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Cardiac Muscle Health Among Women Aging with HIV

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Dr. Zanni is Principal Investigator of an Investigator-Initiated Industry Grant to her Institution from Gilead Sciences, unrelated to the content of today’s presentation.
Among Aging PHIV, Shifting Causes of Morbidity and Mortality


Morlat AIDS 2014
Major Threats to Cardiac Muscle Health

HEART ATTACK

MYOCARDIAL INFARCTION

HEART FAILURE
Myocardial Infarction (MI)

Acute myocardial injury with clinical evidence of myocardial ischemia (myocardial cell death due to oxygen deprivation)

Heart Failure (HF)

A complex clinical syndrome resulting from any structural or functional impairment of the process by which the heart fills with or pumps out blood.

Research spanning nearly 20 years has highlighted MI as a particular threat to cardiac muscle health for PHIV.
PHIV have a 1.5 to 2-fold Increased Risk of MI

North American & European Cohorts

- US Partners Healthcare Database Study

Klein, 2002
Currier, 2003
Triant, 2007
Obel, 2007
Lang, 2010
Durand, 2011
Freiberg, 2013
Differences in MI Rates Among Women with vs. without HIV are Most Prominent

US Partners Healthcare Database Study

Adjusted RR of MI

- Men with vs. without HIV
- Women with vs. without HIV
Myocardial Infarction (MI) Risk Mechanisms

- **TYPE I:** MI caused by **atherothrombosis** (acute disruption of an atherosclerotic plaque with superimposed thrombus, or clot) in a coronary artery supplying the infarcted myocardium.

- **TYPE II:** MI caused by myocardial oxygen supply/demand mismatch (unrelated to atherothrombosis)

**PREVENTION EFFORTS**

**RF:** • Age • Smoking • HTN • High Cholesterol • Inflammation • Clotting Diathesis

Thygesen Circulation 2018; ACC Webpage; Ib.bioninja.com.au; Libby Nature 2011
MI Prevention: Intense Interest in Potential of STATIN Rx Based on Dual Effects

Efficacy/safety of statin Rx for 1st MI prevention have been demonstrated in select patient groups, but never before rigorously assessed among PHIV!
Hypothesis: Statin therapy will prevent atherosclerotic cardiovascular disease (ASCVD) events in PHIV on ART who may not qualify for statin therapy based on algorithms factoring in traditional risk factors alone (but who may benefit from immunomodulatory effects of statins).
>7,500 PHIV on ART with no known CVD recruited from 116 sites globally
4/2015 → 3/2019

Study Design and Progress

Pitavastatin vs. Placebo

Average f/u 4-6 years

CV death MI UA Stroke Revasc PAD

Clinical 1<sup>o</sup> Endpoint

• US • Canada • Haiti • Brazil • Peru
• South Africa • Botswana • Uganda
• Zimbabwe • India • Thailand

Mishka JAMA 2015
• Evidence-based outreach campaign to educate WHIV re: CVD risk and to encourage women’s participation and representation in the REPRIEVE trial.

• Scientific objectives exploring sex-specific mechanisms of CVD risk and risk reduction in HIV.
Myocardial Infarction (MI)

- A complex clinical syndrome resulting from any structural or functional impairment of the process by which the heart fills with and pumps out blood.

Heart Failure (HF)

- Disease of aging
- Poor prognosis: increased morbidity; 5-year mortality rate 50%

Thygesen Circulation 2018; Borlaug Nat Rev Cardiol 2014; Bursi JAMA 2006; Yanci Circulation 2013; Zile NEJM 2004; AHA.
PHIV have a 1.5 to 2-fold Increased Risk of HF

100% men
81% men
93% men

→ f/u Freiberg 2017, 97% men
Heart Failure Incidence & Subtypes: WHIV

HF incidence among Women with vs. without HIV:
• Cumulative incidence rate of HF (any subtype) 4x as high (2.5% vs. 0.74%)

HF Subtype among WHIV with HF:

• Heart Failure with Preserved Ejection Fraction (HFpEF): Clinical heart failure in which the left ventricular ejection fraction ≥ 50%

• Heart Failure with Reduced Ejection Fraction (HFrEF): Clinical heart failure in which the left ventricular ejection fraction ≤ 40%
For **WHIV**, Why Does Predilection to HFpEF Matter?

1) **HFpEF** vs. **HFrEF**: different driving RF and different pathophysiology

2) **HFpEF** more **challenging to diagnose** ...

   diagnosing clinician must rely on H&P and subtle CV imaging findings; must also exclude other causes of dyspnea

For WHIV, Why Does Predilection to HFpEF Matter?

3) **HFpEF** is intransigent to medical rx (in contradistinction to HFrEF)!!
...efforts to prevent heart failure – particularly HFpEF – are paramount!
Pathophysiology Upstream of Established HFpEF

• Diastolic Dysfunction (DD)

DEFINITION:
Pathologic behavior of LV during diastole with abnormal filling dynamics (related to ↓ relaxation +/- distensibility)

PROGNOSIS: Among patients with DD, ~2% per year progress to HF and typically HFpEF!

MODIFIABLE? YES!
Pathophysiology Upstream of Established HFpEF

**MYOCARDIAL FIBROSIS**

**DEFINITION:**

↑ Myocardial tissue collagen volume fraction; may be diffuse or focal

**PROGNOSIS:**

Predicts development of DD and relates to extent of DD

**MODIFIABLE?**

YES!

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Pathophysiology Upstream of Established HFpEF

**MYOCARDIAL STEATOSIS**

DEFINITION: ↑ Deposition of lipids (esp. TG’s) within cardiomyocytes

PROGNOSIS: Predicts development of DD and relates to extent of DD

MODIFIABLE? YES!

Texas Heart Institute; Montet-Abou Int J Obes 2010; Iozzo P Diabetes Care 2011; Rijzewijk JACC 2008; Ng JACC CV Imaging 2015; Mahmod Circ Cardiovasc Imaging 2013.
**Pathophysiology Upstream of Established HFrEF**

- **myocardial infarction**
  - traditional CVD RF: cigarettes, cocaine, HTN
  - systemic inflammation & endothelial dysfunction

- **traditional metabolic RF:**
  - hyperlipidemia (esp ↑TGs)
  - hyperglycemia
  - increased BMI
  - diathesis to ectopic fat deposition

- **MYOCARDIAL STEATOSIS**
- **MYOCARDIAL FIBROSIS**
- **DD**
- **HFrEF**
Among PHIV, Inflammation/Immune Activation and Metabolic Dysregulation may be Expected to Drive HFpEF Development

- **myocardial infarction**

- **traditional CVD RF:**
  - cigarettes, cocaine
  - HTN

- **systemic inflammation**
  & endothelial dysfunction

- **traditional metabolic RF:**
  - hyperlipidemia (esp ↑TGs)
  - hyperglycemia
  - increased BMI

- **diathesis to ectopic fat deposition**

- **MYOCARDIAL STEATOSIS**

- **MYOCARDIAL FIBROSIS**

- **DD** ➔ **HFpEF**
Inflammation/Immune Activation, Metabolic Dysregulation Persist Even in PHIV Treated with ART

- depletion of CD4+ T regulatory cells
- low-level viral replication
- microbial translocation
- viral co-infection (HCV, CMV)
- chronic activation of select monocyte and T cells subtypes
- endothelial cell activation
- systemic inflammation
- altered lipid metabolism
- hyperglycemia
- lipodystrophy

Adapted from Hsue JID 2012
Mechanisms of Cardiac Muscle Dysfunction Among PHIV (with no known CVD) in High-Income Countries:

**Available Evidence**

**Myocardial Steatosis**
Among people with vs. without HIV:
- extent of steatosis ↑
Nelson JACC CV Imaging 2014; Thiara JID 2015

**Myocardial Fibrosis**
Among people with vs. without HIV:
- prevalence and extent of fibrosis ↑
Holloway CJ Circulation 2013; Thiara JID 2015

**Diastolic Dysfunction**
In meta-analyses:
DD observed in up to 43% of asymptomatic ART-treated PHIV (vs. ~10% in general population)
Cerrato Eur Heart J 2013;

**Knowledge Gaps?**
Which are the most Salient Mechanisms of HIV-Associated Cardiac Muscle Dysfunction among Women?
Examining RF Upstream of HFpEF, What Cardiac Muscle Pathology Might We Expect in WHIV?

- **myocardial infarction**

- **traditional CVD RF:**
  - cigarettes, cocaine
  - HTN

- **systemic inflammation** & endothelial dysfunction

- **traditional metabolic RF:**
  - hyperlipidemia (esp ↑TGs)
  - hyperglycemia
  - increased BMI

- **diathesis to ectopic fat deposition**

- **MYOCARDIAL FIBROSIS**

- **MYOCARDIAL STEATOSIS**

- **Diastole**
  - Mitral valve
  - Tricuspid valve

- **DD**
  - **HFpEF**

Texas Heart Institute Borlaug Nat Rev Cardiol 2014; Iozzo Diabetes Care 2011; Mahmod Circ CV Imaging 2013
WHIV in High-Resource Regions Have High Burden of Traditional Metabolic Risk Factors, Not Consistently Treated

US Partners Healthcare Database

Traditional Metabolic risk factors

Dyslipidemia
Diabetes
HTN

RX

WHIV less likely than MHIV to be offered prescription meds targeting equivalent CHD risk factors.

Triant CROI 2014; Willig CID 2008
Examing RF Upstream of HFP EF, What Cardiac Muscle Pathology Can Might We Expect in WHIV?

- Myocardial infarction

- Traditional CVD RF:
  - cigarettes, cocaine
  - HTN

- Systemic inflammation & endothelial dysfunction

- Traditional metabolic RF:
  - hyperlipidemia (esp ↑TGs)
  - hyperglycemia
  - increased BMI

- Diathesis to ectopic fat deposition

- DD ➔ HFP EF

- Myocardial fibrosis

- Myocardial steatosis

Texas Heart Institute Borlaug Nat Rev Cardiol 2014; Iozzo Diabetes Care 2011; Mahmood Circ CV Imaging 2013
Women Have Uniquely Robust Innate Immune Response to HIV Infection (vs. Men)

[Diagram and graph showing the comparison of sCD163 and sCD14 levels in women and men with and without HIV infection.]
Examining RF Upstream of HFpEF, What Cardiac Muscle Pathology Can Might We Expect in WHIV?

- **myocardial infarction**
- **traditional CVD RF:** cigarettes, cocaine, HTN
- **systemic inflammation**
  - hyperlipidemia (esp ↑TGs)
  - hyperglycemia
  - increased BMI
- **diathesis to ectopic fat deposition**

**MYOCARDIAL STEATOSIS**

**MYOCARDIAL FIBROSIS**

**DD** → **HFpEF**

Texas Heart Institute Borlaug Nat Rev Cardiol 2014; Iozzo Diabetes Care 2011; Mahmood Circ CV Imaging 2013
Among WHIV vs. MHIV BMI Increases More with ART

$\Delta$BMI 96 weeks after ART initiation in groups stratified by baseline CD4+ cell count
Examining RF Upstream of HFpEF, What Cardiac Muscle Pathology Can Might We Expect in WHIV?

- Myocardial infarction
- Traditional CVD RF:
  - cigarettes, cocaine
  - HTN
- Systemic inflammation & endothelial dysfunction
- Traditional metabolic RF:
  - hyperlipidemia (esp ↑TGs)
  - hyperglycemia
  - increased adiposity
- Diathesis to ectopic fat deposition

- MYOCARDIAL FIBROSIS
- DD ➔ HFpEF
- MYOCARDIAL STEATOSIS
**WHIV: Observations on Advanced Reproductive Aging Relevant to Ectopic Fat Deposition**

**Antimullerian hormone (AMH)** for characterizing repro aging

- 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** (low levels reflect reduced ovarian reserve/progressive reproductive aging).

**AMH lower among women with vs. without HIV**

- **US WIHS Cohort Study**

\[ \text{In general population studies, repro aging favors } \uparrow \text{ ectopic fat deposition.} \]
Mechanism of HIV-Associated Cardiac Muscle Dysfunction specifically among Women: Collaborative Feasibility Project

Tom Neilan, MD
MGH Cardiology Co-PI

WHIV, no known CVD

Women without HIV, no known CVD

- Cardiac Magnetic Resonance Imaging
- Cardiac Magnetic Resonance Spectroscopy
  - HIV history, CV risk factor history, reproductive history
  - Systemic immune phenotyping including flow cytometry
  - Anthropometric evaluation, metabolic phenotyping, hormonal phenotyping
Findings: Myocardial Fibrosis

Diffuse Myocardial Fibrosis

ECV: 0.34±0.06 vs. 0.29±0.04

Zanni/Neilan, unpublished data
Findings: Myocardial Fibrosis

Upstream Systemic Immune Correlates

Among WHIV: Degree of CCR2 expression on circulating inflammatory monocytes related to degree of myocardial fibrosis and DD.

Zanni/Neilan, unpublished data
**Findings: Myocardial Steatosis**

**Intramyocardial Triglyceride Content (%)**

- IMTG: $1.2(0.4, 3.1)$ vs. $0.4(0.1, 0.5)$%

**Left Atrial Passive Ejection Fraction (%)**

- LAPEF: $26.9 \pm 9.5$ vs. $35.0 \pm 6.8$

**Circumferential Diastolic Strain Rate ($s^{-1}$)**

- Strain Rate: $1.10 \pm 0.23$ vs. $1.39 \pm 0.27$ $s^{-1}$

Among ART-treated WHIV: steatosis $\leftrightarrow$ diastolic $f(x)$ ($\rho=(-)0.62$, $P=0.004$)

Zanni/Neilan, unpublished data
Findings: Myocardial Steatosis

Upstream Hormonal Correlates

Among all Women:

IMTG increased across the continuum of reproductive aging subgroups (P=0.02).

-finding resonates with our observations as clinicians...

Zanni/Neilan, unpublished data
RISK FACTORS FAVORING HEART MUSCLE DYSFUNCTION:

- traditional CVD RF:
  - cigarettes, cocaine
  - HTN

- systemic inflammation & endothelial dysfunction

- traditional metabolic RF:
  - hyperlipidemia (esp ↑TGs)
  - hyperglycemia
  - increased adiposity

- diathesis to ectopic fat deposition

TARGETED STRATEGIES TO PRESERVE HEART MUSCLE FUNCTION:

- Cigarette/drug abstinence
- Antihypertensives (RAAS)
- Anti-inflammatory rx
- Lipid lowering therapies
- Antihyperglycemic therapies
- Diet/Exercise
- Rx affecting fat distribution e.g. tesamorelin // estrogen

Borlaug Nat Rev Cardiol 2014; Iozzo Diabetes Care 2011; Mahmod Circ CV Imaging 2013
Additional Considerations Relevant to PHIV living in HIV-Endemic Regions & Associated Prevention Strategies

HIV

- Mitochondrial dysfunction
- Micronutrient deficiencies
- Pollutant exposures
- Opportunistic infections
- Immune dysfunction & immune activation

Traditional metabolic RF: HTN, DM, dyslipidemia

Behavioral RF including EtOH, illicit drugs

ART +/- micronutrient deficiencies

Zanni Nature Reviews Cardiology 2014; Bloomfield JACC HF 2015
**Strategy: Statin Therapy**

**Central Study Hypothesis:**

- HIV infection
  - Metabolic Dysregulation
  - Systemic Immune Activation
  - Steatosis
  - Fibrosis

**Study Design:**

- Leveraging REPRIEVE study design and operations
- Co-enrolling 130 REPRIEVE participants from 3 US regions and from Cape Town, SA
- Participants undergoing cardiac MRS/MRI and metabolic/immune phenotyping at entry/yr 2
Strategy: Growth Hormone Releasing Hormone

Among PHIV with lipodystrophy, GHRH rx:
• improves lipid profile
• reduces visceral fat and liver fat
• dampens systemic inflammation/immune activation

Stanley/Grinspoon AIDS 2007; Falutz/Grinspoon NEJM 2008; Stanley/Grinspoon JAMA 2014

→ More data on these and other strategies to preserve cardiac muscle health among women and men with HIV will be forthcoming!
Review and Synthesis

- MI and HF represent threats to cardiac muscle health among women and men aging with HIV.

- The REPRIEVE trial will determine whether statin therapy reduces ASCVD events including MI in this population; the REPRIEVE-women’s objectives will assess sex-specific mechanisms of ASCVD risk and risk reduction.

- HF risk is increased among women and men with HIV; WHIV who develop HF tend to develop heart failure with preserved ejection fraction, for which no effective treatments exist.

- We must continue to study upstream mechanisms of HIV-attributable HF risk among women (e.g. processes contributing to myocardial fibrosis and steatosis), with a goal of intervening early to forestall these processes and preserve cardiac muscle health.
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International Workshop on HIV & Women Organizers and Participants!