Judith S. Currier MD

University of California Los Angeles

Presentation Topics

- Heart Disease and Women
  - Role of Statin Therapy
- Review of Emerging Knowledge on Menopause in WWH:
  - Age of Menopause Onset
  - Menopause Symptoms
  - Associated Clinical Conditions
- Considerations for Treatment

Free Image Microsoft 365 Stock

Scope

- This presentation explores the influence of sex-assigned-at-birth on atherosclerotic cardiovascular disease risk and menopause 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 heart disease risks and mechanisms among people living with HIV are also important but will not be covered today.

Cardiovascular Disease in HIV

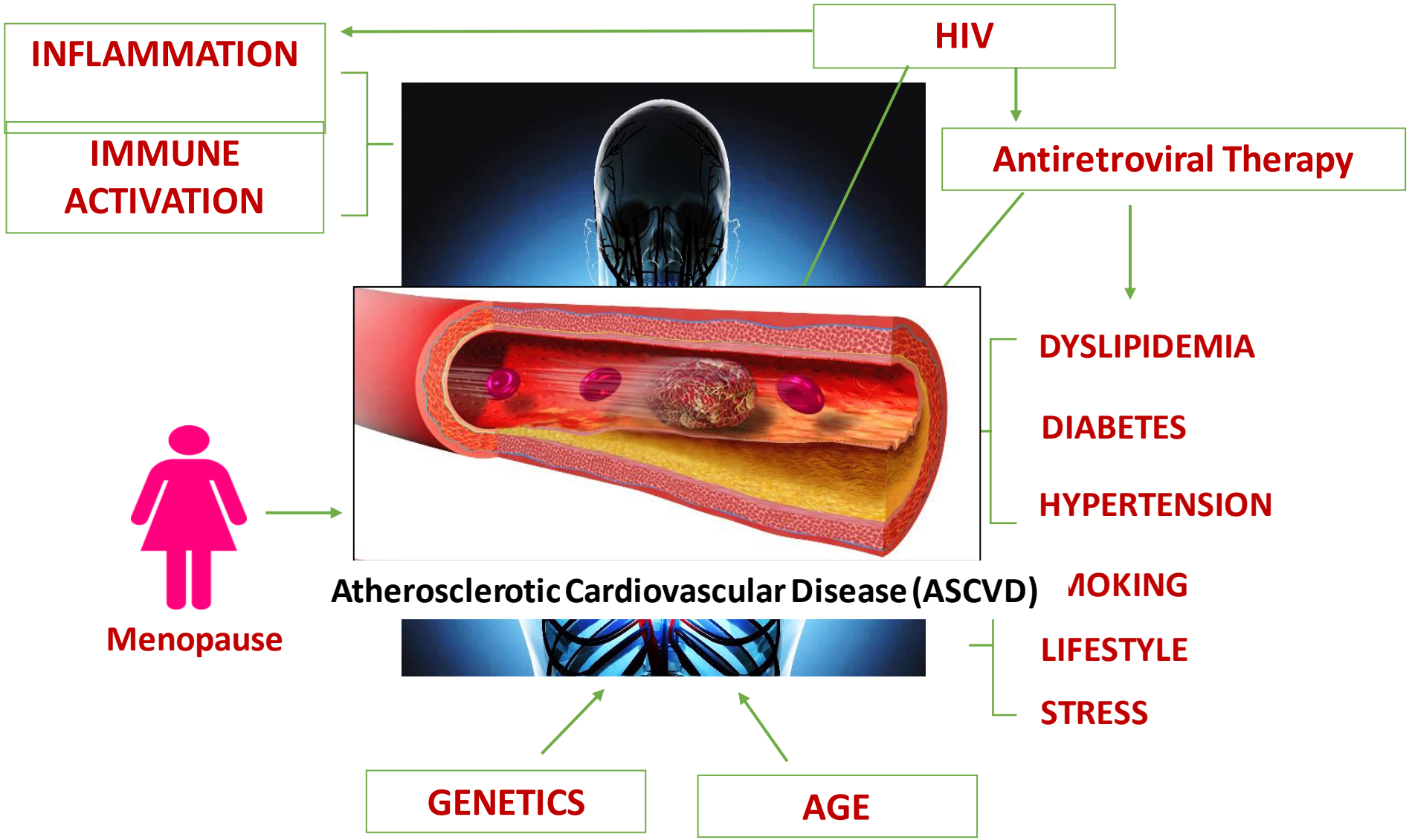
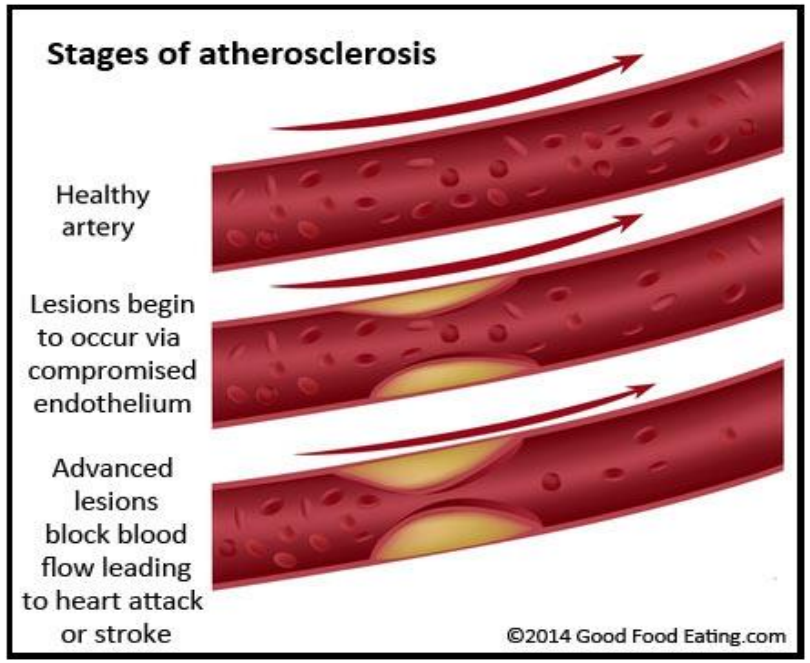
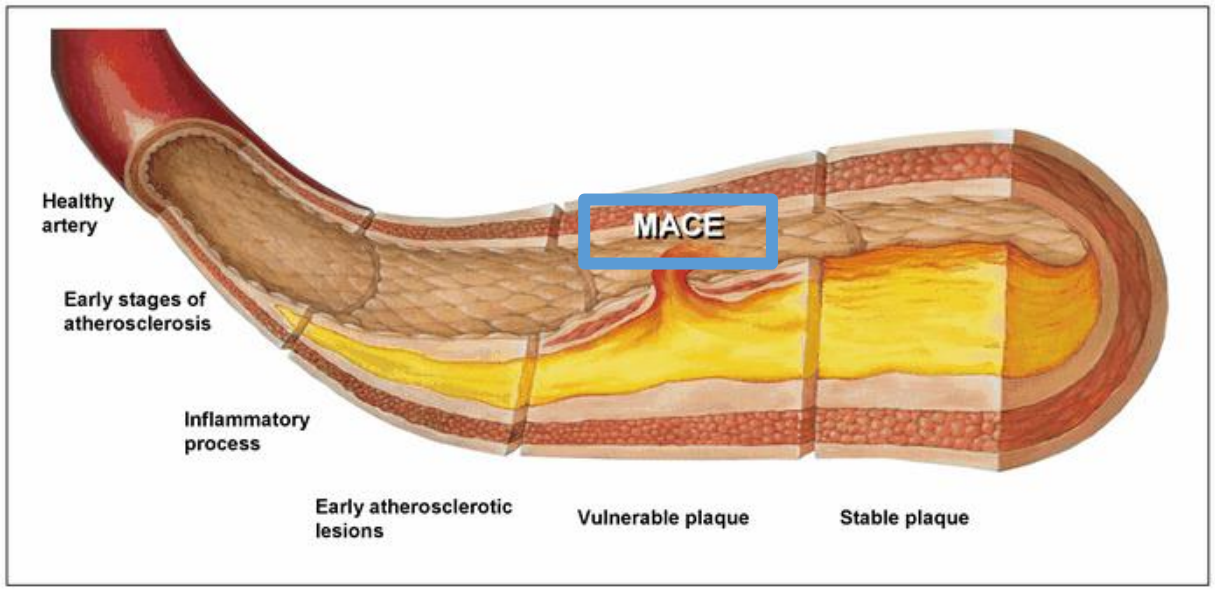


Image purchased from Dollar Photo.

Atherosclerotic cardiovascular disease (ASCVD)



Cardiovascular Disease Events are 1.5 – 2x Higher Among PWH Relative to the General Population



Caused by plaque buildup in arterial walls

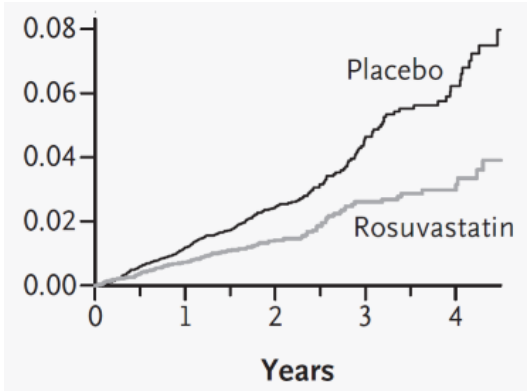
Examples of Conditions or **Major Adverse Cardiovascular Events (MACE)**

- Coronary Heart Disease (CHD), myocardial infarction, angina, and coronary artery stenosis.
- Cerebrovascular disease, such as a transient ischemic attack, ischemic stroke, and carotid artery stenosis.
- Peripheral artery disease, such as claudication(pain from too little blood flow)
- Aortic atherosclerotic disease, such as abdominal aortic aneurysm and descending thoracic aneurysm.
- **Currently, ASCVD- related conditions remain the leading cause of morbidity and mortality globally**

AHA www.heart.org
Picture: Arch Toxicol 2023 97:1529

Statin drugs: reduce cholesterol and prevent heart disease

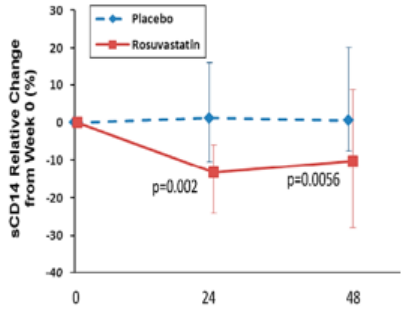
Statins Reduce Vascular Events Among PWOH with Low LDL and Increased CRP



Ridker N Engl J Med 2008; CTTC Lancet 2010

Statins Address Both Traditional and Immune Risk Factors in HIV

- LDL Lowering
- Reduced Immune Activation



Silve …013, Funderburg JAIDS ePUB

Statins are Well-Tolerated/Safe in HIV

- Pitavastatin (Livalo): Recommended in 2013 ACC/AHA guidelines as a moderate dose statin
  - Metabolized primarily by glucoronidation.
  - Minimally metabolized by CYP3A4
  - No known interactions with antiretroviral therapy → no dose limitations.

Sponseller CROI 2014, Aberg Endo 2013, Eckard JID 2014, Stone JACC 2013

Stains are a group of medications that have lower cholesterol, specifically LDL cholesterol known as the "bad cholesterol". These medications have been shown to lower cholesterol and reduce risk for heart disease, stroke, and certain blood clots.

Reprievetrial.org/Kfitch
Mayoclinic.org

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*

***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

Trial PIs: Steven K. Grinspoon, MD; Pamela S. Douglas, MD; Heather Ribaudo, PhD; Michael T. Lu, MD, MPH

As part of REPRIEVE, statin safety and statin effects on non-CVD comorbidities among PLWH also assessed.

The ASCVD risk score is generated from a clinical calculator. It is the calculation of your 10-year risk of having a cardiovascular problem. The risk estimate considers your age, sex, race, cholesterol levels, BP, medication use, diabetic status, And smoking status.

Mishka JAMA 2015; Grinspoon AHJ 201
Intermountain Heart Institute-ASCVD risk score
Slide curtesy of Dr. Markella Zanni.MGH

REPRIEVE Women's Objectives

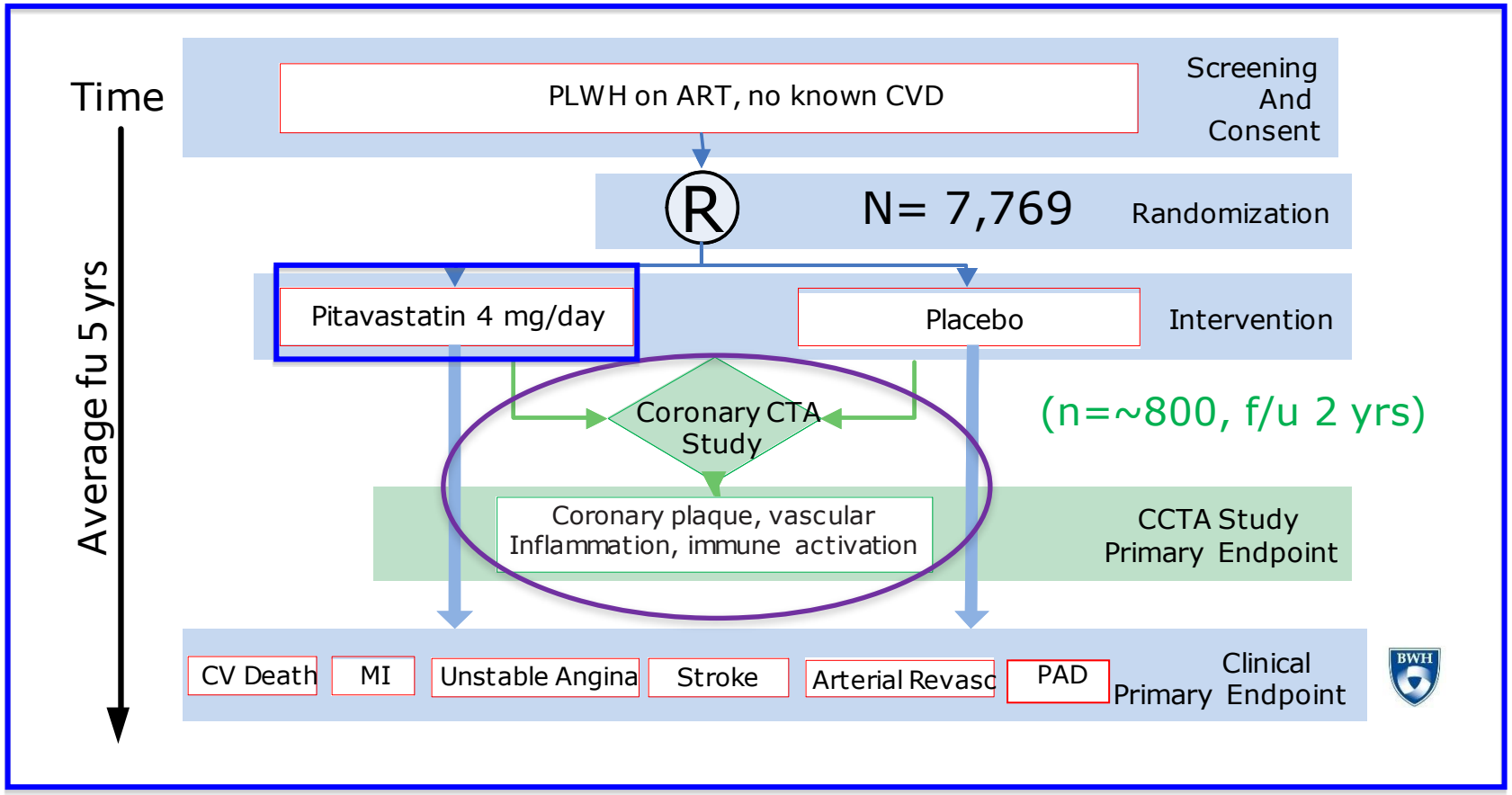
To explore sex-specific mechanisms of CVD risk and risk reduction in people living with HIV

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?
- **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?

NIAID R01AI123001; MPI Looby & Dr. Markella Zanni

REPRIEVE Design



Pitavastatin calcium 4mg

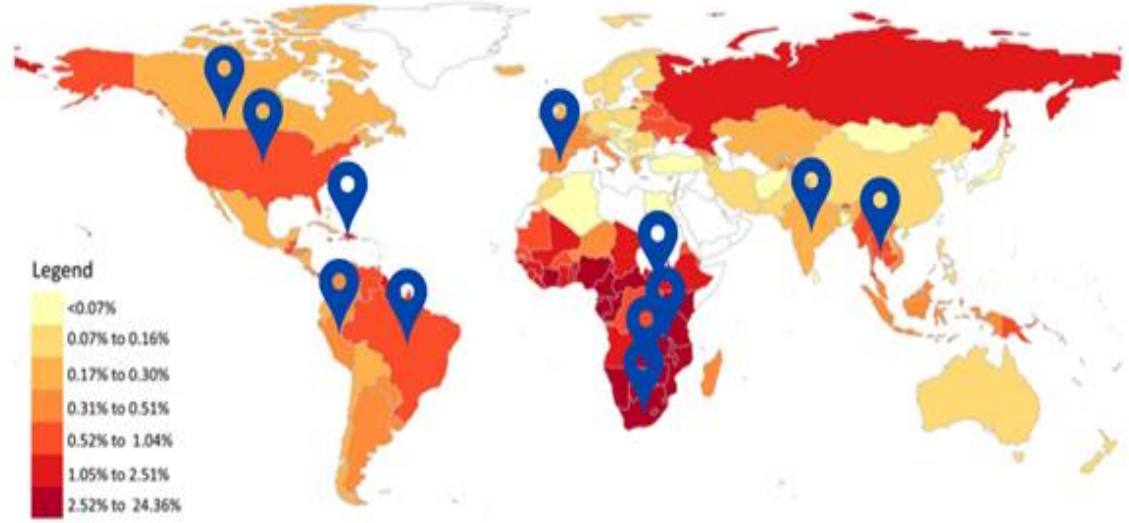
- moderate intensity statin
- does not interact w/ any ART regimen – no dose adjustment
- net neutral effects on glucose in prior studies of PLWH
- potent immune modulatory effects among PLWH

Grinspoon AHJ 2019; Hoffmann AHJ 2019; Aberg Lancet HIV 2017; Toribio AIDS 2017

Slide curtesy of Dr. Markella Zanni. MGH

Study Population

REPRIEVE Study Sites

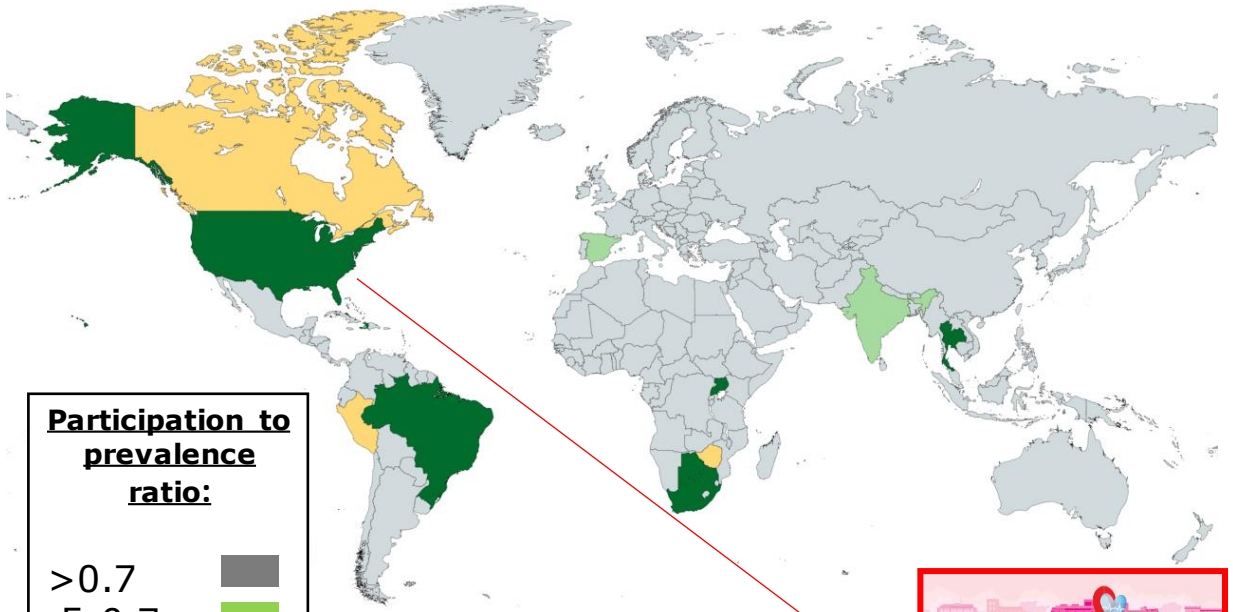


Enrollment by Global Burden of Disease (GBD) Region

	High Income (N=118)	Latin America and Caribbean (N=15)	S. East/East Asia (N=2)	South Asia (N=2)	Sub-Saharan Africa (N=8)	Total (N=145)
Overall Statistics						
Total number screened	5,539	1,953	824	634	1,915	10,865
Total number enrolled	4,095	1,423	590	504	1,157	7,769
Percent of total enrollment	53%	18%	7.6%	6.5%	15%	100%

- **Inclusion Criteria**
  - Documented HIV
  - Receiving stable ART
  - CD4+ > 100 cells/mm3
  - Age ≥ 40 - 75 years
  - No known atherosclerotic cardiovascular disease (ASCVD)
  - 10-yr ASCVD risk score / LDL cholesterol
    - <7.5% / < 190 mg/dL
    - ≥7.5% and ≤ 10% / < 160 mg/dL
    - >10% and ≤15% / < 130 mg/dL
  - Certain laboratory parameters
- **Exclusion Criteria**
  - Current use of statins, gemfibrozil, or PCSK9 inhibitors
  - Diabetes unless LDL < 70 mg/dL
  - Known decompensated cirrhosis

Women's Enrollment in REPRIEVE Main Study



31% Women

	% 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]

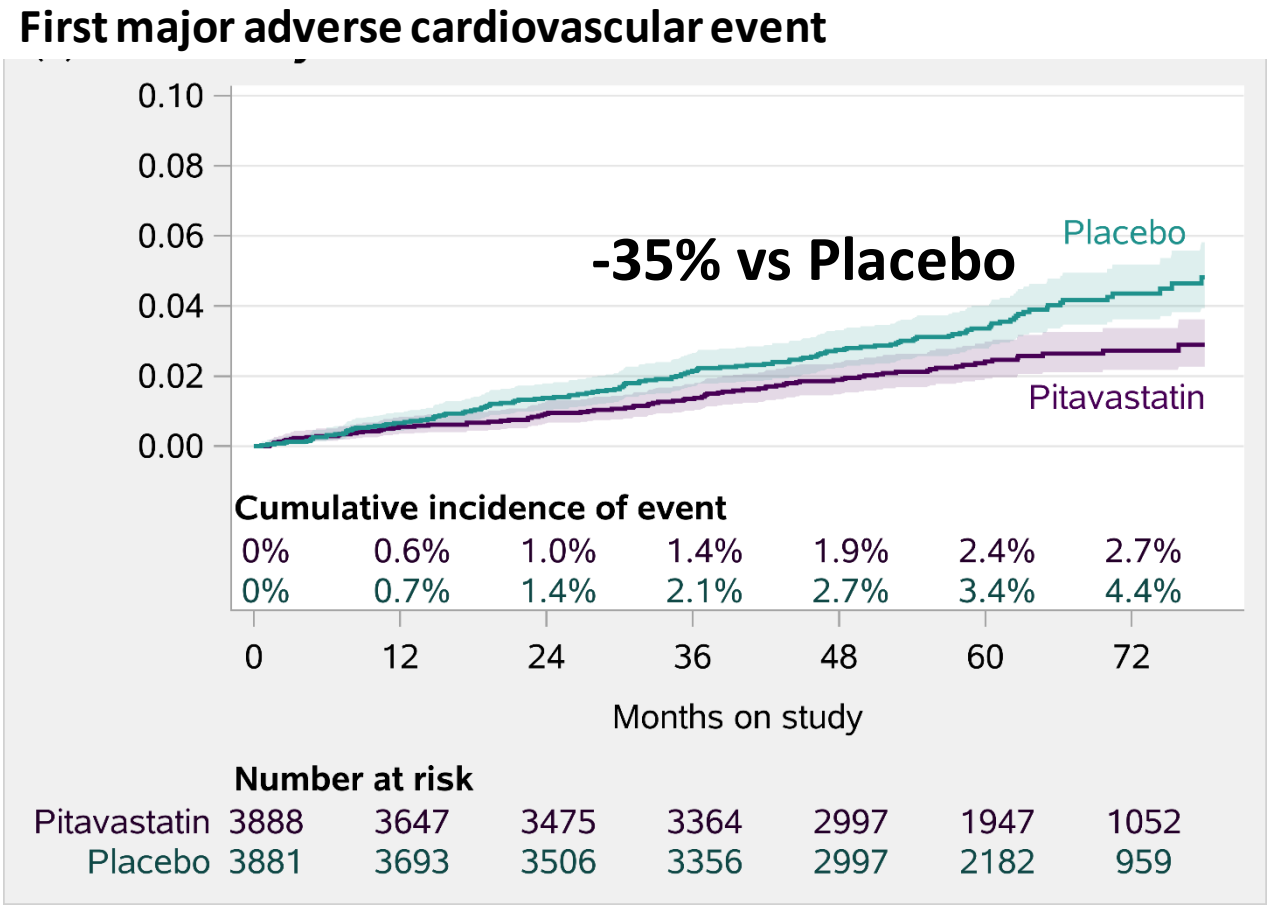
a. UNAIDS Data 2021. Geneva: Joint United Nations Programme on HIV/AIDS, 2021
b. Haddad et al. HIV in Canada Surveillance Report, 2018. Can Commun Dis Rep 2019
c. UNAIDS Data 2022. Geneva: Joint United Nations Programme on HIV/AIDS, 2022
d. AIDSInfo: Global Data on HIV Epidemiology and Responses, UNAIDS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

Slide curtesy of Dr. Markella Zanni. MGH

Treatment with pitavastatin was effective to prevent major adverse cardiovascular events

Over an average of about 5 years of follow up, pitavastatin (4mg/day):

Reduced the risk of heart-related diseases such as heart attack, stroke, peripheral vascular disease, and related illnesses ('MACE') by 35%



Grinspoon et al. NEJM, 2023

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)**

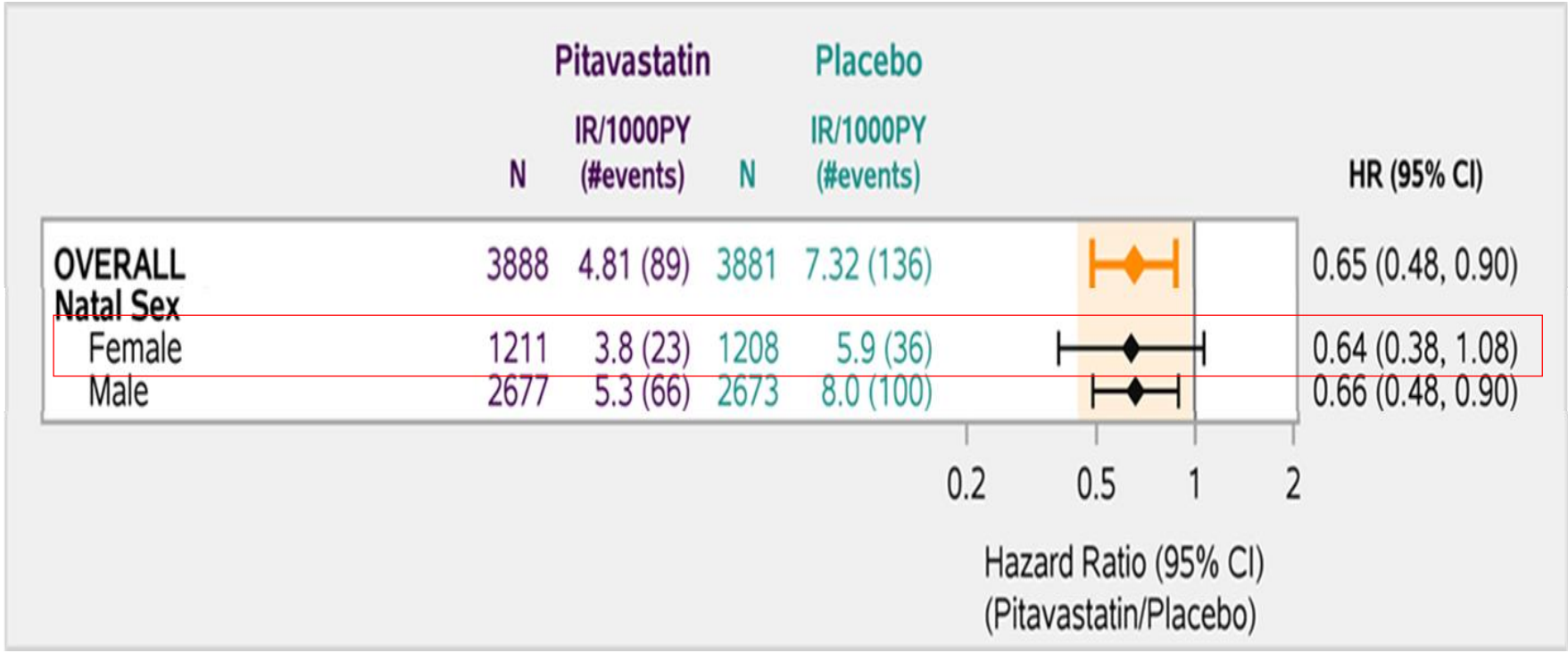
Slide curtesy of Dr. Markella Zanni. MGH

Women experienced more MACE Events than would have been predicted: Rates in 10-year ASCVD Risk Score Subgroups by Sex

Key questions: • 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?

Slide curtesy of Dr. Markella Zanni. MGH

Statin benefit Consistent among Women vs. Men



Slide curtesy of Dr. Markella Zanni. MGH

Safety and Adherence

- Greater than 80% in both groups remained in follow up
- Adherence was *very good to excellent* in the great majority of participants
- Adverse event-related discontinuation was low in each group (2% vs 1% pitavastatin vs placebo)
- All events adjudicated vis a vis relationship to COVID; only one MACE event was definitely related to COVID.

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,©] 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]

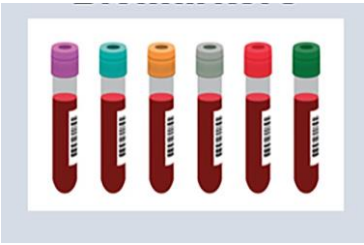
Analyzed baseline data from 755 US REPRIEVE participants enrolled in Mechanistic Substudy

among US REPRIEVE participants

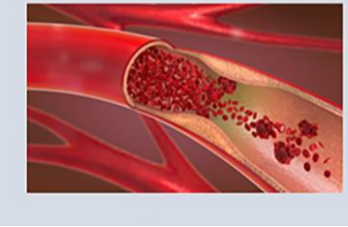
(controlling for 10-y ASCVD risk score + BMI)

women vs. men:

↑ **Immune activation/ inflammatory markers**



↓ **Coronary artery plaque prevalence**



Key Findings & Next Steps

• 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

Slide curtesy of Dr. Markella Zanni. MGH

February 27, 2024: DHHS Recommendations Released

Statin Therapy in People with HIV

Updated: February 27, 2024
Reviewed: February 27, 2024

Recommendations for the Use of Statin Therapy as Primary Prevention of Atherosclerotic Cardiovascular Disease in People with HIV

Statement released: February 27, 2024

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/statin-therapy-people-hiv

Managing Cardiovascular Risk in PWH

Age 40-75 years

10-year ASCVD risk
5 – <20%

Initiate moderate-intensity statin therapy

- Pitavastatin 4 mg
- Atorvastatin 20 mg
- Rosuvastatin 10 mg

Age 40-75 years

10-year ASCVD risk <5%

Favor initiating moderate-intensity statin therapy

Consider HIV-related factors influencing ASCVD risk.

Same statin therapy options as recommended for 5% - <20%.

Age < 40

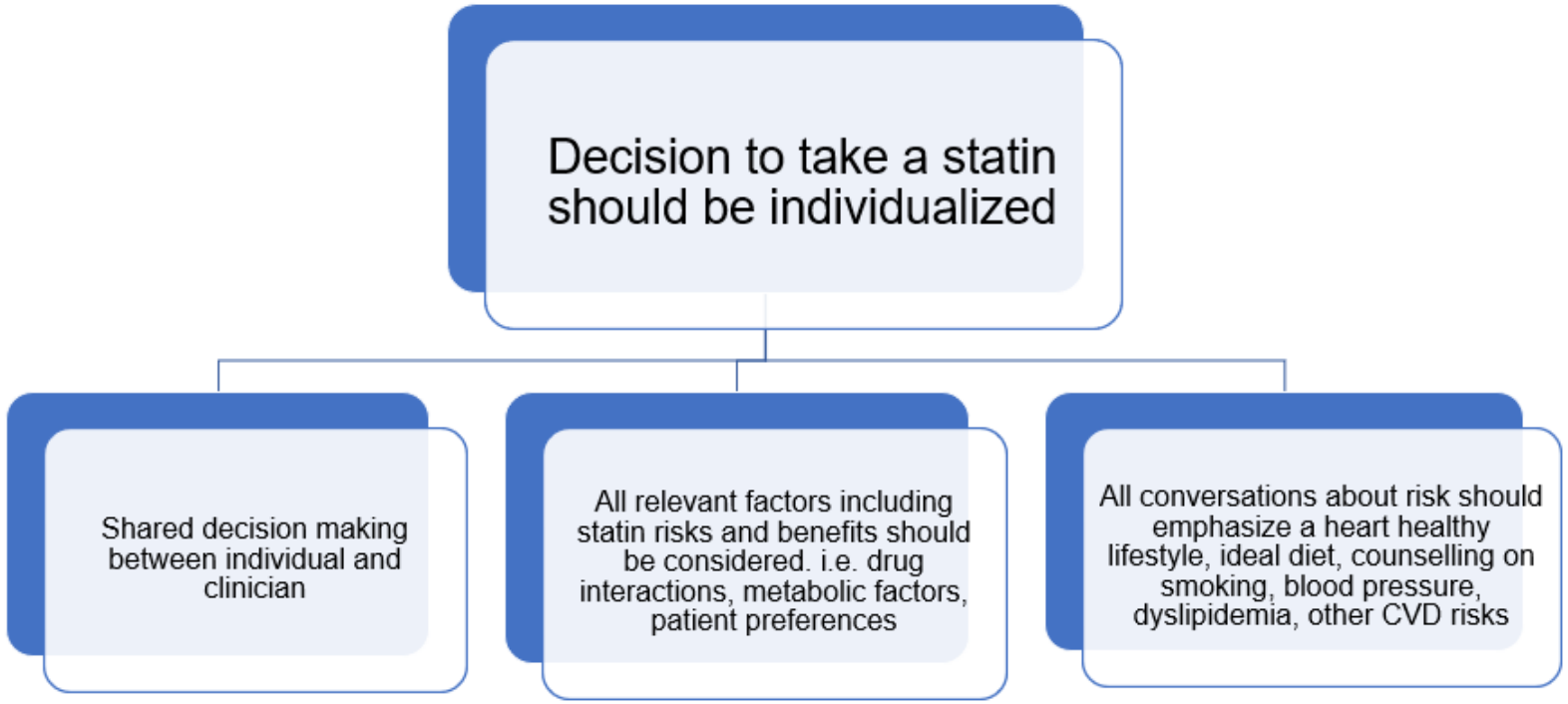
Data insufficient for or against statin therapy as primary prevention of ASCVD in PWH

General population guidance: Lifestyle modifications recommended for age <40

Statin therapy considered selectively depending on ASCVD risk factors

Implications for Care of PWH

Statin therapy, with lifestyle counselling, should be considered, even those with low to moderate predicted traditional risk, to reduce major cardiovascular events and death



Reprievetrial.org/KFitch

Reduce Heart Disease Risk

- Keep doctor's appointment and take prescribed medicines!
- Smoking cessation
- Healthy eating: low salt, low fat, low sugar
- Substance abuse support/limit alcohol
- Maintain healthy weight
- Routine assessment of lipid levels and blood sugar
  - Goals: total cholesterol less <170, good cholesterol (HDL) >50,
- Blood pressure within parameters
  - Systolic blood pressure (top number) <110
- Support for depression and mental health concerns
- Exercise daily- walking!

- Medications:
- Lipid lowering medicines: Statins
- Antihypertensive: lower blood pressure
- Aspirin- if indicated
- Diabetes management to target

Reprievetrial.org

Talking about Menopause and Midlife Women's Health

Free Image Microsoft 365 Stock

"HELL in a HOT FLASH"

Lewis-Thornton R. Hell in a hot flash?
Posit Aware 2016;28:10-11.

"I never want to go to hell, if it feels like a hot flash."

"Sleeping at night, I feel like a zombie in a sauna."

"Some days I don't want to leave the house, that's just not me."

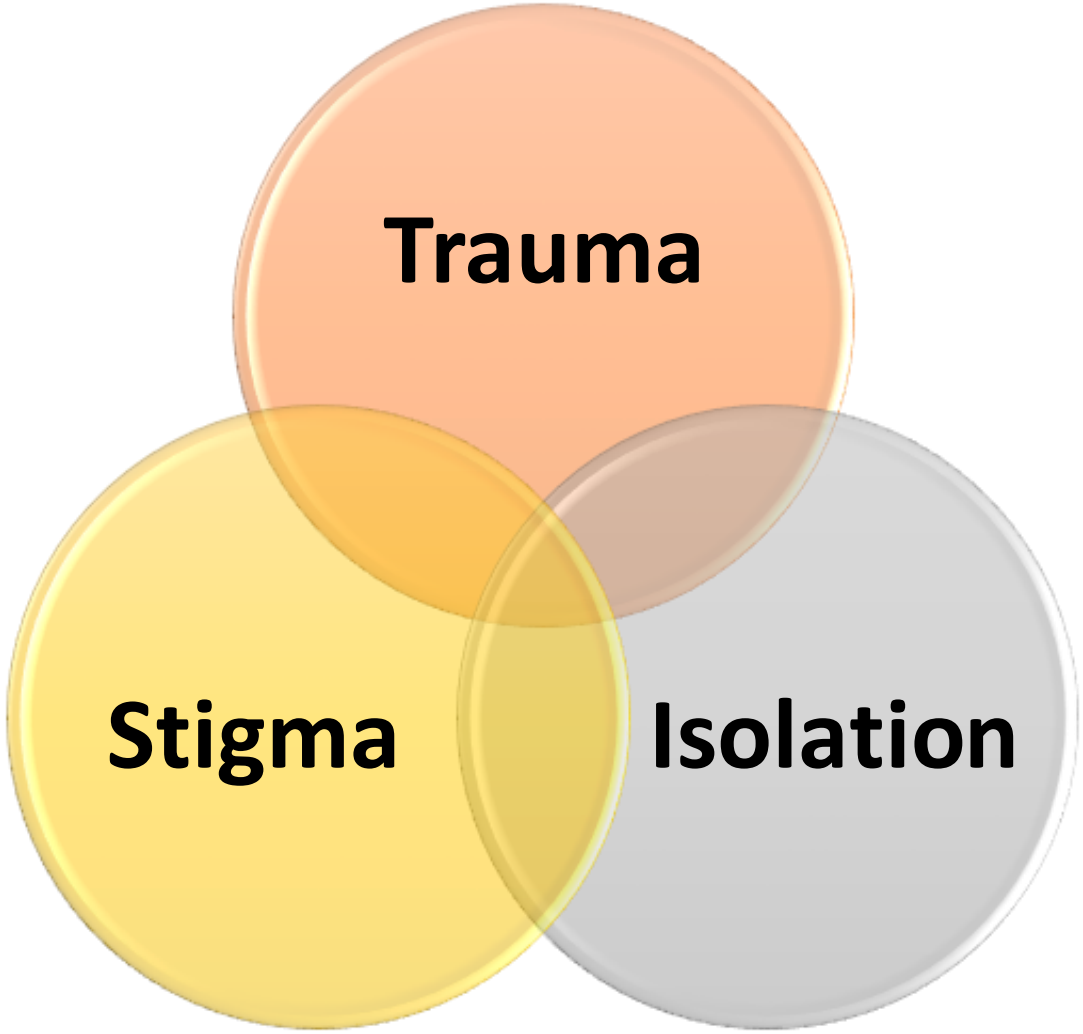
"After a week of waking up in the middle of the night with drenching night sweats, I ran to my doctor in a panic reminiscent of the days when my T-cell count was 8. I just knew something major was wrong with me…"

"I would prefer to deal with the symptoms of menopause over death from AIDS."

Reproductive Health & Trauma Across the Lifespan in Women with HIV

"I am afraid to ask or talk about women's problems."

- Anonymous woman with HIV



Alston C. 2020 https://www.thebodypro.com/article/why-all-hiv-care-must-be-trauma-informed-care
Machtinger EL, et al. *AIDS Behav.* 2012.

Psychological and Social Health Considerations

STRESS

GUILT

SHAME

DEPRESSION

ANXIETY

Limited ACCESS TO CARE

CHILD CARE

FINANCIAL CONCERNS

SINGLE PARENT

DOMESTIC VIOLENCE

PRIMARY CARE GIVER

HOMELESS

INSOMNIA

DISCRIMINATION

SUBSTANCE USE DISORDER AND RECOVERY

LIMITED SOCIAL SUPPORT

LACK OF TRANSPORTATION

Limited EDUCATION

LIMITED HEALTH LITERACY

Free Image Microsoft 365 Stock

Age of Onset of Menopause

Free Image Microsoft 365 Stock

Onset of Menopause in HIV

- Assessment of Reproductive Aging: STRAW+10 (2012)
  - Stages of Reproductive Aging Workshop (STRAW)
  - Staging system for ovarian aging including menstrual & qualitative hormone data to define each stage
  - Existing Gaps: evaluating staging of reproductive aging in women with chronic illness, including HIV

- Prior studies suggest earlier onset of menopause among WWH, though conflicting findings exist
  - Age of onset 46-50 years in WWH
  - Some findings limited by methodological constraints:
    - Use of different methods to document age of menopause
    - Use of laboratory markers verse self report last menstrual period without laboratory verification

Clark et al. 2000; Cejtin et al. 2004, Fantry et al. 2005, Schoenbaum et al. 2005, Ferreira et al., 2007, de Pommerol et al., 2011; Calvet et. al., 2015; Harlow et al., 2012

WWH Experience Irregular Menstrual Patterns

Social, Lifestyle, General Health

- Substance use disorder
- Smoking
- Physical inactivity
- History of low weight
- Hepatitis C
- Medications: psychotropics, narcotics, methadone, corticosteroids

HIV Infection

- Poor immune function
- Current/nadir CD4 count
- History of AIDS diagnosis
- Higher HIV viral load

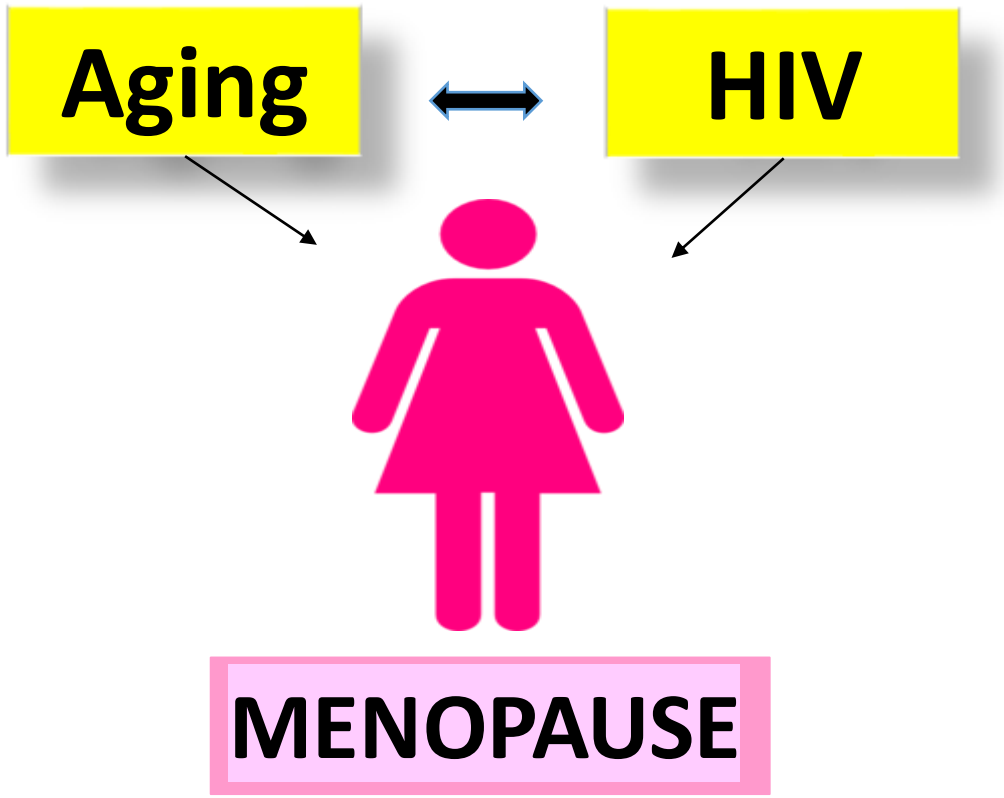
Conde DM, Silva ET, Amaral WN, et al. 2009; Schoenbaum EE, Hartel D, Lo Y, et al. 2005; Cejtin HE., 2008; Clark RA, Mulligan K, Stamenovic E, et al., 2001; Harlow SD, Schuman P, Cohen M, et al., 2000; de Pommerol et al. 2011; Calvet et. al. AJOG, 2015; Scherzer, 2018

Free Image Microsoft 365 Stock

Menopause Symptoms and Clinical Conditions

Free Image Microsoft 365 Stock

Conditions Associated with HIV, Aging & Menopause



- **Cardiovascular Disease**
- Kidney disease
- Liver disease
- **Bone loss/increased fracture risk**
- **Frailty**
- **Cognitive Impairment**
- Cancer
- **Depression**

4 Facts: Menopause Symptoms in WWH

- WWH appear to have more severe depressive symptoms and anxiety compared to women without HIV.

- WWH appear to have more frequent and severe menopausal hot flashes that negatively impact quality of life.

- Urogenital symptoms reported in WWH across menopause transition: vaginal dryness, sexual dysfunction, dyspareunia, unclear if worse than women without HIV.

- VERY few studies to date evaluating menopausal hormone therapy use in WWH in the context of menopause- retrospective chart review, qualitative inquiry.

WWH have a difficult time distinguishing symptoms of menopause from symptoms of HIV

King et al, 2019; Santulli et al. 2016, Scherzer et al. Am J Reprod Immunol 2015, Zanni et al, JID 2020; Looby et al 2016; Andany et al, Int. JWH 2016;Looby et al, 2014; Valadares, 2014; Tariq 2018; Image Microsoft 365 Stock; Schnall et. Al, 2018

Characteristics Associated with Hot Flashes (HF) in WWH

Duff et al., 2017

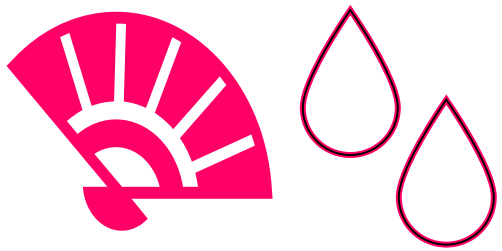
- HF were the most severely experienced somatic symptom on the MRS; 40.4% reported moderate to extremely severe HF.
- In multivariable generalized estimating equation analysis, **severe menopause symptoms,** in addition to injection drug use and physical/sexual based violence**, were independently associated with <95% adherence to antiretroviral therapy** (p<.05).

Rubin et al., 2014

- In multivariable regression analyses, **elevated HF were associated with worse attention and processing speed** (Comalli Stroop test, trials 1 & 2) in WWH and WWOH (p<.05).

Maki et al., 2012

- In logistic regression analyses, **persistent HF predicted elevated depressive symptoms (CES-D) in women with HIV** (p<.05).



Adherence to HIV Clinical Appointments

Solomon D et al.,2021

Rivard, Looby et al. 2019; Image Microsoft 365 Stock

Hot Flashes and Cardiovascular Disease Risk Indices Among Women With HIV

- Among the whole group (n=42) and among WWH (n=23) (but not among women without HIV), women with >1 hot flash per day had higher levels of sCD14 compared with women with ≤1 hot flash per day (P = .004 and P = .02, respectively).
- Among WWH, years since onset of hot flashes related directly to increased intramyocardial steatosis (ρ = 0.80; P = .02) and decreased diastolic function (ρ = –0.70; P = .03) (measured by magnetic resonance imaging/spectroscopy).

Toribio, Fulda, Looby, Zanni, et al. OFID, 2021

2 Facts: Menopause in WWH

- In WWH, increased waist circumference is associated with ovarian aging, conflicting data regarding impact of low CD4/high HIV viral load; reduced ovarian reserve may associate with subclinical CVD and increased markers of immune activation.

- WWH are at increased risk for osteopenia and osteoporosis related to HIV-related factors and have a higher prevalence during the menopause transition.

Looby et al, 2014; Yin et al, 2012; Cortes, et al., 2015; Image Microsoft 365 Stock

Next Steps to Improve the Care of WWH

- Menopause symptom science in HIV
  - What is the interface between menopause symptoms and HIV symptoms?
  - Downstream implications on HIV clinical variables, immunologic/virologic control, antiretroviral therapy use adherence?
  - Treatment modalities in women with HIV-use of menopause hormone therapy?
- Cardiovascular disease risk & bone health in women with HIV
- Education for WWH and Providers- COMMUNITY ENGAGEMENT!

Key Considerations re: Hormone Therapy (HT) Use
(Women without HIV)

Fundamental Concepts: 1) Use of HT for Menopausal Symptoms
2) Use of HT for Prevention of Chronic Diseases

- Age & Timing of Use
- FDA approved indications

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

Age and Timing of Use

- Hormone therapy (HT) is an acceptable option for treating moderate to severe menopausal symptoms in women **below the age of 60 or within 10 years of menopause and healthy.**
- Data show reduced CHD in women who initiate HT aged younger than 60 years and/or within 10 years of menopause onset

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

FDA Approved Indications for Hormone Therapy

(Women without HIV)

Tx of Symptoms

Vasomotor Symptoms

HT has been shown in double-blind RCTs to relieve hot flashes and is approved as first-line therapy for relief of menopause symptoms in appropriate candidates.

Genitourinary Symptoms

Low dose vaginal estrogen has been shown in RCTs to effectively restore genitourinary tract anatomy, increase superficial vaginal cells, reduce vaginal pH, and treat symptoms of vulvovaginal atrophy.

Prevention of Chronic Disease

Prevention of Bone Loss

HT has been shown in double-blind RCTs to prevent bone loss, and in the WHI to reduce hip fractures in postmenopausal women (33%).

Premature Hypoestrogenism

HT is approved for women with hypogonadism, POI, or premature surgical menopause without contraindications, with health benefits for menopause symptoms, prevention of bone loss, cognition and mood issues, until the average age of menopause.

The North American Menopause Society 2017 Hormone Therapy Position Statement Advisory Panel (NAMS). 2018;24(7):728-753.

A5424: Menopausal Hormone Therapy for Women Living with HIV (HoT)

Sponsored by: National Institute of Allergy and Infectious Diseases in collaboration with National Institute on Aging

Co-Chairs: Sara Bares, Michael Yin
Vice-Chair: Sara Looby
Statisticians: Laura Smeaton, Maxine Olefsky
DAIDS Clinical Representative: Beverly Alston-Smith
DAIDS Pharmacist: Justine Beck
NIA Representative: Irina Sazonova
Clinical Trials Specialist: Linda Naini
Community Scientific Subcommittee Representative: Maureen Phiri
Data Managers: Sheldon Tetewsky, Anna Yoder
Lab Data Managers: Christopher Dolina, Kyle Whitson
Lab Center Specialists: Sandy Alvarez, Ceora Beijer Kathie Ferbas

Field Representatives: Romina Chinchay Collahua, Jenny Orihuela
Cardiologist: Chris Longenecker
Endocrinologist: Markella Zanni
Gynecologist: Susan Reed
Immunologist: Adriana Weinberg
Pharmacologist: Kimberly Scarsi
Psychologist: Pauline Maki
Virologist: Sara Gianella Weibel
Investigators: Elizabeth Connick, Jonathan Karn, Rosie Mngqbisa, Eileen Scully, Javier Valencia, Emilia Jalil
Project Manager: Bridget Makhlouf
International Site Specialist: Allegra Cermak

ACTG

Study Hypothesis

- Hormone therapy will be more effective than placebo in reducing VMS in WLWH in late menopausal transition/early post-menopause

Study Schema

Design: Phase 4, randomized, double-blind, placebo-controlled trial of hormone therapy versus placebo

Duration: Up to 17 weeks

Sample Size: Step 1: Up to 300 participants; Step 2: 105 participants (70 Arm B, 35 Arm B)

Population: WLWH aged 40-60 years in late menopausal transition or early postmenopause with moderate to severe VMS who are on ART for at least 48 weeks with no change in ART for at least 60 days prior to entry and have an HIV RNA of <200 copies/mL at screening

Sites: Open to all domestic sites and limited international ACTG sites (Durban, Lima, Rio de Janeiro)

STEP 1 - Active Screening Phase (3-5 weeks)

Daily VMS Diary (Up to 300 participants) → **Eligible via VMS Criteria** → 2:1 randomization →

VMS Eligibility Criteria (based on MSFlash):

- Mean daily VMS frequency at least 2 during wks 1 & 2 AND
- VMS rated as bothersome or severe 4 or more times per week (out of 14 possible) in wks 1 and 2 AND
- VMS frequency in week 3 did not decrease >50% from the average in weeks 1 and 2

STEP 2 - Treatment Phase (12 weeks)

	Arm A (n=70)	Arm B (n=35)
Uterus	Estradiol gel 0.1%, 0.75 g daily + encapsulated micronized progesterone 100mg daily x 12 weeks	Placebo gel daily + placebo capsule daily x 12 weeks
No uterus	Estradiol gel 0.1%, 0.75 g daily x 12 weeks	Placebo gel daily x 12 weeks

NOTE: All participants will be offered optional dose titration from 0.75g (0.75mg estradiol) to 1 g (1mg estradiol) at week R + 6; recommended if VMS symptoms have not decreased in severity or number by ~50%

ACTG

Objectives

Primary Objective:

- Determine the effects of HT on VMS in WLWH in the late menopausal transition or early postmenopause.

Secondary Objectives:

- Evaluate the safety and tolerability of HT as compared to placebo
- Determine the effect of HT on the following: neurocognition, mood, sleep, quality of life, sexual function, and weight, waist circumference and waist-to-hip ratio.

Exploratory Objectives:

- Determine the effect of HT on: Markers of bone turnover, cardiometabolic health, inflammation/immune activation; HIV reservoir activity; Measures of physical function; Rectal and cervical microbiome.
- Explore exposure-response relationships between estradiol pharmacokinetics (PK) and study outcomes in those treated with estradiol.
- Evaluate feasibility and acceptability of ambulatory monitors for VMS and sleep on a subset of participants.
- Explore agreement between subjective VMS frequency with objective VMS frequency in a subset of participants.

ACTG

Safety

- ✓ **Exclusion criteria carefully aligned with FDA approved HT use guidelines**
- ✓ **Estradiol gel-** by avoiding first pass metabolism, transdermal preparations have less effect than oral estrogen on hepatic synthesis of coagulation factors; therefore, pose lower risk of venous thromboembolism and stroke
- ✓ **Detailed safety monitoring throughout study protocol with guidance for the clinical management of safety issues**
- ✓ **Monitoring, grading, and reporting of HT-related AEs**

Key exclusion criteria

- Age>60
- History of breast or endometrial cancer or precancer (e.g., endometrial hyperplasia)
- History of venous thromboembolism (PE, DVT); recent arterial thromboembolic disease; known atherosclerotic CV disease
- Pregnant within 180 days or planning to become pregnant during course of study
- Currently lactating or lactating in the 90 days prior to study entry
- Unexplained vaginal bleeding within 1 year prior to entry

Safety Monitoring on Study

- Clinical breast exam as part of targeted physical exam, vaginal bleeding diary
- Targeted collection and reporting if these occur while on study, regardless of severity
- Pregnancy testing at screening, R and R+12; contraception requirement
- Early treatment discontinuation of pregnant or lactating
- Daily vaginal bleeding diary, telephone call re: vaginal bleeding at R+10, criteria for work-up of endometrial hyperplasia

ACTG

Primary Outcome and Safety Evaluations

- **Primary Outcome Measure**
  - Change in self-reported mean VMS frequency per day from Step 1 observation phase to the one-week period prior to week R + 12.
- **Secondary Safety Outcome Measures**
  - Grade 3+ AEs associated with study treatment.
  - Occurrence of abnormal vaginal bleeding that results in gynecological referral.

Summary

- Heart disease risk management is an important component of care for women living with HIV
- We now have evidence of the benefits of statin therapy and this should be discussed with your care team
- Menopause treatment is being re-examined for women with HIV
- Participation and promotion of research is one way to get the answers we need.

Acknowledgements

- Sara E. Looby, PhD, ANP-BC, FAAN
- Markella Zanni, M.D.
- Sara Bares, M.D.