Atherosclerotic Cardiovascular Disease in HIV: Special Focus on Transgender and Cisgender Women Living with HIV

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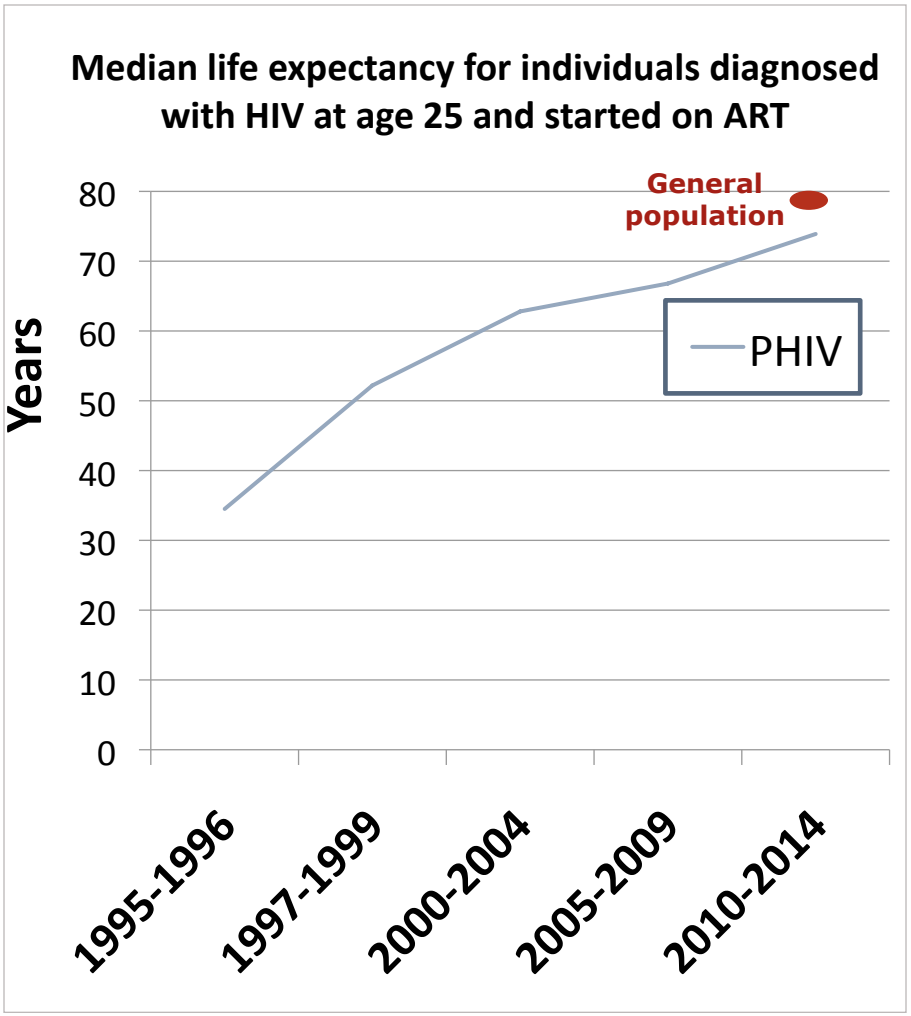
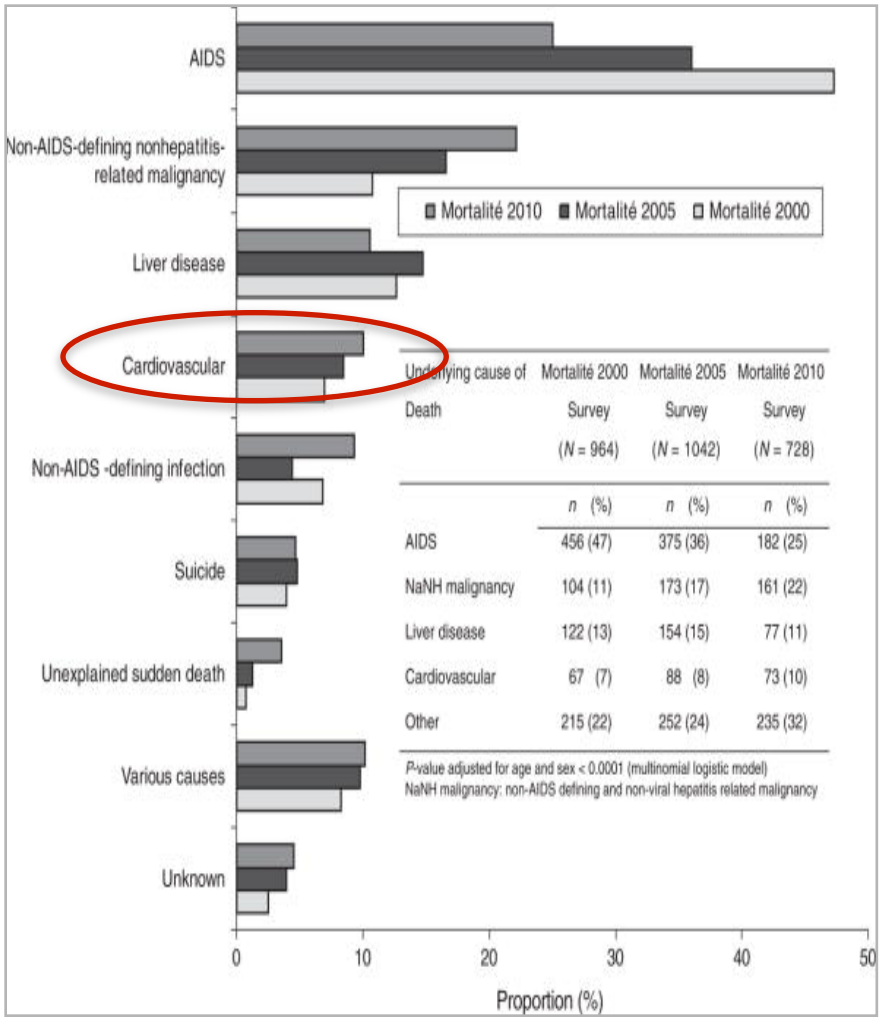
No disclosures

Outline

- Atherosclerotic Cardiovascular Disease (ASCVD) in HIV
  - Heightened ASCVD risk among PHIV
  - Mechanisms of ASCVD among PHIV
  - Prevention and Treatment Strategies
- ASCVD risk among transgender women with HIV (WHIV)
- ASCVD risk among cisgender WHIV

Life expectancy is increasing for PHIV on ART and the percentage of deaths due to CVD is rising among PHIV





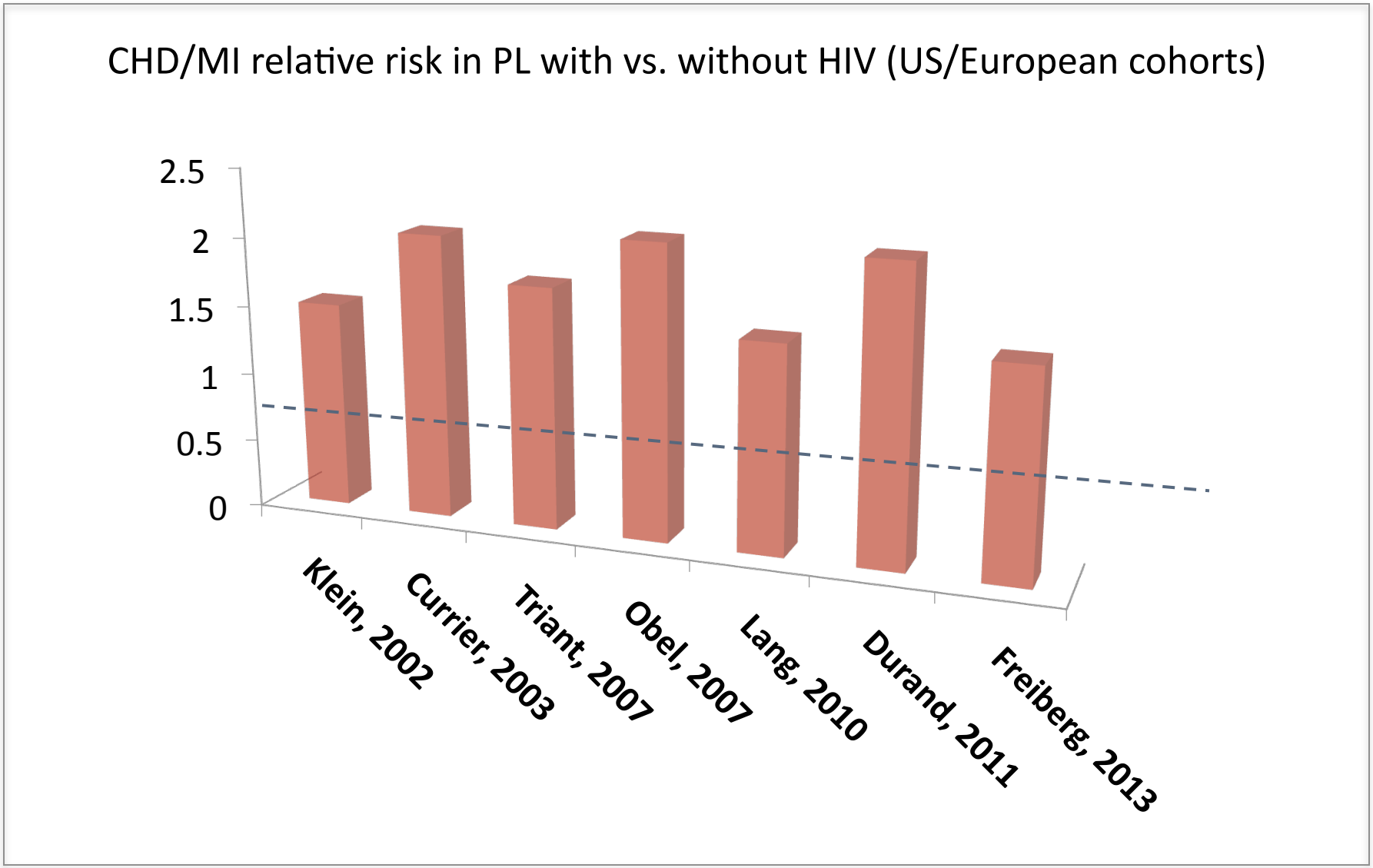
Underlying cause of Death	Mortalité 2000 Survey (N = 964)	Mortalité 2005 Survey (N = 1042)	Mortalité 2010 Survey (N = 728)
	n (%)	n (%)	n (%)
AIDS	456 (47)	375 (36)	182 (25)
NaNH malignancy	104 (11)	173 (17)	161 (22)
Liver disease	122 (13)	154 (15)	77 (11)
Cardiovascular	67 (7)	88 (8)	73 (10)
Other	215 (22)	252 (24)	235 (32)

P-value adjusted for age and sex < 0.0001 (multinomial logistic model)
NaNH malignancy: non-AIDS defining and non-viral hepatitis related malignancy

Slide adapted from Markella V. Zanni
Obel et al. *Annals of Int Med* 2016

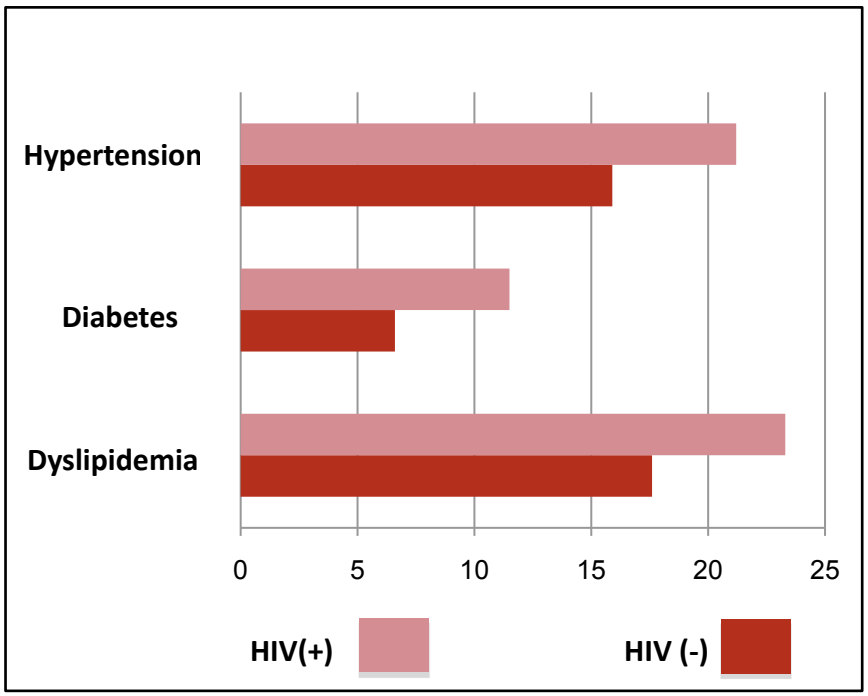
Slide adapted from Markella V. Zanni
Morlat eta al. AIDS 2014

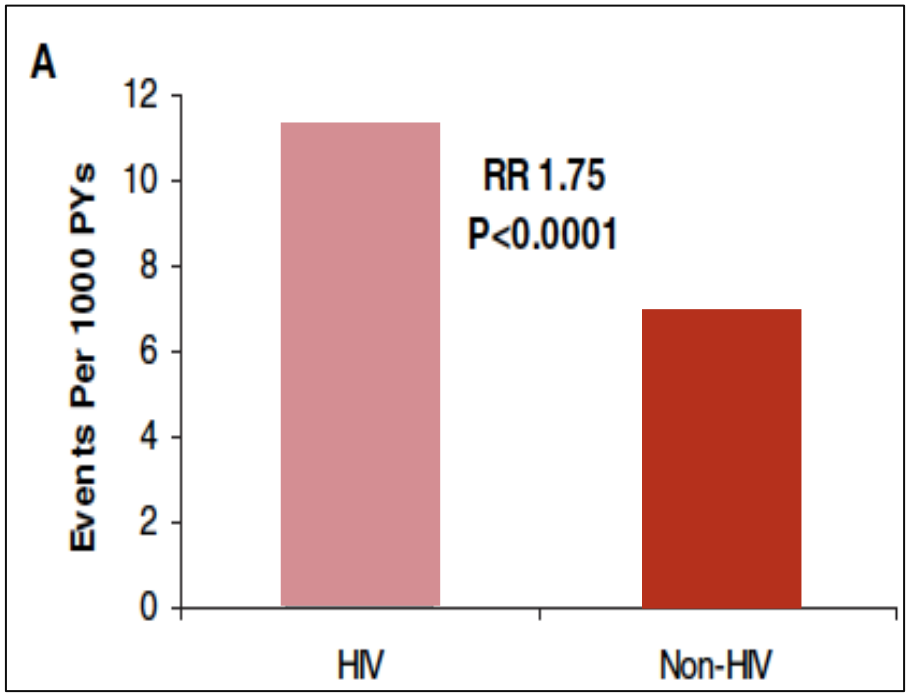
Myocardial infarction risk is increased among PHIV



Slide adapted from Zanni/ Srinivasa /Grinspoon

Increased traditional risk factors account for only a portion of CVD risk in HIV



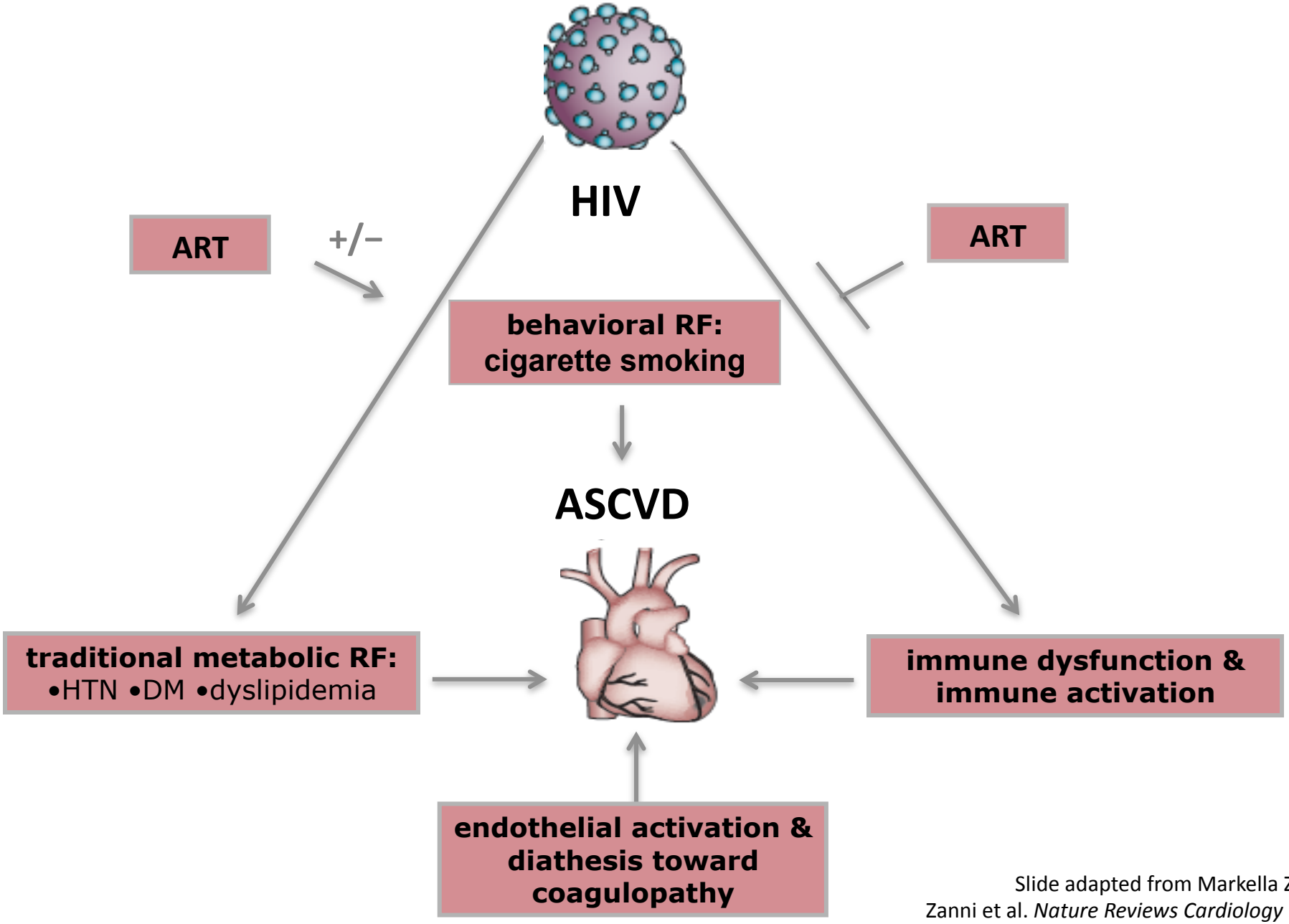


Diabetes, hypertension, and dyslipidemia, though increased, account for only part of the excess risk

Rotger et al. *Clin Infect Dis*. 2013

Slide Adapted from Steven Grinspoon
Triant et al. *JCEM* 2007

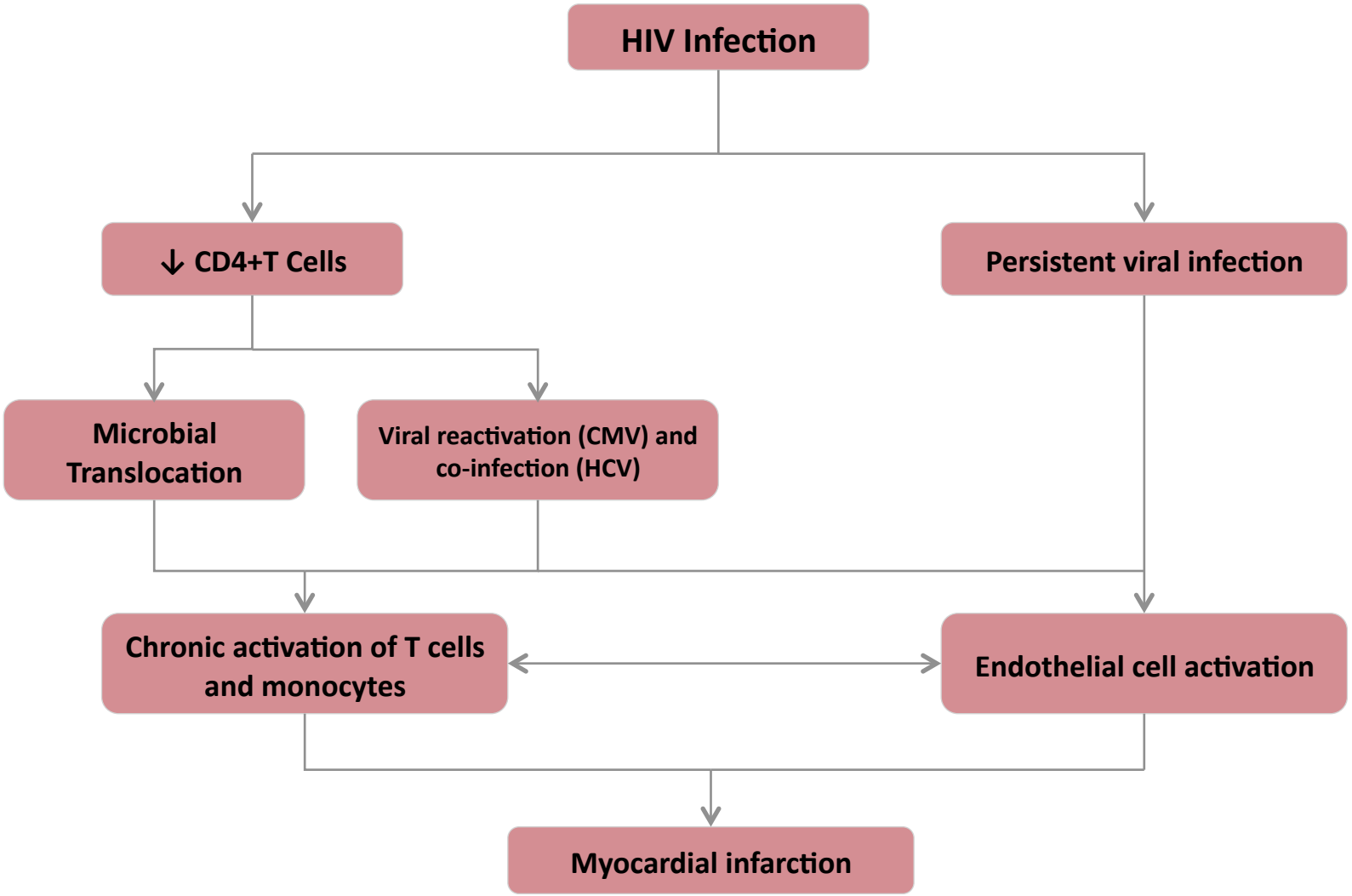
Mechanisms of ASCVD risk in HIV



Slide adapted from Markella Zanni

Zanni et al. *Nature Reviews Cardiology* 2014

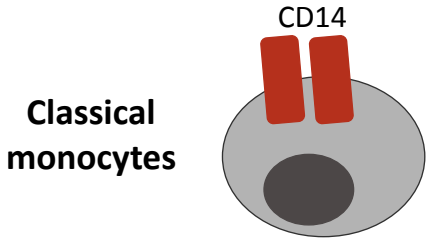
HIV-infection is a state of both immune activation and suppression



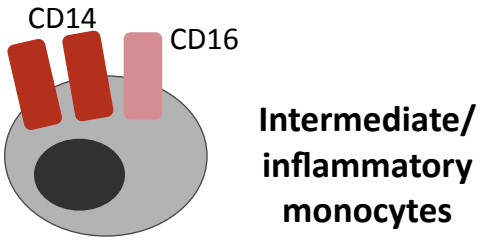
Slide adapted from Steven K. Grinspoon
Hsue et al. *Journal of Infectious Diseases* 2012

Monocytes can be classified into three distinct subsets based on cell surface expression of CD14 and CD16

- Three distinct subsets:
  - Classical: CD14++CD16 –
  - Intermediate/ inflammatory: CD14++ CD16+
  - Non-classical/ patrolling: CD14+ CD16++

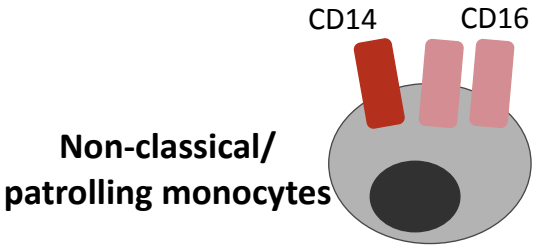


- **Classical monocytes** engulf and present antigen; comprise the largest percentage of monocytes in the bloodstream

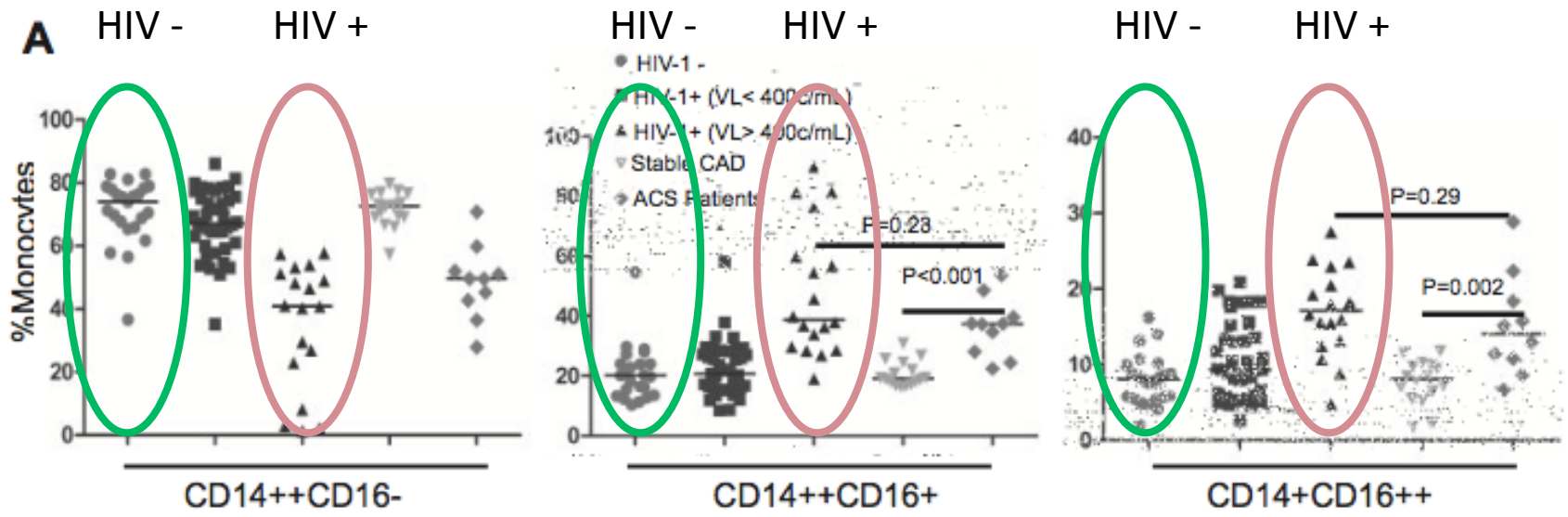


- **Intermediate/inflammatory monocytes** have a pro-inflammatory cytokines production profile in response to stimulation with bacterial TLR ligands

- **Non-classical/ patrolling monocytes** can recognize viral products (and secrete IL6 and IL8 in response to viral products) and hone to the vascular endothelium via expression of CX3CR1



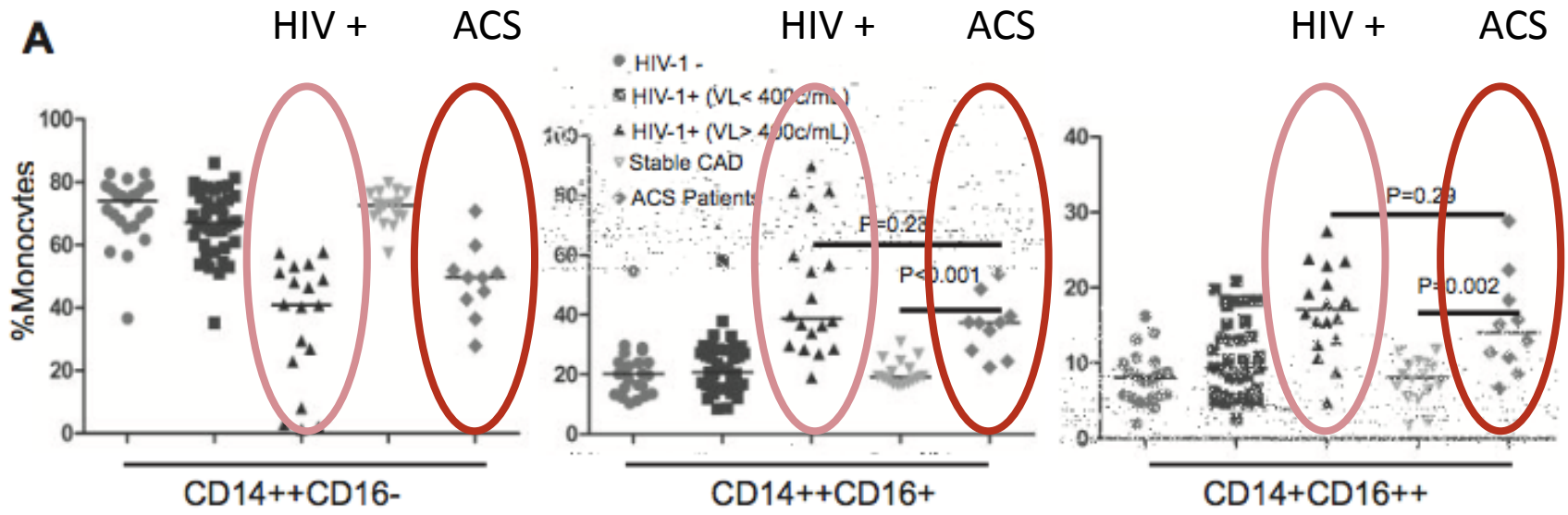
PHIV have an altered monocyte phenotype with increased percentages of inflammatory (CD14++CD16+) monocytes and patrolling (CD14+CD16++) monocytes



Classical monocytes | Inflammatory monocytes | Patrolling monocytes

Funderburg et al. *Blood* 2012

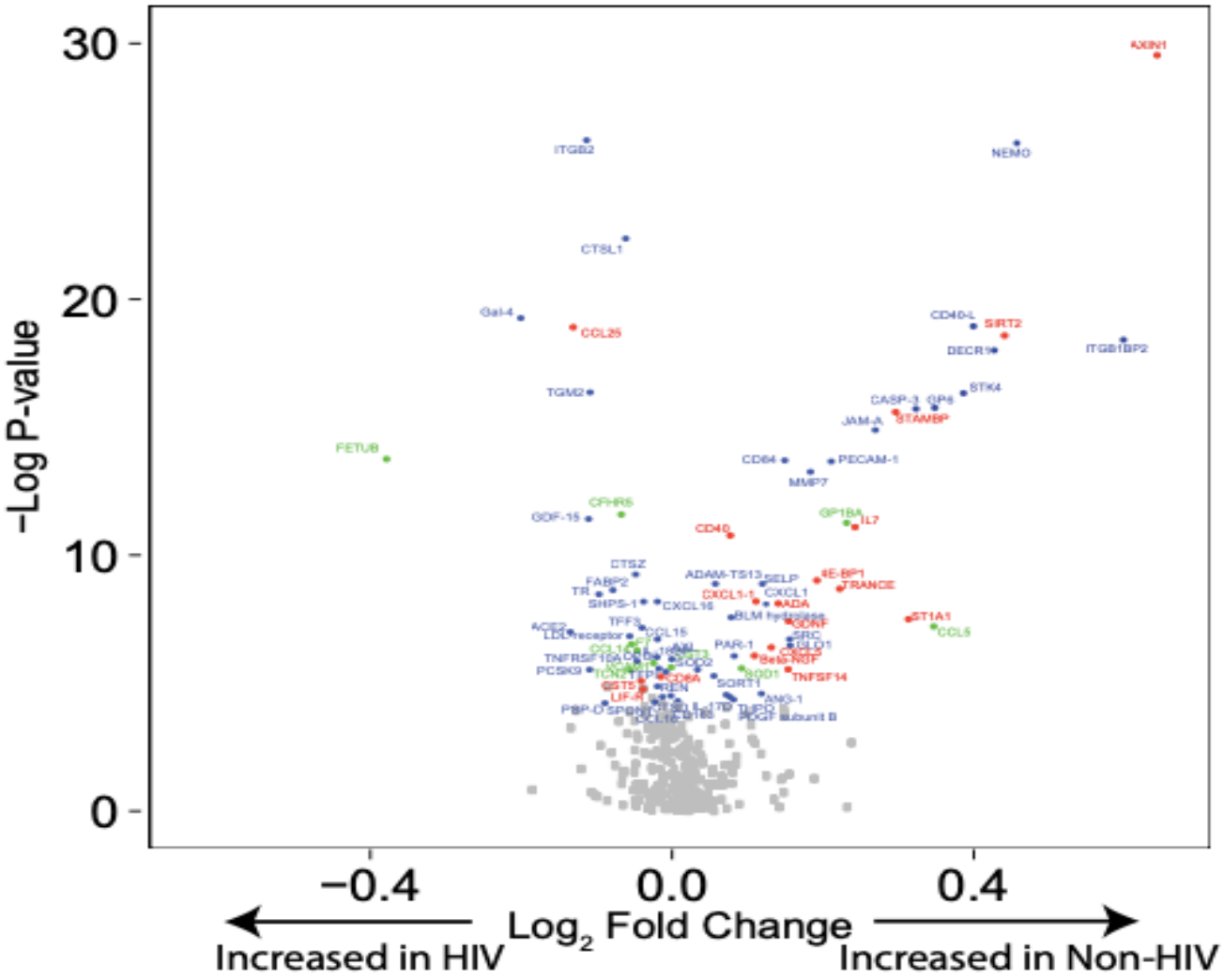
The altered monocyte phenotype in PHIV is similar to the monocyte phenotype seen among patients without HIV presenting with acute coronary syndrome



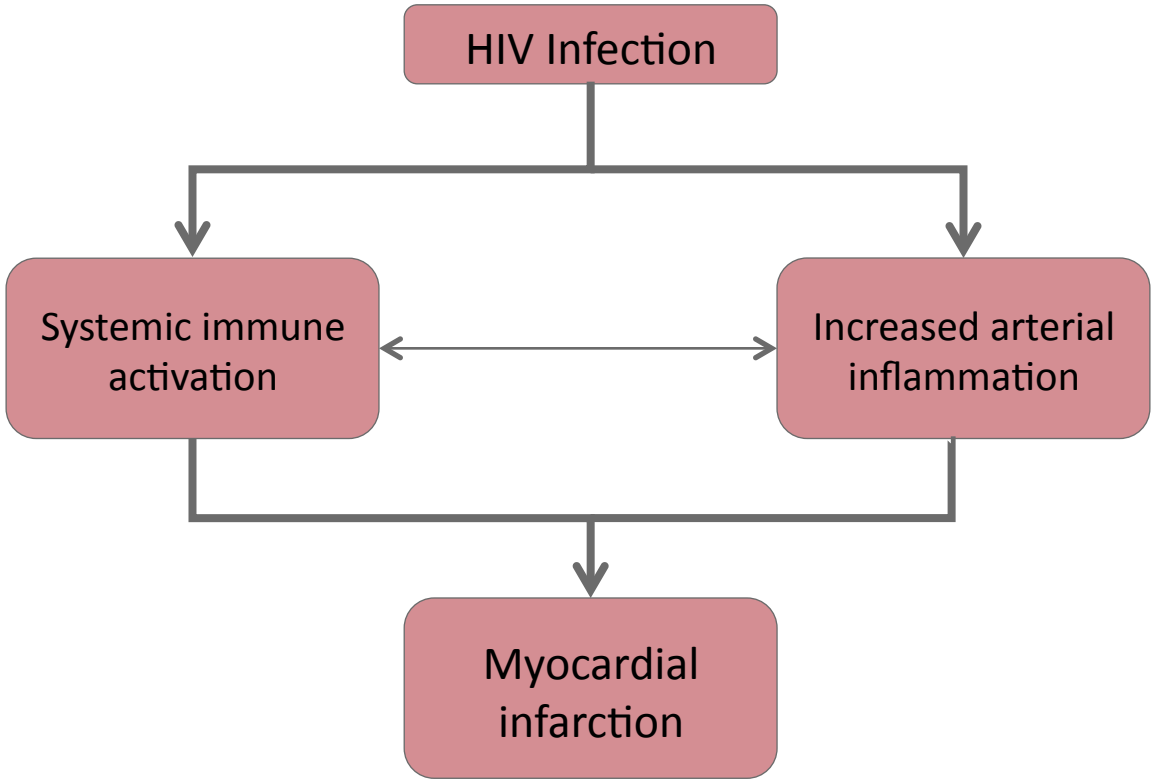
Classical monocytes | Inflammatory monocytes | Patrolling monocytes

Funderburg, et al. *Blood* 2012

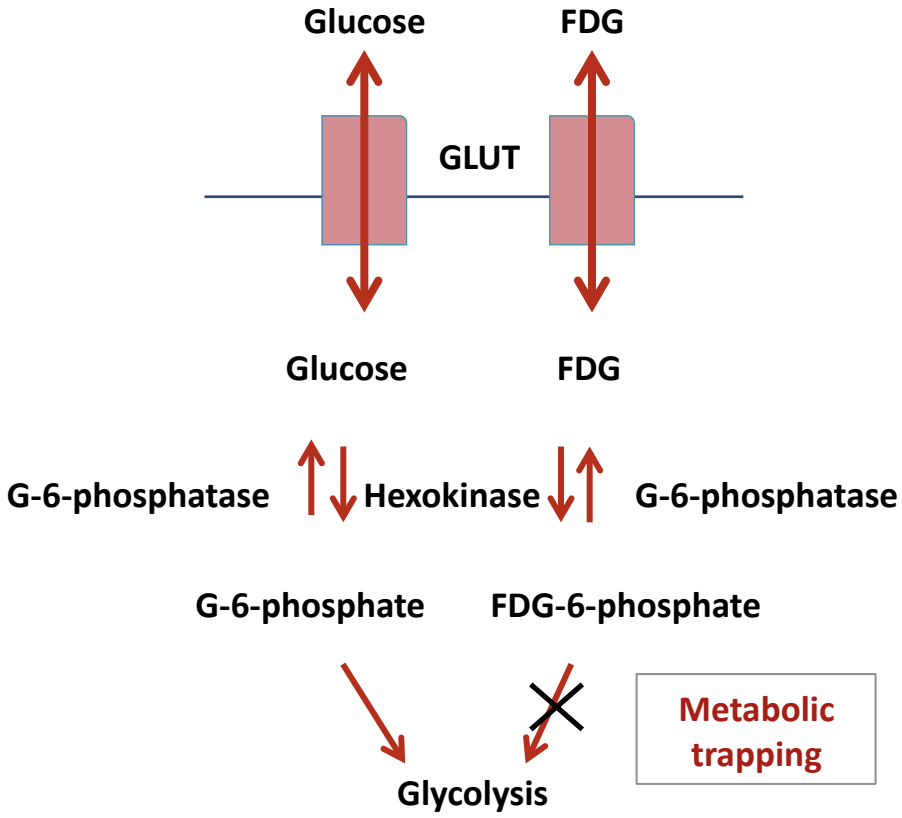
PHIV differentially express proteins relevant to ASCVD, such as proteins involved in collagen processing, platelet and immune cell activation



defillippi et al. *JID* 2020

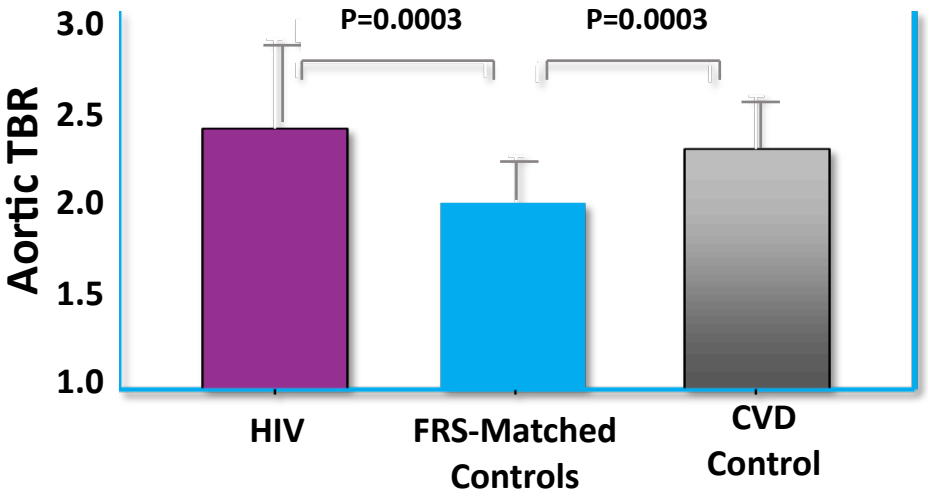

HIV Infection
Systemic immune activation
Increased arterial inflammation
Myocardial infarction

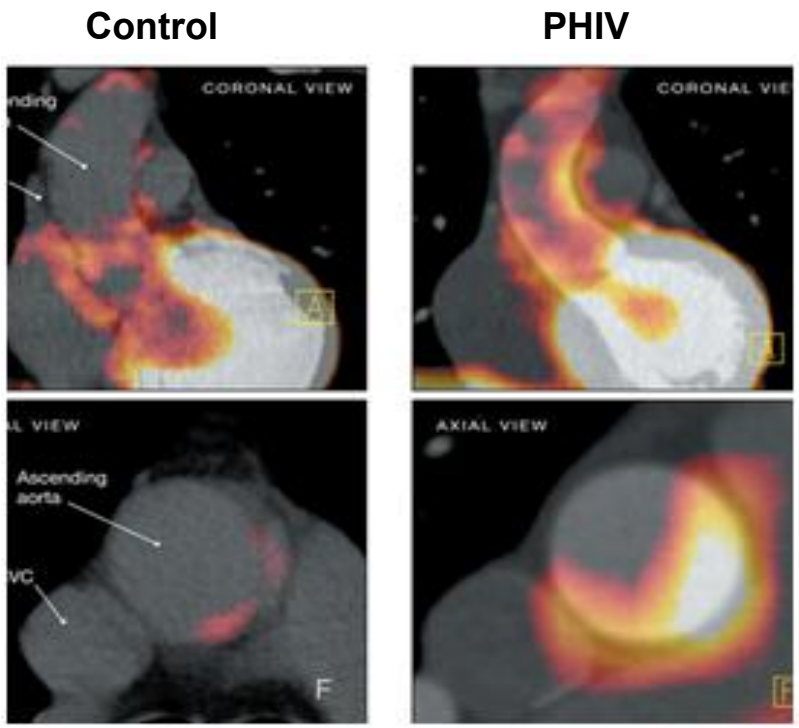
^{18}F-FDG is taken up by metabolically active cells and therefore is taken up by macrophages (which are metabolically active) in the arterial wall, permitting the use of ^{18}F-FDG to image arterial inflammation



Tarkin et al. *Nature Review Cardiology* 2014

PHIV have higher aortic ^{18}F-FDG uptake compared to controls





TBR>1.7 is associated with 40% reduction in CVD event free survival over 3 yrs

TBR>2.25 is associated with increased CVD risk over 5 yrs

Rominger 2009, Figueroa 2011

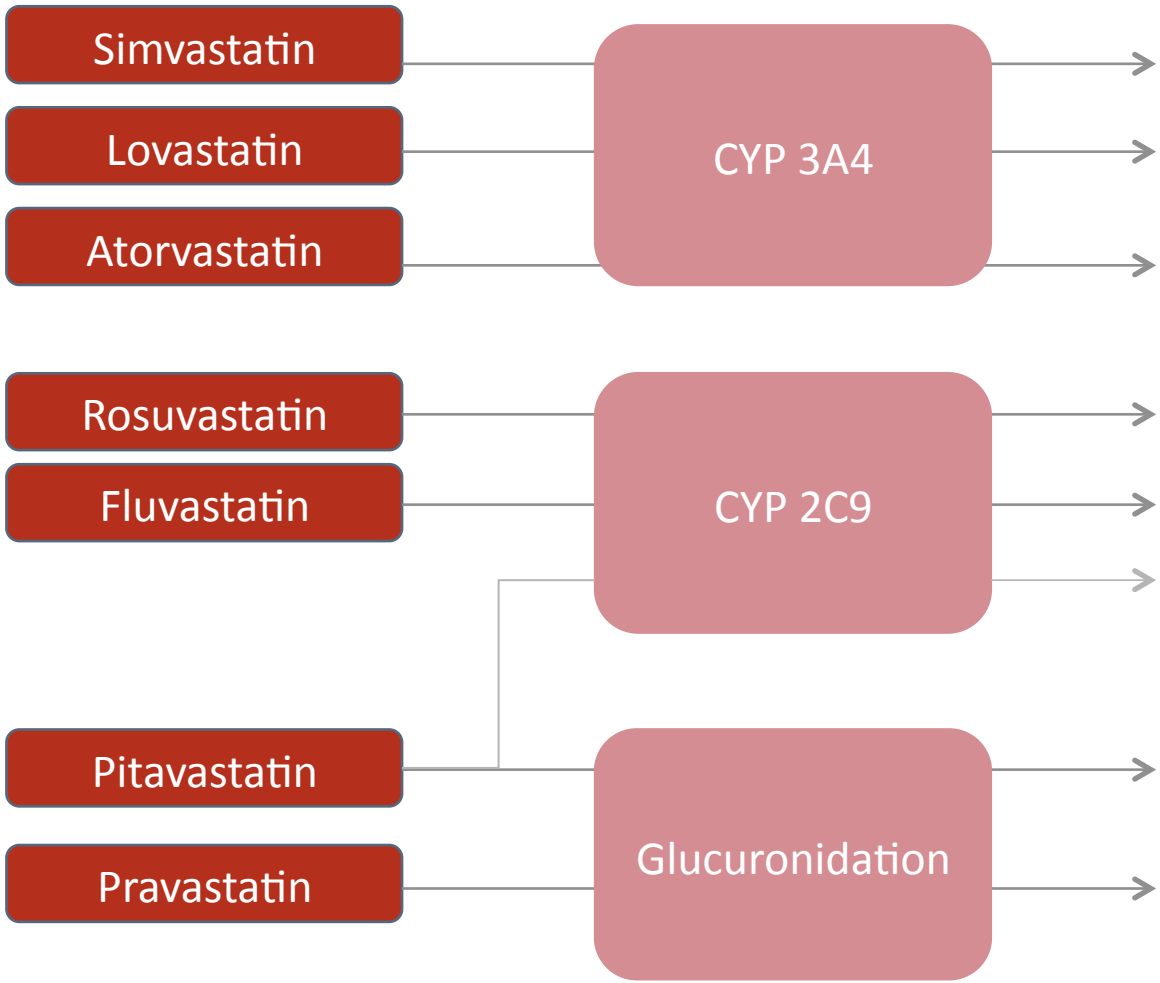
Slide modified from Steven Grinspoon
Subramanian et al. *JAMA* 2012

Prevention of ASCVD in HIV

- Lifestyle Optimization
  - Smoking cessation
  - Diet and exercise

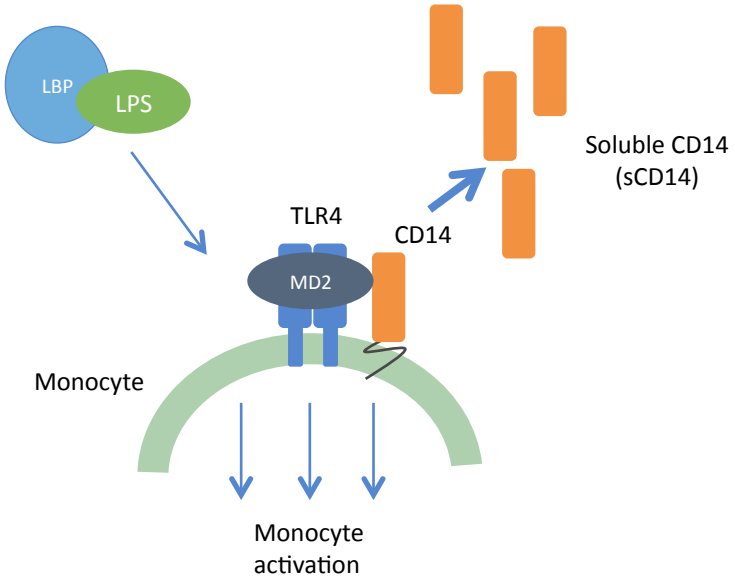
- Pharmacotherapies
  - Statin therapy
  - Immune-modulatory therapies
  - Anti-thrombotic therapies
  - Growth hormone releasing hormone
  - Therapies targeting comorbidities such as diabetes and hypertension

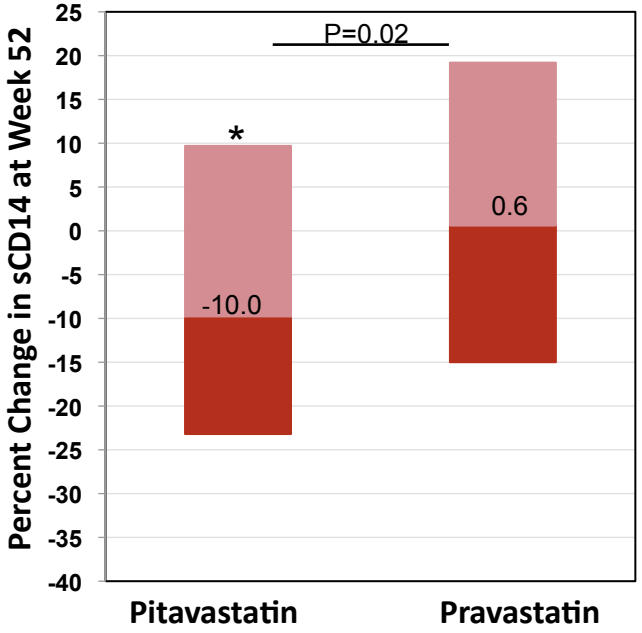
Statin initiation among PHIV needs to be done within the context of understanding the potential drug-drug interactions with ART



Chauvin et al. Clin Pharmacokinet 2013

Statin therapy can significantly decrease markers of systemic immune activation and arterial Inflammation in HIV independent of its LDL-C lowering effects



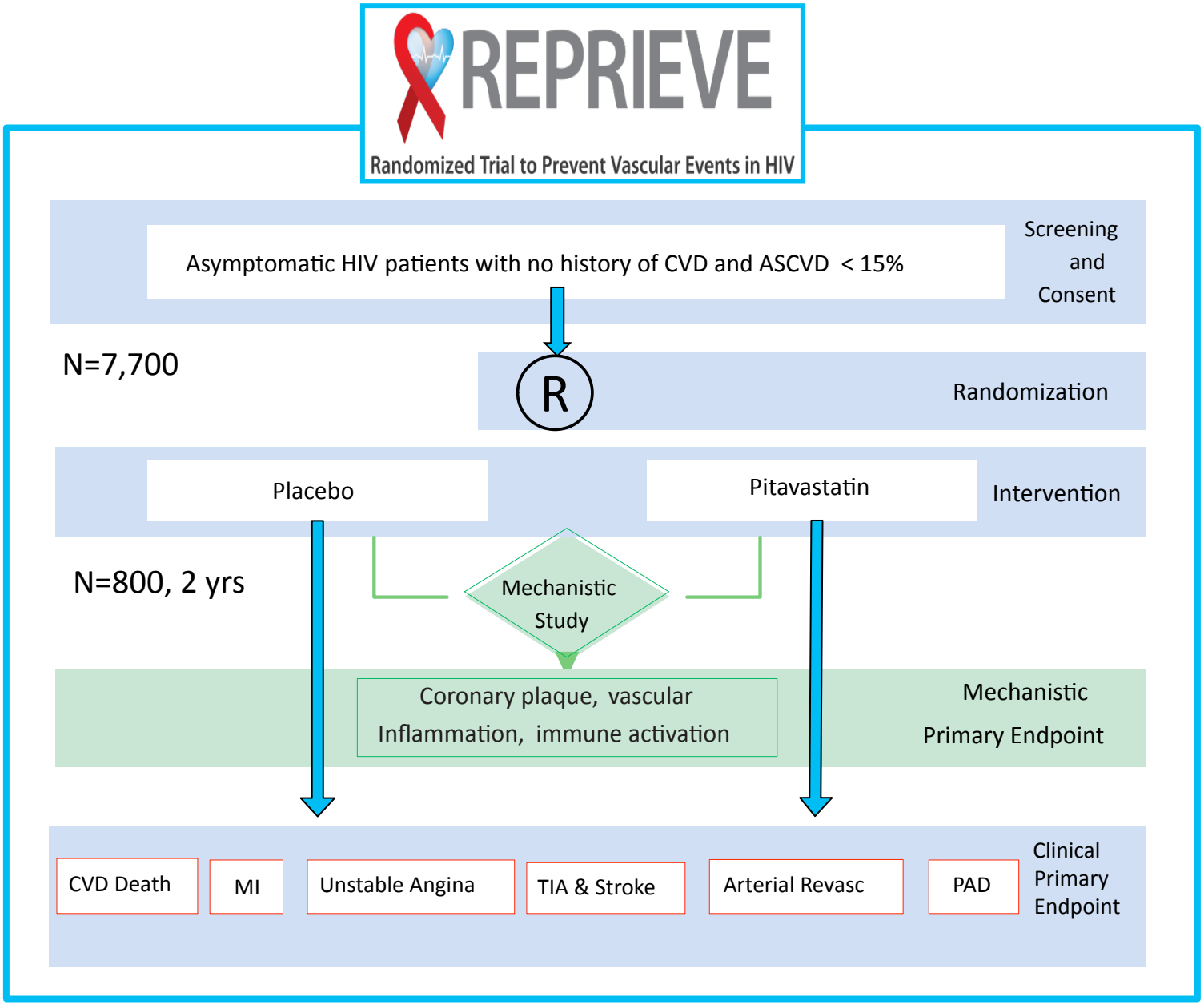


*P<0.05 for within group difference

sCD14 has been found to be a predictor of progression of ***subclinical atherosclerosis*** and ***mortality*** in PHIV

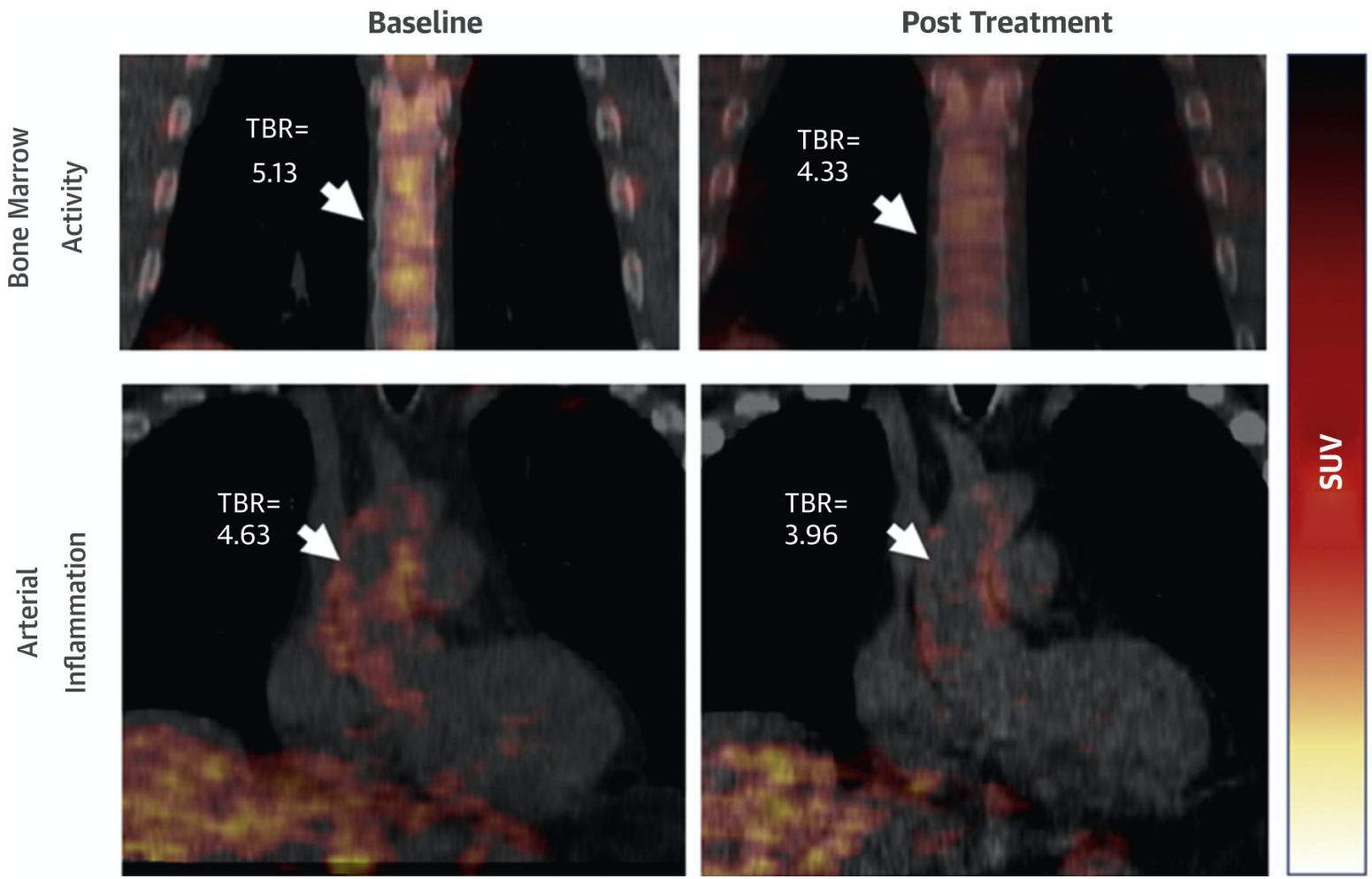
Kelesidis, et al. *Journal of Infectious Diseases*, 2012.
Sandler, et al. *Journal of Infectious Diseases*, 2011

Toribio et al. *AIDS* 2017



Slide Adapted from Steven Grinspoon

IL-1β inhibition reduces arterial inflammation in HIV

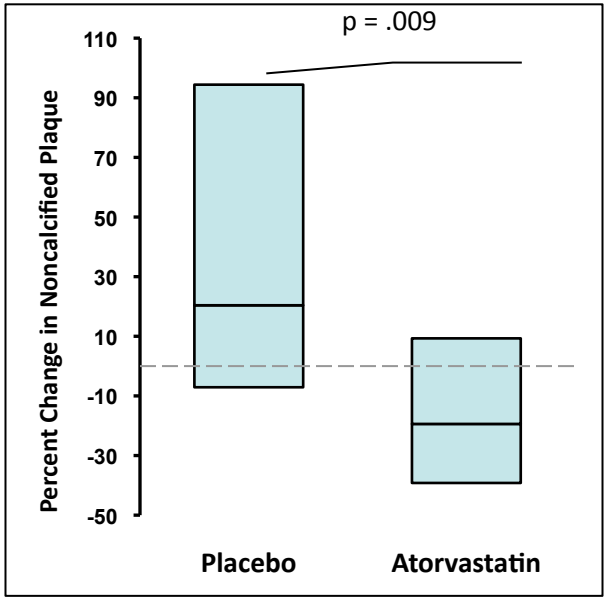


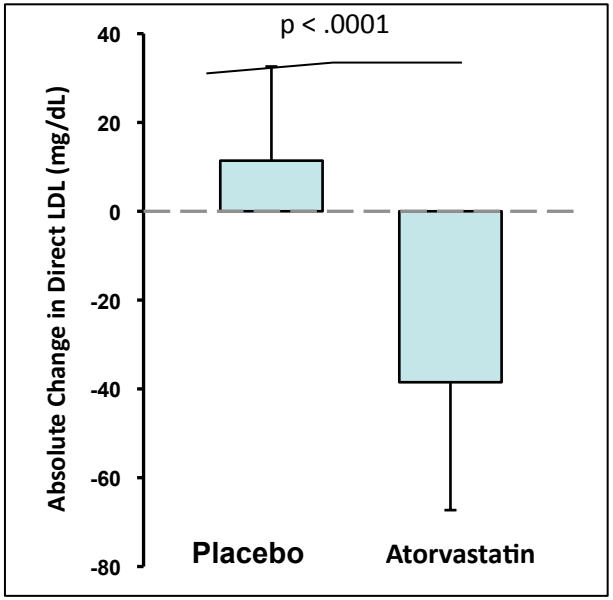
Hsue et al. *JACC* 2018

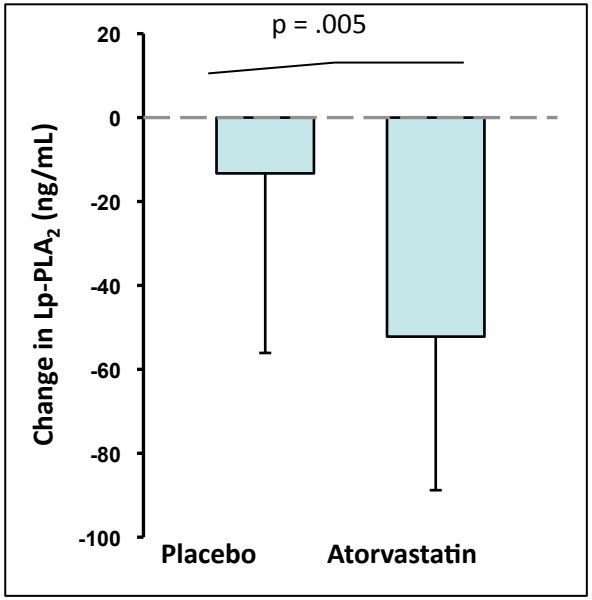
Treatment and Secondary Prevention of ASCVD in HIV

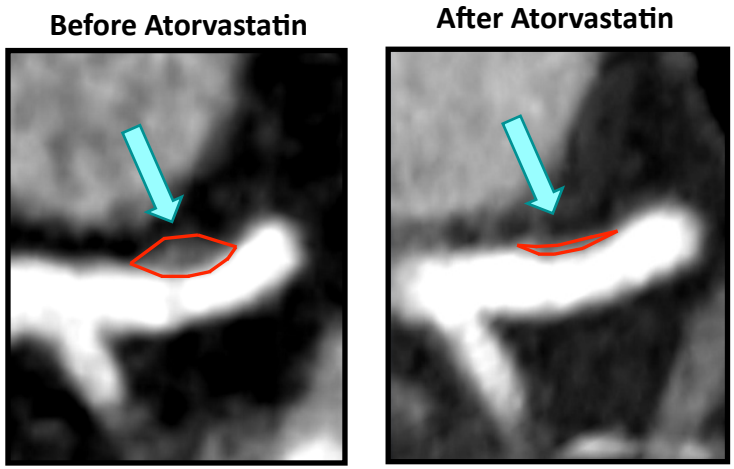
- Percutaneous coronary interventions
- Other revascularization procedures (CABG)
- High-intensity statin therapy
- Anti-thrombotic therapies

Statins decrease coronary artery plaque volume in HIV







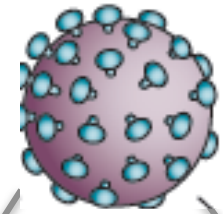


Decreasing non-calcified plaque in proximal left anterior descending (LAD) coronary artery in patient on atorvastatin for 12 months.

Slide modified from Steven K. Grinspoon

Lo et al., *Lancet HIV,* 2015

Summary of Part I



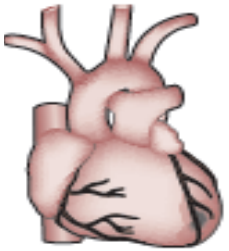
HIV

Avoid Metabolically Unfriendly ART: PIs +/−

ART

Smoking Cessation

ASCVD



- Life-style modification
- Targeted therapies (i.e DLD, DM and HTN meds)
- GHRH

-Use ART that reduces immune activation: INSTI
- Statin therapy also reduces immune activation

- Not enough evidence to recommend anti-platelet therapy for primary prevention

What is gender identity, incongruence, and dysphoria?

- **Gender identity** is an individual's sense of being male, female, a combination, or neither male or female
  Examples: Transgender, Non-binary, Cisgender

- **Gender incongruence** is a marked and persistent incongruence between an individual's **gender identity** and their assigned sex or gender

- **Gender dysphoria** is marked distress and/or discomfort due to **gender incongruence**

Poll Question 1

Adults in the US who identify as being transgender

Transgender women in the US

Sex Assigned At Birth

Gender Identity or Expression

4 out of 10 transgender women have attempted suicide

3 out of 10 transgender women have engaged in sex work

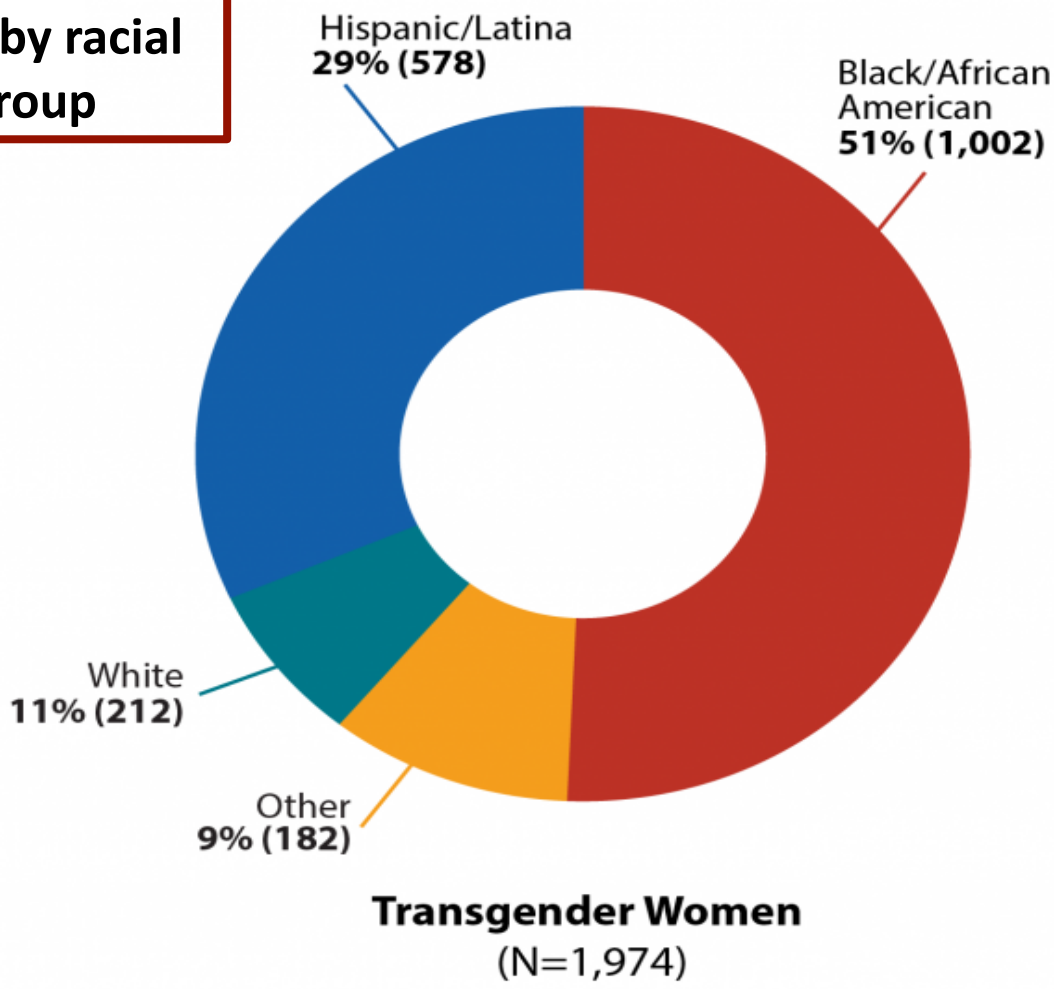
3 out of 10 transgender women are living in poverty

2-3 out of 10 transgender women are living HIV

2015 US Transgender Survey; Baral et al. Lancet Infect Dis 2013; Poteat, et al., Curr Opin HIV AIDS 2018; Herbst et al. AIDS Behav 2008

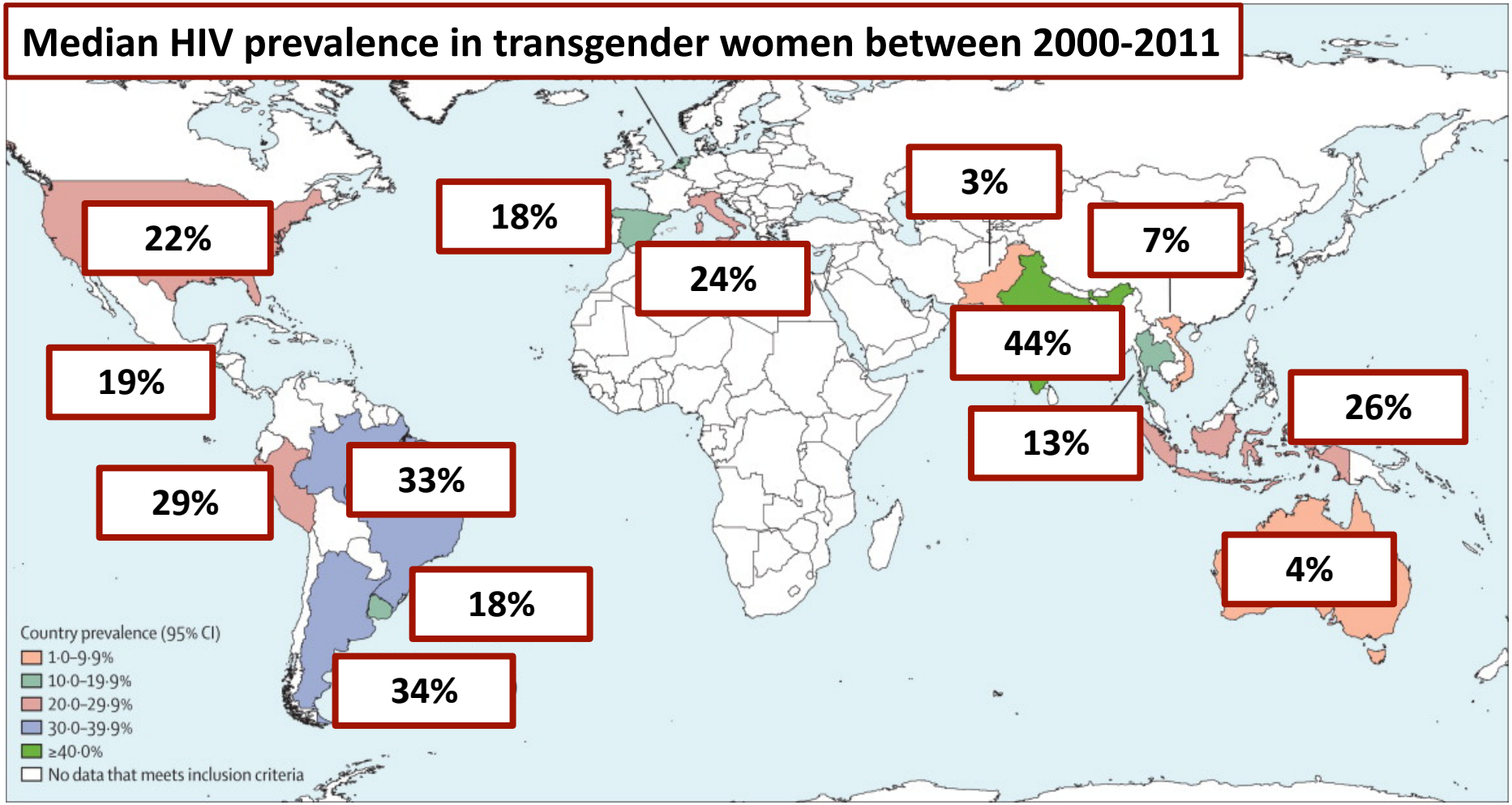
HIV prevalence is highest among Black/African American and Hispanic/Latina transgender women

HIV prevalence by racial and/or ethnic group



Clark et al. AIDS Behav 2017; Becasen et al. AJPH 2019

Prevalence of HIV among transgender women is increased globally



Baral et al. Lancet ID 2013; Poteat et al. Curr Opin HIV AIDS 2018; Herbst et al. AIDS Behav 2008

Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy

Results From a Large Cohort Study

Table. Standardized Incidence Ratios for Acute Cardiovascular Events in Transwomen and Transmen Receiving Hormone Therapy

Acute Cardiovascular Events	OCs (IR)*	Using Women as Reference		Using Men as Reference	
		ECs	SIR (95% CI)	ECs	SIR (95% CI)
Transwomen					
Stroke	29 (127)	12.01	2.42 (1.65–3.42)†	16.08	1.80 (1.23–2.56)†
Myocardial infarction	30 (131)	11.38	2.64 (1.81–3.72)†	38.03	0.79 (0.54–1.11)
Venous thromboembolism	73 (320)	13.22	5.52 (4.36–6.90)†	16.04	4.55 (3.59–5.69)†
Transmen					
Stroke	6 (55)	3.49	1.72 (0.70–3.58)	4.10	1.46 (0.59–3.04)
Myocardial infarction	11 (100)	2.98	3.69 (1.94–6.42)†	10.99	1.00 (0.53–1.74)
Venous thromboembolism	2 (18)	4.84	0.41 (0.07–1.37)	5.56	0.36 (0.06–1.19)

ECs indicates expected cases; IR, incidence rate; OCs, observed cases; and SIR, standardized incidence ratio.
*Per 100 000 person-years.
†Significant finding.

Nota et al. *Circulation* 2019

Poll Question 2

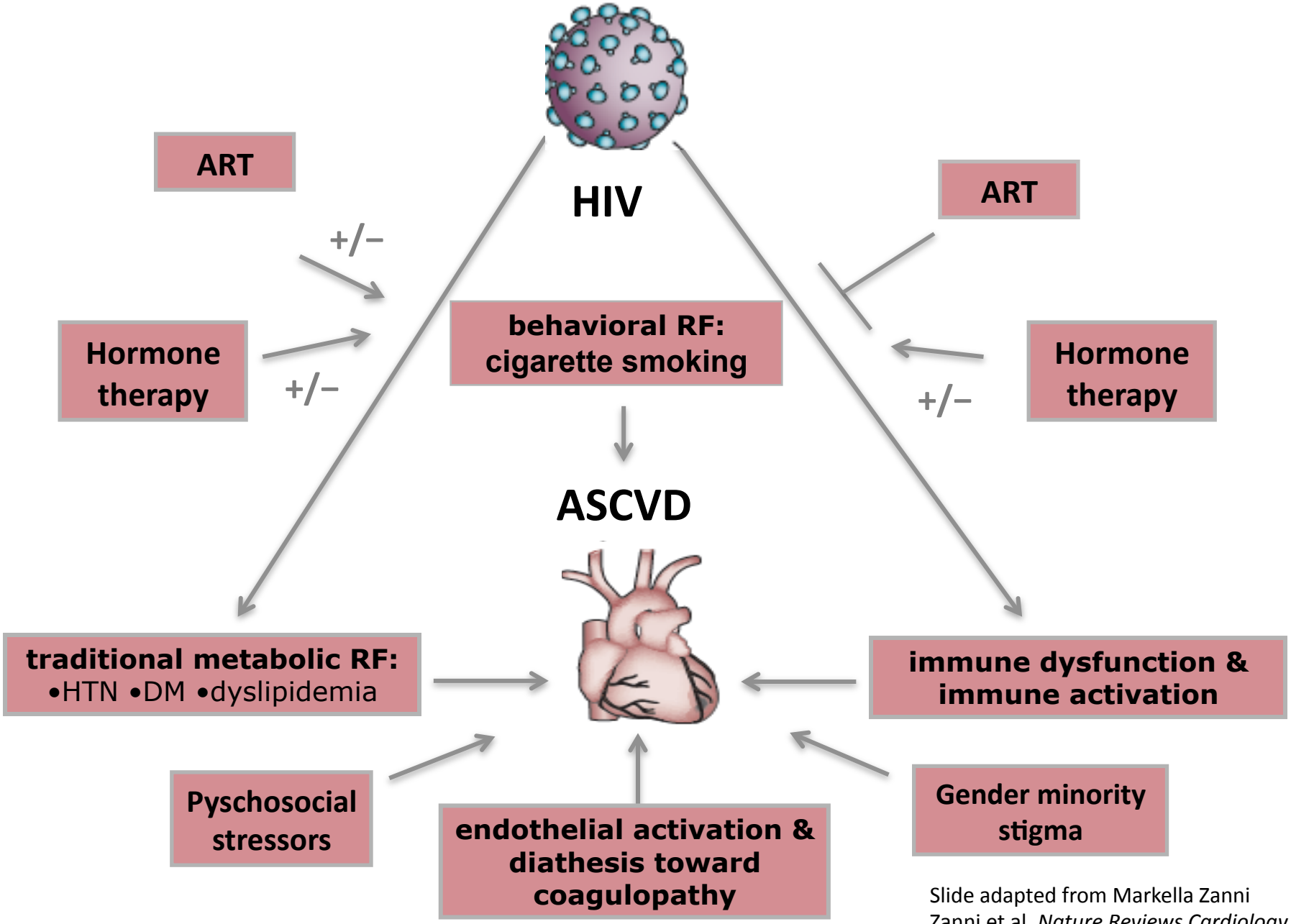
ASCVD risk calculation among Transgender WHIV dependent on how sex variable in calculators is chosen

Table 3. Associations Between Sex and Gender and Elevated CVD Risk Scores Among 221 Transgender Women, 2,983 Cisgender Women, and 13,467 Cisgender Men Alive and Engaged in Continuity HIV Care in the CNICS, 2014–2018 (or contributing cohort-specific administrative censoring date)*.

	Pooled Cohort Equation (PCE)				Framingham Risk Score (FRS)			
	Crude		Adjusted*		Crude		Adjusted*	
	Prevalence Ratio	95% CI	Prevalence Ratio	95% CI	Prevalence Ratio	95% CI	Prevalence Ratio	95% CI
Transgender Women Classified by Birth Sex† Compared to:								
Cisgender Women	1.03	(0.65, 1.63)	2.52	(1.08, 5.86)	1.06	(0.79, 1.43)	2.58	(1.71, 3.89)
Cisgender Men	0.77	(0.49, 1.21)	1.25	(0.54, 2.87)	0.70	(0.53, 0.94)	1.25	(0.84, 1.86)
Transgender Women Classified According to History of Exogenous Sex Hormone Use† Compared to: PresentFemalesb by Present Sex (Female)								
Cisgender Women	0.75	(0.44, 1.28)	2.14	(0.79, 5.81)	0.77	(0.54, 1.10)	1.77	(0.97, 3.24)
Cisgender Men	0.56	(0.33, 0.96)	1.06	(0.40, 2.85)	0.51	(0.36, 0.72)	0.86	(0.47, 1.55)
Transgender Women Classified by Current Gender Compared to:								
Cisgender Women	0.35	(0.14, 0.84)	1.52	(0.38, 6.08)	0.48	(0.30, 0.76)	1.26	(0.53, 2.96)
Cisgender Men	0.26	(0.11, 0.62)	0.75	(0.19, 2.99)	0.32	(0.20, 0.50)	0.61	(0.26, 1.42)

Gosiker et al. *Plos One* 2020

Mechanisms of ASCVD risk in Transgender WHIV



Slide adapted from Markella Zanni

Zanni et al. *Nature Reviews Cardiology* 2014

Effects of hormone therapy among transgender women without HIV

- ↑ Visceral Adipose Tissue
- ↓ Lean Body Mass
- ↓ Insulin Sensitivity
- ↑ Fasting Insulin Levels
- ↑ Triglycerides

PHIV on ART compared to people without HIV

- ↑ Visceral Adipose Tissue
- ↓ Lean Body Mass
- ↓ Insulin Sensitivity
- ↑ Fasting Insulin Levels
- ↑ Triglycerides

Elbers et al. *Amer Phy Soc* 1999
Auer et al. *Sci Rep* 2016
Deutsh et al. *Obstet Gynecology* 2015
Elbers et al. *Clin Endocrinology* 2003

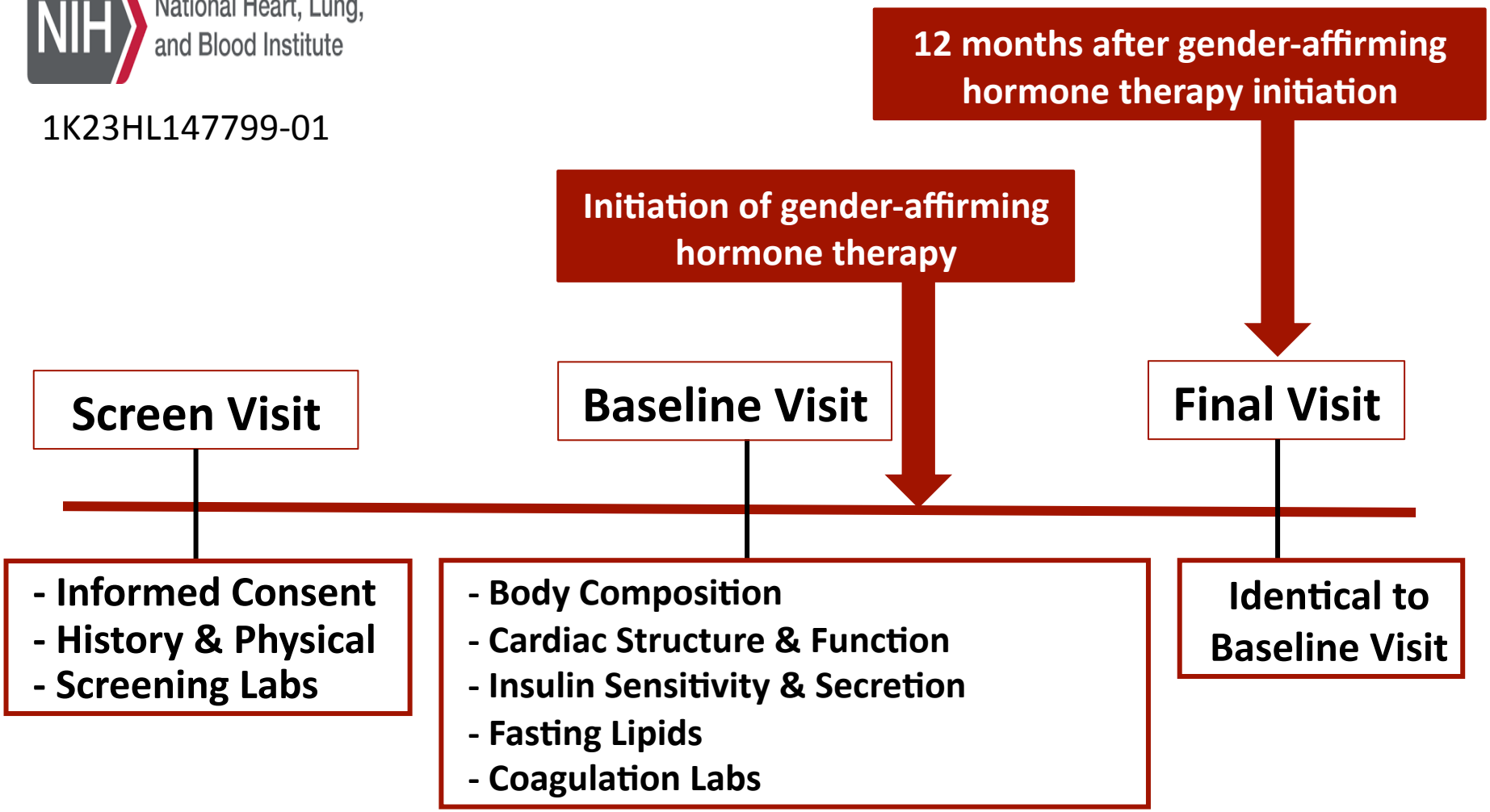
Stanley et al. *JID* 2012
Grant et al. *AIDS* 2016
Hadigan et al. *JCEM* 2000

What are the cardiometabolic effects of gender-affirming hormone therapy among transgender women with HIV – a group that faces heightened cardiometabolic disease risk?

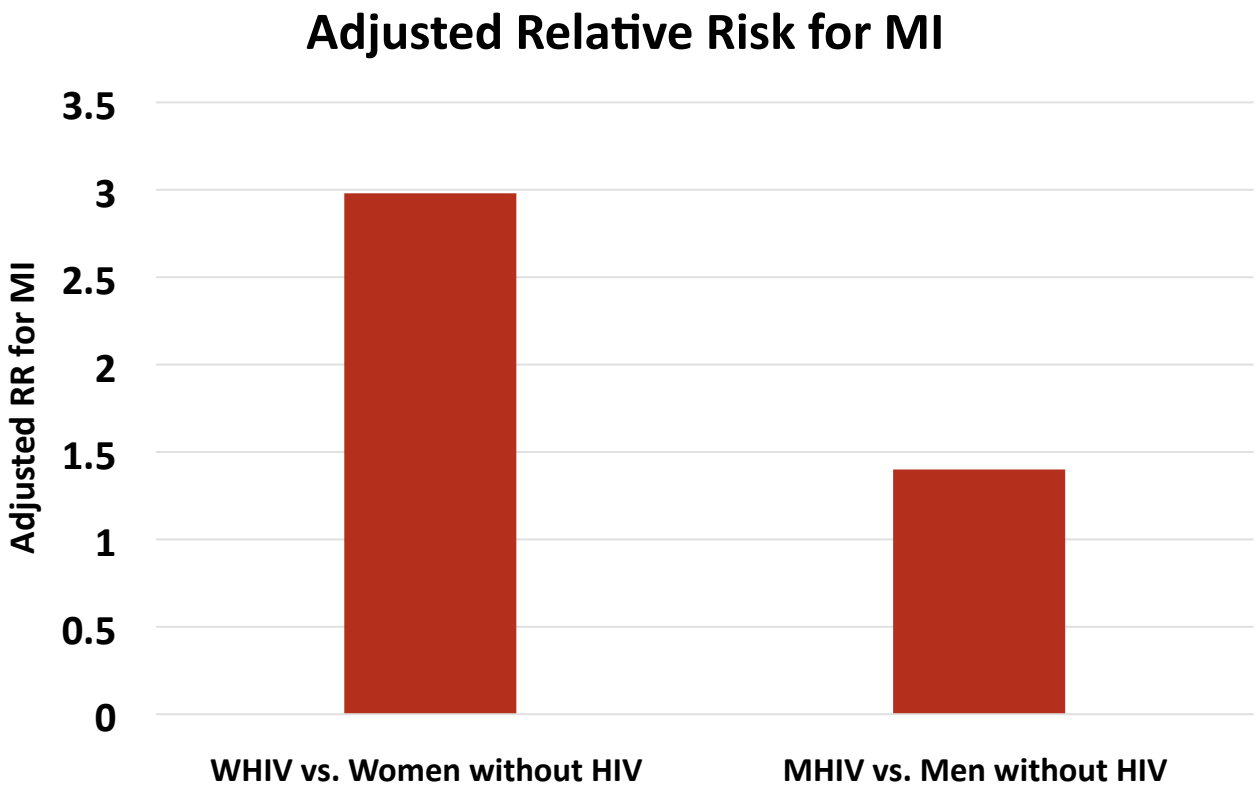
Cardiometabolic Effects of Gender-Affirming Hormone Therapy among Transgender Women with HIV

National Heart, Lung, and Blood Institute

1K23HL147799-01

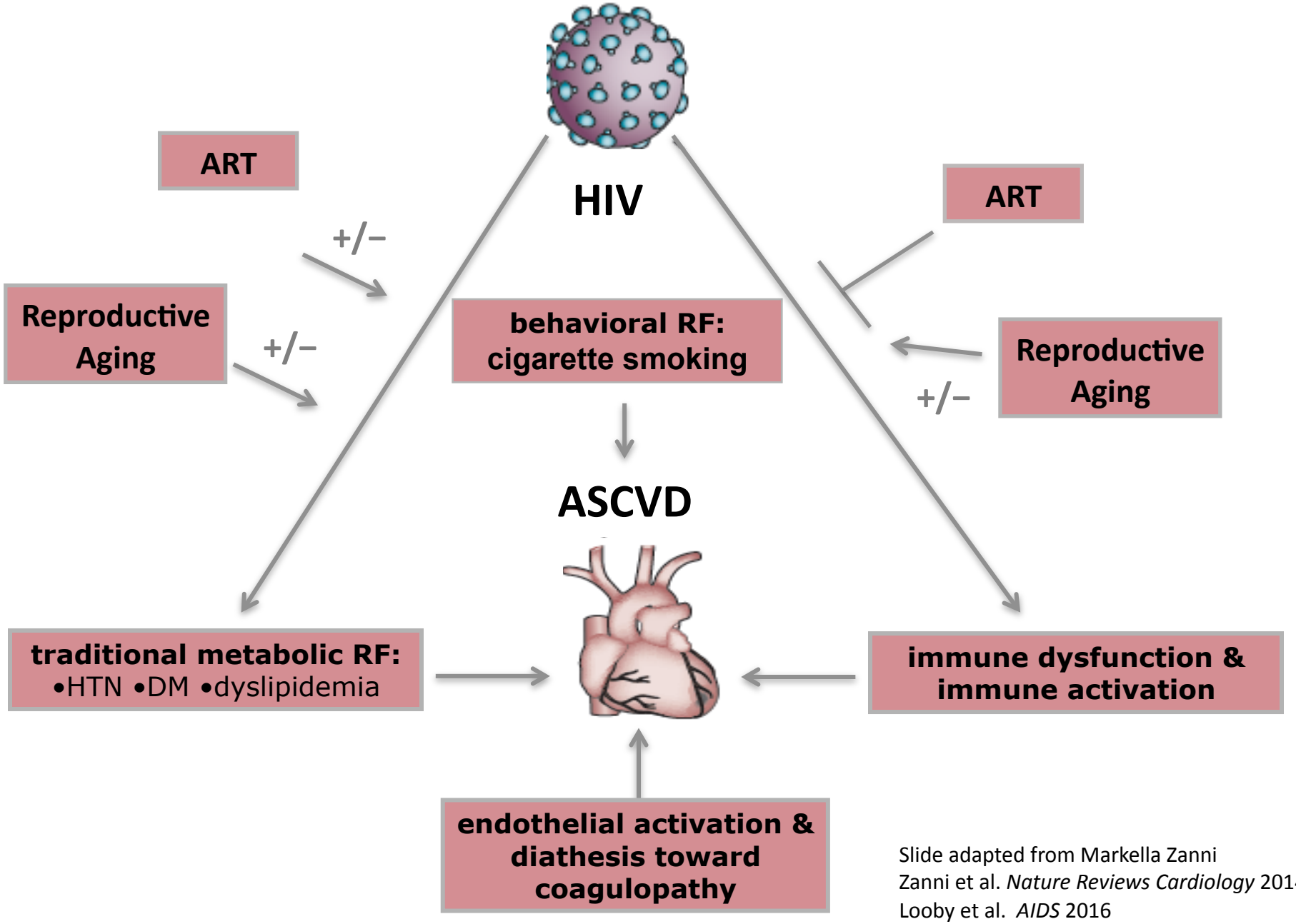


Cisgender WHIV have heightened ASCVD risk



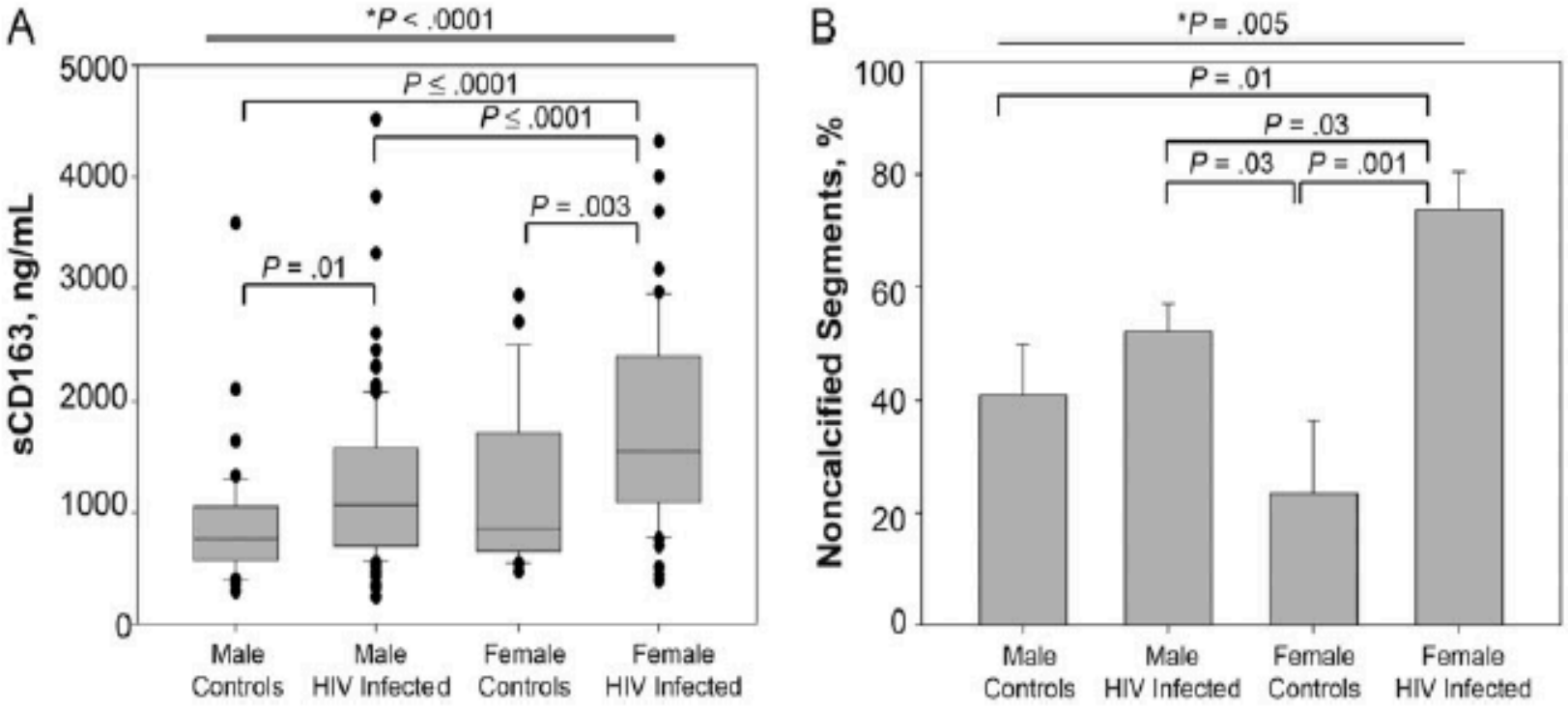
Triant et al. *JCEM* 2007

Mechanisms of ASCVD risk in Cisgender WHIV



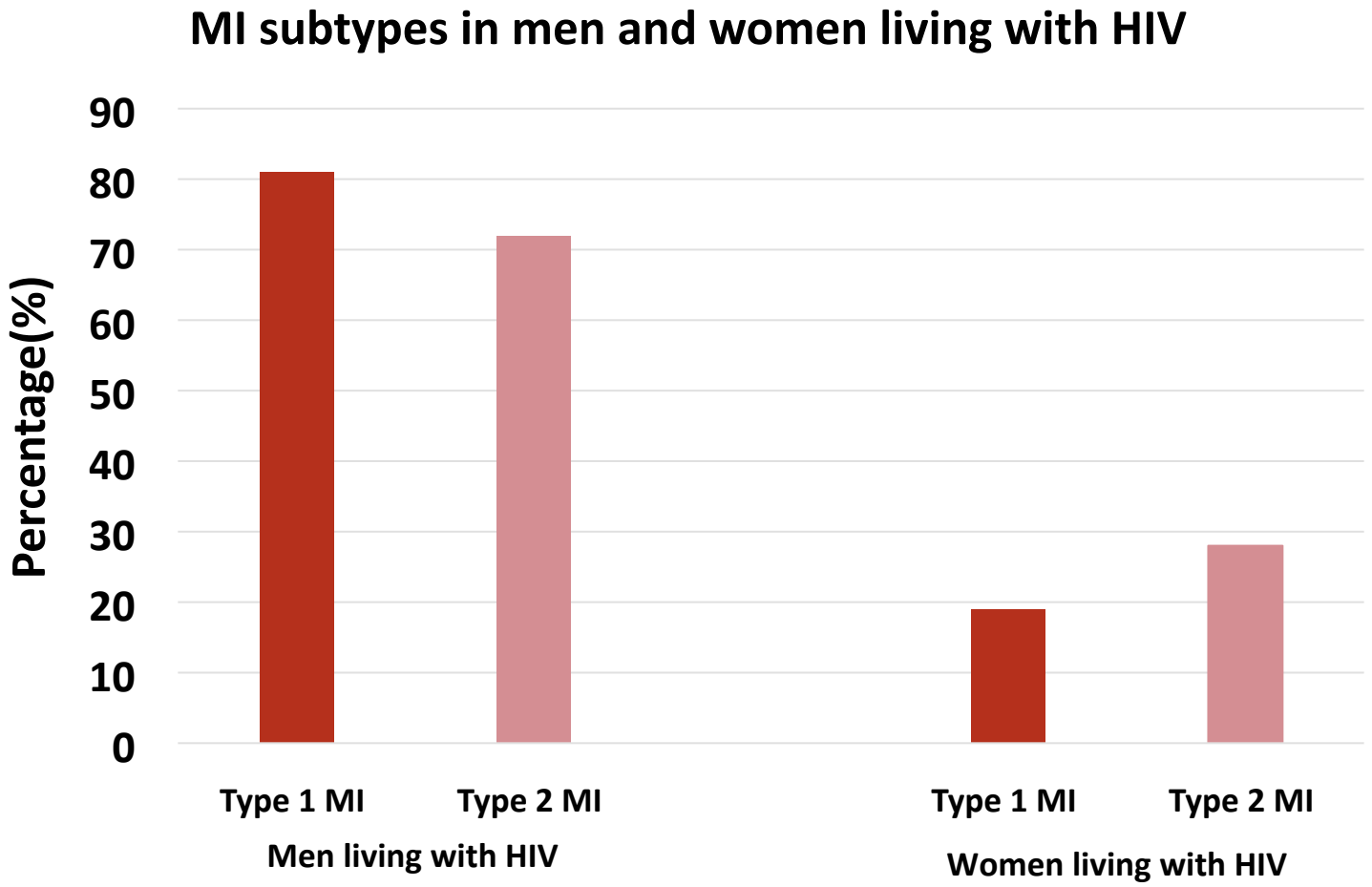
Slide adapted from Markella Zanni
Zanni et al. *Nature Reviews Cardiology* 2014
Looby et al. *AIDS* 2016

Cisgender WHIV have increased systemic immune activation and non-calcified coronary plaque



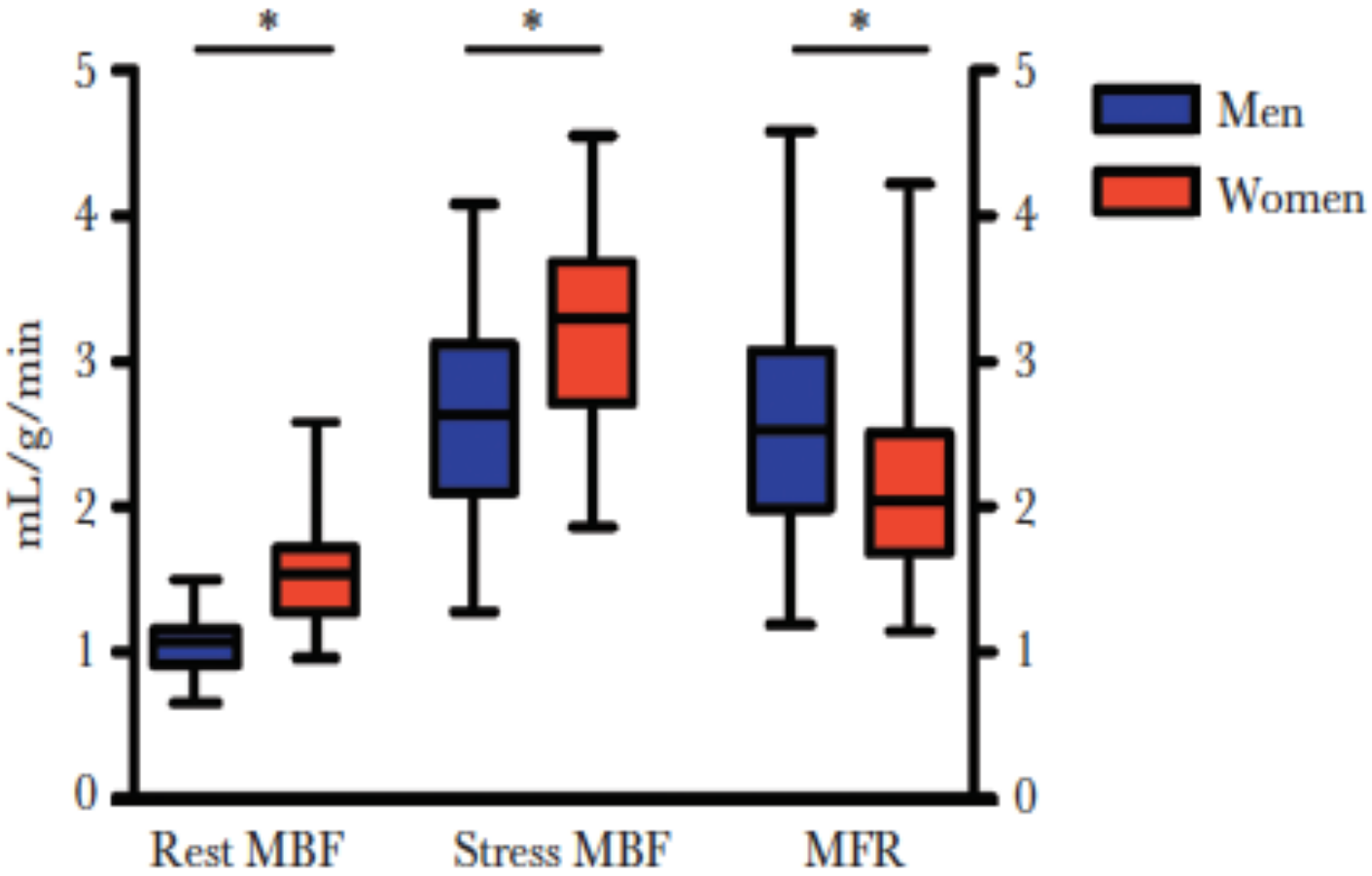
Fitch et al. *Journal of Infectious Disease* 2013

Cisgender WHIV have more type 2 MIs vs type 1 MIs



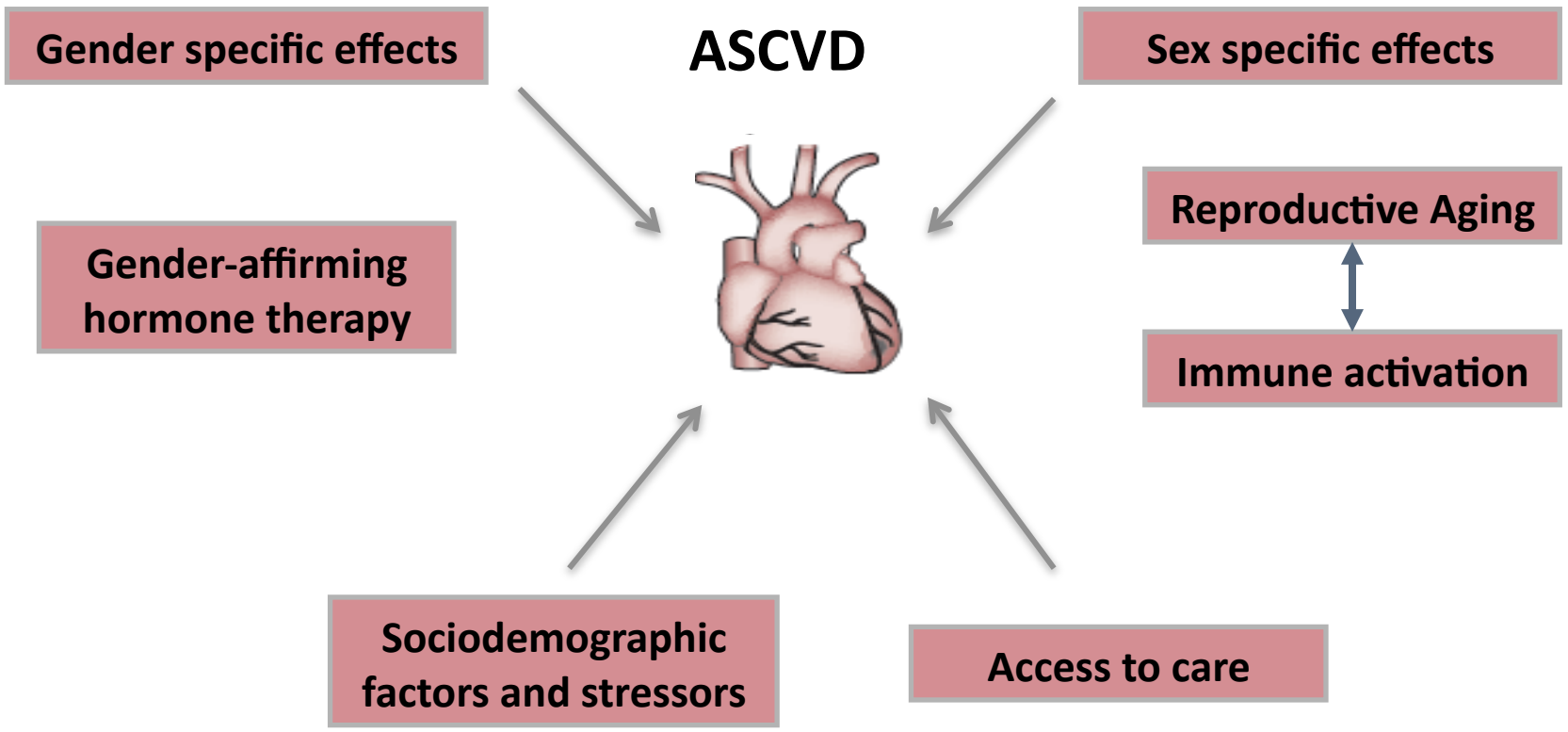
Crane et al. *JAMA Cardiology* 2017

Cisgender WHIV have lower myocardial flow reserve (MFR) compared to cisgender MHIV



Knudsen et al. *Open Forum Infectious Diseases* 2018

Summary Part II



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