Update on Inflammation, Aging, and CMV Co-Infection in Treated HIV

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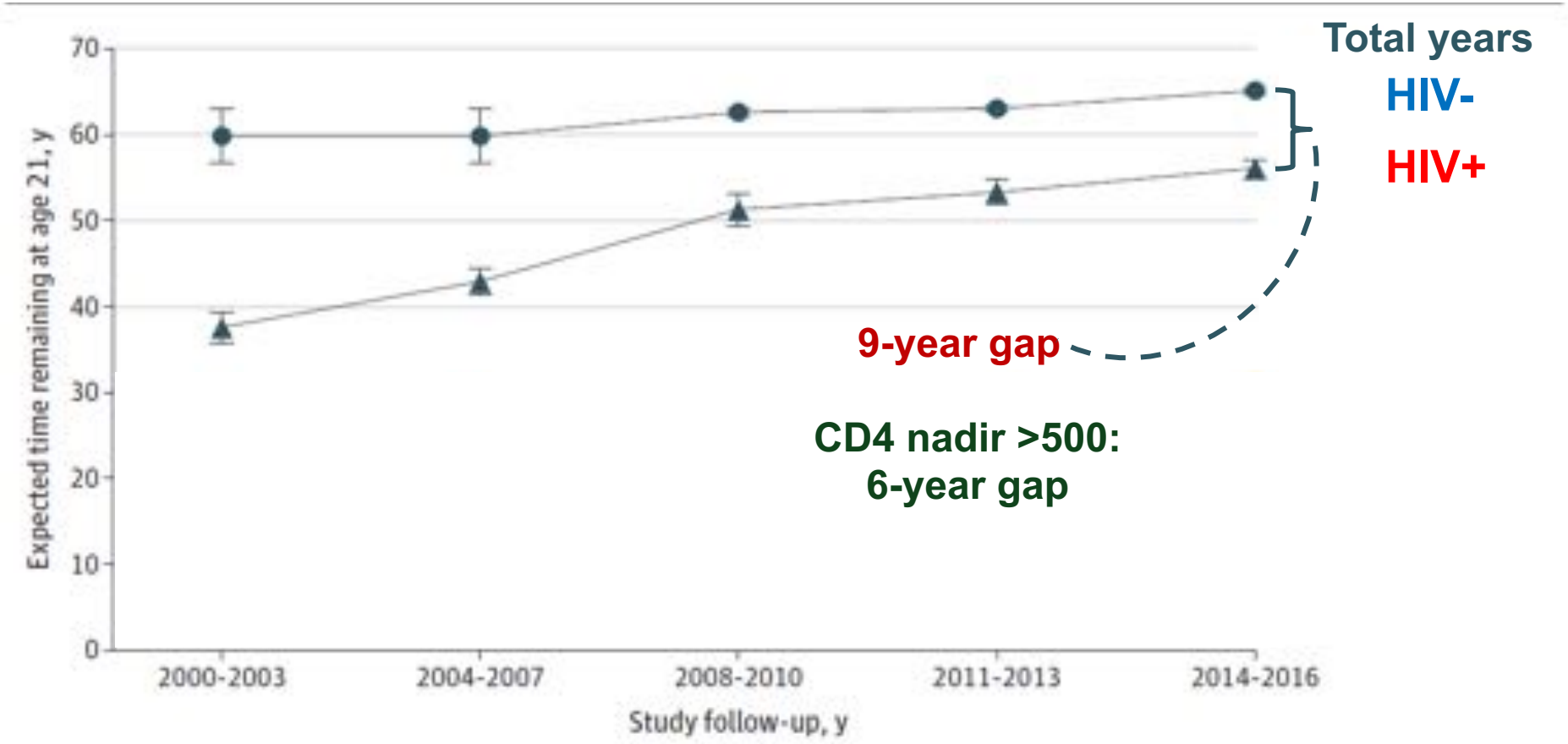
- Merck: consultant, donated drug for NIH-sponsored trial
- Gilead: honorarium, research grant recipient
- Viiv: consultant, honorarium
- Biotron: consultant

Life expectancy gap in HIV is narrowing

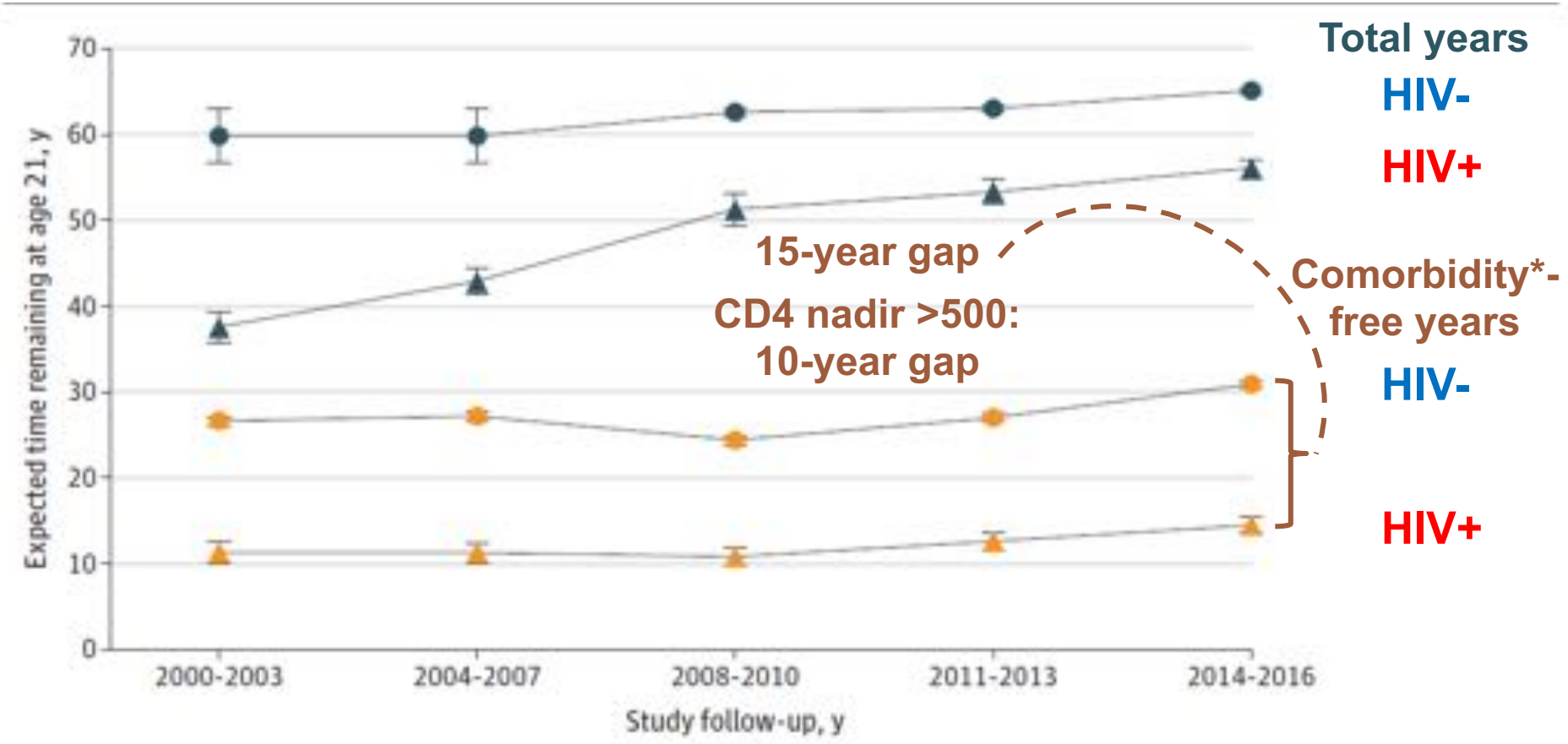
Particularly those with high CD4 nadir



Marcus et al, JAMA Network Open 2020

The comorbidity gap still lags

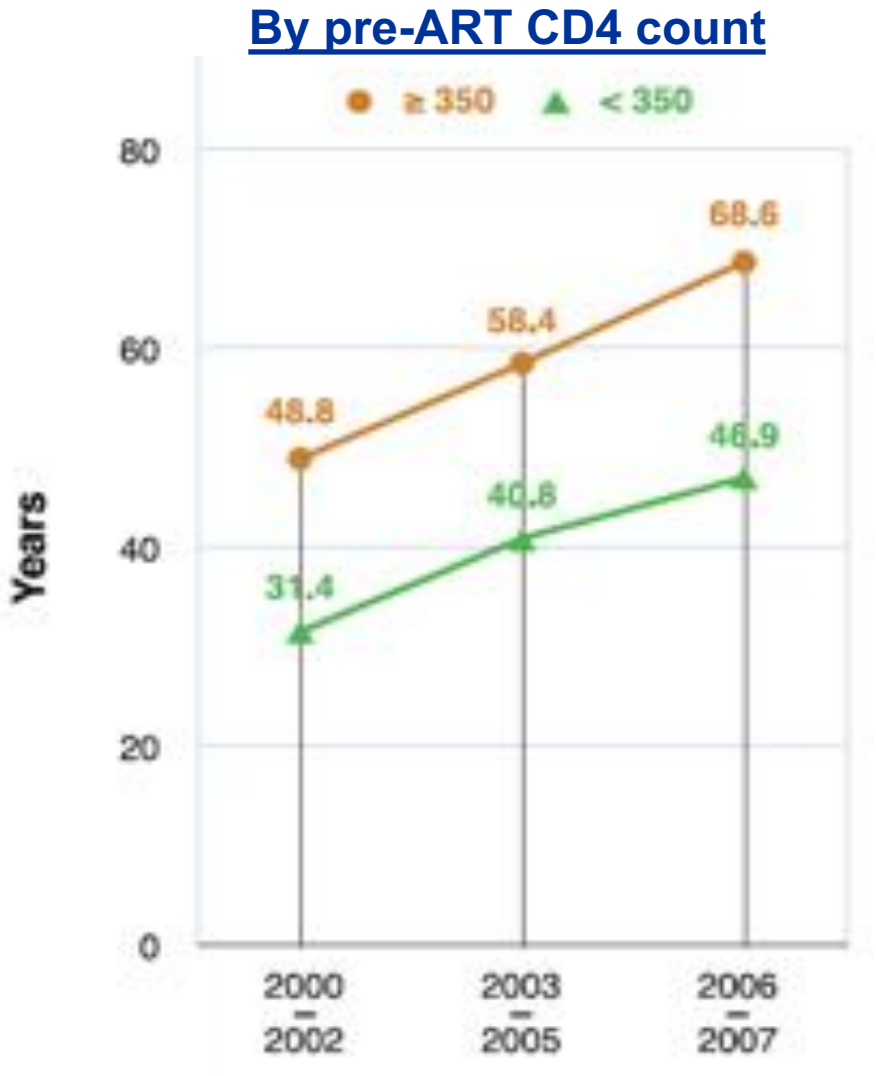
Even in those with high CD4 nadirs



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

Marcus et al, JAMA Network Open 2020

Life Expectancy Further Reduced By Low CD4 Nadir



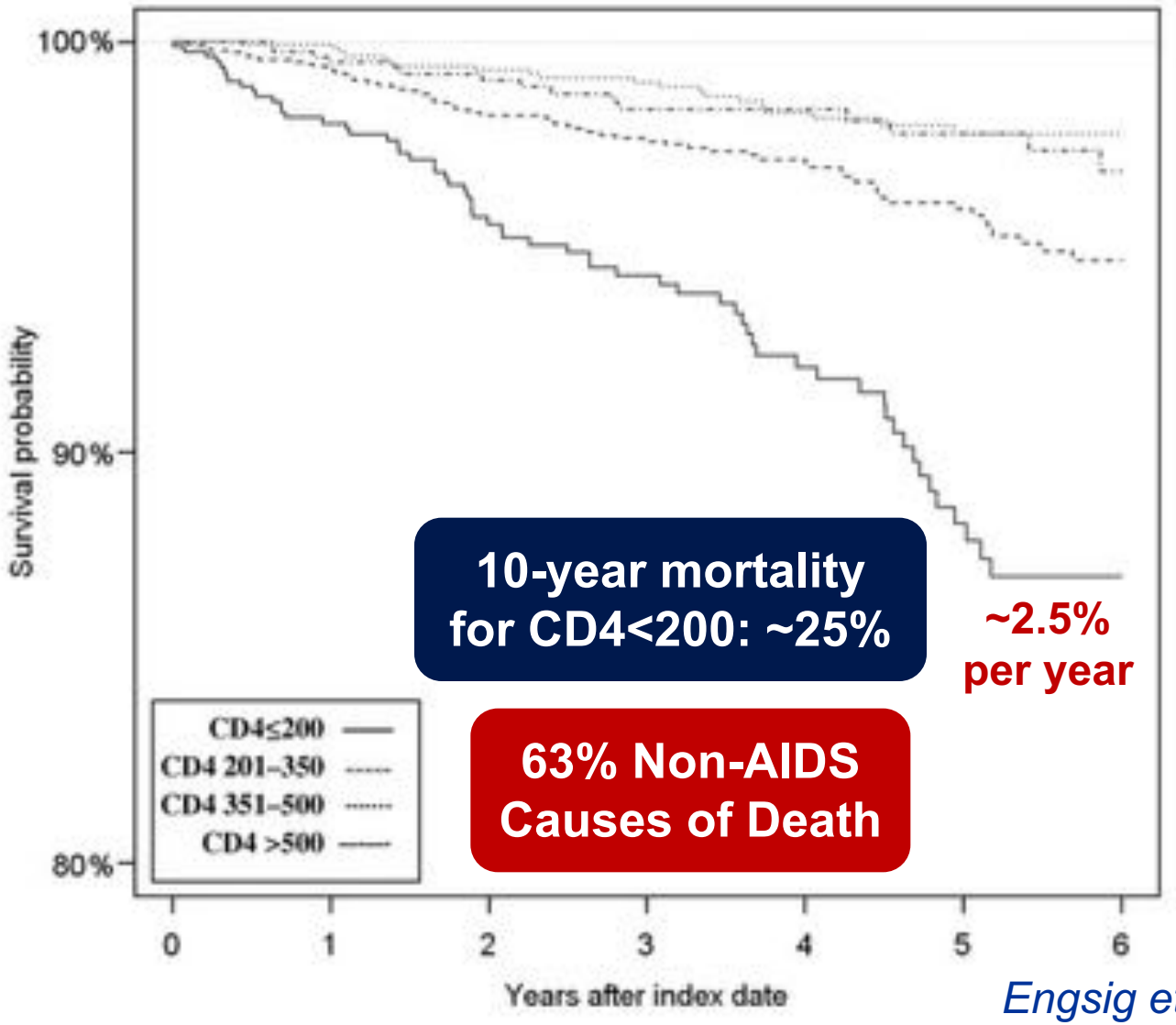
- 20-year reduction in life expectancy with CD4 nadir <350
- Of ~20 million people on ART globally, vast majority started ART at CD4 <350.

*For 20-year old initiating ART

Samji for NA-ACCORD, PLoS One, 2013

Mortality Even Higher in Those with Poor CD4 Recovery during ART

ART-CC and COHERE



CD4 after 3y ART

>500

351-500

200-350

≤200

(15% of cohort)

Engsig et al, CID, 2014

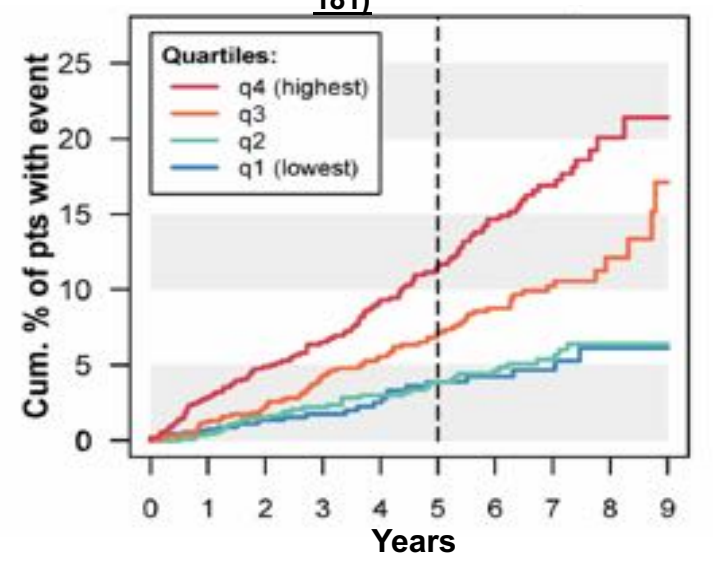
Many age-associated morbidities are increased in treated HIV

- Cardiovascular disease [1-3]
- Cancer (non-AIDS) [4]
- Bone fractures / osteoporosis [5,6]
- COPD [12]
- Liver disease [7]
- Type 2 Diabetes [8]
- Cognitive decline [9]
- Non-AIDS infections [10]
- Intermediate-Stage 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 a. 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

Inflammation Strongly and Durably Predicts Morbidity / Mortality in Treated HIV Infection
(IL-6 + D-dimer Score)

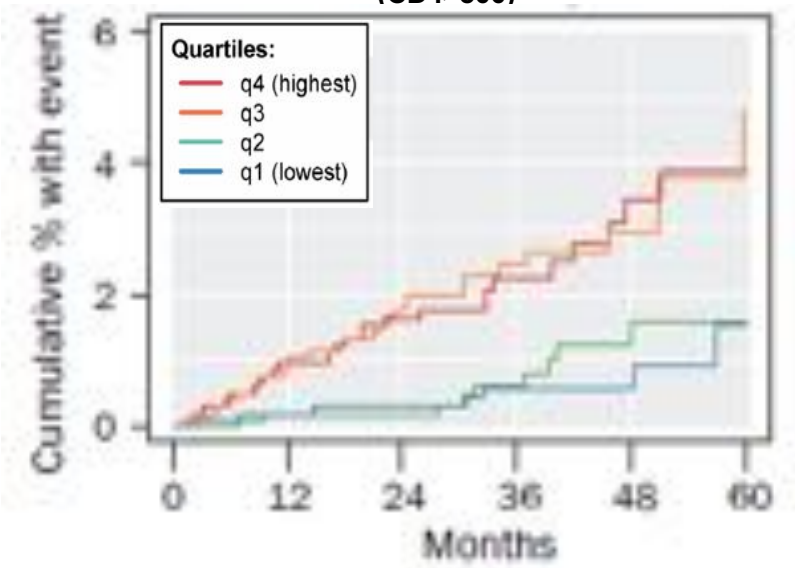
SMART / ESPRIT / SILCAAT
(Median Current CD4: 500; Nadir: 181)



HR: 1.64 per 2-fold increase

Even in those starting ART early…

START
(CD4>500)



HR: 1.61 per 2-fold increase

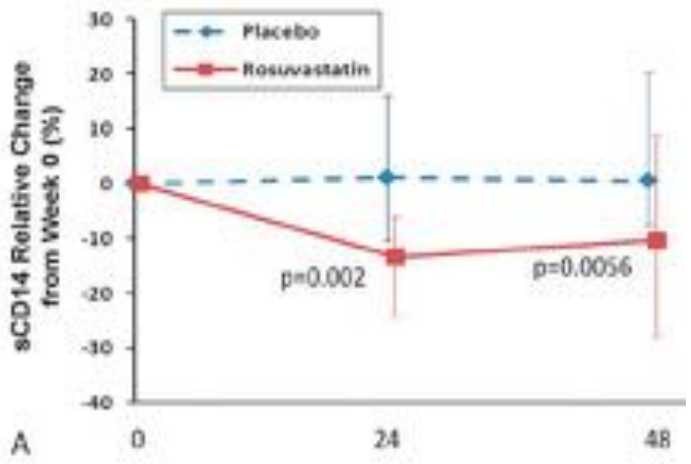
Grund, PLoS One, 2016; Baker, OFID, 2017; see also: Ledwama, PLoS One, 2012

insight

How can we target the inflammatory state?

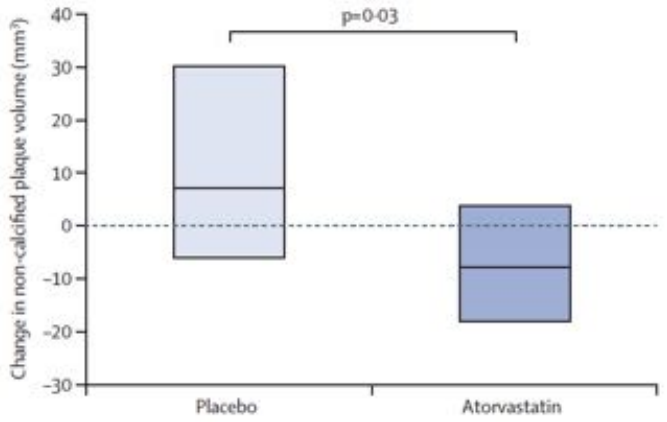
Statins Decrease Immune Activation and Aortic Plaque in Treated HIV Infection

sCD14 Declines with Rosuvastatin



Funderburg/McComsey, JAIDS, 2015

Plaque Regression with Atorvastatin



Lo/Grinspoon, Lancet HIV, 2015

Press Release Yesterday!

- 7,769 adults (40-75) with treated HIV, low-mod CVD risk
  - Pitavastatin 4mg vs placebo x 6 years (stopped early)
  - Primary outcome: MACE (CV death, MI, unstable angina, stroke/TIA, arterial revascularization)
- Pitavastatin **decreased MACE by 35%**
- Not in press release:
  - Time to MACE and/or death (may be **~20% reduction**)
  - Incident T2DM (may be modest increase)
  - Secondary endpoints including non-AIDS cancers, AIDS events, renal, liver events.
- This is major news and is likely to change treatment guidelines.
- But… There is still much we don't know and I doubt statins will be all that we will need…

Caveats

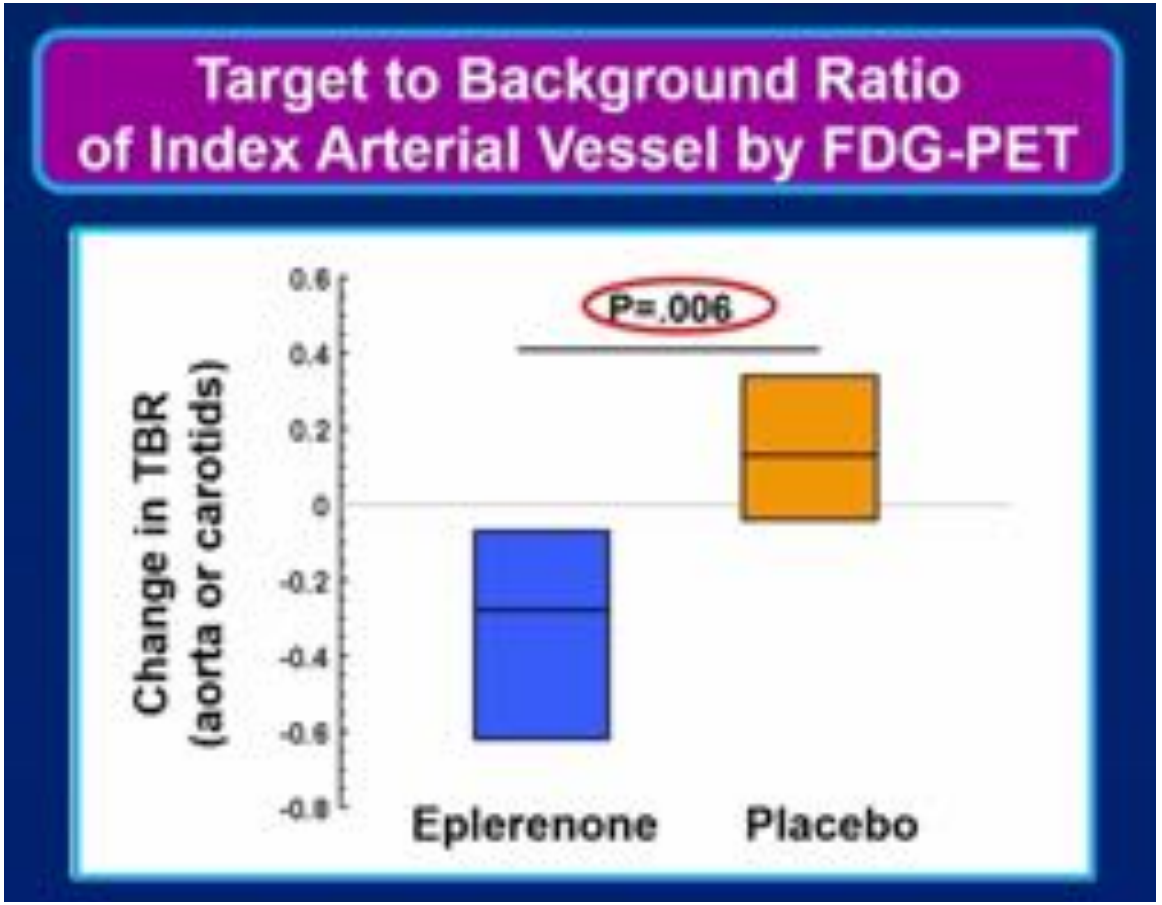
- In a pooled analysis of all primary prevention trials in people without HIV, statins reduced MI by **28-33%** (USPSTF, JAMA 2022)
  - Nearly identical to effect in REPRIEVE
- In JUPITER, in those with low-mod CVD risk, but high hsCRP, rosuvastatin decreased MI by **47%** (Ridker, NEJM 2008)
  - Stronger effect than seen in REPRIEVE, though rosuvastatin may be higher intensity than pitavastatin
- Unclear thus far if statins will decrease other non-AIDS events in PWH
- Type 2 Diabetes will remain an important complication in HIV
- Not clear that statins reverse all the HIV-associated inflammatory pathways.

Eplerenone (Aldosterone Receptor Inhibitor) Decreases Vascular Inflammation and Improves Myocardial Function in Treated PWH

Also Improved:
-LV End Diastolic Volume
-Global strain
-Stress Myocardial Blood Flow

Unclear if these represent greater effects in PWH

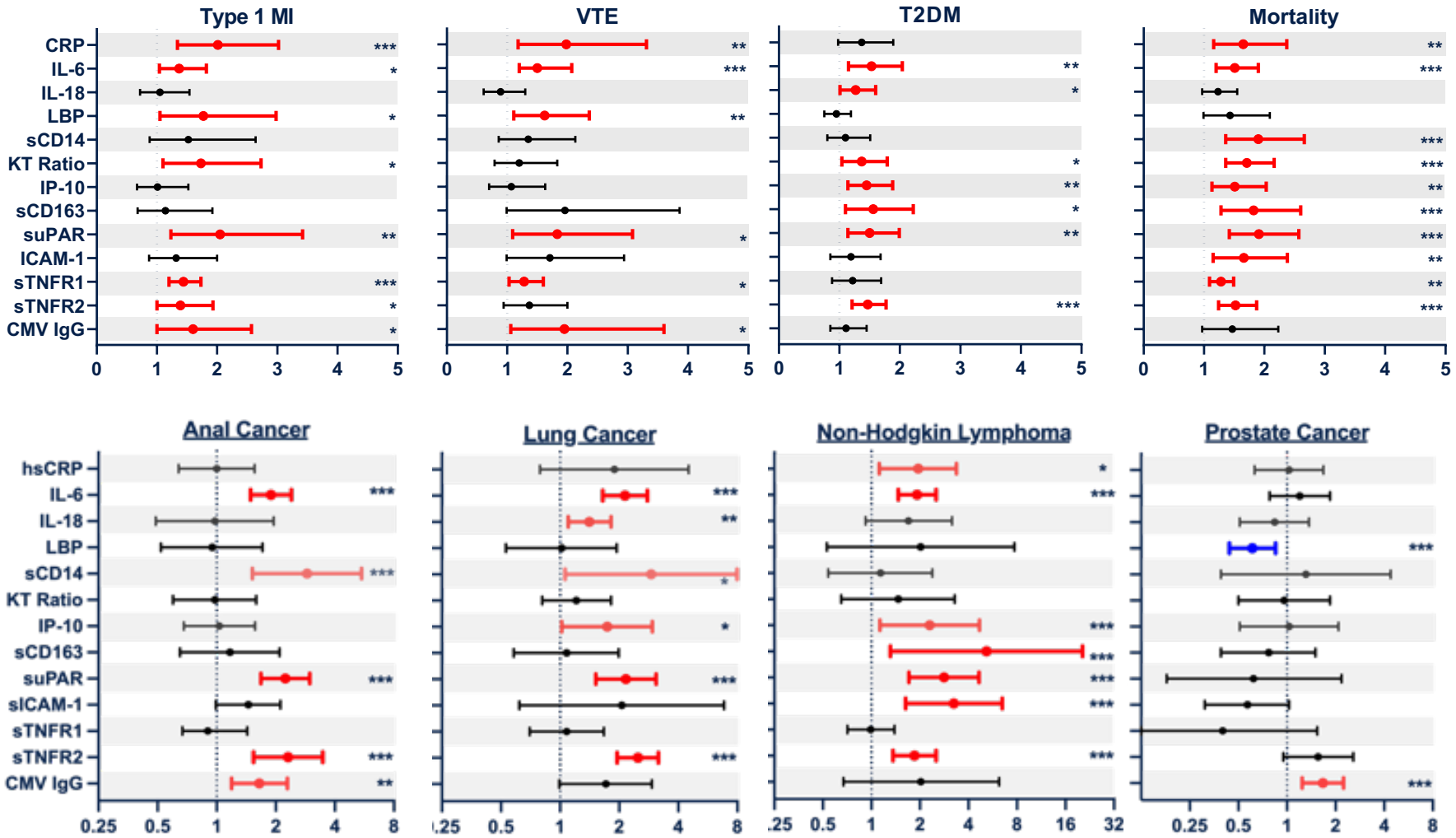
Not yet clear if all relevant immune activation pathways decreased



Srinavasa et al, #144

Developing an ”Atlas” of Inflammatory Predictors of Age-related Morbidities in Treated HIV

CNICS Case-Cohort Study



Adjusted for: age, natal sex, IDU history, ASCVD score, nadir CD4 (and BMI, statin for T2DM; smoking for cancers)

Schnittman et al, CROI 2021, Abstract #98; Alba et al, CROI 2022, Abstract #36; Schnittman et al, CROI 2022, Abstract #552

Is Inflammation Like a Tree?

Branches

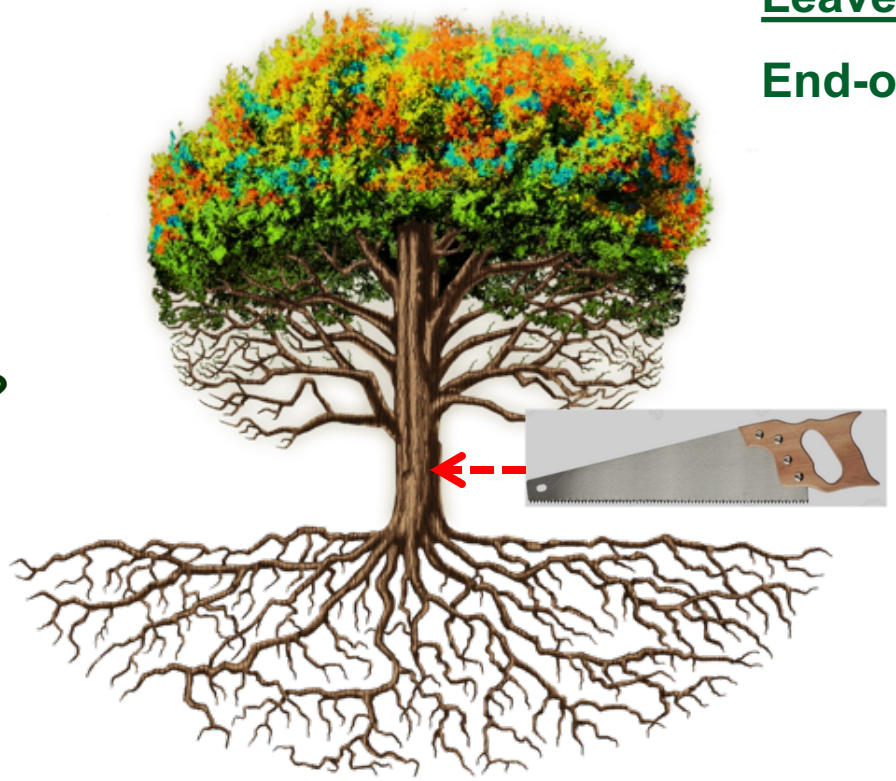
Adaptive immune fn
TNFa
D-dimer
Lymphoid fibrosis

Trunk

IL-1b (canakinumab)?
IL-6 (tocilizumab)?
mTOR (sirolimus)?

Roots

HIV reservoirs
CMV
Microbial translocation



Leaves

End-organ diseases

Justice, Hunt, Tracy, JID, 2018

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

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

Low-dose Methotrexate Fails to Reduce Inflammation or Vascular Dysfunction in HIV

ACTG 5314, N=176

Reduced:

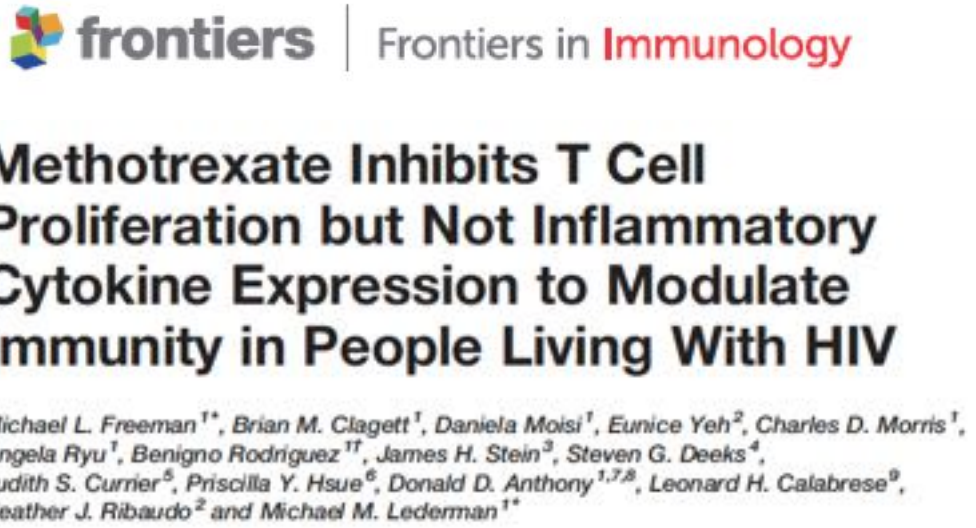
-CD4 and CD8 counts

No effect on:

-Flow-mediated dilatation

-Inflammatory markers:

IL-6, CRP, D-dimer, IP-10, sCD163, sCD14, sVCAM-1



frontiers | Frontiers in Immunology

Methotrexate Inhibits T Cell Proliferation but Not Inflammatory Cytokine Expression to Modulate Immunity in People Living With HIV

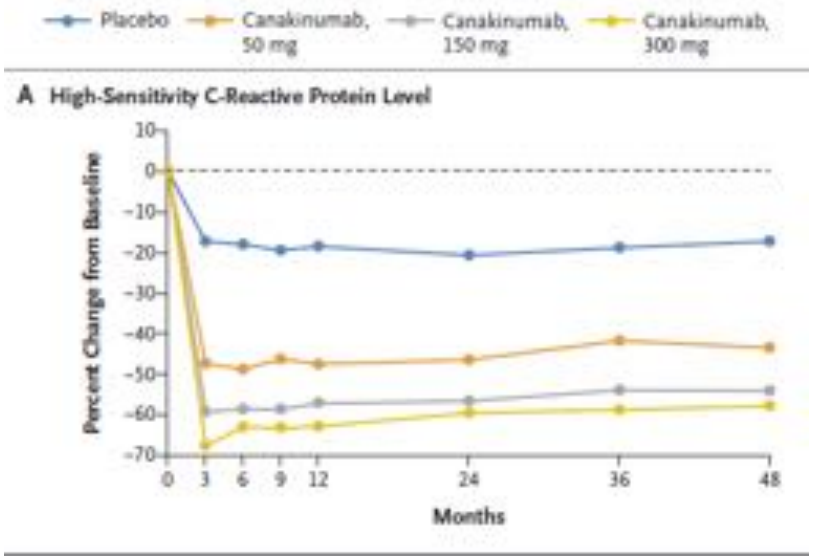
Michael L. Freeman[1], Brian M. Clagett[1], Daniela Moisi[1], Eunice Yeh[2], Charles D. Morris[1], Angela Ryu[1], Benigno Rodriguez[1†], James H. Stein[3], Steven G. Deeks[4], Judith S. Currier[5], Priscilla Y. Hsue[6], Donald D. Anthony[1,7,8], Leonard H. Calabrese[9], Heather J. Ribaudo[2] and Michael M. Lederman[1*]*

(Hsue, CID, 2019; Freeman, Frontiers Immunol, 2022)

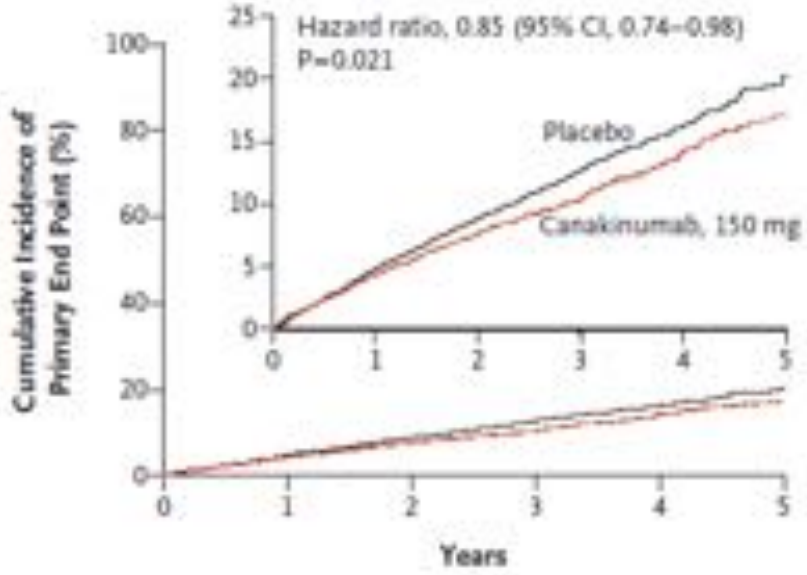
CANTOS: IL-1b Inhibitor Canakinumab Decreases CAD Events and Cancer Death

HIV-negative People with CAD

Canakinumab reduces hsCRP



Canakinumab reduces CAD Events



Proof that inflammation causes disease risk

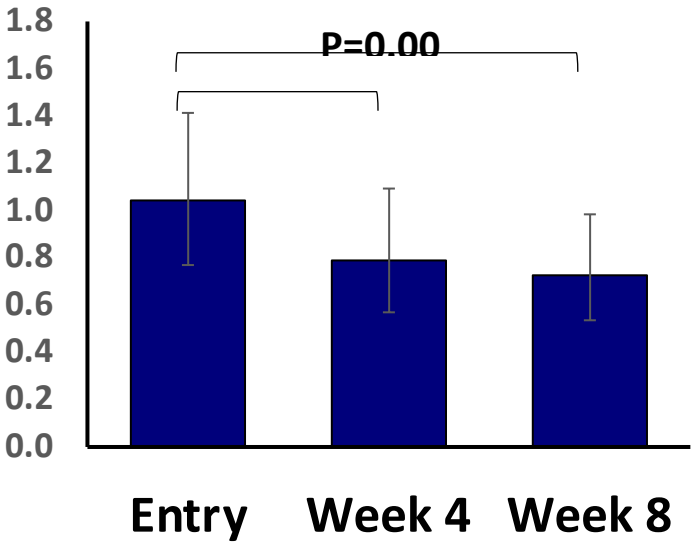
↑ Death from Sepsis

Ridker, NEJM, 2017

IL-1b Inhibition with Canakinumab* Appears to Reduce Inflammation in Treated HIV

(N=10 Uncontrolled Pilot Study)

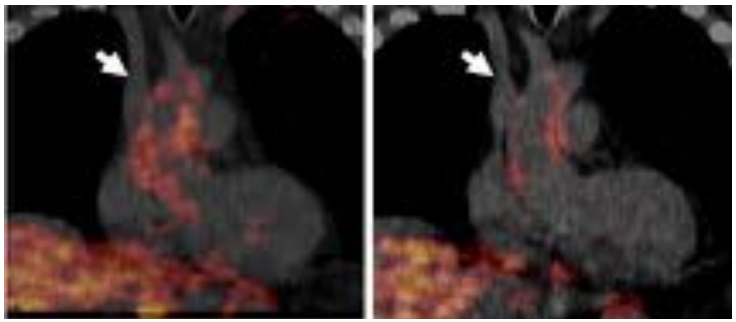
Plasma IL-6 (pg/ml)



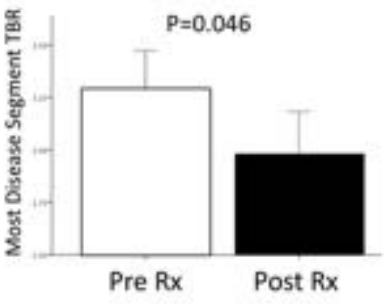
A 30% ↓ in IL-6 associated with a 25% ↓ odds of Non-AIDS event (Tenorio, JID 2014)

**Single subcutaneous dose of 150mg*

Aortic Inflammation



Pre-canakinumab Post-canakinumab



Concerns?

No effect on T cell activation.

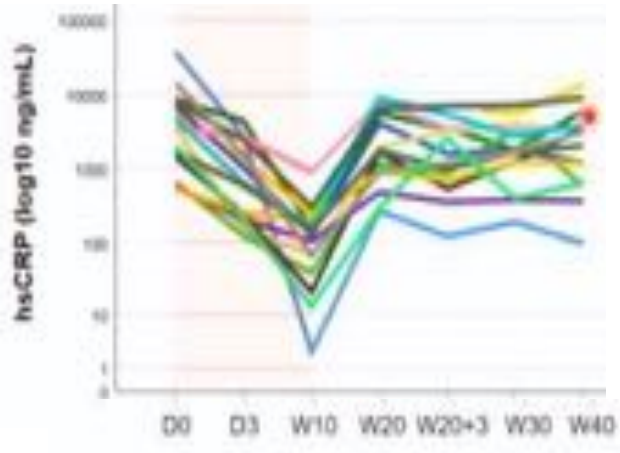
Other pathways affected?

Infection risk?

Hsue, JACC, 2018

IL-6 Receptor Inhibition with Tocilizumab Reduces Inflammation in Treated HIV

Plasma hsCRP



Immune Activation

Activity	Est. effect	P-value
sCD14	⬇ -312 ng/mL	0.01
sCD40L	⬇ -608 pg/mL	<0.01
sTNFR1	⬇ -115 pg/mL	0.02
D-dimer	⬇ -42 ng/mL	0.02
sTNFR2	-86 pg/mL	0.48
sCD163	70 ng/mL	0.06
IP10	⬆ 33 pg/mL	0.04
IL-22	-0.7 pg/mL	0.84
I-FABP	416 pg/mL	0.27
Zonulin	-2.7 ng/mL	0.07

Concerns?

Some pathways appeared to worsen.

Atherogenic lipid levels increased.

Unclear effects on gut barrier (gut study pending)

Infection risk?

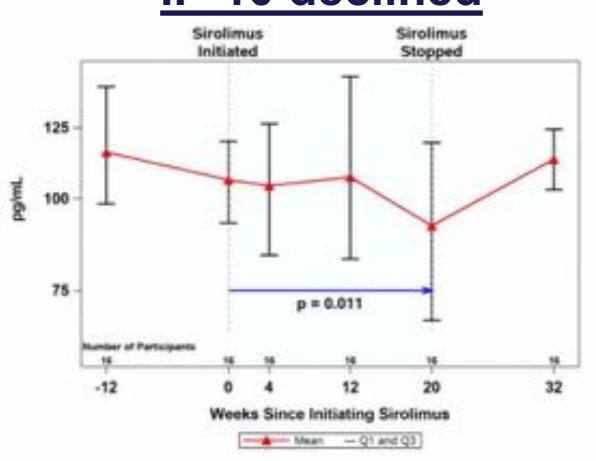
Rodriguez, CROI 2020, #113

mTOR Inhibition with Sirolimus Reduces T cell Proliferation but Increased Inflammation in Treated HIV

Potentially Beneficial Changes

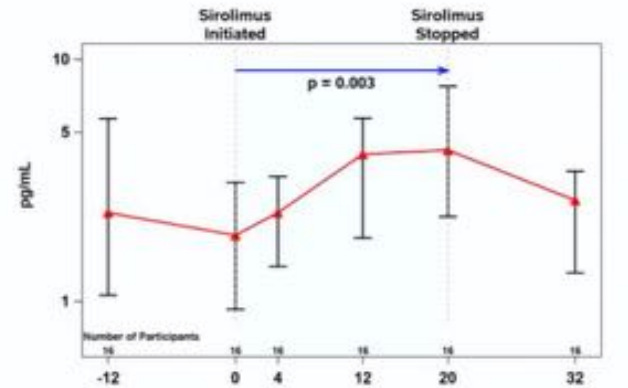
- ↓ T cell exhaustion (PD-1)
- ↓ T cell proliferation (Ki67)
- ↓ HIV DNA levels

IP-10 declined

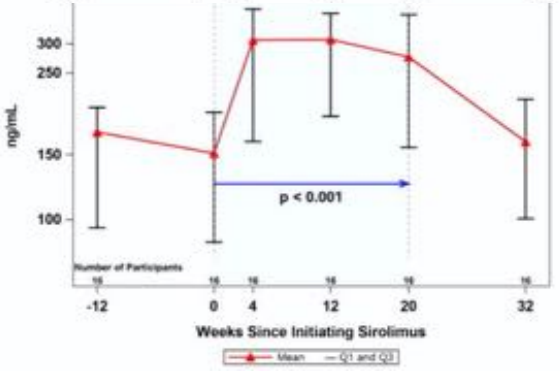


Concerning Changes

IL-6



D-dimer



Henrich, CROI 2019, #131

Perhaps inflammation in treated HIV is like a Banyan Tree?

In **autoimmune diseases**, the immune system is responding *inappropriately* to the host.

The problem = immune system

In **treated HIV**, the immune system is responding *appropriately* to several abnormal root drivers of inflammation.

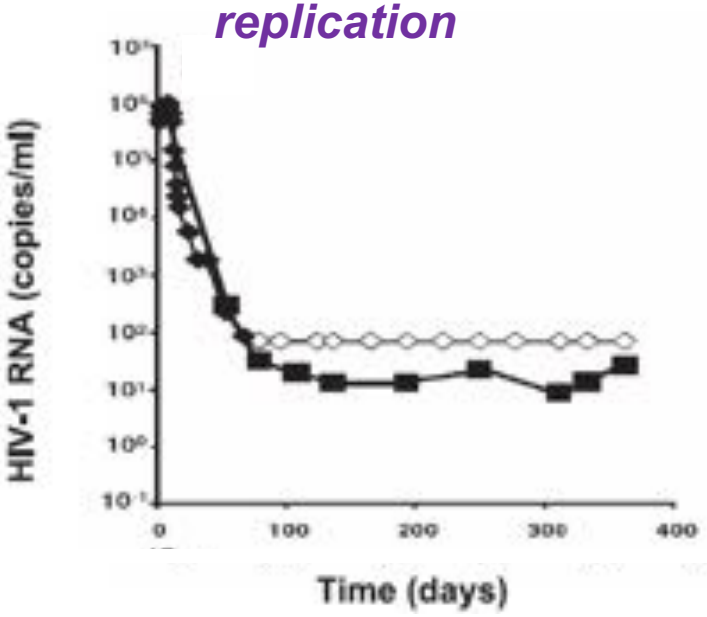
The problem = root drivers

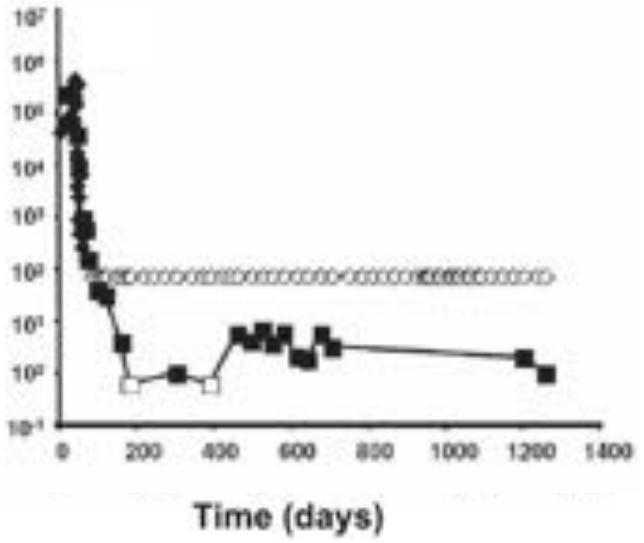
-HIV reservoirs
-Microbial Translocation
-CMV

HIV Reservoirs Established in First Week of Infection and Continue to Release Virus on ART

Mostly reflects release of virus from infected cells without productive replication

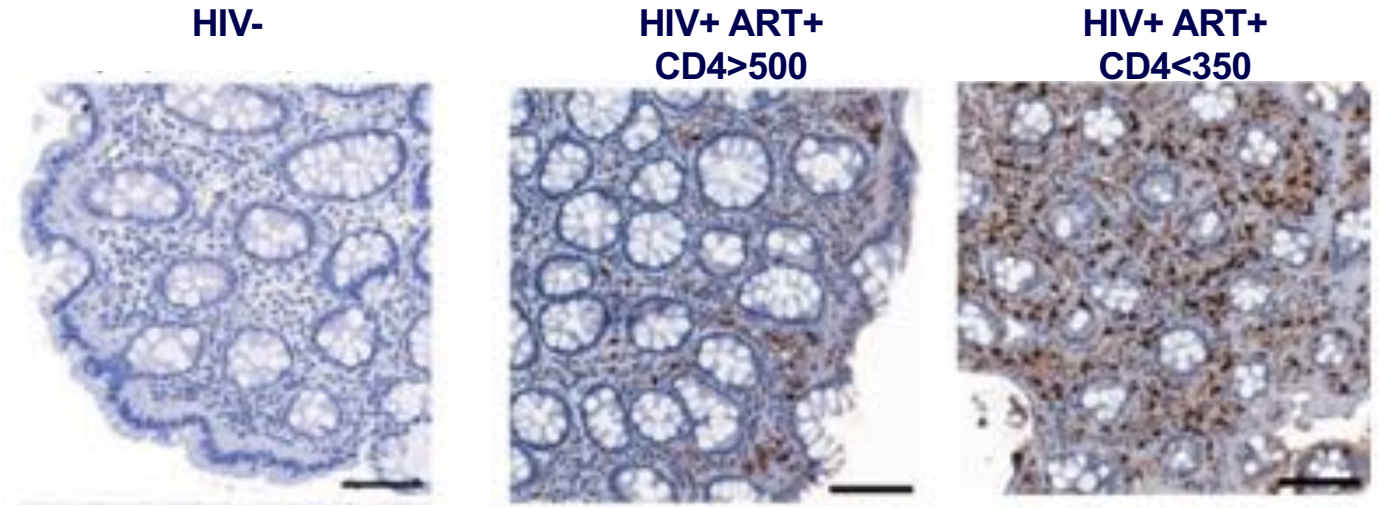
We lack interventions that block HIV expression.





Maldarelli F. *et al., PLOS Path*, 2007; Palmer S. et al, *PNAS*, 2008.

Microbial Translocation Persists on ART
Particularly in Those with Low CD4 Nadirs and Poor CD4 Recovery

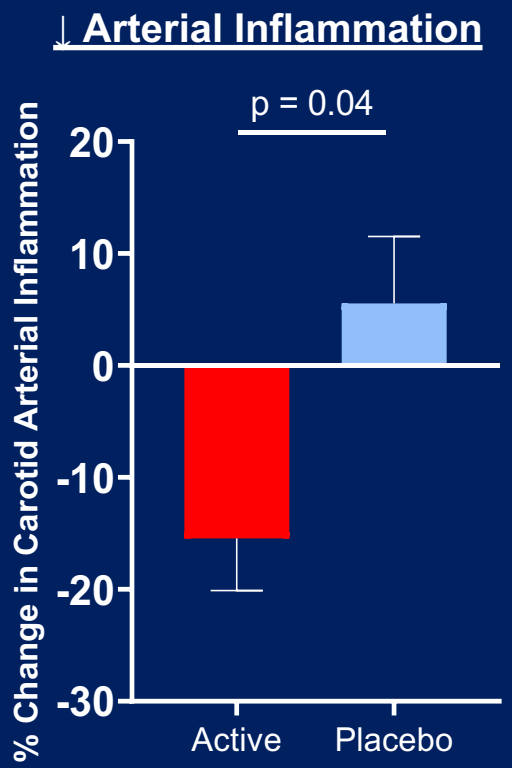


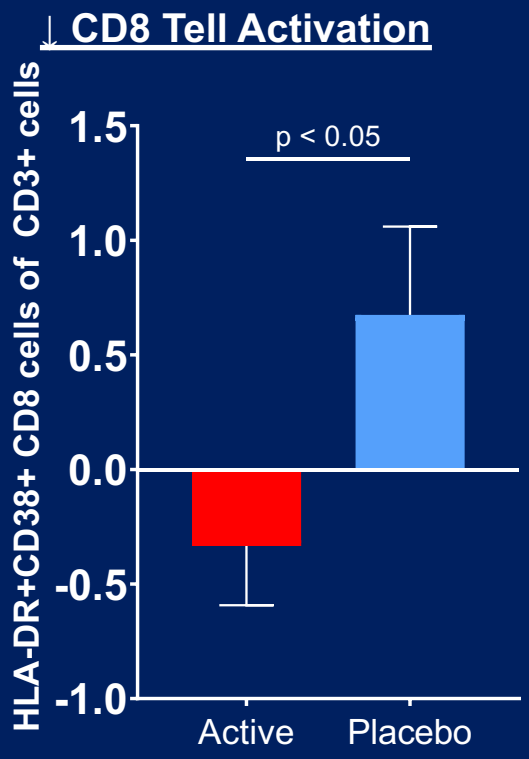
Persistent neutrophil infiltration in rectal mucosa during treated HIV infection in response to mucosal barrier breach

Interventions to reduce microbial translocation have been unsuccessful to date (sevelamer, rifaximin, mesalamine, probiotics).

Somsouk, AIDS, 2014 (also Marchetti, AIDS, 2008; Jiang et al, JID, 2009)

Improving Gut Barrier Function with GLP2 Agonist Teduglutide Decreased Immune Activation

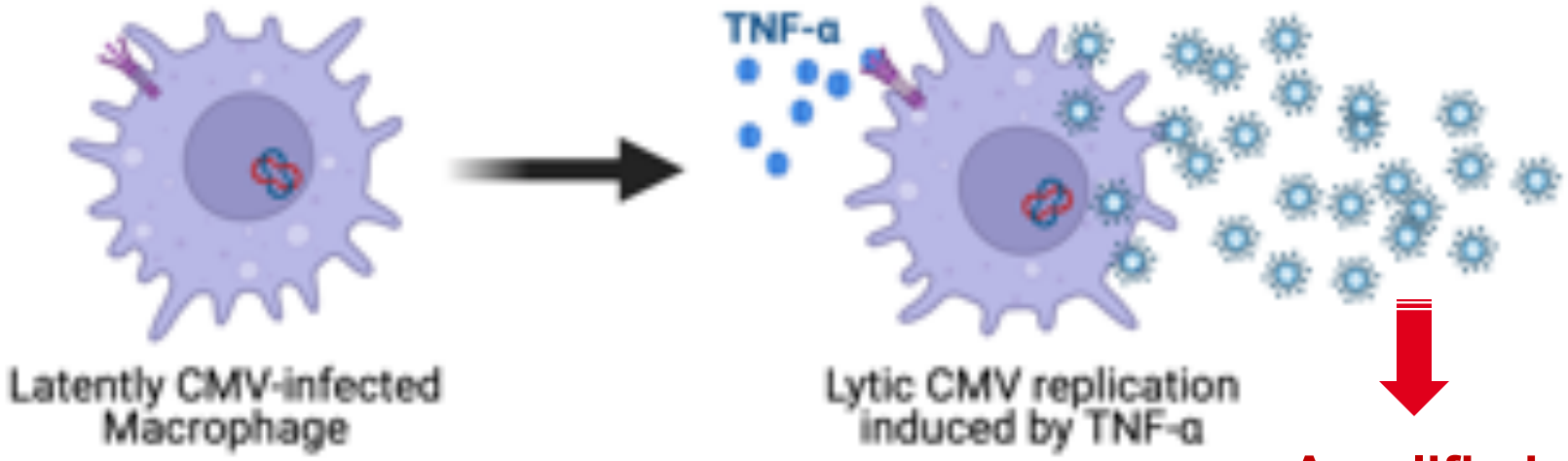




Lots of tolerability issues (bloating, etc), but first proof-of-concept that improving gut barrier function might reduce immune activation.

Lo et al, CROI 2022, #134

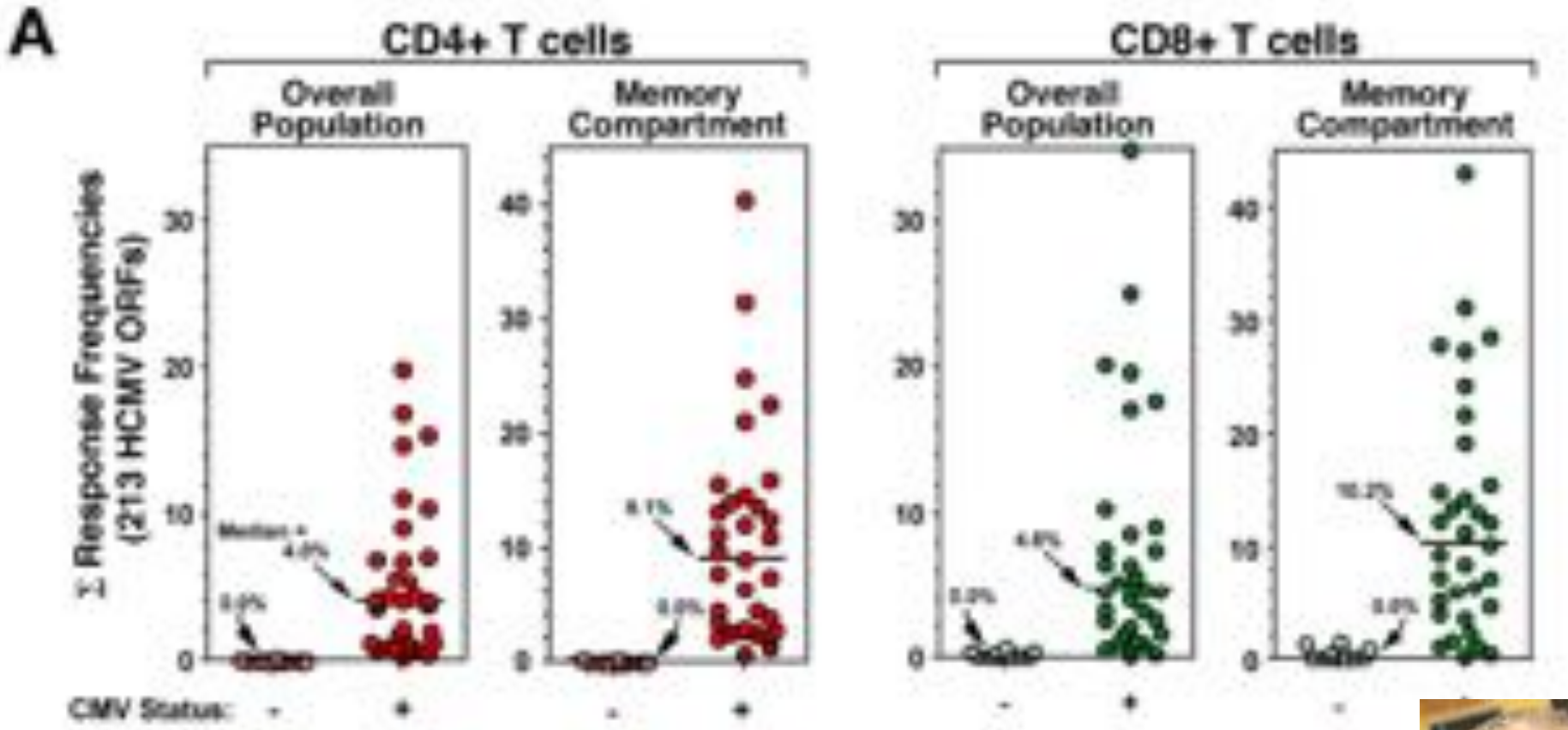
CMV as an Amplifier of Inflammation



Amplified Inflammation
(but also vIL-10)

Forte et al, mBio 2018

CMV elicits massive immune responses even in asymptomatic HIV- individuals

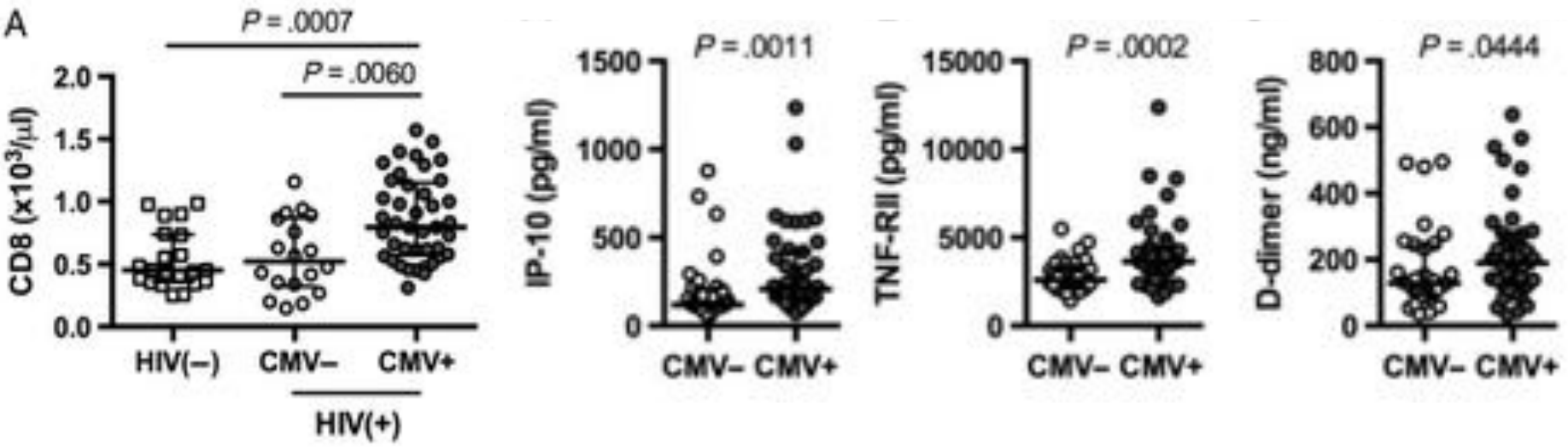


Sylwester/Picker, JEM, 2005

Louis Picker, MD
OHSU

CMV Causes CD8 Expansion and Inflammation in HIV Infection

CD8+ T Cell Counts | **IP-10** | **sTNF-RII** | **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

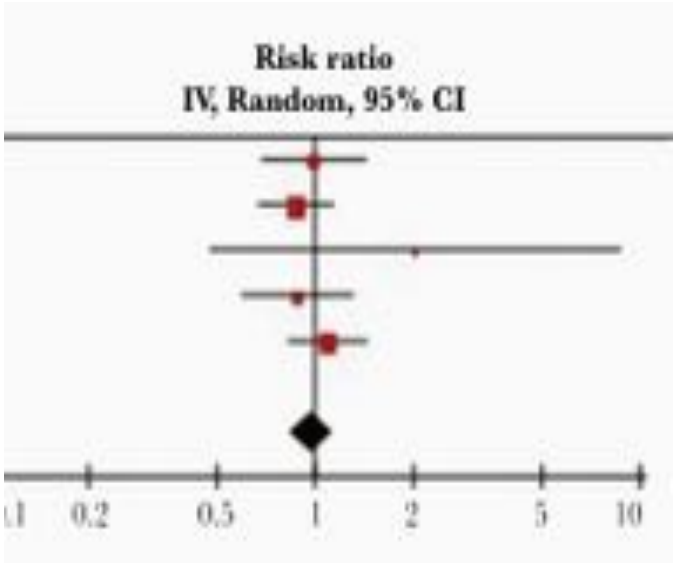
Freeman, JID, 2014 (see also: Sacre, AIDS, 2011; Mudd, JID, 2016; Musselwhite, AIDS 2011)

Cardiovascular Effects of CMV in People without HIV

Inflammation and Immunosuppression Likely Key

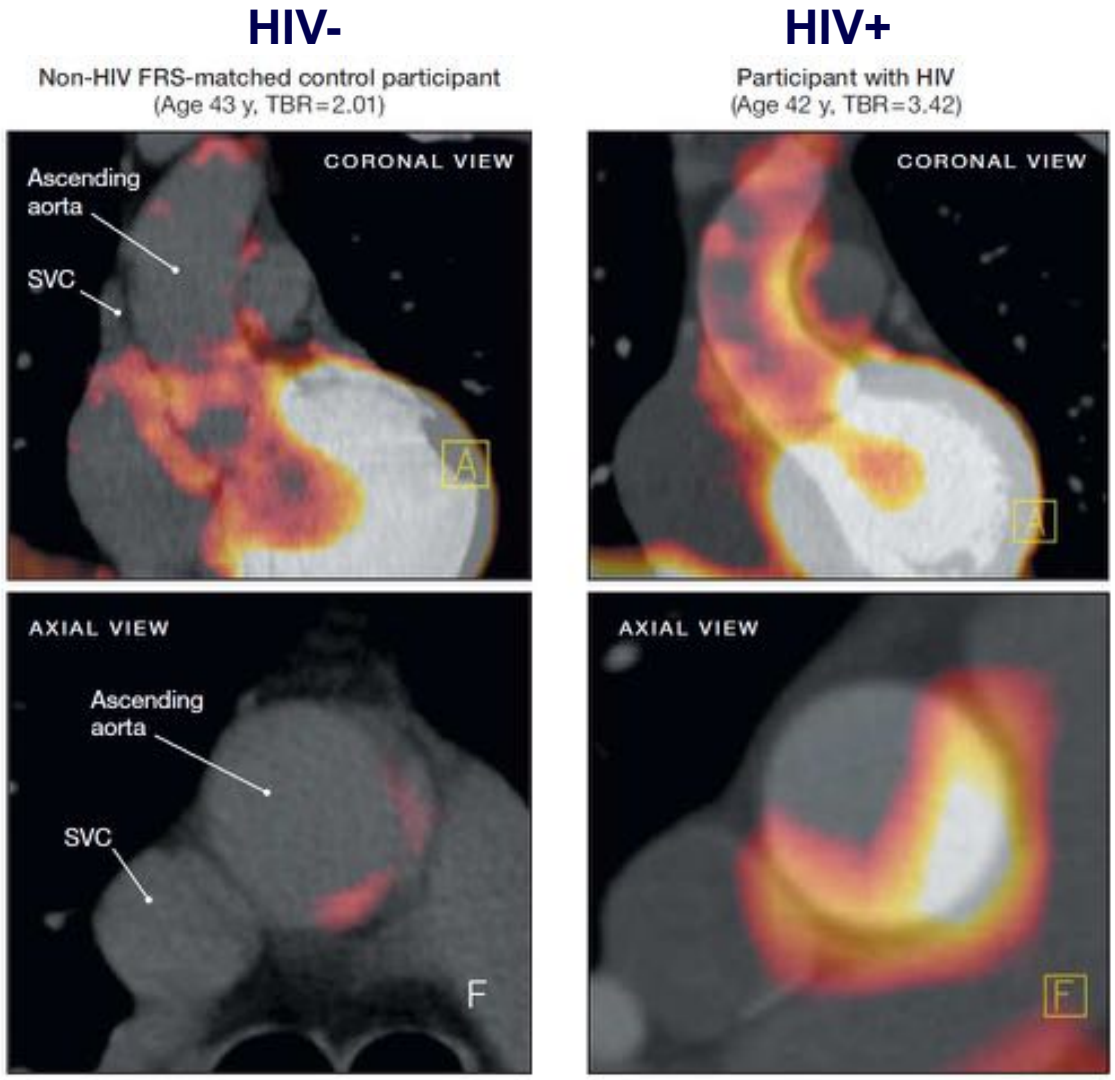
- CMV replicates in vascular endothelium
- 82% of carotid plaques from endarterectomy CMV DNA+(Nikitskaya, JAHA, 2016).
- In MI patients without HIV, 78% had CMV DNA detectable in plasma (Nikitskaya, JAHA, 2017).
- CMV IgG+ predicts ↑ mortality in ACS patients with **elevated IL-6** during MI (Blankenburg, Circulation, 2001).
- CMV prophylaxis with ganciclovir appears to decrease **transplant vasculopathy** (Valantine, Circ, 1999)

CVD Mortality Meta-Analysis



Chen, JID, 2021

Increased Arterial Inflammation in HIV

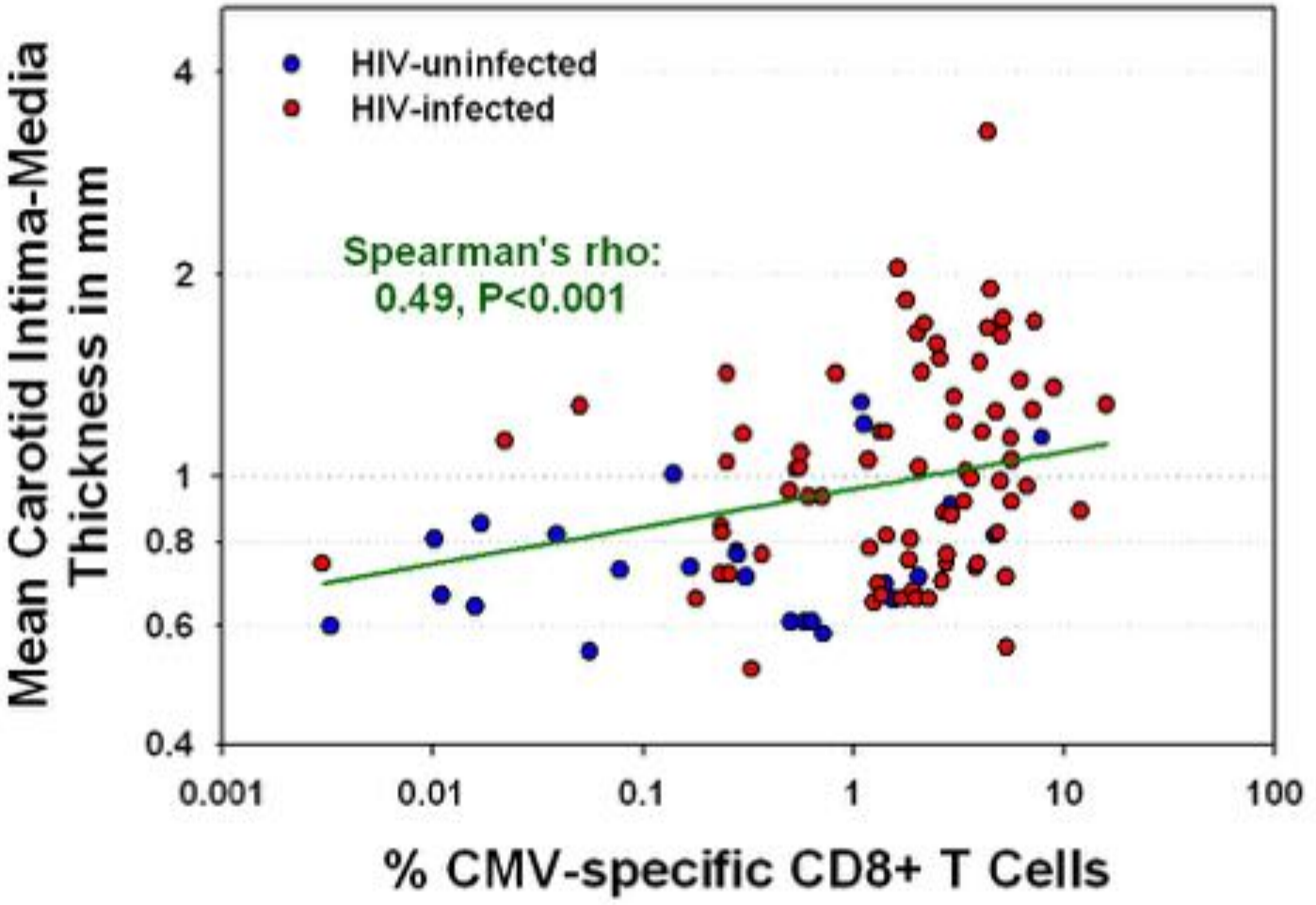


Ahmed Tawokol, MD

Aortic Inflammation associated with ↑sCD163 levels (monocyte/macrophage activation)

Subramanian/Grinspoon, JAMA, 2012

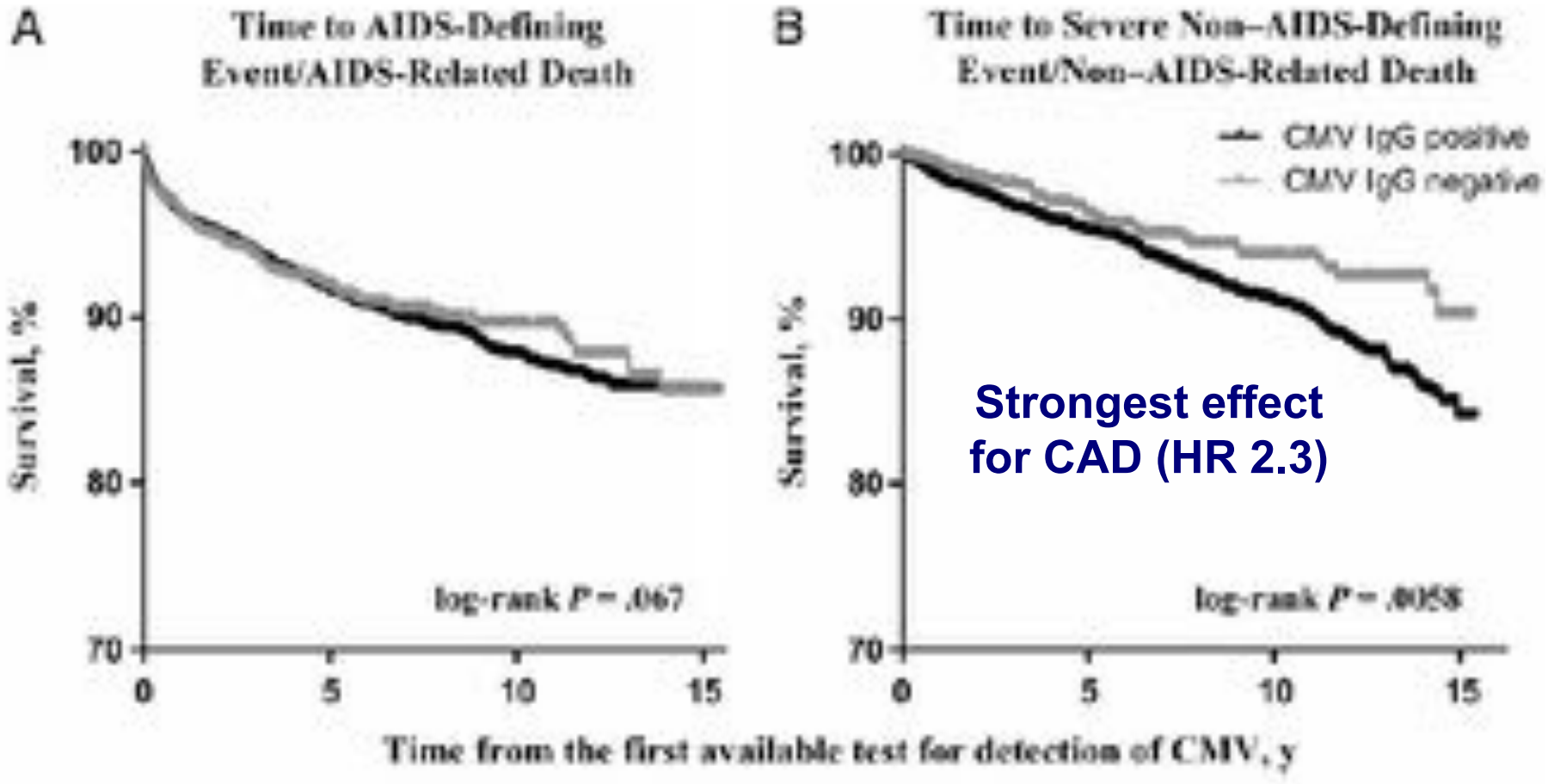
Higher CMV-specific CD8 IFN-g Production Associated with More Atherosclerosis



Priscilla Hsue, UCSF

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

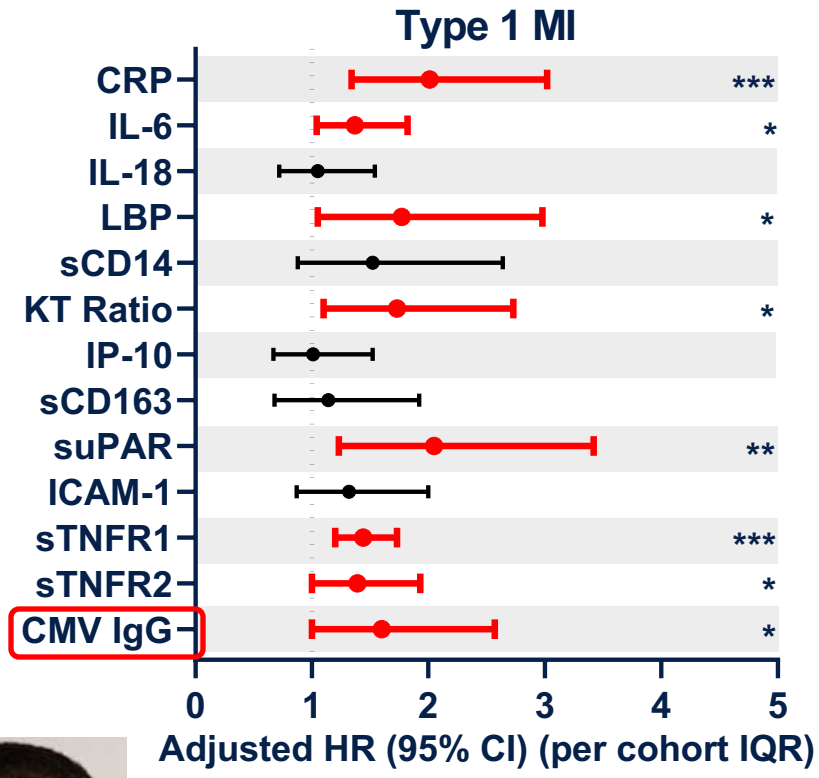
CMV Sero-status Predicts Non-AIDS Events (and less so AIDS…): ICONA Cohort

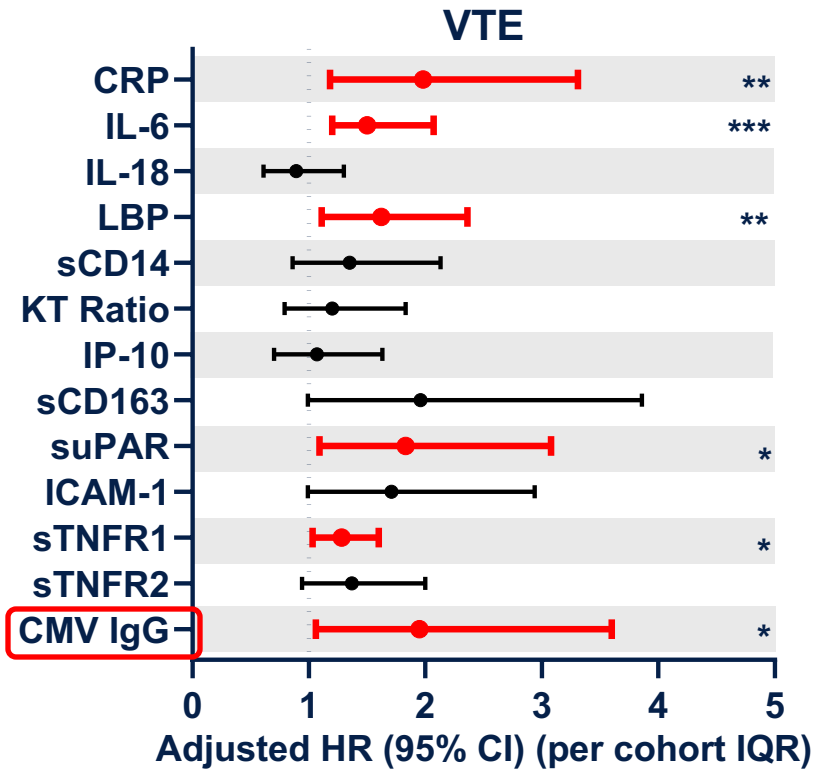


Strongest effect for CAD (HR 2.3)

Lichtner et al, JID, 2015 (see also Hsue, AIDS, 2006)

Higher CMV IgG Titer Also Predicts Type I MI and Venous Thromboembolism in Treated HIV

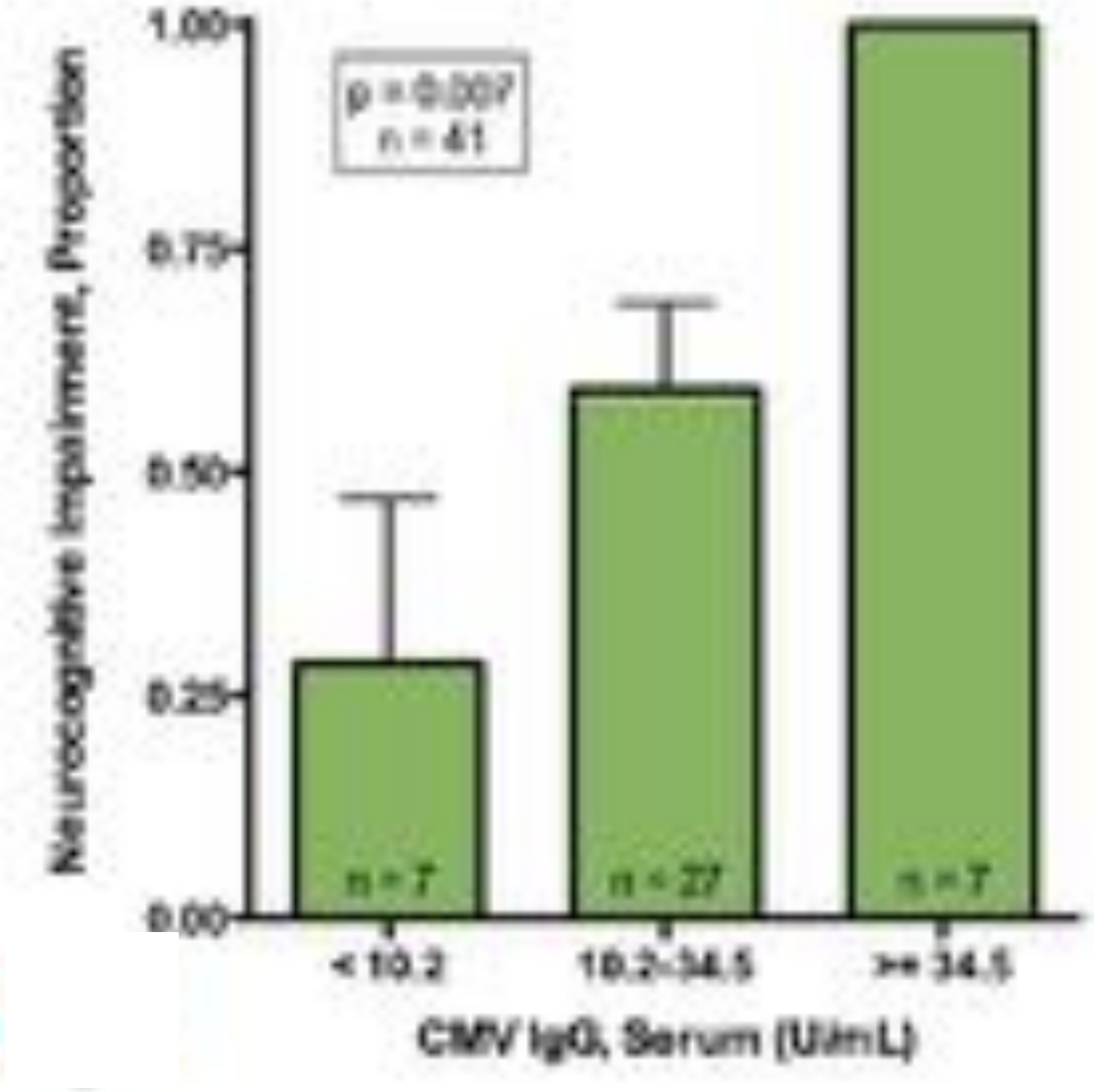




Sam Schnittman, MD
UCSF Medical Resident
Current Harvard ID Fellow

Schnittman et al, CROI 2021, #98

CMV IgG Titer Associated with Neurocognitive Impairment in Treated HIV Infection



Similar relationship seen in elderly HIV-populations (Vescovini, JI, 2010)

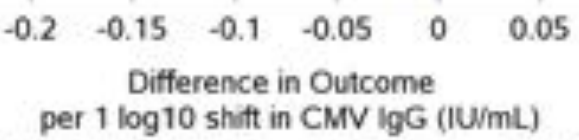
Scott Letendre, MD
UCSD

Letendre, CID, 2018

Higher CMV IgG Titers Associated with Impaired Physical Function and Frailty in PWH

REPRIEVE substudy

Outcome	N	Estimate	95% CI	P-value
Composite MSPPB				
Unadjusted	161	-0.08	(-0.14, -0.01)	0.025
Adjusted	155	-0.09	(-0.15, -0.02)	0.008
Chair Rise (cMSPPB)				
Unadjusted	161	-0.05	(-0.08, -0.01)	0.006
Adjusted	155	-0.05	(-0.08, -0.01)	0.005
Gait Speed (cMSPPB)				
Unadjusted	161	-0.04	(-0.07, -0.01)	0.009
Adjusted	155	-0.05	(-0.07, -0.02)	0.002



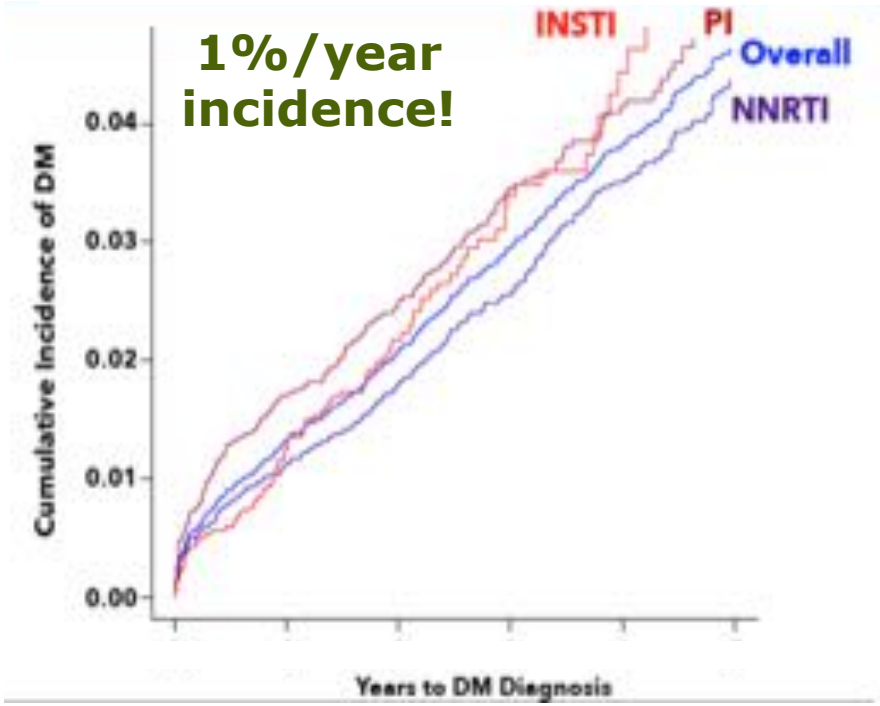
Estimates are from linear regression models with CMV IgG as risk factor and physical function measures as outcomes, unadjusted and adjusted for age, sex, BMI, nadir CD4 and hsCRP.

Kristine Erlandson, MD
U Colorado

Erlandson, poster 697

Might CMV Increase T2DM Risk?

T2DM common in treated HIV



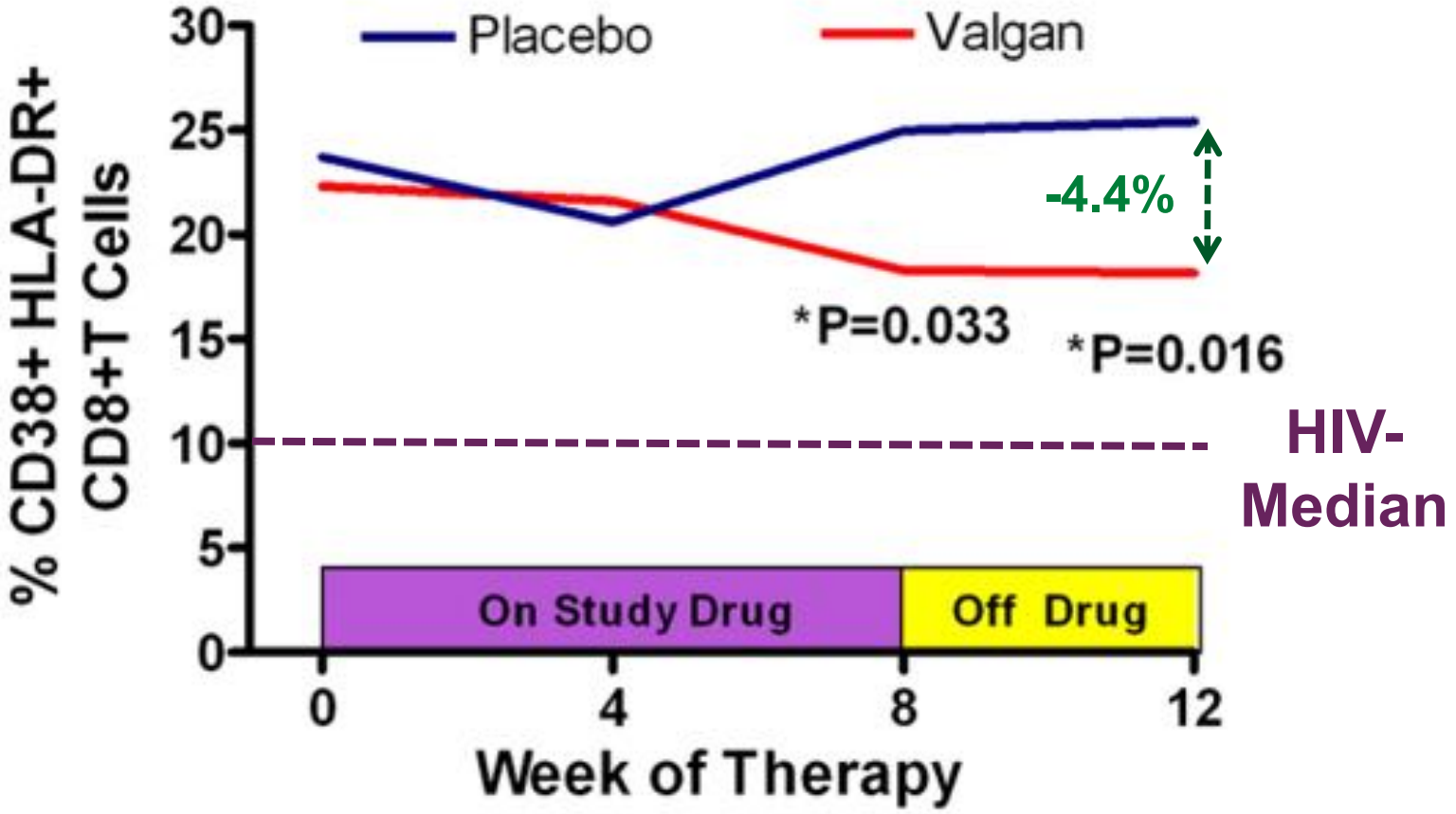
Rebeiro for NA-ACCORD, CID, 2020

Might CMV Play a Role?

- ↑T2DM incidence post solid organ transplant (Shivaswamy, Endocrine Rev, 2016)
- CMV expressed in adipose tissue (Shnayder, mBio, 2018)
- CMV causes adipose tissue inflammation, fibrosis and insulin resistance in mice (Contreras, PLoS Path, 2019)
- ↑Putatively CMV-specific CD8+ T cell infiltration of fat in HIV/SIV (Wanjalla, Front Immunol, 2018)
- ↑Adipose tissue fibrosis in HIV (Couturier, AIDS, 2015)
- CD8 infiltration of adipose tissue and fibrosis precede NASH and insulin resistance in obesity (Nishimura, Nat Med, 2009)

Blocking Asymptomatic CMV Replication with Valganciclovir ↓ Immune Activation

in HIV+ Patients with CD4<350 despite ART

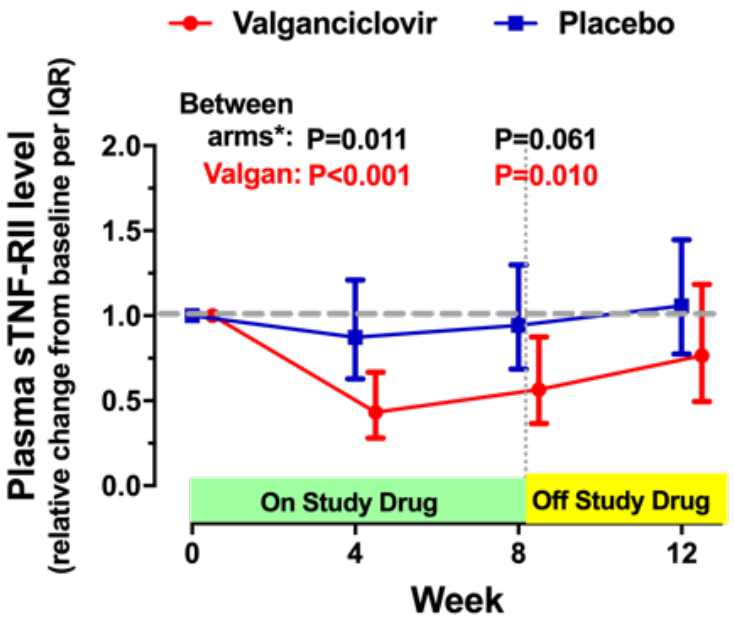


*P for difference in the change from week 0 between valgan- and placebo-treated groups.

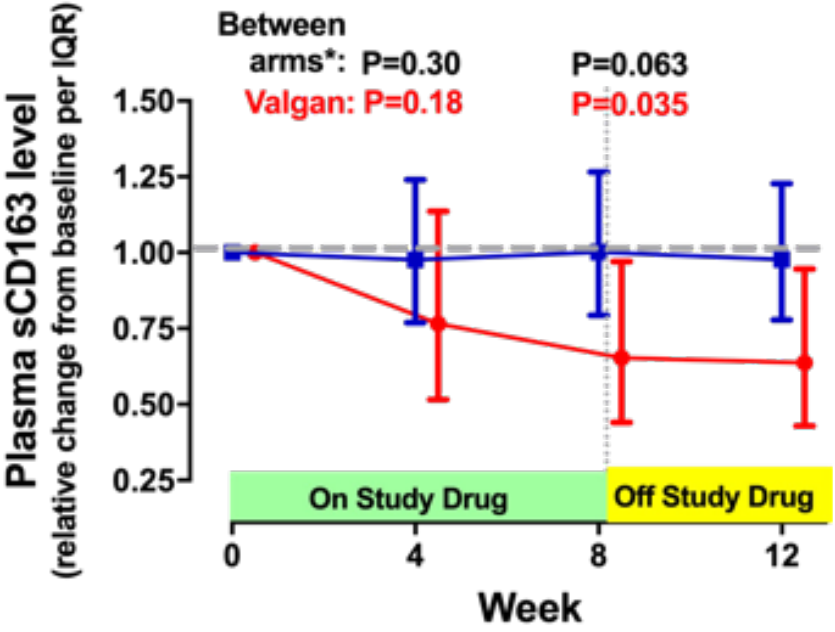
Hunt et al, JID, 2011

Valganciclovir Broadly Decreased Innate Immune Activation in Treated HIV

sTNF-RII



sCD163

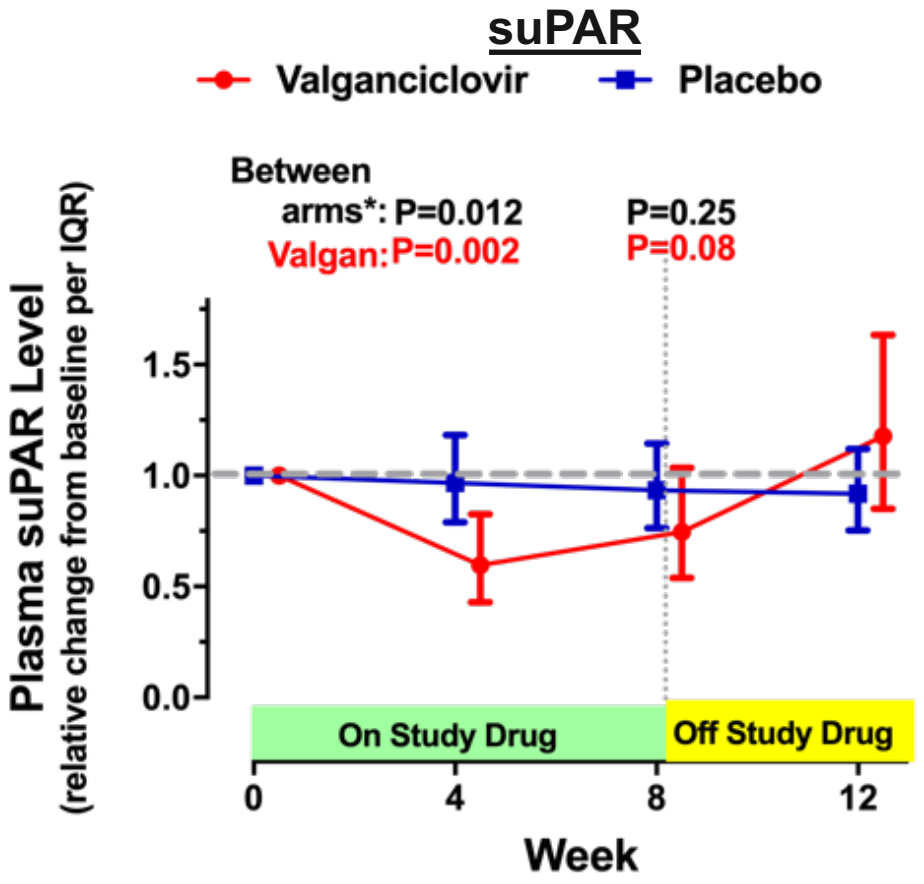


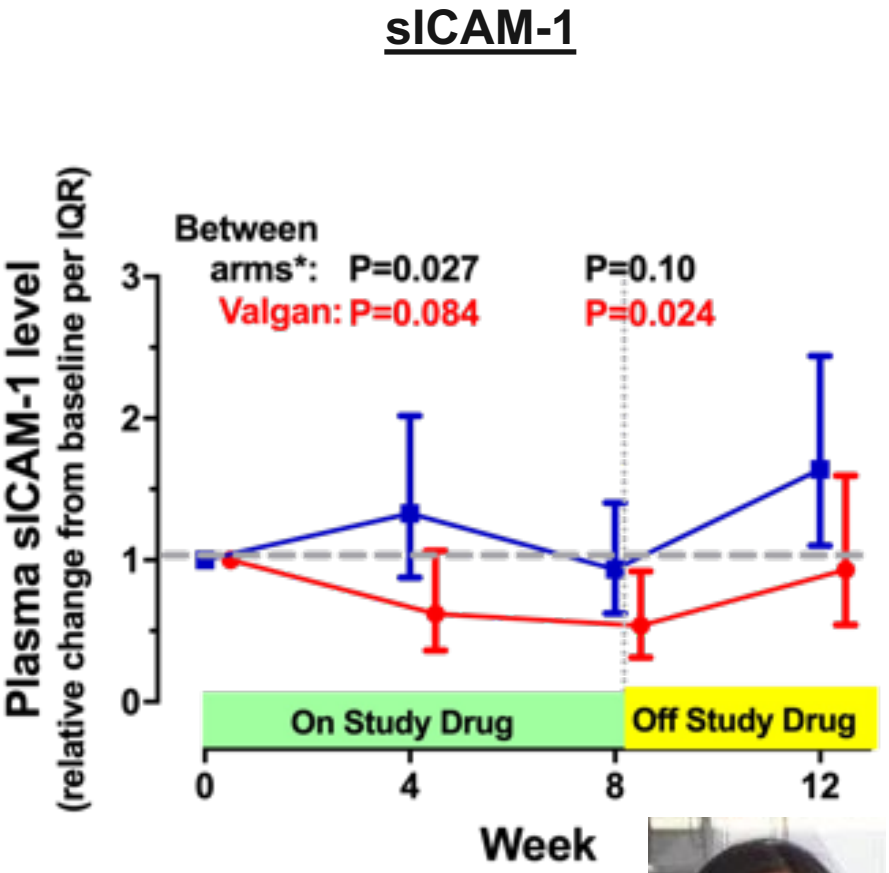
*P values test difference in the change from baseline between treatment arms at each timepoint (linear mixed model).

Gaby Beck-Engeser

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

Valganciclovir Also Decreased Other Markers of Cardiovascular Risk



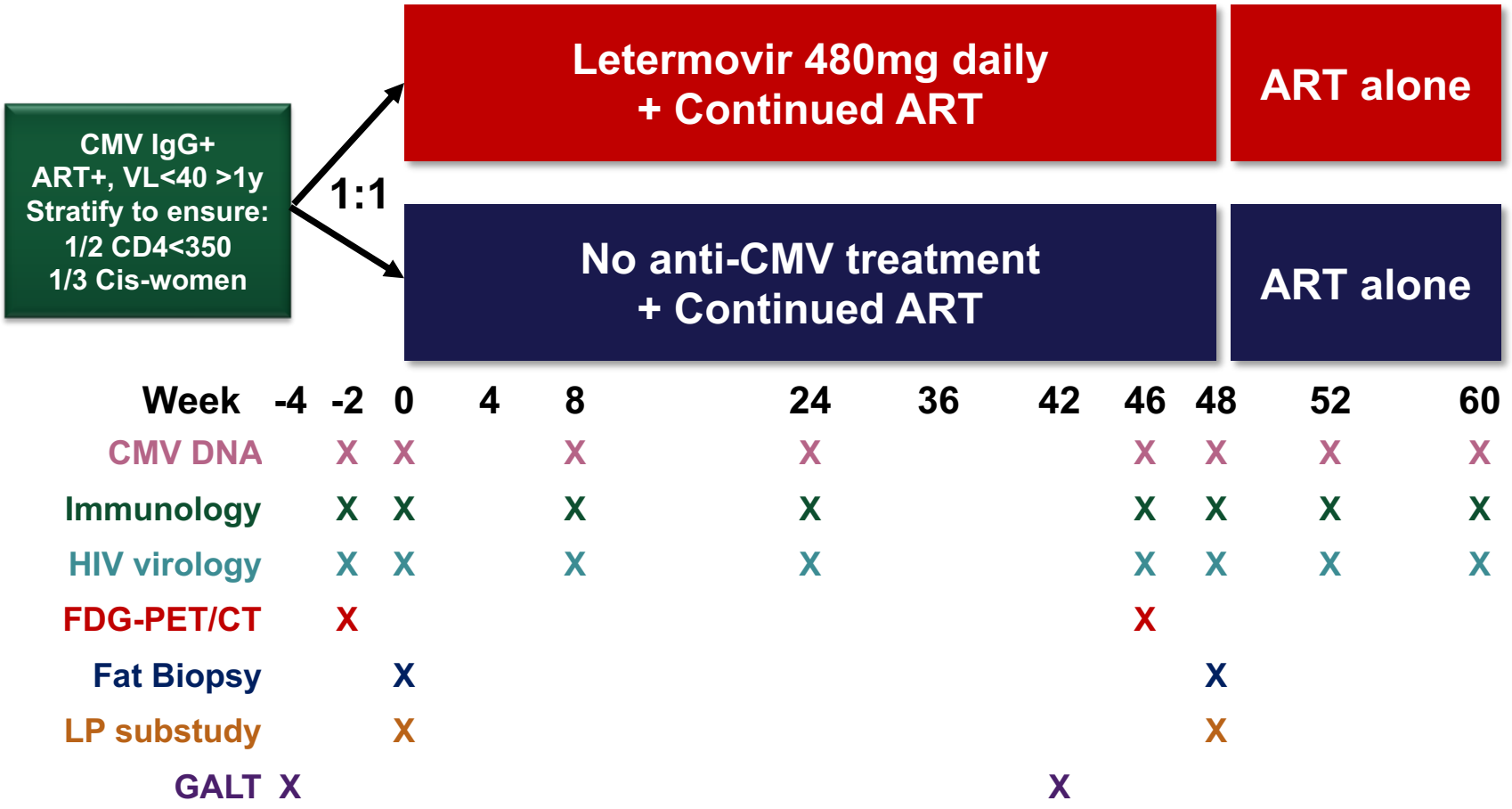


Wk4 suPAR effect corresponds to 24% decrease in MI/Stroke (Hoenigl, CID, 2018)

No evidence for Δ in sVCAM-1, P-selectin, or sTF

Priscilla Hsue,
UCSF

A5383: Letermovir to Reduce Immune Activation in Treated HIV Infection (n=180)

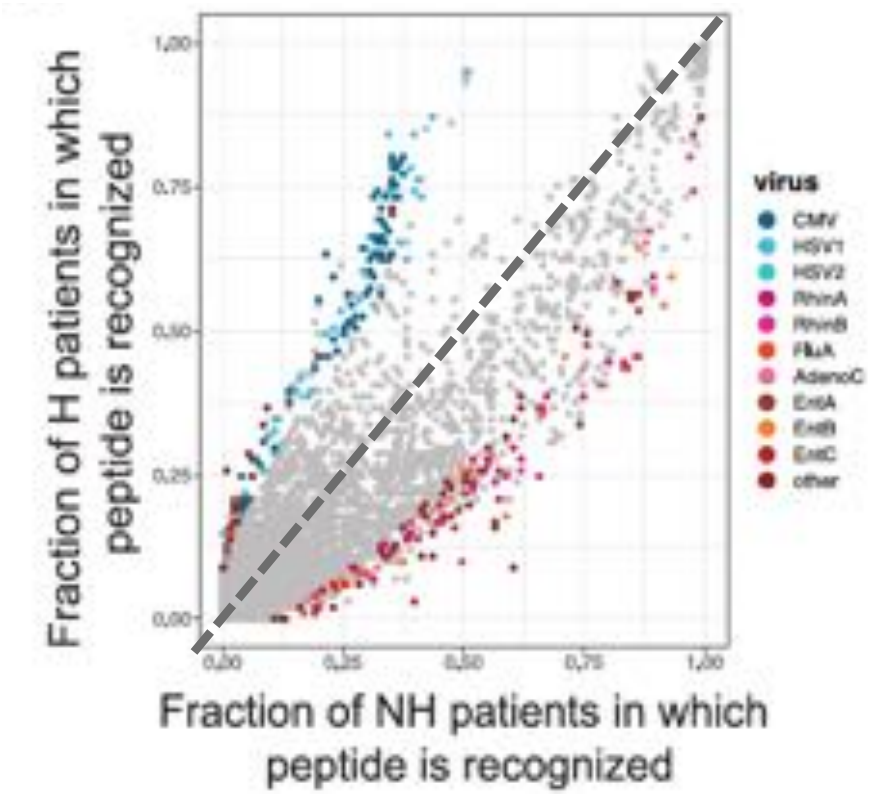


N=42 enrolled, awaiting results of futility analysis in May, 2023

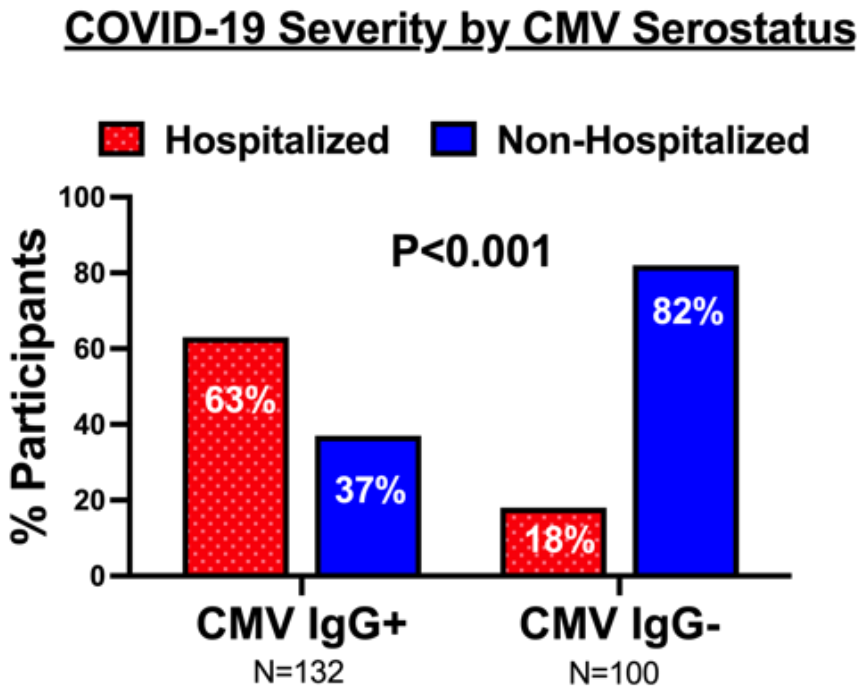
Might CMV Also Potentiate COVID-19 Pathogenesis?

- CMV lives in the same anatomic spaces where COVID-19 causes disease (lung, vasculature, etc)
- CMV reactivation common in critically ill patients
- Treatment of CMV with ganciclovir improved oxygenation and decreased time on ventilator by 3 days among patients with ARDS in the GRAIL trial (Limaye, JAMA, 2017)
  - Comparable to effect of remdesivir on time on ventilator in patients with COVID-19

CMV Seropositivity *Appears* Associated with Hospitalization for COVID-19

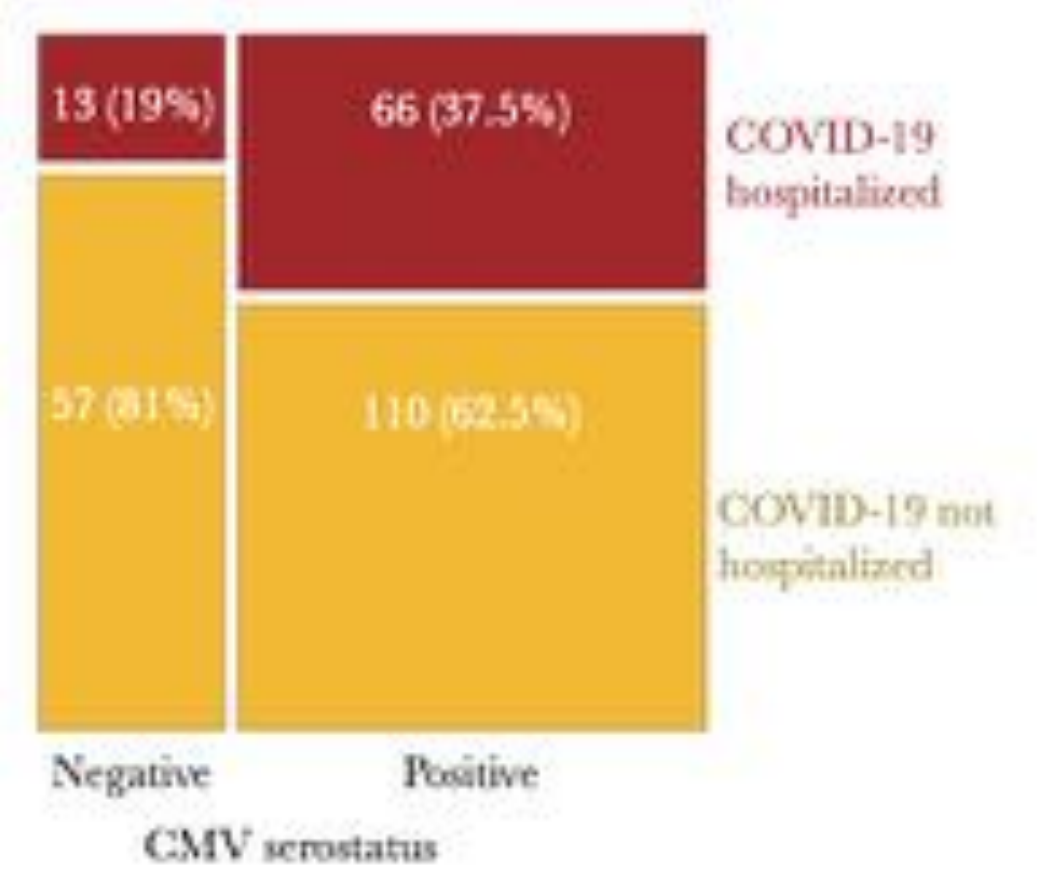


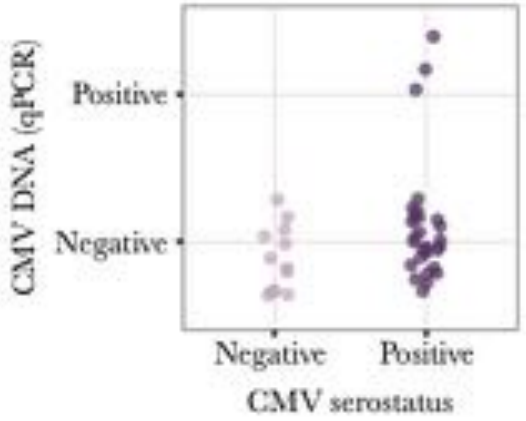
H=hospitalized, NH=Non-Hospitalized



Shrock / Elledge, Science, 2020

CMV Seropositivity *Appears* Associated with Hospitalization for COVID-19





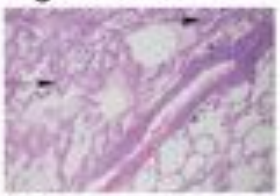
CMV-specific T cells expand over time during hospitalization

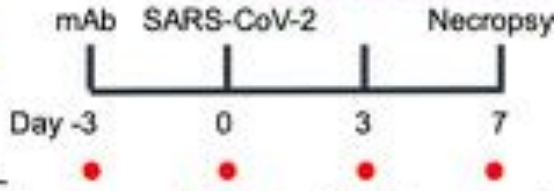
Alonio / Wherry, JID, 2022

Does RhCMV reactivate after SARS-CoV-2 Infection?

Hypothesis: CMV is reactivated following SARS-CoV-2 infection

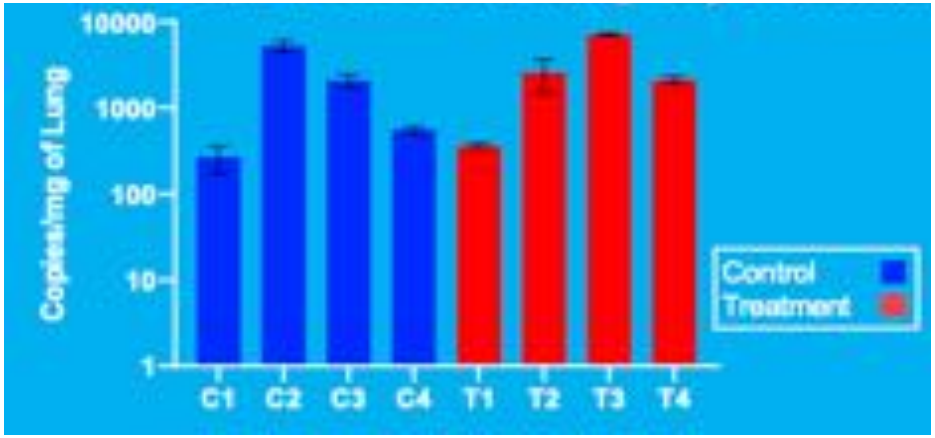
♀ Aged:18-23 years Treatment (T) : n=4 Control (C) : n=4





- 8 female rhesus macaques with type 2 diabetes, aged 18-23 years naturally infected with Rhesus (Rh) CMV were infected with SARS-CoV-2 ($2.5x10^6$ PFU) and monitored for 7 days.
- Animals were given either SARS-CoV-2 neutralizing monoclonal antibodies or control antibodies
- Lung, liver, ileum, and colon were collected at necropsy. Blood was sampled pre infection, day 3, and day 7

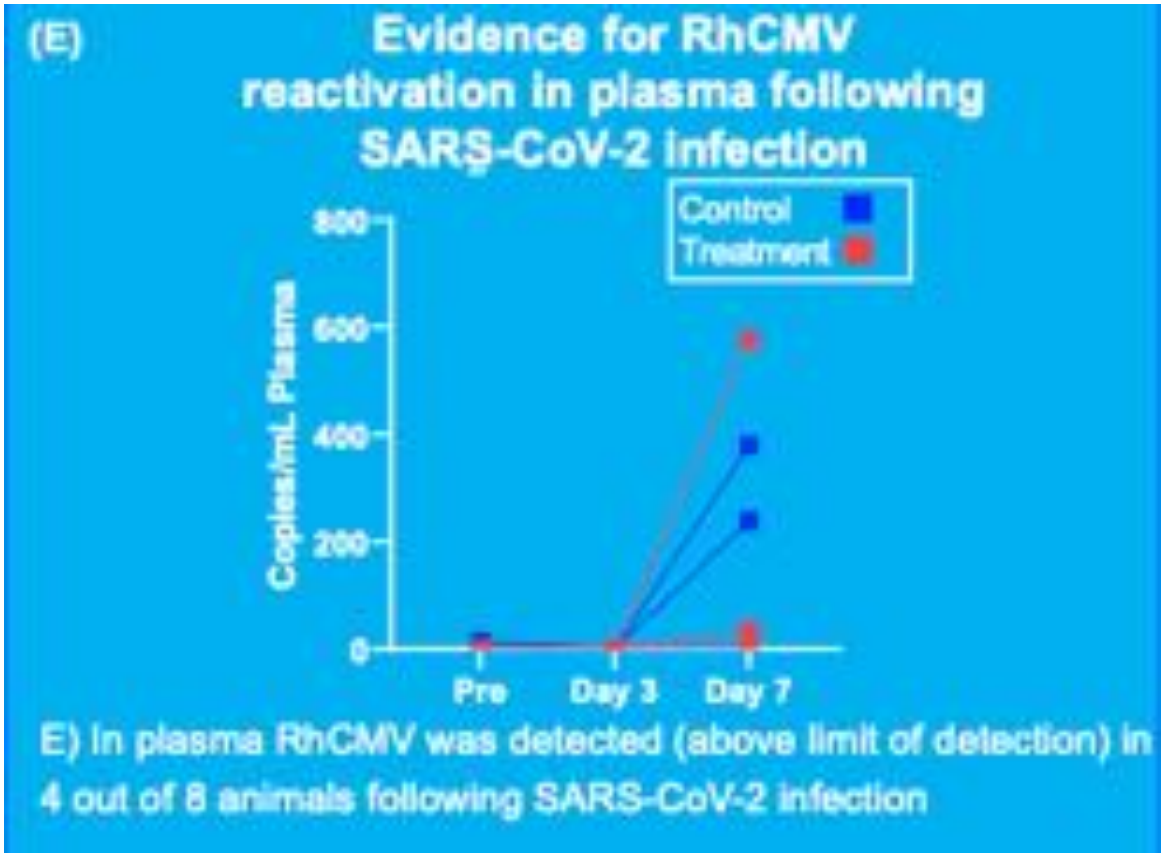
RhCMV Reactivation detected in <u>all animals</u> at d7 regardless of receipt of SARS-CoV-2-specific bNabs



Smita Iyer, UC Davis (now U Pitt)

Roh/Iyer, CROI 2022, #200

Less robust *Rh*CMV reactivation in plasma during SARS-CoV-2 infection



Smita Iyer,
UC Davis
(now U Pitt)

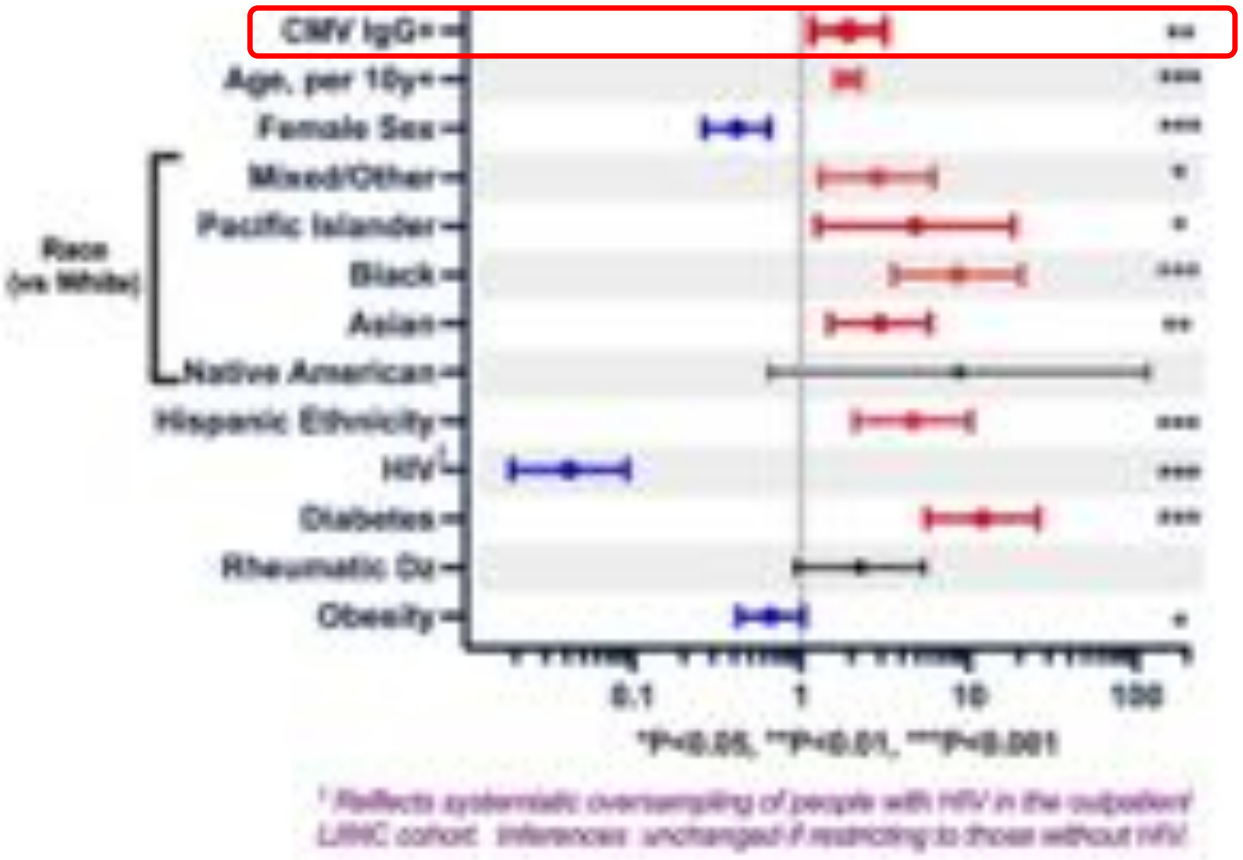
Roh/Iyer, CROI 2022, #200

Does CMV *Independently* Increase the Risk of Hospitalization in People with COVID-19?

CMV Seropositivity Independently Predicts Hospitalization in People with COVID-19

IMPACC/COMET/LIINC Cohorts

N=519 Hospitalized, N=271 Non-Hospitalized

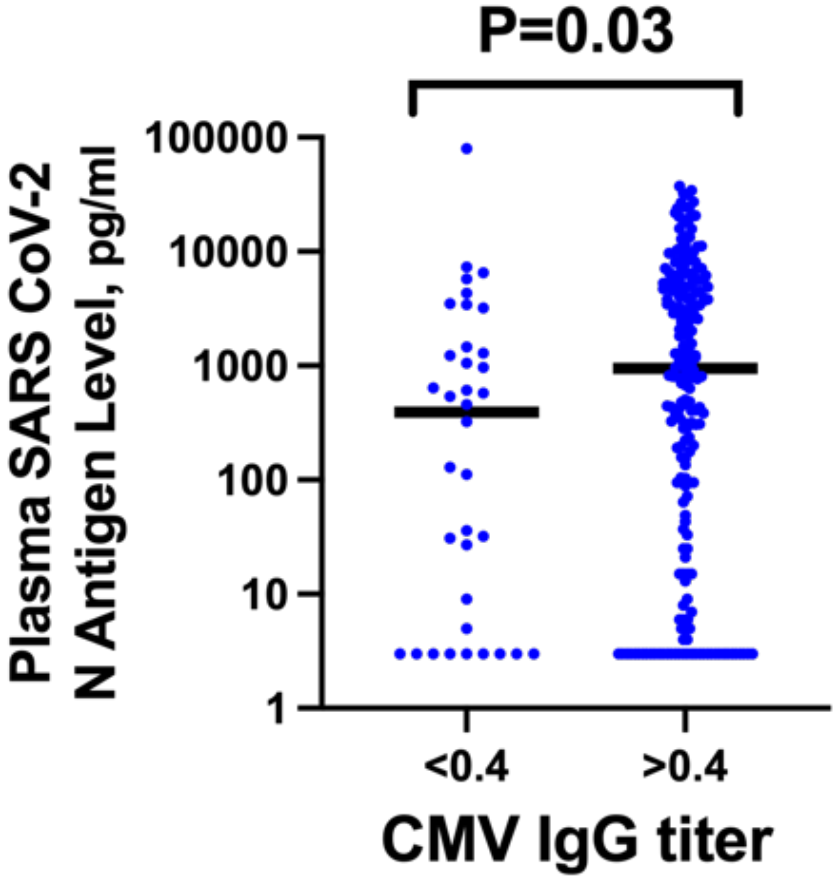


Mean 2-fold Increased Risk!

Michael Peluso,
UCSF HIV-ID Division

Peluso et al, CROI 2023, #273

CMV Seropositives Had Higher SARS CoV-2 N antigen Burden

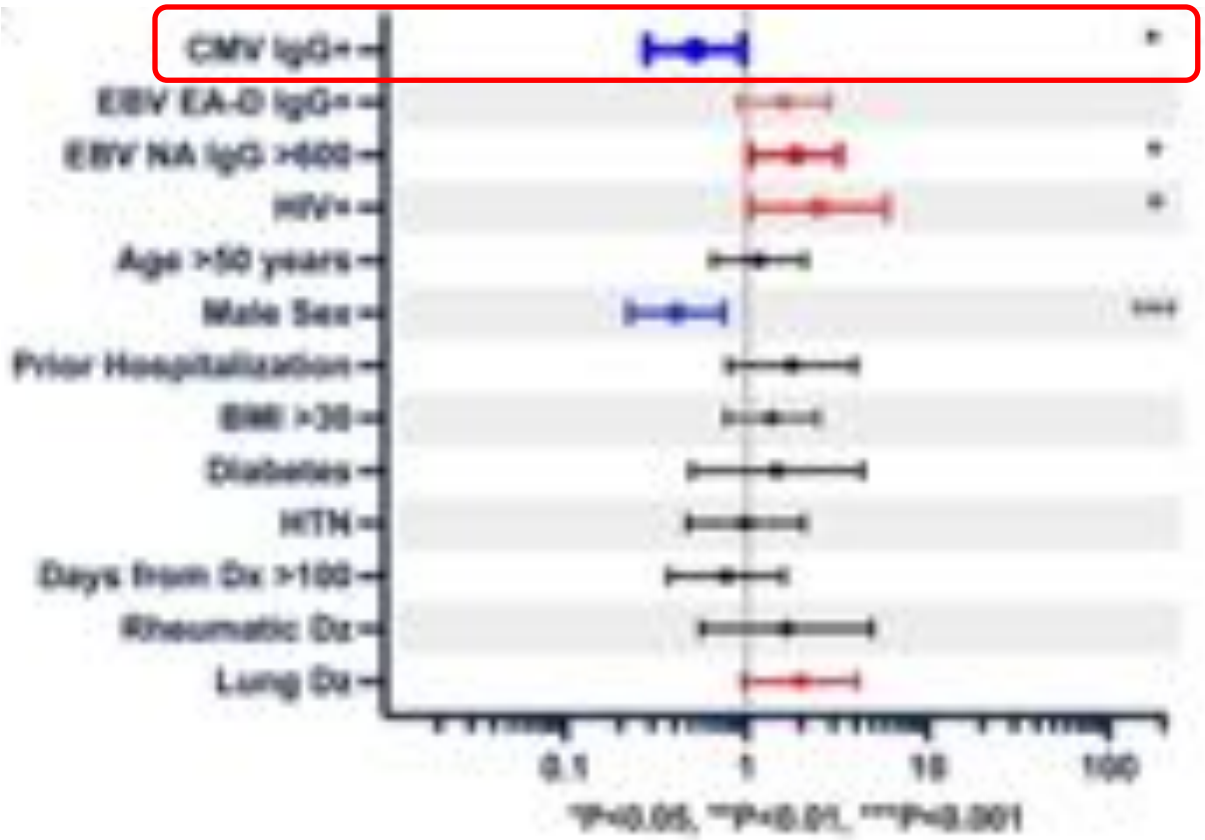


No evidence for association with risk of ICU admission or death among hospitalized patients

Michael Peluso,
UCSF HIV-ID Division

Peluso et al, CROI 2023, #273

CMV Associated with a 50% *Decreased* Risk of Neurologic Long COVID



Peluso et al, JCI, 2023

Might immunoregulatory effects of CMV (i.e., vIL-10) increase SARS-CoV-2 burden but limit its inflammatory consequences?

Conclusions / Implications

- Targeting immune activation pathways in treated HIV has had mixed results (whack-a-mole).
  - Statins and eplerenone may be promising
- Targeting root drivers (microbial translocation, CMV) also holds promise.
  - Teduglutide and Letermovir actively being assessed
  - Field needs an intervention that blocks HIV expression from cells
- CMV increases hospitalization risk from COVID-19, and SARS-CoV-2 Ag burden, but decreases long COVID risk.
  - Ongoing work to understand mechanisms (immunoregulatory?)

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