Sex-Specific Mechanisms of Coronary Heart Disease Risk among Women Aging with HIV

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Massachusetts General Hospital
Director of Women’s Health Research, Program in Nutritional Metabolism
Overview

• Coronary heart disease risk **epidemiology** among **PLHIV** and **WLHIV**

• Coronary heart disease risk **mechanisms** among **PLHIV** and **WLHIV** (including sex-specific mechanisms)

• **Future Directions:** new research geared towards improving the cardiovascular health of **WLHIV**
Coronary heart disease risk epidemiology among PLHIV
Life expectancy increasing for PLHIV with access to ART

Danish HIV Cohort Study:
- 5,701 persons with HIV
- 28,505 matched controls
  → 60,270 PY of observation

Median life expectancy for individuals dx with HIV at age 25 and started on ART

Proportion of adults with HIV 50 or older is increasing

> 3.6 million adults with HIV ≥ 50 years old

UNAIDS 2013
Percentage of deaths due to CVD is rising among PLHIV

Causes of death among PLHIV, French national surveys 2000 → 2005 → 2010

*MRI leading cause of CVD death
CHD/MI risk is increased among PLHIV

CHD/MI relative risk in PL with vs. without HIV (US/Euro cohorts)
Risk for heart failure, stroke, SCD also increased

-data internally consistent
-dovetail with data among patients with autoimmune diseases

Slide adapted from Srinivasa /Grinspoon
Coronary heart disease risk epidemiology in HIV

A focus on women
CDC estimates, a high proportion of WLHIV in US are ≥ 40
Percentage of deaths due to CVD are rising among WLHIV

Trends in causes of death among US WLHIV
WIHS Study of 2792 women with HIV who died during observation period

French et al. JAIDS 2009
Wise WIHS!

- Launched in 1993 to investigate the impact, over time, of HIV infection on women in the United States
- Funded by NICHD, NIAID, NCI, NIDA, NIMH
- Includes 10 clinical sites in and around 10 US cities
- Currently following a diverse group of >3,090 US WLHIV and 1,047 matched US women without HIV; study visits include detailed clinical, biological, neurocognitive, and behavioral assessments
- Largest and longest ongoing US study of WLHIV
- Has yielded >550 high-impact scientific papers/observations
Relative risk of CHD/MI higher among WLHIV than MLHIV!

In HIV: CHD-protective effect of being a woman appears to be lost

US Partners Healthcare Database
Coronary heart disease risk mechanisms in HIV
Mechanisms of CHD risk

HIV

ART +/-

behavioral RF including

CHD

traditional metabolic RF: • HTN • DM • dyslipidemia

immune dysfunction & immune activation

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Cigarette smoking prevalence and influence on mortality in HIV

- Smoking prevalence is 40-75% among US adults with HIV
Mechanisms of CHD risk in HIV

**traditional metabolic RF:**
- HTN
- DM
- dyslipidemia

**behavioral RF including**

**immune dysfunction & immune activation**

**ART**

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ART EFFECTS: Select older ART regimens had an effect to induce lipodystrophy, as well as insulin resistance and dyslipidemia but many contemporary regimens are considered more “metabolically friendly.”

Triant JCEM 2007; Brown Archives 2003; Capeau AIDS 2012; Brown Nat Rev Endo 2011; Riddler JAMA 2003; Anastos JAIDS 2007
MI risk in HIV not fully explained by traditional risk factors

**Objective:** To assess relationship between HIV and acute myocardial infarction risk

**Design:** Data from 82,459 patients without known CVD in the Veterans Aging Cohort Study Virtual Cohort from 2003-2009

**Results:** Veterans with HIV had a ~50% increased risk of incident AMI vs. veterans without HIV after adjusting for age, sex, race/ethnicity, cigarettes, lipids, DM, HTN, BMI, renal dz, anemia, hep C, substance use (HR, 1.48; 95% CI, 1.27-1.72)
Mechanisms of CHD risk in HIV

- **ART**

- **behavioral RF**
  - including smoking

- **traditional metabolic RF:**
  - HTN
  - DM
  - dyslipidemia

- **immune dysfunction & immune activation**

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HIV = state of immune dysfunction and activation

HIV infection

- depletion of CD4+ T cells
- microbial translocation
- viral co-infection (HCV, CMV)

- persistent viral replication
- chronic activation of select monocyte and T cells subtypes
- systemic immune activation/inflammation
- altered lipid function
- altered platelet reactivity

endothelial cell activation

CHD

Adapted from Hsue JID 2012
Markers of systemic immune activation/inflammation are increased in HIV

- percentage of circulating activated monocytes, T cells

- **soluble markers of monocyte activation**
  e.g. sCD163, LPS, sCD14, and CXCL10

- **pro-inflammatory cytokines and soluble cytokine receptors**
  e.g. IL-6, sTNFR1

- **acute phase proteins**
  e.g. CRP

- **soluble leukocyte adhesion markers**
  e.g. sICAM-1 and VCAM-1

- **fibrin degradation products**
  e.g. d-dimer

ART dampens immune activation but abnormalities persist

Cross-sectional data from the MACS Cohort
Immune activation persists in treated HIV: possible drivers

- HIV infection
  - depletion of CD4+ T cells
  - microbial translocation
  - viral co-infection (HCV, CMV)
  - chronic activation of select monocyte and T cells subtypes
  - altered lipid function
  - altered platelet reactivity

- persistent viral replication
  - endothelial cell activation

Adapted from Hsue JID 2012
Immune activation persists in treated HIV: possible drivers

HIV infection

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- microbial translocation
- viral co-infection (HCV, CMV)

persistent viral replication

- chronic activation of select monocyte and T cells subtypes
- endothelial cell activation

- altered lipid function
- altered platelet reactivity

systemic immune activation/inflammation

CHD

Adapted from Hsue JID 2012
Inflammation ↔ plaque formation and remodeling

“high-risk morphology plaque features” may predispose to plaque rupture

- necrotic core; thin fibrous cap
- tendency to remodel eccentrically

Individuals with HIV (vs. age and FRS-matched individuals without HIV) have higher levels of arterial inflammation on 18F FDG PET scanning and a higher prevalence of plaque and high-risk plaque on coronary CT, in relation to systemic immune markers. These are powerful risk surrogates which help us understand which systemic immune pathways increase CHD risk.
Mechanisms of CHD risk in HIV

- ART +/-
- HIV
- behavioral RF including
  - traditional metabolic RF: HTN, DM, dyslipidemia
  - immune dysfunction & immune activation

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Coronary heart disease risk mechanisms in HIV

A focus on women
Mechanisms of CHD risk in WLHIV

HIV

ART +/-

behavioral RF including

traditional metabolic RF: •HTN •DM •dyslipidemia

immune dysfunction & immune activation

CHD

Zanni Nature Reviews Cardiology 2014
# Traditional MI risk factors by sex / HIV status

<table>
<thead>
<tr>
<th></th>
<th>All HIV control</th>
<th>Female HIV control</th>
<th>Male HIV control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>4467</td>
<td>1467</td>
<td>3000</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>42</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>52</td>
<td>40</td>
<td>57</td>
</tr>
<tr>
<td>Black / AA</td>
<td>21</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td><strong>HTN (%)</strong></td>
<td>13</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td><strong>DM (%)</strong></td>
<td>7</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td><strong>Dyslipidemia (%)</strong></td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

*Partners Database*
Increased prevalence of metabolic abnormalities, MetS, among women with vs. without HIV

Dolan et al. JAIDS 2005
- 100 women with HIV; 75 women without HIV (matched on age, race, BMI)
  - ↑ visceral adiposity; ↑ WHR
  - ↑ TG; ↓ HDL
  - ↑ 2h blood sugar on OGTT; ↑ fasting insulin
  - ↓ adiponectin

Sobieszczyk et al. JAIDS 2008
- 2393 women with HIV; 668 women without (WIHS)
  - ↑ prevalence of MetS
    defined by ATP III guidelines
    33% vs. 22% (P<0.0001)
    adjusted OR 1.79 (CI 1.48, 2.16)
### Increased prevalence of non-traditional CHD RF among women with vs. without HIV

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No HIV (1477, m age 44)</th>
<th>HIV (710, m age 44)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Framingham risk score</td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.1 (3.0)</td>
<td>3.2 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3 (1 to 5)</td>
<td>3 (1 to 5)</td>
<td></td>
</tr>
<tr>
<td>Framingham risk factors, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>28.0</td>
<td>22.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12.6</td>
<td>10.4</td>
<td>0.14</td>
</tr>
<tr>
<td>Lipids, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol ≥160</td>
<td>12.3</td>
<td>8.2</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL cholesterol &lt;50</td>
<td>41.1</td>
<td>53.8</td>
<td>&lt;0.001</td>
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<td>TGs ≥150</td>
<td>23.4</td>
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<tr>
<td>Smoking, %</td>
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<tr>
<td>Current</td>
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<td>Past</td>
<td>12.3</td>
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<tr>
<td>Never</td>
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Increased prevalence of mental health CHD RF among women with vs. without HIV

Schwartz et al. AIDS Care 2012
- 562 women with HIV; 132 women without (WIHS)

• Trend toward ↑ prevalence of chronic depressive symptoms (22.8% vs. 15.9%, p=0.08)

• In pooled cohort, follow-up Framingham Risk Score higher among women with chronic depressive symptoms, adjusting for baseline FRS and other covariates
## Preventative Rx: prescribing patterns among women with vs. without HIV

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Womack JAHA 2014
### Preventative Rx: prescribing patterns among WLHIV vs. MLHIV

**D:A:D study**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Before adjustment</th>
<th>RR (95% CI); p-value</th>
<th>After adjustment</th>
<th>RR (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid-lowering drugs</td>
<td>0.52 (0.49, 0.56); p = 0.0001</td>
<td></td>
<td>0.80 (0.75, 0.86); p = 0.0001</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>0.60 (0.56, 0.65); p = 0.0001</td>
<td></td>
<td>0.80 (0.74, 0.87); p = 0.0001</td>
<td></td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td>0.81 (0.75, 0.86); p = 0.0001</td>
<td></td>
<td>1.16 (1.07, 1.25); p = 0.0001</td>
<td></td>
</tr>
<tr>
<td>ICPs</td>
<td>0.25 (0.20, 0.32); p = 0.0001</td>
<td></td>
<td>0.49 (0.38, 0.63); p = 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Sex-specific differences in immune activation in HIV

Addo JID 2013; Fitch JID 2013
Immune activation relevant to CVD risk surrogates among WLHIV:
1) coronary atherosclerotic plaque type ...

![Immune activation relevant to CVD risk surrogates among WLHIV](image)

- % noncalcified plaque

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Male Controls</td>
<td></td>
</tr>
<tr>
<td>Male HIV Infected</td>
<td></td>
</tr>
<tr>
<td>Female Controls</td>
<td></td>
</tr>
<tr>
<td>Female HIV Infected</td>
<td></td>
</tr>
</tbody>
</table>

*P = 0.005
P = 0.01
P = 0.03
P = 0.03
P = 0.001

Fitch JID 2013
... 2) epicardial adipose tissue
Sex hormones among premenopausal women with vs. without HIV

Karim et al. JCEM 2013

Methods:
- 414 women with HIV; 170 women without (WIHS)
- Cycle-specific measures of sex hormones, including total estradiol E2
- 771 women with HIV; 323 women without (WIHS)
- Random concentrations of sex hormones including T

Results:
• E2, T lower among women with vs. without T
• Relationships with arterial distensibility
AMH: a hormone permitting assessment of reproductive aging (reduced ovarian reserve)

- Made by ovarian granulosa cells
- Drops to undetectable levels a few years prior to menopause
- Serves as a molecular biomarker for measuring ovarian reserve (low levels reflect reduced ovarian reserve or reproductive aging)
- Levels relatively consistent throughout the cycle
AMH levels lower among premenopausal women with vs. without HIV

Unadjusted AMH in WIHS Cohort (by age)

- Women with HIV
- Women without HIV
AMH: predictive of age at menopause among WLHIV

**STUDY DESIGN:**
AMH measured in 2461 women with HIV (WIHS) and used to model age at final menstrual period. MV normal mixture models for censored data used to identify factors associated with age at final menstrual period.

**RESULTS:**
Median age at final menstrual period ranged from 45 years for those in the 10th percentile of AMH to 52 years for those in the 90th percentile.
Reproductive aging relates to immune activation, atherogenesis in HIV

<table>
<thead>
<tr>
<th>MENSTRUAL HISTORY</th>
<th>PREMENOPAUSAL</th>
<th>POSTMENOPAUSAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menses within the past 12 months</td>
<td>No menses within the past 12 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AMH LEVELS</th>
<th>PREMENOPAUSAL</th>
<th>POSTMENOPAUSAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable AMH; variable by age</td>
<td>Undetectable AMH</td>
<td>Undetectable AMH</td>
</tr>
</tbody>
</table>

Group 1: Premenopausal with measurable AMH
Group 2: Premenopausal with reduced ovarian reserve
Group 3: Postmenopausal

• Select markers of systemic immune activation increase across the reproductive aging spectrum.

• Reduced ovarian reserve relates to subclinical coronary plaque plaque after controlling for traditional CVD risk factors, including age.
Perimenopause/menopause among WLHIV: CHD risk considerations

![Chart showing various indices (MRS, HFRDIS, ISI, GAD-7, CESD) with red and green bars representing HIV and Controls, respectively. An arrow points to a note: ART non-adherence.]

Looby Menopause 2014
Maki et al. Menopause 2012
Mechanisms \rightarrow prevention strategies

HIV

traditional metabolic RF:  
•HTN •DM •dyslipidemia

behavioral RF including

ART +/-

ART

immune dysfunction & immune activation

CHD

Zanni Nature Reviews Cardiology 2014
• **Future Directions**: new research geared towards improving the cardiovascular health of WLHIV
REPRIEVE is a multisite, international randomized controlled trial testing whether statin therapy will prevent atherosclerotic cardiovascular disease (ASCVD)-related major adverse cardiovascular events (MACE) in 6500 PLHIV on antiretroviral therapy (ART) in whom traditional CVD risk is not significantly increased.
Asymptomatic HIV+ patients with no history of CVD

Randomization

Pitavastatin 4mg/day

Placebo

Coronary plaque, vascular inflammation, immune activation

Coronary CTA Study

CCTA Study

Primary Endpoint

Secondary Endpoints

All cause death

Incidence/Progression of noncalcified plaque – high risk plaque

Inflammatory, immune, metabolic effects

Predictors of statin effects

Statin safety and effects on AIDS-defining events, CA, kidney/liver, DM

Aberg Endo 2013
site engagement:
- ~100+ sites
- US, Canada, Thailand, Brazil, S. Africa (+ more)

participants:
2742 since 4/2015
- 69% men, 31% women
- 44% white, 38% black or AA, 13% Asian
- median 49 years, LDL 107 mg/dl
- median duration ART 10 yrs
- median CD4 628
REPRIEVE Women’s Objectives

Objective: To explore sex-specific mechanisms of CVD risk and risk reduction within the context of REPRIEVE

Hypotheses:

• Sex-based differences in immune activation and statin-induced immunomodulation will relate to clinical CVD events.

• Menopause status and ovarian reserve will relate to immune activation, statin-induced immunomodulation, and clinical CVD events.
Supplemental Objective: To design, implement, and test the efficacy of an evidence-based educational awareness campaign to augment women’s enrollment in REPRIEVE

- Women underrepresented in HIV research and CVD research - women make up 19.2% of participants in ARV trials and 11.1% of participants in CURE trials

- Robust representation of women in HIV-CVD clinical trials is essential to understanding sex-specific mechanisms of CVD risk and risk reduction!
Pilot study and available literature as evidence basis for women’s campaign

Pilot study:

• Surveys distributed among a community sample of women with or at risk for HIV. N=40; mean age 53±13

• Questions centered on factors which might influence enrollment and/or sustained participation in a large-scale clinical research study focused on heart disease

Literature:
Including (but not limited to) ACTG Guide

Unpublished data Looby, Zanni 2016
REPRIEVE Follow YOUR Heart Campaign

Themes:

• Inclusion
• Empowerment through knowledge
• Peer to peer communication
• Provider communication
• Altruism / sense of community

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
Follow YOUR Heart
Campaign Components & Outreach

Components of the Recruitment Campaign
- Video designed to engage and educate women on clinical research participation and REPRIEVE consisting of education on women’s CVD/HIV research participation, personal experiences from HIV+ women & demonstration of a REPRIEVE screening visit.
- Website highlighting women’s health, CVD, HIV
- Social Media Strategies: FaceBook, Twitter, to leverage HIV-women’s networks and improve dissemination regarding the REPRIEVE Women’s objectives.
- Educational Packet including posters, brochures, a DVD of the video will be distributed to REPRIEVE study sites and staff at the HIV community centers.
- Training, guidance & support regarding the use of the recruitment intervention will be provided by our staff and representatives from the Global Community Advisory Board to study site outreach coordinators and the staff at the HIV community organizations.

Women living with HIV
REPRIEVE
Study site outreach coordinators
Staff at HIV community organizations

Unpublished data Looby, Zanni 2016
REPRIEVE Follow YOUR Heart Website

http://followyourheart.reprievetrial.org/
REPRIEVE Follow YOUR Heart Video

Follow YOUR Heart

Learning about research from peers

Brief demonstration of a study visit

6,500 women and men

✓ HIV + on Antiretroviral Therapy
✓ Age 40-75
✓ NO history of heart attack or stroke (heart healthy)

Study Details

Learning about the study from healthcare providers
A “model for future research”: “REPRIEVE is unique because it prioritizes the analysis of sex differences in the onset, severity, and course of HIV and heart disease, as well as in the response of participants to statins. Beyond focusing on the physiological issues unique to women, the study will also assess the best ways to recruit and retain women as trial participants, thus informing the design of future studies.”
Review and synthesis

- Men and women with HIV and with access to ART are living longer and are facing increased CV morbidity and mortality

- Among PLWH:
  - Traditional CVD RF contribute to, but do not fully account for, the heightened risk of MI in HIV
  - Persistent immune activation among ART-treated individuals may contribute to a unique coronary atherosclerotic phenotype in HIV

- Among WLHIV:
  - Mechanisms of increased CVD risk involve a complex interplay between traditional CVD risk factors, non-traditional / behavioral CVD risk factors, heightened systemic immune activation, and hormonal milieu

- Ongoing progress in the effort to improve cardiovascular health among WLHIV will require conscientious processes of research study design (taking into account biological and social factors relevant to women) concerted efforts to promote robust recruitment of women into impactful trials and translation of new knowledge into practice guidelines which are uptaken, benefitting the community of WLHIV
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