

HOPE Nurses Conference

December 18th, 2019

HIV and Cardiovascular Disease: The REPRIEVE Trial

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Disclosures

- Educational grant from Gilead Sciences, Inc.

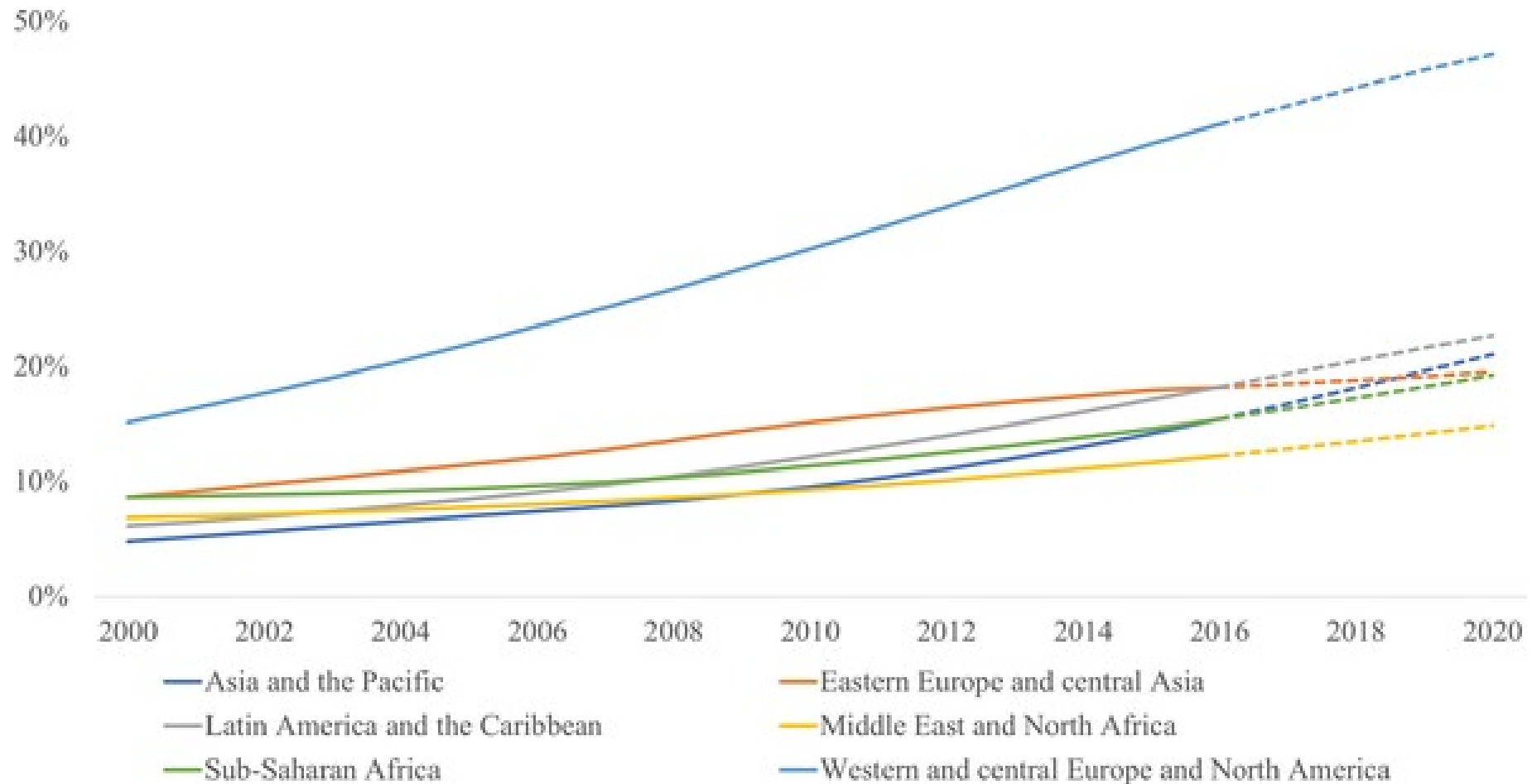
Overview

- Cardiovascular disease (CVD) in the setting of HIV
 - Epidemiology
 - Mechanisms
 - Preventive therapies
- The REPRIEVE Trial
 - Study status
 - Baseline data
 - REPRIEVE substudies/ancillary objectives
 - Novel strategies to promote recruitment and engagement

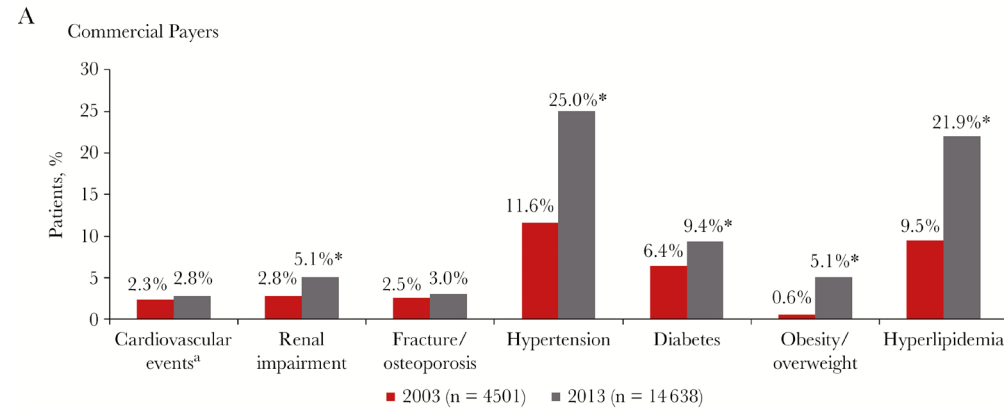
Background: HIV and CVD

- People living with HIV (PWH) are aging globally
- Comorbid medical conditions, including cardiovascular disease (CVD) are increasing in prevalence among PWH
- CVD disease is unique in HIV
 - Occurs in asymptomatic, young people
 - Traditional risk factors are often not present and may account for only a portion of excess CVD risk in HIV
 - Non-traditional risk factors such as increased inflammation and immune activation are associated with CVD
- No current recommendations for prevention of CVD in HIV which consider the unique pathophysiology of atherosclerosis in this population.

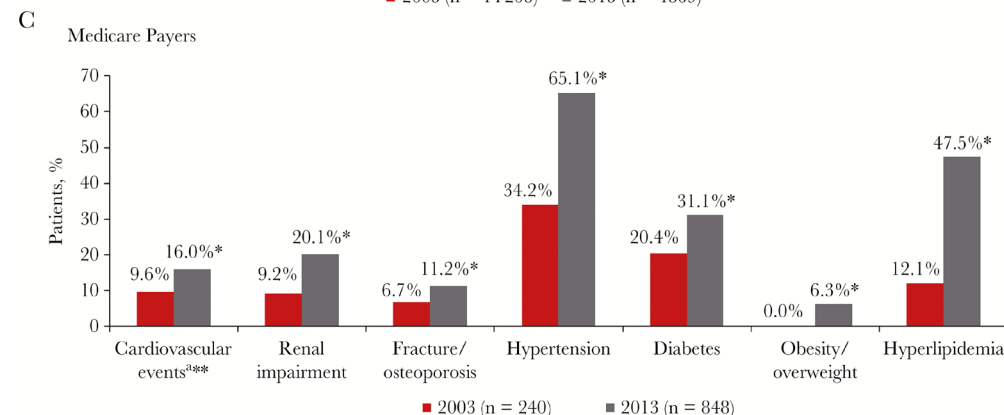
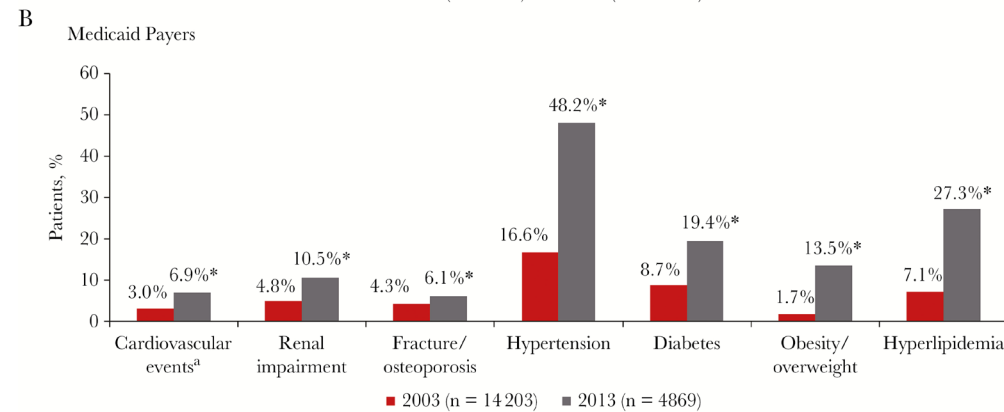
People Living with HIV (PWH) are Aging *Globally*



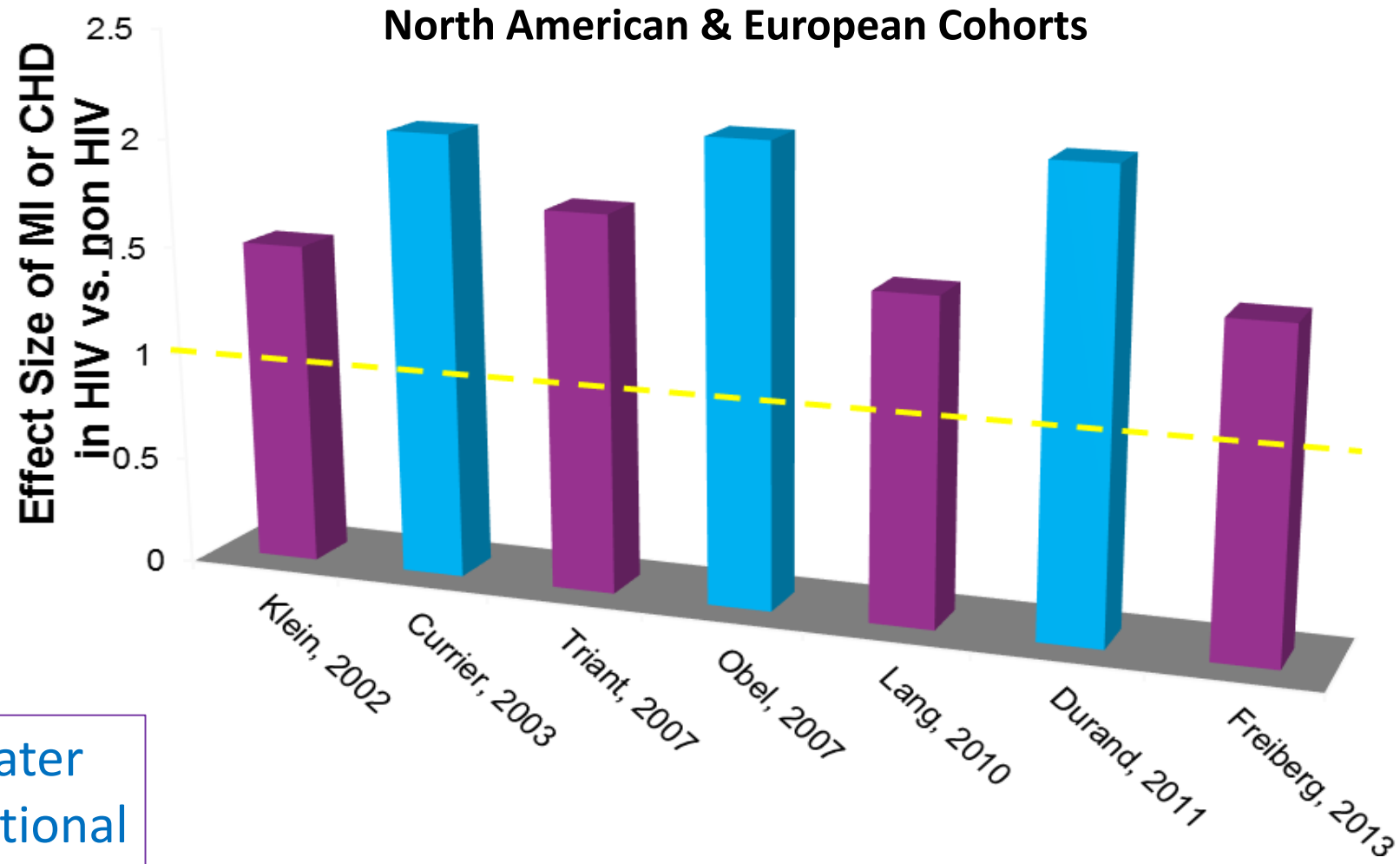
Increased Burden of Comorbid Medical Conditions



Significant increases in comorbidities among PWH between 2003-2013

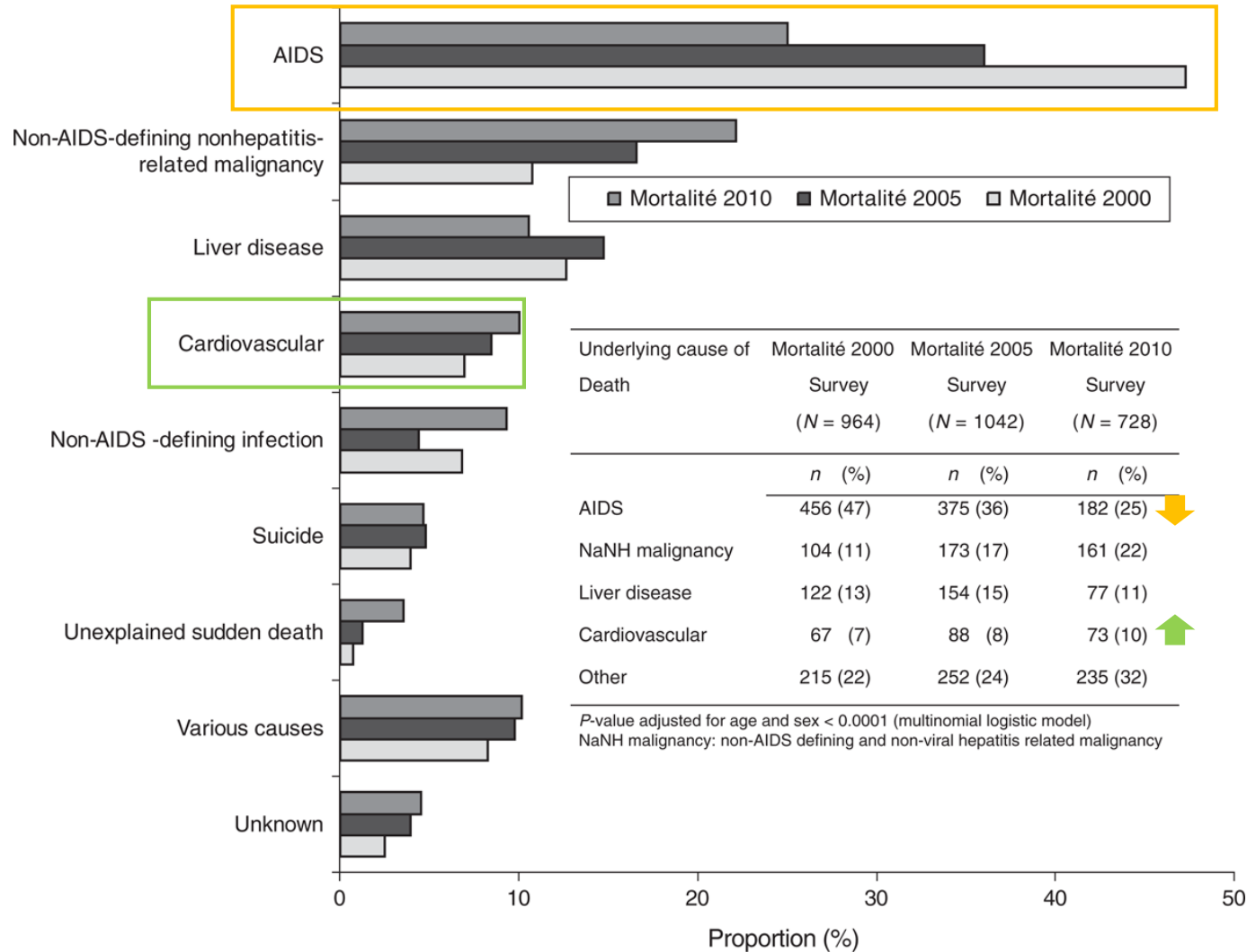


Relative Risk of MI is Increased Among PWH (vs. PWOH) in High-Income Countries



CVD risk in HIV is greater than predicted by traditional risk factors alone

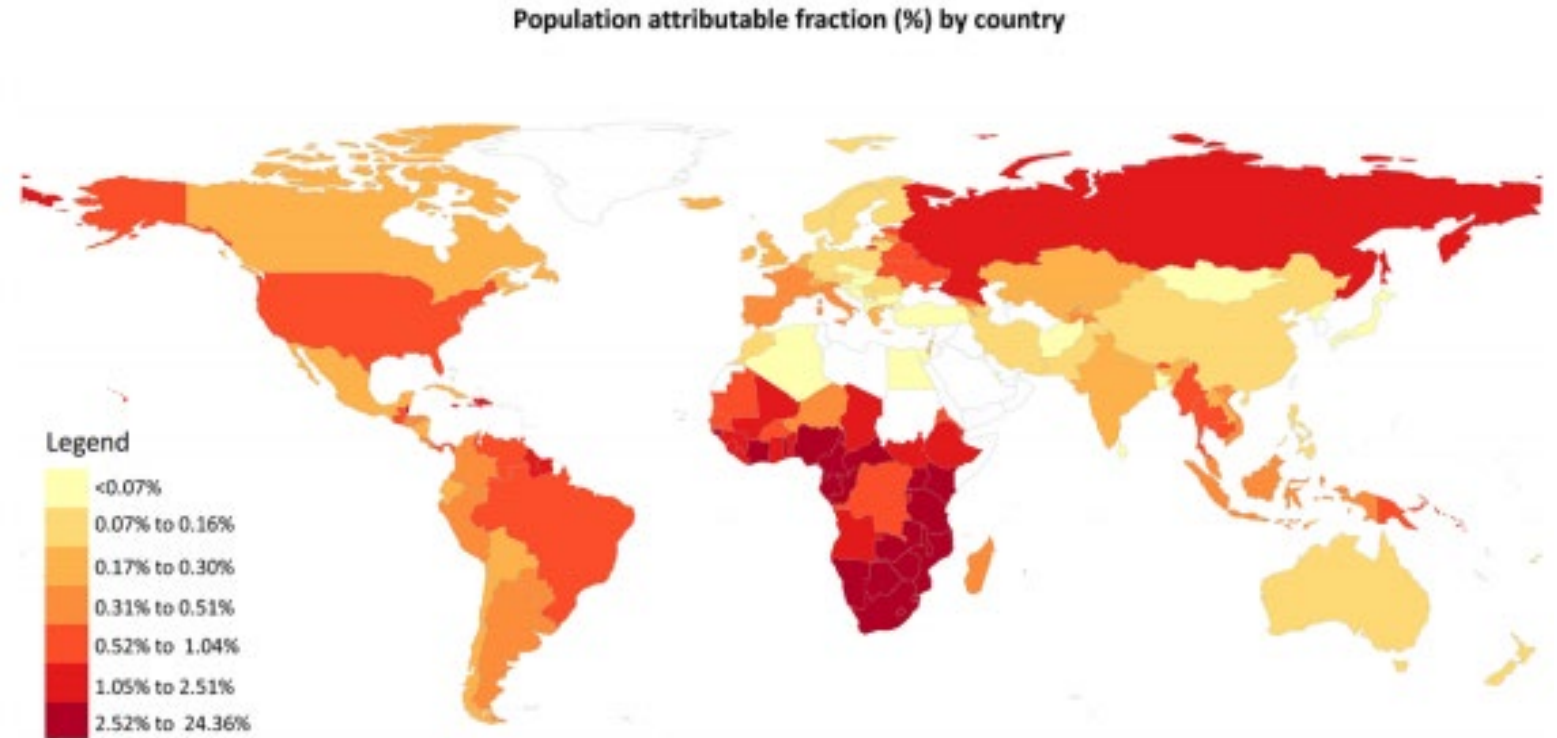
CVD Related Mortality is Increasing Among PWH



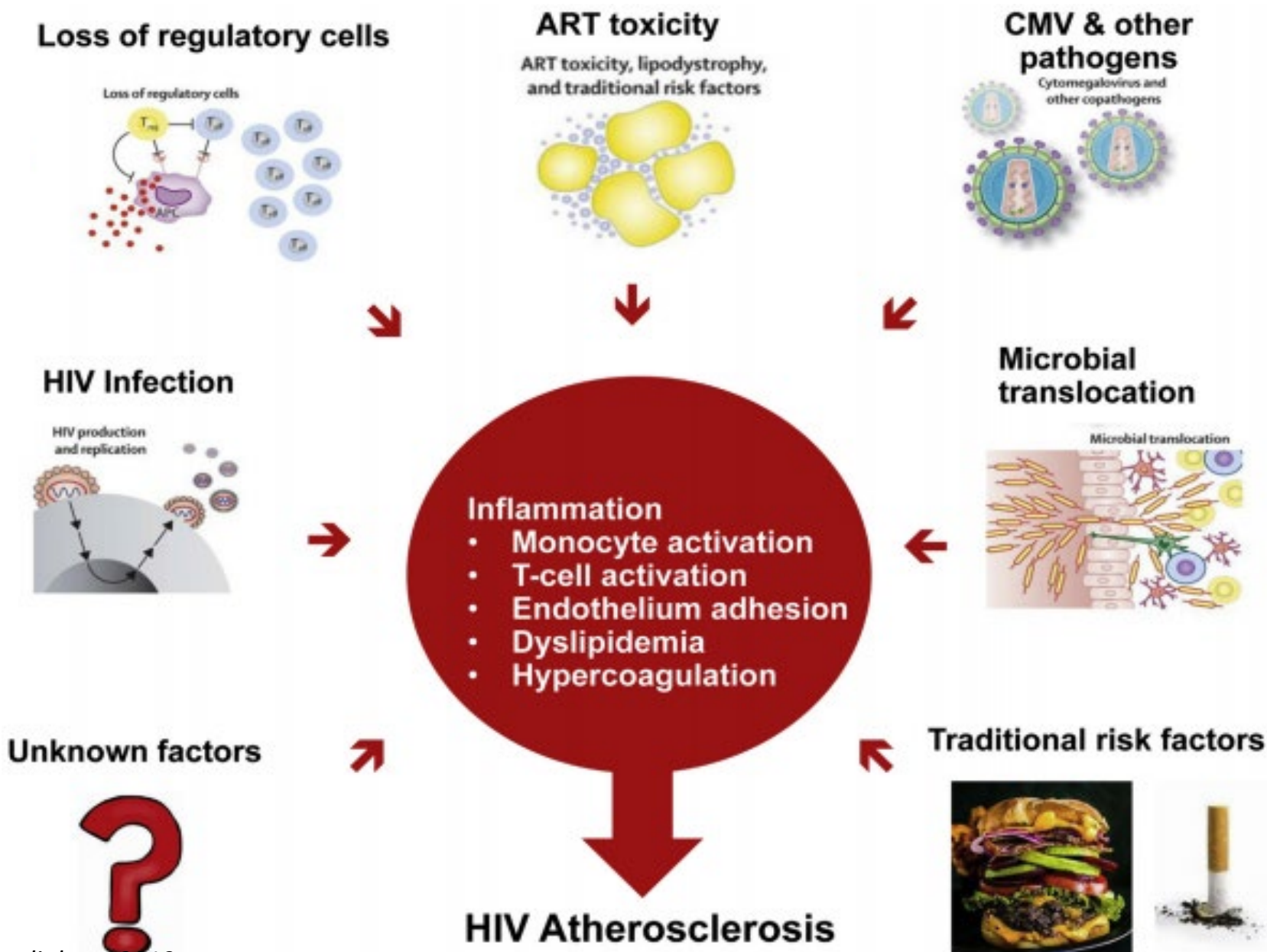
- Cause of death among HIV adults, France, 2000-2010 at clinical sites providing HIV care and treatment
- Proportions of deaths from non-AIDS defining malignancy and CVD increased while AIDS-related deaths decreased

Population Attributable Fraction (%) of Prevalence of CVD by Country

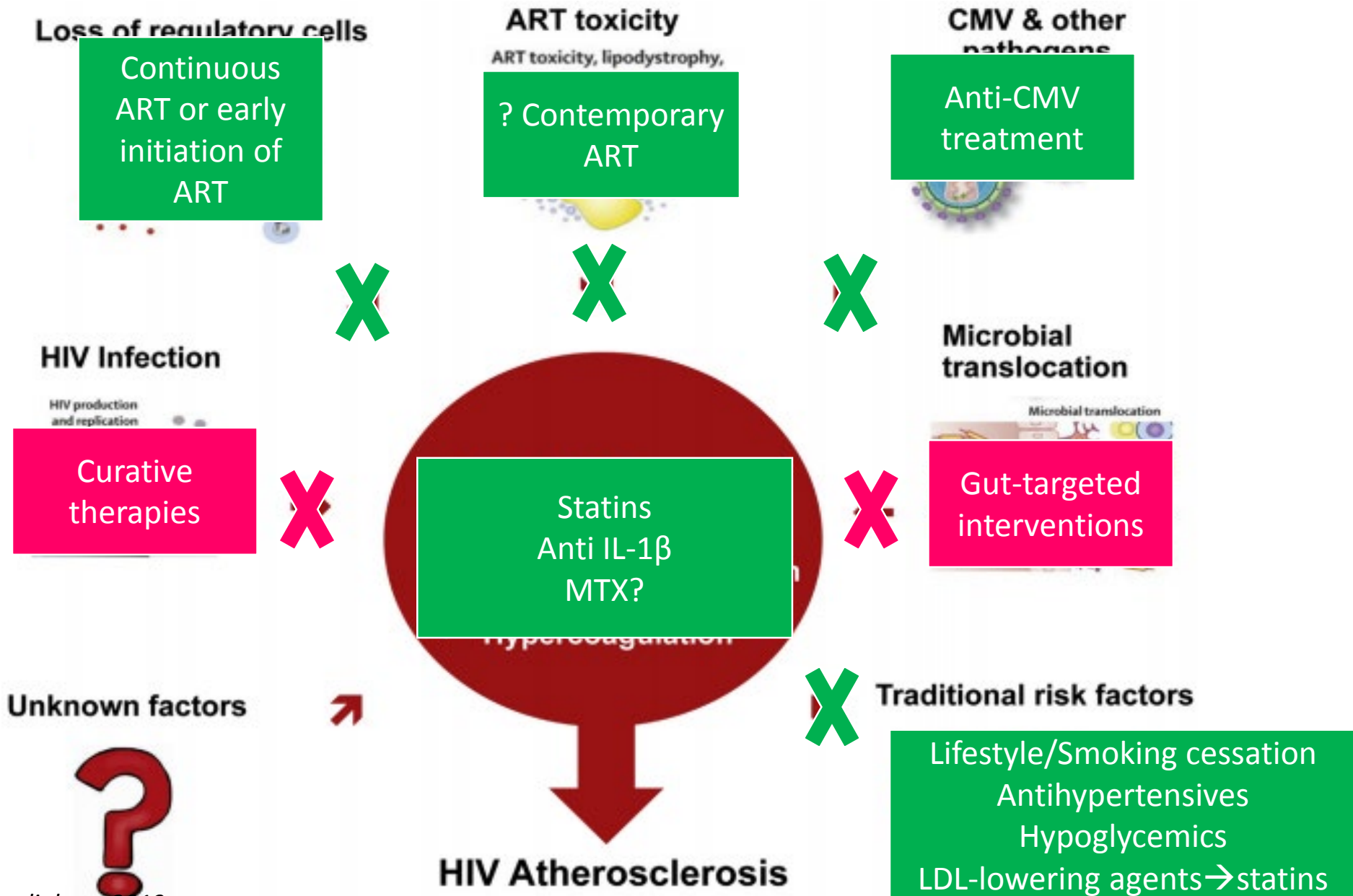
- Systematic review of longitudinal studies on CVD in HIV, 80 studies with ~800,000 individuals with HIV and a follow-up of 3.5 million person years
- Relative risk of CVD in persons living with HIV is 2.16 (95% CI, 1.68–2.77) compared to PWOH
- Authors report impact of HIV and CVD was highest among individuals in sub-Saharan Africa



What Are the Mechanisms Associated with CVD in HIV?

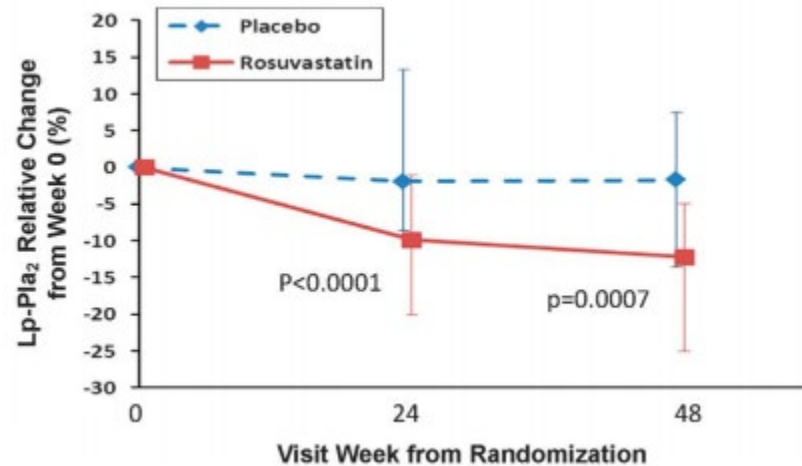
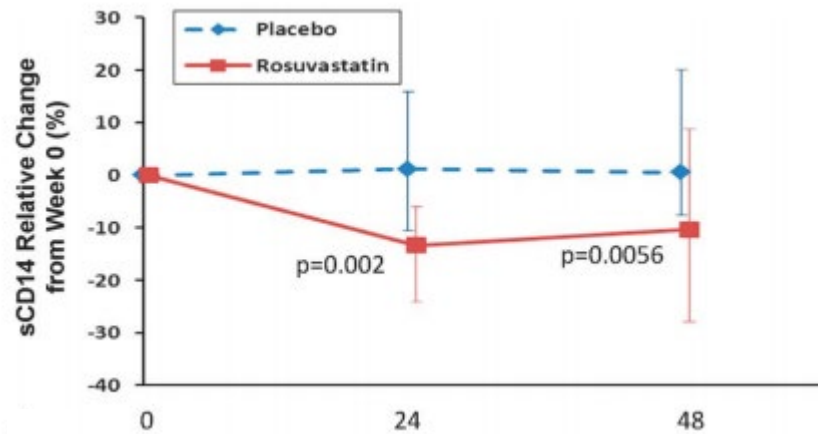


Established and Potential Treatments for CVD Prevention in HIV



Statins Address Both Traditional and Immune Risk Factors in HIV

- LDL Lowering: Statins lower LDL by similar amounts in people with and without HIV (-26.2% vs -26.9%)
- Reduced Immune Activation: Decreased monocyte activation with decreased circulating levels of sCD14 and the macrophage-derived phospholipase Lp-PLA2



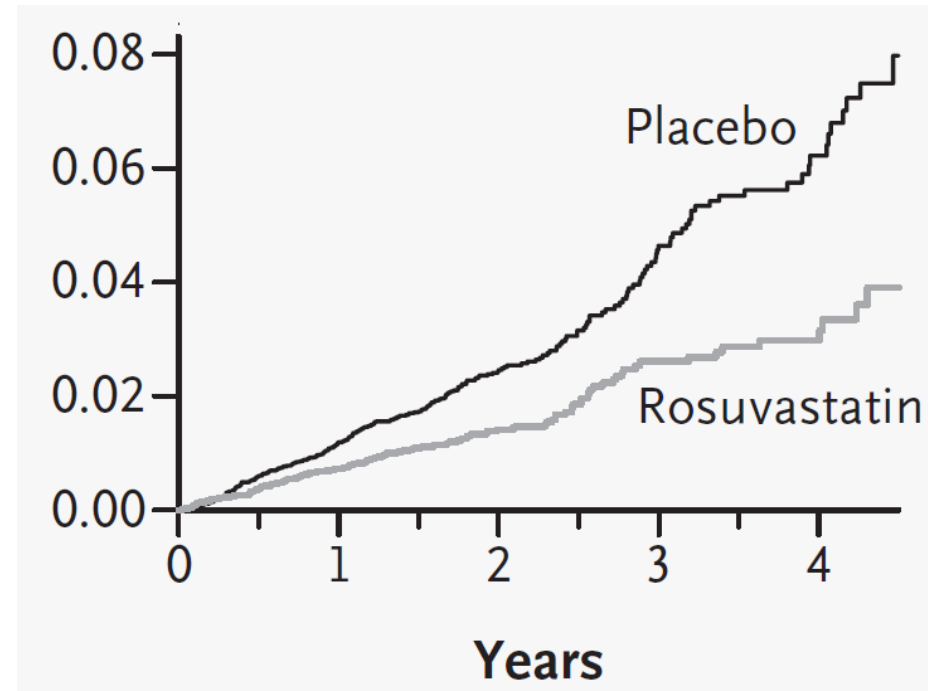
Statins are Well-Tolerated/Safe in HIV

- Low rates of ↑LFTs, myalgias (<3%) (Silverberg AIM 2009)
- Despite immune suppressant effects, no adverse effects on viral replication (Moncunill AIDS 2005, Negrodo AIDS 2006)
- Newer statins may not increase glucose (metabolic syndrome) and do not interact with PIs
- Pitavastatin (Livalo): Recommended in 2013 ACC/AHA guidelines as a *moderate dose* statin
 - Metabolized primarily by glucuronidation. Minimally metabolized by CYP3A
 - No known interactions with antiretroviral therapy → no dose limitations. (Sponseller CROI 2014, Aberg Endo 2013, Eckard JID 2014, Stone JACC 2013)

Do Statins Prevent
Cardiovascular Disease *Events* in
PWH?

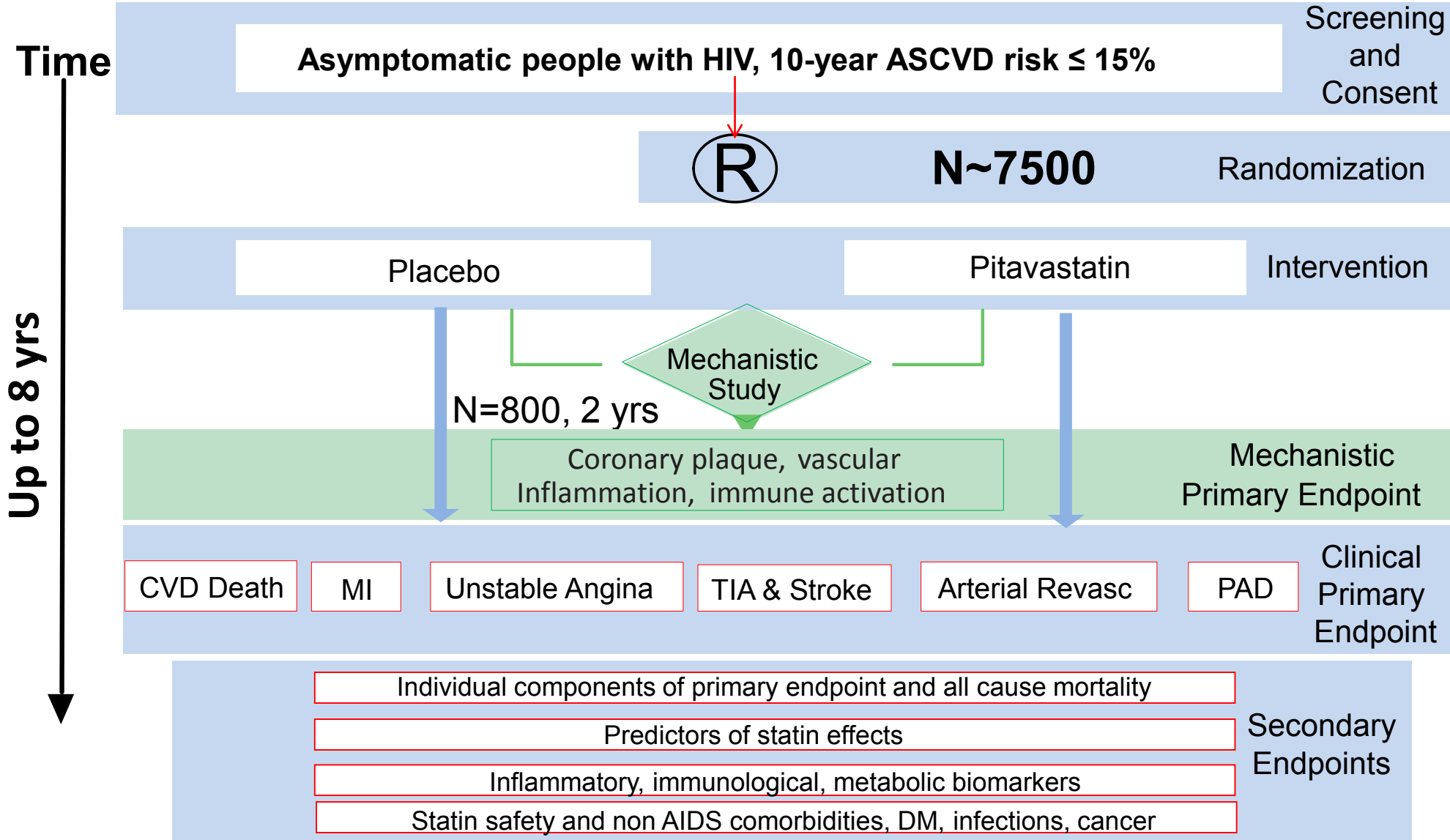
Statins Reduce Vascular Events in People Without HIV With Low LDL and Increased CRP

Events/100p-y:
Placebo: 1.36
Rosuva: 0.77
HR 0.56



- Instead JUPITER showed a HR of 0.56, greater than expected based on LDL lowering alone

REPRIEVE Trial Schema



ASCVD = atherosclerotic cardiovascular disease

Key Inclusion/Exclusion Criteria

- **Inclusion criteria**

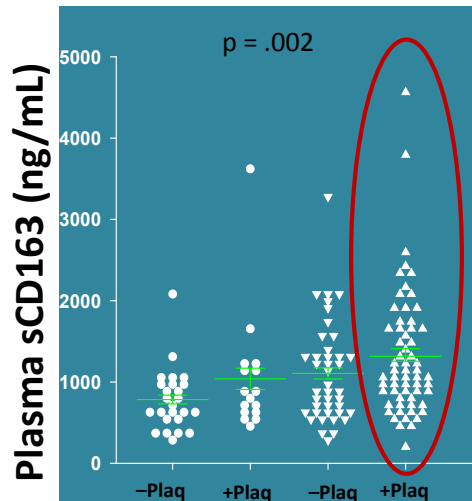
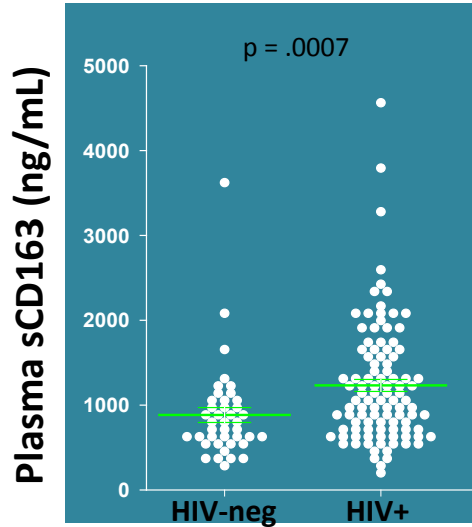
- HIV-infected adults, 40-75 yrs; No known ASCVD
- 10 year ASCVD risk score $\leq 15\%$
- On ART > 6 mos; CD4 count > 100 cells/mm³
- LDL < 190 mg/dL; TG < 500 mg/dL; ALT ≤ 2.5 ULN; CrCl ≥ 60 mL/min
- Allowed: HBV and HCV (FIB-4 ≤ 3.25); Diabetes (LDL < 70mg/dL)

- **Exclusion criteria**

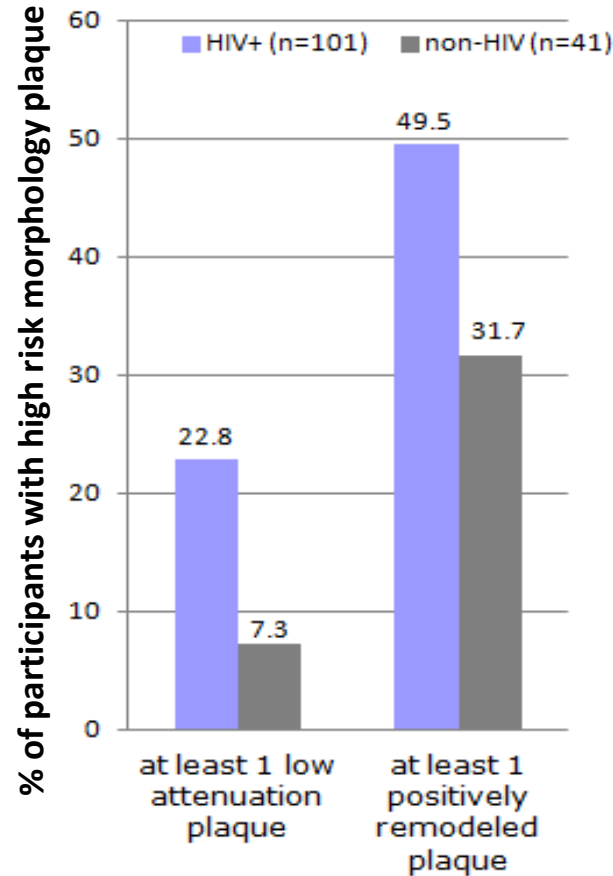
- Active cancer within 12 months
- Known decompensated cirrhosis
- Exclusionary meds and other conditions

Mechanistic Substudy of REPRIEVE

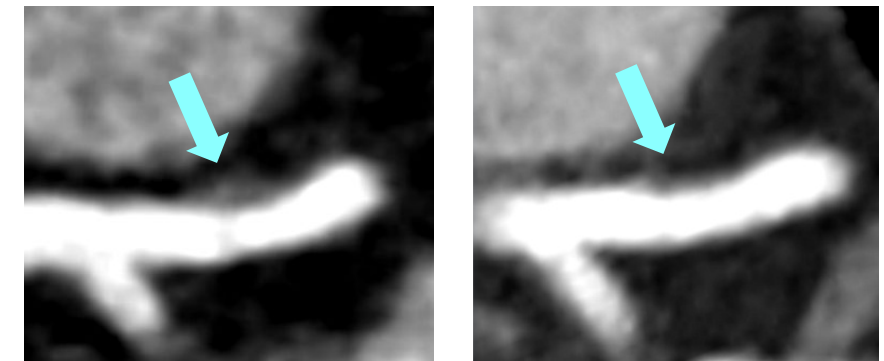
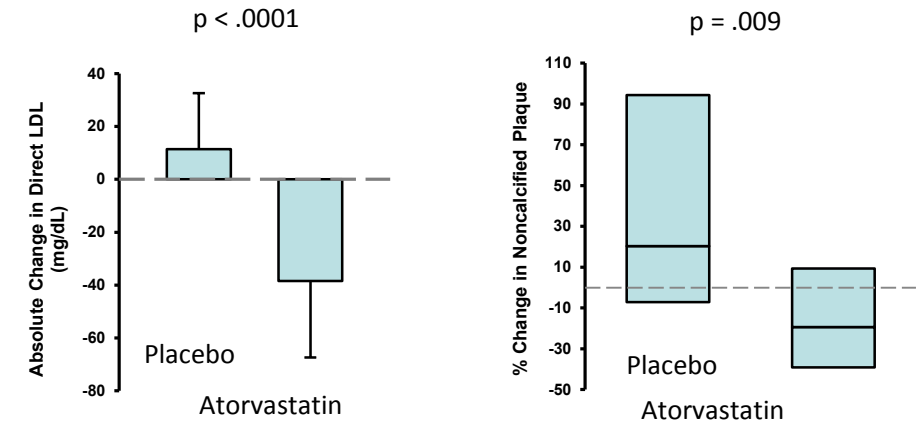
OBJECTIVE: Determine the effects of pitavastatin on coronary plaque architecture by serial CCTA and on serum markers of immune activation, inflammation, and CVD risk



Burdo, TH et al. JID, 2011



Zanni MV, et al. AIDS. 2013



Decreasing non-calcified plaque in LAD after 12 mo atorvastatin

Lo CROI 2015, Lancet HIV 2015

REPRIEVE's Progress to Date

7770

participants enrolled

12

countries worldwide

32

percent women
enrolled

~5.0

years
ongoing

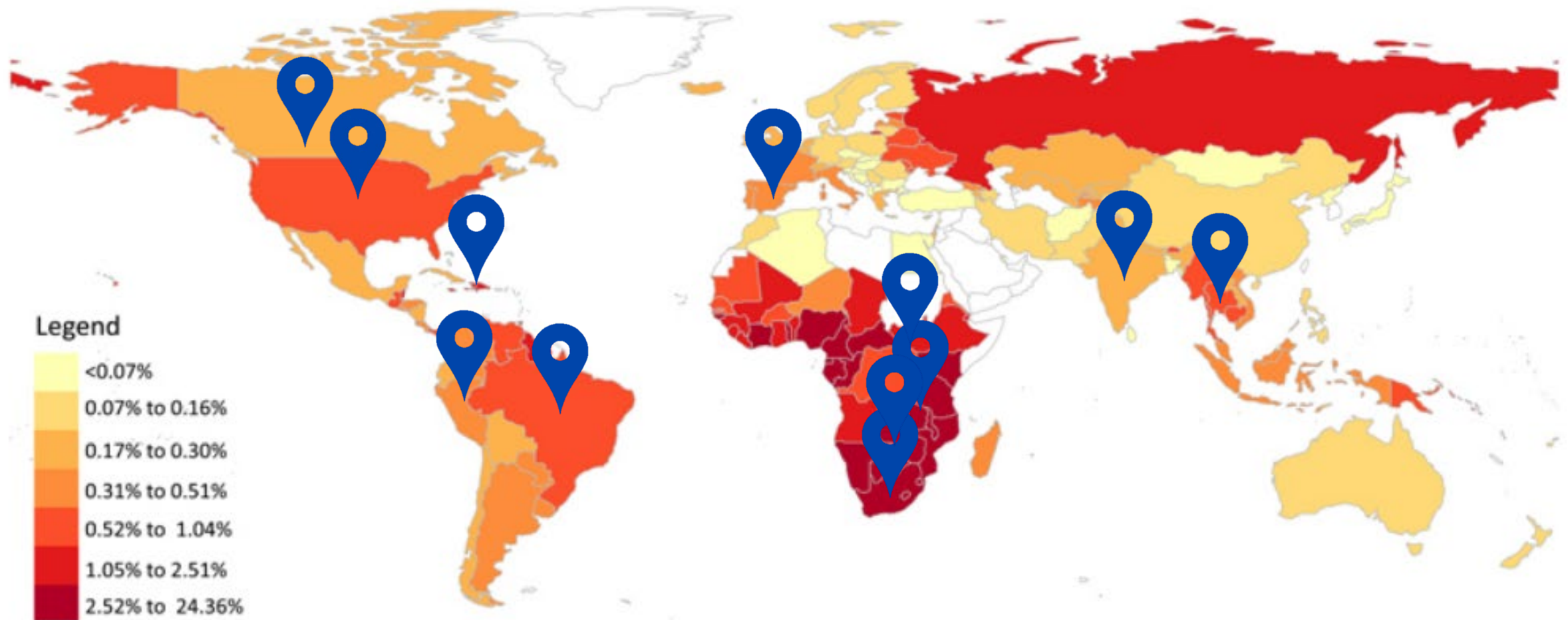
Over 110 clinical sites in 12 countries globally, sites are part of the AIDS Clinical Trial Group as well as outside the ACTG



- Mechanistic Substudy (A5333s) completed enrollment February, 2018. **805** participants enrolled.
- REPRIEVE (A5332) completed enrollment of **7557** participants (March 2019)
- REPRIEVE-EU (EU5332) completed enrollment of **213** participants (July 2019)
- Design and rationale for REPRIEVE and Substudy published in American Heart Journal

Population Attributable Fraction (%) of Prevalence of CVD by Country

and REPRIEVE Sites by Country



Baseline Demographics

Characteristics	Total (N=7770)	
Sex at Birth, N(%)	Male	5158 (68%)
	Female	2399 (32%)
Age (years)	Median (Q1-Q3)	50 (45-55)
Ever Been on a Statin, N(%)	No	7045 (94%)
	Yes	474 (6%)
Race, N(%)	White	2444 (32%)
	Black or African American	3324 (44%)
	Asian	1139 (15%)
Ethnicity, N(%)	Hispanic or Latino	1896 (25%)

Baseline HIV-Related Medical History

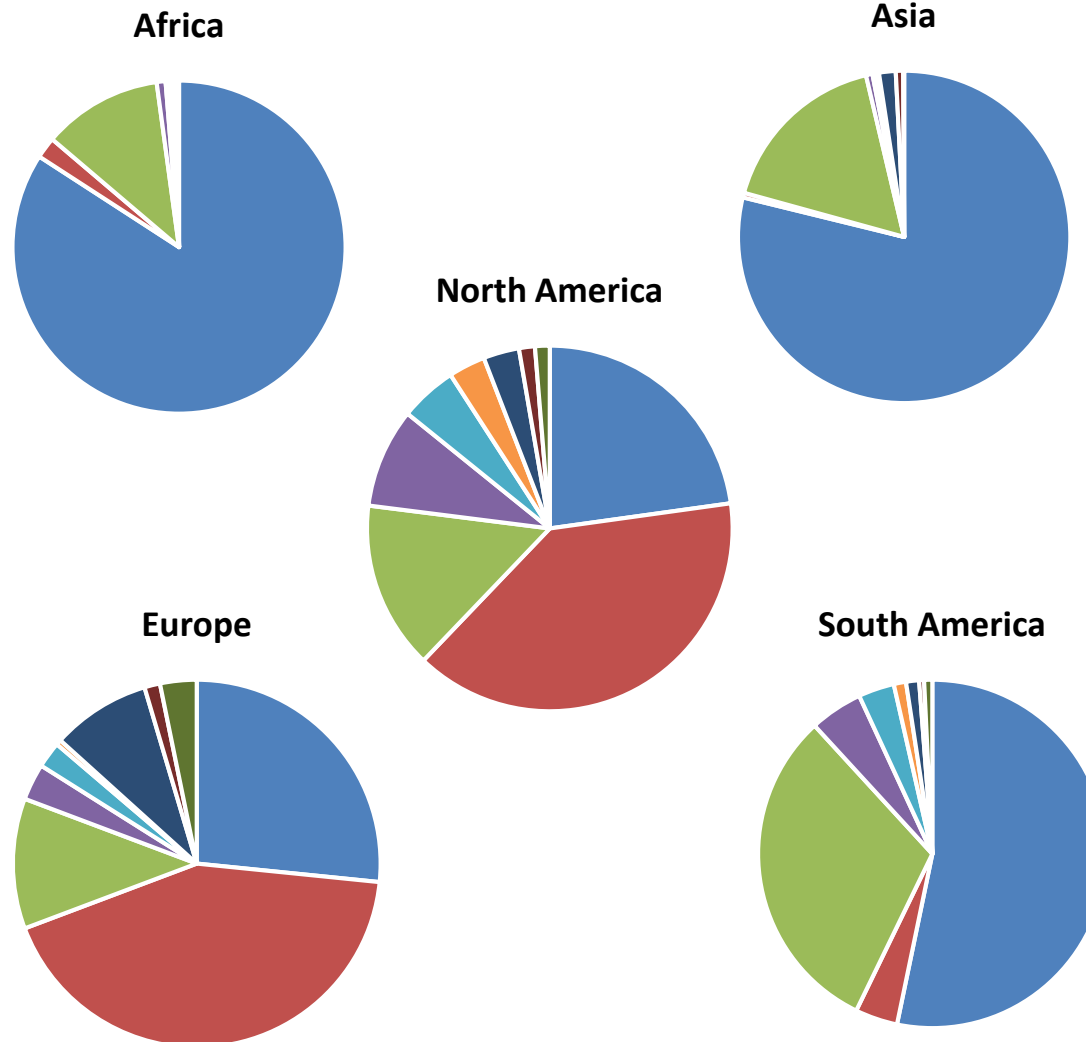
Characteristic	Total (N=7770)	
Years Since HIV Diagnosis	Median (Q1-Q3)	12 (7-19)
CD4 count (cells/mm ³)	Median (Q1,Q3)	617 (447-821)
HIV-1 RNA (cp/mL) No. (%)	<20	2743 (48%)
	<40	2138 (37%)
	<400	146 (3%)
	Quantifiable	728 (13%)
ARV use (years)	Median (Q1-Q3)	9.4 (5.2-14.5)

Baseline CVD History and Risk Factors

Characteristics	Total (N=7770)	
Total cholesterol (mg/dL)	Median (Q1-Q3)	184 (162-208)
LDL calculated (mg/dL)	Median (Q1-Q3)	107 (87-127)
HDL-C (mg/dL)	Median (Q1-Q3)	48 (39-59)
Systolic BP (mm HG)	Median (Q1-Q3)	122 (113-132)
BMI (kg/m ²)	Median (Q1-Q3)	25.8 (22.8-29.4)
Smoking status, N(%)	Current	1798 (24%)
	Former	1834 (25%)
	Never	3873 (52%)
Family History of CVD, N(%)	No	5913 (79%)
	Yes	1353 (18%)

ART Use Among REPRIEVE Participants by Continent

- NRTI + NNRTI
- NRTI + II
- NRTI + PI
- Other NRTI-containing
- Other NRTI-containing: PI + II
- Other NRTI-containing: Other
- NRTI-sparing
- NRTI-sparing: PI + II
- NRTI-sparing: Other



REPRIEVE Ancillary Objectives and Substudies

Sex-Specific Mechanisms of CVD Risk and Risk Reduction

CKD Ancillary Objective

PREPARE Substudy (A5361s)

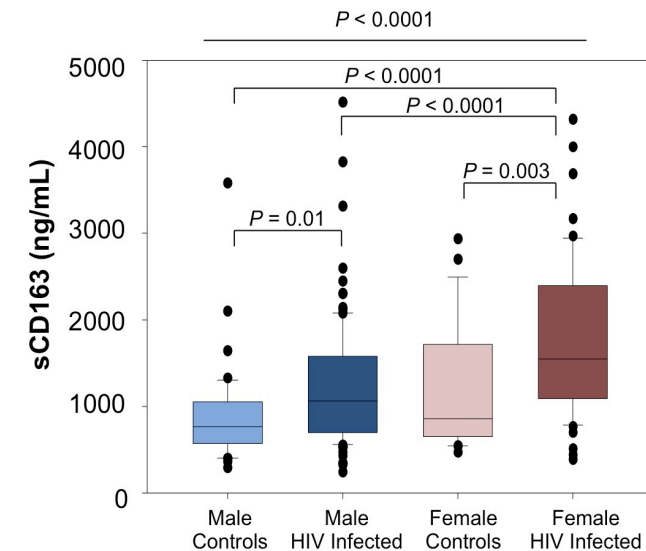
Cardiovascular Disease Risk in HIV-infected Women: Sex-Specific Mechanisms of Risk and Risk Reduction among REPRIEVE Trial Participants

Principal Investigators: Sara Looby, PhD & Markella Zanni, MD

Background: Women with HIV have greater relative rates inflammation than HIV-infected men (see figure below), the mechanism and consequences of this with respect to CVD is unknown.

Aims: To assess the relationship between reproductive aging, immune activation, and cardiovascular disease risk and risk reduction among women with HIV.

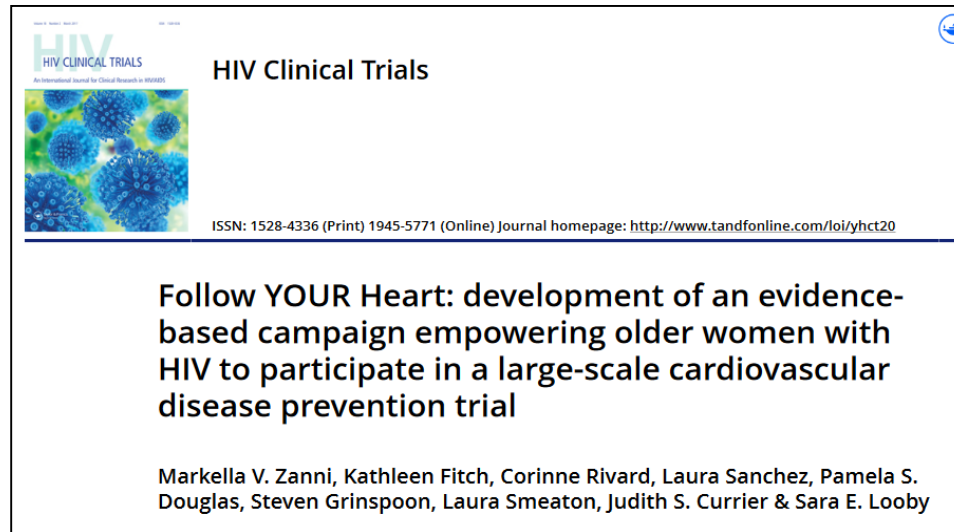
- Among **HIV+ Women and Men:**
 - How do sex-based differences in immune activation influence CVD risk?
 - How do sex-based differences in statin-induced immunomodulation influence statin effects to *reduce* CVD risk?
- Among **HIV+ Women:**
 - How does ↓ ovarian reserve influence immune activation and CVD risk?
 - How does ↓ ovarian reserve influence statin-induced immunomodulation and CVD risk reduction?



Fitch, JID 2013

Supplemental Women's Grant Aim: to design, implement, and test the efficacy of an education-based awareness campaign to augment female enrollment in REPRIEVE.

- Women underrepresented in HIV research
 - women make up 19.2% of participants in ARV trials and 11.1% of participants in CURE trials
- Women underrepresented in CVD preventive care research
 - women make up 25% of participants in CAD prevention trials
 - 29 % of participants in HF prevention trials



- Explored strategies to improve awareness of research studies, as well as factors that enhance research participation, including sustained enrollment in longitudinal trials.
- Surveys among a community sample of women with or at risk for HIV.
 - N=40; mean age 53 ± 13

REPRIEVE Follow YOUR Heart (FYH)

Campaign

COMPONENTS




Follow YOUR Heart

- ♥ Women with HIV are 3 times more likely to have a heart attack than women without HIV.
- ♥ The heart health of women with HIV matters.

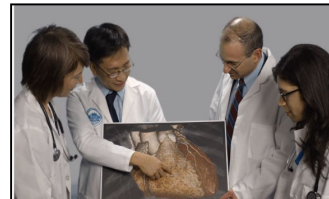
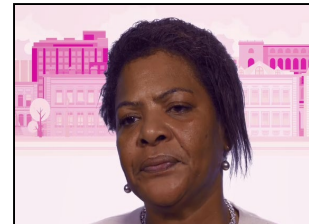
Learn more about the REPRIEVE trial and how to sign up!

www.reprievetrial.org

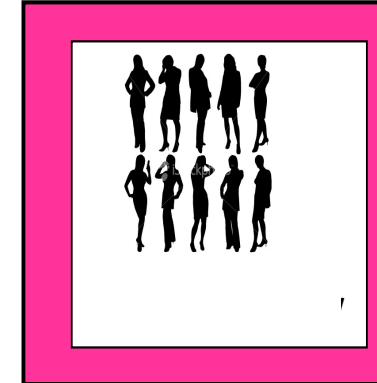
 **REPRIEVE**
Randomized Trial to Prevent Vascular Events in HIV

WEBSITE:

- Participant-centered FYH video
- "My Heart Matters" blog
- Women's CV health resources



Outreach



Press



Health Affairs Blog

HOME TOPICS JOURNAL BRIEFS EVENTS PODCASTS ARCHIVE

ASSOCIATED TOPICS: EQUITY AND DISPARITIES, POPULATION HEALTH, PUBLIC HEALTH

A Reprieve For Women: Embracing Inclusive Scientific Research

Barbra Streisand and Anthony S. Fauci

September 13, 2016



Follow YOUR Heart Video © The General Hospital Corp. All rights reserved.

REPRIEVE CKD Ancillary Objective

Effect of Pitavastatin on Kidney Function in HIV-infected Persons

Principal Investigator: Turner Overton, MD

Background: More recently a decline in HIV-associated nephropathy and increase in comorbid kidney disease likely due to prevalent CKD risk factors in PWH such as Black race, diabetes, hypertension as well as HIV treatment toxicity including history of indinavir use, TDF (proximal tubular injury), use of ritonavir and boosted PIs

AIM 1: Evaluate the effects of pitavastatin 4mg daily on clinically relevant parameters of kidney function.

Aim 2: Assess whether the effect of pitavastatin on eGFR and albuminuria is stronger in high-risk groups.

Aim 3: Determine whether the effect of pitavastatin on kidney function is mediated through anti-inflammatory effects.



National Institute on Aging

PREPARE Substudy

Effects of Pitavastatin on Physical Function

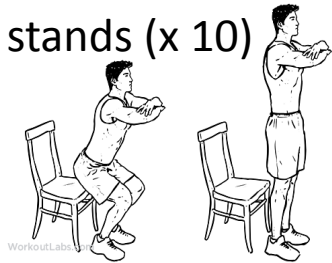
Principal Investigators: Kristine Erlandson, MD and Todd Brown, MD

Background: Physical function appears to decline more quickly in persons living with HIV. A key objective of health for older adults is to maintain a high level of physical function and preserve independence. Through decreased inflammation, statins may have a beneficial effect on muscle function

AIM: Determine the impact of statin therapy on physical function and muscle quality (by fat density on CT scans)

Annual Assessments

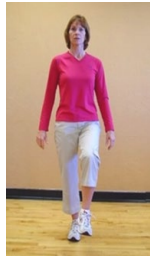
Chair stands (x 10)



4-meter walk



Standing balance

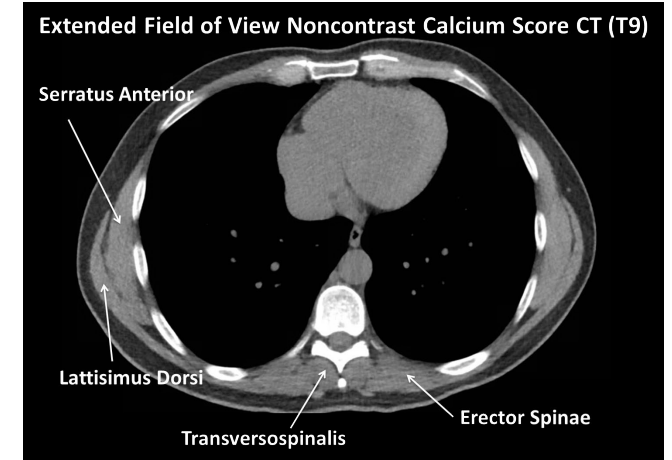
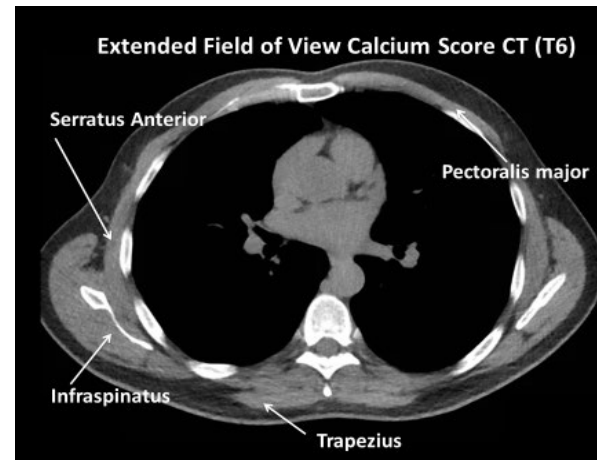


Grip Strength



Muscle Fat Outcome:

Trunk Muscles From Non-contrast Calcium Score CT



No other randomized controlled statin trial has measured objective physical function outcomes past 1 year, although statin therapy is typically prescribed for a decade or more.

Next Steps....Publication of Baseline Data in JID Supplement

1. Intro/overview
2. Baseline kidney function and correlates
3. Baseline muscle function and correlates (PREPARE)
4. Baseline women's reproductive aging and correlates
5. Baseline ART by geographic region in relation to immune virologic status
6. Baseline myocardial steatosis and correlates (REPRIEVE-MR)
7. Baseline transgender characteristics

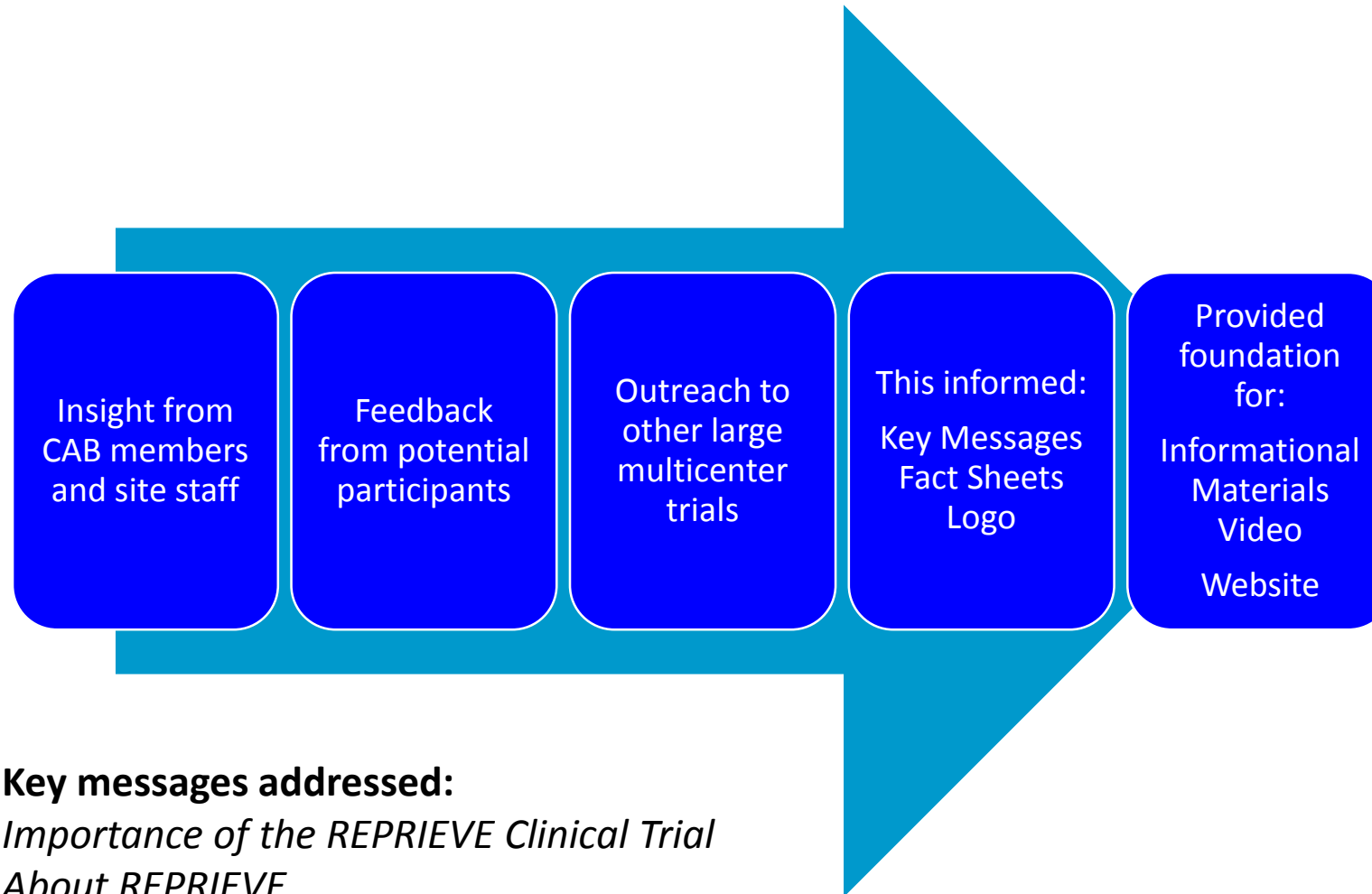
Novel Strategies to Recruit a Multi-
site, International RCT:
Perspectives From the Clinical
Coordinating Center

What Makes REPRIEVE Unique?

- Primary prevention trial
- Cardiovascular study in ID settings
- Number of participants
- Number of clinical sites
- Duration of follow up
- Sex-specific biologic aims and supplemental aim to augment female participation
- Studies evaluating comorbidities in HIV (CKD and frailty)



Developing Approach To Engage Participants



Key messages addressed:

Importance of the REPRIEVE Clinical Trial

About REPRIEVE

Goal for REPRIEVE

Selection of study treatment

REPRIEVE Website www.reprievetrial.org

Home About REPRIEVE » Join the Study » Find a Site Site Resources » Follow YOUR ❤️ Contact

English ▾

Q1. Thank you for your interest in the REPRIEVE Trial. REPRIEVE, which stands for the Randomized Trial to Prevent Vascular Events in HIV is the first large-scale, randomized clinical research trial to test a strategy for heart disease prevention among people living with HIV. Specifically, REPRIEVE will test whether a daily dose of a statin (pitavastatin) reduces the risk of heart disease among people living with HIV. To see if you may qualify for the study, please answer the questions below. If it appears you may qualify, with your permission, we will contact a clinical site near you so that they may contact you about participating in REPRIEVE.

Q4. How old are you?

- Less than 40 years old
- 40-75 years old
- Greater than 75 years old

Prescreening Tool

Participant Information

What You Need to Know About REPRIEVE

48

Length of Participation
48 months on average



of Participants
6,500 enrolling participants



Multiple Locations
100 sites across the U.S. and abroad



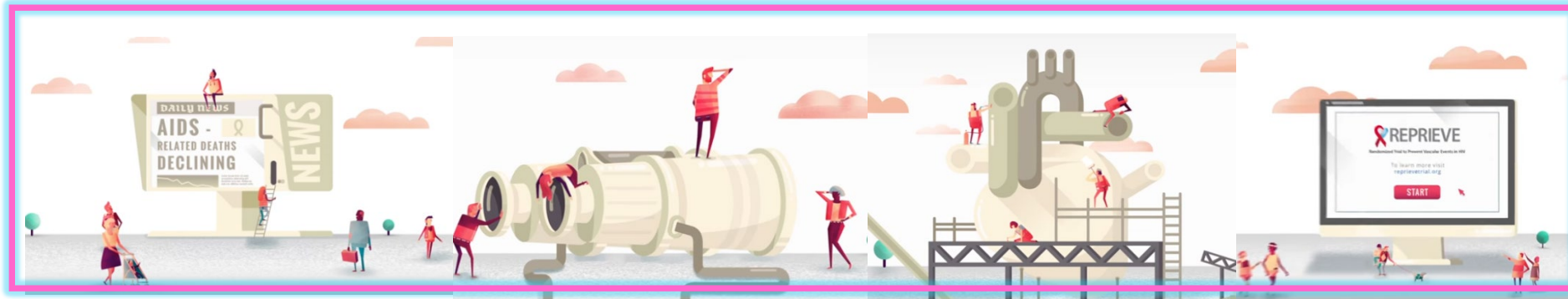
Simple Time Commitment
Visits every 4 months on average



Interactive Site Map

REPRIEVE Videos

- 50 second video, on home page of REPRIEVE website, also distributed to clinical sites to play in waiting room, available on YouTube
- Basic introduction to REPRIEVE
- Main point: REPRIEVE is getting ahead of CVD in HIV, by finding a solution now rather than later



- Video featuring trial participants and CAB members

Social Media: Facebook and Twitter



Profile picture: A red and blue heart with a white pulse line.

Header image: A silhouette of a person with a heart on their chest, set against a yellow circle on a dark background.

TWEETS 633 FOLLOWING 445 FOLLOWERS 553 [Edit profile](#)

REPRIEVE Trial
@reprivetrial

Landmark @NIH-funded trial on #HIV-related #cardiovascular disease prevention. One of largest HIV clinical trials in world. Learn more: reprivetrial.org

#HIVheartchat

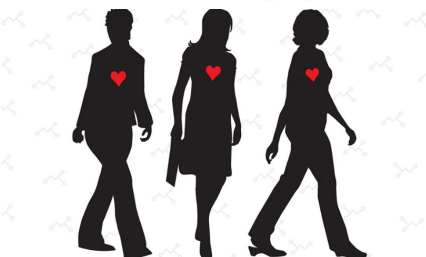


Wednesday, Feb 17 at 1pm EST
#HIVheartchat
hosted by @reprivetrial and @ACTGNetwork



#HIVAgingChat

Hosting Twitter chats about topics related to REPRIEVE with other groups: ACTG, ACRIA



WOMEN WITH HIV
are 3x more likely to have a heart attack than women without HIV.

Tweets from supporting agencies: Women's Heart Alliance and DAIDS



REPRIEVE Trial @reprivetrial · Oct 4
REPRIEVE now has 2000 participants! Dr. Dieffenbach of @NIAIDNews has a special message about this exciting milestone



REPRIEVE Reaches 2,000 Participants!
Dr. Carl W. Dieffenbach, Director of the Division of AIDS (DAIDS), congratulates the REPRIEVE Trial on enrolling 2,000 participants.
youtube.com

Informational Materials



Randomized Trial to Prevent Vascular Events in HIV

Participant Newsletter #1 | Spring 2016



Annual Participant Newsletter

Participant Materials:
Brochure, Infographics,
Flyers, Postcards
English and Spanish

REPRIEVE 4x6 Postcard



PDF Download 4x6 Postcard
Clic aquí para la versión en español

REPRIEVE Informational Brochure

A 2 sided tri-fold brochure with a more detailed overview of REPRIEVE



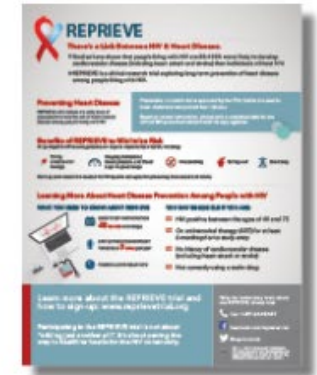
PDF Download LETTER Size (8.5x11) brochure
Clic aquí para la versión en español

REPRIEVE Flyer/Poster



PDF Download LETTER Size (8.5x11) flyer
 PDF Download Poster size (11x17) poster
Clic aquí para la versión en español

REPRIEVE Infographics
A more detailed overview of REPRIEVE



PDF Download LETTER Size (8.5x11) infographics
Clic aquí para la versión en español

Online and Print Media



OPINIONS

REPRIEVE for Heart Disease in HIV

By Steven Grinspoon and Aaron Laxton Why is heart disease increased among people living with HIV?



New Med Could Prevent Heart Disease in People With HIV

Call it a PrEP to protect against heart disease in people with HIV.



NIH to fund first large-scale trial for heart disease prevention among people with HIV

Posted by Steve Lee, Editor Online Only, Top Highlights, Around the Nation



Medical News & Perspectives

Exploring Statins to Decrease HIV-Related Heart Disease Risk

Mike Mitka, MSJ

- Approximately 50 articles about REPRIEVE published between 2014-2017
- Location: In US and internationally
- Target audiences: PWH, clinicians, general public

Engagement is Essential Due to Prolonged Follow Up

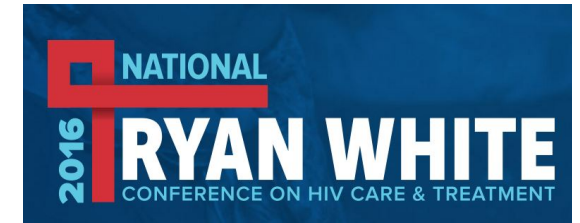
Enrollment Challenges



Team Building!



Promotional Materials Distributed at Conferences



Recruitment Materials Distribution



FREE 1 time order Kit

Description: 50 each of Flyers, Postcards and Brochures. value paid for by Reprieve.

Strategies for Long-term Engagement

Current Participant Engagement Activities

Annual Participant Newsletter

Available in 7 languages



REPRIEVE Tokens of Appreciation



My Heart Matters Blogpost on REPRIEVE Website

<http://www.reprievetrial.org/for-participants/my-heart-matters-blog/>



September 4, 2019

What YOU need to know about the salt in your diet!

By: Corinne Rivard Have you ever been told by your healthcare provider that you need to reduce the salt in your diet? Have you been wanting [...]

May 30, 2019

Tips to Get 30 Minutes of Exercise Every Day

By: Diana Cagliero Exercise is one the best things you can do for your health! While we hear about how exercise can lead to great health [...]

Updated Website

Focus is engagement of participants

Over 7500 Participants Have Joined REPRIEVE!

Here are two of their stories.

**Karina McClanahan,
Dallas Texas, USA**

"Doing something that can help me and others in the future is invaluable. Prevention is the keyword to help to improve quality of life and REPRIEVE is investing into prevent vascular sicknesses that can be fatal to many. It is an honor to be part of the REPRIEVE Study."

REPRIEVE Community Advisory Board

Quarterly meetings via teleconference, monthly email updates



Engagement Activities: Site Teams and Investigators

2 meetings held annually at CROI and ACTG Annual Network Meeting



Sites are recognized for the efforts to enroll in REPRIEVE and team awards were handed out to top-performing sites!



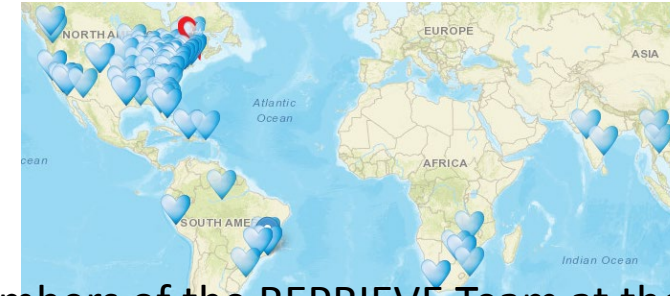
Site 11201: Durban International Clinical Research Site

Located in Durban, South Africa, site 11201 has been a tremendous contributor to REPRIEVE, enrolling a total of 161 participants! Having successfully retained 98% of their participants, we asked the Durban Int'l team to share their retention tips:

- Ensure adequate staff time and effort to retention
- Host gatherings for study participants
- Perform random acts of kindness to participants.

Thank you, Durban Int'l team, for all your efforts in REPRIEVE!

REPRIEVE Ambassador Initiative



Members of the REPRIEVE Team at the Clinical Coordinating Center are making an effort to visit REPRIEVE sites

Goal: Ensure that REPRIEVE sites feel supported and to identify any barriers to retention.

Visits consist of 1-hour informal meetings with REPRIEVE team members to discuss trial updates, retention, protocol amendment, and address any questions from the site.

To date: 43 sites visits have taken place

Additional strategies include: provider slide presentations, monthly site calls, monthly site newsletters with Site Teams featured, biannual site evaluations, monthly score cards, Retention Champion Initiative

Summary

- Traditional and nontraditional RFs increase CVD risk: Statins are a proven strategy for 1° prevention in inflammatory atherosclerosis
- In HIV, the importance of inflammation is manifest by excess CV risk and non-calcified high-risk plaque w immune activation
 - Modulation of both risk pathways is necessary to prevent CVD in HIV
- REPRIEVE is the first major CVD prevention trial in HIV and the largest ever focused on HIV-related CVD
 - New paradigm of research geared toward preventing in the long-term chronic comorbidities (kidney function, muscle function) associated with HIV
- REPRIEVE will inform standard of care in HIV and have implications for treatment of other inflammatory CVDs
- Novel strategies are needed for successful accrual and continued engagement of a trial of this magnitude

REPRIEVE Core Team

Principal Investigators:

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Udo Hoffmann, MD, MPH
Heather Ribaud, PhD

Biostatisticians:

DAIDS Pharmacists:

Field Representatives:

Lab Technologists:

Lab Data Managers:

Data Managers:

NHLBI Program Officer:

NIAID Medical Officer:

Project Manager:

Clinical Trials Specialists:

Community Scientific Committee:

Co-Investigators:

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Allergy and
Infectious Diseases

