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

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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
Myocardial infarction risk is increased among PHIV

CHD/MI relative risk in PL with vs. without HIV (US/European cohorts)

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


Slide Adapted from Steven Grinspoon
Triant et al. *JCEM* 2007
Mechanisms of ASCVD risk in HIV

HIV

+/-

ART

behavioral RF: cigarette smoking

ASCVD

traditional metabolic RF: •HTN •DM •dyslipidemia

immune dysfunction & immune activation

endothelial activation & diathesis toward coagulopathy

Slide adapted from Markella Zanni Zanni et al. Nature Reviews Cardiology 2014
HIV-infection is a state of both immune activation and suppression.
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.

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

- Simvastatin
- Lovastatin
- Atorvastatin

CYP 3A4

- Rosuvastatin
- Fluvastatin

CYP 2C9

- Pitavastatin
- Pravastatin

Glucuronidation

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

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

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

Toribio et al. *AIDS* 2017
Intervention
Screening and Consent

Asymptomatic HIV patients with no history of CVD and ASCVD < 15%

N=7,700

Randomization

Placebo  Pitavastatin

N=800, 2 yrs

Mechanistic Study

Coronary plaque, vascular Inflammation, immune activation

Mechanistic Primary Endpoint

CVD Death  MI  Unstable Angina  TIA & Stroke  Arterial Revasc  PAD

Clinical Primary Endpoint

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

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

ART

- Use ART that reduces immune activation: INSTI
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

Twice the population of the city of Boston (~1.4 million)
Transgender women in the US

- 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

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

Median HIV prevalence in transgender women between 2000-2011

- 22%
- 18%
- 24%
- 3%
- 7%
- 44%
- 13%
- 26%
- 4%

Country prevalence (95% CI)
- 1.0–9.9%
- 10.0–19.9%
- 20.0–29.9%
- 30.0–39.9%
- ≥40.0%
- No data that meets inclusion criteria

Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy
Results From a Large Cohort Study

<table>
<thead>
<tr>
<th>Acute Cardiovascular Events</th>
<th>OCs (IR)*</th>
<th>Using Women as Reference</th>
<th>Using Men as Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECs</td>
<td>SIR (95% CI)</td>
<td>ECs</td>
</tr>
<tr>
<td>Transwomen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>29 (127)</td>
<td>12.01</td>
<td>2.42 (1.65–3.42)†</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>30 (131)</td>
<td>11.38</td>
<td>2.64 (1.81–3.72)†</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>73 (320)</td>
<td>13.22</td>
<td>5.52 (4.36–6.90)†</td>
</tr>
<tr>
<td>Transmen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (55)</td>
<td>3.49</td>
<td>1.72 (0.70–3.58)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (100)</td>
<td>2.98</td>
<td>3.69 (1.94–6.42)†</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2 (18)</td>
<td>4.84</td>
<td>0.41 (0.07–1.37)</td>
</tr>
</tbody>
</table>

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)*.

<table>
<thead>
<tr>
<th></th>
<th>Pooled Cohort Equation (PCE)</th>
<th>Framingham Risk Score (FRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted*</td>
</tr>
<tr>
<td></td>
<td>Prevalence Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Transgender Women Classified by Birth Sex† Compared to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisgender Women</td>
<td>1.03</td>
<td>(0.65, 1.63)</td>
</tr>
<tr>
<td>Cisgender Men</td>
<td>0.77</td>
<td>(0.49, 1.21)</td>
</tr>
<tr>
<td>Transgender Women Classified According to History of Exogenous Sex Hormone Use‡ Compared to: Present Females by Present Sex (Female)</td>
<td></td>
<td></td>
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<tr>
<td>Cisgender Women</td>
<td>0.75</td>
<td>(0.44, 1.28)</td>
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<tr>
<td>Cisgender Men</td>
<td>0.56</td>
<td>(0.33, 0.96)</td>
</tr>
<tr>
<td>Transgender Women Classified by Current Gender§ Compared to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisgender Women</td>
<td>0.35</td>
<td>(0.14, 0.84)</td>
</tr>
<tr>
<td>Cisgender Men</td>
<td>0.26</td>
<td>(0.11, 0.62)</td>
</tr>
</tbody>
</table>

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

HIV

+/-

ART

+/-

Hormone therapy

+/-

behavioral RF: cigarette smoking

immune dysfunction & immune activation

Gender minority stigma

endothelial activation & diathesis toward coagulopathy

traditional metabolic RF: HTN DM dyslipidemia

Psychosocial stressors
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

References:
Elbers et al. Amer Phy Soc 1999
Deutsh et al. Obstet Gynecology 2015
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

Screen Visit
- Informed Consent
- History & Physical
- Screening Labs

Baseline Visit
- Body Composition
- Cardiac Structure & Function
- Insulin Sensitivity & Secretion
- Fasting Lipids
- Coagulation Labs

Final Visit
- Identical to Baseline Visit

12 months after gender-affirming hormone therapy initiation

Initiation of gender-affirming hormone therapy

1K23HL147799-01
Cisgender WHIV have heightened ASCVD risk

![Adjusted Relative Risk for MI](chart)

Triant et al. *JCEM* 2007
Mechanisms of ASCVD risk in Cisgender WHIV

- ART
- Reproductive Aging
- traditional metabolic RF: HTN, DM, dyslipidemia
- behavioral RF: cigarette smoking
- immune dysfunction & immune activation
- endothelial activation & diathesis toward coagulopathy

Slide adapted from Markella Zanni et al. "Nature Reviews Cardiology" 2014
Looby et al. "AIDS" 2016
Cisgender WHIV have increased systemic immune activation and non-calcified coronary plaque
Cisgender WHIV have more type 2 MIs vs type 1 MIs

Percentage(%) of MI subtypes in men and women living with HIV:

- Men living with HIV: Type 1 MI > Type 2 MI
- Women living with HIV: Type 2 MI > Type 1 MI

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

- Gender specific effects
- Gender-affirming hormone therapy
- Sociodemographic factors and stressors
- Access to care
- ASCVD
- Sex specific effects
- Reproductive Aging
- Immune activation
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