CROI:
novità in tema di patogenesi dell'infezione da HIV

Camilla Tincati MD, PhD

Clinica di Malattie Infettive

Dipartimento di Scienze della Salute

ASST Santi Paolo e Carlo-Presidio San Paolo

Università degli Studi di Milano

Immunologic concepts and knowledge gaps

- **Immunopathogenesis of untreated HIV**

-cellular and humoral immune responses

- **Immunopathogenesis of HIV during cART**

-immune activation and inflammation

- **Immunopathogenesis of CVD**

- focus on Reprieve

Immunologic concepts and knowledge gaps

- **Immunopathogenesis of untreated HIV**

-cellular and humoral immune responses

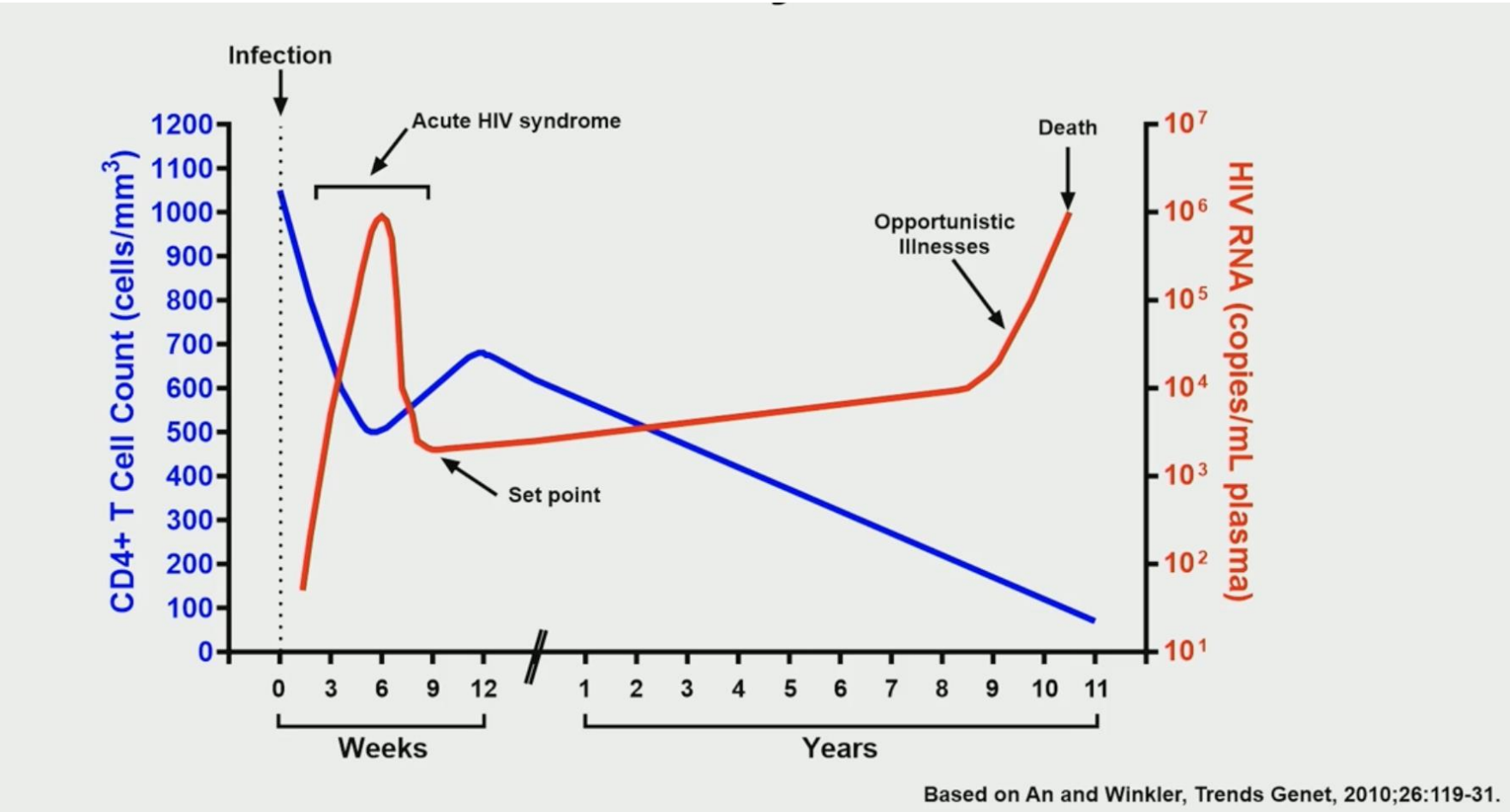
- **Immunopathogenesis of HIV during cART**

-immune activation and inflammation

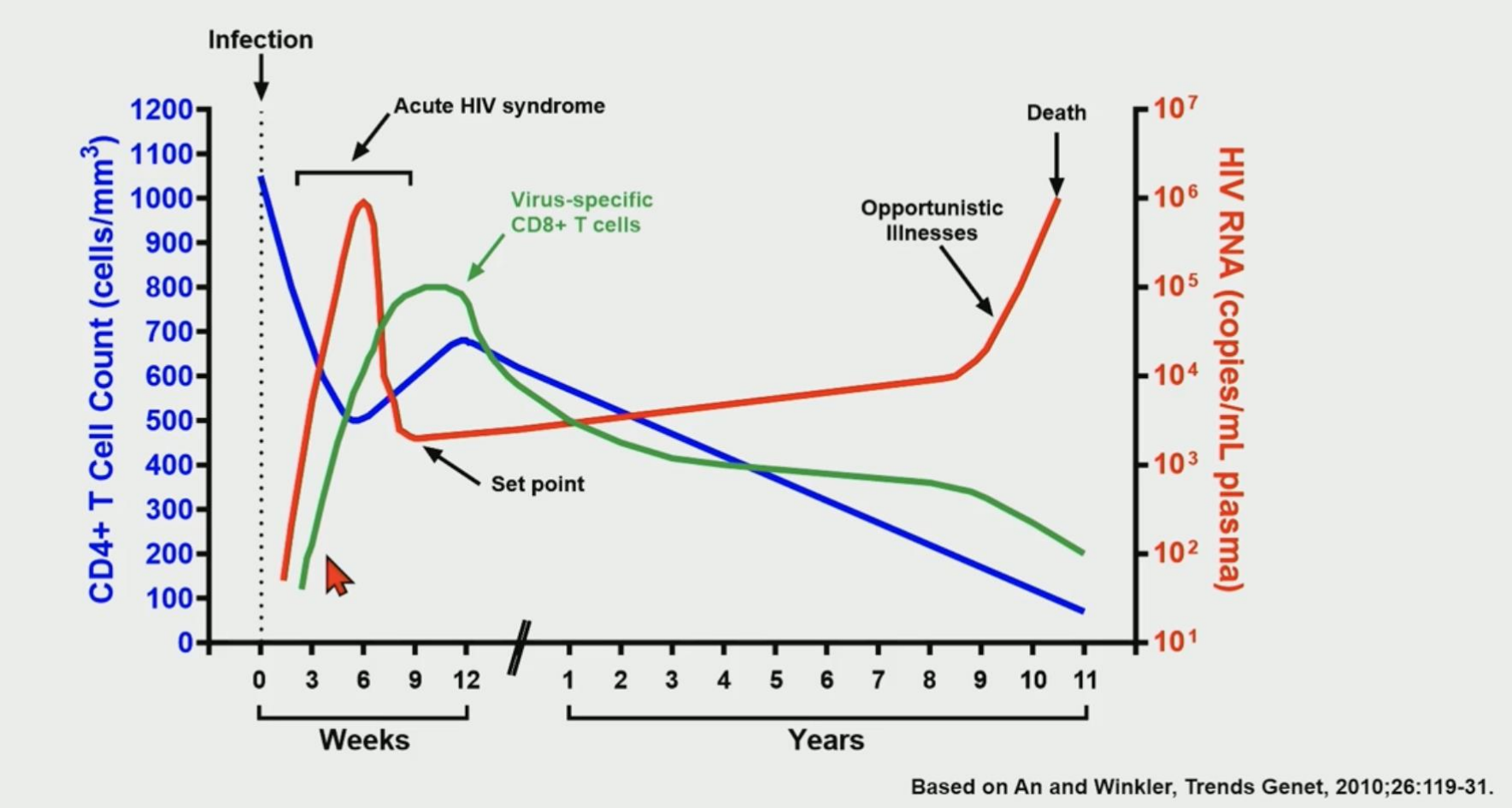
- **Immunopathogenesis of CVD**

- focus on Reprieve

Viro-immunological parameters in untreated HIV



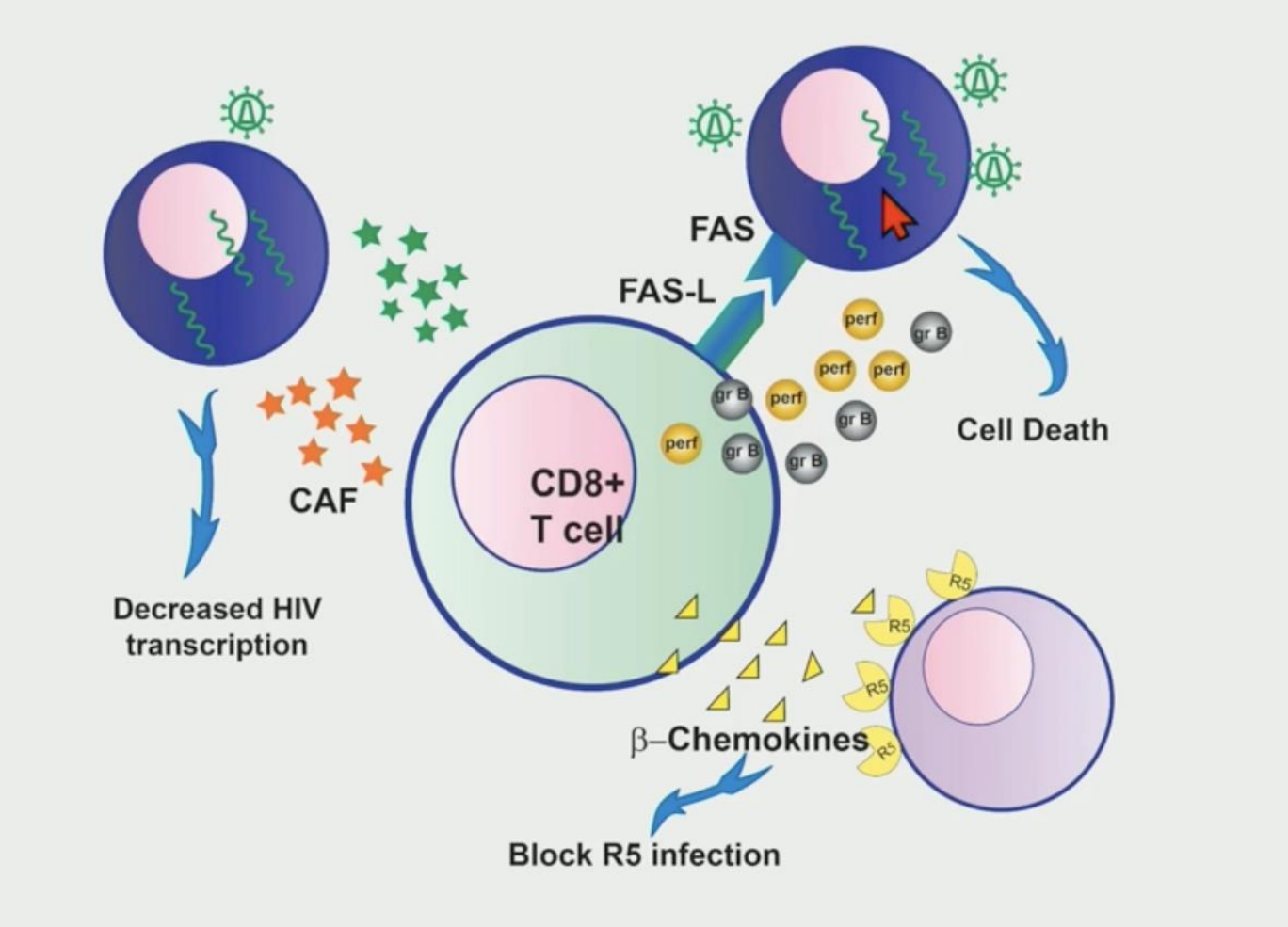
Viro-immunological parameters in untreated HIV



CD8 T-cell depletion leades to increased viremia in SIV-infected macaques

Jin, J Exp Med, 1999

HIV/SIV-specific CD8+ T-cells reduce viral replication



Yet are unable to fully suppress HIV replication:

- indadequate numbers
- viral escape from viral recognition
- impaired effector mechanisms (cure arena: check-point inhibitors, IL-15 agonists…)
- Immune privileged cell (Bcl-2 expression)/site (secondary lymphoid tissues: different location of viral expression vs CD8+ T-cells)

Connick, CROI 20

Single-Cell, Multi-Omics Analysis of SIV-Specific CD8⁺ T Cells Across Multiple Anatomical Sites

444

Jennifer Simpson[1], Paul Schaughency[2], Justin Lack[2], Jason M. Brenchley[1]

1.Barrier Immunity Section, Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA. 2. Integrated Data Sciences Section, Research Technologies Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

BACKGROUND

Antigen-specific CD8⁺ T cells play a key role in the host's antiviral response. T cells recognize viral epitopes via the T cell receptor (TCR). During chronic simian immunodeficiency virus (SIV) infection of rhesus macaque nonhuman primates, tissue specific TCR clonotypes were identified among SIV-specific CD8⁺ T cells. We sought to answer the following questions:

- Do SIV-specific CD8⁺ T cells exhibit altered transcriptional profiles and TCR repertoires in different anatomical sites?
- Do SIV-specific CD8⁺ T cells with tissue-specific TCR sequences show distinct transcriptional profiles compared to cells with TCR sequences shared across multiple sites?

METHODS

- SIV gag CM9 (CTPYDINQM)-specific CD8⁺ T cells were sorted from the peripheral blood mononuclear cells (PBMCs), multiple non-gut draining lymph nodes (LNs), mesenteric lymph nodes (MeLN), spleen and liver of chronically SIV infected Mamu-A*01⁺ rhesus macaques.
- Single-cell RNA and TCR sequencing libraries were generated from the CM9-specific CD8⁺ T cells via the 10x Genomics pipelines.
- Sequencing libraries were sequenced via the NovaSeq or NextSeq platforms and data was analyzed using software programs CellRanger, Seurat and scRepertoire.

SIV-specific CD8⁺ T cells with tissue-specific TCR sequences show distinct transcriptional profiles compared to cells that share TCR sequences across multiple anatomical sites.

RESULTS: Overlap of RNAseq profiles of multiple anatomical sites.

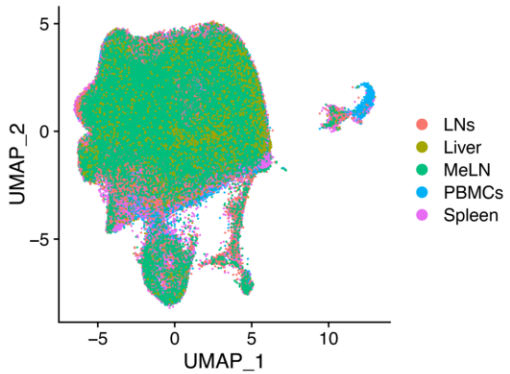


Figure 1: RNAseq profiles of CM9 specific CD8⁺ T cells isolated from PBMCs, LNs, MeLN, spleen and liver. n= 6.

RESULTS: TCRseq data shows similar TCR repertoire diversity and TCR repertoire composition across anatomical sites.

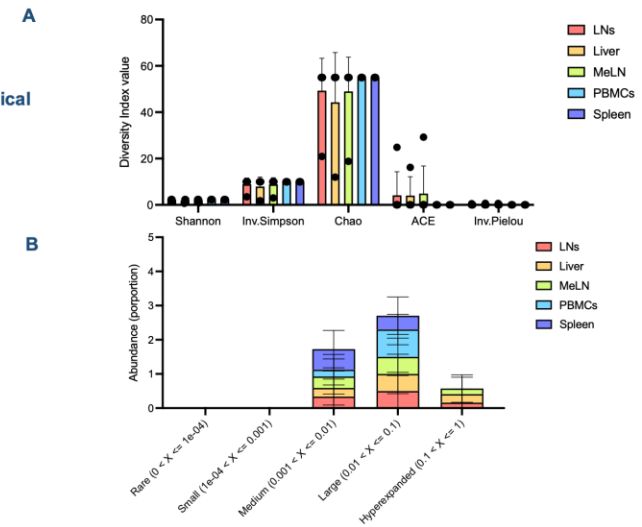


Figure 2: TCR repertoire diversity and composition of CM9 specific CD8+ T cells isolated from PBMCs, LNs, MeLN, spleen and liver. (A) TCR repertoire diversity index values. (B) TCR sequence abundance. n= 6.

RESULTS: GSEA identified distinct transcriptional profiles between cells with shared/tissue specific TCRs.

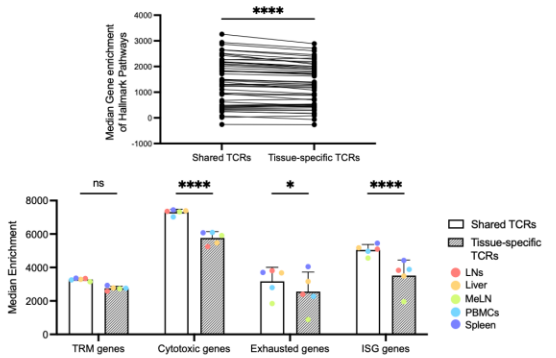


Figure 3: Gene set enrichment analysis (GSEA) of CM9 specific CD8+ T cells isolated from PBMCs, LNs, MeLN, spleen and liver. (A) Median enrichment scores for GSEA using Hallmark gene sets. (B) Median enrichment scores for GSEA using targeted (TRM, Cytotoxic, Exhausted and ISG) gene sets. n= 6.

RESULTS: Average gene expression analysis showed distinct transcriptional profiles between cells with shared/tissue specific TCRs in the liver.

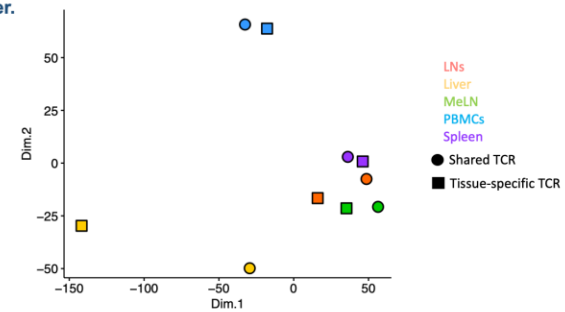


Figure 4: MDS plot of average gene expression of CM9 specific CD8+ T cells isolated from PBMCs, LNs, MeLN, spleen and liver. n= 6.

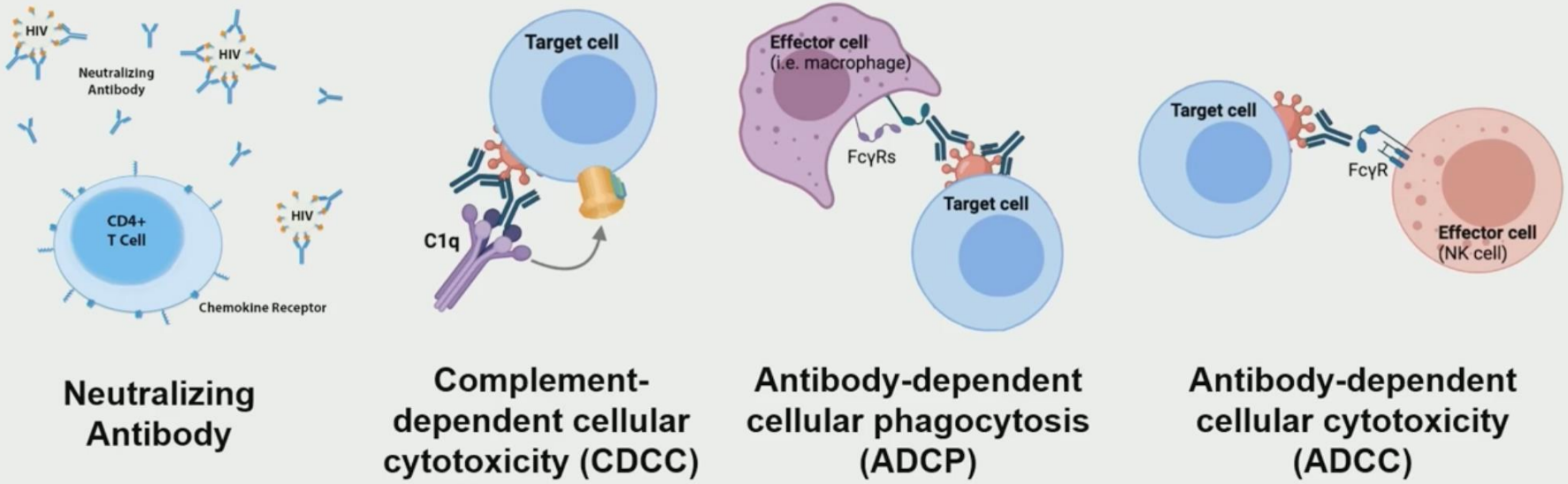
CONCLUSIONS

- CM9 specific CD8+ T cells expressing tissue specific TCR sequences exhibit distinct transcriptional profiles, including reduced expression of cytotoxic and exhausted genes compared to cells with shared TCRs.
- These data illustrate the presence of distinct tissue-specific antiviral responses, which may lead to novel therapeutic strategies to enhance T cell mediated defenses against viruses.

ADDITIONAL KEY INFORMATION

Funding for this study was provided in part by the Division of Intramural Research/NIAID/NIH. The content of this publication does not necessarily reflect the views or policies of DHHS, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Antibodies suppress HIV through different mechanisms



Adapted from: Phelps and Balazs, Front. Immunol, 2021 and Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (8th Edition), 2015, Neutralizing Antibody

bNAbs

- Low CD4+ cells
- High viral load/no cART
- Younger age (children)
- Non-subtype B
- Not enriched in EC

- Passive transfer inhibits viral replication

Barouch, Nature, 2013

T003 Study Design and Objectives

Group	mAbs	Dose (mg/kg IV)	Frequency	HIV	ART	Viral Load (Log_{10} cp/ml)	N	ATI
1	PGT121/ VRC07-523LS	30/30	Once	No	-	-	3	-
	PGT121/ VRC07-523LS/PGDM1400	20/20/20	Once	No	-	-	3	-
2	PGT121/ VRC07-523LS/PGDM1400	20/20/20	D0 + D28 + D56 [+ D84 + D112 + D140]	Yes	Yes	<1.7	12	Yes Stop ART D1
	Total						18	

Sponsor
IAVI

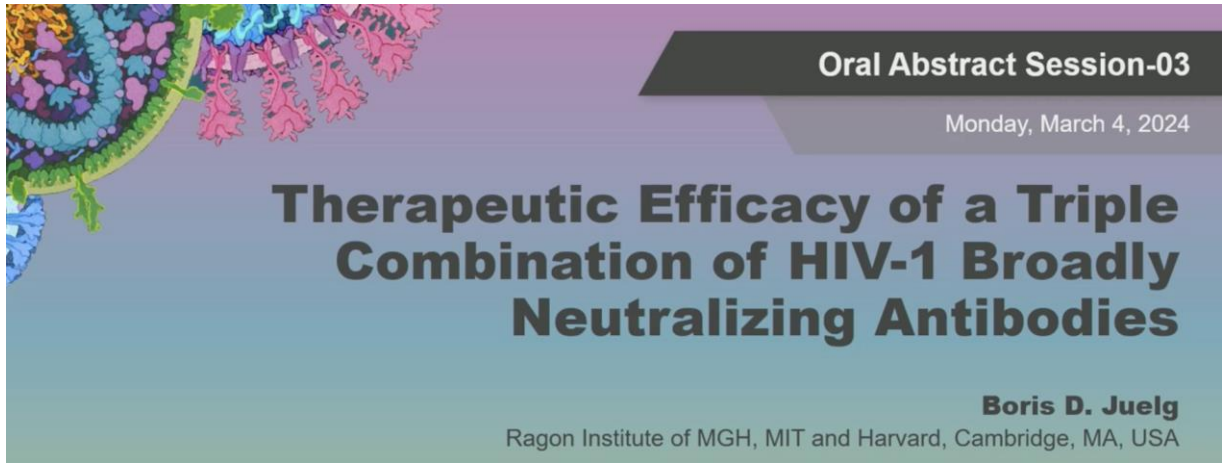
Funder
Ragon Institute of Mass General, MIT and Harvard

Collaborator
Vaccine Research Center, NIH

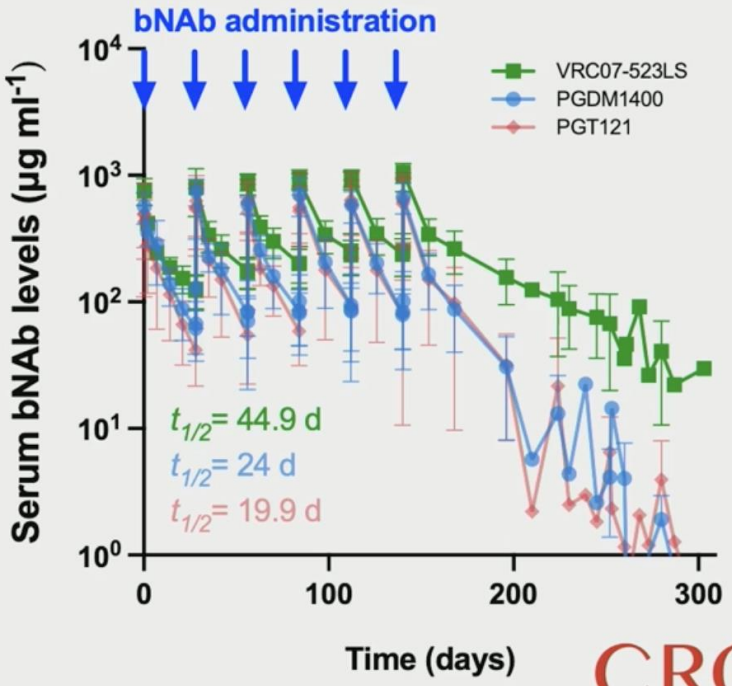
Study Sites
Boston, MA
Orlando, FL (PI Dr Rolle)
Houston, TX (PI Dr Arduino)

Objectives: Safety, tolerability and PK of IV PGT121, PGDM1400 and VRC07-523LS in adults with and without HIV.

Antiviral activity of a combination of PGT121, PDGM1400 and VRC07-523LS, in PLWH that are undergoing an ATI

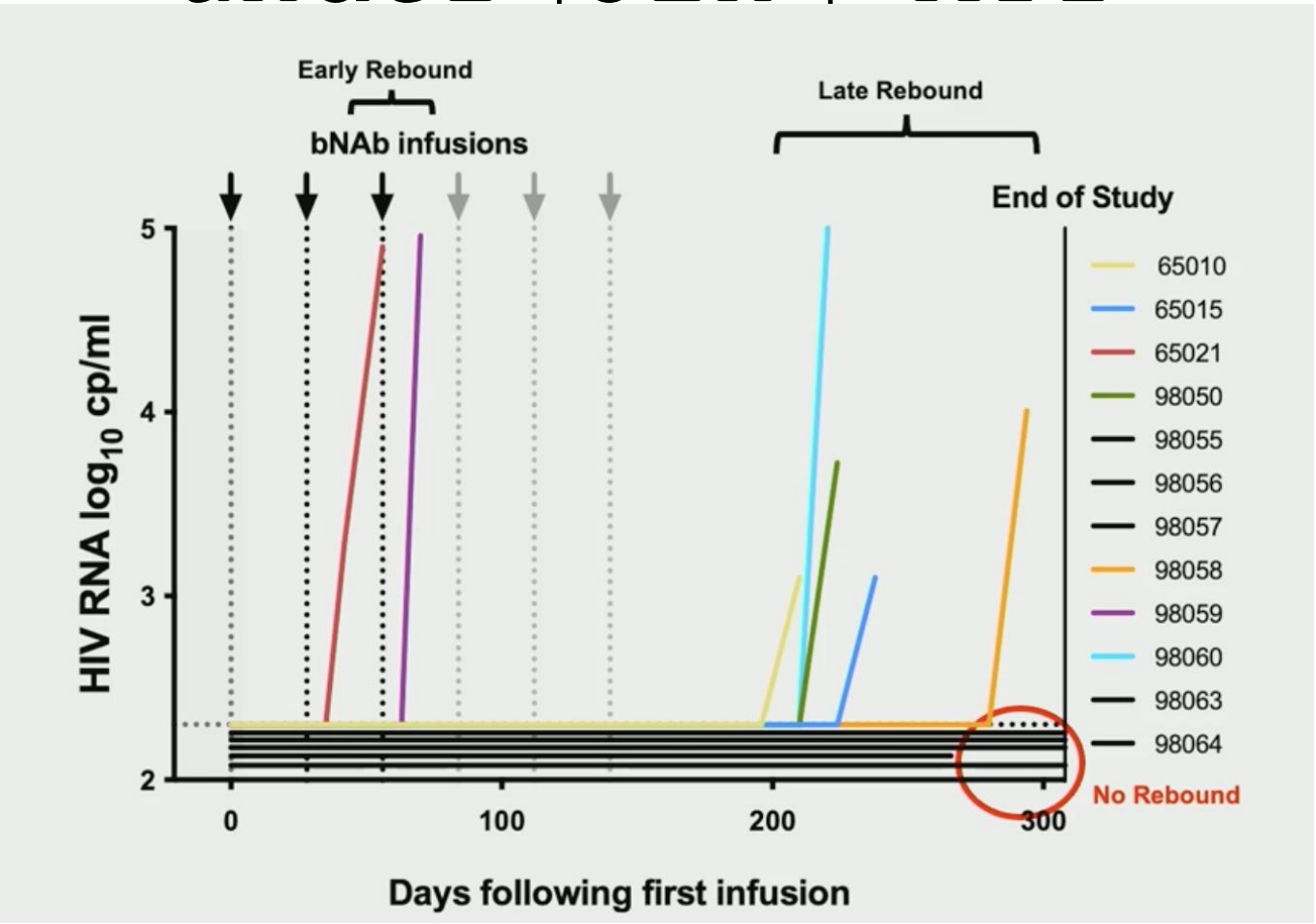


- All three antibodies were generally safe and well tolerated in participants without and with HIV-1. Four serious adverse event (SAE) and/or a Grade 3 or higher AE or reactogenicity (appendicitis, chest pain, malaise and headache) were determined unrelated.
- Median elimination half-life estimates were 19.9 days for PGT121, 23.9 days for PGDM1400, and 44.9 days for VRC07-523LS in PLWH.
- Pharmacokinetic profiles of PGT121, PGDM1400, and VRC07-523LS were not altered by multiple administrations over a period of 20 weeks.



CROI 2024

Antiviral activity of multiple doses of triple bNAbs in PLWH undergoing ATI



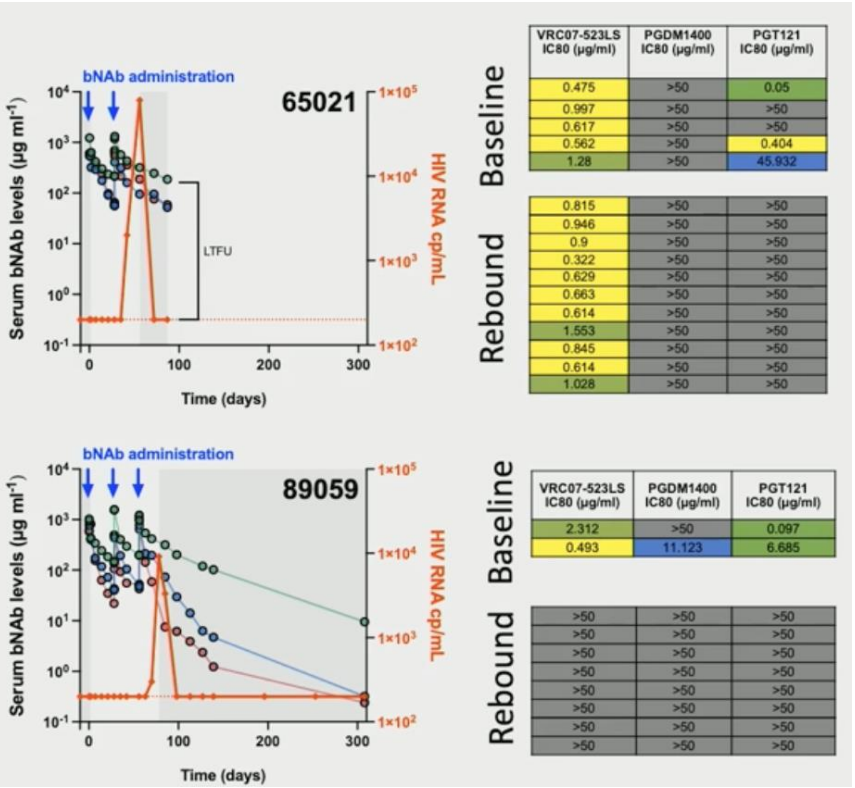
- 83% (10/12) maintained virologic suppression for at least 28 weeks

- 36% (4/11 FU completion) demonstrated virologic suppression at the end of study week 44

Juelg, # 121 LB, CROI 2024

bNAbs resistance and viral rebound

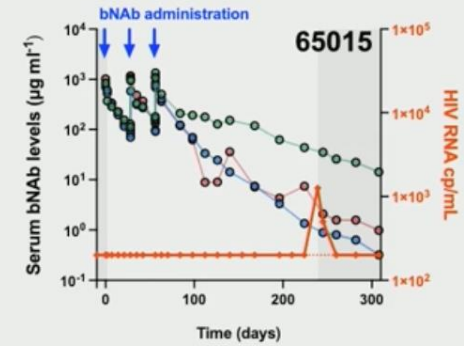
Early:
BL resistance to PGT121/PGDM1400



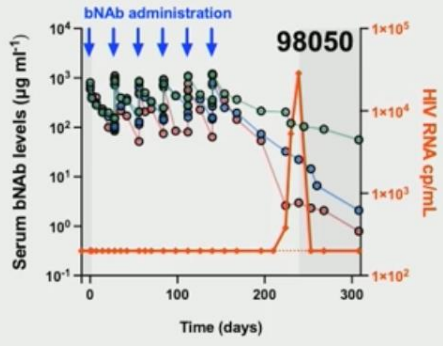
	VRC07-523LS IC80 (μg/ml)	PGDM1400 IC80 (μg/ml)	PGT121 IC80 (μg/ml)
Baseline	0.475	>50	0.05
	0.997	>50	>50
	0.617	>50	>50
	0.562	>50	0.404
	1.28	>50	45.932
Rebound	0.815	>50	>50
	0.946	>50	>50
	0.9	>50	>50
	0.322	>50	>50
	0.629	>50	>50
	0.663	>50	>50
	0.614	>50	>50
	1.553	>50	>50
	0.845	>50	>50
	0.614	>50	>50
	1.028	>50	>50

	VRC07-523LS IC80 (μg/ml)	PGDM1400 IC80 (μg/ml)	PGT121 IC80 (μg/ml)
Baseline	2.312	>50	0.097
	0.493	11.123	6.685
Rebound	>50	>50	>50
	>50	>50	>50
	>50	>50	>50
	>50	>50	>50
	>50	>50	>50
	>50	>50	>50
	>50	>50	>50
	>50	>50	>50

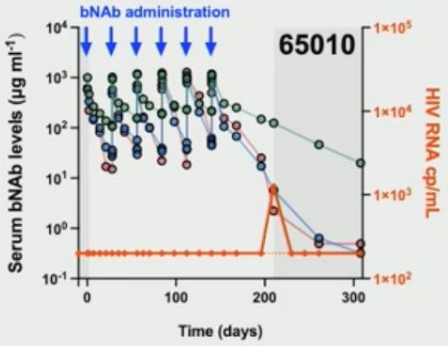
Late:
Sensitive and resistant rebound virus



	VRC07-523LS IC80 (μg/ml)	PGDM1400 IC80 (μg/ml)	PGT121 IC80 (μg/ml)
Rebound	0.352	0.648	0.127
	0.418	0.424	0.089
	1.251	0.815	0.176
	0.865	0.877	0.247
	0.714	0.436	0.075
	0.881	1.002	0.293
	0.727	0.792	0.229



	VRC07-523LS IC80 (μg/ml)	PGDM1400 IC80 (μg/ml)	PGT121 IC80 (μg/ml)
Rebound	1.435	>50	>50
	2.293	>50	>50
	0.553	>50	>50
	0.237	>50	>50
	0.654	>50	>50
	1.174	>50	>50
	1.166	>50	>50
	2.254	>50	>50



	VRC07-523LS IC80 (μg/ml)	PGDM1400 IC80 (μg/ml)	PGT121 IC80 (μg/ml)
Rebound	0.301	0.98	43.078
	0.639	>50	0.155
	0.402	0.887	0.139
	0.241	0.798	0.135
	0.228	0.681	0.159
	0.639	>50	0.155
	0.313	0.79	0.098

Juelg, #121 LB, CROI

CROI
Presentation #2258

Lenacapavir Plus bNAbs for People with HIV and Susceptibility to Either Teropavimab or Zinlirvimab

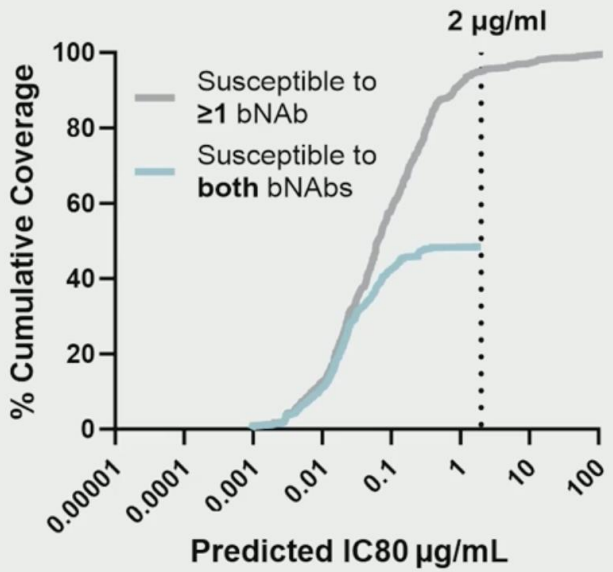
Joseph J Eron,[1] Paul P Cook,[2] Megha L Mehrotra,[3] Hailin Huang,[3] Marina Caskey,[4] Gordon E Crofoot,[5] Edwin DeJesus,[6] Linda Gorgos,[7] Laurie A VanderVeen,[3] Olayemi O Osiyemi,[8] Cynthia Brinson,[9] Sean E Collins[3]

[1]University of North Carolina, Chapel Hill, NC; [2]East Carolina University, Greenville, NC; [3]Gilead Sciences, Foster City, CA; [4]The Rockefeller University, New York, NY; [5]The Crofoot Research Center, Houston, TX; [6]Orlando Immunology Center, Orlando, FL; [7]AXCES Research Group, Santa Fe, NM; [8]Triple O Research Institute PA, West Palm Beach, FL; [9]Central Texas Clinical Research, Austin, TX

Background

- Teropavimab (TAB) and zinlirvimab (ZAB) are broadly neutralizing antibodies (bNAbs) against the CD4-binding site of gp120 and a non-overlapping epitope on the V3 glycan of HIV-1 Env, respectively[1]
- Approximately 50% of clade B viruses are highly susceptible to both TAB and ZAB with a 90% inhibitory concentration (IC90) ≤2 µg/mL, while over 90% are highly susceptible to either TAB or ZAB[2]
- TAB and ZAB have extended half-lives that allow for dosing every 6 months[1]
- Lenacapavir (LEN) is a first-in-class, small molecule capsid inhibitor with high potency and a long half-life that can be administered subcutaneously every 6 months and is indicated in heavily treatment-experienced people with HIV-1 (PWH)[3]

bNAb Susceptibility Breadth[4]

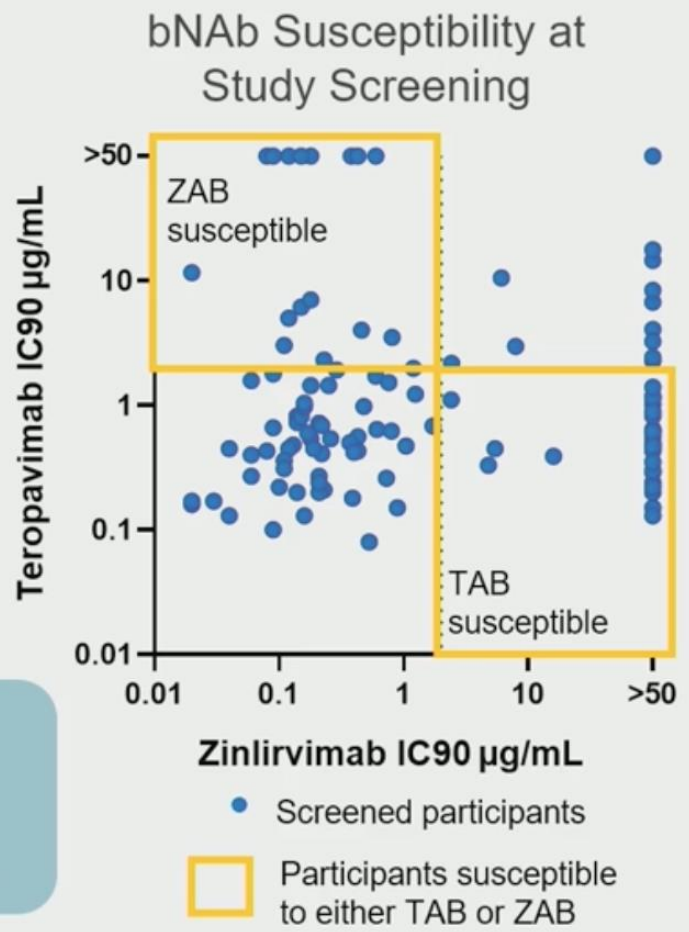


1. Gautam R, et al. *Nat Med* 2018; 24(5): 610-6. 2. Selzer L, et al. Presented at CROI 2023. Poster 580. 3. Sunlenca® Prescribing Information, available at https://www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.pdf (accessed February 2024). 4. Estimated coverage given predicted IC90 closely resembles coverage given IC80 shown here. Data from CATNAP CombiNAber (Yoon H, et al. *Nucleic Acid Res*. 2015;43:W213-9, Wagh K, et al. *PLoS Pathog*. 2016 Mar30;12(3)) using 479 Clade B viruses.

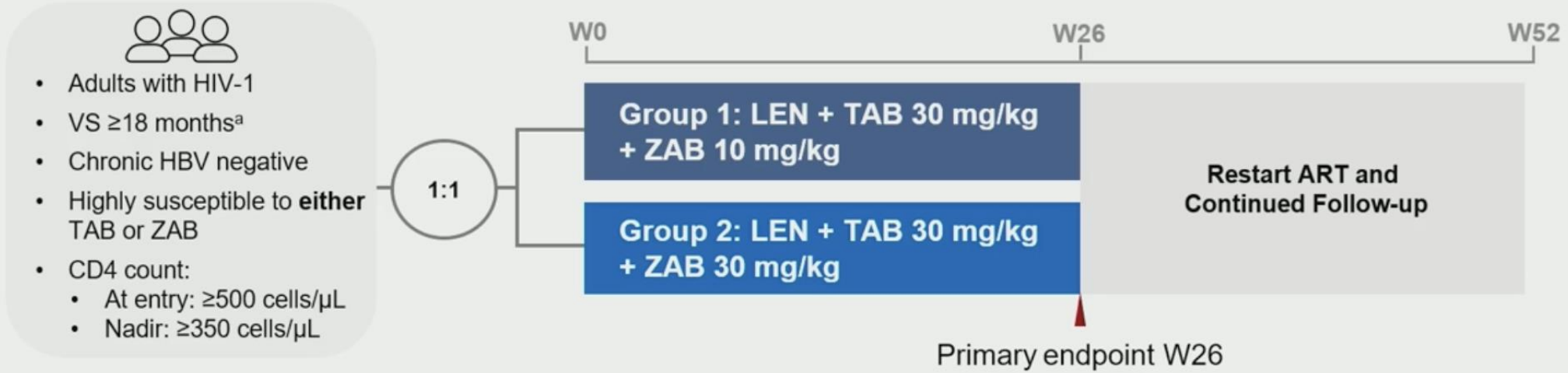
Background and Objective

- In a Phase 1b study (NCT04811040), a single dose of the long-acting combination of LEN, TAB, and ZAB maintained virologic suppression (VS) for 6 months in 18/20 participants with HIV-1 highly susceptible to both bNAbs[1]
- The optimal threshold for required bNAb sensitivity to achieve efficacy in the context of HIV-1 treatment has not been established

Objective: To evaluate safety and efficacy of LEN + TAB + ZAB in virologically suppressed participants highly susceptible to **either** TAB or ZAB, **but not both** bNAbs



Study Design

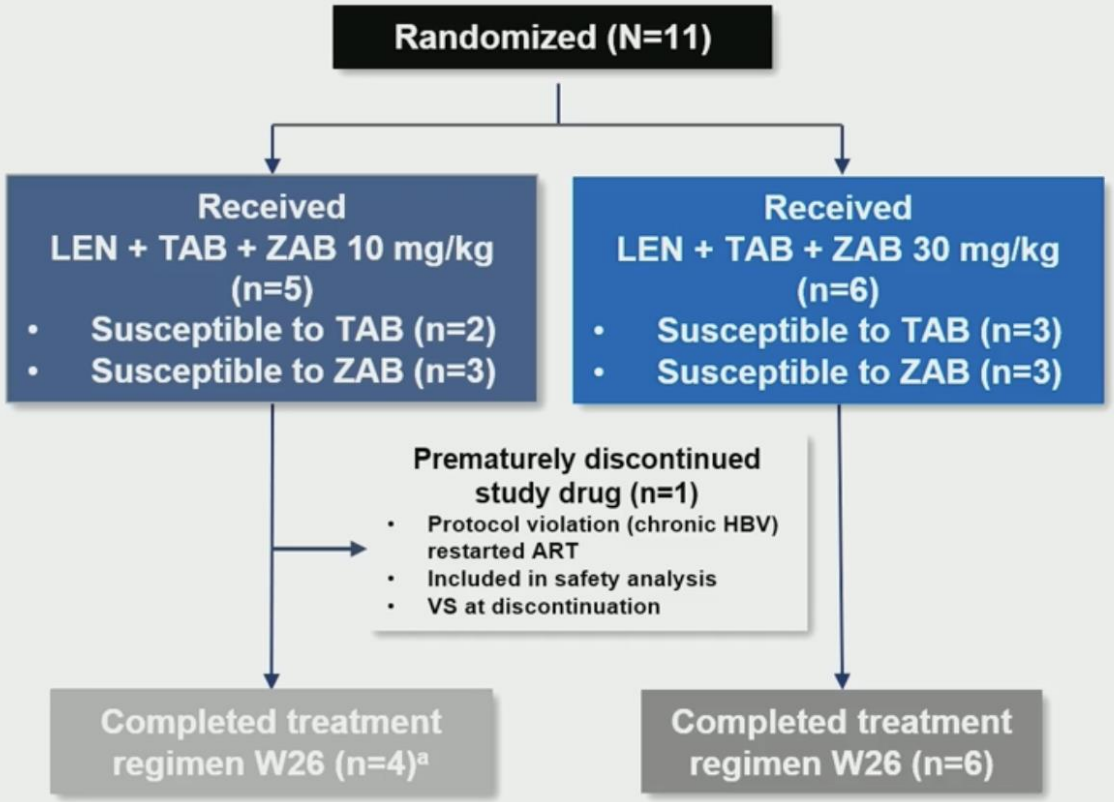


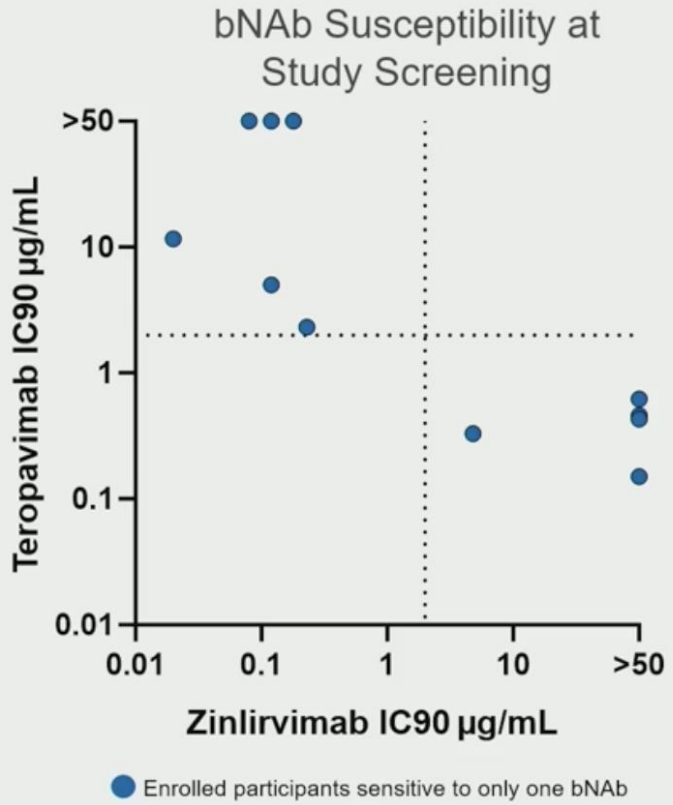
Participants

- After primary cohort sensitive to both bNAbs completed study, a cohort of participants with susceptibility to **either** TAB **or** ZAB was enrolled
- bNAb susceptibility defined as IC90 ≤2 µg/mL by PhenoSense mAb Assay (Monogram Biosciences)
- Randomization to treatment groups was stratified by bNAb susceptibility (TAB or ZAB)

[a]Previous virologic failure was allowed if participants were VS (HIV-1 RNA ≤50 copies/mL) for ≥18 months prior to screening
ART, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **HBV**, Hepatitis B virus; **IC90** 90% inhibitory concentration; **LEN**, lenacapavir; **TAB**, teropavimab; **VS**, virologic suppression; **W**, Week; **ZAB**, zinlirvimab.

Participant Disposition and Susceptibility





[a]1 and 3 participants were susceptible to TAB and ZAB, respectively

ART, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **HBV**, Hepatitis B virus; **LEN**, lenacapavir; **TAB**, teropavimab; **VS**, virologic suppression; **W**, Week; **ZAB**, zinlirvimab.

Eron, #121, CROI 2

Baseline Characteristics

	LEN + TAB + ZAB 10 mg/kg (n=5)	LEN + TAB + ZAB 30 mg/kg (n=6)	Total (N=11)
Age (years), median (range)	49 (28–63)	51 (29–57)	49 (28–63)
Female sex at birth, n	2	1	3
Race, n			
Black	2	2	4
White	3	3	6
Other	0	1	1
Hispanic or Latino ethnicity, n	2	1	3
Weight (kg), median (range)	86.4 (67.6–104.5)	86.3 (84.2–117.6)	86.4 (67.6–117.6)
CD4 cell count (per mL), median (range)	861 (449–1916)	942 (673–1196)	916 (449–1916)
Duration of baseline ART (years), median (range)	2.5 (1.0–5.5)	4.9 (3.1–6.4)	3.7 (1.0–6.4)
Time since HIV-1 diagnosis (years), median (range)[a]	16 (5–25)	13.5 (3–24)	16 (3–25)

Eron, #121, CROI 2

Viral Suppression at Week 26

	LEN + TAB + ZAB 10 mg/kg (n=4)[a]	LEN + TAB + ZAB 30 mg/kg (n=6)	Total (N=10)
HIV-1 RNA ≥50 copies/mL, **n** (%; [95% CI])	**2** (50; [7, 93])	**0** (0; [0, 46])	**2** (20; [3, 56])
HIV-1 RNA <50 copies/mL, **n** (%; [95% CI])	**2** (50; [7, 93])	**6** (100; [54, 100])	**8** (80; [44, 98])

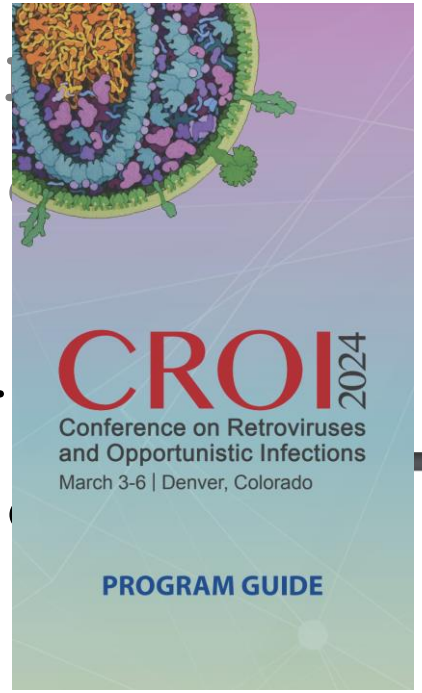
- Eight out of 10 participants remained virologically suppressed with HIV-1 RNA <50 copies/mL 6 months after dosing
- All participants in the higher dose group (n=6; ZAB 30 mg/kg) remained suppressed at Week 26

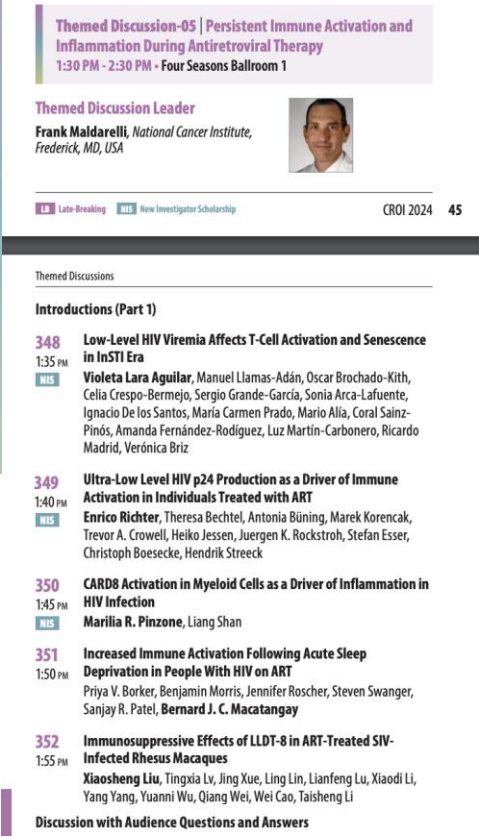
Immunologic concepts and knowledge gaps

- **Immunopathogenesis of untreated**
  - cellular and humoral immune resp

- **Immunopathogenesis of HIV during**
  - immune activation and inflammati

- **Immunopathogenesis of CVD**
  - focus on Reprieve





Themed Discussion-05 | Persistent Immune Activation and Inflammation During Antiretroviral Therapy
1:30 PM - 2:30 PM • Four Seasons Ballroom 1

Themed Discussion Leader
Frank Maldarelli, *National Cancer Institute, Frederick, MD, USA*

LB Late-Breaking NIS New Investigator Scholarship CROI 2024 45

Themed Discussions

Introductions (Part 1)

348 1:35 PM NIS
Low-Level HIV Viremia Affects T-Cell Activation and Senescence in InSTI Era
Violeta Lara Aguilar, Manuel Llamas-Adán, Oscar Brochado-Kith, Celia Crespo-Bermejo, Sergio Grande-García, Sonia Arca-Lafuente, Ignacio De los Santos, María Carmen Prado, Mario Alía, Coral Sainz-Pinós, Amanda Fernández-Rodíguez, Luz Martín-Carbonero, Ricardo Madrid, Verónica Briz

349 1:40 PM NIS
Ultra-Low Level HIV p24 Production as a Driver of Immune Activation in Individuals Treated with ART
Enrico Richter, Theresa Bechtel, Antonia Büning, Marek Korencak, Trevor A. Crowell, Heiko Jessen, Juergen K. Rockstroh, Stefan Esser, Christoph Boesecke, Hendrik Streeck

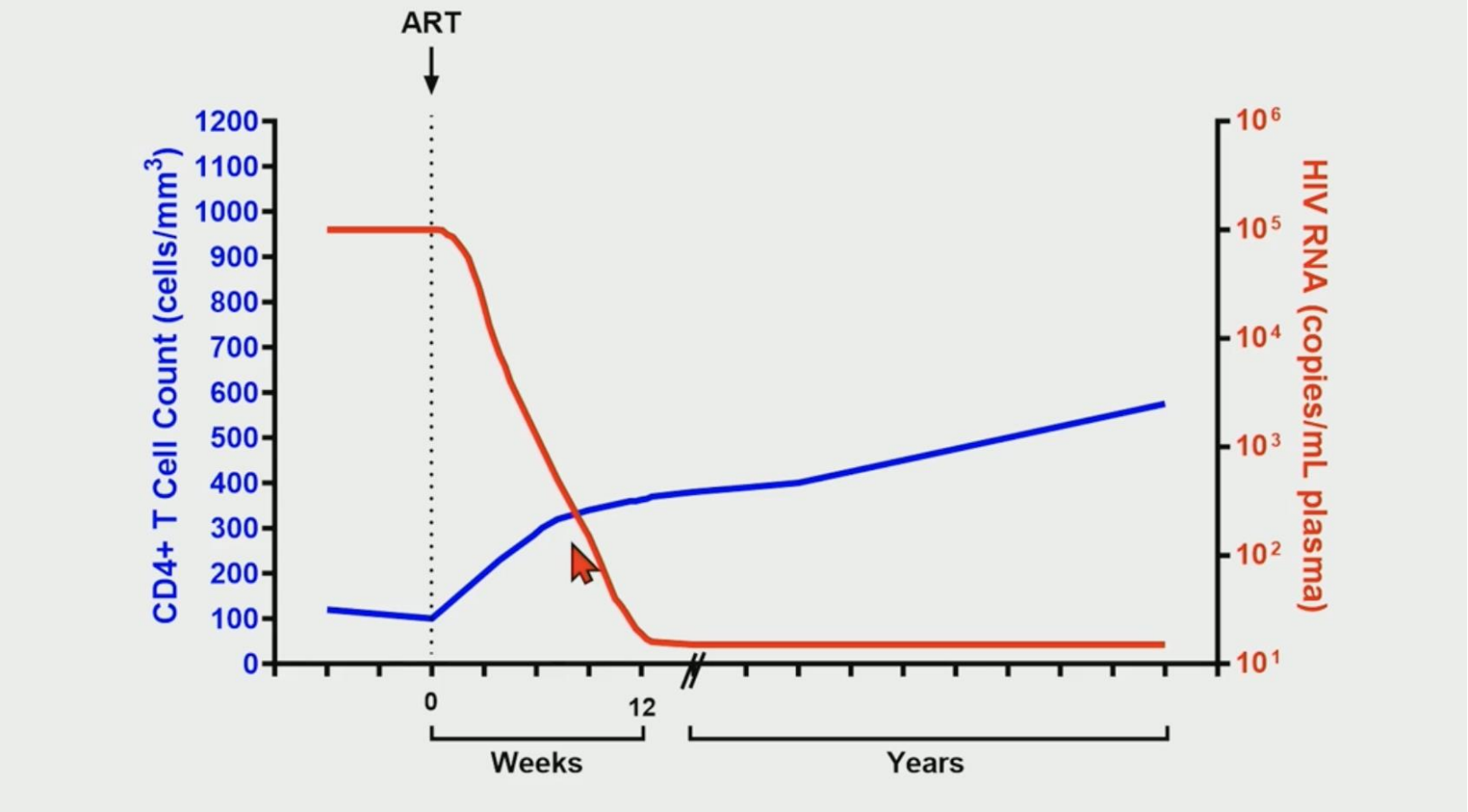
350 1:45 PM NIS
CARD8 Activation in Myeloid Cells as a Driver of Inflammation in HIV Infection
Marilia R. Pinzone, Liang Shan

351 1:50 PM
Increased Immune Activation Following Acute Sleep Deprivation in People With HIV on ART
Priya V. Borker, Benjamin Morris, Jennifer Roscher, Steven Swanger, Sanjay R. Patel, **Bernard J. C. Macatangay**

352 1:55 PM
Immunosuppressive Effects of LLDT-8 in ART-Treated SIV-Infected Rhesus Macaques
Xiaosheng Liu, Tingxia Lv, Jing Xue, Ling Lin, Lianfeng Lu, Xiaodi Li, Yang Yang, Yuanni Wu, Qiang Wei, Wei Cao, Taisheng Li

Discussion with Audience Questions and Answers

Viro-immunological parameters on cART



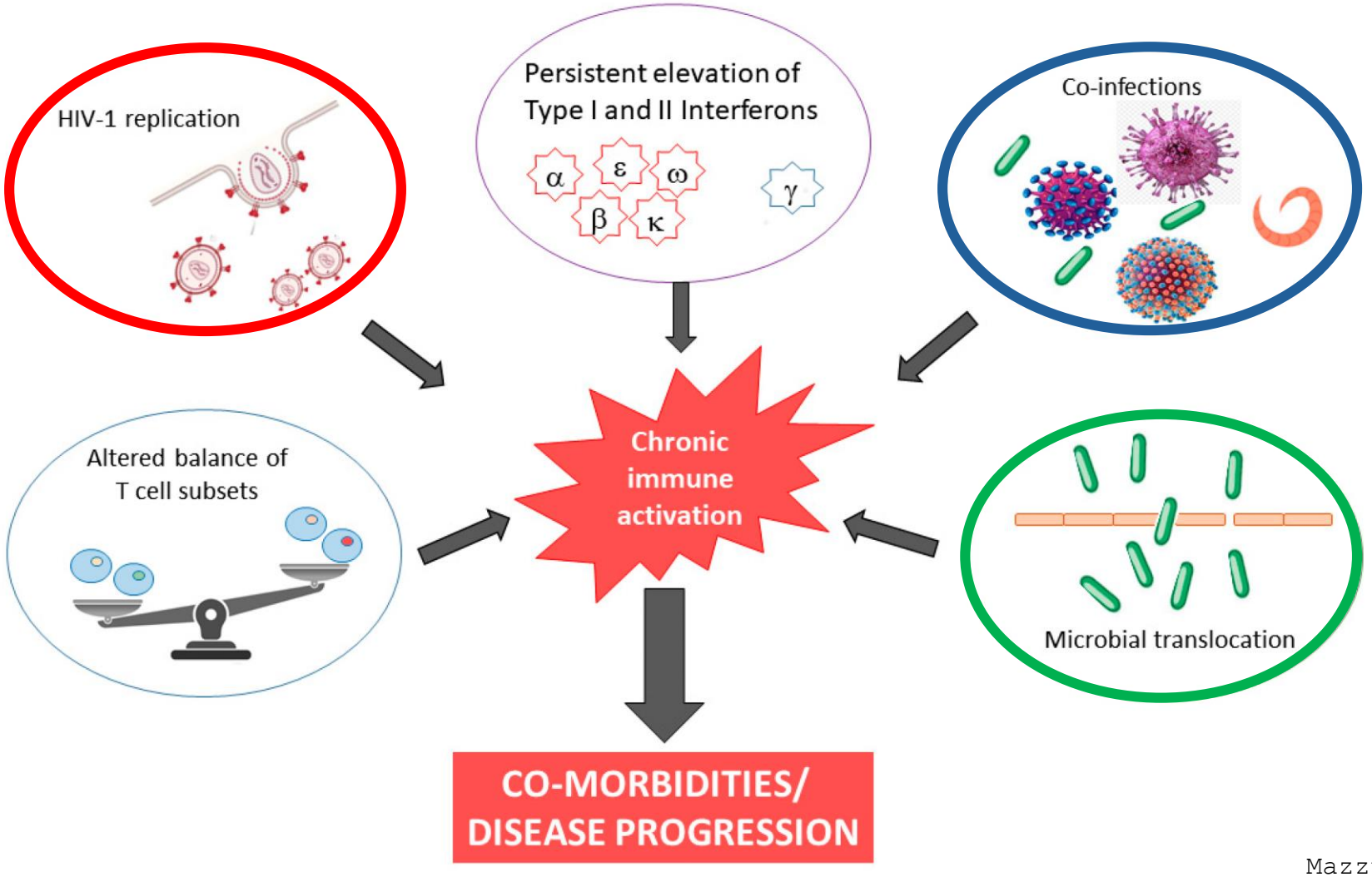
Connick, CROI 2(

Role of immune activation on cART

- **Central pathogenic mechanism during ART**
  - **Life threatening complications upon ART initiation**
    - **Immune Reconstitution Inflammatory Syndrome (IRIS)**
    - **Kaposi Sarcoma Inflammatory Cytokine Syndrome (KICS)**
- **Elevated biomarkers are characteristic of long term ART**
  - **All cause morbidity and mortality**
  - **Biomarker profiles vary among persons with HIV**
    - **Pregnant women**
    - **Pediatric**
    - **Biological and chronological age**
- **Roles in pathogenesis remains uncertain**
  - Correlation-Rich but Causality-Poor
- **Interventional studies**

Maldarelli, CROI 2

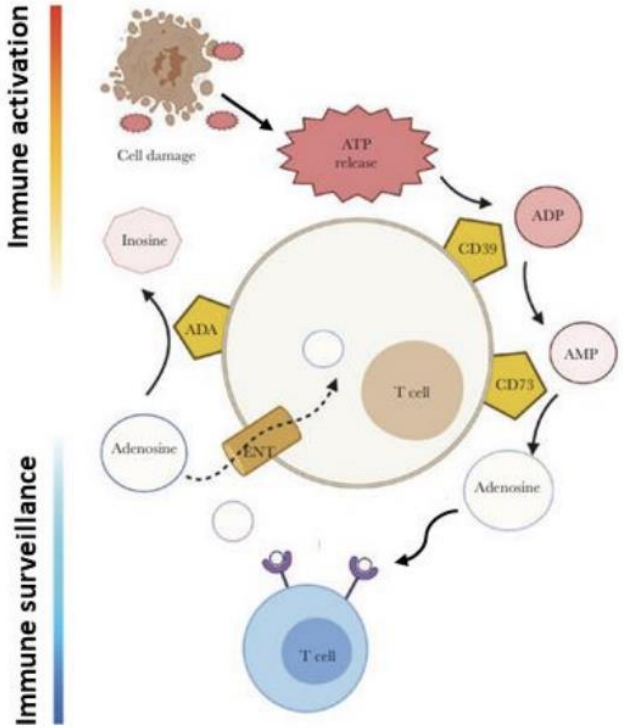
Determinants of immune activation

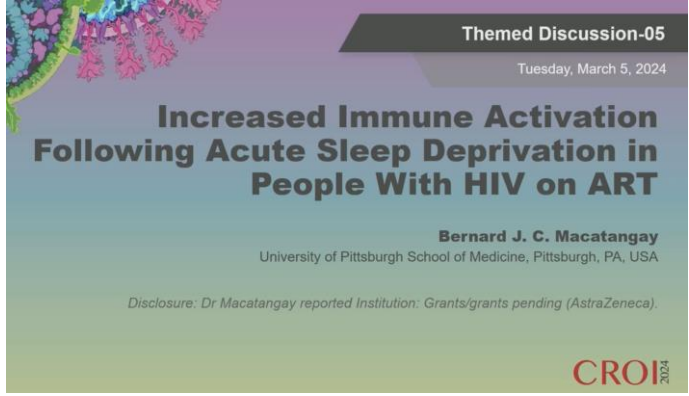


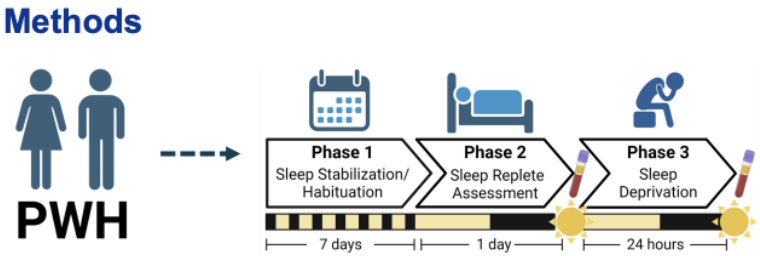
+behaviour

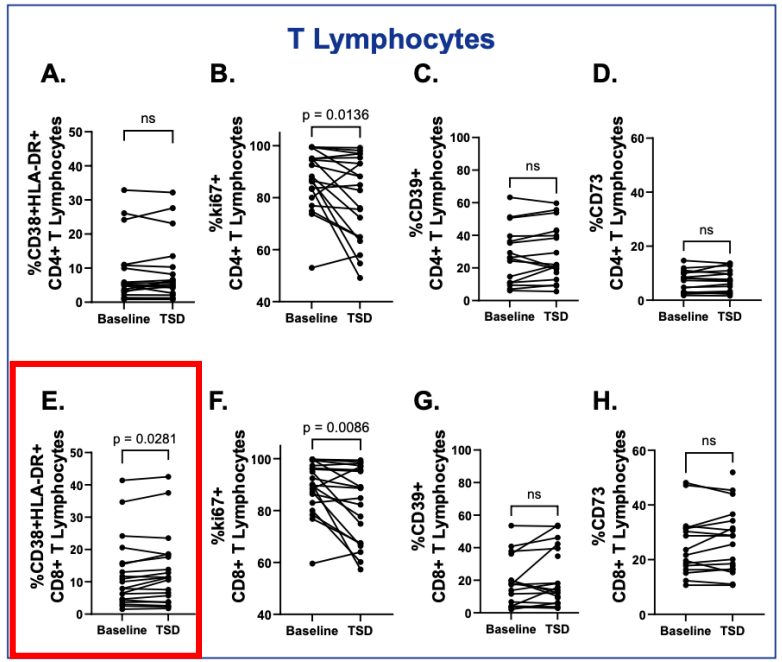
Mazzuti, Biomedicines, 2023

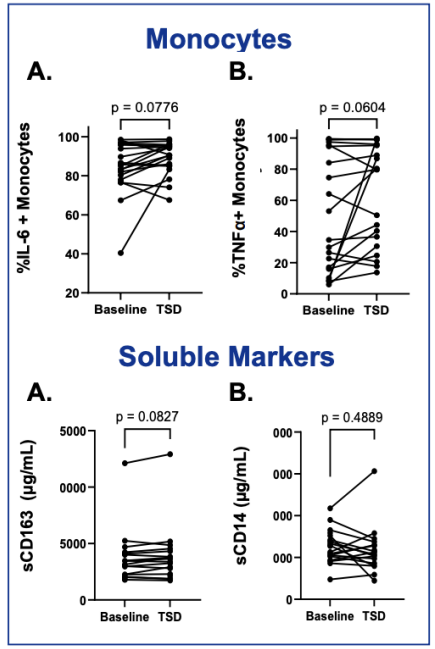
Sleep deprivation and immune activation

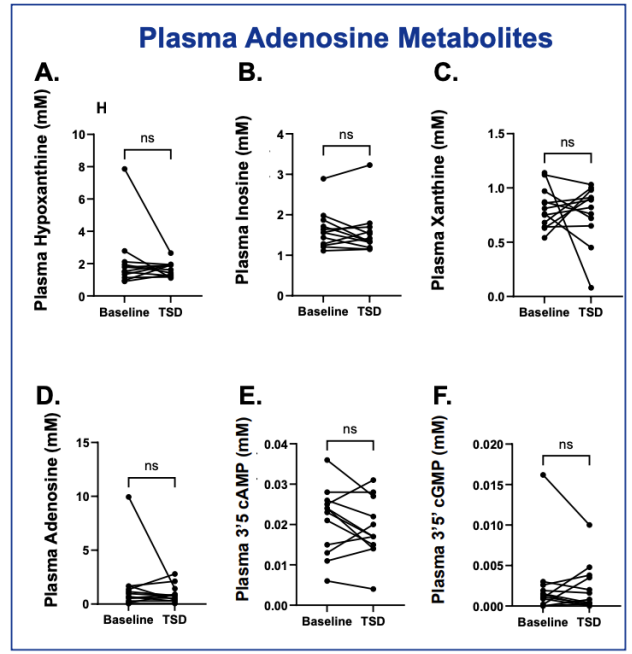












- Extracellular adenosine (ADO) is a potent immune regulatory nucleoside that mediates immune activation
- ADO metabolism is dysregulated in PWH
- Sleep behaviors alter ADO metabolism

Borker, Macatangay #351,

PWH on cART who use MA have increased proinflammatory responses and enhanced HIV transcription

Figure 1. Univariate analyses demonstrated that long-term MA use was associated with increased inflammation (plasma IL-6) and residual HIV reservoir transcription (Pol)

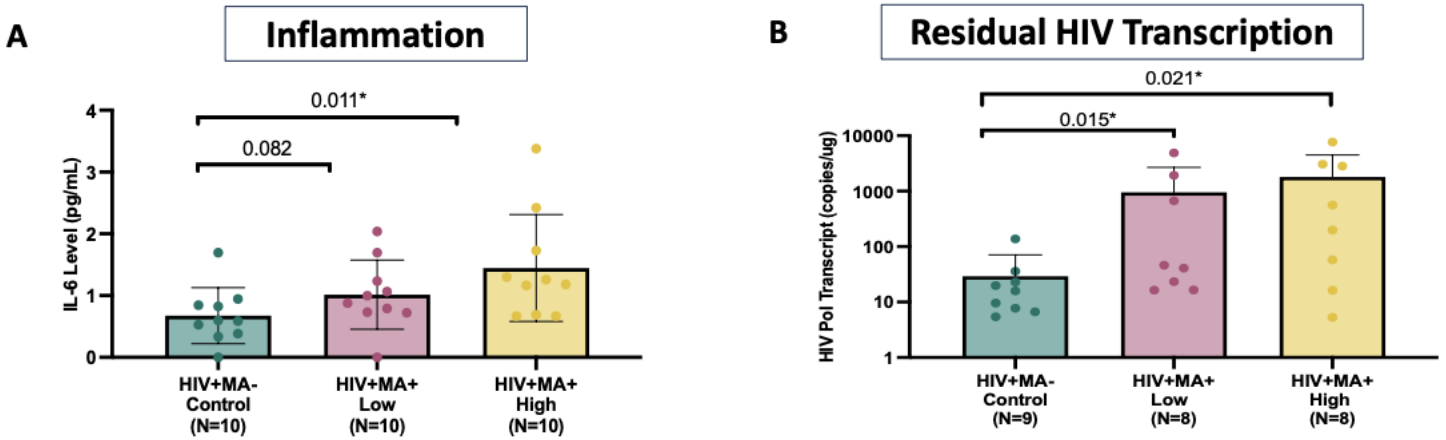
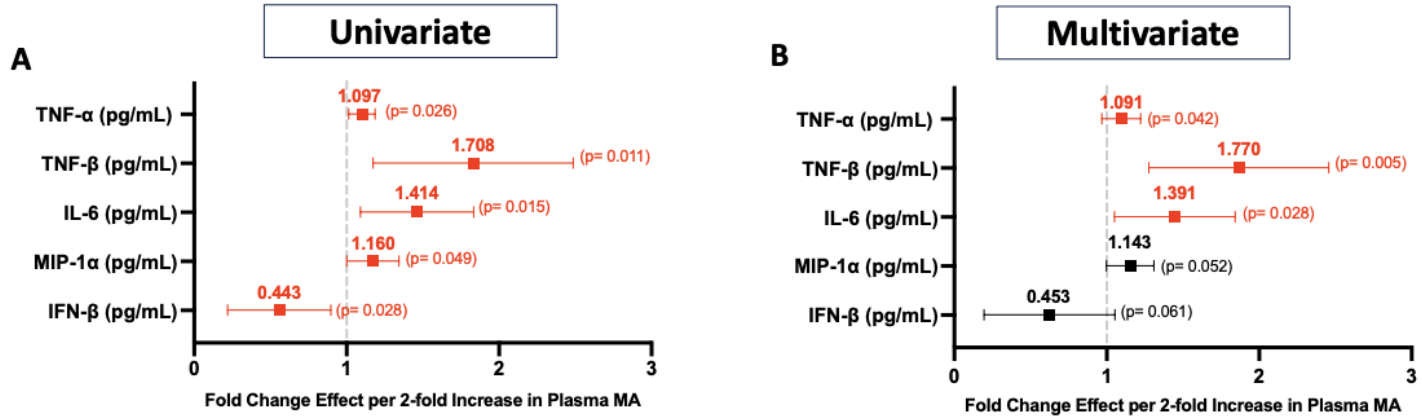


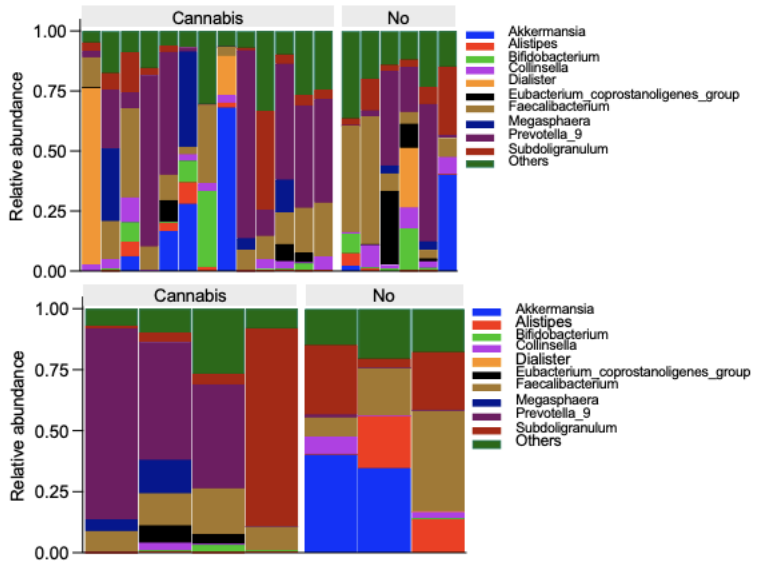
Figure 2. Multivariate modeling among PWH on ART with long-term MA use demonstrated that higher concentrations of MA were significantly associated with inflammatory cytokines (IFN-β, TNF-α, -β, MIP-1α, IL-6)

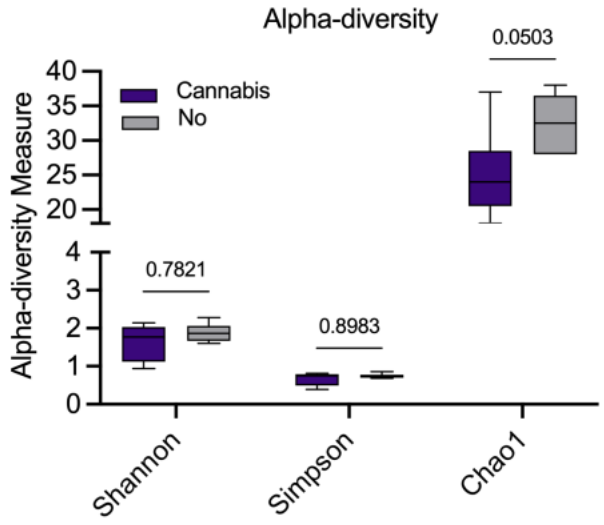


Donaire #356;
CROI 2024

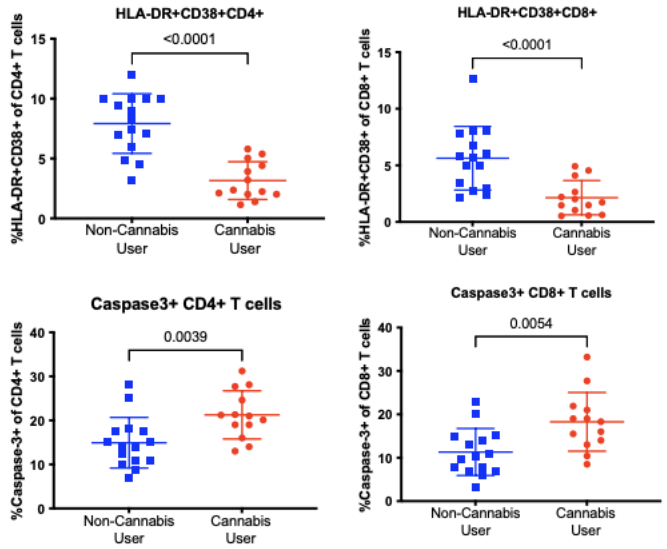
Cannabis enhances mucosal immunity and the microbiome in PLWH

Cannabis alters the gut microbiome in people living with HIV and may increase the abundance of beneficial bacteria

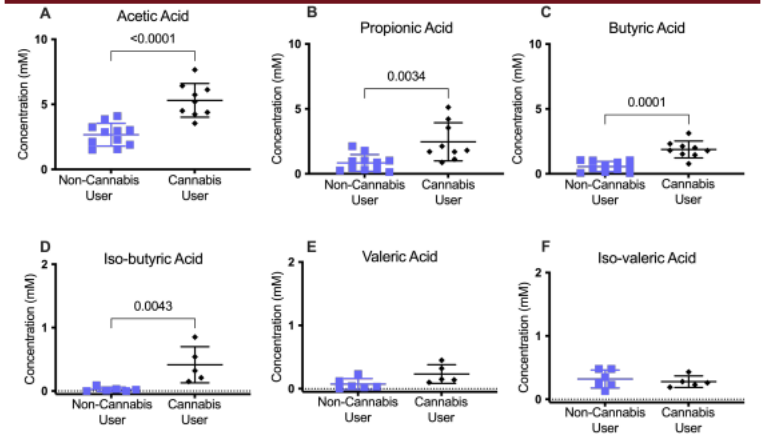




Cannabis use decreases T-cell activation and increases cell death



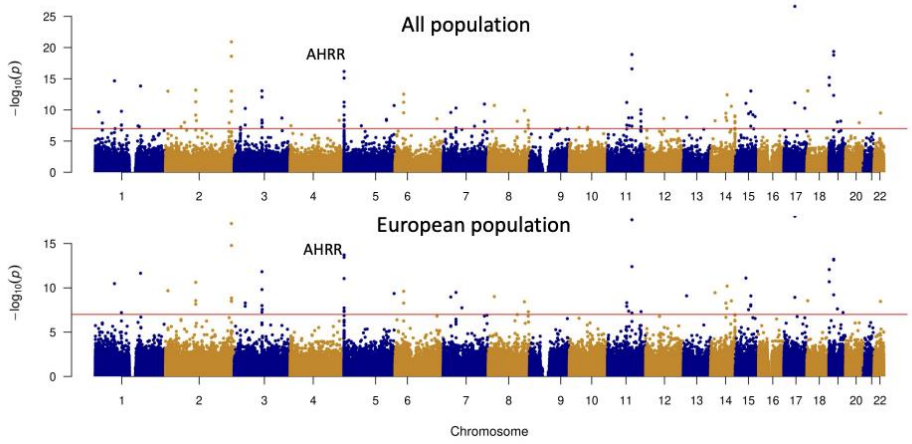
Cannabis use increases short-chain fatty acid production

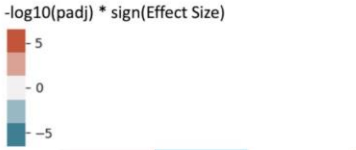


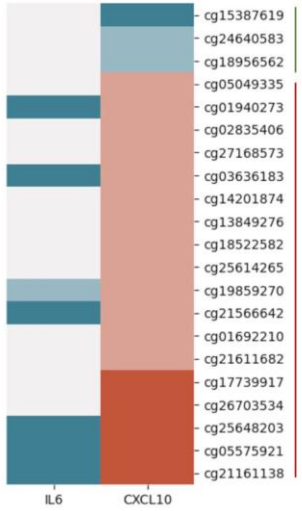
Langat #329; CROI 2024

Cannabis induces DNA methylation and has anti-inflammatory effects

Fig1. Cannabis use induced significant DNA methylation change





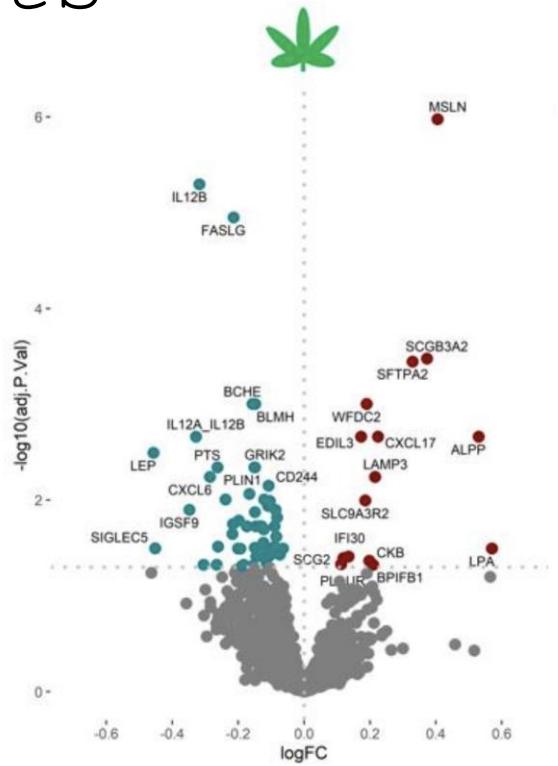


Increased DMS in Cannabis users

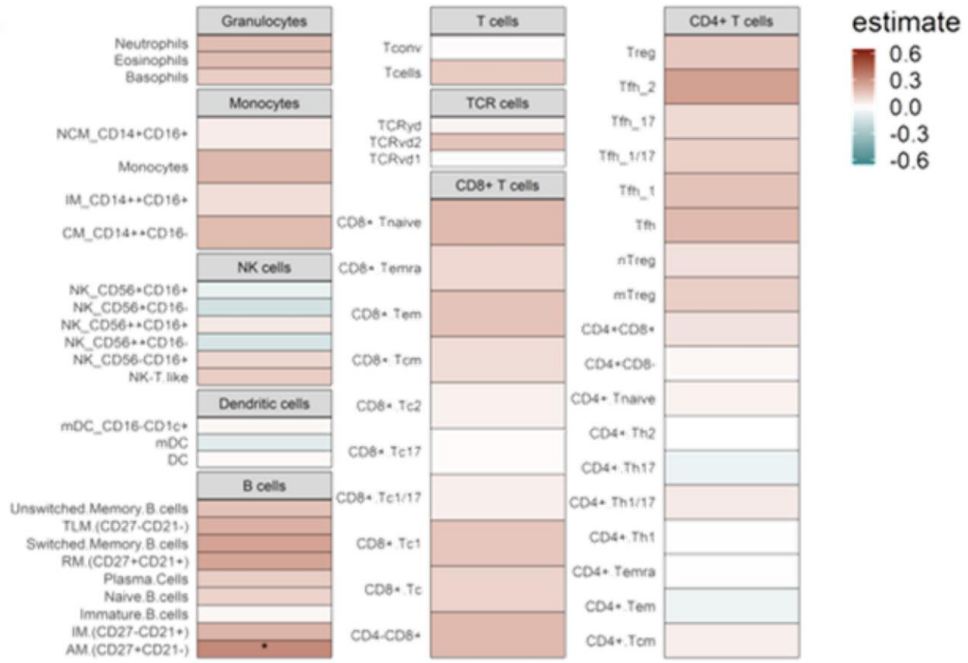
Decreased DMS in Cannabis users

The DMS-associated plasma proteins suggested that DMSs are associated with leukocyte differentiation and cytokine expression, such as IL6 upregulation and CXCL10 downregulation.

The causal inference test suggested that cannabis-induced DMSs may modulate immune response in PLHIV, such



Cannabis use was associated with an upregulation of 15 and a downregulation of 50 proteins. Downregulated proteins in cannabis users were involved in leukocyte-mediated cytotoxicity and NK cell-mediated cytotoxicity



Cannabis use was associated with increased levels of CD27+CD21- B-cells

Jiang #448; Meeder #449
CROI 2024

Low CD4 counts and inflammation associate with herpesvirus reactivation after cART initiation

- 187 WLWH not on ART, aged ≥18 years in south-central Uganda.
- CMV and HSV-2 shedding quantified by PCR on vaginal secretions
- HHV-8` shedding on oral swabs

Fig1. Herpesvirus shedding during the study time points

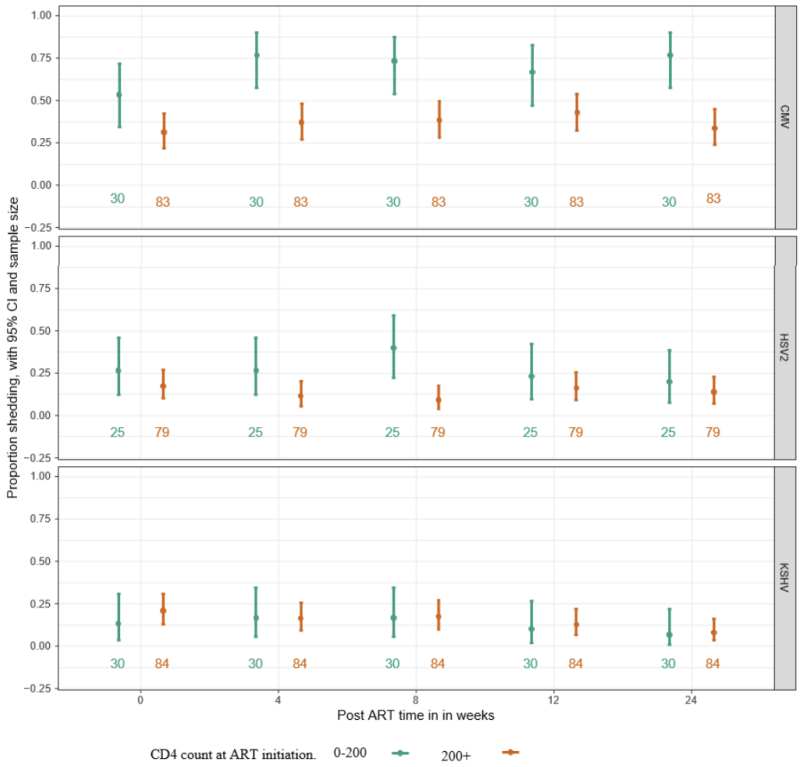


Fig2. Heatmap of median cytokine values over time by ever-shedding status and baseline CD4 count of 0-200 versus >200 cells /µL

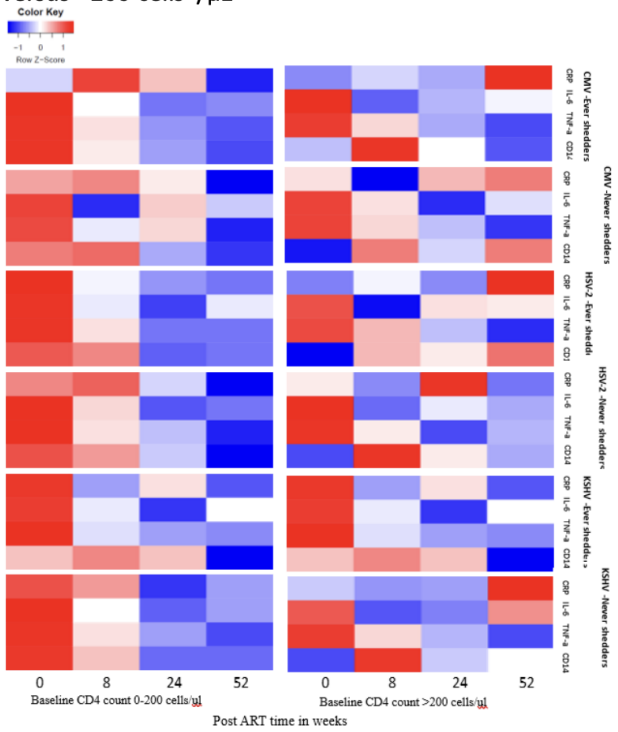


Table 1: Primary Outcome Table
Proportion of women shedding herpesviruses at baseline, week 4 and 8 of ART

Herpes virus type	Baseline CD4 category	Baseline proportion (95% CI)	Week 4 proportion (95% CI)	Week 4 p-value	Week 8 proportion (95% CI)	Week 8 p-value
CMV	**0-200**	**0.53 (0.34, 0.72)**	**0.77 (0.58, 0.90)**	**0.016**	**0.73 (0.54, 0.88)**	**0.027**
	>200	0.31 (0.22, 0.42)	0.37 (0.27, 0.48)	1.000	0.38 (0.28, 0.49)	0.719
HSV2	0-200	0.27 (0.12, 0.46)	0.27 (0.12, 0.46)	1.000	0.40 (0.23, 0.59)	0.302
	>200	0.17 (0.10, 0.27)	0.12 (0.06, 0.20)	0.689	0.09 (0.04, 0.18)	0.081
KSHV	0-200	0.13 (0.04, 0.31)	0.17 (0.06, 0.35)	0.221	0.17 (0.06, 0.35)	0.683
	>200	0.21 (0.13, 0.31)	0.16 (0.09, 0.26)	0.383	0.17 (0.10, 0.27)	0.823

Table 3. Association of shedding herpesviruses at week 8 of ART with the level of plasma biomarkers at baseline

Type of herpes virus at 8 weeks	Plasma Biomarker (log10 pg/mL) at baseline	Herpes virus shedding at baseline	Odds ratio	95% CI	p-value (Main effects)	p-value (Interaction effect
CMV	IL-6		1.454	(0.552, 3.926)	0.450	
	CRP		**1.826**	**(1.027, 3.358)**	**0.044**	
	TNF-α		**7.790**	**(1.117, 62.337)**	**0.044**	
	CD14		2.970	(0.194, 55.124)	0.448	
HSV2	**IL-6**	**No**	**4.372**	**(0.796, 27.187)**	**0.097**	**0.014**
		Yes	**0.173**	**(0.016, 1.163)**		
	CRP		1.096	(0.552, 2.221)	0.793	
	TNF-α		1.223	(0.121, 12.203)	0.863	
	CD14	**No**	**1.625**	**(0.031, 191.813)**	**0.829**	**0.035**
		Yes	**0.001**	**(0.000, 0.288)**		
KSHV	IL-6		0.939	(0.245, 3.463)	0.925	
	CRP		1.536	(0.697, 3.468)	0.291	
	TNF-α		1.744	(0.149, 19.703)	0.652	
	CD14		2.192	(0.063, 138.189)	0.690	

Ssempijja #322; CROI 2024

Letermovir reduces immunologic and cardiometabolic biomarkers in PLWH

Figure 1. Futility Analysis: Letermovir unexpectedly increased sTNFR2 and had little effect on sCD163

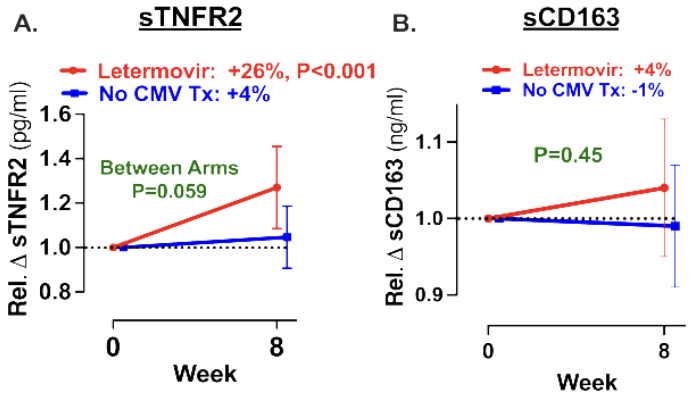


Figure 2. Suppression of CMV viral IL-10 may have contributed to the increase in plasma sTNFR2.

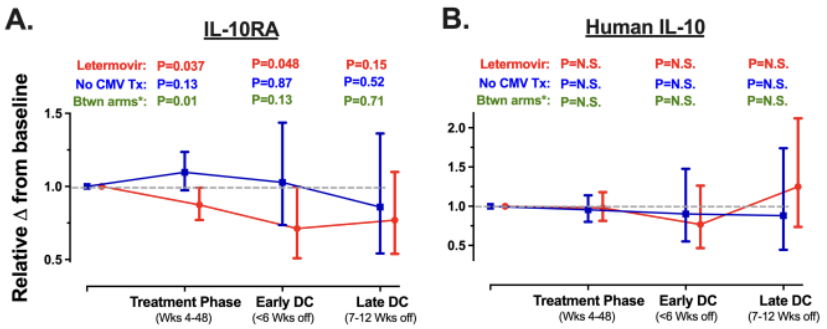
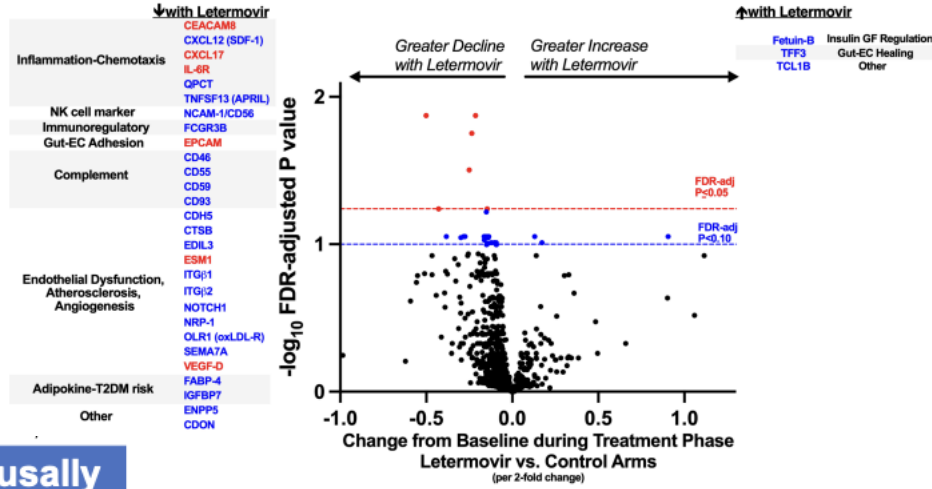


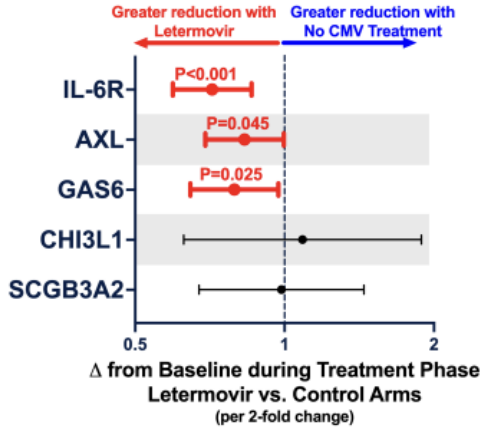
Figure 3. Letermovir broadly impacts immunologic and cardiometabolic biomarkers in people with HIV.



Evaluate the antiinflammatory efficacy of letermovir 480 mg once daily for 48 weeks in PWH and asymptomatic CMV with ART-mediated suppression

Letermovir, n=18
No treatment, n=21

Figure 4. Letermovir suppresses 3/5 proteins causally linked to CVD Events by Mendelian Randomization



- Reilly et al conducted the first Mendelian Randomization study of causal determinants of CVD events in treated HIV. (Reilly et al, JID, 2023)
- These 5 proteins were the only ones causally linked to CVD events.
- Letermovir decreased three of them (IL-6R, AXL, GAS6) to a greater degree than in the control arm.
- AXL and GAS6 are unique causal predictors of CVD in HIV.
- AXL/GAS6 also linked to transplant vasculopathy (Glinton, J Heart Lung Transpl, 2021)

Weibel #354 CROI 2024

Oral microbial trans

ORAL MICROBIOME CHANGES WITH HIV

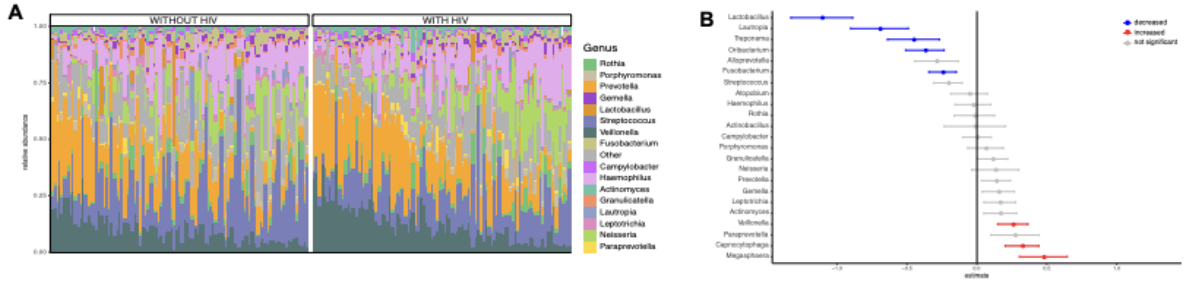


Figure 1. Oral microbiome composition is altered in HIV. (A) Oral microbiome composition in saliva shown as relative abundance between MSM with HIV (right, n=99) and without HIV (left, n=99). **(B)** Forest plot showing significant changes in oral microbiome in MSM with HIV and without HIV. Significantly increased (red) or decreased (blue) taxa were determined using zero-inflated negative binomial models with FDR-adjusted q<0.05.

ORAL BACTERIA ARE SIGNIFICANT CONTRIBUTORS TO INFLAMMATORY CYTOKINES

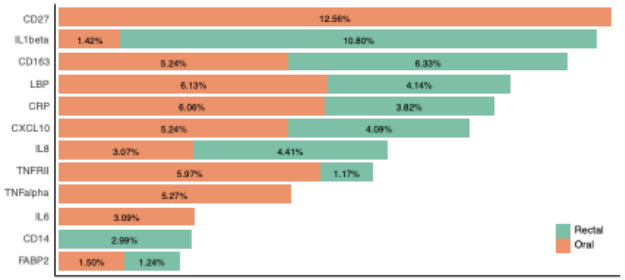


Figure 2. Relative contributions of oral and gut bacteria to cytokine variation in HIV. Relative contribution of the gut (green) or oral (orange) microbiome to serum cytokine variation as determined by PERMANOVA.

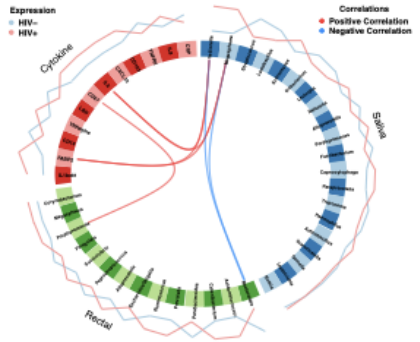


Figure 3. Relationships between oral and gut bacteria with inflammatory cytokines in HIV. Circos plot showing positive correlations (red) between *Porphyromonas* in the gut and *Veillonella* and *Megasphaera* in the saliva with inflammatory cytokines (analysis performed using mixOmics).

VEILLONELLA PARVULA IgG TITERS CORRELATE WITH MARKERS OF MICROBIAL TRANSLOCATION

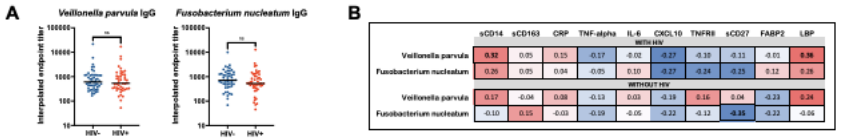


Figure 4. Serum anti-bacteria IgG endpoint titers in HIV. (A) Anti-bacteria IgG endpoint titers were measured in serum by ELISA. Endpoint titers were interpolated from serial dilutions using negative pooled serum as cutoff. Titers were compared between HIV serogroups using Kruskal-Wallis tests. **(B)** Spearman correlation between inflammatory cytokines/biomarkers and anti-bacteria endpoint titers. Heatmap shows results separated by HIV status. Numbers are Spearman rho values with significant values (p<0.05) in bold.

EXPOSURE TO VEILLONELLA PARVULA ALTERS ORAL BARRIER FUNCTION AND INFLAMMATORY RESPONSES

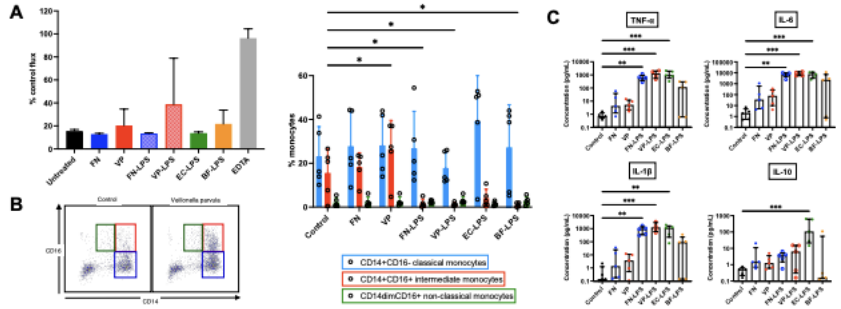
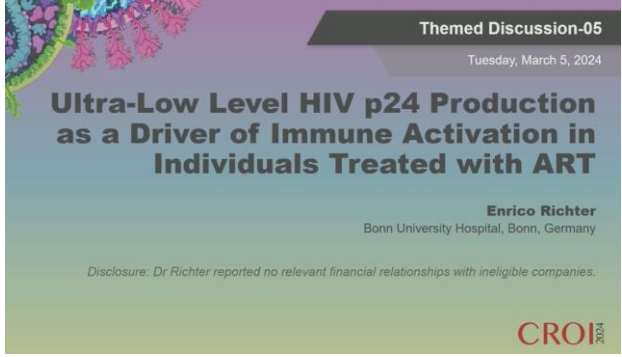


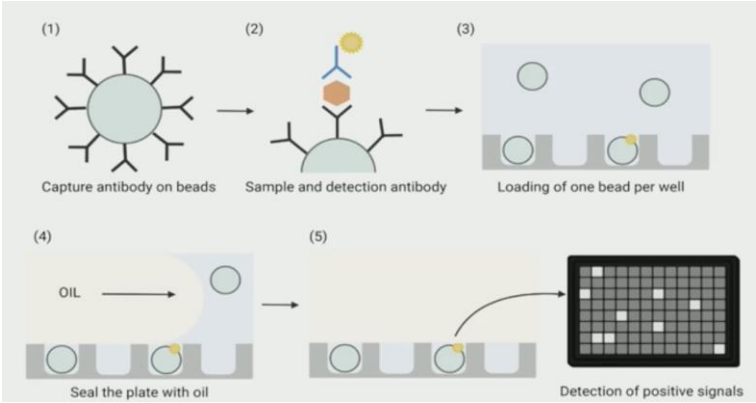
Figure 5. Effects of *Veillonella parvula* on oral epithelial barrier function and PBMC responses. (A) FITC-dextran permeability assay showing increased permeability following treatment with either heat-inactivated bacteria or isolated LPS from VP. Mean standard deviation from 3 independent experiments. **(B)** Altered monocyte subsets with increased CD14+CD16+ intermediate monocytes (red) following co-culture with heat-inactivated VP bacteria. **(C)** Increased inflammatory cytokines production in supernatant from PBMC co-cultures with heat-inactivated bacteria or isolated LPS. Data shown includes five independent donors. *p<0.05; **p<0.005; ***p<0.001
FN, *Fusobacterium nucleatum*; VP, *Veillonella parvula;* EC-LPS, lipopolysaccharide from *E.Coli*; BF-LPS, lipopolysaccharide from *Bacteroides fragilis*

Cho #333, CROI 2024

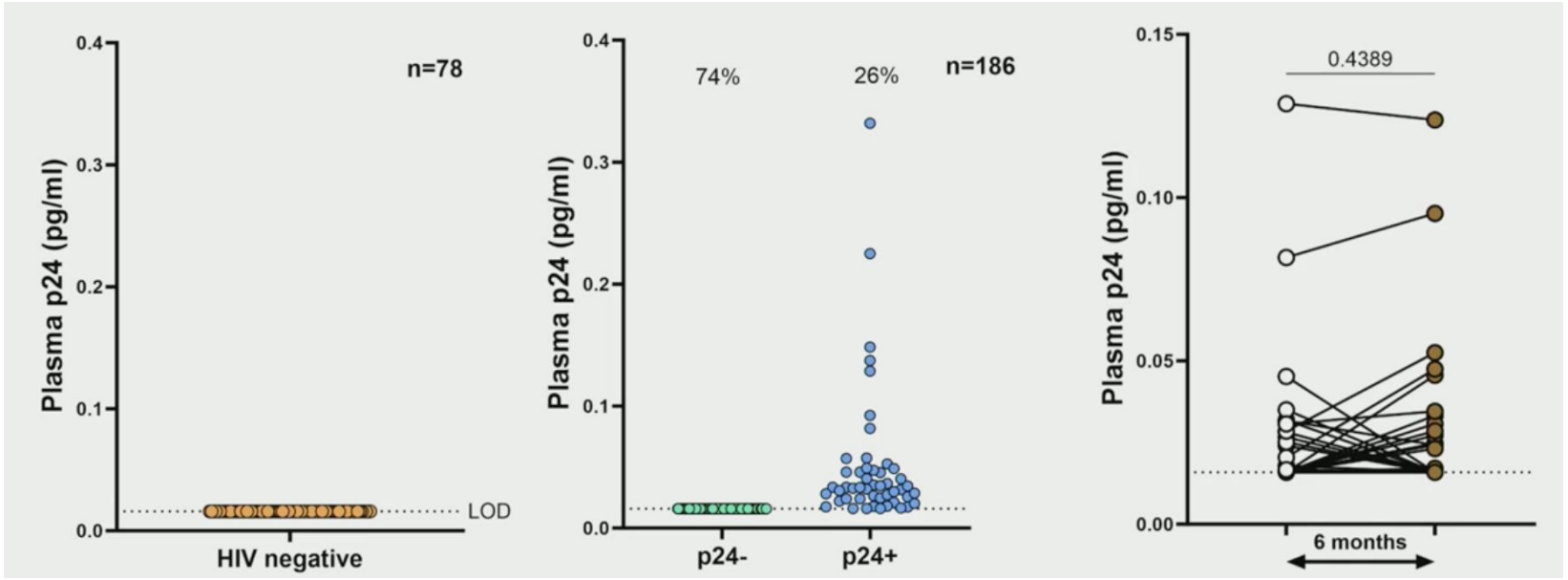
p24 is detectable in 26% of PLWH on suppressive cART

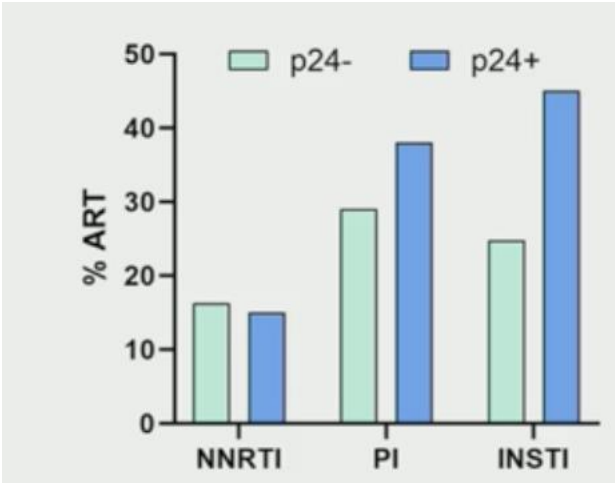


We used an ultrasensitive p24 single-molecule array from SIMOA™ to detect p24 in plasma at a 1000-fold lower concentration compared to previous assays.



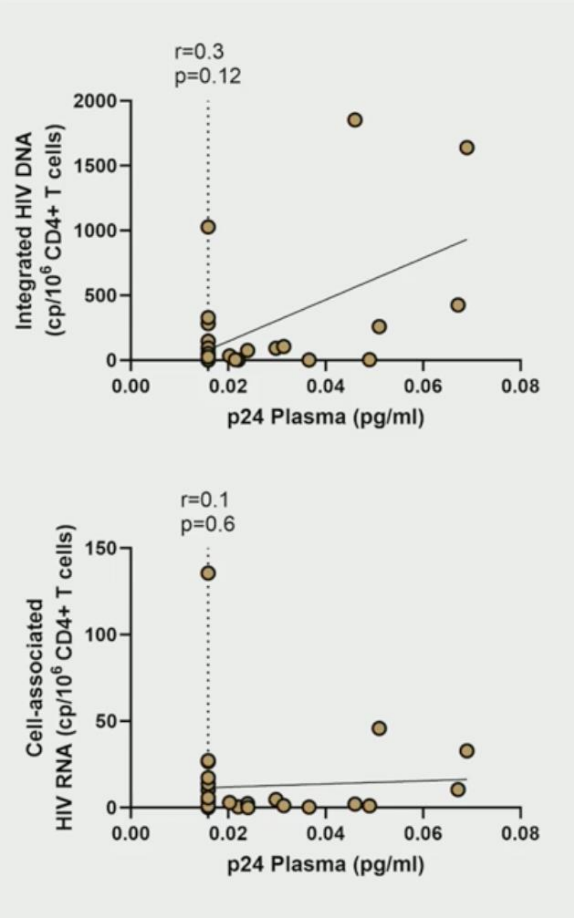
- All on suppressive cART (mean duration 8.4 years
- No association with gender, age, CD4 and CD4/CD8 ratio

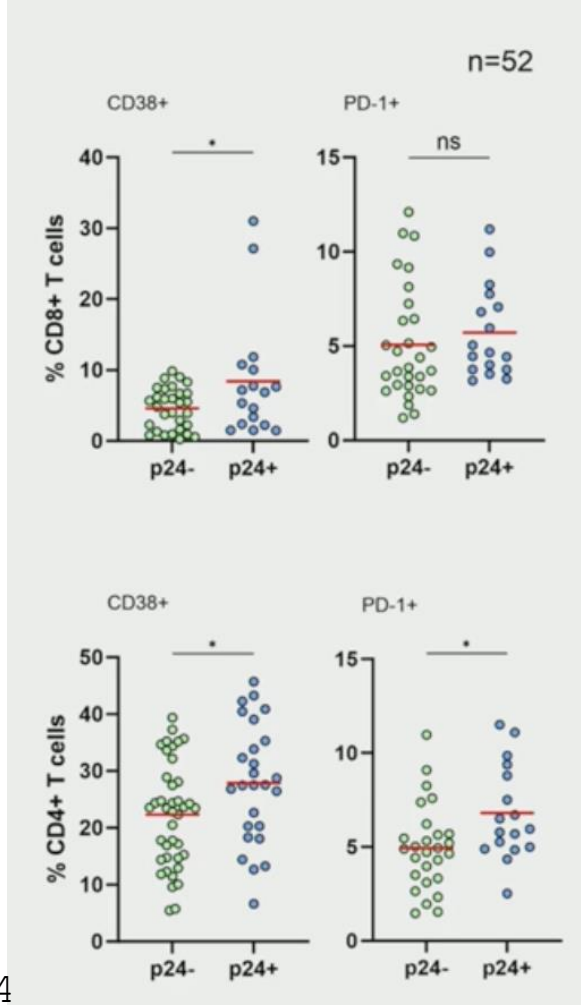


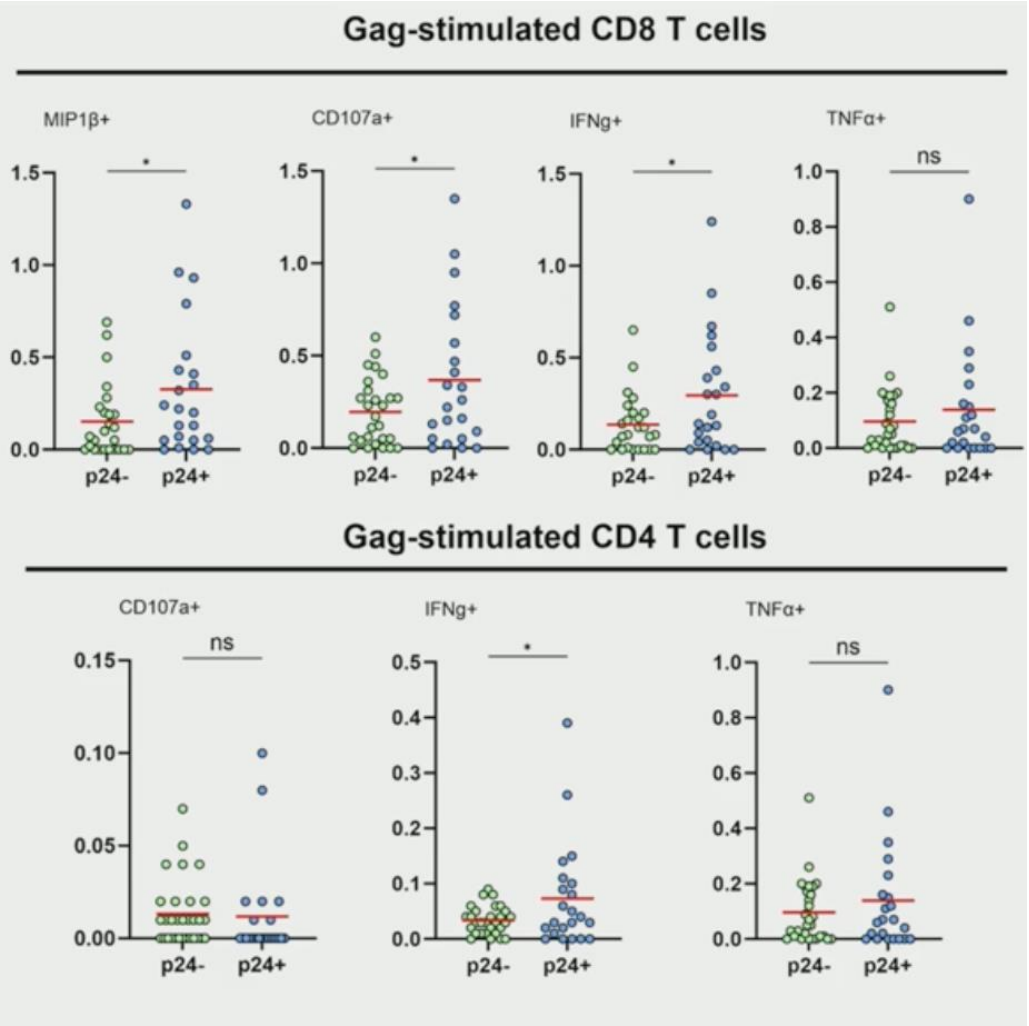


Richtner #349, CROI 2024

p24 associates with immune activation and HIV-specific T-cell responses







Richtner #349, CROI 2024

LLV leads to higher activatio (EM, TEMRA)

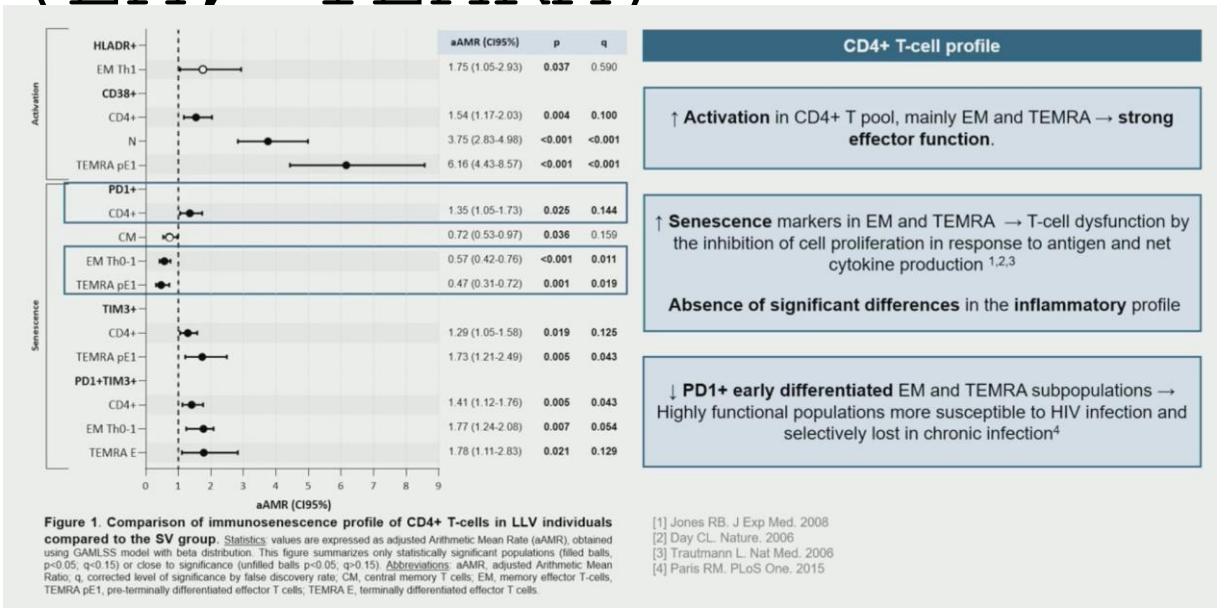


Figure 1. Comparison of immunosenescence profile of CD4+ T-cells in LLV individuals compared to the SV group. Statistics: values are expressed as adjusted Arithmetic Mean Rate (aAMR), obtained using GAMLSS model with beta distribution. This figure summarizes only statistically significant populations (filled balls, p<0.05; q<0.15) or close to significance (unfilled balls p<0.05; q>0.15). Abbreviations: aAMR, adjusted Arithmetic Mean Ratio; q, corrected level of significance by false discovery rate; CM, central memory T cells; EM, memory effector T cells; TEMRA pE1, pre-terminally differentiated effector T cells; TEMRA E, terminally differentiated effector T cells.

CD4+ T-cell profile

↑ **Activation** in CD4+ T pool, mainly EM and TEMRA → **strong effector function**.

↑ **Senescence** markers in EM and TEMRA → T-cell dysfunction by the inhibition of cell proliferation in response to antigen and net cytokine production [1,2,3]

Absence of significant differences in the **inflammatory** profile

↓ **PD1+ early differentiated** EM and TEMRA subpopulations → Highly functional populations more susceptible to HIV infection and selectively lost in chronic infection[4]

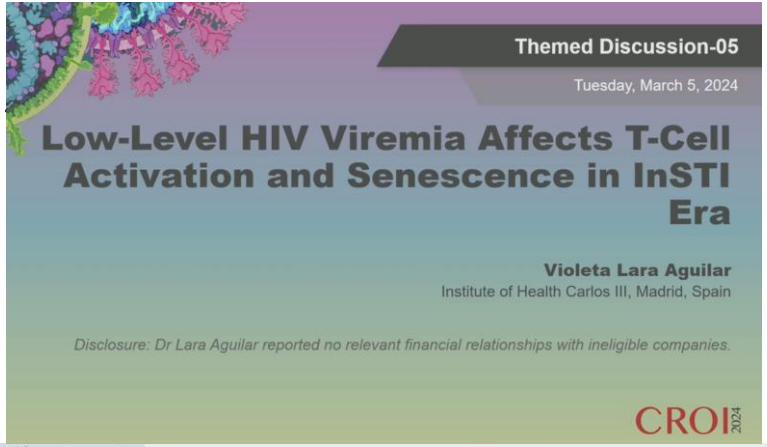
[1] Jones RB. J Exp Med. 2008
[2] Day CL. Nature. 2006
[3] Trautmann L. Nat Med. 2006
[4] Paris RM. PLoS One. 2015

Table 1. Epidemiological and clinical characteristics of participants enrolled in this study

Characteristics	LLV (n=27)	SV (n=27)	p
Age (years)	53.00 (47.50-58.00)	54.00 (49.00-59.00)	0.775
Sex at birth (male) [n(%)]	21 (77.80%)	21 (77.80%)	1.000
Ethnicity (caucasian) [n(%)]	25 (92.60%)	25 (92.60%)	1.000
BMI (kg/m²)	26.90 (24.65-28.70)	24.90 (23.00-28.10)	0.228
HIV infection (years)	16.00 (10.50-21.50)	16.50 (12.25-24.00)	0.454
Transmission route [n(%)]			
MSM	14 (56.00%)	13 (54.20%)	
Heterosexual contact	8 (32.00%)	7 (29.20%)	1.000
IDU	3 (12.00%)	4 (16.70%)	
Time on ART (years)	14.00 (9.50-19.00)	16.00 (11.50-22.00)	0.401
Classes of ART [n(%)]			
INSTI+2NRTI	13 (48.10%)	5 (18.50%)	
INSTI+NRTI	3 (11.10%)	4 (14.80%)	
INSTI+NNRTI	-	4 (14.80%)	
INSTI+IP	1 (3.70%)	-	
INSTI+IP+2NRTI	1 (3.70%)	-	<0.001
INSTI+IP+NRTI	2 (7.40%)	-	
IP+2NRTI	6 (22.20%)	1 (3.70%)	
IP+NRTI	1 (3.70%)	1 (3.70%)	
NNRTI+2NRTI	-	12 (44.40%)	
Régimen of ART [n(%)]			
Bitherapy	5 (18.50%0%)	9 (33.30%0%)	0.352
Tritherapy	22 (81.50%0%)	18 (66.70%0%)	
Lymphocyte count (cell/mm³)			
CD4+ T-cells	716.50 (514.50-992.50)	1005.00 (673.00-1161.00)	0.104
CD4+ T nadir	231.50 (85.25-376.25)	275.50 (188.00-391.75)	0.174

53 years old
78% men

ART based on INSTI
- 74% LLV (n=20)
- 48% SV (n=13)



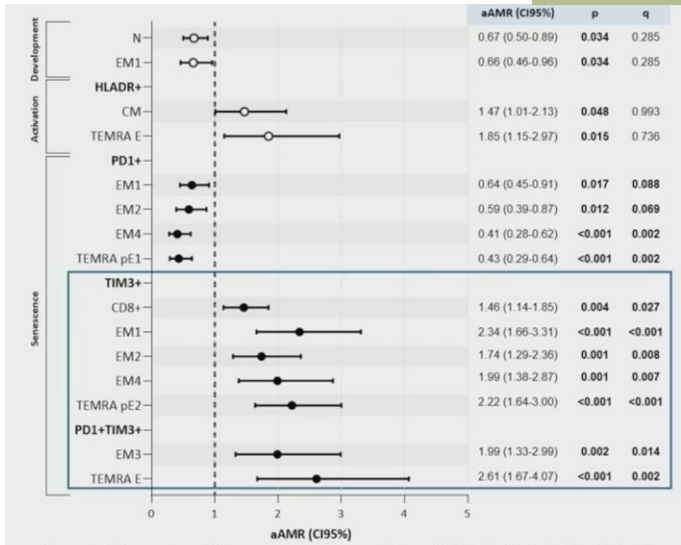


Figure 1. Comparison of immunosenescence profile of CD4+ T-cells in LLV individuals compared to the SV group. Statistics: values are expressed as adjusted Arithmetic Mean Rate (aAMR), obtained using GAMLSS model with beta distribution. This figure summarizes only statistically significant populations (filled balls, p<0.05; q<0.15) or close to significance (unfilled balls p<0.05; q>0.15). Abbreviations: aAMR, adjusted Arithmetic Mean Ratio; q, corrected level of significance by false discovery rate; CM, central memory T cells; EM, memory effector T cells; TEMRA pE1, pre-terminally differentiated effector T cells; TEMRA E, terminally differentiated effector T cells.

CD8+ T-cell profile

Upward trend in **activated CM** and **TEMRA E** subpopulations → higher viremias (40-999 copies/mL).
Strong immune activation + ↑ circulating viral antigens → T-cell **exhaustion**[5,6]

↑ **TIM3+** and **PD1+TIM3+** in **EM and TEMRA subpopulations** → Reduced effector functions and clonal elimination of antigen-specific T cells[7]

Absence of significant differences in the **inflammatory** profile

[5] Douek DC. Nature 2002
[6] Papagno L. PloS Biol. 2004
[7] Guerville F. AIDS. 2023

Aguilar #348, CROI 202

Immunologic concepts and knowledge gaps

- **Immunopathogenesis of untreated HIV**

-cellular and humoral immune responses

- **Immunopathogenesis of HIV during cART**

-immune activation and inflammation

Immunopathogenesis of CVD

- focus on Reprieve

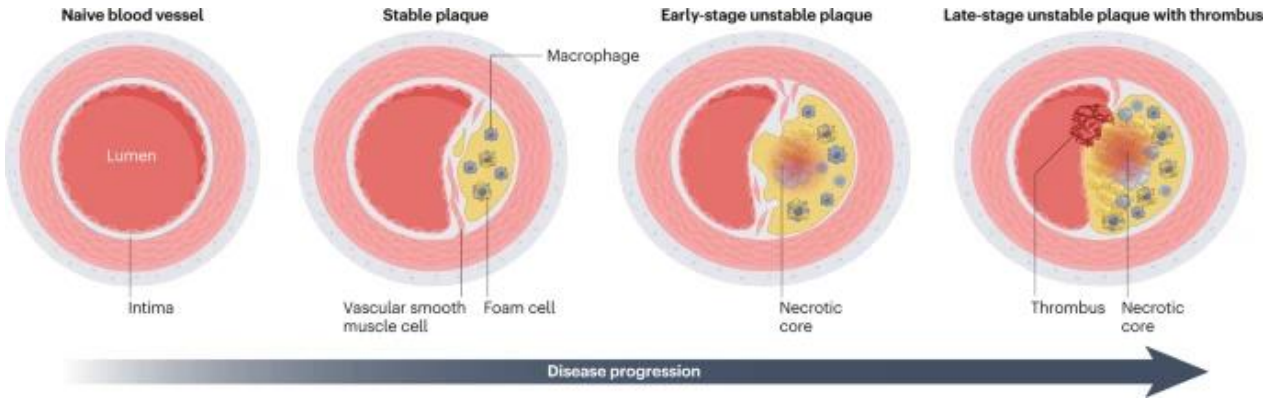
Rationale of the Reprieve Study

- Increased CVD in PLWH

- low- to-moderate traditional risk factors

- unique atherosclerotic phenotype: vulnerable, non-calcified plaque

- Hypothesis: statin could prevent CVD with pleiotropic effects beyond LDL lowering

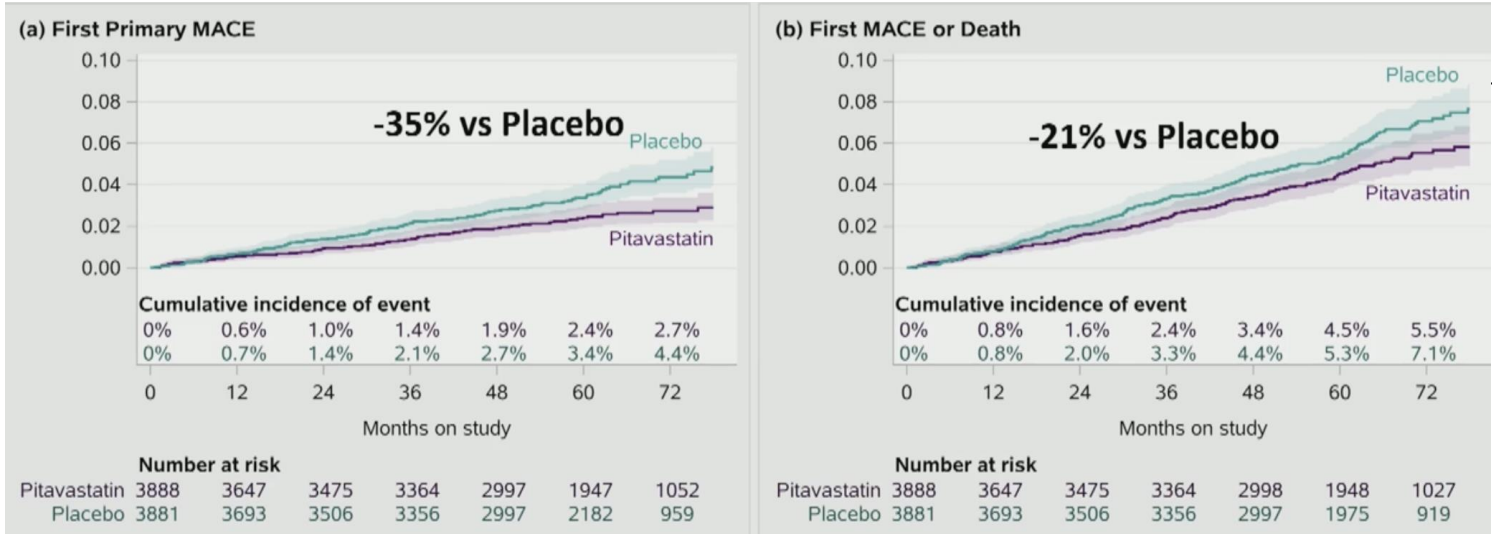


De Meyer, Nat Rev Cardiol, 2024

Primary and Key Secondary Endpoints

- RCT of 7769 participants, age 50, low to moderate Pooled Cohort Equation (PCE*) risk: 4.5%, LDL 108 mg/dL
- Trial stopped early for efficacy (average 5 year duration FU):

– first primary MACE: -35% vs placebo



acebo

*estimates the risk of ASCVD within a 10-year period among patients who have never had one of these events in the past.

Grinspoon, NEJM, 2

REPRIEVE in comparison with other key studies: larger effect size

SELECT:
-20%

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Lincoff AM et al. DOI: 10.1056/NEJMoa2307563

CLINICAL PROBLEM

Glucagon-like peptide-1 (GLP-1) receptor agonists can reduce the risk of adverse cardiovascular events in patients with diabetes. Whether the GLP-1 receptor agonist semaglutide can also reduce cardiovascular risk in patients with overweight or obesity but without diabetes is unknown.

CLINICAL TRIAL

Design: An international, double-blind, event-driven, randomized, placebo-controlled, superiority trial assessed the safety and efficacy of semaglutide in patients with preexisting cardiovascular disease, overweight or obesity (body-mass index, ≥27), and no history of diabetes.

Intervention: 17,604 adults ≥45 years of age were assigned to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo. The primary cardiovascular end point was a composite of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis.

RESULTS

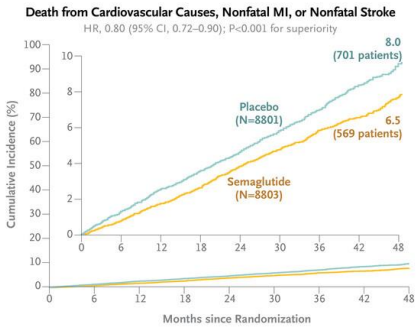
Efficacy: Semaglutide was superior to placebo in reducing the incidence of primary end-point events during a mean follow-up of approximately 40 months.

Safety: More patients discontinued semaglutide than placebo because of adverse events, a result driven largely by a higher incidence of gastrointestinal symptoms with semaglutide.

LIMITATIONS AND REMAINING QUESTIONS

- The trial was limited to patients with preexisting cardiovascular disease.
- The diversity of the trial population did not duplicate a globally representative population; specifically, women and patients identifying as Black were underrepresented.

Links: Full Article | NEJM Quick Take | Editorial



CONCLUSIONS

In patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, once-weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke during a mean follow-up of approximately 40 months.

CANTOS:
-15%

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

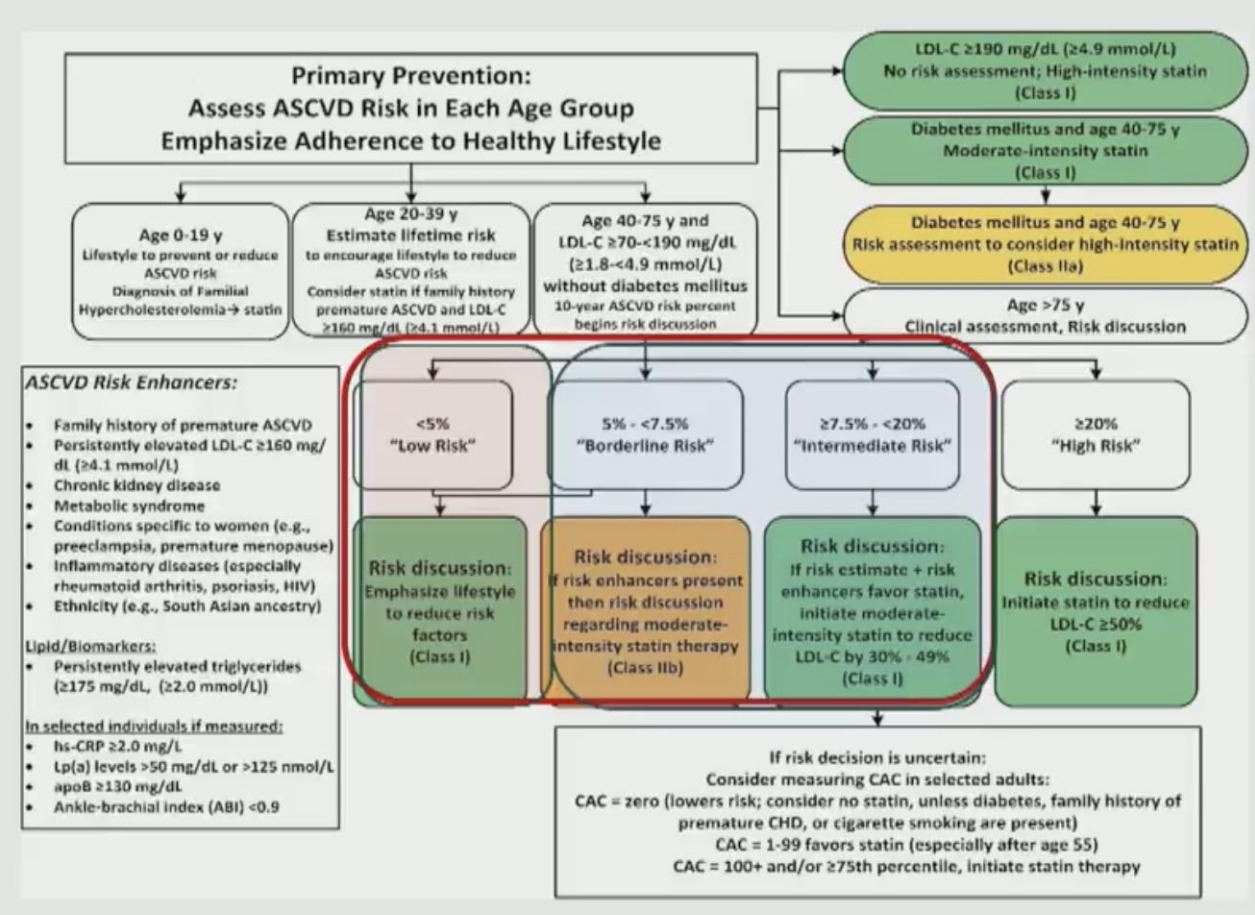
Authors: Paul M Ridker, M.D., Brendan M. Everett, M.D., Tom Thuren, M.D., Jean G. MacFadyen, B.A., William H. Chang, Ph.D., Christie Ballantyne, M.D., Francisco Fonseca, M.D., +21, for the CANTOS Trial Group* Author Info & Affiliations

Published September 21, 2017 | N Engl J Med 2017;377:1119-1131 | DOI: 10.1056/NEJMoa1707914
VOL. 377 NO. 12

CONCLUSIONS

Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)

DHHS/HIVMA/AHA/ACC Guidelines Expanded 29/2/24* to Include Data from REPRIEVE



AI Recommendation
Pitava 4 mg/d

All Recommendation
Rosuva 10 mg/d
Atorva 20 mg/d

C1 Recommendation

*Before: unclear what to do between 5

Why was the study intervention in REPRIEVE so effective?

Mechanicistic study embedded in REPRIEVE

Designed to determine:

- potential statin effects to reduce noncalcified plaque volume and progression as assessed by entry and 2-year coronary computed tomography angiography (CTA)

- effects on lipid parameters and circulating biomarkers of inflammation: LDL and non–high-density lipoprotein cholesterol, hsCRP, LpPLA2, oxLDL, monocyte chemoattractant protein 1, IL-6, IL-10, IL-1β, IL-18, soluble CD14, and soluble CD163

Lu, JAMA Cardiology, 20

Pitavastatin reduced noncalcified plaque volume and progression

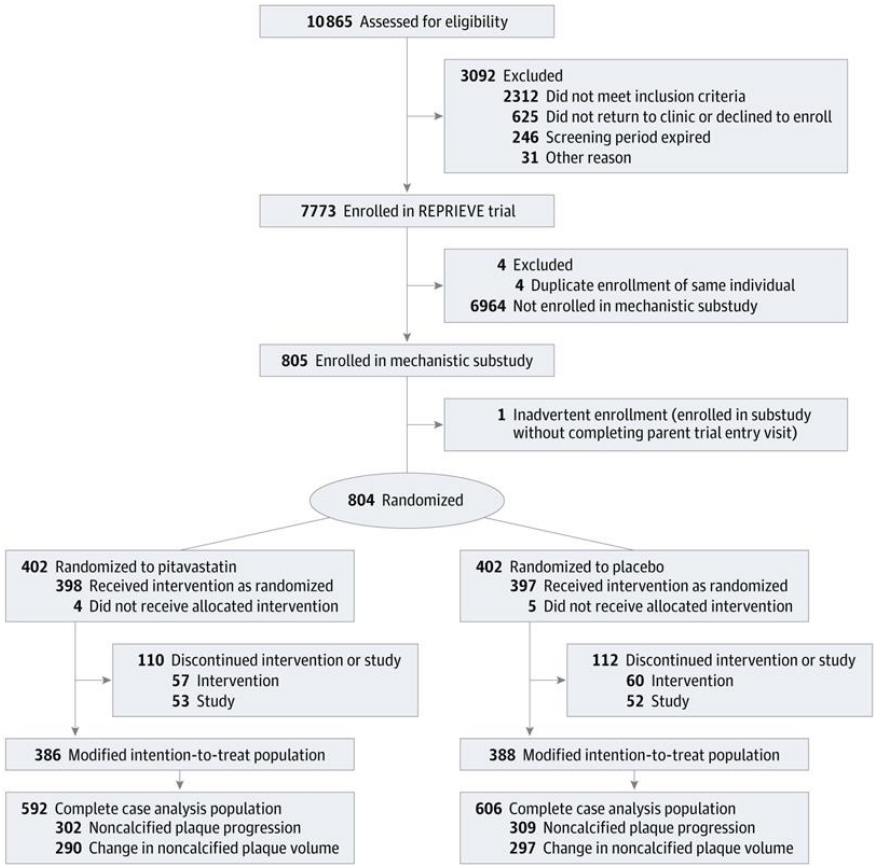


Table 2. Coronary Artery Plaque Changes by Treatment Arm[a]

Outcome	Treatment arm		Treatment effect[b]	
	Pitavastatin (n = 302)	Placebo (n = 309)	Estimated difference adjusted for baseline (95% CI)	*P* value
Primary outcomes				
NCP volume, mean (SD), mm^3[c]				
Baseline	52.3 (193.5)	57.7 (109.2)	NA	NA
Month 24	50.6 (192.8)	60.4 (113.7)	NA	NA
Change from baseline	−1.7 (25.2)	2.62 (27.1)	−4.3 (−8.6 to −0.1)	.04
Fold change from baseline (95% CI)	0.95 (0.91-1.00)	1.02 (0.99-1.05)	0.93 (0.88-0.99)	.02
Progression of NCP, No. (%)	53 (18)	85 (28)	0.67 (0.52-0.88)	.003
Secondary outcomes				
Total plaque volume, mean (SD), mm^3				
Baseline	65.6 (211.7)	72.2 (135.9)	NA	NA
Month 24	67.9 (218.4)	79.1 (149.1)	NA	NA
Change from baseline	2.34 (28.7)	6.89 (32.3)	−4.3 (−9.2 to 0.62)	NA
Progression of total plaque, No. (%)	80 (28)	100 (34)	0.89 (0.74-1.08)	NA
Reduction in NCP percentage, mean (SD)	−6.6% (14.3)	−2.6% (9.21)	−4.1% (−7.0 to −1.3)	NA
Exploratory outcomes				
Low-attenuation plaque volume, mean (SD), mm^3				
Baseline	3.32 (16.5)	4.25 (15.3)	NA	NA
Month 24	2.43 (9.91)	4.17 (12.8)	NA	NA
Change from baseline	−0.9 (9.97)	−0.1 (8.16)	−1.2 (−2.2 to −0.1)	NA

Abbreviations: NA, not applicable; NCP, noncalcified plaque.

[a] NCP defined as plaque voxels with attenuation <350 Hounsfield units. Total plaque includes all plaque voxels (noncalcified + calcified). Low-attenuation plaque defined as <30 Hounsfield units.

[b] For continuous outcomes, the treatment effect is given as the mean difference or relative fold change between treatment groups; for binary outcomes, it is a relative risk. All treatment effects and associated *P* values are adjusted for baseline values. Intention-to-treat analyses were conducted with the exception of reduction in NCP percentage, which is calculated in the subgroup with plaque present at baseline.

[c] Change in NCP volume could be assessed in a subset of 587 participants (297 in the pitavastatin arm and 290 in the placebo arm).

Lu, JAMA Cardiology, 20

Table 3. Distributions of Inflammatory and Immune Biomarkers at Entry and Month 24

Measure[a]	Median (IQR)				
	Entry		Month 24		
	Pitavastatin (n = 402)	Placebo (n = 402)	Pitavastatin (n = 340)	Placebo (n = 350)	P value
Inflammatory markers					
LpPLA2					
Total, No.	398	391	335	333	NA
LpPLA2 level, ng/mL	126 (94.8-169)	131 (89.6-163)	119 (84.0-160)	143 (105-186)	<.001
Change from baseline	NA	NA	−9.77 (−33.6 to 16.8)	19.9 (−5.6 to 43.0)	<.001
Mean fold change (95% CI)	NA	NA	0.93 (0.89-0.96)	1.14 (1.10-1.18)	NA
oxLDL					
Total, No.	398	392	335	333	NA
oxLDL level, U/L	53.0 (42.2-69.8)	53.6 (41.7-69.9)	37.6 (30.0-47.3)	48.2 (38.9-58.4)	<.001
Change from baseline	NA	NA	−14.9 (−28.9 to −3.93)	−6.45 (−20.2 to 5.26)	<.001
Mean fold change (95% CI)	NA	NA	0.71 (0.68-0.74)	0.87 (0.83-0.91)	NA
hsCRP[b]					
Total, No.	397	391	343	335	NA
hsCRP level, mg/dL	0.18 (0.08-0.39)	0.18 (0.09-0.33)	0.17 (0.07-0.36)	0.19 (0.10-0.40)	.02
Change from baseline	NA	NA	−0.01 (−0.10 to 0.08)	0.01 (−0.09 to 0.11)	.09
Mean fold change (95% CI)	NA	NA	0.89 (0.79-1.01)	1.06 (0.94-1.20)	NA
Immune markers					
MCP-1					
Total, No.	398	390	335	330	NA
MCP-1 level, pg/mL	189 (148-245)	183 (144-238)	192 (157-235)	193 (154-247)	.77
Change from baseline	NA	NA	2.11 (−37.8 to 47.5)	3.91 (−33.3 to 53.2)	.46
Mean fold change (95% CI)	NA	NA	1.02 (0.98-1.06)	1.05 (1.01-1.09)	NA
Soluble CD14					
Total, No.	398	392	335	333	NA
Soluble CD14 level, ng/mL	1840 (1544-2176)	1810 (1496-2200)	1541 (1284-1809)	1534 (1324-1850)	.52
Change from baseline	NA	NA	−289 (−588 to −5.08)	−237 (−528 to 36.1)	.54
Mean fold change (95% CI)	NA	NA	0.83 (0.81-0.86)	0.86 (0.83-0.88)	NA
Soluble CD163					
Total, No.	398	391	335	333	NA
Soluble CD163 level, ng/mL	849 (651-1163)	845 (613-1074)	1013 (728-1419)	1003 (745-1384)	.65
Change from baseline	NA	NA	149 (−60.8 to 420)	143 (−46.0 to 453)	.88
Mean fold change (95% CI)	NA	NA	1.21 (1.16-1.27)	1.23 (1.18-1.29)	NA
IL-6					
Total, No.	398	391	335	333	NA
IL-6 level, pg/mL	1.64 (0.99-2.76)	1.46 (0.98-2.59)	1.64 (0.99-2.73)	1.53 (0.93-2.62)	.24
Change from baseline	NA	NA	0 (−0.95 to 0.77)	−0.12 (−0.81 to 0.59)	.46
Mean fold change (95% CI)	NA	NA	0.98 (0.89-1.08)	0.94 (0.86-1.03)	NA
IL-1β					
Total, No.	377	375	320	320	NA
IL-1β level, fg/mL	75.9 (43.9-151)	87.0 (44.9-168)	88.6 (50.2-164)	96.4 (52.6-191)	.09
Change from baseline	NA	NA	2.01 (−41.4 to 58.1)	11.4 (−28.9 to 69.2)	.06
Mean fold change (95% CI)	NA	NA	1.05 (0.93-1.17)	1.19 (1.07-1.33)	NA
IL-18					
Total, No.	377	375	320	320	NA
IL-18 level, pg/mL	245 (179-330)	232 (169-310)	236 (169-310)	230 (176-308)	.79
Change from baseline	NA	NA	−8.53 (−48.2 to 35.3)	−3.77 (−43.3 to 44.1)	.26
Mean fold change (95% CI)	NA	NA	0.96 (0.92-1.00)	1.01 (0.97-1.04)	NA
IL-10					
Total, No.	363	353	305	300	NA
IL-10 level, pg/mL	0.24 (0.17-0.37)	0.22 (0.16-0.35)	0.21 (0.15-0.34)	0.22 (0.16-0.33)	.53
Change from baseline	NA	NA	−0.02 (−0.12 to 0.06)	0 (−0.09 to 0.09)	.08
Mean fold change (95% CI)	NA	NA	0.96 (0.87-1.05)	0.99 (0.91-1.07)	NA
Caspase-1					
Total, No.	377	375	320	320	NA
Caspase-1 level, pg/mL	66.6 (47.0-93.8)	69.6 (50.1-107)	69.6 (48.6-102)	74.2 (52.6-113)	.08
Change from baseline	NA	NA	−3.41 (−22.2 to 26.2)	5.61 (−18.6 to 30.5)	.07
Mean fold change (95% CI)	NA	NA	1.02 (0.94-1.10)	1.07 (0.98-1.16)	NA

Abbreviations: hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LpPLA2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemoattractant protein 1; NA, not applicable; oxLDL, oxidized low-density lipoprotein.

SI conversion factor: To convert hsCRP to mg/L, multiply by 10.

[a] Data are reported for all enrolled participants with available biomarker results.

[b] For hsCRP, censored values below the assay limit are randomly imputed based on a uniform distribution; otherwise, censored values below the assay limit are imputed as the result −0.01; values above the assay limit are imputed as result 0.1.

Pitavastatin reduced markers of lipid oxidation and arterial inflammation

Effects on localized plaque stabilization may be more important than systemic effects on inflammation

Lu, JAMA Cardiology, 20

Effects on Novel Mechanistic Pathways

Primary objective

To investigate mechanistic pathways of statin effects on plaque in PWH

People with HIV

Randomized to pitavastatin or placebo

Olink target 96 panels

Proteomic markers
Cardiovascular
Cardiometabolic
Immuno-oncological

Coronary CT
Noncalcified plaque volume

Repeated at 2-year follow-up

We first used a targeted approach to evaluate statin effects on plasma proteomic markers

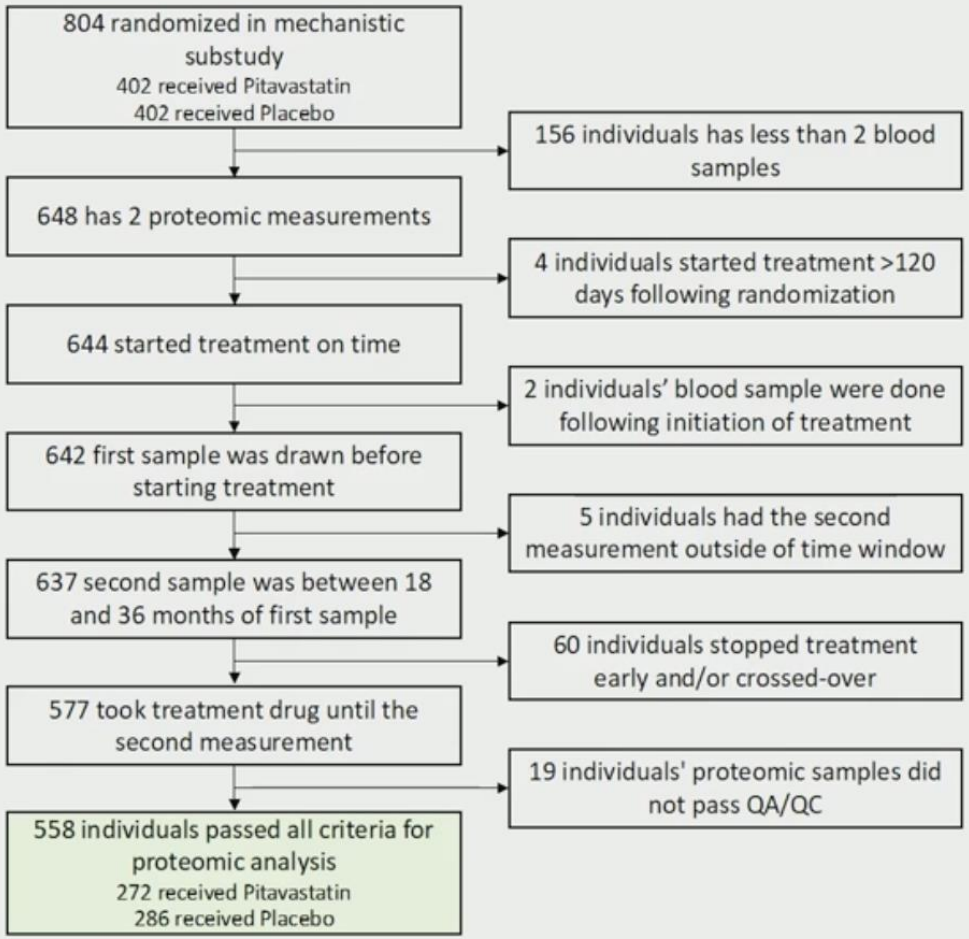
We then evaluated the association between changes in LDL / proteins and changes in coronary plaque

Finally, we investigated the degree to which changes in key proteins mediated statin effects on coronary plaque

CROI 2024

Kolossvary, CROI 2024

Participant characteristics

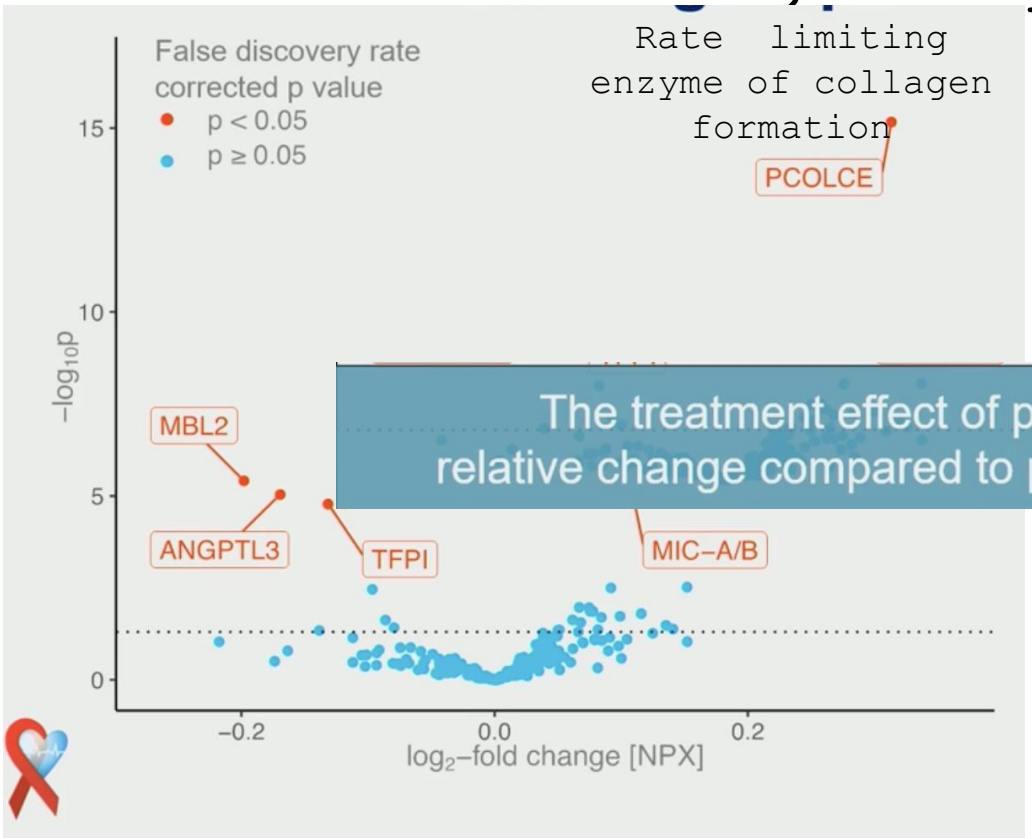


Variable	Overall N = 558	Placebo N = 286	Pitavastatin N = 272
Age (years)	51 ± 6	51 ± 6	51 ± 6
Male natal sex	455 (82%)	233 (81%)	222 (82%)
Race			
Asian	5 (1%)	4 (1%)	1 (0.3%)
Black or African American	206 (37%)	106 (37%)	100 (37%)
White	293 (53%)	154 (54%)	139 (51%)
Other	54 (10%)	22 (8%)	32 (11.7%)
Cardiovascular risk factors			
BMI (kg/m²)	27.3 ± 4.4	27.3 ± 4.3	27.3 ± 4.5
ASCVD risk score (%)	5.0 ± 3.1	4.9 ± 2.9	5.0 ± 3.2
Total cholesterol (mg/dL)	186 ± 36	186 ± 37	185 ± 35
LDL-C (mg/dL)	108± 30	108 ± 31	108 ± 29
Non-HDL-C (mg/dL)	134 ± 35	134 ± 36	134 ± 34
Triglycerides (mg/dL)	133 ± 74	133 ± 77	132 ± 72
HIV-related health history			
Total ART use (years)	12 ± 7	12 ± 6	12 ± 7
Nadir CD4 (cells/mm³)			
<50	116 (21%)	58 (21%)	58 (22%)
50-199	168 (31%)	92 (32%)	76 (28%)
200-349	155 (28%)	78 (28%)	77 (29%)
350+	106 (20%)	52 (19%)	54 (21%)
HIV-1 RNA (copies/mL)			
<LLQ	482 (88%)	245 (88%)	237 (88%)
LLQ -< 400	54 (10%)	29 (10%)	25 (9%)
400+	14 (2%)	6 (2%)	8 (3%)

CROI 2024

Kolossvary, CROI 2024

Proteins differentially expressed over time in the two treatment groups



255 individual proteins

Proteins showing differential expression between treatment groups	
Decreased expression	
ANGPTL3	*Angiopoietin-related protein 3*: Involved in regulation of lipid and glucose metabolism.
MBL2	*Mannose-binding protein C*: Calcium-dependent lectin involved in innate immune defense.
	Tissue factor pathway inhibitor: Inhibits factor
	member 10: Induces apoptosis.
Increased expression	
MIC-A/B	*MHC class I polypeptide-related sequence A-B*: Acts as a stress-induced self-antigen that is recognized by gamma delta T-cells. Binding to KLRK1 leads to cell lysis.
NRP1	*Neuropilin-1*: Receptor involved in the development of the cardiovascular system, in angiogenesis.
PCOLCE	*Procollagen C-endopeptidase enhancer 1*: Binds to the C-terminal propeptide of type I procollagen and enhances procollagen C-proteinase activity

The treatment effect of pitavastatin was largest on PCOLCE; relative change compared to placebo: 24% [95% CI: 18-31%, p<0.001]

vs placebo

Kolossvary, CROI 2024

PCOLCE associates with reduced non-calcified plaque

Variable	Univariable regression			Multivariable regression		
	% change in NCP	95% Confidence interval	p	% change in NCP	95% Confidence interval	p
LDL	1.5	[-1.2; 4.3]	0.26	-0.1	[-3.0; 2.9]	0.95
ANGPTL3	-19.8	[-34.0; -2.6]	0.026	2.3	[-20.3; 31.3]	0.86
MBL2	-18.7	[-31.5; -3.5]	0.018	-11.0	[-26.9; 8.4]	0.25
MIC-A/B	-11.1	[-36.2; 23.7]	0.48	-	-	-
NRP1	-30.0	[-53.0; 4.3]	0.08	-	-	-
PCOLCE	-31.9	[-42.9; -18.7]	<0.001	-31.2	[-45.3; -13.4]	0.002

Doubling in PCOLCE expression was associated with a decrease in noncalcified plaque by -31%, [95%CI: -45%; -13%, p=0.002]

Model estimates are for per doubling in protein expression

CROI 2024

Kolossvary, CROI 2024

PCOLCE associates with plaque stabilization

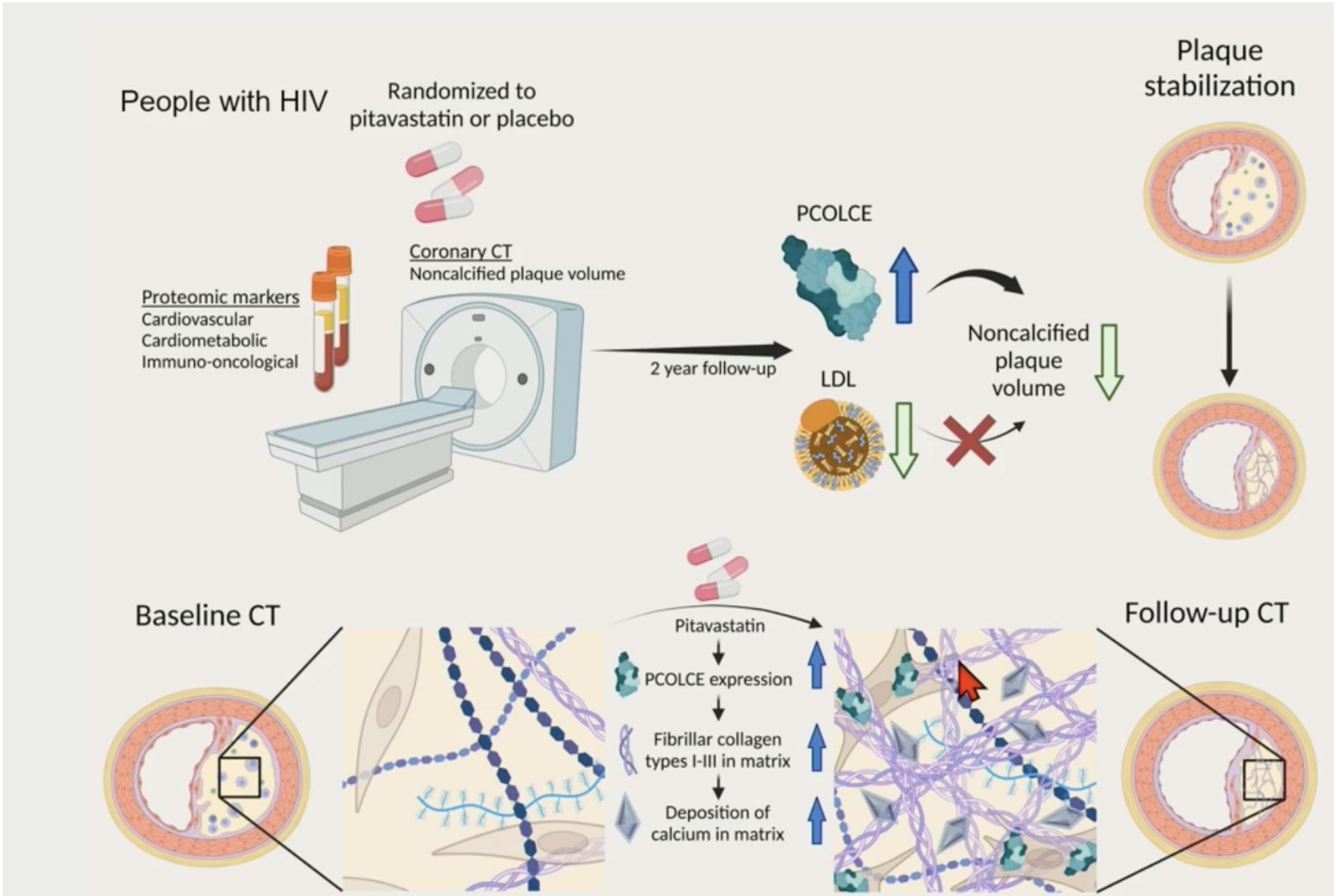
Protein changes vs. plaque components changes

	Calcified plaque			Noncalcified plaque					
Variable	Calcified plaque volume (>350HU)			Fibro-fatty plaque volume (<130HU)			Fibrous plaque volume (130-350HU)		
	% change	95% Confidence interval	p	% change	95% Confidence interval	p	% change	95% Confidence interval	p
LDL	-3.7	[-9.5; 2.3]	0.22	6.1	[0.5; 11.8]	0.032	0.4	[-1.9; 2.6]	0.74
ANGPTL3	-1.2	[-33.8; 47.5]	0.95	-28.0	[-52.3; 8.9]	0.12	-20.7	[-32.3; -7.0]	0.004
MBL2	7.3	[-25.1; 53.6]	0.70	-25.9	[-48.5; 6.8]	0.11	-13.5	[-25.0; -0.4]	0.044
MIC-A/B	6.7	[-46.4; 112.3]	0.85	-25.7	[-63.0; 49.4]	0.40	-3.3	[-26.4; 27.1]	0.81
NRP1	13.8	[-50.1; 159.5]	0.76	-46.6	[-77.0; 24.1]	0.14	-13.9	[-38.1; 19.8]	0.37
PCOLCE	34.4	[-7.9; 96.2]	0.12	-38.5	[-58.1; -9.7]	0.013	-22.2	[-32.9; -9.7]	0.001
TFPI	77.3	[-0.4; 215.4]	0.051	-0.6	[-43.8; 75.8]	0.98	-8.1	[-26.4; 14.9]	0.46
TRAIL	9.6	[-40.2; 100.7]	0.77	18.2	[-37.7; 124.1]	0.61	-9.9	[-29.8; 15.6]	0.41

Increased PCOLCE expression was associated with a shift in plaque components promoting plaque stabilization

Model estimates are for per doubling in protein expression

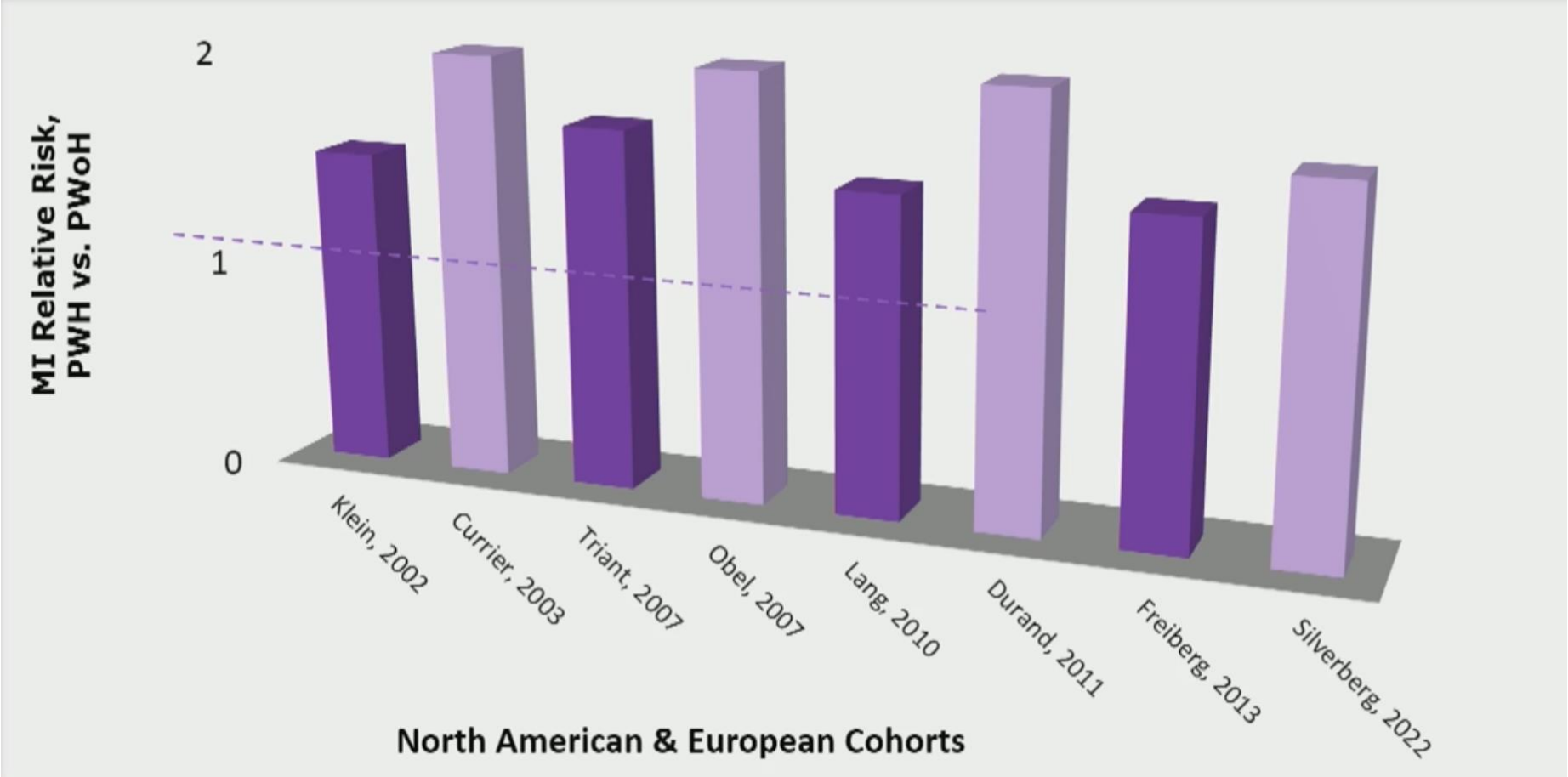
CROI 2024



Kolossvary, CROI 2024

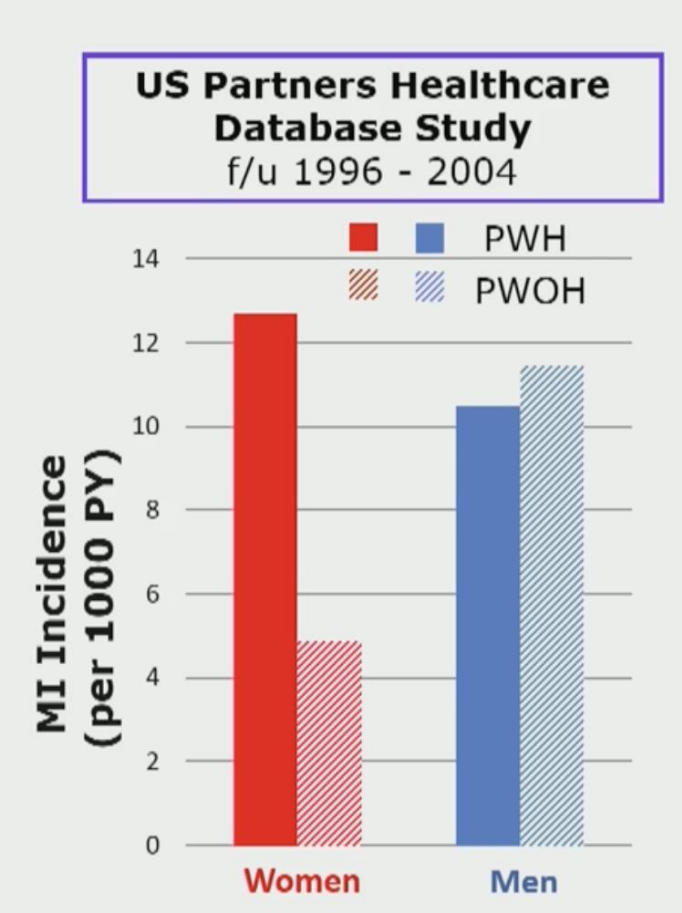
Sex Differences in Atherosclerotic Cardiovascular Disease Risks

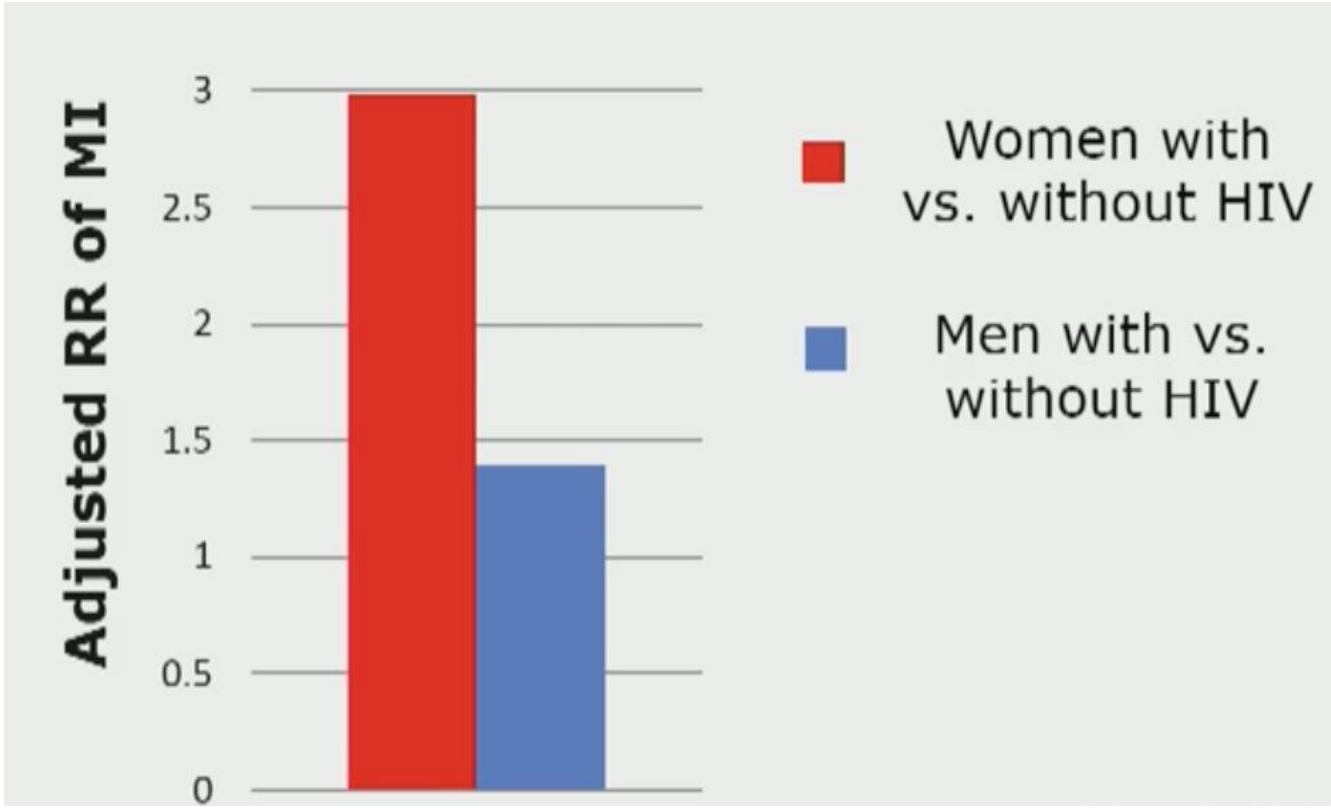
Relative Risk of MI in High Income Countries among PLWH vs PLWOH: ranges from 1.5-2



Zanni, CROI, 2024

Sex Differences in MI Incidence and HIV-Attributable MI Risk among PLWH





Double the risk of MI in women vs men

MI Incidence comparable in WLWH and MLWH

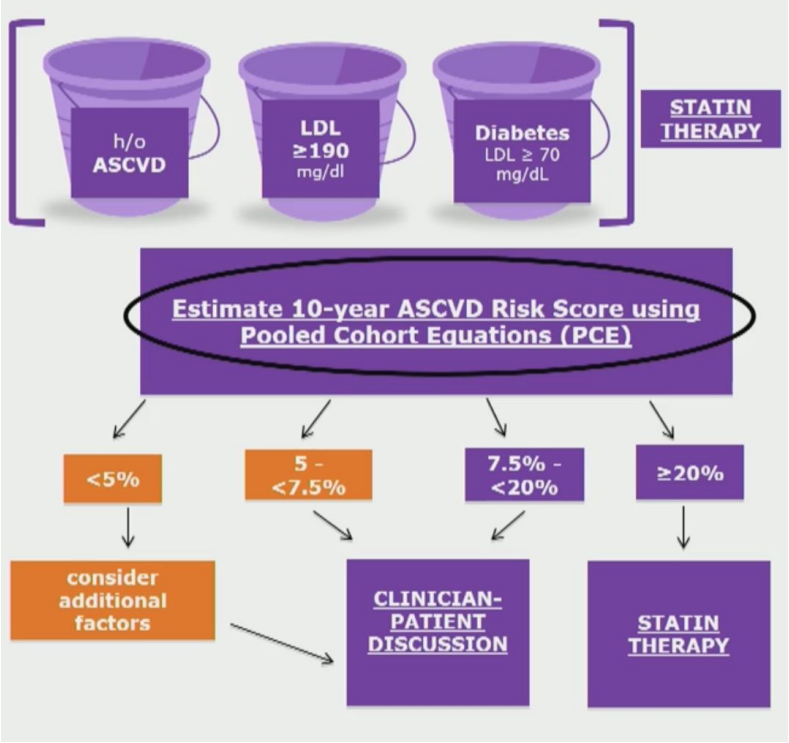
MI Incidence signficantly lower in WWOH than MWOH

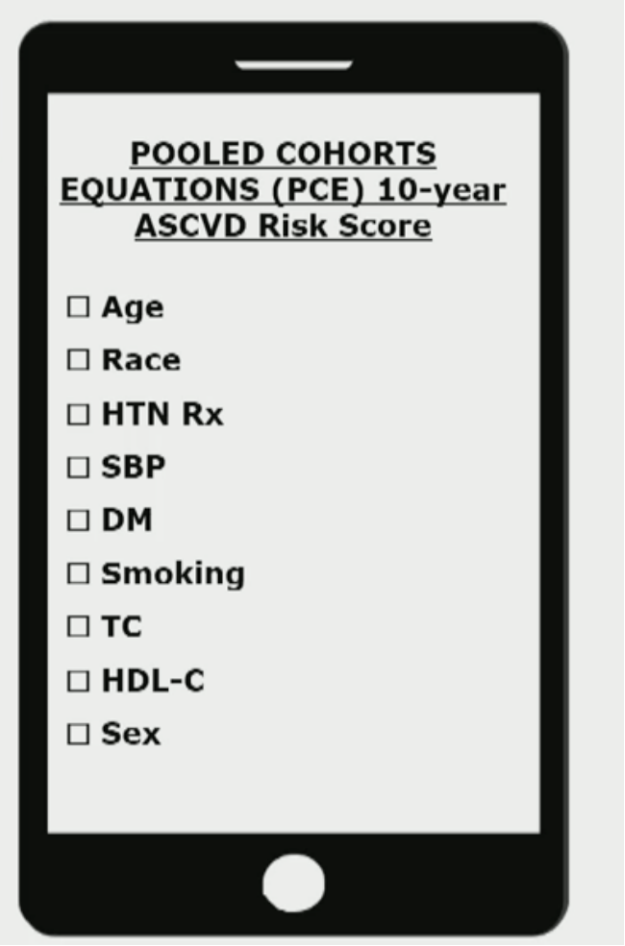
Triant, JCEM, 20(

Limitations of PCE 10 year score

- Does not integrate data on HIV parameters or indeces of activation/systemic inflammation
- Female sex lowers the calculated

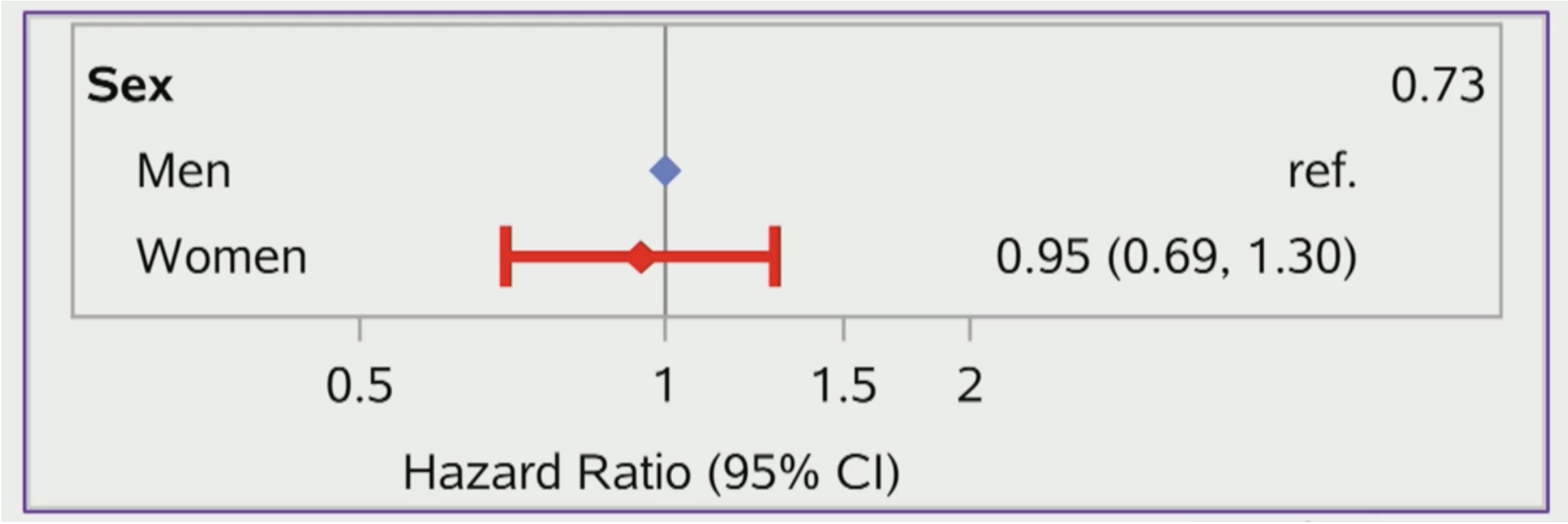
2013 and 2018 ACC/AHA Guidelines on ASCVD Prevention





Zanni, CROI, 2024

Female Sex **Not Protective** vs MACE in Controlling for Other Risk Factors*



***Risk Factors:**
Demographic: •age •race •region •FHx premature CVD
Behavioral: •cigarette smoking
Metabolic: •HTN •BMI •glucose •cholesterol levels •eGFR
HIV-specific: •HIV-1 RNA •CD4 count

Among a global cohort of PWH, modifiable factors associated with first MACE included cigarette smoking, hypertension, and detectable VL, with no apparent protective effect of female sex.

PCE Risk Score underestimates MACE in Women Living in High-Income Countries

		Calibration GND statistic		Observed/Expected Events		
		X^2 (df)	P-value	Obs	Exp	O:E
Overall		**4.47 (8)**	**0.81**	**84**	**81**	**1.03**
By Sex	Women	2.69 (3)	0.44	21	14	**1.42**
	Men	1.96 (4)	0.74	64	67	**0.95**
By Region	High Income	7.21 (5)	0.21	63	49	**1.30**
	Non-High Income	10.52 (3)	0.015	22	32	**0.69**

		Calibration GND statistic		Observed/Expected Events		
		X^2 (df)	P-value	Obs	Exp	O:E
High Income Region Only						
By Sex	Women	5.90 (2)	0.05	17	7	2.56
	Men	2.79 (4)	0.59	46	42	1.10

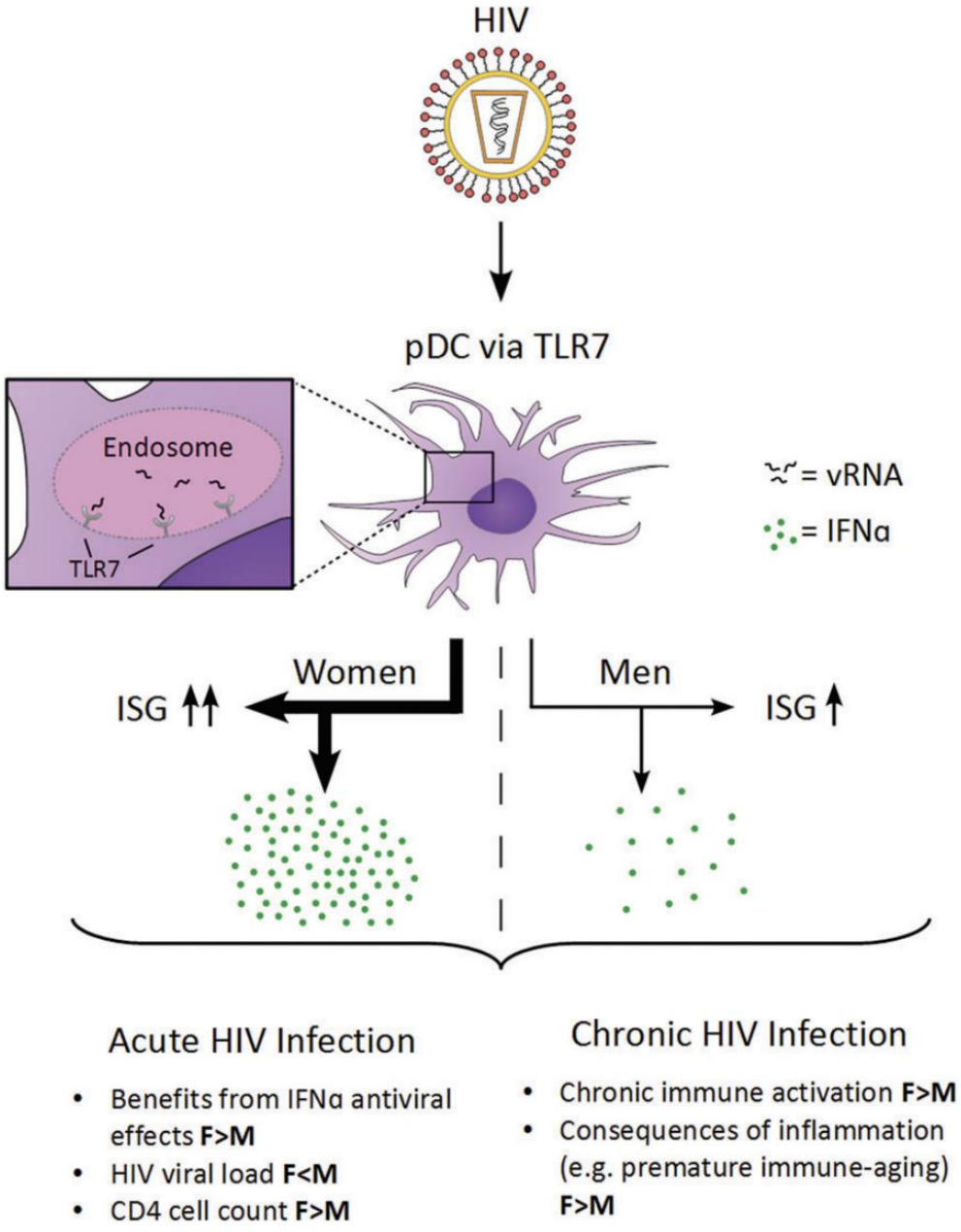
REPRIEVE

Among a global cohort of PWH, the Pooled Cohort Equation over-predicted events among participants in non-High Income regions and under-predicted events in female and Black or African American participants from High Income regions.

Grinspoon, #782, CROI 2024

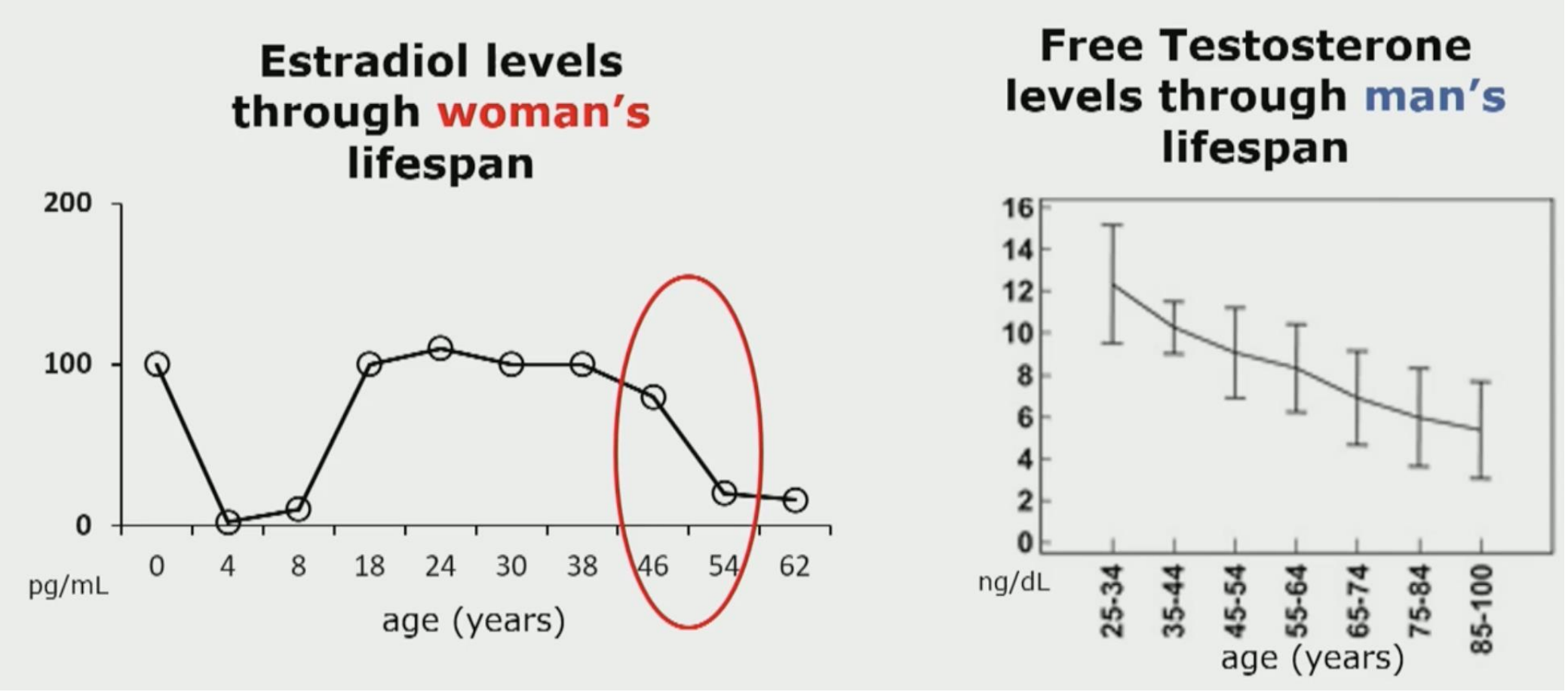
See also: CNICS cohort
Feinstein et al. JAMA Cardiology 2017

More Robust Innate Response to HIV Infection in Women



Addo, JID, 2014

Patterns of Reproductive Aging through the Lifespan Vary Significantly by Sex of Relevance to ASCVD Risk



Dimitrakakis, BCR 2009; Starka, JSBM

REPRIEVE Women's Objectives

To explore sex-specific mechanisms of CVD risk and risk reduction in people living with HIV

Zanni, CROI, 2024

"Immune-Plaque Paradox" Among US Women with HIV

Possible explanatory hypotheses ....

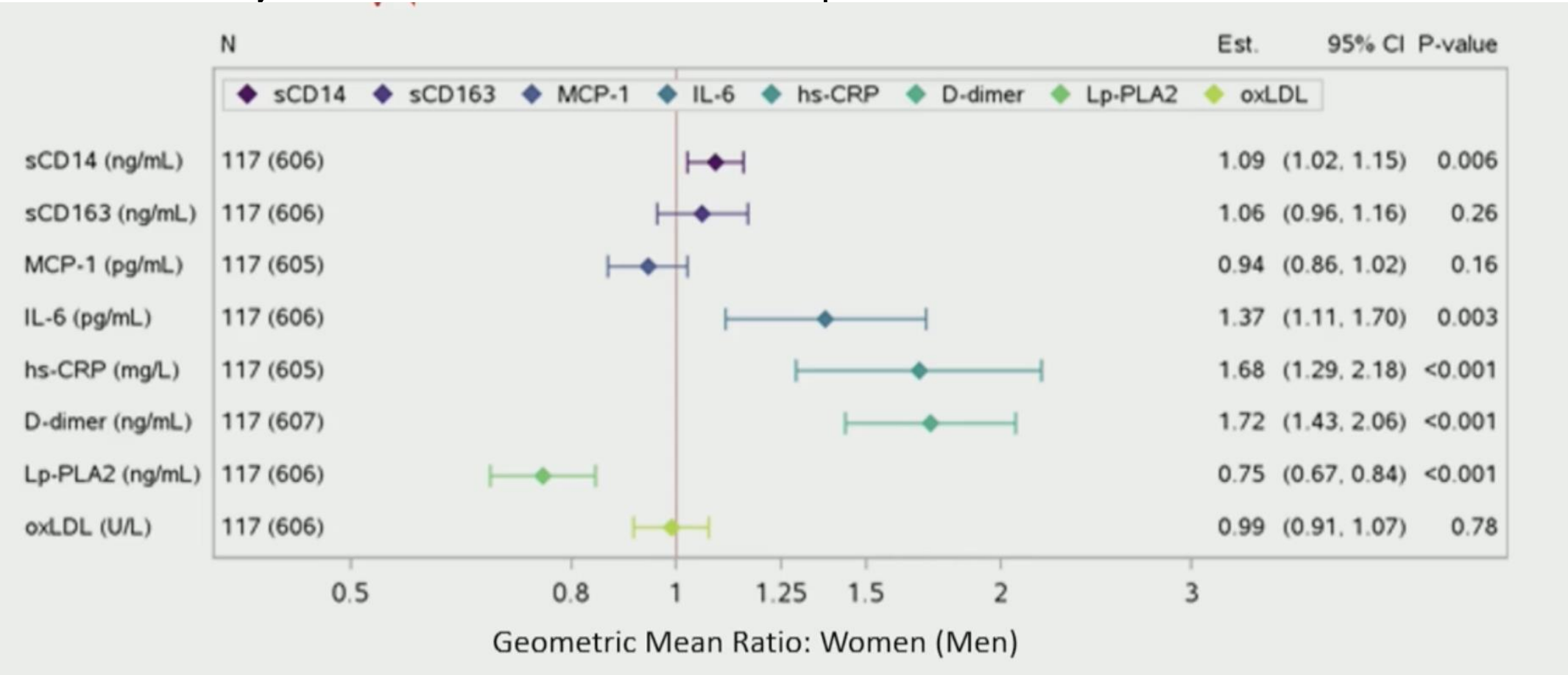
- Hypothesis 1: Among **women with HIV,** subclinical coronary atherosclerotic plaque has higher prognostic value for atherothrombosis

- Hypothesis 2: Among **women with HIV**, MI risk may also be mediated through pathways not directly involving epicardial artery plaque (e.g. coronary microvascular dysfunction)

- ***See Knudsen et al. OFID 2018 & Zanni/Chu/Toribio NCT04224181***

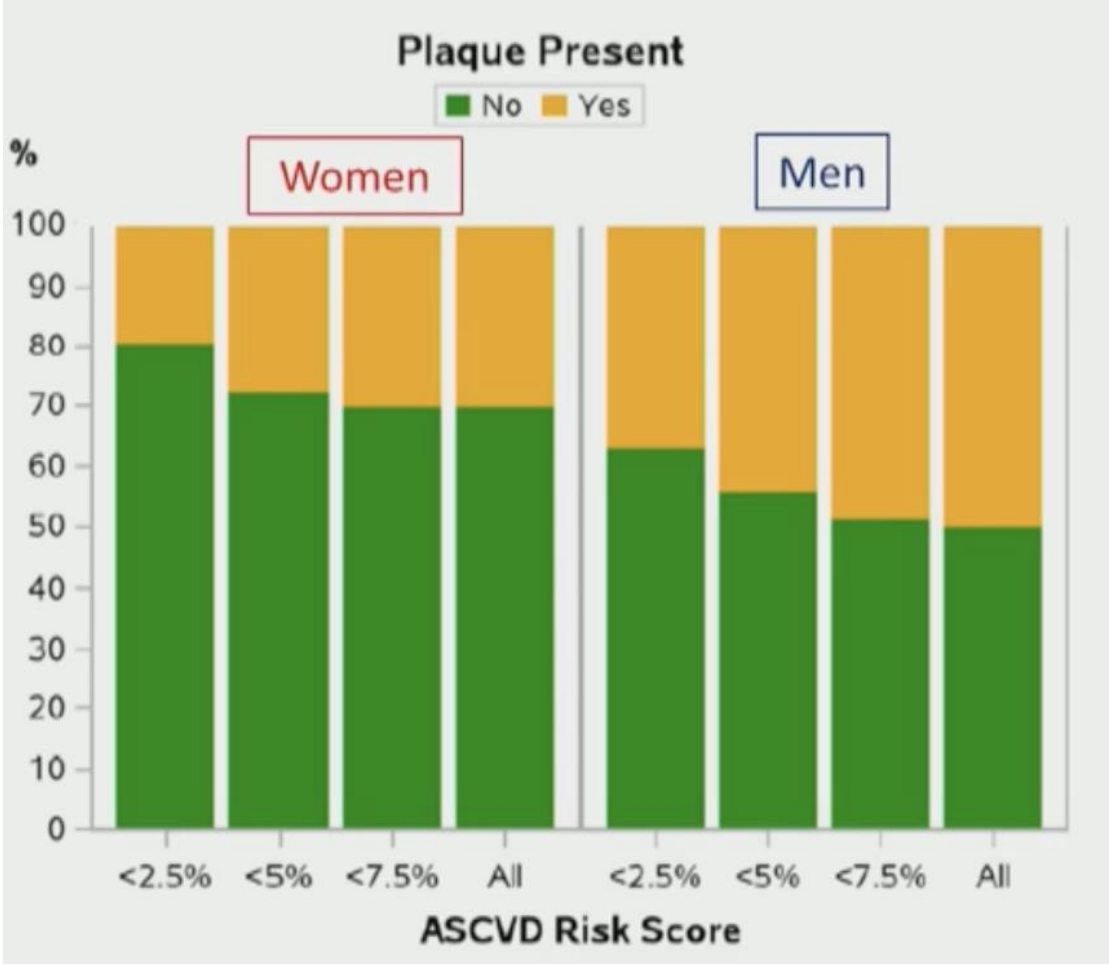
ACC/AHA website; Galli Nature Reviews Cardiology 2023

In REPRIEVE, women (vs men): increased IL-6, hs CRP, D-dimer; reduced LpPLA-2



Zanni, CID, 2023

In REPRIEVE, Women (vs Men) had a Lower Prevalence of Coronary Artery Plaque



Zanni, CID, 2023

Acknowledgmen

Clinica di Malattie Infettive
Dipartimento di Scienze della Salute
ASST Santi Paolo e Carlo-Presidio Ospedaliero San Paolo
Università degli Studi di Milano
Valeria Bono
Matteo Augello
Sabrina Marozin
Maria Sgarlata
Roberta Rovito
Giulia Marchetti

INACTION
ITALIAN NETWORK ACUTE HIV INFECTION

Italian Cohort I. C. O. N. A. Naive Antiretrovirals
Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS
Conceived by Professor Mauro Moroni

EUCARE
Funded by the European Union

TRANSCAN
Fondazione Regionale per la Ricerca Biomedica
Regione Lombardia