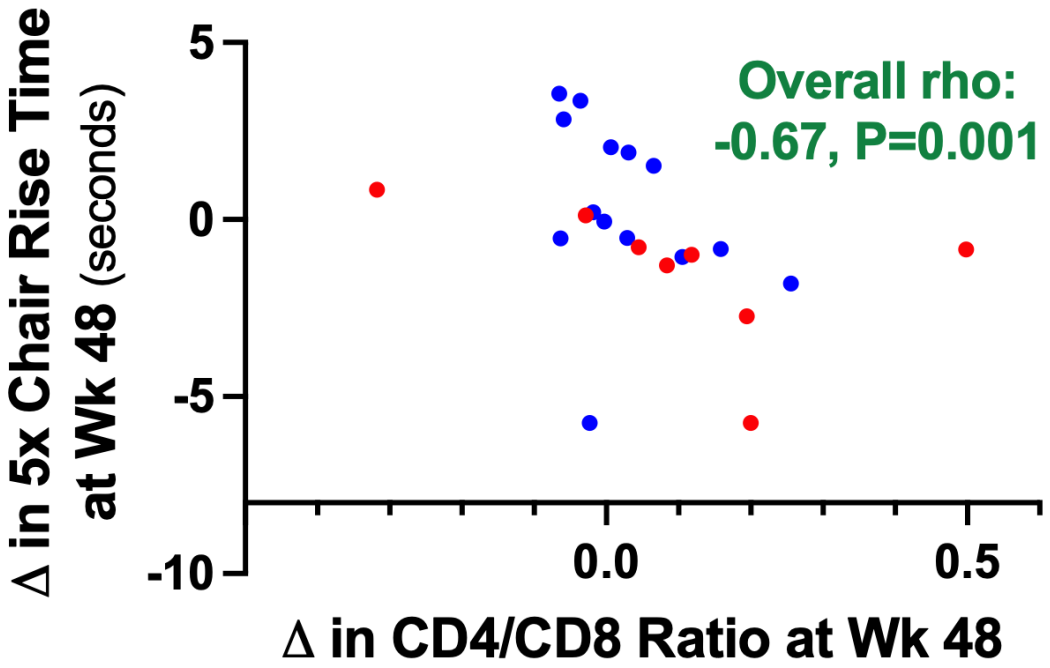


Letermovir Improved physical function, which Correlated with Immunologic Improvement

Change in 5x Chair Rise Time



Change in Chair Rise Time by Change in CD4/CD8 Ratio

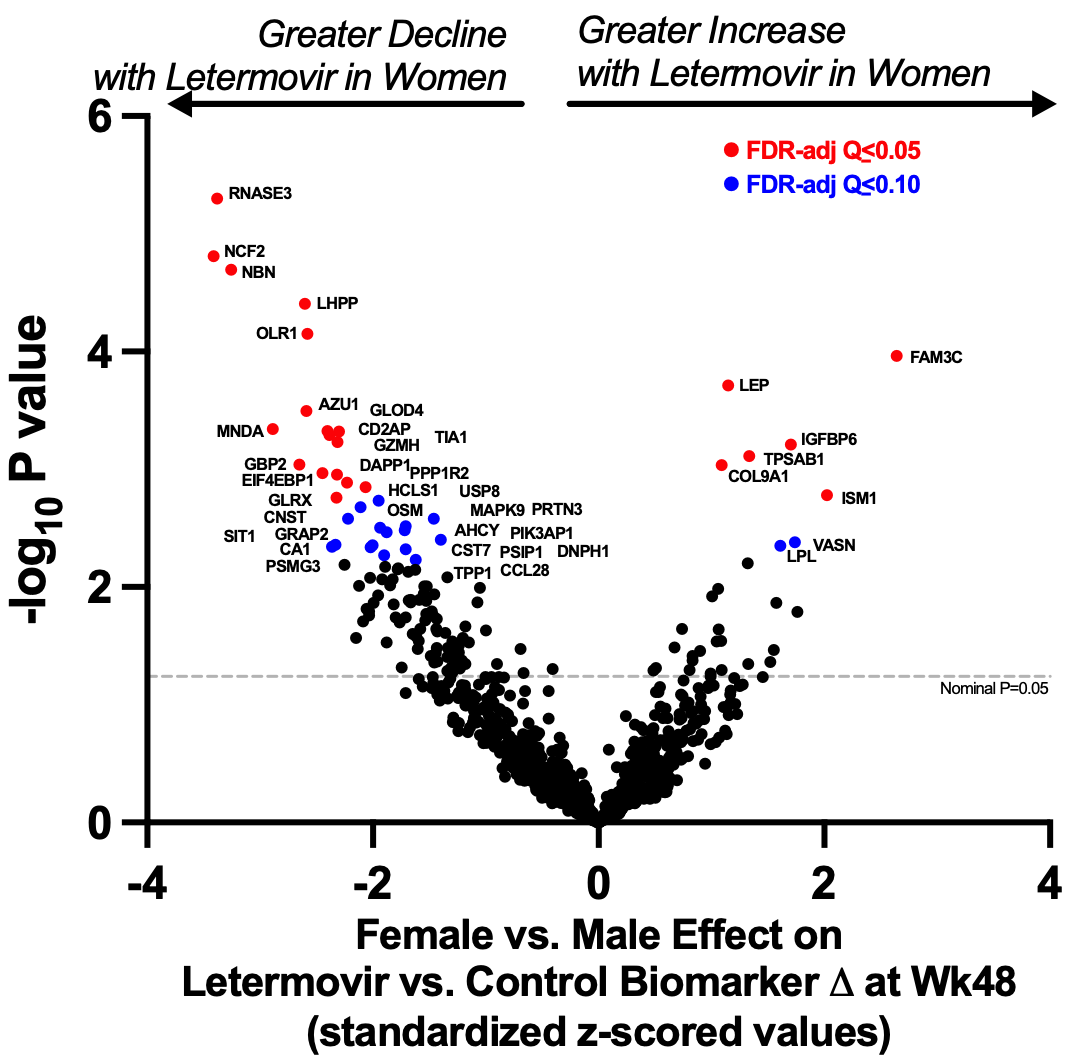


Significant correlations also for IL-6R and IL-1β

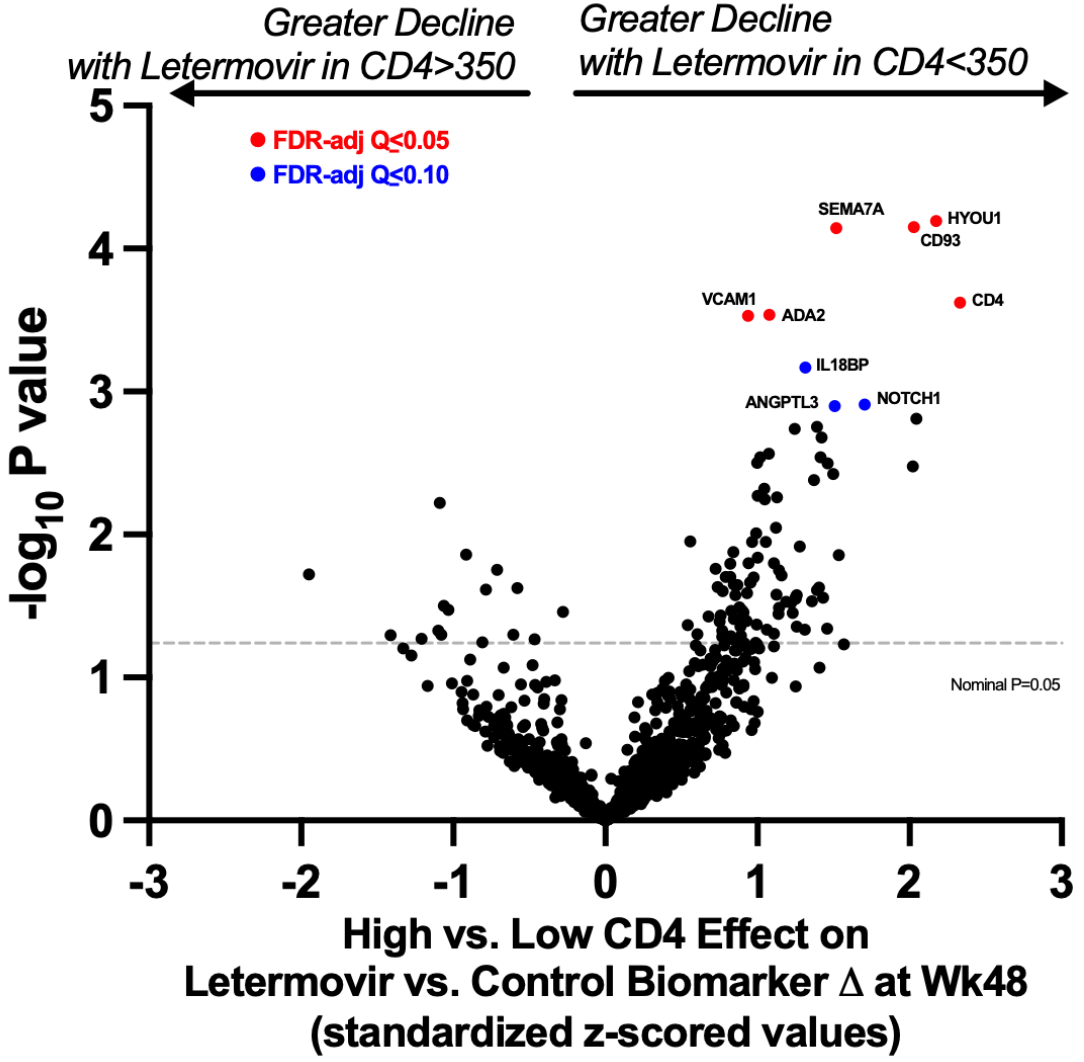
Gianella et al, #182 LB, CROI 2025

Greater Improvement in Women and with CD4<350

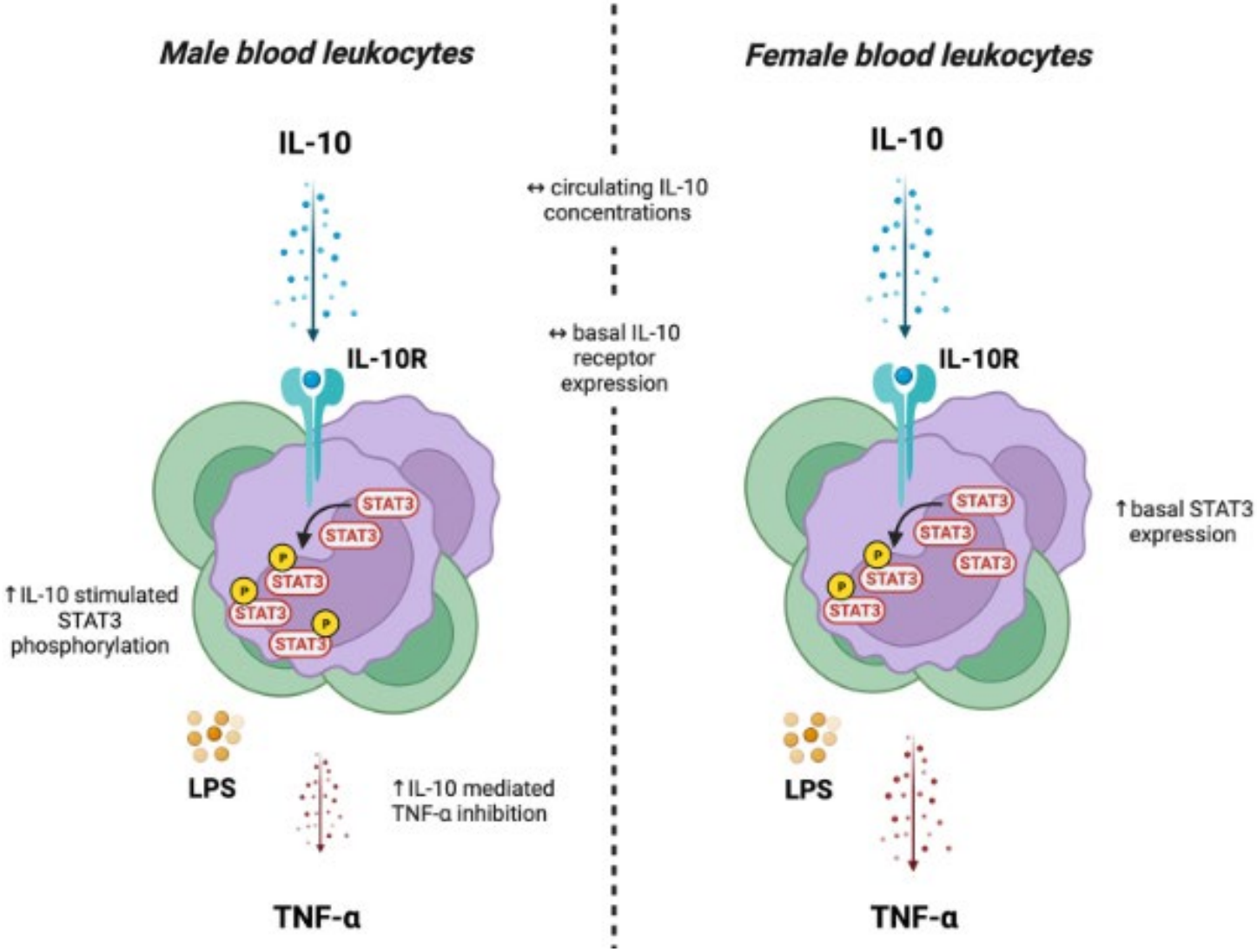
Interaction by Sex



Interaction by CD4 Count



Women Have Impaired IL-10R Signaling via STAT3

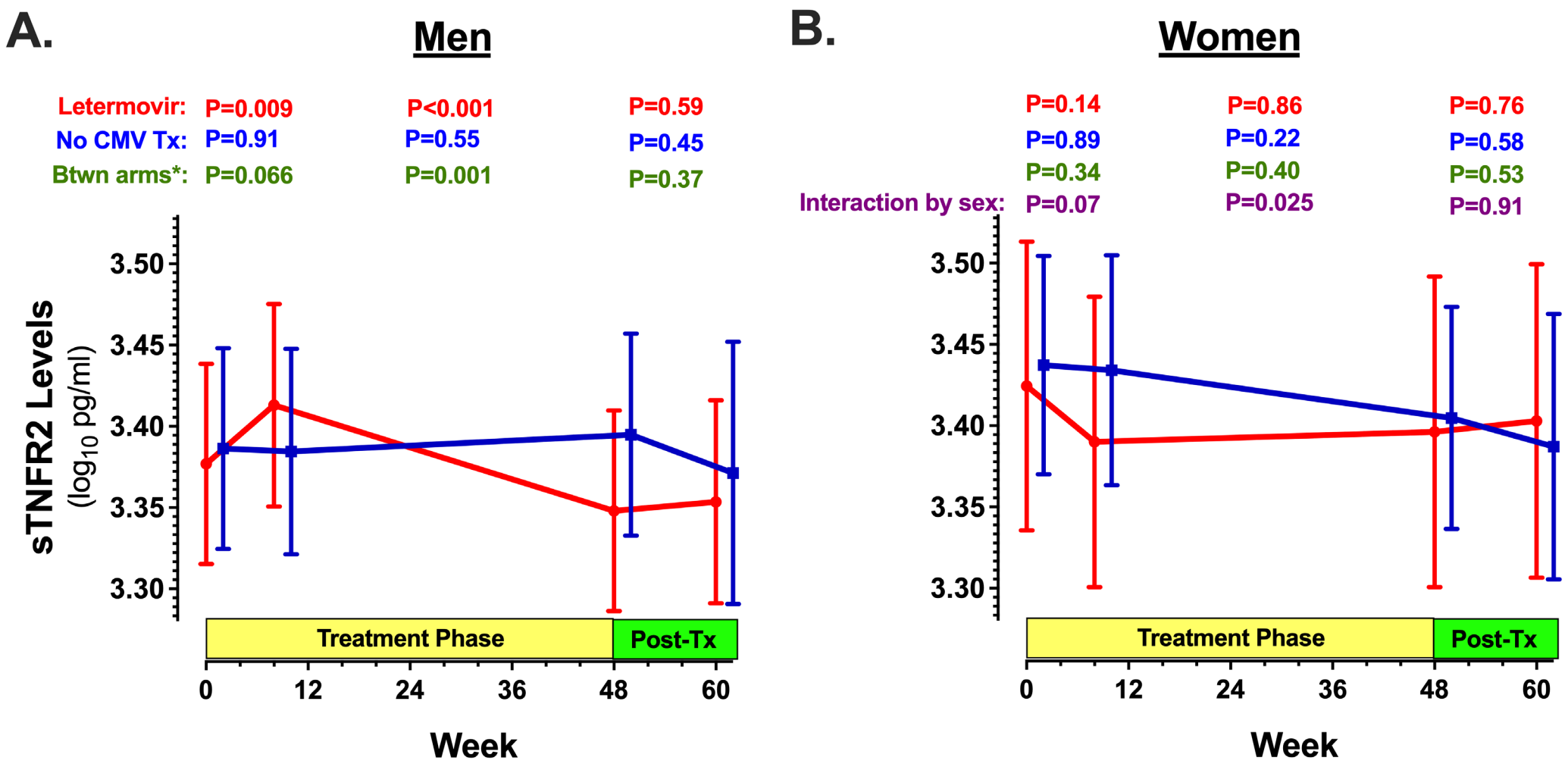


If we think that the early letermovir-mediated increase in inflammation was the result of loss of CMV vIL10 signaling through the IL-10R...

Might that increase inflammation be more prominent in men than women?

Islam, Am J Physiol Cell Physiol, 2022

Women Have Qualitatively Different Early Immune Response to Letermovir than Men



P values for slope during segment

Also NO CHANGE in IL-10RA levels in women with letermovir

Treating Asymptomatic CMV with Letermovir Improves Immunologic and Functional Aging in Treated HIV

- Transient ↑ in some inflammatory markers (sTNFR2, IL-6, CRP)
  - Thought to be due to suppression of immunoregulatory CMV vIL-10
- Early and sustained ↓ in inflammatory markers that increase CVD/cancer risk
- ↑ CD4/CD8 ratio over 48 weeks
- Improved physical function/leg strength (5x chair rise test) at 48 weeks, correlating with CD4/CD8 ratio improvement
- Better immunologic improvement in women and those with CD4<350
  - Early inflammation and reduction of IL-10R activity was *only observed in men*
- Transient early inflammation also not observed with valganciclovir
  - Perhaps because valganciclovir also suppresses the EBV vIL-10 *partial agonist*?
- While clinical implications remain unclear, actively planning next study
- These findings may have broader implications (aging, transplant fields)

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