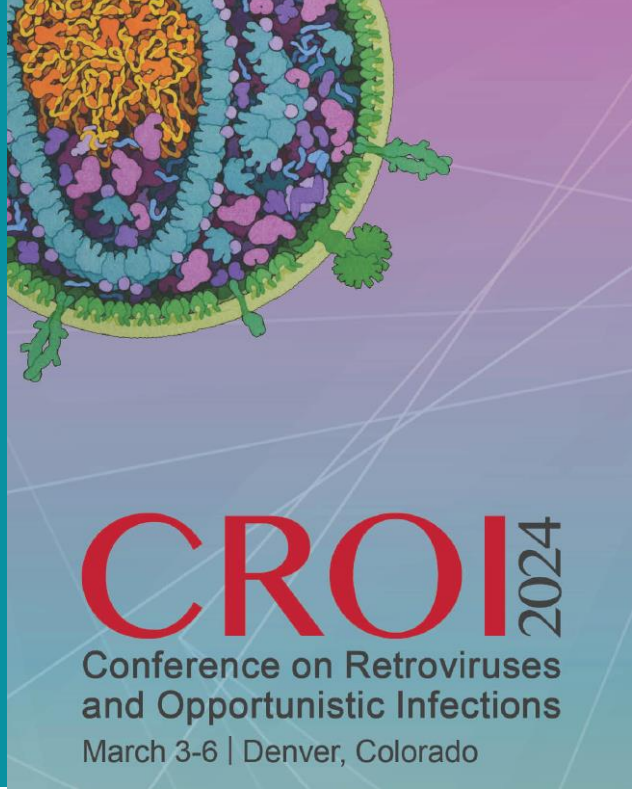
Envejecimiento y comorbilidades

Eugènia Negredo
Fundació lluita contra les Infeccions
Hospital Germans Trias I Pujol
Badalona



Fundació Lluita contra les Infeccions

SEMAGLUTIDE

CROI 2024

Is the Weight Over?: GLP-1 Receptor Agonists Are Here

Todd T. Brown, MD, PhD
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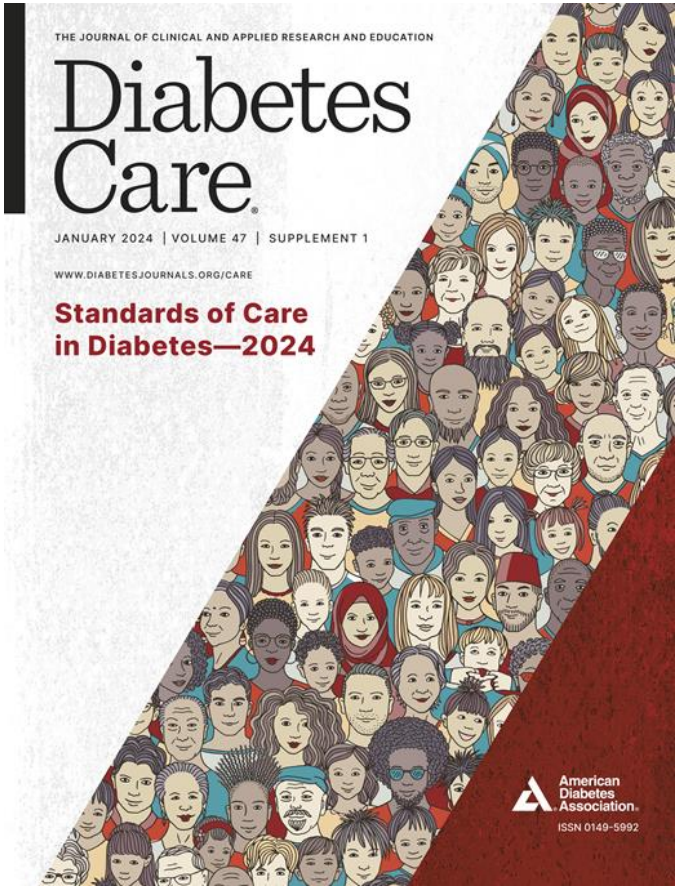
GLP1 RAs: Revolutionary Drugs for Diabetes

CROI 2024

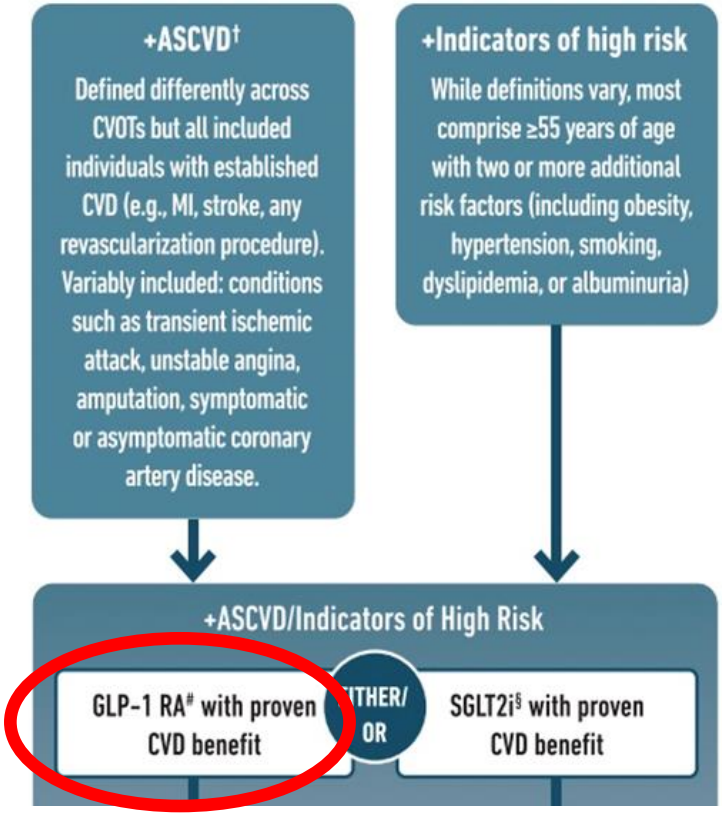


The Reign of Metformin as THE First Line Drug 2007- …

GLP1 RAs: Revolutionary Drugs for Diabetes

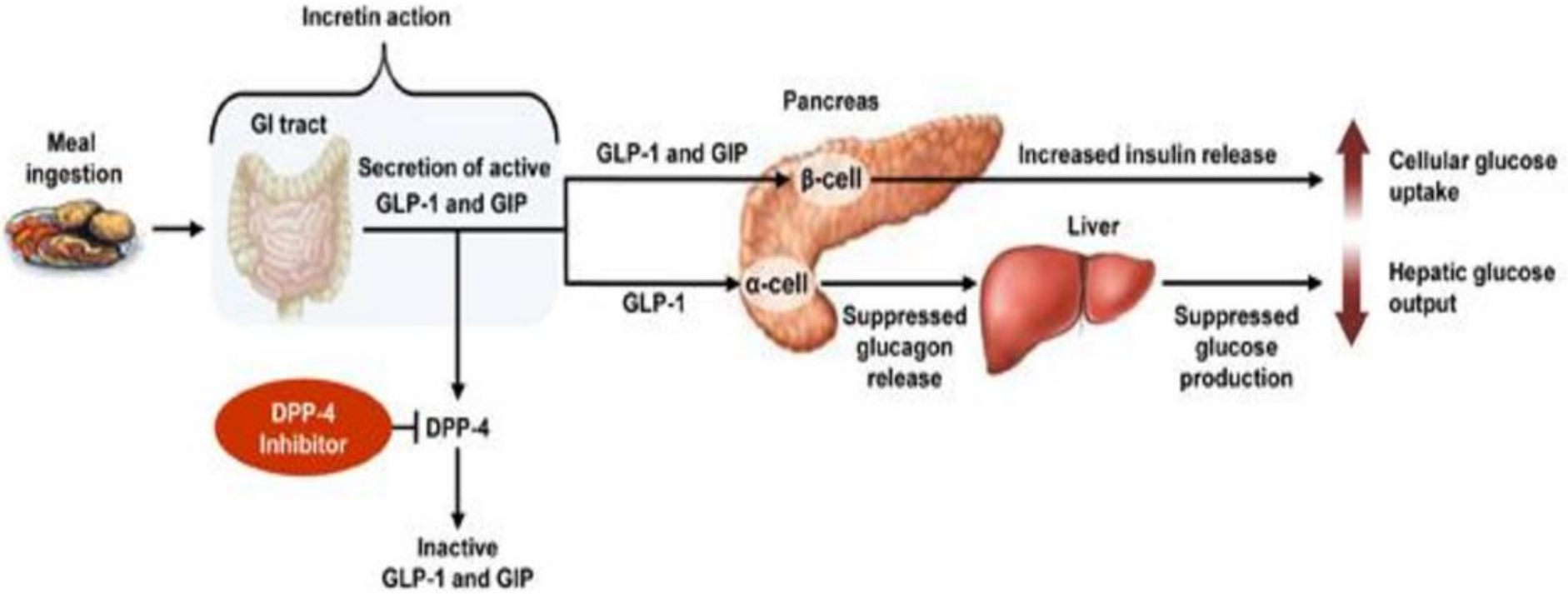
CROI 2024

The Reign of Metformin as THE First Line Drug
2007-2023



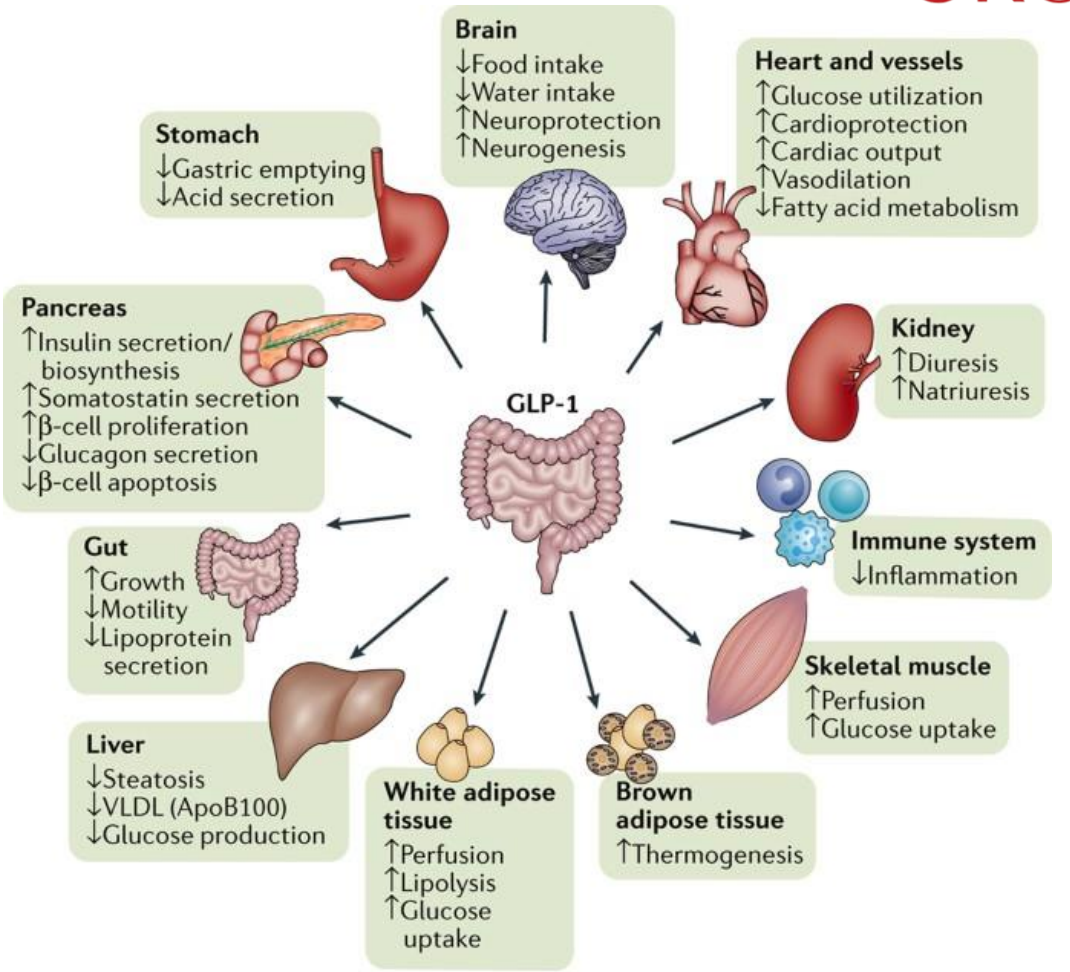
ADA, Standard of Medical Care in Diabetes, 2023

Incretins: Mechanisms of Action



Gothwal, IOSR Journal of Pharmacy, 2013

Multiple Sites of Action of GLP-1 RA



Muskiet, NatureReviewsNephrology, 2017

GLP1 RAs in Diabetes: Effects on Cardiovascular Events

Drug	Duration	Glucose Effect	Weight Effect	Reduction in MACE
Exenatide	24 weeks	-0.9%	-2.9 kg	NO
Liraglutide	52 weeks	-1.1 %	-2.5 Kg	↓ 14%
Lixisenatide	24 weeks	-0.72%	-2.7 kg	NO
Dulaglutide	36 weeks	-1.8%	-4.6 kg	↓ 12%
Semaglutide	40 weeks	-2.1%	-6.4 kg	↓ 26%

Glucose and weight data from FDA Package Inserts at highest approved dose

Dual Incretin (GLP-1 & GIP) Receptor Agonist: Tirzepatid

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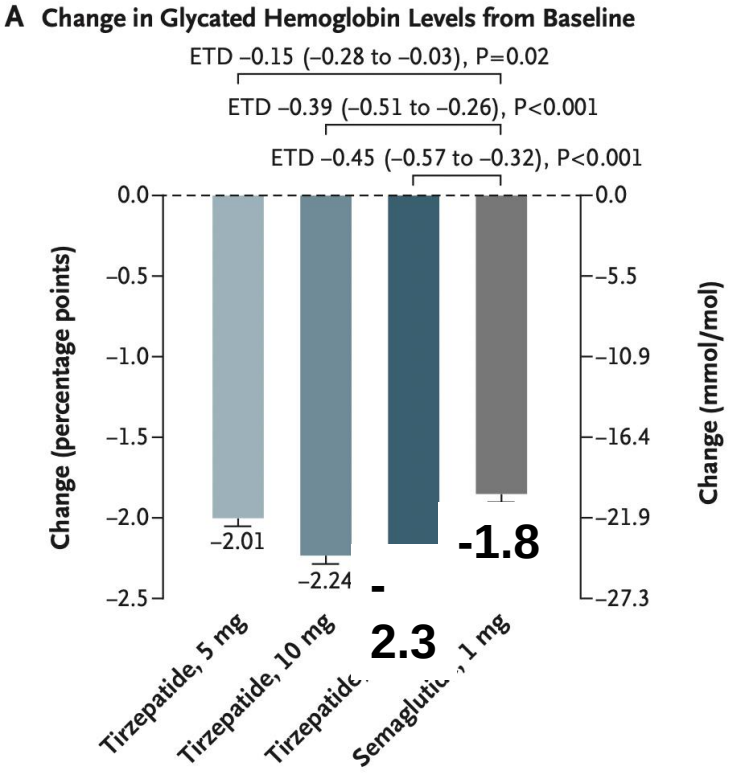
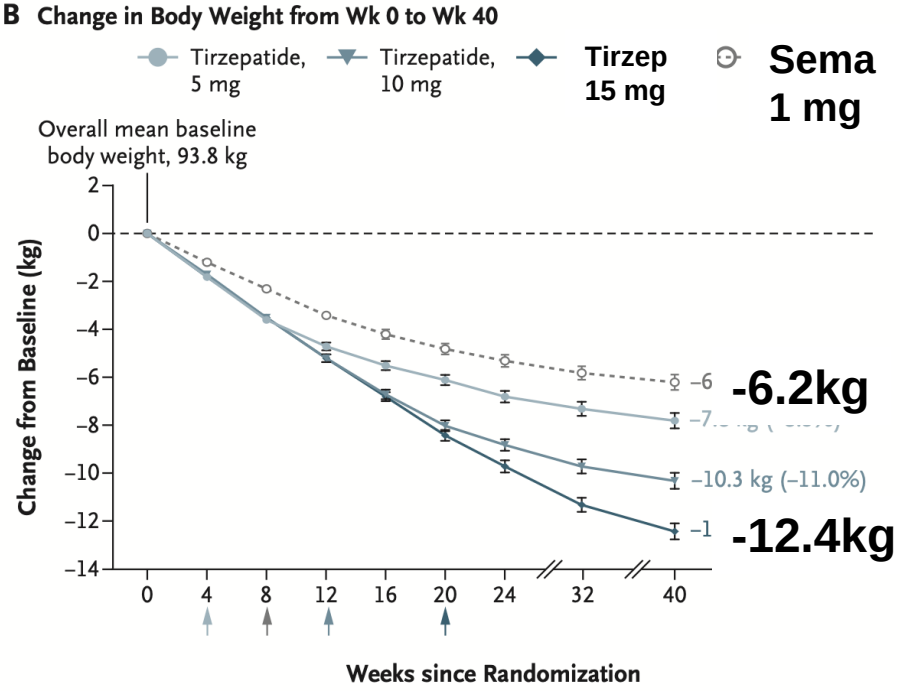
Effect on HbA1c



Effect on Weight



Frias, NEJM, 2021

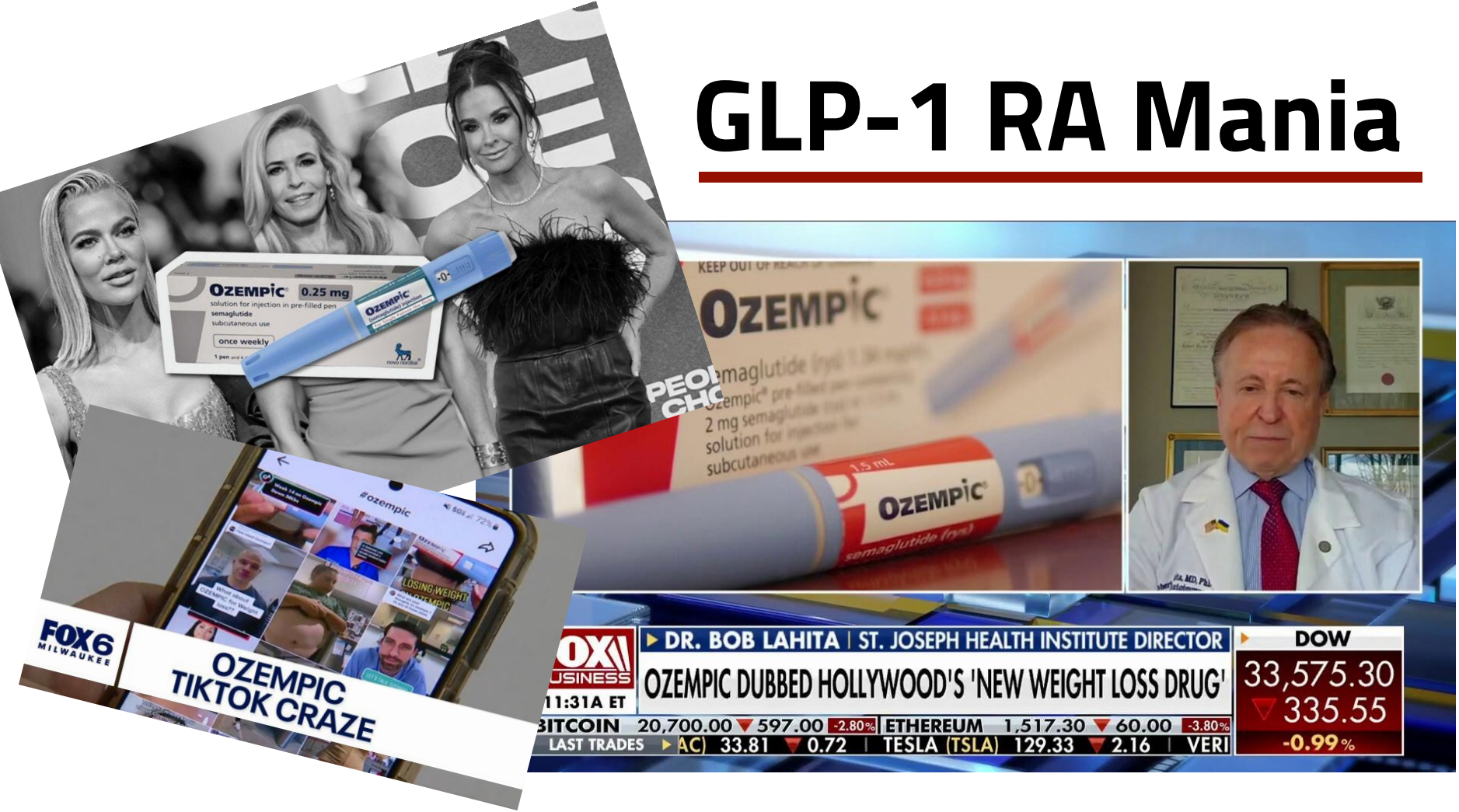
GLP1 RA for Obesity

Drug	Duration	Max Dose	Weight Effect	% Non-responder*	% D/C in Treatment Arm
Liraglutide	72 w	3.0 mg	-8.4 kg/-8%	46%	9.9%
Semaglutide	68 w	2.4 mg	-18.4 kg/-16%	13%	5.9%
Tirzepatide	72 w	15 mg	-22 kg/-18.4%	12.5%	10%

*weight loss < 5%

Pi-Sunyer, NEJM, 2015; Wadden, JAMA, 2021; Wadden, Nature Med, 2023

GLP-1 RA Mania



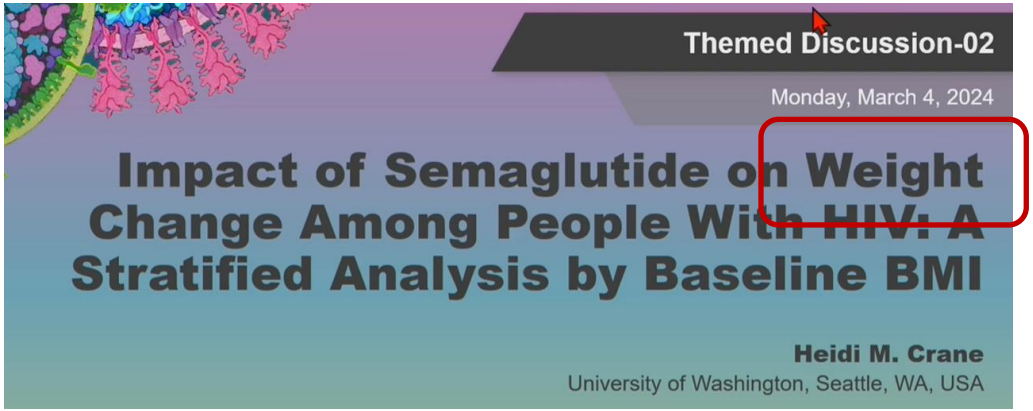
GLP1 RA: Adverse Effects & Long-Term Benefits

Possible Adverse Effects

- Nausea/Diarrhea
- Pancreatitis
- Gastroparesis
- Bowel Obstruction
- Decreased muscle mass
- Facial lipoatrophy (“Ozempic Face”)
- Suicidal ideation (Wang, Nat Med, 2024)
- ? Medullary thyroid cancer

Possible Long-term Benefits

- Diabetes Prevention
- ↓ CVD Risk (SELECT: ↓ 20% MACE)
- ↓ Liver Fat
- ↓ Systemic and Adipose Inflammation
- ↓ Ectopic Fat
- Renal function preservation (FLOW)
- ↑ Physical function (SF-36)



- A quien?
- Qué y cómo?
- Cuanto tiempo?

- *Setting*: Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) Cohort
- *Observation Period*: 2018-2022
- *Participants*: PWH who initiated injectable or oral semaglutide and had ≥2 weight measurements
- *Outcome*: at 1-year post-initiation: (1) bodyweight change in kg, and (2) percent bodyweight change
- *Analysis*: linear mixed models adjusted for age, sex, race/ethnicity, CNICS site, diabetes status, CD4 cell count, HIV viral load, and time
- *Sensitivity analyses* stratifying by:
  - Baseline BMI class
  - Diabetes status
  - Semaglutide dose (low vs. high)

Analytic Cohort & Weight loss over 1 year

N=222

25% Female
75% Male

Avg follow-up: 1.1 years

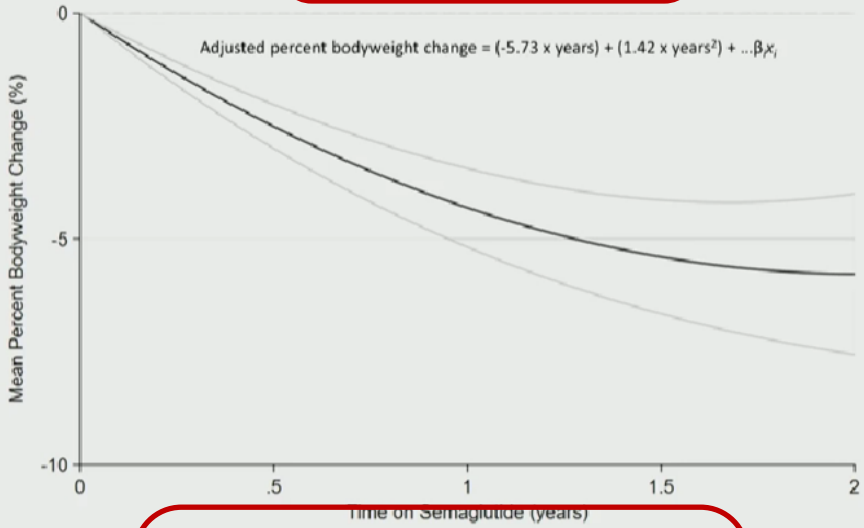
Average age: 53 years

77% Diabetic

Avg HbA1c: 7.7%

89% virally suppressed

Avg CD4 count: 796



On average, PWH lost 5.7% of bodyweight (95% CI: -6.9, -4.5)

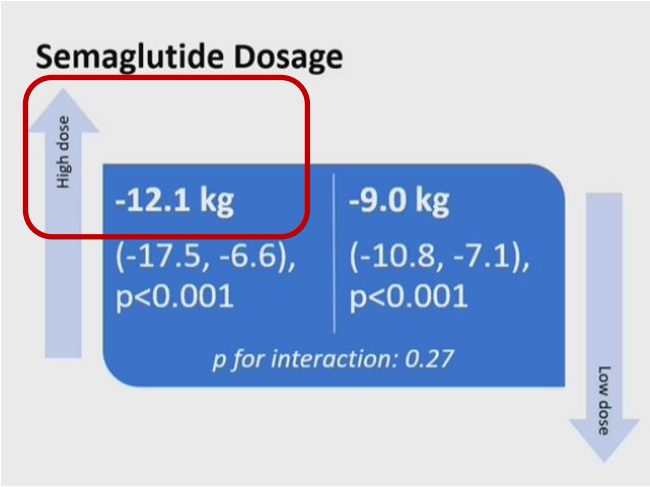
On average, PWH lost 6.5kg (95% CI: -7.7, -5.2)

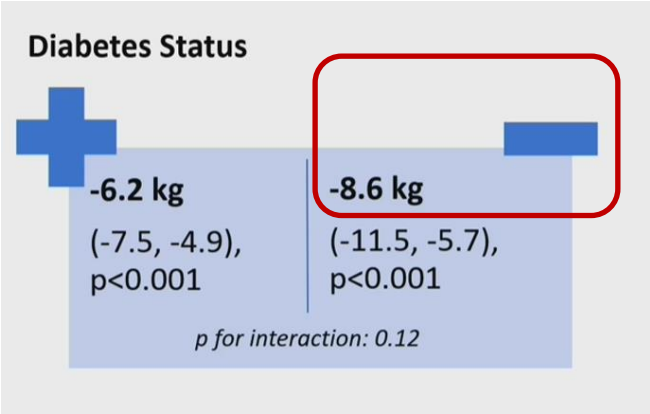
Stratified by baseline BMI

Table 1. Weight loss results stratified by BMI class

BMI Class	n (%)	Weight loss, kg (95% CI)
Normal (18.5 – 24.9 kg/m^2)	11 (4.9)	-4.1 (-7.9, -0.2)
Overweight (25.0 – 29.9 kg/m^2)	36 (16.2)	−4.6 (−6.9, −2.3)
Obesity Class I (30.0 – 34.9 kg/m^2)	65 (29.3)	−5.4 (−7.3, −3.4)
Obesity Class II (35.0 – 39.9 kg/m^2)	60 (27.0)	−7.6 (−9.5, −5.7)
Obesity Class III (≥ 40.0 kg/m^2)	50 (22.5)	−8.8 (−10.9, −6.7)

- PWH in Obesity Class III lost significantly more weight than PWH with normal, overweight, and Obesity Class I BMI (p-value for interaction <0.05)





Themed Discussion-02

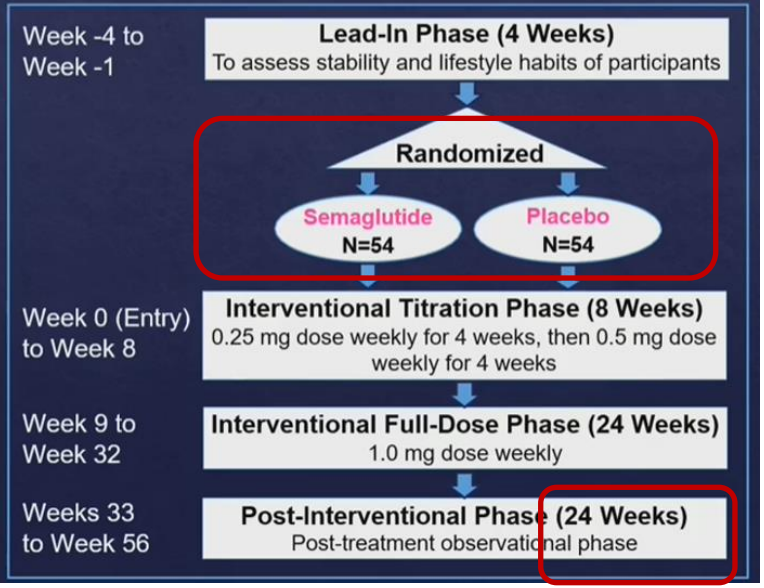
Monday, March 4, 2024

Effects of Semaglutide on Inflammation and Immune Activation in HIV-Associated Lipohypertrophy

Allison Ross Eckard
Medical University of South Carolina, Charleston, SC, USA

- A quien?
- Qué y cómo?
- Cuanto tiempo?

- **HIV-associated lipohypertrophy** → characterized by abnormal accumulation of visceral adiposity and ectopic fat deposition
- Contributes to chronic inflammation and cardiometabolic risk in HIV
- Glucagon-like peptide 1 receptor agonists shown effective in diabetes & obesity



Inclusion/Exclusion & Baseline Characteristics

Key inclusion criteria:

- Age ≥18 years
- Stable ART ≥12 weeks
- HIV RNA <400 cps/mL ≥6 mo.
- Body mass index ≥25 kg/m^2
- Waist circumference/waist-to-hip ratio: >95 cm/>0.94 (men), >94 cm/>0.88 (women)
- Subjective ↑ abdominal girth after ART

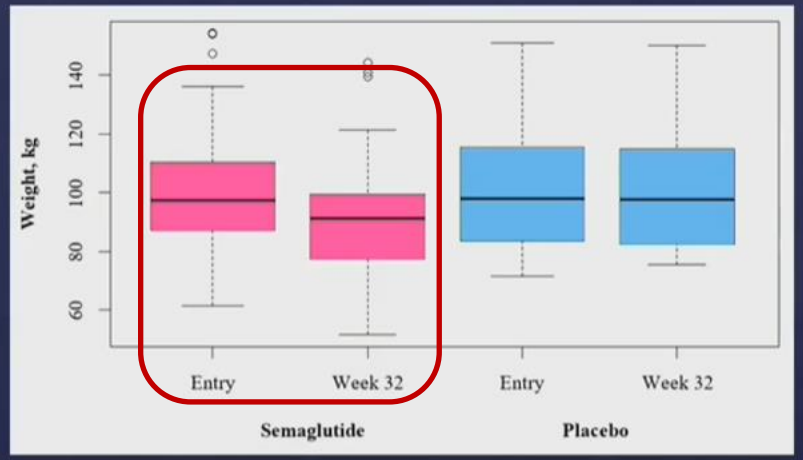
Key exclusion criteria:

- Diabetes, cardiovascular disease, pregnancy, severe lipoatrophy

Median (Q1, Q3) or No. (%)	Semaglutide (N=54)	Placebo (N=54)
Age, years	53 (40, 57)	53 (41, 57)
Male sex	38 (70%)	27 (50%)
Black race	33 (61%)	34 (63%)
Smoking	15 (28%)	23 (43%)
CD4+ count, cells/μL	826 (407, 1058)	793 (579, 994)
ART duration, mo.	168 (98, 230)	148 (98, 198)
Current INSTI use	45 (83%)	43 (80%)
Current PI use	10 (19%)	8 (15%)
Abdominal TAT, cm^2	416 (350, 476)	446 (385, 503)
Abdominal SAT, cm^2	302 (226, 362)	333 (231, 389
Abdominal VAT, cm^2	101 (78, 143)	118 (84, 152)
Total body fat, kg	34.4 (27.4, 40.2)	35.5 (28.3, 49.7)
Limb fat, kg	15.6 (12.6, 19.2)	17.9 (11.6, 22.3)
Lean body mass, kg	60.1 (50.7, 66.8)	56.9 (47.6, 65.6)
Weight, kg	97.5 (87.3, 110.6)	97.9 (83.6, 115.5)
Body mass index, kg/m^2	32.9 (28.4, 36.0)	33.8 (29.9, 39.7)
HbA1c, %	5.5 (5.1, 5.8)	5.6 (5.3, 5.8)

Groups well-balanced except smoking & male sex $p<0.05$

TAT, SAT, VAT = total, subcutaneous, visceral adipose tissue



32 weeks of semaglutide use caused significant decreases in abdominal VAT, SAT, TAT, trunk fat, limb fat, total body fat, lean body mass & weight.**

*previously presented at IDWeek 2023, abstract #1984

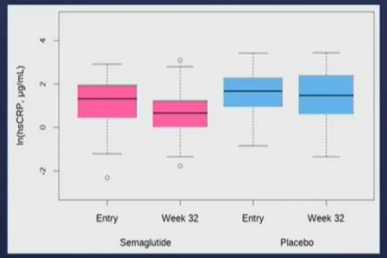
Visceral adipose tissue
-30.6%
Subcutaneous adipose tissue
-11.2%
(abdominal fat area measured by CT at L4-L5)

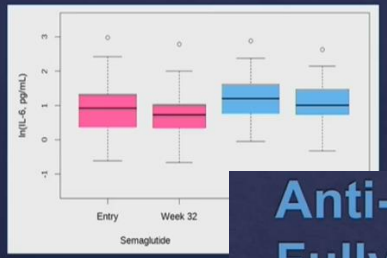
Body weight
-10.4%
Lean body mass
-5.7%
(measured by whole-body DXA)

**effect sizes based on β coefficient in sex-adjusted multiplicative GEE regression models; % changes exponentiated with formula: $100(e^{\beta}-1)$

Effects of Semaglutide on Inflammation and Immune Activation

Summary of key linear regression models adjusted for baseline marker values, smoking, male sex ± age*





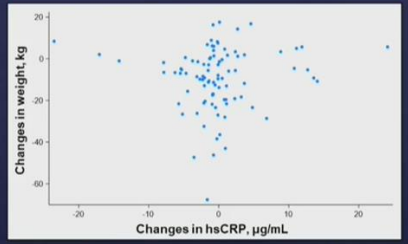
hsCRP
-39.9%

IL-6
-18.8%

*β coefficients estimate adjusted effects of semaglutide treatment vs. placebo at 32 weeks; % change estimates calculated using the formula: $100(e^{\beta}-1)$

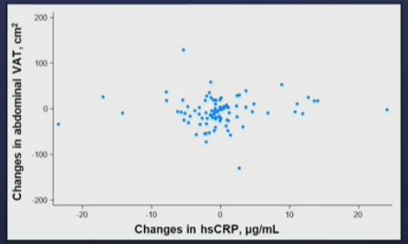
Anti-Inflammatory Effects of Semaglutide Not Fully Explained by Decreases in Weight

A. CORRELATION BETWEEN CHANGES IN hsCRP & CHANGES IN WEIGHT



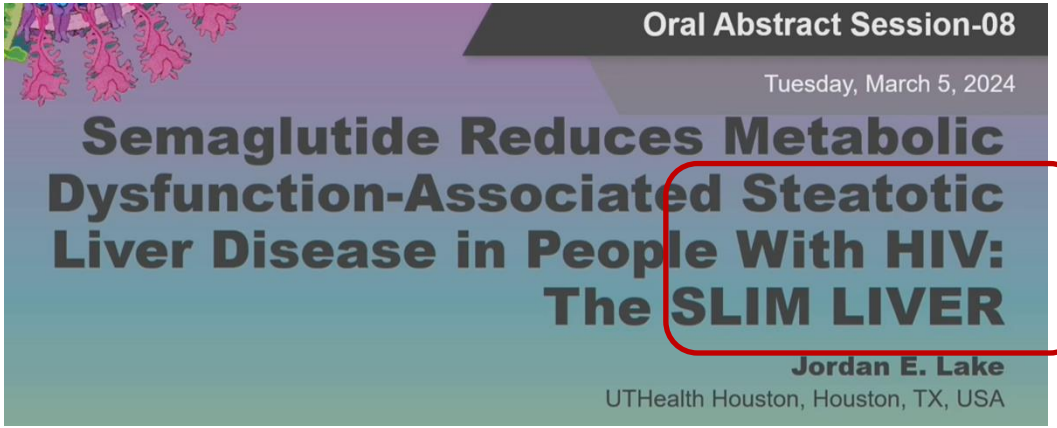
r = 0.043; p = 0.69

B. CORRELATION BETWEEN CHANGES IN hsCRP & CHANGES IN ABDOMINAL VAT



r = 0.067; p = 0.53

Semaglutide use caused notable decreases in several key biomarkers independent of VAT & weight loss in people with HIV-associated lipohypertrophy & w/o diabetes.



- A quien?
- Qué y cómo?
- Cuanto tiempo?

- We hypothesized that semaglutide could be an effective treatment for MASLD in PWH
- ACTG A5371, the SLIM LIVER study, was a phase IIb, single-arm, open-label, pilot study of the effects of semaglutide on magnetic resonance imaging-proton density fat fraction (MRI-PDFF)-quantified intrahepatic triglyceride (IHTG) content

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ACTG A5371 Study Design

Inclusion Criteria

- Adult PWH on suppressive ART
- Elevated minimum waist circumference

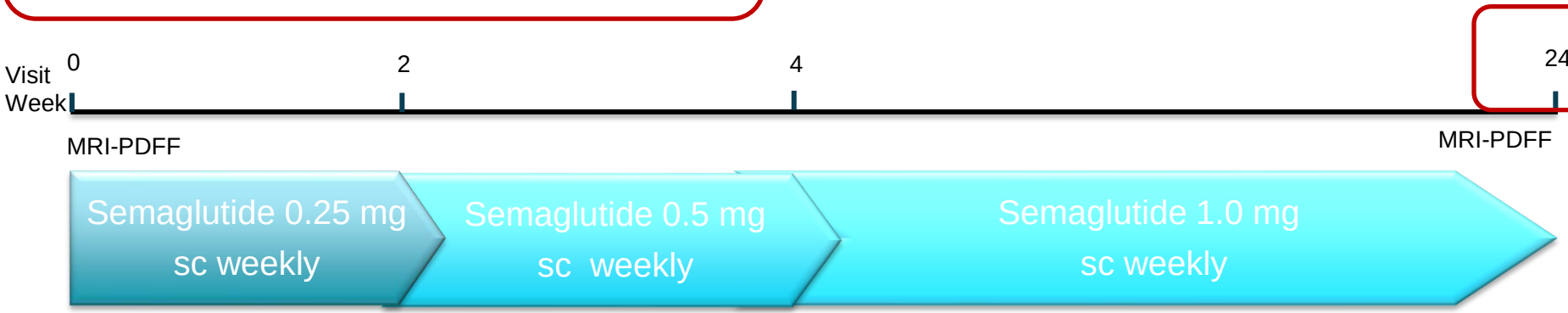
-WC≥95 cm ♂ / WC 94≥cm ♀

- Insulin resistance or pre-diabetes
- ≥5% IHTG on MRI-PDFF

- **51 enrolled, 49 completed per-protocol**
- **Reasons for exclusion from analysis:**

-Nausea Grade 3 (n=1)

-Withdrawal of Informed Consent (n=1)

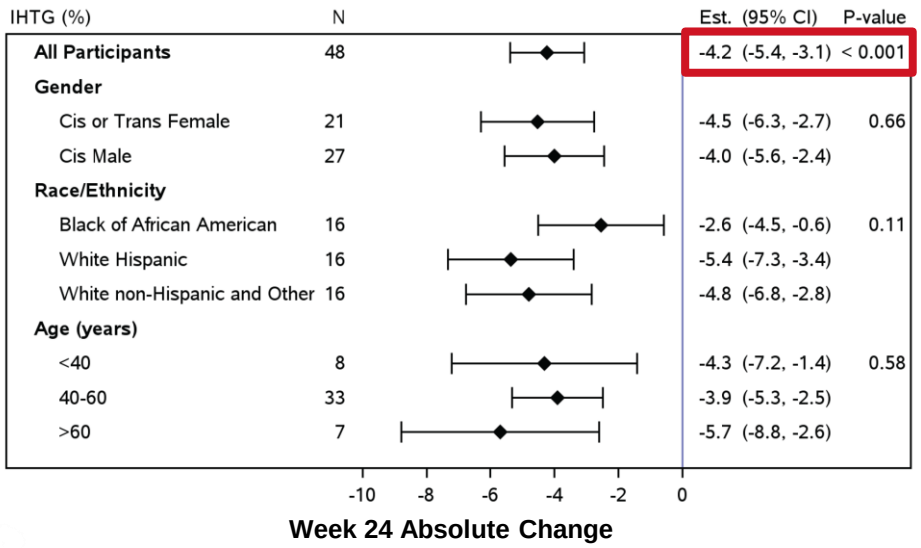


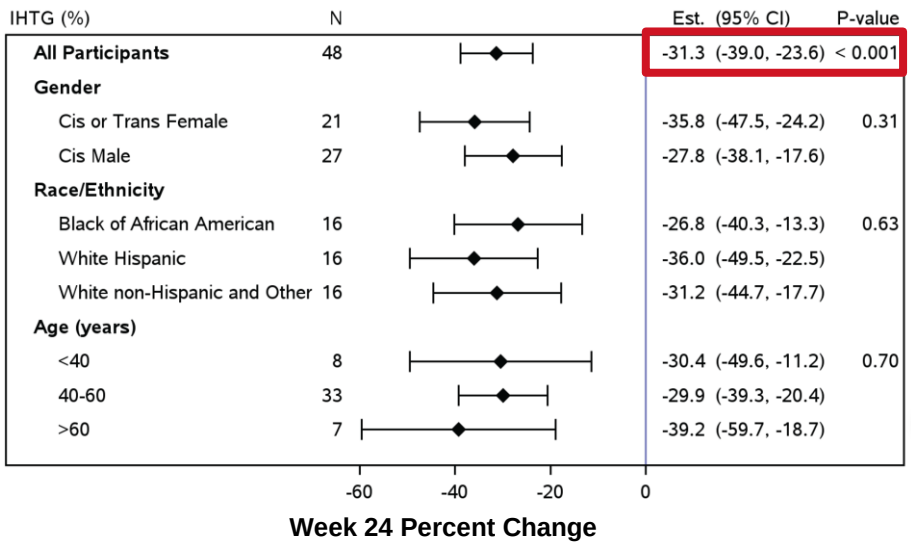
Baseline Characteristics*

	N=49
Age	52 (42, 58)
Gender	
Cis woman	18 (37%)
Trans woman	3 (6%)
Cis man	28 (57%)
Race/ethnicity	
White non-Hispanic	13 (27%)
Black or African American*	16 (33%)
Hispanic	19 (39%)
American Indian or Alaskan Native	1 (2%)
BMI (kg/m^2)	35 (31, 39)
Waist circumference (cm)	114 (107, 124)
$CD4^+$ T lymphocyte count ($cells/mm^3$)	701 (586, 869)
ART regimen	
PI	2 (4%)
NNRTI	10 (22%)
INSTI	40 (82%)
History of hepatitis C virus	4 (8%)

*Median with interquartile range or frequency presented from protocol defined analysis group.

Primary Outcome: Changes in IHTG

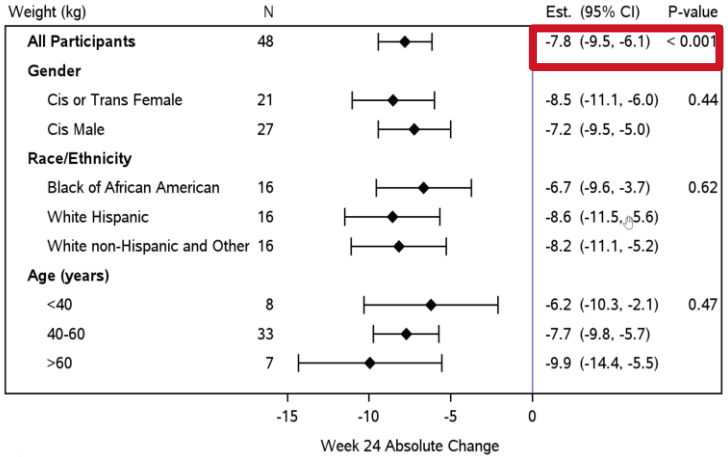


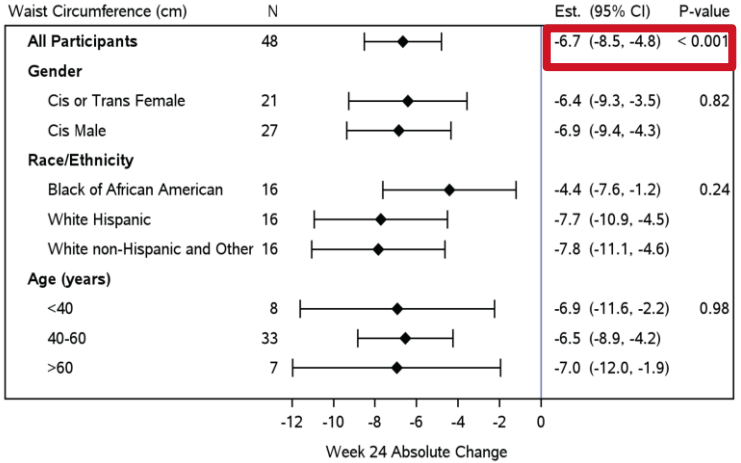


- Overall clinically significant reductions in IHTG
- 58% of participants had a ≥30% relative reduction in IHTG
- 29% of participants had complete MASLD resolution (absolute IHTG <5%)
- Greater reductions in IHTG were observed among*:
  - Women
  - Hispanic and non-Hispanic white participants
  - Participants with age >60 years

*A5371 was not powered to detect differences between subgroups.

Anthropometric Changes





- Mean weight loss was 7.8 kg (17 lbs) over 24 weeks, with greater losses among*
  - Women
  - Hispanic and non-Hispanic white participants
  - Persons ≥40 years of age
- IHTG improvements correlated with weight loss (r=0.54, p<0.0001)
- Amongst persons who lost >2.27 kg (5 lbs) on semaglutide (n=38), the mean absolute and relative changes in IHTG were -5.1% and -39.0%, respectively

*A5371 was not powered to detect differences between subgroups.

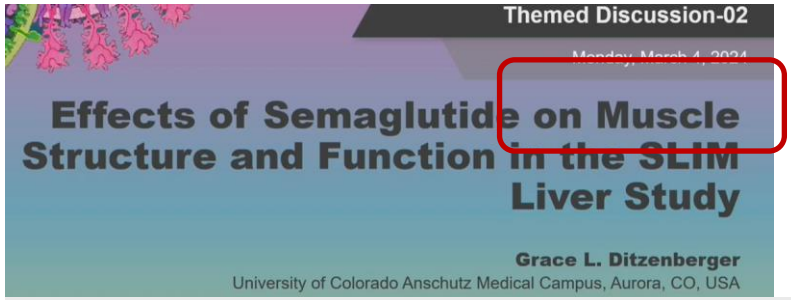
Changes in Circulating Lipids and Glucose Homeostasis

	24-week Change*	P value
Glucose (mg/dL)	-9.9 (-14.7, -5.1)	<0.001
HOMA-IR	-1.5 (-2.3, -0.8)	<0.001
Hemoglobin A1c (%)	-0.3 (-0.3, -0.2)	<0.001
Total Cholesterol (mg/dL)	-4.0 (-10.8, 2.9)	0.25
LDL Cholesterol (mg/dL)	-1.0 (-7.1, 5.1)	0.73
HDL Cholesterol (mg/dL)	2.0 (-0.02, 4.1)	0.053
Triglycerides (mg/dL)	-26.8 (-46.0, -7.5)	0.007

*Mean (95% confidence interval)

- Larger glucose reductions among[1, 2]
  - Women
  - Black participants
  - Persons ≥40 years of age
- Larger triglyceride reductions among[1]
  - Men
  - Hispanic participants
  - Persons <40 years of age

[1]A5371 was not to detect differences between subgroups. [2]HbA1c and HOMA-IR trends similar except that Hispanics and non-Hispanic whites had greater declines than Blacks.



- A quien?
- Qué y cómo?
- Cuanto tiempo?

SLIM LIVER study details

- **Patient population**: PWH with ≥5% IHTG content on MRI scan, waist circumference of ≥ 95cm for male sex at birth or ≥94cm for female sex at birth, at least 1 criteria for insulin resistance or pre-diabetes
- Received open-label, subcutaneous semaglutide for 24 weeks
- Semaglutide dose-escalated up to 1.0 mg/week by week 4

However, weight loss is typically accompanied by muscle loss

- Little is known about change in physical function with weight loss medications
- SLIM LIVER included muscle measures and physical function
- Primary outcome (change in IHTG and weight) presented tomorrow (**Abstract # 00159**)

Age (years)	50 (11)
Sex at birth	
Female	18 (37%)
Male	31 (63%)
Gender Identity	
Cis Female	18 (37%)
Cis Male	28 (57%)
Transgender Female	3 (6%)
Race	
American Indian or Alaska Native	1 (2%)
Black or African American	16 (33%)
Multiple	1 (2%)
Unknown	2 (4%)
White	29 (59%)
Ethnicity	
Hispanic or Latino	19 (39%)
Not Hispanic or Latino	30 (61%)
Weight Characteristics	
BMI (kg/m^2)	35.5 (5.6)
Weight (kg)	103.1 (20.8)
Waist circumference (cm)	114.7 (11.8)

Methods

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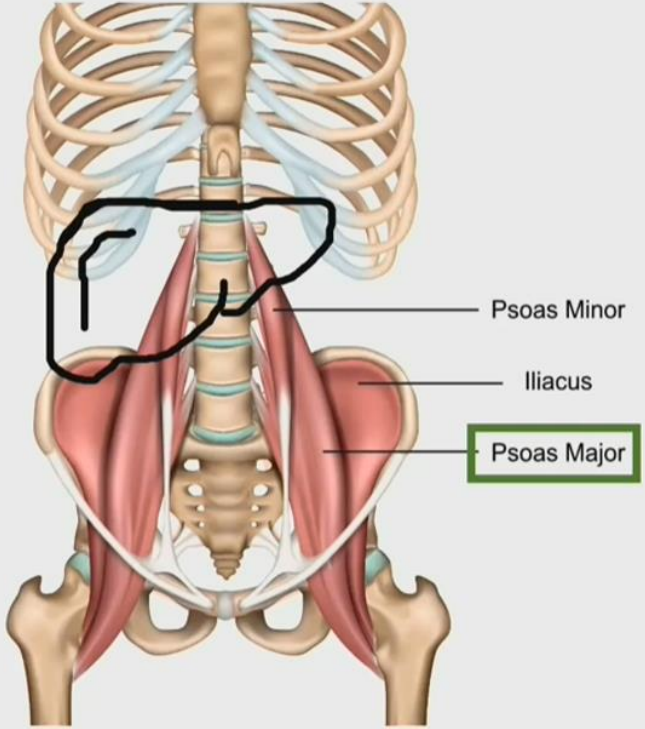
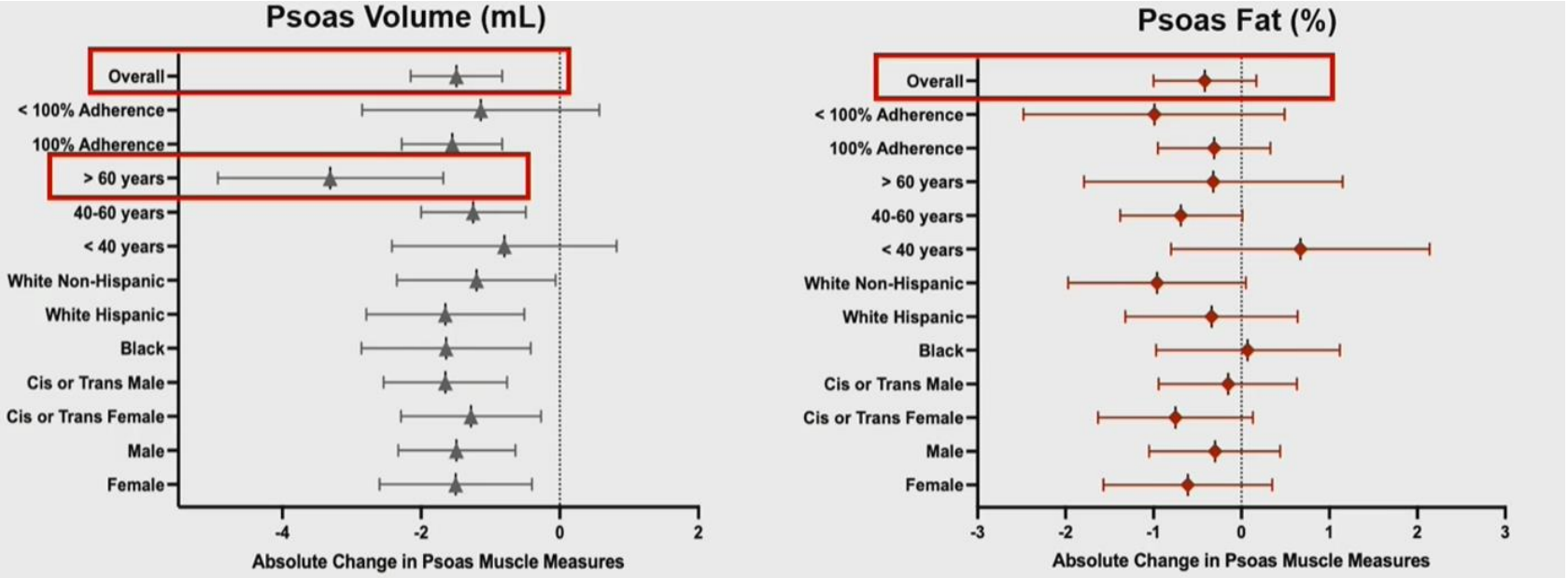
Outcomes (baseline → week 24)

- Psoas volume/fat fraction: captured from the liver magnetic resonance imaging proton-density fat fraction (MRI-PDFF)
- Physical function: timed chair rise test & 4-meter gait speed

Statistical Analysis

- Mean change from baseline estimated with linear regression models
- Spearman's correlations used to examine associations between MASLD markers and muscle measures





Overall psoas muscle volume **declined**, but psoas muscle fat content did not significantly change. PWH >60 years had the greatest decline in muscle volume.

Results: Change in physical function

CROI 2024

Parameter	Baseline	Week 24	Change, Baseline to Week 24 (estimate, 95% CI)	P-value
5x Chair Rise (seconds)	12.5 (3.6)	11.9 (3.3)	-0.66 (-1.4, 0.07)	0.077
10x Chair Rise (seconds)	26.2 (7.0)	25.0 (6.8)	-1.27 (-2.7, 0.10)	0.069
Gait speed (meters/second)	0.93 (0.23)	0.98 (0.24)	0.05 (-0.01, 0.10)	0.078
Presence of slow gait speed (<1 meters/second)	No: 18 (37%) Yes: 31 (63%)	No: 26 (54%) Yes: 22 (46%)	RR: 0.73 (0.55, 0.97)	0.029

Chair rise time and gait speed were **preserved** despite loss of psoas muscle volume. These changes in function were not correlated with change in overall weight or BMI.

SEMAGLUTIDE

1

Sobre el peso

- Descenso del peso 5,7kg
- Hasta -8,8kg si IMC alto

2

Mayor beneficio si

- IMC alto
- No DM
- Lipohipertrofia
  - Descenso VAT/SAT
- Dosis dependiente

3

Sobre el hígado

- Descenso de grasa hepática

4

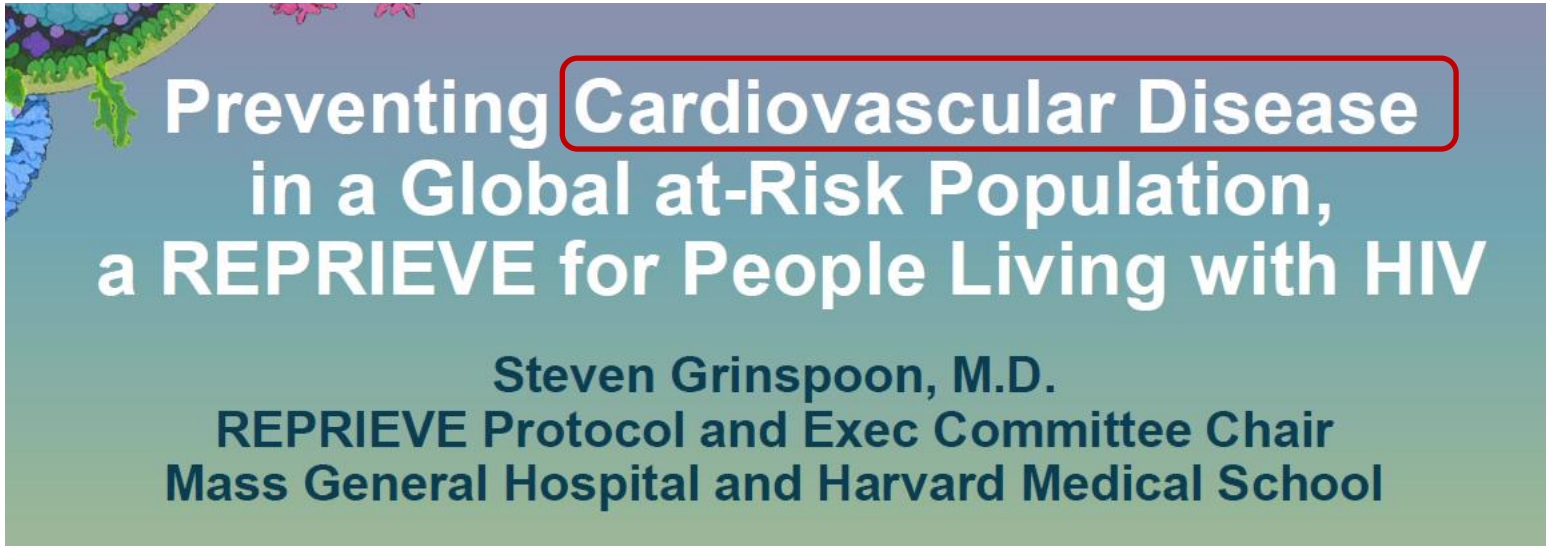
- Descenso cintura/cadera
- Descenso glucosa, HOMA-IR, HbA1c y TG
- Descenso inflamación

5

Sobre el músculo

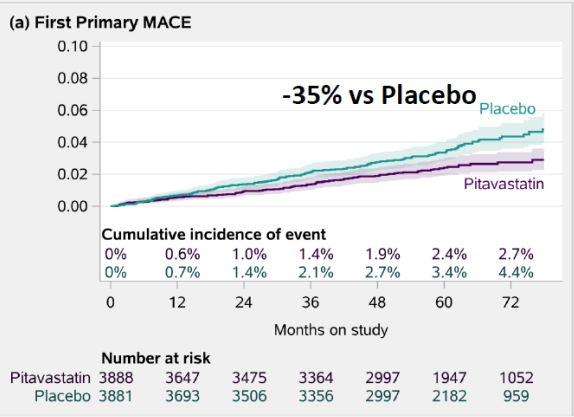
- Descenso **volumen** muscular
- No descenso de **grasa** en músculo
- **Función** muscular preservada

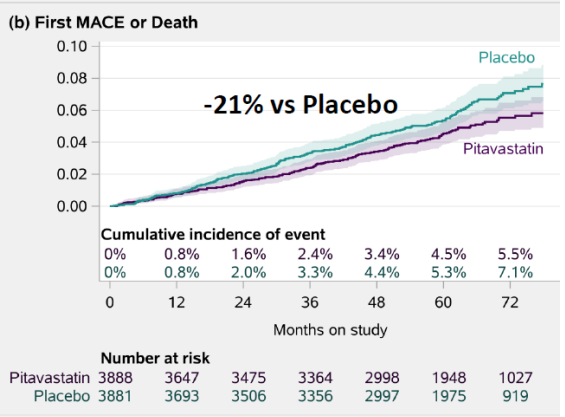
REPRIEVE


Preventing Cardiovascular Disease
in a Global at-Risk Population,
a REPRIEVE for People Living with HIV
Steven Grinspoon, M.D.
REPRIEVE Protocol and Exec Committee Chair
Mass General Hospital and Harvard Medical School

Primary and Key Secondary Endpoints

Among 7769 participants, age 50, ASCVD risk 4.5%, LDL 108:





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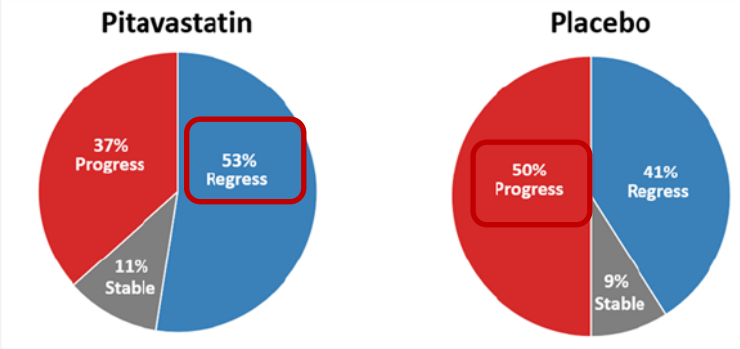
Grinspoon NEJM 2023

Other Key Findings

- No treatment modification based on LDL, age, sex, CD4, nadir CD4, HIV RNA, ART Duration
- Only 1% vs 0.5% (pitava vs placebo) withdrew for muscle-related symptomatology
- Diabetes rates were higher 5.3% vs 4% (pitava vs placebo), but c/w other studies and protective effect of statin seen among diabetics receiving pitava vs placebo
  - ➢50% reduction in MACE among diabetics in pitava vs placebo

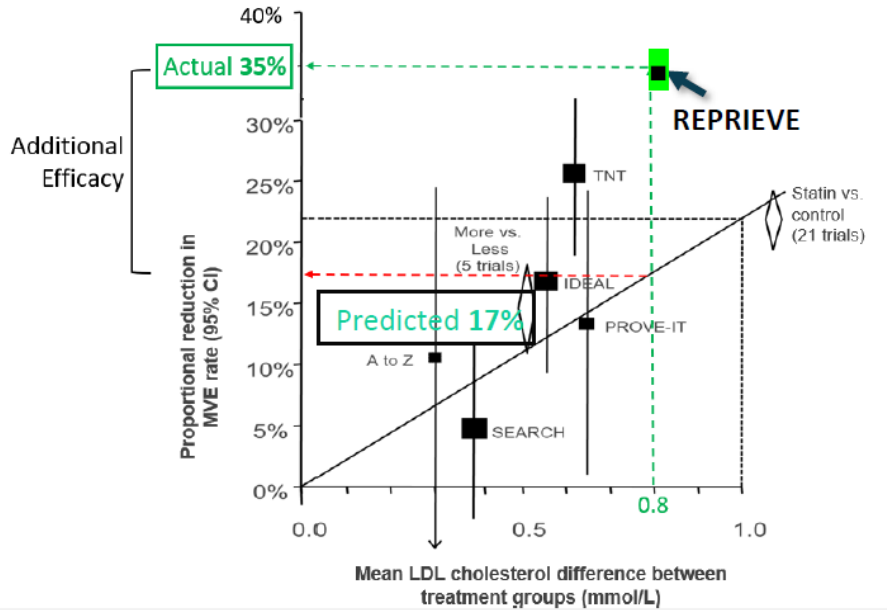
Effects on Plaque

Outcome	Treatment arm		Treatment effect[1]		
	Pitavastatin (N=386)	Placebo (N=388)	Difference (95% CI)	P	Difference (95% CI)[2]
Noncalcified plaque volume, mm^3					
Change from baseline, mean (SD)	-1.7 (25.2)	2.62 (27.1)	-4.3 (-8.6, -0.1)	0.044	-8.8 (-17.9, 0.36)
Fold-change from baseline (95% CI)	0.95 (0.91, 1.0)	1.02 (0.99, 1.05)	0.93 (0.88, 0.99)	0.024	0.88 (0.77, 1.00)
Progression of noncalcified plaque, N (%)	53 (18%)	85 (28%)	0.67 (0.52, 0.88)	0.003	0.71 (0.55, 0.93)
Low attenuation plaque volume, mm^3					
Change from baseline, mean (SD)	-0.9 (9.97)	-0.1 (8.16)	-1.2 (-2.2, -0.1)	0.026	-2.4 (-4.7, -0.2)



Lu et al. AHA 2023

Effect Larger than Anticipated Based on Lowering of LDL



- LDL lowering matters but statin effect is beyond what is expected for LDL lowering alone

Note: 35% is point estimate, CI % is 17 – 52%

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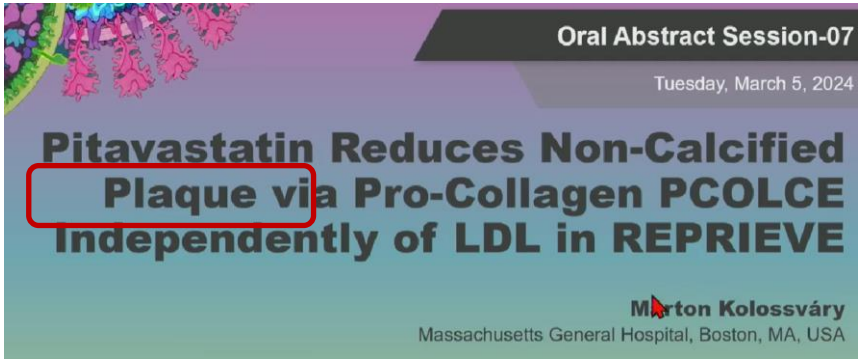
Lancet 2010; 376: 1670-81

Clinical Implications and Future Considerations

- Consideration should be given to incorporating results from REPRIEVE into clinical guidelines
- Further work is needed to understand how to utilize PCE scoring in subpopulations of PWH in whom the PCE underpredicts risk, e.g. in blacks and females
- Further work is needed to assess effects on key inflammatory and immune pathway changes in response to statin therapy in REPRIEVE, as well as role of genetics, lifestyle and other risk factors

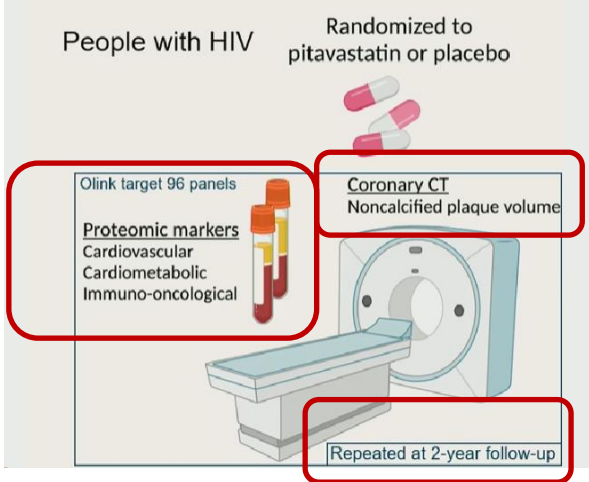
PCE = pooled cohort equations



- A quien?
- Qué y cómo?
- Cuanto tiempo?

Changes in LDL and biomarkers were not significantly associated with changes in noncalcified plaque volume

To investigate mechanistic pathways of statin effects on plaque in PWH



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

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%)

Protein changes vs. noncalcified plaque change

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

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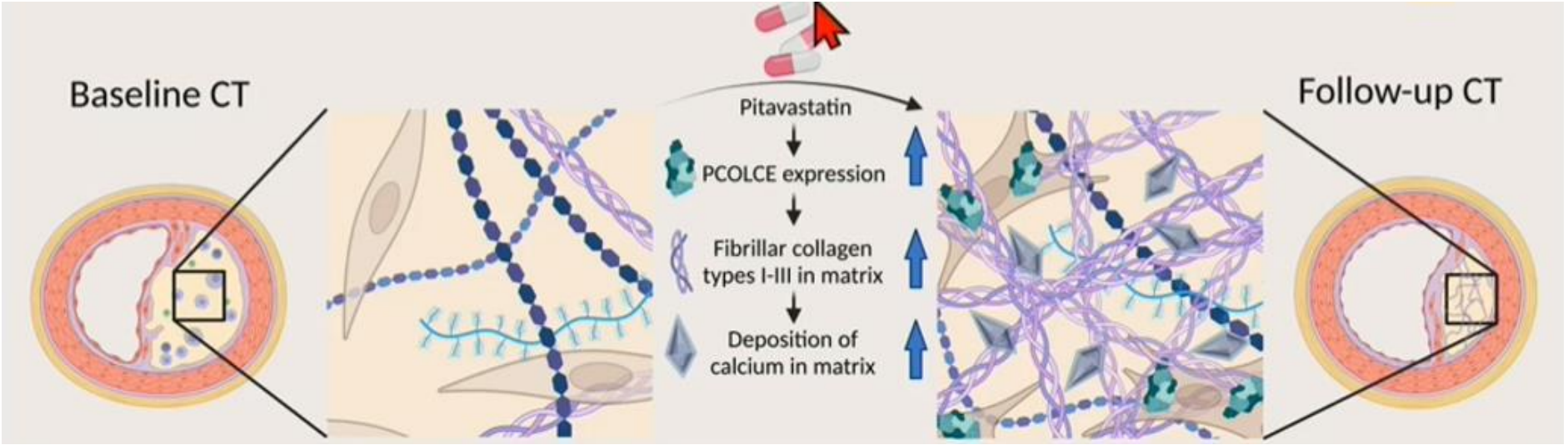
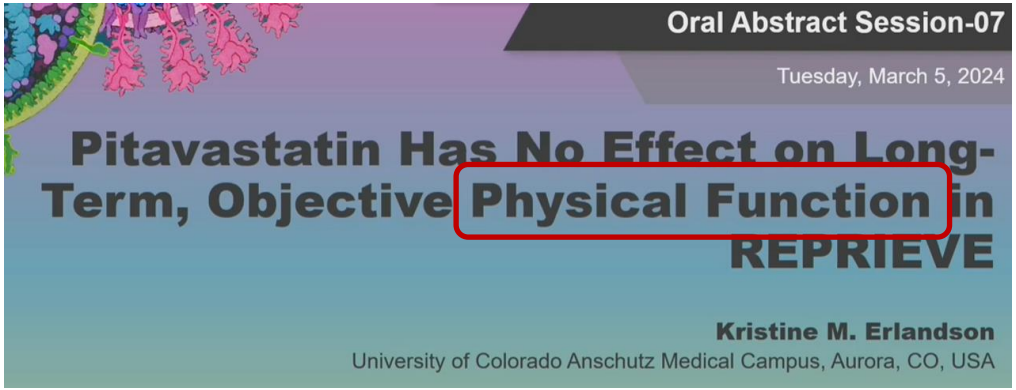
Increased PCOLCE expression was associated with a shift in plaque components promoting plaque stabilization

84% of the total effect of statins on NCP volume change was mediated through PCOLCE, independent of LDL change or achieved LDL


Baseline CT
Pitavastatin
PCOLCE expression
Fibrillar collagen types I-III in matrix
Deposition of calcium in matrix
Follow-up CT



- A quien?
- Qué y cómo?
- Cuanto tiempo?

- Physical function (10x chair rise, 4-m gait, balance, grip strength, mSPPB) was evaluated annually for up to 5 years

Results

- 602 enrolled into PREPARE
  - 45% prospective (at initiation)
  - 55% retrospective (within <2 years)
- No difference in function at entry
- Median (Q1, Q3) follow-up duration:
  - 5.0 (4.9, 5.1) years for prospective
  - 4.4 (4.3, 4.7) years for retrospective
  - Linear mixed effects models allowed inclusion of data from both
- 81% completed follow-up

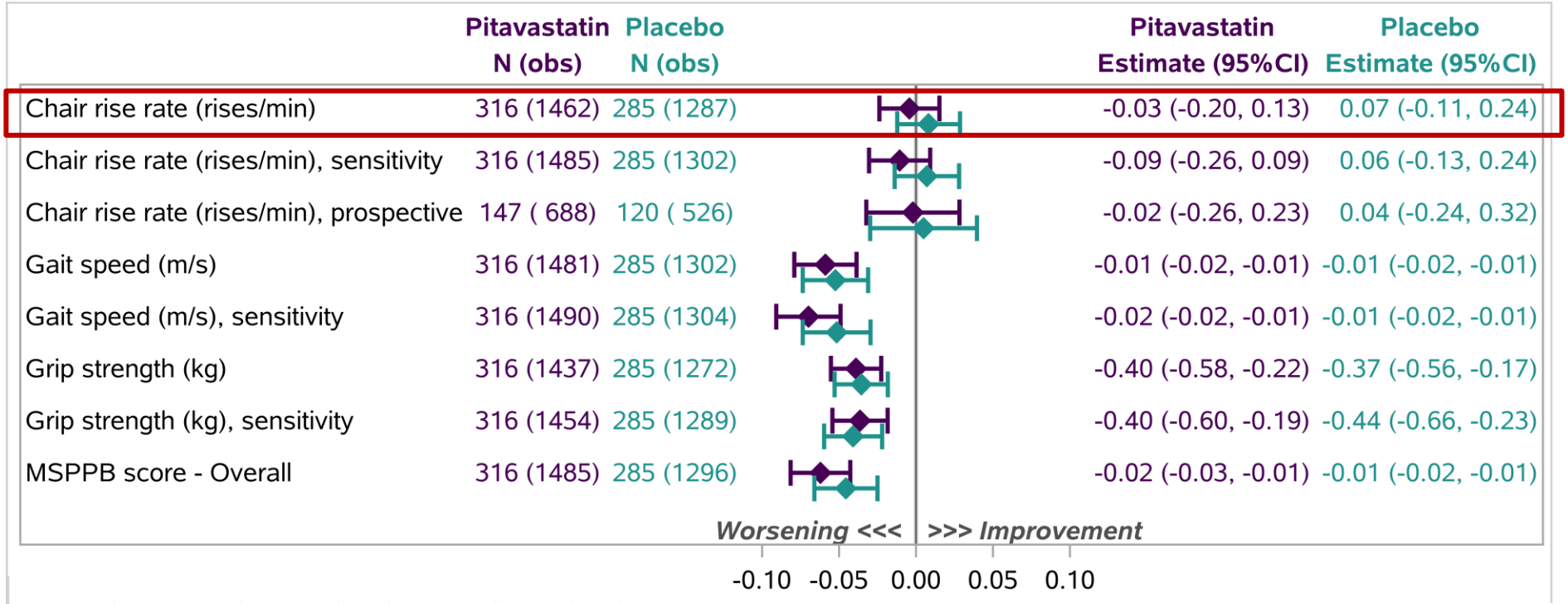
	Pitavastatin N= 316	Placebo N= 286
Age (years)	51	51
Female sex	21%	16%
Transgender	2%	2%
Black	40%	39%
Hispanic	18%	18%
BMI (kg/m^2)	27.3	27.1
Current smoker	30%	24%

For age and BMI, medians are shown

Results

Minimal changes in rise change in either group

- Similar results seen when restricted to prospective only group
- Smaller change than anticipated 0.58 rise/min/year

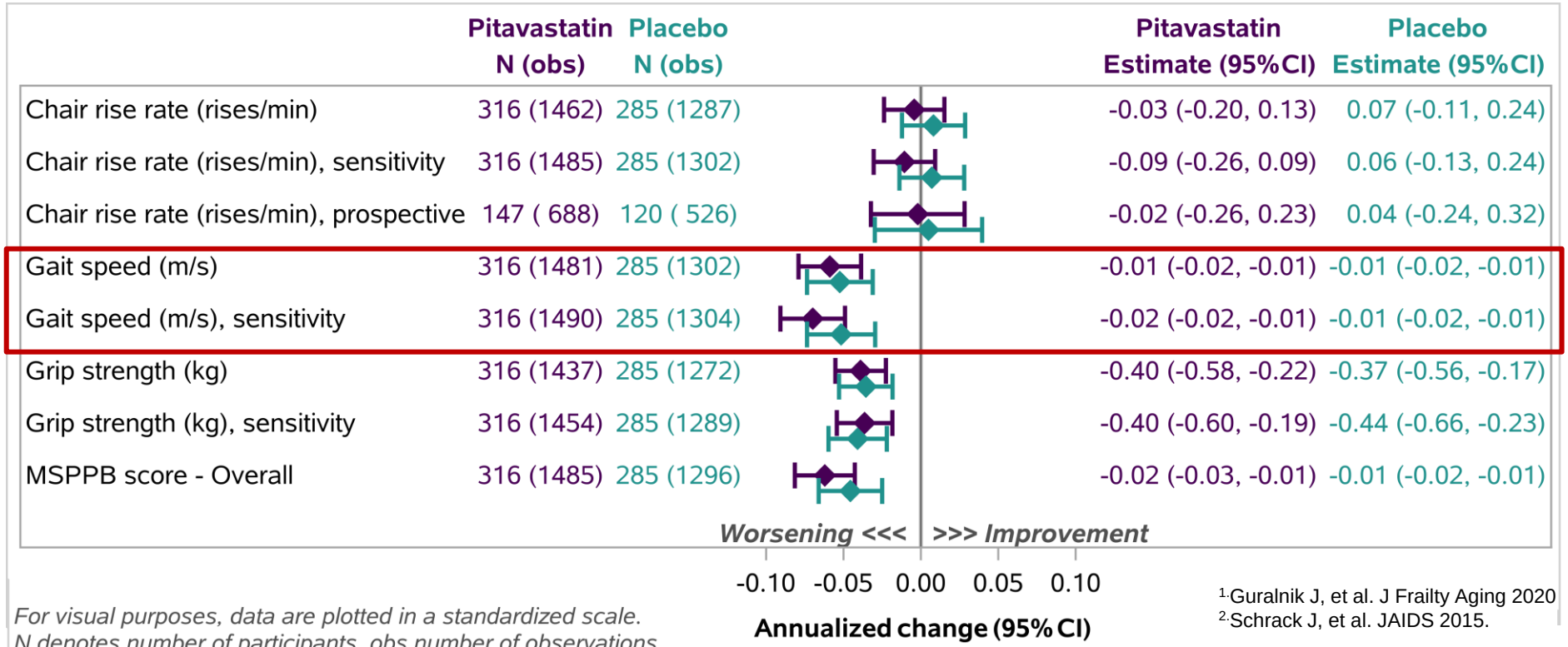


For visual purposes, data are plotted in a standardized scale.
N denotes number of participants, obs number of observations.
Sensitivity analyses = evaluations not attempted for non-administrative reasons were considered worst outcomes.

Results

Small declines in gait speed:

- Smallest clinically meaningful change = 0.03-0.05 m/s[1]
- Change per year with aging in PWH = 0.012 m/s/year[2]



For visual purposes, data are plotted in a standardized scale.
N denotes number of participants, obs number of observations.
Sensitivity analyses = evaluations not attempted for non-administrative reasons were considered worst outcomes.

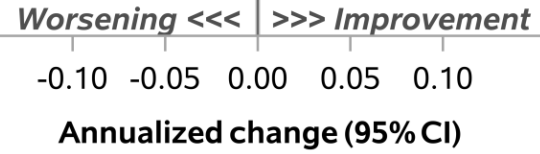
[1] Guralnik J, et al. J Frailty Aging 2020
[2] Schrack J, et al. JAIDS 2015.

Results

Small declines in grip strength:

- Smallest clinically meaningful change = 5.0-6.5 kg[1]
- Change per year with aging in PWH = 0.37-0.40 kg/year[2]

	Pitavastatin N (obs)	Placebo N (obs)	Pitavastatin Estimate (95%CI)	Placebo Estimate (95%CI)
Chair rise rate (rises/min)	316 (1462)	285 (1287)	-0.03 (-0.20, 0.13)	0.07 (-0.11, 0.24)
Chair rise rate (rises/min), sensitivity	316 (1485)	285 (1302)	-0.09 (-0.26, 0.09)	0.06 (-0.13, 0.24)
Chair rise rate (rises/min), prospective	147 (688)	120 (526)	-0.02 (-0.26, 0.23)	0.04 (-0.24, 0.32)
Gait speed (m/s)	316 (1481)	285 (1302)	-0.01 (-0.02, -0.01)	-0.01 (-0.02, -0.01)
Gait speed (m/s), sensitivity	316 (1490)	285 (1304)	-0.02 (-0.02, -0.01)	-0.01 (-0.02, -0.01)
Grip strength (kg)	316 (1437)	285 (1272)	-0.40 (-0.58, -0.22)	-0.37 (-0.56, -0.17)
Grip strength (kg), sensitivity	316 (1454)	285 (1289)	-0.40 (-0.60, -0.19)	-0.44 (-0.66, -0.23)
MSPPB score - Overall	316 (1485)	285 (1296)	-0.02 (-0.03, -0.01)	-0.01 (-0.02, -0.01)



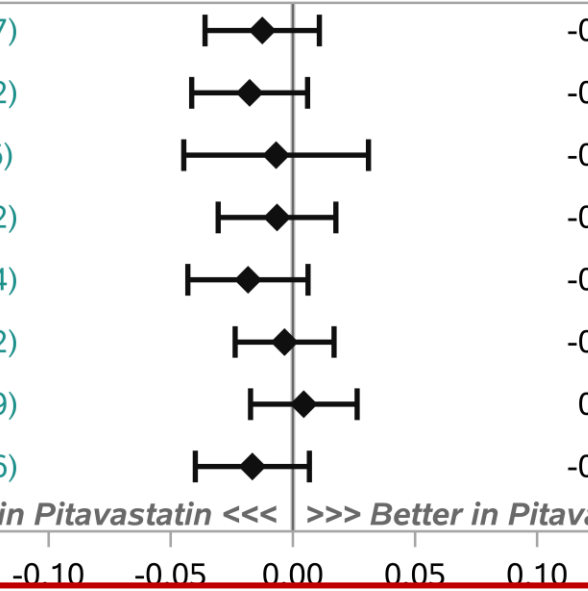
For visual purposes, data are plotted in a standardized scale.
N denotes number of participants, obs number of observations.
Sensitivity analyses = evaluations not attempted for non-administrative reasons were considered worst outcomes.

1. Bohannon, RW. J Phys Ther Sci 2019.
2. Schrack J, et al. AIDS 2016.

Results

No differences seen by treatment arm on any physical function outcomes

	Pitavastatin N (obs)	Placebo N (obs)	Estimate (95% CI)	P-value
Chair rise rate (rises/min)	316 (1462)	285 (1287)	-0.100 (-0.296, 0.095)	0.31
Chair rise rate (rises/min), sensitivity	316 (1485)	285 (1302)	-0.146 (-0.350, 0.058)	0.16
Chair rise rate (rises/min), prospective	147 (688)	120 (526)	-0.053 (-0.355, 0.248)	0.73
Gait speed (m/s)	316 (1481)	285 (1302)	-0.001 (-0.007, 0.004)	0.61
Gait speed (m/s), sensitivity	316 (1490)	285 (1304)	-0.004 (-0.010, 0.002)	0.16
Grip strength (kg)	316 (1437)	285 (1272)	-0.035 (-0.254, 0.184)	0.75
Grip strength (kg), sensitivity	316 (1454)	285 (1289)	0.049 (-0.200, 0.298)	0.70
MSPPB score - Overall	316 (1485)	285 (1296)	-0.005 (-0.013, 0.002)	0.18



For visual purposes, data are plotted in a standardized scale.
N denotes number of participants, obs number of observations.
Sensitivity analyses = evaluations not attempted for non-administrative reasons were considered worst outcomes.

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REPRIEVE

1 General (7769 pacientes / 5 años)

- Descenso 35% MACE
- Descenso de placa atheroma
- Mujer:
- Mas inflamación/activación
- Menos placas ateroma

- Afectación muscular:
  1% vs 0,5%
- DM: 5,3% a 4%

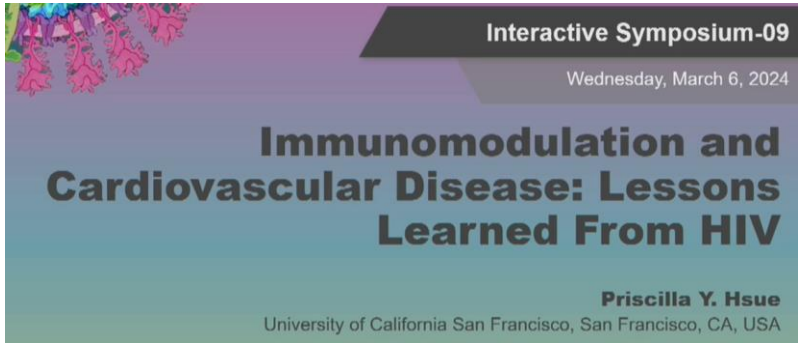
2 Mecanismo (disminución placa)

- Aumento expression PCOLCE
- Aumento de la matriz en la placa
- Aumento del depósito de calcio en la matriz

3 Afectación muscular

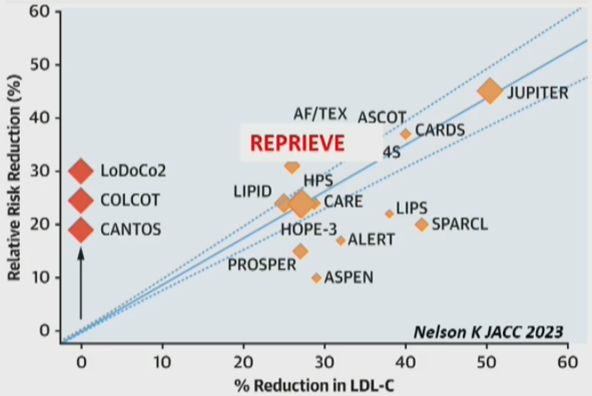
- Seguridad de las estatinas con pitavastatina (vs placebo)

Otras



- Una classe magistral

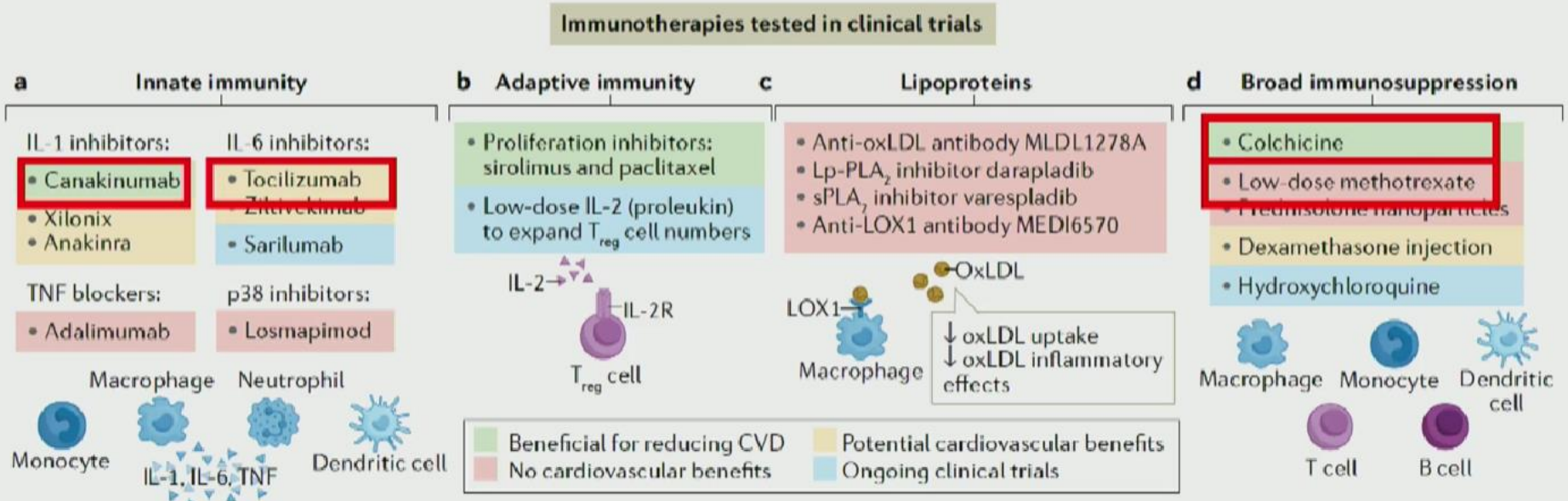
Residual inflammatory risk in the general population



Colchicine and canakinumab reduce CV risk without reducing LDL-C, while statins reduce both

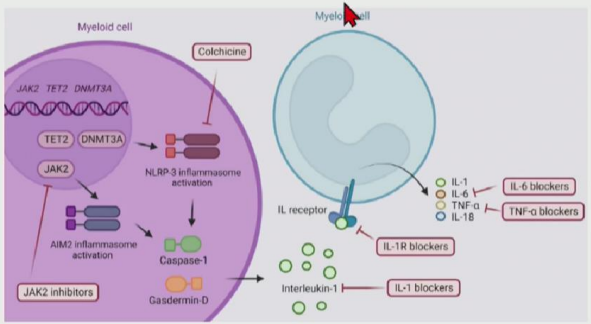
"We believe that combined use of aggressive lipid-lowering and anti-inflammatory therapies might become standard of care for atherosclerotic disease in the future" (Ridker PM Lancet 2023).

Multiple anti-inflammatory drugs/strategies have advanced to clinical testing in the cardiology space



Engelen SE Nature Reviews Cardiology 2022

Potential therapies for clonal hematopoiesis of indeterminate potential (CHIP)-related inflammation

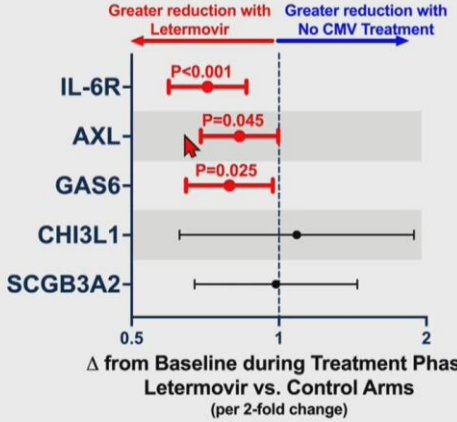


Upstream targets of inflammatory cytokines (JAK inhibitors, colchicine)

Downstream targets (IL-6, TNF-alpha, IL-1R,IL-1 blocker)

Sikking MA JAHA 2023

Emerging role of CMV as a cause of inflammation and cardiovascular disease in PWH



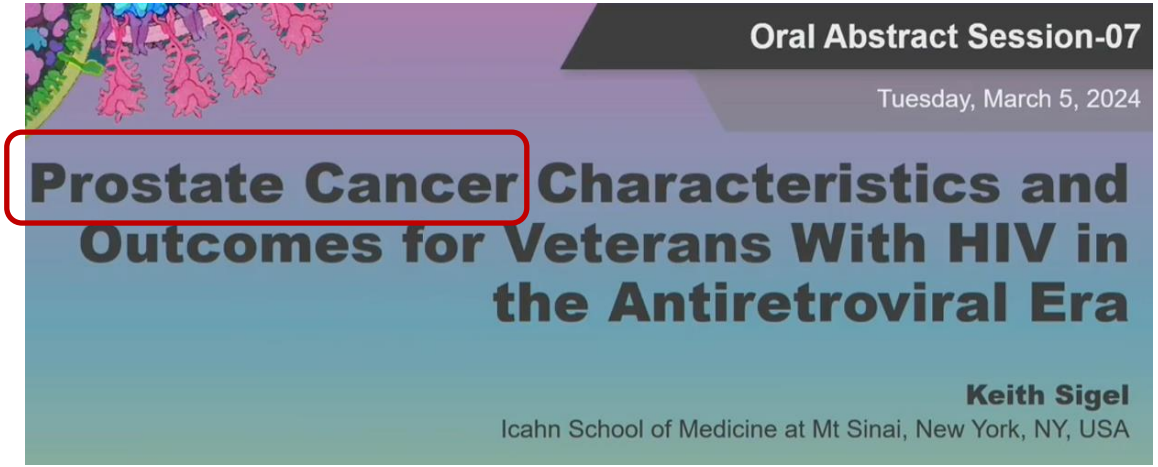
- ACTG 5383: RCT of letermovir vs placebo in PWH (n=40)
- Letermovir decreased 3/5 of the plasma proteins causally linked to CVD events in treated HIV (IL-6R, AXL, GAS6). (Reilly et al, JID, 2023)
- AXL and GAS6 are unique causal predictors of CVD in HIV

Gianella et al, Poster 354 LB, CROI 2024

Immunology 101: Most of the host inflammatory response is immunoregulatory in nature

Schnittman et al, Tuesday, Oral #143, CROI 2024

- Inflammation is harmful
- Inflammation stimulates a potent and sustained immunosuppressive response
  - T regulatory cells (TGF-β, IL-10)
  - Immune checkpoint receptors
  - Myeloid-derived suppressor cells
- These immunosuppressive responses can blunt immune responses to infection (HIV) and cancer



- Cambio de mensaje

- A quien?
- Qué y cómo?
- Cuanto tiempo?

Objective: Examine prostate cancer characteristics and survival by HIV

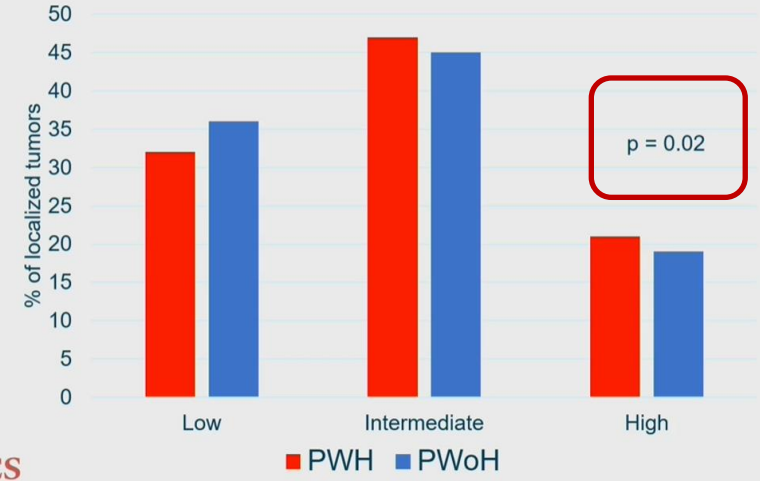
VACS
Veterans Aging Cohort Study

Characteristic	PWH n=791	PWoH n=2,778	p
Age, median (IQR)	62 (56-66)	61 (57-65)	0.31
Race, %			0.43
Non-Hispanic White	22	21	
Non-Hispanic Black	67	66	
Hispanic	4	5	
Diagnosis year, %			<0.001
2001-2007	19	25	
2008-2018	81	75	

Prostate cancer characteristics by HIV

Characteristic	PWH n=791	PWoH n=2,778	p
PSA at dx, median	6.8	6.3	0.005
Metastatic at dx, %	4.1	2.7	0.048

D'Amico risk classification of localized tumors



VACS
Veterans Aging Cohort Study

PWH vs PWoH:

Higher risk prostate cancer diagnosis

Less frequent PSA testing

Higher non-cancer mortality

- May impact benefits of aggressive prostate cancer tx strategies vs active surveillance

- Para acabar donde lo dejamos en el CROI 2023
  - A quien?
  - Qué y cómo?
  - Cuanto tiempo?

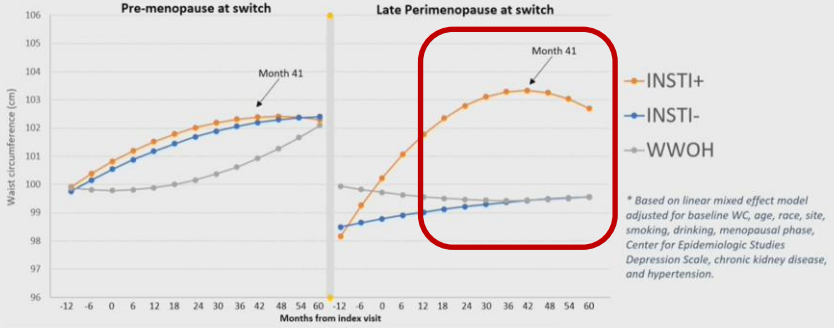
- Longitudinal study of retrospective data from women with and without HIV in the MACS-WIHS Combined Cohort Study (MWCCS) from 2006-2019.
  - Leveraged the SPPACE INSTI sub-study (PI: Lahiri)
- Inclusion criteria:
  - ART suppressed for at least two years
  - Did not have prior exposure to an INSTI before the switch visit
- Women were divided into menopausal categories [premenopause, early and late perimenopause, and postmenopause] using anti-Müllerian hormone (AMH) levels, a biomarker of ovarian reserve

- Women were categorized into three groups:
  - Women with HIV who newly started on an INSTI (INSTI+)
  - Women with HIV who were not on an INSTI at a similar timepoint (INSTI-)
  - A comparison group of demographically similar women without HIV (WWOH)

N (%)	INSTI+	INSTI-	WWOH
Median (IQR)	(n=424)	(n=733)	(n=904)
Age (y)	52 (46-58)	49 (43-54)	47 (38-53)
Race/Ethnicity			
White	21%	22%	16%
African American	67%	61%	71%
Other‡	12%	17%	13%
Hispanic	20%	25%	19%
Menopausal status			
Premenopause	14%	26%	37%
Early Perimenopause	7.3%	10%	11%
Late Perimenopause	32%	30%	25%
Menopause	47%	35%	27%
Current Smoking	32%	35%	48%
Chronic Kidney disease	19%	9.9%	7.4%
HIV-related factors			
CD4 (cells/mm^3)	713 (552-893)	629 (456-829)	
Tenofovir disoproxil fumarate (TDF) use	64%	79%	-
Efavirenz use	1.9%	29%	-

- Small numbers of women on TAF-containing regimens
  - We performed a sensitivity analysis limiting to women on TDF and the findings appeared similar

Waist circumference trajectories by menopausal phase



* Based on linear mixed effect model adjusted for baseline WC, age, race, site, smoking, drinking, menopausal phase, Center for Epidemiologic Studies Depression Scale, chronic kidney disease, and hypertension.

	Pre-menopause		Late Perimenopause	
	Δcm/6 month (95% CI)	P-value	Δcm/6 month (95% CI)	P-value
INSTI+*time interaction	0.06 (-0.27, 0.38)	0.73	**0.96 (0.45, 1.46)**	**<.001**
INSTI+*time^2			**-0.07 (-0.13, -0.003)**	**0.04**
INSTI-*time	0.08 (-0.11, 0.28)	0.40	0.14 (-0.06, 0.33)	0.16

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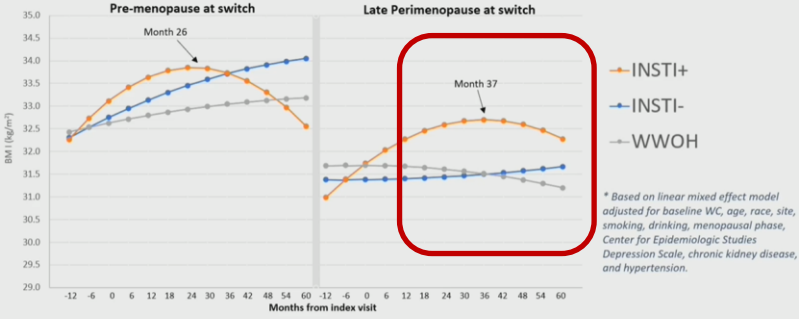
BMI trajectories by menopausal phase



* Based on linear mixed effect model adjusted for baseline WC, age, race, site, smoking, drinking, menopausal phase, Center for Epidemiologic Studies Depression Scale, chronic kidney disease, and hypertension.

	Pre-menopause		Late Perimenopause	
	Δ/6 month (95% CI)	P-value	Δ/6 month (95% CI)	P-value
INSTI+*time interaction	**0.24 (0.03, 0.45)**	**0.02**	**0.35 (0.20, 0.49)**	**<0.001**
INSTI+*time^2	**-0.04 (-0.06, -0.01)**	**0.01**	**-0.03 (-0.04, -0.01)**	**0.01**
INSTI-*time	**0.09 (0.02, 0.15)**	**0.01**	0.06 (-0.004, 0.12)	0.07

CI

EXTRA-CVD: A Nurse-led Intervention to Extend the HIV Treatment Cascade for Cardiovascular Disease Prevention

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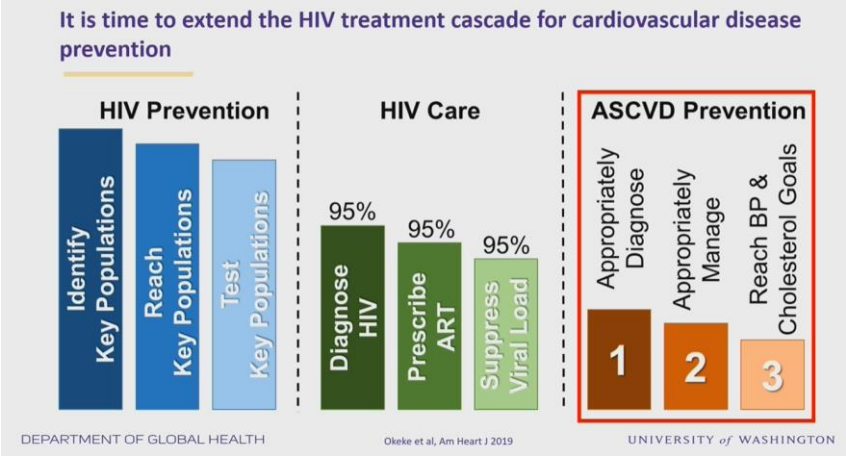
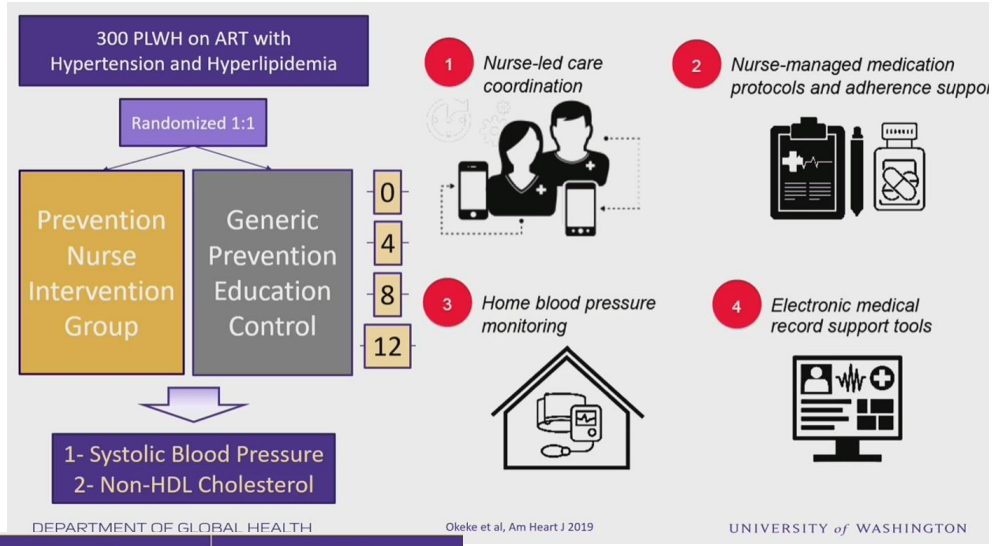
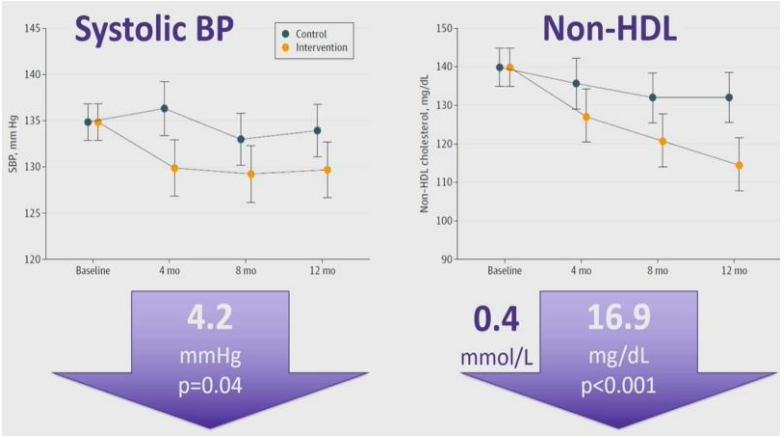
DEPARTMENT OF GLOBAL HEALTH

- Una estratègia a implementar





	Overall N=297	Intervention N=149	Control N=148
Age (IQR)	59 (53, 65) years	59 (53, 65) years	60 (53, 64) years
Male	233 (79%)	113 (76%)	120 (81%)
Black/African American	176 (59%)	79 (53%)	97 (66%)
Public insurance	181 (61%)	85 (57%)	96 (65%)
Diabetes	89 (30%)	45 (30%)	44 (30%)
Mental health disorder	158 (53%)	85 (57%)	73 (49%)
10-yr ASCVD risk ≥7.5%	163 (85%)	82 (80%)	91 (90%)
Systolic BP (SD)	135 (19) mmHg	136 (18) mmHg	134 (20) mmHg
≥3 BP medications	64 (22%)	31 (21%)	33 (22%)
Non-HDL (SD)	139.9 (44.6) mg/dL	139.5 (44.6) mg/dL	140.3 (44.9) mg/dL
On a statin	202 (68%)	101 (68%)	101 (68%)



	4 months		8 months		12 months	
Tertiary outcomes	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Hypertension cascade						
Treated	0.9 (0.3, 2.6)	.85	1.6 (0.4, 5.8)	.46	1.3 (0.4, 4.0)	.61
At treatment goal	1.6 (0.6, 4.4)	.38	3.0 (0.9, 10.6)	.08	2.9 (1.0, 8.3)	.05
Cholesterol cascade						
Treated	1.2 (0.4, 4.1)	.74	1.3 (0.4, 4.9)	.68	1.1 (0.3, 4.5)	.84
At treatment goal	1.8 (0.6, 5.1)	.30	3.2 (1.0, 10.2)	.05	**7.3 (2.3, 23.3)**	**< .001**
Exploratory outcomes	Mean difference (95% CI)	*p*	Mean difference (95% CI)	*p*	Mean difference (95% CI)	*p*
Total cholesterol, mg/dL	-7.3 (-15.8, 1.2)	.09	**-10.0 (-18.4, -1.5)**	**.02**	**-15.5 (-23.9, -7.0)**	**< .001**
HDL cholesterol, mg/dL	0.9 (-1.3, 3.2)	.43	1.7 (-0.6, 3.9)	.15	0.9 (-1.3, 3.2)	.43
LDL cholesterol, mg/dL	-7.4 (-23.4, 8.6)	.36	-10.3 (-26.0, 5.5)	.20	-9.6 (-25.5, 6.3)	.24
Triglycerides, mg/dL	-12.2 (-36.5, 12.1)	.33	**-34.1 (-58.2, -10.1)**	**.006**	**-29.5 (-53.7, -5.3)**	**.02**

Gracias

Próximo CROI 2025

San Francisco