Epidemiological Data: CVD Events in HIV-Patients

- Retrospective cohort studies
- Prospective HIV cohort studies
- Administrative/clinical databases
- Randomized clinical trails of ART

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of patients/No. of events</th>
<th>Event rate per 1,000 HIV+</th>
<th>Event rate per 1,000 HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAD I²</td>
<td>23,468/126</td>
<td>3.5</td>
<td>NA</td>
</tr>
<tr>
<td>DAD I³</td>
<td>23,437/345</td>
<td>3.6</td>
<td>NA</td>
</tr>
<tr>
<td>VA⁴</td>
<td>36,766/1,207</td>
<td>8.1</td>
<td>NA</td>
</tr>
<tr>
<td>Kaiser 2002⁵</td>
<td>4,159/47</td>
<td>4.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Kaiser 2007</td>
<td>5,000/162</td>
<td>3.7</td>
<td>2.2</td>
</tr>
<tr>
<td>MGH⁶</td>
<td>3,851/189</td>
<td>11.13</td>
<td>6.98</td>
</tr>
<tr>
<td>MediCal⁷</td>
<td>28,512/294</td>
<td>4.12</td>
<td>3.32</td>
</tr>
</tbody>
</table>

Infection with HIV is associated with a 50% increased risk of AMI beyond that explained by recognized risk factors.
## Cause of Death in D:A:D

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Percentage(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-related</td>
<td>29</td>
</tr>
<tr>
<td>Liver-related</td>
<td>13</td>
</tr>
<tr>
<td>Non-AIDS cancers</td>
<td>15</td>
</tr>
<tr>
<td>CVD-related</td>
<td>11</td>
</tr>
<tr>
<td>Non-natural</td>
<td>10</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>7</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
</tr>
<tr>
<td>Lactic acidosis/pancreatitis</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Others/Unknown</td>
<td>15</td>
</tr>
</tbody>
</table>

\(^1\)Smith Lancet 2014; \(^2\)ATCC, Clin Infect Dis 2010

7.9 (ATCC)
## Cause of Death in D:A:D

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<tr>
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<td>15</td>
</tr>
</tbody>
</table>

\(^1\)Smith Lancet 2014

\(^2\)7.9 (ATCC)
No Differences in Incidence of MI for HIV+ and HIV- Individuals in Recent Years

Klein et al. CROI 2014

Graph showing the incidence of MI per 100,000 person-years (py) for HIV-positive (red, n=24,768) and HIV-negative (blue, n=257,600) individuals from 1996-99 to 2010-11. The incidence rate for HIV-positive individuals was slightly higher than that for HIV-negative individuals, but the difference was not statistically significant.
### Role of Traditional Risk Factors in HIV+ and HIV-

<table>
<thead>
<tr>
<th>Unit</th>
<th>% increase in risk per unit for each study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+</td>
</tr>
<tr>
<td></td>
<td>Iloeje²</td>
</tr>
<tr>
<td>Age</td>
<td>Per 1 y ↑</td>
</tr>
<tr>
<td>Sex</td>
<td>Male vs female</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes vs No</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes vs No</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes vs No</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Per 1 mm/L ↑</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Per 1 mm/L ↑</td>
</tr>
</tbody>
</table>

Traditional risk factors

- Smoking (47-71%)\(^1,2\)
- Obesity (40-60%)\(^3\)
- Hypertension (31%)\(^4\)
- Dyslipidemia (40-60%)\(^5\)
- Glucose intolerance
- Type 2 diabetes

Traditional risk factors powerfully predict cardiovascular risk in HIV patients

BUT: Lack of specificity

# Incidence of the Metabolic Syndrome in HIV

<table>
<thead>
<tr>
<th>Reference</th>
<th>Incident metabolic syndrome cases</th>
<th>Person-years</th>
<th>Incidence rate (per 100 person-years)</th>
<th>Timeframe of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palacios et al. 2007 [23]</td>
<td>7</td>
<td>50</td>
<td>14</td>
<td>2002-2003</td>
</tr>
</tbody>
</table>
## Incidence of Type 2 Diabetes in HIV

<table>
<thead>
<tr>
<th>Reference</th>
<th>Incident DM cases</th>
<th>Person-years</th>
<th>Adjusted risk estimates* (95% confidence interval)</th>
<th>Timeframe of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected</td>
<td>47</td>
<td>100</td>
<td>4.11 (1.85, 9.16)</td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td>14</td>
<td>100</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>HIV-infected</td>
<td>76</td>
<td>4905</td>
<td>1.90 (1.04, 3.48)</td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td>15</td>
<td>1774</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>HIV-infected</td>
<td>18</td>
<td>4,768</td>
<td>2.83 (1.57, 5.09)</td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td>29</td>
<td>20,992</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Rasmussen et al. 2012 [42••]</td>
<td></td>
<td></td>
<td></td>
<td>1999-2010</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>87</td>
<td>23,574</td>
<td>0.90 (0.72, 1.13)</td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td>499</td>
<td>115,374</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>HIV-infected</td>
<td>491</td>
<td>39,737</td>
<td>0.55 (0.46, 0.65)</td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td>595</td>
<td>39,994</td>
<td>ref</td>
<td></td>
</tr>
</tbody>
</table>
D:A:D: Traditional Risk Factors for CHD in an HIV-infected Population

Multivariable Poisson model adjusted for age, sex, BMI, HIV risk, cohort, calendar year, race, family history of CVD, smoking, previous CVD event, TC, HDL, hypertension, diabetes.

Lipid Profile before HIV Infection

- Total cholesterol
- LDL cholesterol
- Triglycerides
- HDL cholesterol
Lipid Profile due to HIV Infection
Lipid Profile due to Several ARTs
571 HIV+ with first MI, 1304 matched HIV neg. controls

Contribution of the Genetic Background to CAD in HIV Patients
HIV, ART and Aging: A Rough Estimate

- Total world population
- Population over 60 years of age
- German HIV+ > 60 years of age

Population (Billion)

2000: 10%
2015: 15%
2025: 22%
2050: 60%

Population over 60 years of age
Increased Risk for CVD with Age in HIV
HAART and Cardiovascular Disease

- Insulin resistance
  - Type 2 diabetes

- Dyslipidemia
  - High FFA
  - Small dense LDL
  - Low HDL
  - High TG

- Central obesity

Age, genetics, diet, hypertension, sedentary lifestyle, renal disease…
D:A:D: Recent and/or Cumulative Antiretroviral Exposure and Risk of MI

<table>
<thead>
<tr>
<th>NRTI</th>
<th>RR of recent* exposure yes/no</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>ddI</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>ddC</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>d4T</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>3TC</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>ABC</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

*Current or within last 6 months. †Approximate test for heterogeneity: $P = 0.02$

Lundgren JD, et al. CROI 2009. Abstract 44LB.

Only >30,000 PY of follow up
D:A:D: Abacavir and Myocardial Infarction

Stratified by recent* ABC use

Predicted 10-year CHD risk

- Overall
- Low
- Moderate
- High
- Not known

Events
- No recent abacavir: 325, 192, 60, 79, 100, 86
- Recent abacavir: 192, 42, 33, 68, 49

PY
- No recent abacavir: 126581, 57628, 13372, 6293, 49288
- Recent abacavir: 27728, 14754, 4300, 2095, 10182
HIV Drug-Specific Associations to CVD

Insulin resistance
Type 2 diabetes

Dyslipidemia
High FFA
Small dense LDL
Low HDL
High TG

Central obesity

Inflammation ?

HAART

Abacavir
Didanososine
Indinavir
Lopinavir

CVD
# Abacavir and Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Event Ascertainment</th>
<th>Patients (n=)</th>
<th>MI (n=)</th>
<th>Abacavir-effect?</th>
</tr>
</thead>
<tbody>
<tr>
<td>D:A:D</td>
<td>Prospective observ. cohort</td>
<td>Prospective predefined</td>
<td>33,347</td>
<td>580</td>
<td>Yes</td>
</tr>
<tr>
<td>FHDB</td>
<td>Case control in observ. cohort</td>
<td>Prospective, MI retrospectively validated</td>
<td>289 cases</td>
<td>289</td>
<td>Yes, first year of exposure</td>
</tr>
<tr>
<td>SMART</td>
<td>RCT, Observ. analysis</td>
<td>Prospective predefined</td>
<td>2,752</td>
<td>19</td>
<td>Yes</td>
</tr>
<tr>
<td>STEAL</td>
<td>RTC</td>
<td>Prospective</td>
<td>357</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>QPHID</td>
<td>Case control in observ. cohort</td>
<td>ICD 9 code acute MI Not validated</td>
<td>142 cases</td>
<td>142</td>
<td>Yes</td>
</tr>
<tr>
<td>GSK Analysis</td>
<td>RCT (n=54)</td>
<td>Retrospective Data base search</td>
<td>14,174</td>
<td>11</td>
<td>No</td>
</tr>
<tr>
<td>ALLRT ACTG</td>
<td>Long term follow up of 5 RCT</td>
<td>Retrospective 2 independent reviewer</td>
<td>3,205</td>
<td>27</td>
<td>No</td>
</tr>
<tr>
<td>VACCR</td>
<td>Retrospective observ. cohort</td>
<td>ICD 9 code acute MI Not validated</td>
<td>19,424</td>
<td>278</td>
<td>No</td>
</tr>
</tbody>
</table>
Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data

Mario Cruciani\textsuperscript{a}, Veronica Zanichelli\textsuperscript{b}, Giovanni Serpelloni\textsuperscript{a}, Oliviero Bosco\textsuperscript{a}, Marina Malena\textsuperscript{a}, Romualdo Mazzi\textsuperscript{a}, Carlo Mengoli\textsuperscript{b}, Saverio G. Parisi\textsuperscript{b} and Graeme Moyle\textsuperscript{c}

\begin{table}
\centering
\begin{tabular}{llll}
\hline
Study & ABC & Others & Risk Difference \\
\hline
Clumek 2001 & 0 & 104 & 2 & 103 & 10.8\% & 0.20 [0.01, 4.08] \\
CNA 30024 & 1 & 324 & 0 & 325 & 2.1\% & 3.01 [0.12, 73.60] \\
CNAAB3003 & 0 & 83 & 0 & 80 & Not estimable \\
CNAAB3005 & 1 & 262 & 0 & 264 & 2.1\% & 3.02 [0.12, 73.87] \\
CNAB3001 & 0 & 46 & 1 & 48 & 6.3\% & 0.35 [0.01, 8.32] \\
CNAB3002 & 0 & 91 & 0 & 91 & Not estimable \\
CNAF3007 & 1 & 96 & 1 & 91 & 4.4\% & 0.95 [0.06, 14.93] \\
ESS100327 & 0 & 137 & 1 & 141 & 6.3\% & 0.34 [0.01, 8.35] \\
ESS40002 & 1 & 85 & 0 & 166 & 1.5\% & 5.83 [0.24, 141.50] \\
NZTA4002 & 0 & 150 & 3 & 151 & 14.9\% & 0.14 [0.01, 2.76] \\
Opravi 2002 & 0 & 84 & 1 & 79 & 6.6\% & 0.31 [0.01, 7.59] \\
Vibhagool 2004 & 0 & 165 & 0 & 164 & Not estimable \\
Subtotal (95\% CI) & 1627 & 1703 & 55.1\% & 0.66 [0.28, 1.55] \\
\hline
\end{tabular}
\end{table}

Test for overall effect: \( Z = 0.46 (P = 0.64) \)

1.1.2 ABC vs Others

Total events: 4 vs 9

Heterogeneity: \( \chi^2 = 5.75, df = 8 (P = 0.68); \hat{I} = 0\% \)

Test for overall effect: \( Z = 0.96 (P = 0.34) \)

Total (95\% CI): 3488 vs 3566

Total events: 12 vs 19

Heterogeneity: \( \chi^2 = 7.68, df = 12 (P = 0.81); \hat{I} = 0\% \)

Test for overall effect: \( Z = 1.01 (P = 0.31) \)

Cruciani et al. AIDS 2011
The Cruciani Meta Analysis

- No channelling bias!

But

- Low baseline cardiovascular risk
- Low event rates
- Comparator arm +/- PI/r?
- No data on viral replication at the time of the event
- Mostly first line therapy
ABC in vitro:
- induces Mac-1 on leukocytes, which interacts with ICAM-1 on endothelial cells
- increases platelet activity through inhibition of soluble guanylyl cyclase
- facilitates collagen-induced platelet aggregation

ABC in patients:
- STEAL Study
- WIHS and HOPS Cohort
- BICOMBO Study
- HEAT Study

No differences in biomarkers (hsCRP, IL-6, D-dimer, MCP-1…)

1 de Pablo CROI 2010 #716; 2 Baum CROI 2010 #717; 3 Satchell CROI 2009 #151LB7; 4 Martin CROI 2010, #718; 5 Palella AIDS 2010; 6 Martinez AIDS 2010; 7 McComsey CROI 2009 # 732
Search for Independent CVD Risk Factors
Challenges of Useful Independent Risk Factors for CVD (Biomarkers)

- Tells you nothing about clinical utility
- Scientifically: Tells you nothing about causality
- Markers with strong independent associations (adj. RR 2-3) usually will not improve discrimination for CVD
- Biggest challenge: Showing that therapy based on identification of a new marker must improve long-term outcomes (RCT)
Predictive Value of High-Sensitivity C-Reactive Protein

The Mendelian Randomization Approach to Identifying a Causal Association

- **Genetic Variant**
  - Determined
  - Observed = Predicted?

- **Biomarker**

- **Disease**
  - Determined

The Mendelian Randomization Approach to Identifying a Causal Association

SNP CRP gene

CRP level
- Determined

IVD*
- Observed ≠ Predicted

If CRP >3 mg/L, risk increased by a factor of 2.2 versus ≤3 mg/L

* Ischemic Vascular Disease

Atherosclerosis and Immune Cells

Modified from Hansson & Libby.
Atherosclerosis and Immune Cells

Modified from Hansson & Libby.
HIV and Cardiovascular Risk

**HIV induces**

- Apoptosis ↑ in endothelial cells (gp120, Tat)\(^1\text{-}^3\)
- Endothelial dysfunction\(^4\)
- Leukocyte activation\(^5\)
- HDL ↓, IL-6 ↑, sICAM ↑, D-dimer ↑
- MCP-1-CCR2 axis activation\(^6\)
- MCP-1 polymorphism associated with atherosclerosis in HIV\(^7\)
- a distinct (inflammatory) atherosclerosis process?\(^8\)

MCP-1: Monocyte chemotactic protein-1

\(^1\)Sudano, Am Heart J 2006; \(^2\)Huang, J AIDS 2001; \(^3\)Jia, Biochem Biophys Res Commun 2001; \(^4\)Solages, CID 2006; \(^5\)de Gaetano, Lancet Infect Dis 2004; \(^6\)Park Blood 2001; \(^7\)Alonso-Villaverde Circulation 2004; \(^8\)Mehta, Angiology 2003, Baker CID 2010
HIV and Cardiovascular Risk

HIV as a risk factor

- **HIV+HCV**: - sICAM-1 + sVCAM-1 ↑
  - endothelial dysfunction
  - increased risk for MI

- Low CD4 count is risk factor for MI and carotid lesions
- Low CD4 nadir is associated with reduced arterial stiffness
- HAART improves FMD, but not to normal (ACTG 5152s)
- HIV is an independent predictor of increased carotid IMT
- HIV increases tissue factor expression on monocytes

FMD: Flow-mediated dilatation

---

Changes in Immune Activation with Treatment Interruption (ATG 5102)

CD$^+$/HLA-DR+/CD38+

Soluble TNFR II

Conclusion for treatment interruption: Lipids ↓, immune activation ↑
Arterial Inflammation in Patients With HIV

Subramanian et al JAMA 2012
## Signs for CVD in Elite Controllers

<table>
<thead>
<tr>
<th></th>
<th>Elite Controllers (n=10)</th>
<th>Chronic HIV (n=103)</th>
<th>HIV negative (n=43)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary plaques</strong>*</td>
<td>78%</td>
<td>60%</td>
<td>42%</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Total plaque segments</strong></td>
<td>2.5 (0.3, 6.6)</td>
<td>1 (0, 3)</td>
<td>0 (0, 3)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>sCD14 (ng/ml)</strong></td>
<td>1530 (499, 1919)</td>
<td>416 (218, 1614)</td>
<td>241 (134, 395)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>sCD163 (ng/ml)</strong></td>
<td>2841 (1722, 3427)</td>
<td>1247 (829, 1883)</td>
<td>847 (624, 1230)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>hsCRP (mg/l)</strong></td>
<td>0.4 (0.3, 2.4)</td>
<td>1.4 (0.6, 3.9)</td>
<td>1.2 (0.5, 3.1)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*CT Angiopgraphy*
Inflammation and Cardiovascular Disease

- Insulin resistance
- Type 2 diabetes
- Dyslipidemia
  - High FFA
  - Small dense LDL
  - Low HDL
  - High TG
- Central obesity
- HAART
- HIV
- CVD
- Inflammation?
What Does it Mean for Clinical Care?

Viral load
Inflammation
Risk for myocardial infarction

5%

HAART

VL<50 copies

2%
What Does it Mean for Clinical Care?

HAART, lipodystrophy, lipids, insulin resistance, type 2 diabetes...

5%

7%

Viral load

Inflammation

HAART

Risk for myocardial infarction

VL<50 copies

What Does it Mean for Clinical Care?
What Does it Mean for Clinical Care?

Viral load

Inflammation

HAART, lipodystrophy, lipids, insulin resistance, type 2 diabetes…

Risk for myocardial infarction 10%

HAART

VL<50 copies
EACS Guidelines 2014

- Assess CVD risk in the next 10 years
  - Advise on diet and lifestyle in all patients
  - Consider ART modification, if 10 year CVD risk ≥20%

- Smoking

- Blood pressure
  - Drug treatment if: SBP ≥ 140 or DBP ≥ 90 mmHg (especially if 10 year CVD risk ≥ 20%)

- Coagulation
  - Drug treatment if: Established CVD or Age ≥ 50 and 10 year CVD risk ≥ 20%

- Glucose
  - Confirm DM and treat

- Lipids
  - Drug treatment if: Established CVD or T2D or 10 year CVD risk ≥ 20%

---

EACS Guidelines, 2014 www.eacs.com
EACS Guidelines 2014

Assess CVD risk in the next 10 years

Advise on diet and lifestyle in all patients
Consider ART modification, if 10 year CVD risk ≥20%

Identify key modifiable risk factors

**Smoking**

**Blood pressure**

- Target: If T2D or prior CVD or CKD + proteinuria
  - Others
  - SBP<130: <140
  - DBP<80: <90

**Coagulation**

- Target: N/A
- Consider to treat with acetylsalicylic acid 75-150mg

**Glucose**

- Target: HbA1c <6.5-7%

**Lipids**

<table>
<thead>
<tr>
<th>TC</th>
<th>Best</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 (155)</td>
<td>≤5 (190)</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>≤2 (80)</td>
<td>≤3 (115)</td>
</tr>
</tbody>
</table>

Smoking Cessation Decreases Risk of CVD in HIV-infected Patients

*Adjusted for: age, cohort, calendar yr, antiretroviral treatment, family history of CVD, diabetes, time-updated lipids and blood pressure assessments.

Petoumenos et al. HIV Medicine 2011
The ART Drug Profile

- Antiviral activity
- Metabolisation
- Resistance profile
- Pharmacokinetics
- Drug-drug interaction
- $C_{\text{max}}$
- Lipid profile…
Atheroma formation and growth

Plaque instability and rupture

Hyper-coagulability

Age

Nicotine

Hypertension

Obesity

Lipids

Glucose

HIV

Inflammation

Lipids

Glucose

Fat tissue

HIV-therapy

Behrens & Reiss Curr Opin Infect Dis 2010
Summary

1995  2005  2015  2025

Drug-associated „Metabolics“  Inflammation

Clinical end points  Ageing