Beyond MI: Cardiovascular Disease in the ART-Treated Patient

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Objectives

1. Describe the clinical impact of myocardial infarction (MI), stroke, heart failure, and sudden cardiac death in the current ART treatment era

2. Identify special considerations for evaluating and managing the spectrum of cardiovascular disease in patients with HIV

3. Summarize important unanswered questions regarding cardiovascular disease and HIV infection
• 50 years old
• AIDS in 2002; on ART since
• Nadir/current CD4+: 20/600
• BP 140/70 on amlodipine 10 mg daily
• LDL 100 mg/dl on atorvastatin 40 mg daily

• 50 years old
• HIV-negative
• BP 150/90
• LDL 160 mg/dl

• 50 years old
• HIV+ 2010; on ART since
• Nadir/current CD4+: 600/1000
• BP 120/70
• LDL 100 mg/dl on atorvastatin 40 mg daily
HIV is associated with higher risk of myocardial infarction

Adapted from S. Grinspoon
1.5-2x Higher Risk

**MI**
- Freiberg et al, JAMA Intern Med 2013 (MI)
- Freiberg et al, Circ Cardiovasc Qual Outcomes 2011 (CAD)
- Chow et al, JAIDS 2012 (stroke)

**Stroke**
- Butt et al, Arch Intern Med 2011 (HF)
- Freiberg et al, CROI 2013 (HFpEF)
- Hsu et al, JACC 2013 (Afib)

**Heart Failure**

**Atrial Fibrillation**
Cardiovascular Events in VACS 2003-2012

- Heart Failure
- MI
- Stroke

Marconi et al. CROI 2017
Atherosclerotic CVD

A known entity
Atherosclerotic CVD

Koenig et al, ATVB 2007
Thygesen et al, Circulation 2012

HIV Management
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What accounts for the 1.5-2x higher risk seen in HIV?
What accounts for the 1.5-2x higher risk seen in HIV?

2017

HIV risk

Traditional risk

ART risk
Population Attributable Risk

Prevalence + Hazard Ratio = Population Attributable Fraction

Proportional reduction in risk that would occur if that risk factor were absent or reduced to “normal”
Population attributable fractions (PAFs) for myocardial infarction

- Total Cholesterol: 43%
- Hypertension: 41%
- Smoking: 38%
- CD4+: 10%
- HCV+: 8%
- Viral Load: 6%
- Chronic Kidney Disease: 3%
- Diabetes: 2%
- AIDS: 2%

Althoff et al. CROI 2017
# Comparison with other non-AIDS comorbidities

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Traditional risk factor PAF</th>
<th>HIV-related risk factor PAF</th>
</tr>
</thead>
</table>
| **Cancer**  
(CROI 2015) | 1. Smoking: 35%  
• 26% after excluding lung cancer | 2. Clinical AIDS diagnosis: 10%  
3. Low CD4+ count: 4% |
| **ESRD**  
(unpublished) | 1. Elevated total cholesterol: 22% | 2. Detectable HIV RNA: 20%  
3. Low CD4+ count: 17% |
| **ESLD**  
(CROI 2016) | 1. At-risk alcohol use: 33%  
2. HCV infection: 31% | 3. Low CD4+ count: 25% |
| **MI**  
(CROI 2017) | 1. Elevated total cholesterol: 43%  
2. Hypertension: 41%  
3. Smoking: 38% | |

ESRD=end-stage renal disease. ESLD=end-stage liver disease. MI=myocardial infarction.

Althoff et al. CROI 2017
Predicted Reduction in ASCVD Risk from 2017–2030, with 50% or 100% Success in Reducing Risk Factors: A Dutch Modeling Study

Van Zoest et al, CROI 2017
Netherlands ATHENA observational HIV cohort
What accounts for the total risk of ASCVD events in HIV?
Primary prevention of ASCVD

► Diet and exercise
► Smoking cessation
► Statin
► Aspirin
► Appropriate management of comorbidities (blood pressure, diabetes, CKD, etc...)

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2013 ACC/AHA Guidelines: Statin benefit groups

1. Clinical ASCVD
   - Age <75: High-dose statin
   - Age >75: Moderate-dose statin

2. LDL > 190 mg/dL
   - High-dose statin

3. Diabetes
   - Age 40-75
     - >7.5% risk: High-dose statin
     - <7.5% risk: Moderate-dose statin

4. >7.5% estimated risk
   - Age 40-75
     - Moderate- to high-dose statin

Stone et al, Circulation, 2014
# Pooled Cohort Equations Calculator

## ASCVD Risk Estimator

### 10-Year ASCVD Risk
- **7.5%** calculated risk
- **3.7%** risk with optimal risk factors

### Lifetime ASCVD Risk
- **69%** calculated risk
- **5%** risk with optimal risk factors

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**Gender**
- Male
- Female

**Age**
- 49

**HDL - Cholesterol (mg/dL)**
- 56

**Total Cholesterol (mg/dL)**
- 320

**Diabetes**
- Yes
- No

**Treatment for Hypertension**
- Yes
- No

**Race**
- White
- African American
- Other

**Systolic Blood Pressure**
- 114

**Smoker**
- Yes
- No

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*Intended for use if there is not ASCVD and the LDL cholesterol is <190 mg/dL.

**Optimal risk factors include: Total cholesterol of 170 mg/dL, HDL cholesterol of 50 mg/dL, Systolic BP of 110 mm Hg. Not taking medications for hypertension, Not a diabetic, Not a smoker.
The ACC/AHA calculator may underestimate risk in HIV
Data from the CFAR Network (CNICS)
Statins in HIV: Beware of drug interactions

Many protease inhibitors (PIs), especially those boosted with ritonavir or cobicistat will increase statin levels in the blood (through CYP3A4)

- Lovastatin (Mevacor)
- Simvastatin (Zocor)
- Atorvastatin (Lipitor)
- Rosuvastatin (Crestor)
- Pravastatin (Pravachol)
- Pitavastatin (Livalo)

CONTRAINDIATED
CAUTION
NO INTERACTION

Efavirenz INDUCES CYP3A4

Jacobson et al, J Clin Lipidol 2015
HIV + Chronic Inflammation

ART
Contemporary ART and blood lipids

TDF = Tenofovir
RAL = Raltegravir
RPV = Rilpirivine
DTG = Dolutegravir
ETV = Etravirine
ABC = Abacavir
EFV = Efavirenz
ATV = Atanazavir
RTV = Ritonivir
EVG = Elvitegravir
COBI = Cobicistat

Adapted from K. Aspry
clinicaloptions.com/hiv
Abacavir and MI Risk: The D:A:D Study

Sabin et al, Lancet, 2008
• Adjusted RR of MI while on ABC ~2.0
• No difference in pre-vs. post-2008 periods
Association Between CVD & Cumulative ATV/r and DRV/r Use; Additional Time-updated Adjustment for Factors Potentially on the Causal Pathway between PI/r use and CVD

CD4, BMI, CKD, Dyslipidaemia, Diabetes

Ryom et al.  CROI, 2017
Data from the D:A:D Study
## Is risk of MI declining over time? The Kaiser Permanente story

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>Incidence Rate/100 000 py</th>
<th>Rate Ratio(^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-positive</td>
<td>HIV-negative</td>
</tr>
<tr>
<td>1996–2011</td>
<td>268</td>
<td>165</td>
</tr>
<tr>
<td>1996–1999</td>
<td>276</td>
<td>136</td>
</tr>
<tr>
<td>2000–2003</td>
<td>324</td>
<td>162</td>
</tr>
<tr>
<td>2004–2007</td>
<td>270</td>
<td>178</td>
</tr>
<tr>
<td>2008–2009</td>
<td>245</td>
<td>167</td>
</tr>
<tr>
<td>2010–2011</td>
<td>195</td>
<td>165</td>
</tr>
</tbody>
</table>
ASCVD— Clinical Pearls

► MI and Stroke Prevention:
  – Focus on traditional risk factors
  – Risk calculators may underestimate risk
  – ART does more good than harm, but consider avoiding certain drugs in high-risk individuals

► Statins:
  – Beware drug interactions
  – Despite interactions, don’t be scared to use a potent statin with proper dosing and monitoring
  – Will statins prevent ASCVD events in low-risk individuals?
ASCVD– When prevention fails

► Revascularization:
  – After a stent, restenosis rates are similar but recurrent acute events higher in HIV+
  – Stents are great, but HIV+ can safely undergo surgery as well

• Beware drug interactions:
  – Clopidogrel: efavirenz and etravirine decrease effectiveness
  – Ticagrelor: PI/cobicistat increase risk of bleeding
  – Prasugrel: ritonavir/cobicistat decrease effectiveness
Heart Failure

The coming epidemic
Two Kinds of Heart Failure

**Systolic**

- ↓ Ejection Fraction (HFrEF)
  - MI/Ischemic Heart Disease
  - Hypertension
  - Alcohol
  - Diabetes
  - AIDS

**Diastolic**

- Normal EF (HFpEF)
  - Hypertension
  - Kidney Disease
  - Aging
  - Chronic HIV
Heart failure is a disease of old age... and the HIV+ population is aging

Alkindi and Longenecker. In Review, 2017
Heart failure is prevalent in HIV+  

![Graph showing prevalence of heart failure in HIV+ patients across different age groups and gender](image-url)

Alkindi et al (Longenecker), Int J Card 2016
HIV is associated with higher incidence of HF

Butt et al, Arch Int Med 2011

Overall

Coronary artery disease and alcohol excluded
Survival may be worse for women with HIV and HF

Metabolic disease and inflammation may affect HF progression in HIV

- Diabetes
- High BP
- Low HDL
- High TGL

Adiposopathy
- Visceral Fat
- Ectopic Fat
- Peripheral Fat

Aging, ART, Microbial Translocation

Inflammation

Stage A HF
Stage B HF
Stage C HF
Stage D HF

Cardiac Cachexia

Buggey and Longenecker, In Preparation.
**Class I Recommendations for HF Management**

<table>
<thead>
<tr>
<th>Pharmacologic Therapy</th>
<th>Yancy et al. Circulation 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
</tr>
<tr>
<td>All HFrEF with retention</td>
<td>Improve symptoms</td>
</tr>
<tr>
<td>ACE Inhibitor/ARB</td>
<td>All HFrEF</td>
</tr>
<tr>
<td>Improve symptoms and mortality</td>
<td></td>
</tr>
<tr>
<td>ARB + Neprilysin Inhib (ARNI)</td>
<td>NYHA II - III who can tolerate ACE/ARB</td>
</tr>
<tr>
<td>Improve symptoms and mortality</td>
<td></td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>All HFrEF</td>
</tr>
<tr>
<td>Improve symptoms and mortality</td>
<td></td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists (MRA)</td>
<td>NYHA class II - IV</td>
</tr>
<tr>
<td>LVEF &lt; 35%</td>
<td>Beware advanced CKD or hyperkalemia</td>
</tr>
<tr>
<td>Improve symptoms and mortality</td>
<td></td>
</tr>
<tr>
<td>Hydralazine/isosorbide dinitrate</td>
<td>African Americans</td>
</tr>
<tr>
<td>NYHA III - IV</td>
<td>Receiving ACE/BB</td>
</tr>
<tr>
<td>Improve symptoms and mortality</td>
<td></td>
</tr>
</tbody>
</table>

0 Studies in HIV
# Class I Recommendations for HF Management

## Device Therapy

### Implantable Cardioverter Defibrillator (ICD)
- 40 days post-MI
- LVEF ≤35%
- NYHA class II or III
- On good medical therapy
- Expected survival >1 year
- Primary prevention of sudden cardiac death
- Reduce mortality

### Cardiac Resynchronization Therapy with or without defibrillator (CRT or CRT-D)
- LVEF ≤35% or less
- QRS duration ≥150 ms
- Left bundle-branch block (LBBB)
- NYHA class II, III, or IV ambulatory IV
- On good medical therapy
- Improve symptoms
- Reduce mortality

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Studies in HIV

Yancy et al. Circulation 2013

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Sudden cardiac death is common in the modern ART treatment era. The rate of SCD was 4.5-fold higher in HIV+ compared with general population in San Francisco.
Ejection fraction is a powerful predictor of sudden cardiac death in HIV.

### Sudden Cardiac Death

<table>
<thead>
<tr>
<th>EF Category</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF &lt;40*</td>
<td>13.7 (4.1-46.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF 40-50†</td>
<td>1.9 (0.3-10.9)</td>
<td>0.47</td>
</tr>
<tr>
<td>EF 30-39†</td>
<td>9.5 (1.7-53.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>EF &lt;30†</td>
<td>38.5 (7.6-195.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF &lt;40, VL &lt;50*</td>
<td>2.7 (0.3-27.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>EF &lt;40, VL &gt;50*</td>
<td>11.7 (2.9-47.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>14.8 (4.0-55.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic dysfunction, adjusted†</td>
<td>8.0 (2.5-25.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### AIDS Death

<table>
<thead>
<tr>
<th>EF Category</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF 40-50†</td>
<td>1.1 (0.5-2.7)</td>
<td>0.75</td>
</tr>
<tr>
<td>EF 30-39†</td>
<td>1.3 (0.5-3.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>EF &lt;30†</td>
<td>1.8 (0.5-5.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>0.5 (0.1-2.0)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Moyers et al, Am J Cardiology, 2014
Advanced therapies in HIV

► In 2012, 60% of US institutions still considered HIV infection a contraindication for transplant
  – 20% for left-ventricular assist devices

► Case series suggest good outcomes

► Concerns:
  – Infection
  – Progression of HIV disease
  – Pump thrombosis

Heart Failure—Clinical Pearls

- Diastolic and systolic heart failure are both common
- Little is known about medical therapy
  - Treat as in general HIV-uninfected population
- ART does more good than harm
  - Avoid drugs with high mitochondrial toxicity (ZDV, didanosine, stavudine)
- ICD implantation must be a shared decision between patient and providers
- HIV+ on ART can safely undergo advanced therapies
  - Less is known for those with low CD4+ T-cell counts or AIDS
In Conclusion

Imagine a world where HIV+ patients achieve better outcomes and longer lifespan compared with those without HIV.
Team-based cardiovascular risk reduction

Primary HIV care

Dietitian

Nursing Staff

Social Work

Smoking Cessation

HIV Cardiometabolic Risk Clinic