Unique Aspects of Cardiovascular Disease among Women with HIV: Lessons from REPRIEVE

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Disclosures

I am Principal Investigator of NIH grants R01AI123001, R01HL146267, R01HL137562, R01HL 167645, and K24AI157882, as well as an Investigator-Initiated Industry Grant from Gilead Sciences to my Institution (MGH).

Scope

- This presentation explores the influence of sex-assigned-at-birth on atherosclerotic cardiovascular disease (ASCVD) risks and mechanisms among people living with HIV.

- Terms “female” and “women” are used in reference to sex-assigned-at-birth.

- Efforts to better understand the influence of gender identification and gender-affirming therapies on ASCVD risks and mechanisms among people living with HIV are also important but will not be covered today.

Discussion Map

- REPRIEVE overview
- Unique aspects of CVD risk mechanisms among women living with HIV
- Insights from REPRIEVE specifically relevant to women living with HIV
- Synthesis and future directions

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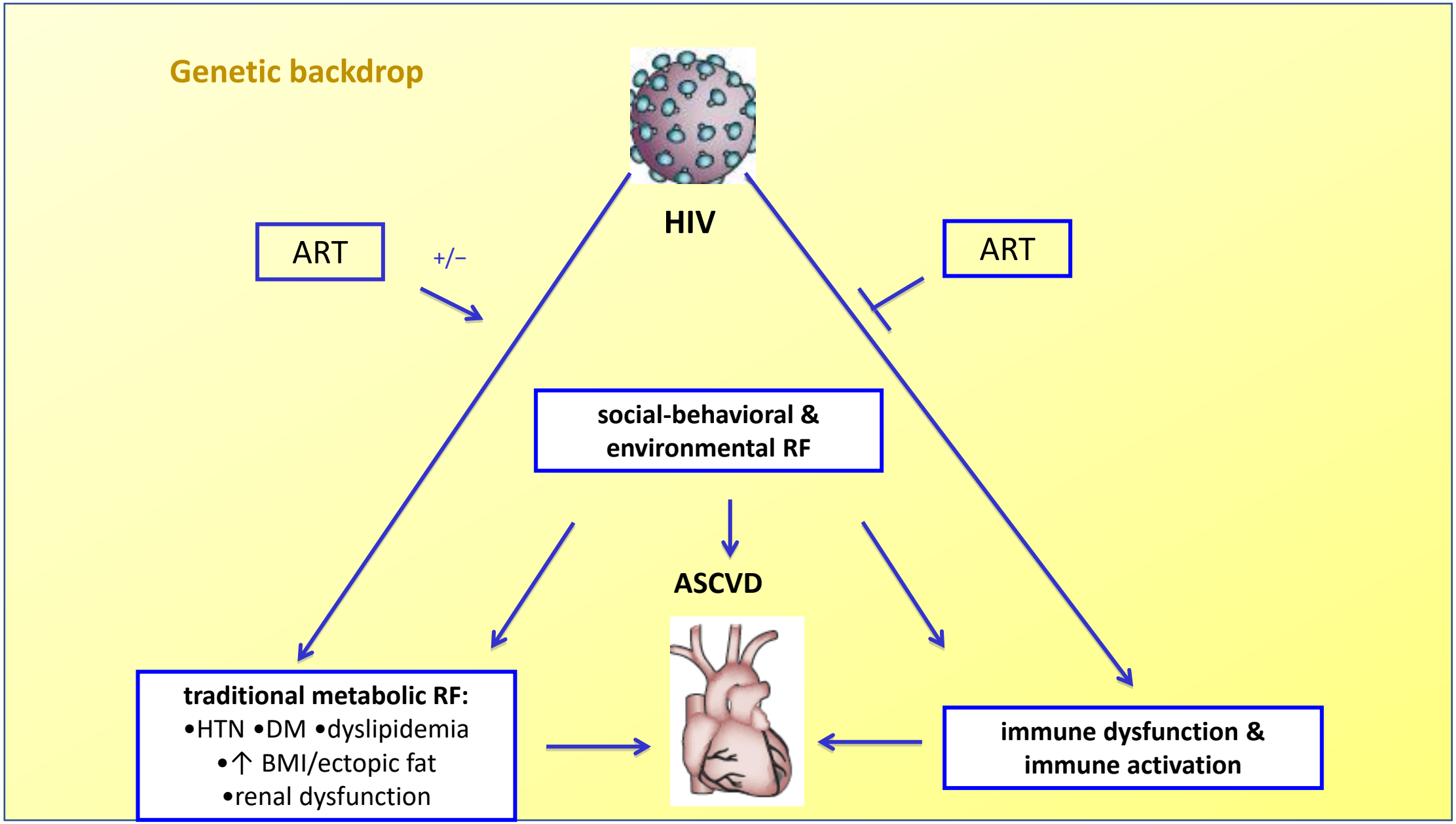
ASCVD Risk Mechanisms Among PLWH



Adapted from Zanni Nature Reviews Cardiology 2014

10-year ASCVD Risk Score - Part of the 2013 + 2018 ACC/AHA Guidelines

Other groups (age <40, age >75, LDL<70)

Primary Prevention (40-75, LDL 70-189): Estimate 10-y ASCVD risk q4-6 yrs using Pooled Cohort Equations

<5%

5 - <7.5%

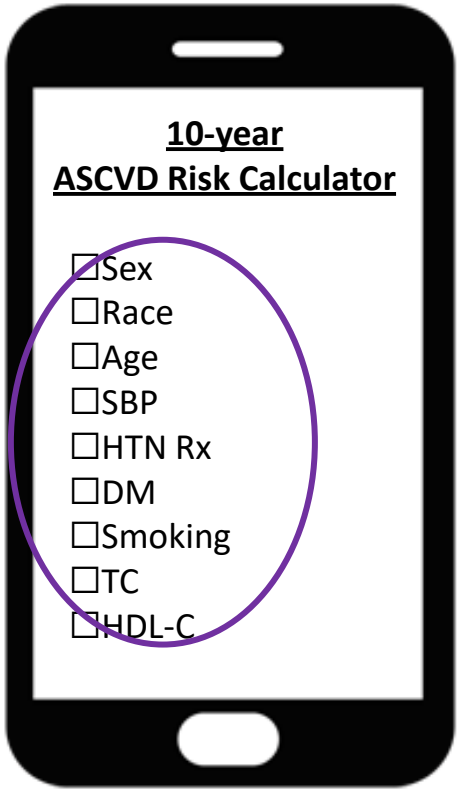
***7.5% - <20%**

≥20%

consider additional factors

CLINICIAN-PATIENT DISCUSSION

High-intensity statin rx



*2018 guidelines add if score 7.5%-19.9%, risk enhancing factors may favor initiation of statin rx.

Stone Circ 2014; Grundy JACC 2018

REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV

A Priori Hypothesis: Statin therapy will prevent atherosclerotic cardiovascular disease (ASCVD)-related major adverse cardiovascular events (MACE) among people living with HIV on ART in whom traditional CVD risk is not significantly increased*, e.g:

***entry criteria**

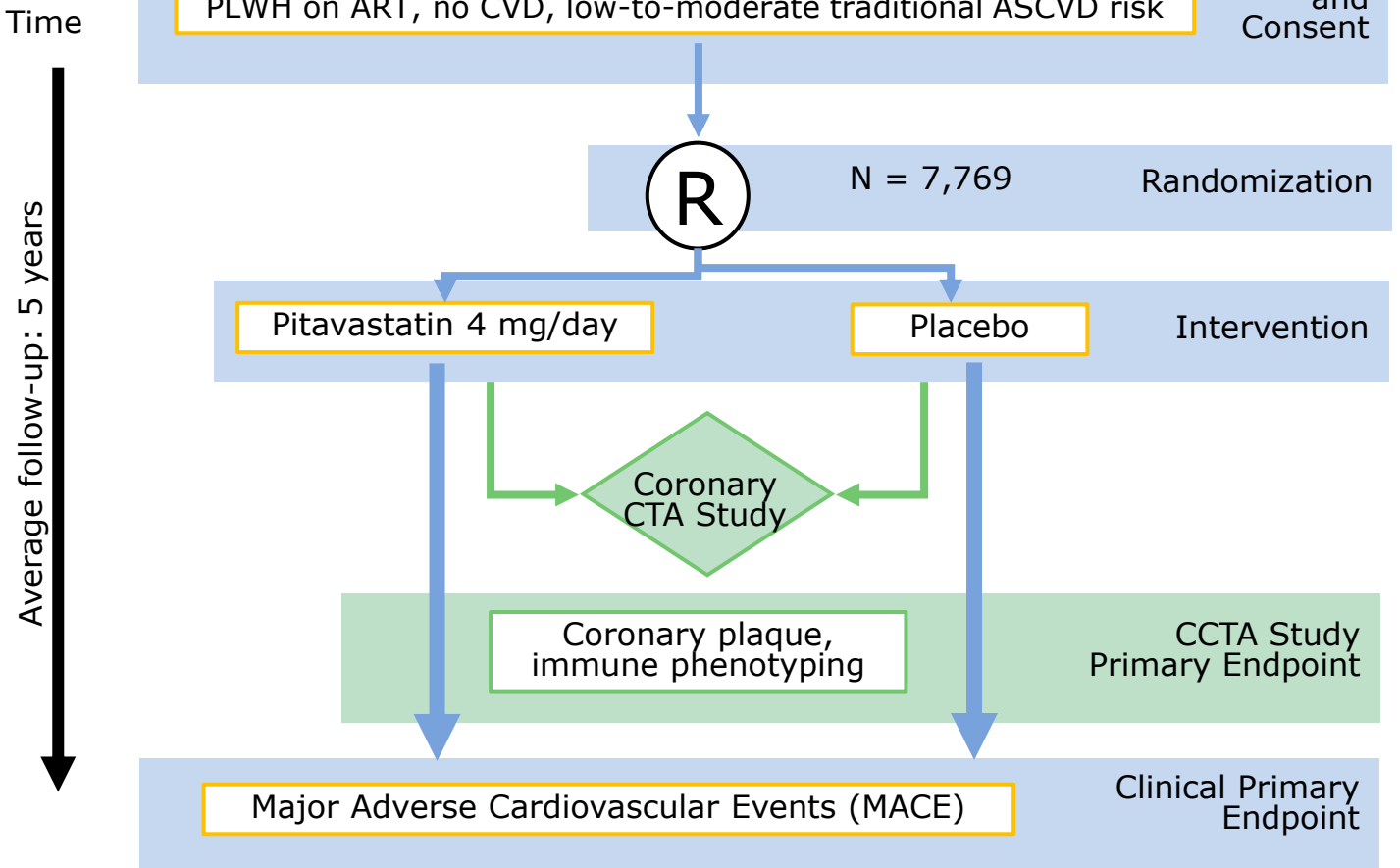
10-YEAR ASCVD RISK SCORE (%)	LDL
<7.5%	LDL < 190 mg/dl
7.5 - 10%	LDL < 160 mg/dl
>10 - 15%	LDL < 130 mg/dl

Mishka JAMA 2015; Grinspoon AHJ 2019

Appreciation of ASCVD Risk Mechanisms among PLWH Informed Design of REPRIEVE

Steven Grinspoon, MD MGH, Co-PI

Pamela Douglas,MD Duke, Co-PI



Michael Lu, MD MGH, Co-PI

Heather Ribaudo, PhD, HSPH, Co-PI

Grinspoon AHJ 2019; Hoffman AHJ 2019

REPRIEVE Population
Baseline Characteristics

		Total
Age (years)	Median (Q1-Q3)	50 (45, 55)
Sex (female)	%	31%
Race	Black/African-American, N (%)	41%
	White, N (%)	35%
	Asian, N (%)	15%
Current Cigarette Smoking	(%)	25%
Hypertension	(%)	36%
LDL-C (mg/dL)	Median (Q1-Q3)	108 (87, 128)
10-y ASCVD Risk Score (%)	Median (Q1-Q3)	4.5 (2.1, 7.0)
BMI (kg/m2)	Median (Q1-Q3)	25.8 (22.8, 29.4)
Viral Load < LLQ	(%)	88%
CD4 count (cells/mm3)	Median (Q1-Q3)	621 (448, 827)

10-year ASCVD Risk Score - Part of the 2013 + 2018 ACC/AHA Guidelines

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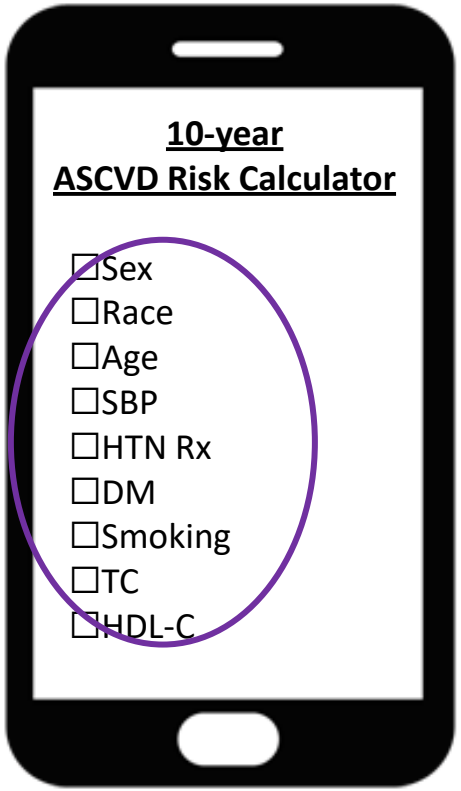

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Stone Circ 2014; Grundy JACC 2018

Recent Events and Trial Closure

- REPRIEVE was designed as an events driven trial with 85% power to detect a HR of 0.70 with 288 planned events.
- ***The DSMB convened at 75% of information and closed the trial for efficacy***, concluding there were no unanticipated safety concerns and that the benefits outweighed the risk of statin therapy in this group.

DSMB = data and safety monitoring board

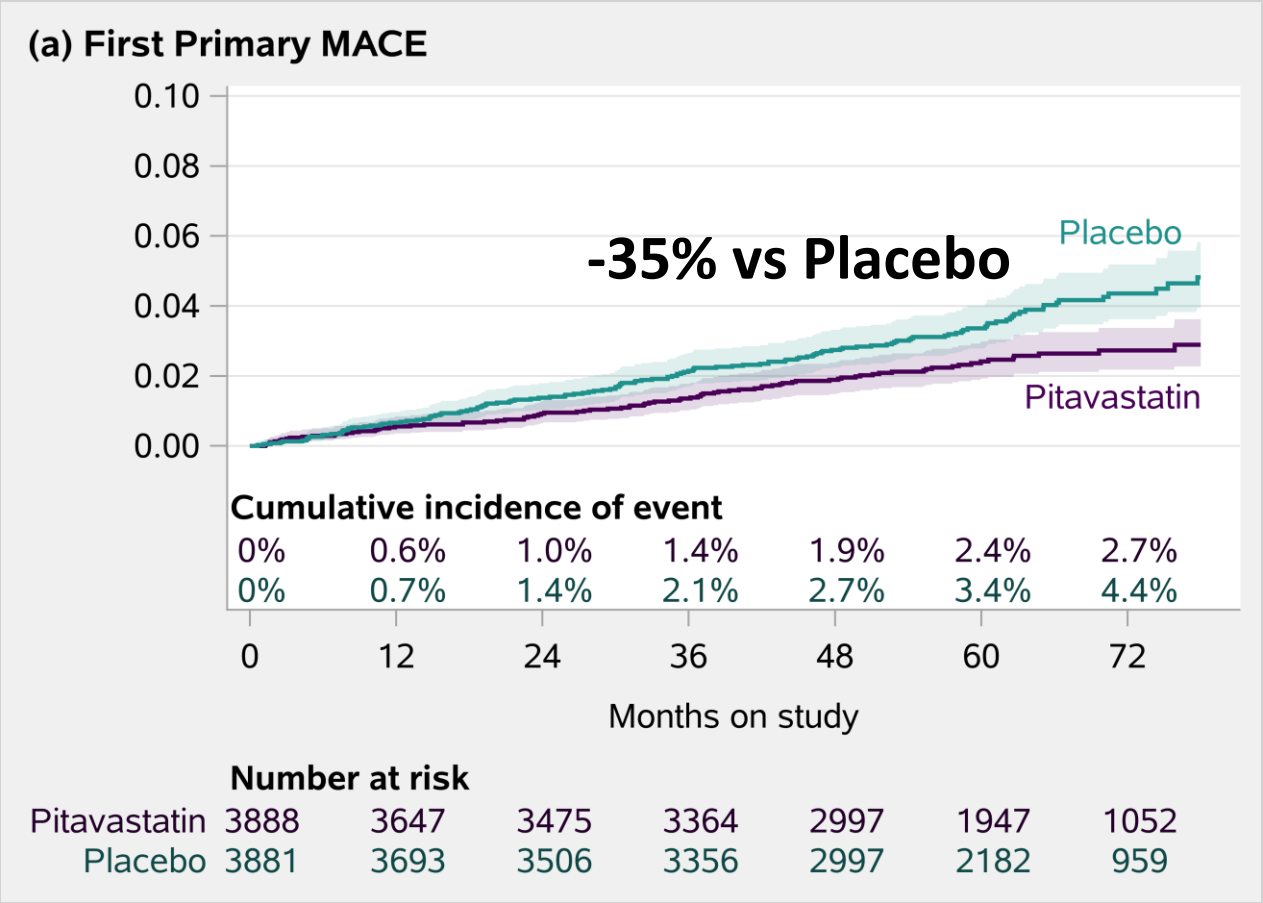
The NEW ENGLAND JOURNAL of MEDICINE

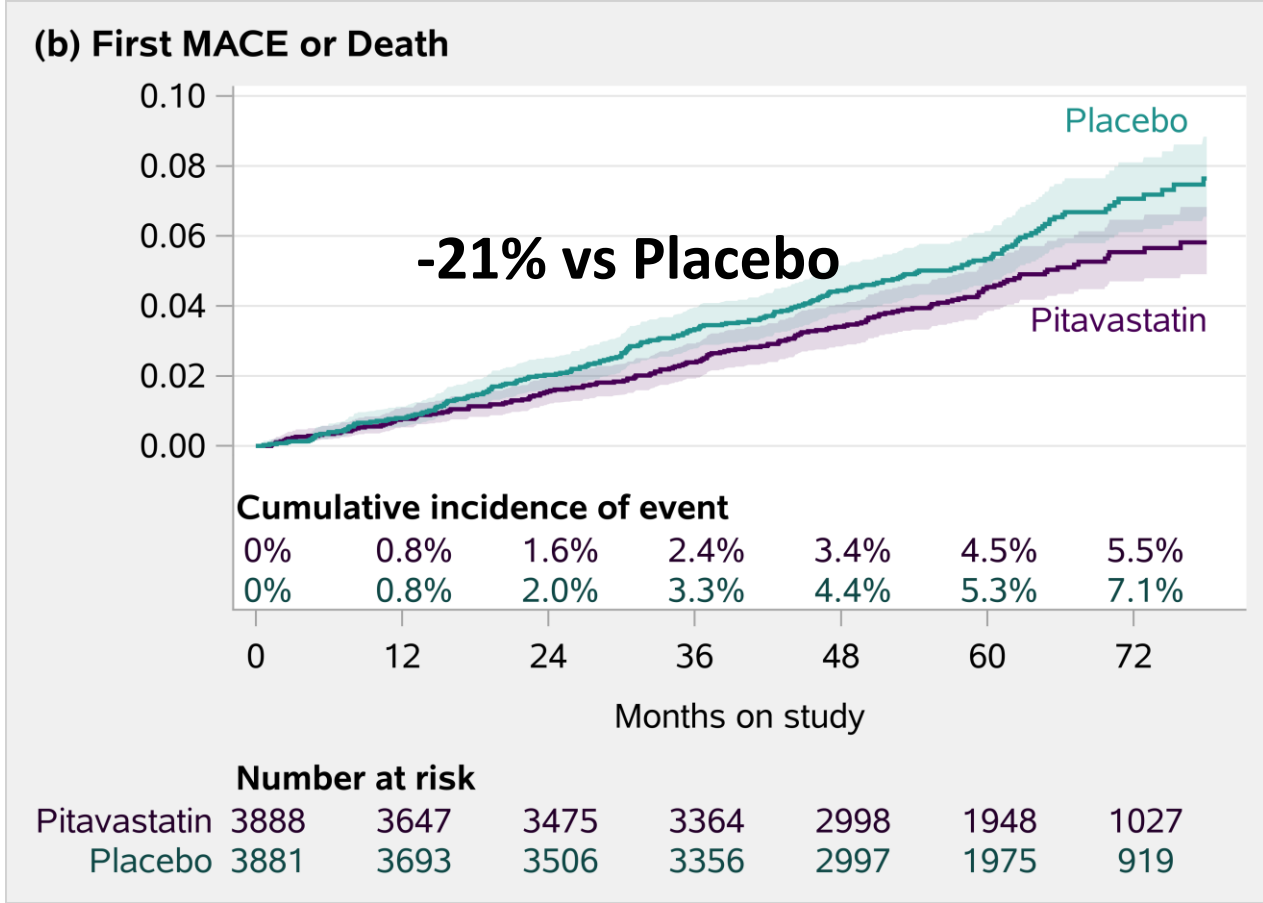
ORIGINAL ARTICLE

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

Primary and Key Secondary Endpoints





Additional Findings

- Greater than 80% of participants in both groups remained in follow-up
- Adherence was *very good to excellent* in majority of participants
- Clinical initiation of a non-study statin occurred in 5.7% of pitavastatin-treated and 9.6% of placebo-treated participants, below threshold of concern
- All events were adjudicated vis-a-vis relationship to COVID; only one MACE event was determined to be definitely related

Safety

- Serious adverse events similar in each group: IRR 1.02 (0.92-1.14)
- Muscle-related symptoms were higher in the pitavastatin group (2% vs. 1% in placebo) but were mostly mild and only 1% withdrew for muscle-related symptomatology
- Adverse event-related discontinuation was low in each group (2% pitavastatin vs 1% placebo)
- Diabetes rates were increased in the pitavastatin group (5.3% vs 4.0% in placebo), but were not significantly above rates observed in the general population

IRR: incidence rate ratio

Discussion Map

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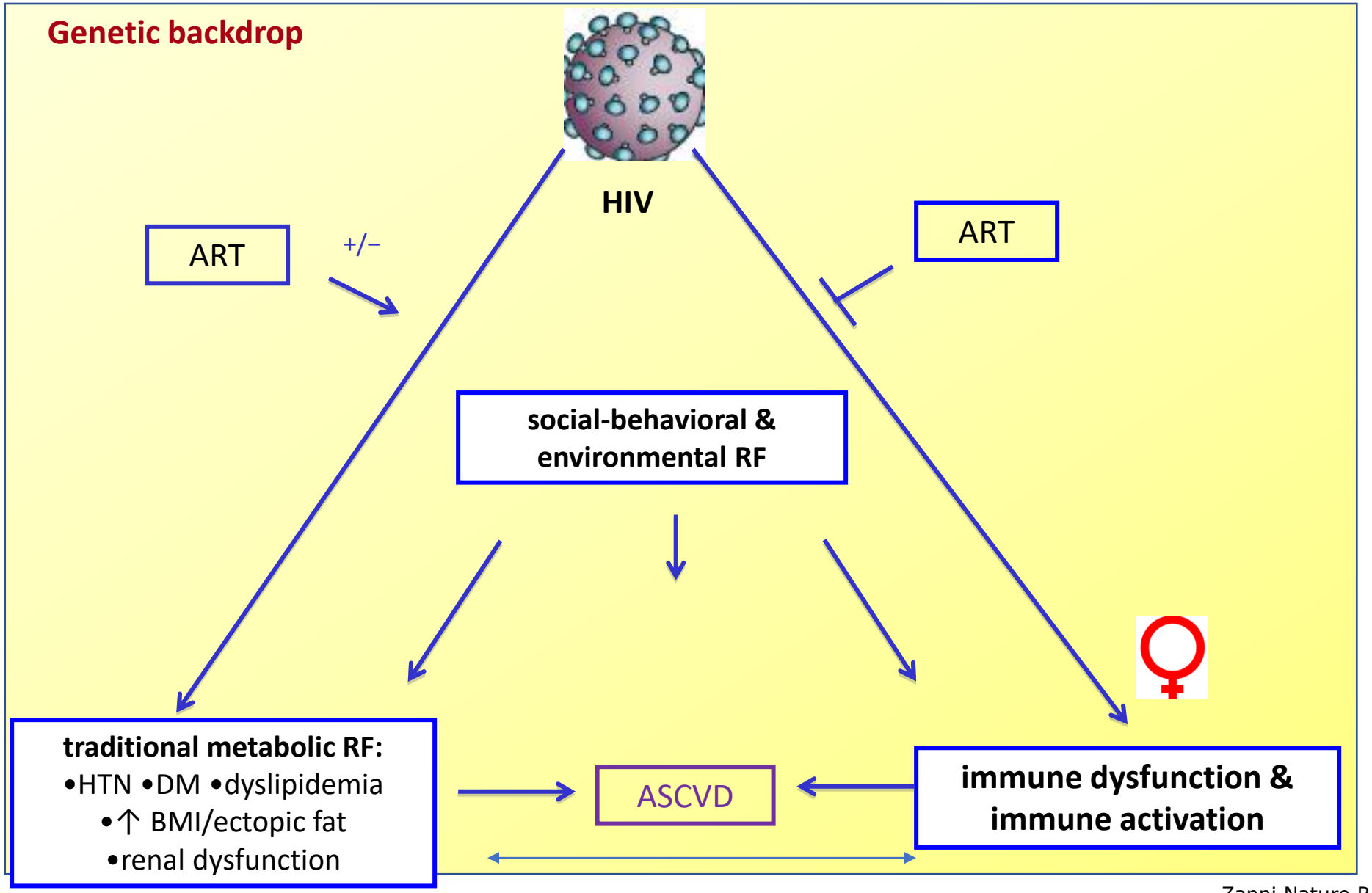
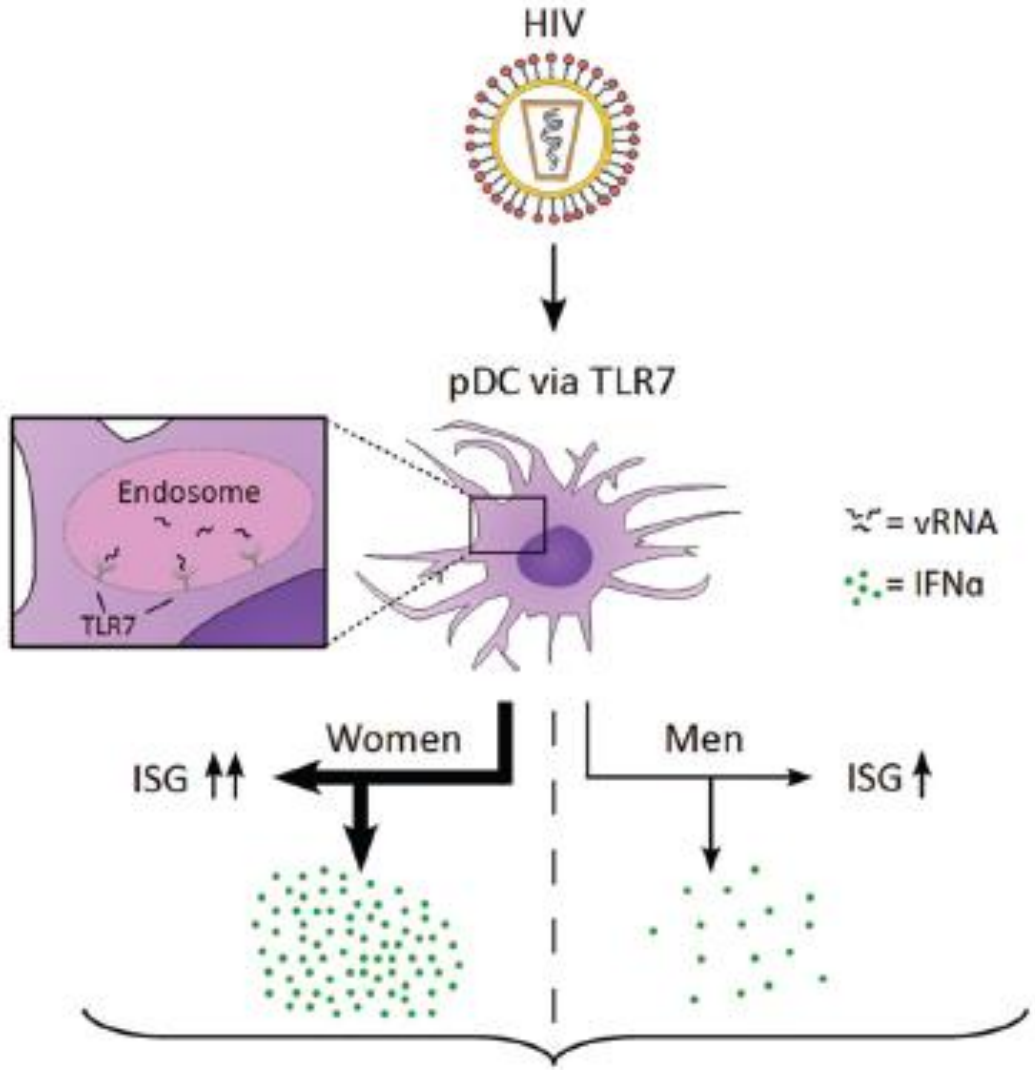
ASCVD Risk Mechanisms Among People Living with HIV:
Sex-Specific Considerations



Zanni Nature Reviews Cardiology 2014

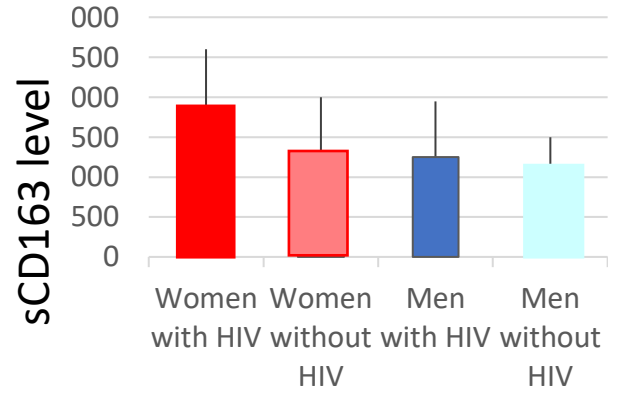
Women Have a More Robust Innate Immune Response to HIV Infection (vs. Men)

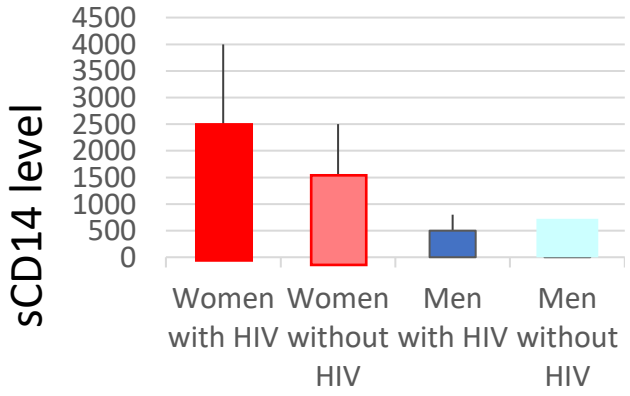


Addo JID 2014

Levels of Select Systemic Immune Activation Markers are Highest Among Women Living with HIV

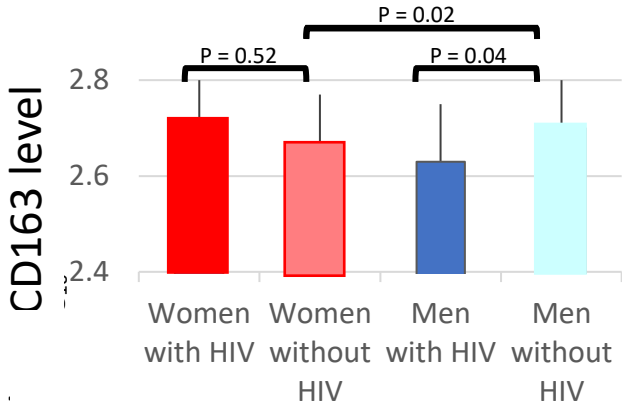
Prospective US Cohort (N=233)

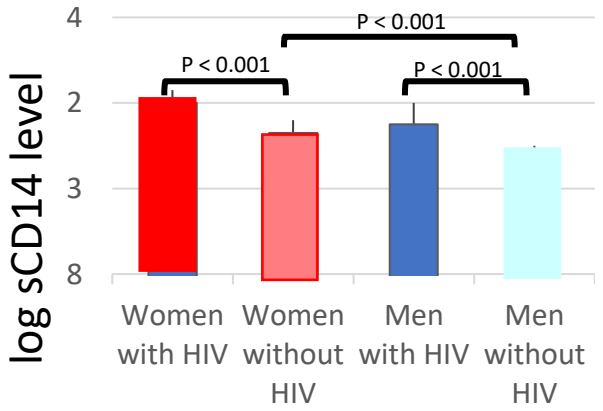




-Fitch JID 2014

Prospective Ugandan Cohort (N=308)





-Siedner JID 2018

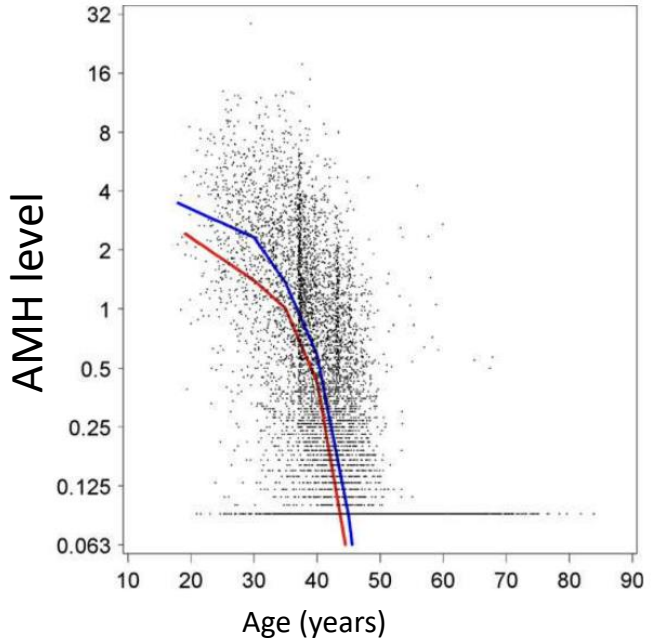
Women Living with HIV (vs. Women without HIV) Show Evidence of Advanced Reproductive Aging

Antimullerian hormone (AMH):

- Produced by ovarian granulosa cells
- Levels drop to undetectable a few years prior to menopause; levels predict age at menopause
- Serves as a molecular biomarker for **ovarian reserve**

AMH among WLWH vs. Women without HIV

US WIHS Cohort Study



↑ *reproductive aging*

↓

↑ *immune activation*

Women Living with HIV, n=2621

Women without HIV, n=941

Scherzer Am J Reprod Immunol 2015; Looby/Zanni AIDS 2016

Appreciation of Sex-Specific ASCVD Risk Mechanisms among PLWH Informed Design of REPRIEVE

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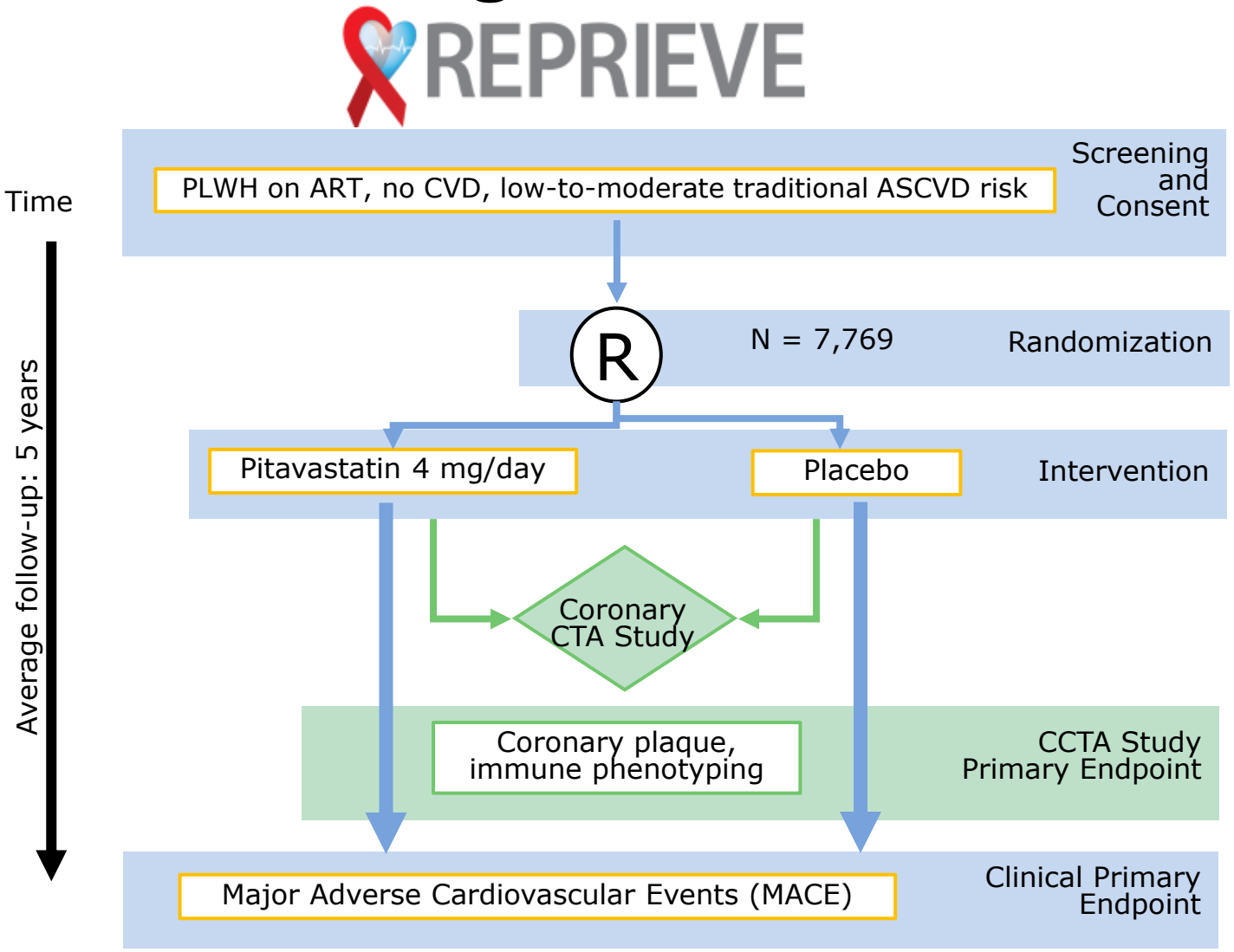
Pamela Douglas,MD Duke, Co-PI



Michael Lu, MD MGH, Co-PI

Heather Ribaudo, PhD, HSPH, Co-PI

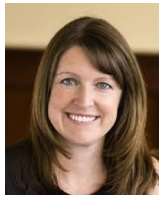
Grinspoon AHJ 2019; Hoffman AHJ 2019

REPRIEVE Women's Objectives

National Institute of Allergy and Infectious Diseases

R01AI123001

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



Sara Looby, PhD,
MGH – Co-PI

Aim 1) Among people living with HIV:

- How do sex-based differences in immune activation influence ASCVD risk?

- How do sex-based differences in statin-induced immunomodulation influence ASCVD risk reduction?

Insights from a Key REPRIEVE Baseline Analysis

(prior to recent unblinding of REPRIEVE)

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

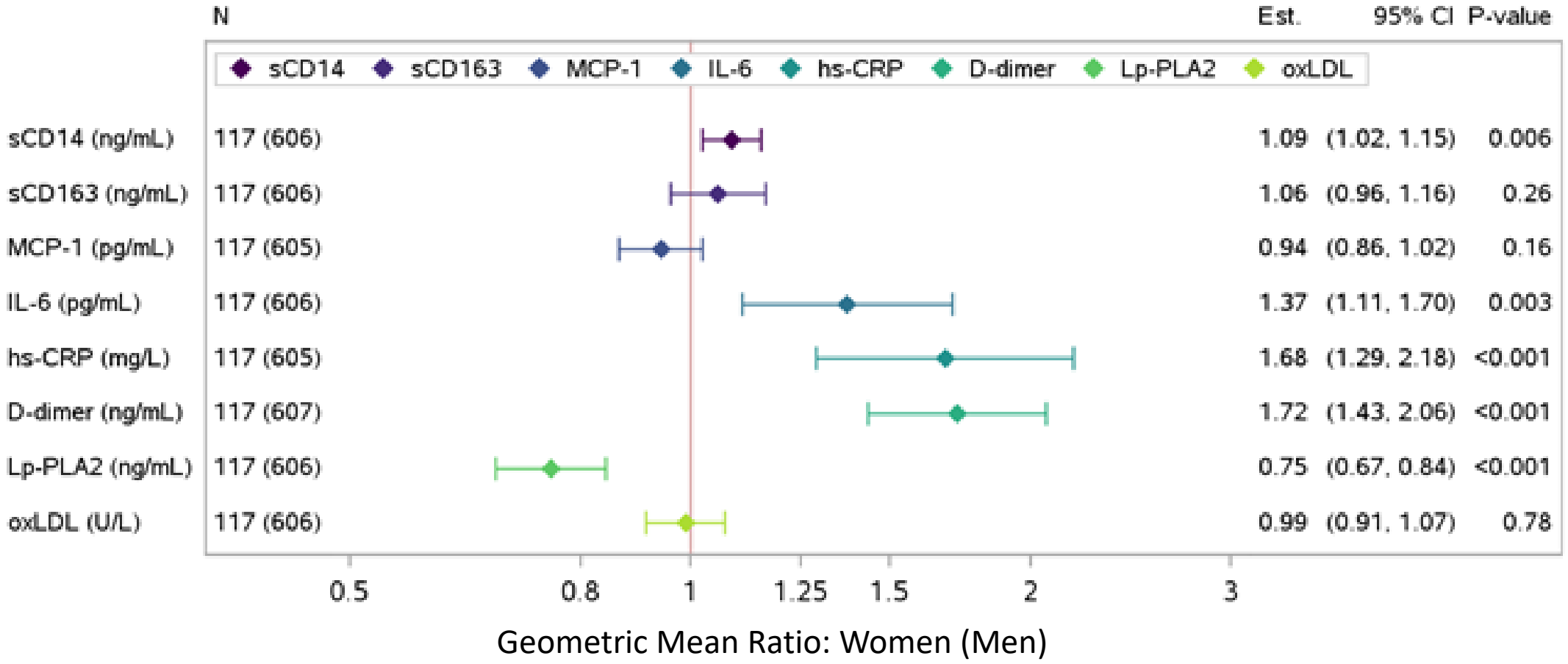
OXFORD

Sex Differences in Subclinical Atherosclerosis and Systemic Immune Activation/Inflammation Among People With Human Immunodeficiency Virus in the United States

Markella V. Zanni,[1,a] Borek Foldyna,[2,a] Sara McCallum,[1] Tricia H. Burdo,[3] Sara E. Looby,[1,4] Kathleen V. Fitch,[1] Evelynne S. Fulda,[1] Patrick Autissier,[5] Gerald S. Bloomfield,[6] Carlos D. Malvestutto,[7] Carl J. Fichtenbaum,[8] Edgar T. Overton,[9] Judith A. Aberg,[10] Kristine M. Erlandson,[11] Thomas B. Campbell,[11] Grant B. Ellsworth,[12] Anandi N. Sheth,[13] Babafemi Taiwo,[14] Judith S. Currier,[15] Udo Hoffmann,[2] Michael T. Lu,[2] Pamela S. Douglas,[16] Heather J. Ribaudo,[17] and Steven K. Grinspoon[1]

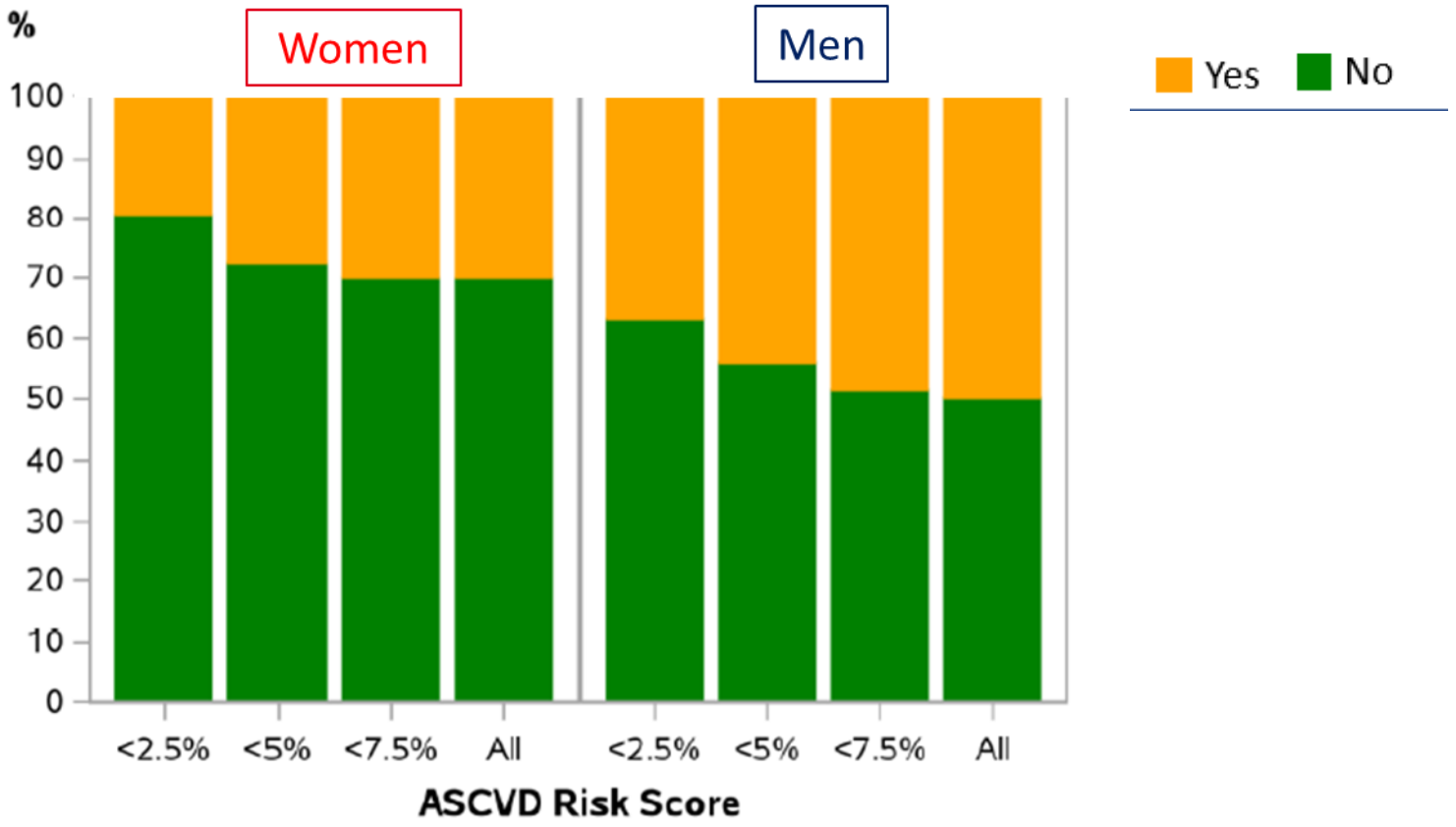
analyzed data from 755 US REPRIEVE participants enrolled in Mechanistic Substudy

Sex-Differences in Immune Activation/Inflammatory Markers



- Women living with HIV (vs. men living with HIV) showed higher levels of IL-6, hsCRP, and D-Dimer and lower levels of LpPLA-2 (*P<0.001 for* all, controlling for 10y ASCVD risk score + BMI).

Sex Differences in Coronary Artery Plaque Prevalence by 10-year ASCVD Risk Score



- Prevalence of coronary artery plaque was lower among women living with HIV vs. men living with HIV overall and controlling for 10y ASCVD risk score + BMI (RR=0.67; 95%CI: 0.50–0.92)

Clinical Infectious Diseases
MAJOR ARTICLE

Sex Differences in Subclinical Atherosclerosis and Systemic Immune Activation/Inflammation Among People With Human Immunodeficiency Virus in the United States

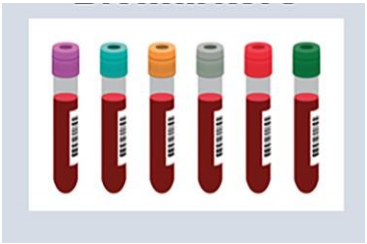
Markella V. Zanni,[1,a] Borek Foldyna,[2,a] Sara McCallum,[1] Tricia H. Burdo,[3] Sara E. Looby,[1,4] Kathleen V. Fitch,[1] Evelynne S. Fulda,[1] Patrick Autissier,[5] Gerald S. Bloomfield,[6] Carlos D. Malvestutto,[7] Carl J. Fichtenbaum,[8] Edgar T. Overton,[9] Judith A. Aberg,[10] Kristine M. Erlandson,[11] Thomas B. Campbell,[11] Grant B. Ellsworth,[12] Anandi N. Sheth,[13] Babafemi Taiwo,[14] Judith S. Currier,[15] Udo Hoffmann,[2] Michael T. Lu,[2] Pamela S. Douglas,[16] Heather J. Ribaudo,[17] and Steven K. Grinspoon[1]

among US REPRIEVE participants

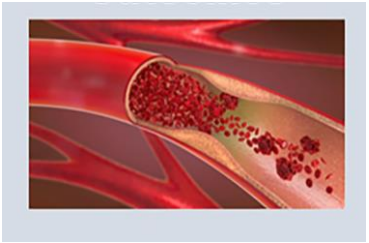
(controlling for 10-y ASCVD risk score + BMI)

women vs. men:

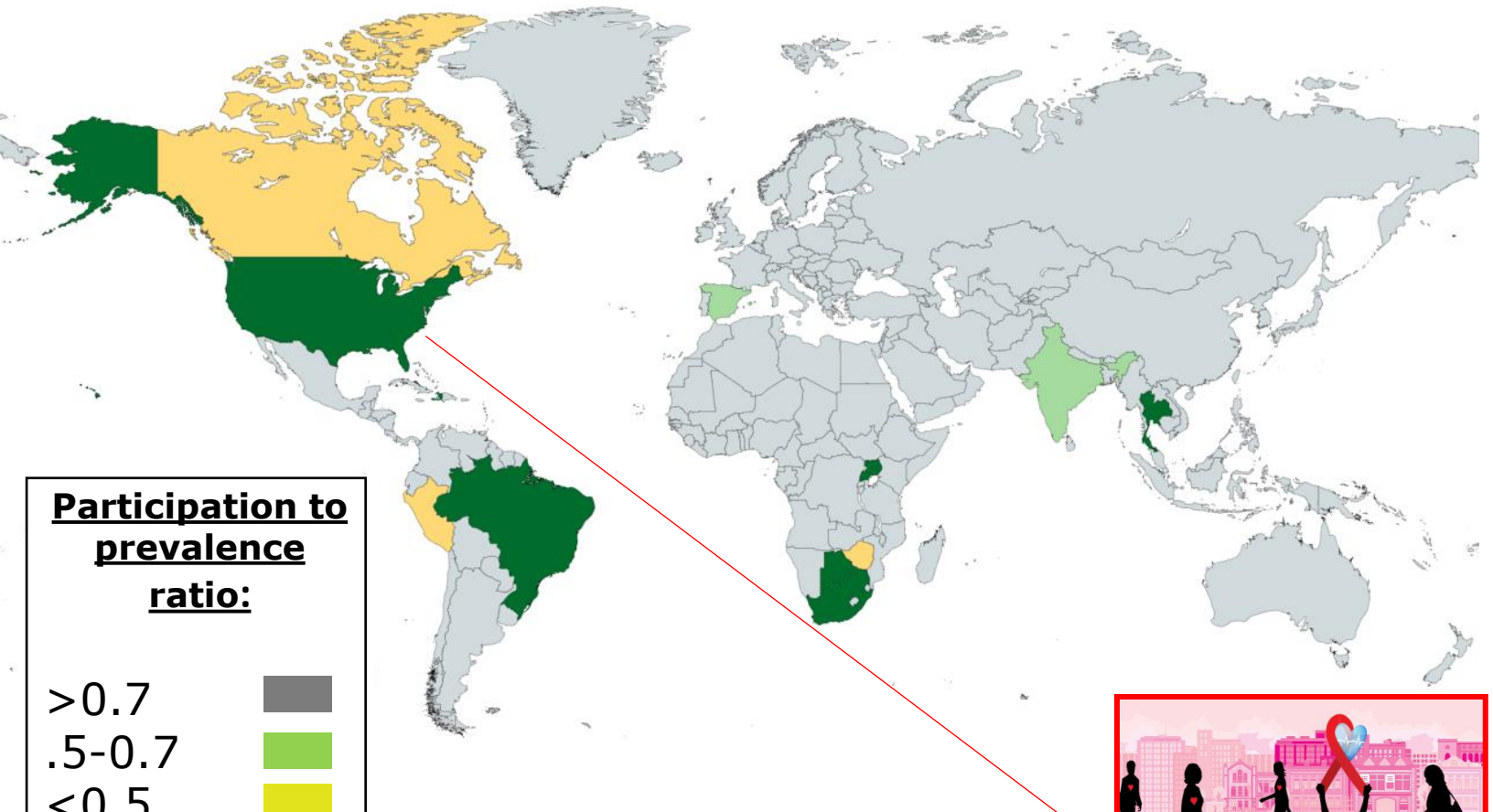
↑ **Immune activation/ inflammatory markers**



↓ **Coronary artery plaque prevalence**



Women's Enrollment in REPRIEVE Main Study



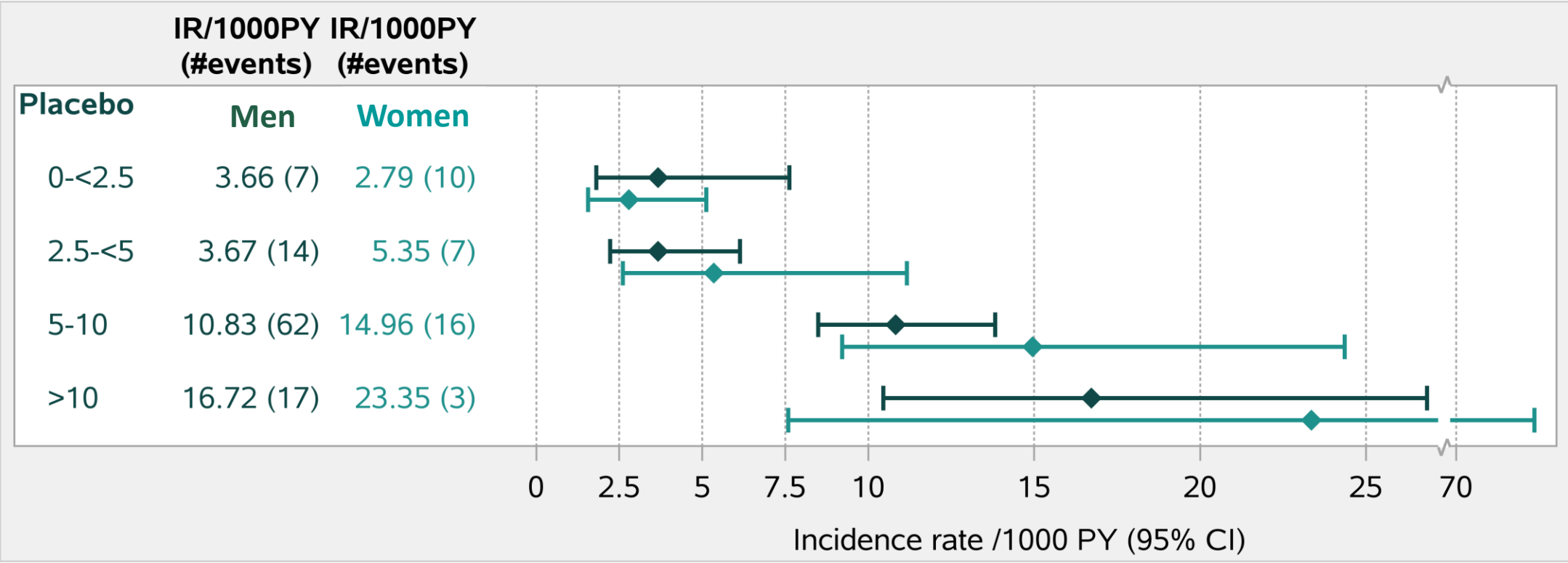
	% Women enrolled in REPRIEVE, by country	% Women among population living with HIV, by country
US	23	23[a]
Canada	10	29[b]
Spain	9	18[c]
Brazil	29	34[d]
Peru	8	24[c]
Haiti	42	57[c]
Thailand	56	42[c]
India	26	39[e]
South Africa	66	64[c]
Botswana	63	61[c]
Uganda	51	60[c]
Zimbabwe	24	58[c]

a. UNAIDS Data 2021. Geneva: Joint United Nations Programme on HIV/AIDS, 2021
b. Haddad et al. HIV in Canada Surveillance Report, 2018. Can Commun Dis Rep 2019
c. UNAIDS Data 2022. Geneva: Joint United Nations Programme on HIV/AIDS, 2022
d. AIDSInfo: Global Data on HIV Epidemiology and Responses, UNAIDS 2022
e. HIV/AIDS in India. Worldbank.org, 2021.

REPRIEVE Population
Baseline Characteristics by Sex

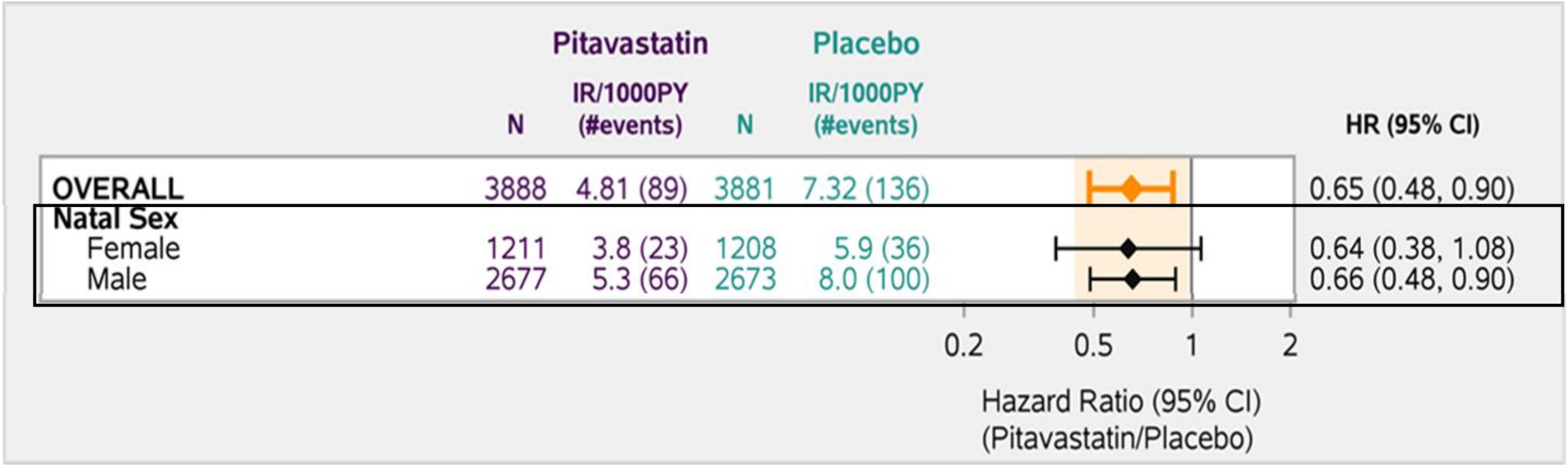
		Total	Men (N=5350)	Women (N= 2419)
Age (years)	Median (Q1-Q3)	50 (45, 55)	**50 (46, 55)**	**49 (44, 55)**
Race	Black/African-American, N (%)	41%	**34%**	**58%**
	White, N (%)	35%	**44%**	**15%**
	Asian, N (%)	15%	**13%**	**19%**
Current Cigarette Smoking	(%)	25%	**28%**	**18%**
Hypertension	(%)	36%	**34%**	**39%**
LDL-C (mg/dL)	Median (Q1-Q3)	108 (87, 128)	**107 (86, 126)**	**111 (90. 131)**
10-y ASCVD Risk Score (%)	Median (Q1-Q3)	4.5 (2.1, 7.0)	**5.4 (3.3, 7.8)**	**1.9 (0.8, 4.3)**
BMI (kg/m2)	Median (Q1-Q3)	25.8 (22.8, 29.4)	**25.3 (22.6, 28.3)**	**27.2 (23.4, 32.1)**
Viral Load < LLQ	(%)	88%	**87%**	**88%**
CD4 count (cells/mm3)	Median (Q1-Q3)	621 (448, 827)	**598 (426, 795)**	**679 (496, 898)**

MACE Rates in 10-year ASCVD Risk Score Subgroups by Sex



Key questions:
- Might 10y ASCVD risk score underestimate risk in women > men?
- Is it possible that systemic immune activation (not well captured by ASCVD risk score) is driving MACE to a greater extent in women (vs. men) living with HIV?

Effect Size of Statin Rx to Reduce MACE = Consistent among Women vs. Men



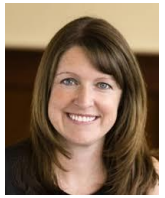
Key question: Are there sex-differences in the mechanisms of statin-induced efficacy – i.e. might reduction in MACE be driven to a greater extent by immune modulation among women (vs. men) living with HIV?

REPRIEVE Women's Objectives

National Institute of Allergy and Infectious Diseases

R01AI123001

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



Sara Looby, PhD,
MGH – Co-PI

Aim 2) Among women living with HIV:

- How does reproductive aging influence immune activation and ASCVD risk?

- How does reproductive aging influence statin-induced immunomodulation and ASCVD risk reduction?

Why Did We Build REPRIEVE Women's Objective #2 Around "Reproductive Aging" Instead of "Menopause"?

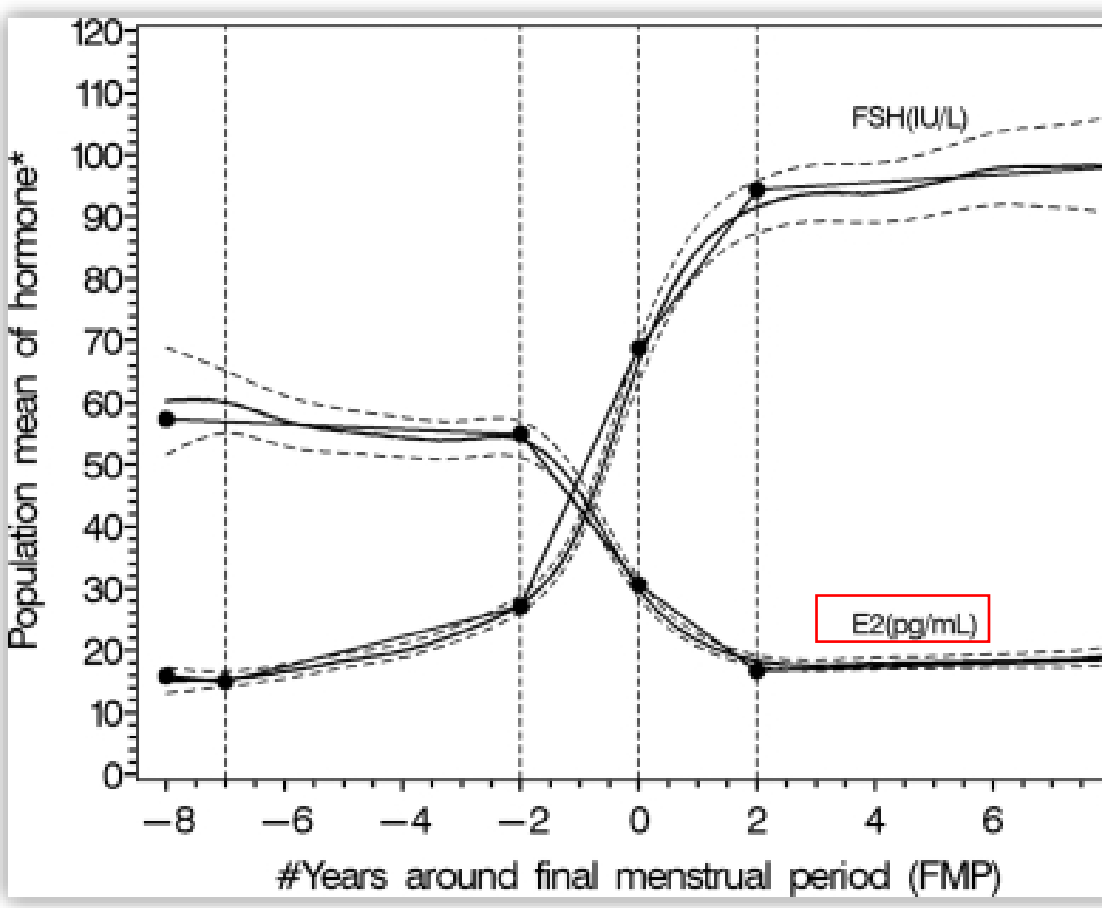
WHO Definition of Menopause:

"The term `natural menopause' is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause. Menopause occurs with the final menstrual period (FMP), which is known with certainty only in retrospect, a year or more after the event. An adequate independent biological marker for the event does not exist."

WHO. 1996.

Female Reproductive Aging - Characterized by Loss of Cyclic Endogenous Estrogen Production - Occurs Along a Continuum

≠



Harlow JCEM 2012 / Kaufman Endocr Rev 2005

Postmenopausal Women Experience Increased Rates of Cardiovascular Diseases (vs. Premenopausal):

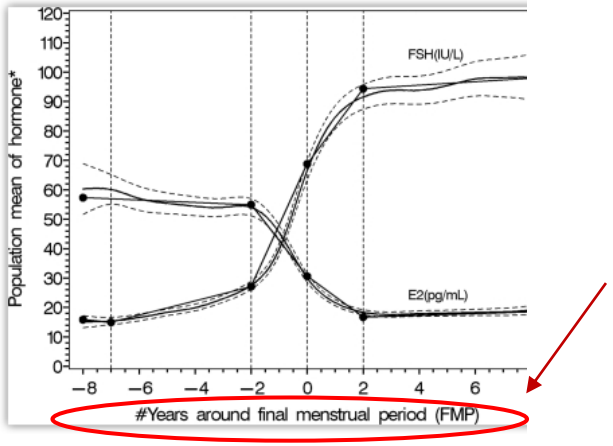
To Address this Problem, We Need to Consider Downstream Changes & Timing:

nature of downstream pathology predisposing to CV events

Loss of endogenous estrogen production

- **Immune changes**
- **Changes in vascular biology**
- **Metabolic changes**

timing of acceleration of downstream changes



CVD Preventive Rx Goal = intervene on **right processes** at the **right time** to preserve women's CM health across menopausal transition (MT)

Synthesis & Future Directions

• Among women living with HIV: traditional metabolic risk factors, immune risk factors, and accelerated reproductive aging all likely contribute to increased ASCVD risk

• Among a subset of REPRIEVE participants from the US: women (vs. men) exhibited higher levels of immune activation/inflammatory markers but a lower prevalence of coronary artery plaque

• Among all REPRIEVE participants, globally:
  -MACE rates increased along the ASCVD risk score continuum, with estimated rates trending higher among women (vs. men) harboring a 10y ASCVD risk score ≥ 2.5%
  -Statin rx (vs. placebo) reduced MACE by 35%; effect size consistent among women and men

• Future REPRIEVE analyses will examine:
  1) sex differences in immune-mediated ASCVD risk and risk reduction
  2) influence of women's reproductive aging on ASCVD risk and risk reduction

THANK YOU:

REPRIEVE Participants and CAB Members

REPRIEVE Site Teams

REPRIEVE CCC and DCC and Supportive Teams

NHLBI, NIAID

Kowa, Gilead, ViiV

ACTG

NCHIV Conference Team & Participants