HIV and CVD
Do we really understand the risk?

Dr Paddy Mallon

UCD HIV Molecular Research Group
Associate Dean for Research and Innovation
UCD School of Medicine and Medical Science

paddy.mallon@ucd.ie

UCD School of Medicine & Medical Science
Scoil an Leighis agus Eolaíocht an Leighis UCD

HIV and CVD – incidence of MI

• AMI commonest cause of death in ART-treated patients¹
• Rates of MI higher in HIV-positive versus HIV-negative²

Within age group P<0.05

AMI=acute myocardial infarction; CI=confidence interval.

AMI rates / 1000 patient years (95% C.I)

• RR of MI with age not different between HIV and the general population risk estimates³


CVD – assessing risk

D:A:D and ASCVD lower risk profile than FHS-CVD¹

HIV and MI

Characteristics of those with MI in D:A:D

<table>
<thead>
<tr>
<th>Year of MI</th>
<th>99-02</th>
<th>03-04</th>
<th>05-06</th>
<th>07-08</th>
<th>09-11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MIs</td>
<td>212</td>
<td>194</td>
<td>157</td>
<td>171</td>
<td>110</td>
</tr>
<tr>
<td>Male (%)</td>
<td>91.0</td>
<td>92.8</td>
<td>90.5</td>
<td>89.5</td>
<td>92.7</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>48</td>
<td>49</td>
<td>49</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td>398</td>
<td>444</td>
<td>454</td>
<td>434</td>
<td>546</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>49.5</td>
<td>46.9</td>
<td>46.9</td>
<td>57.3</td>
<td>58.2</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>14.2</td>
<td>13.9</td>
<td>14.7</td>
<td>15.2</td>
<td>13.6</td>
</tr>
<tr>
<td>High risk (%)</td>
<td>28.8</td>
<td>23.2</td>
<td>22.3</td>
<td>26.9</td>
<td>32.7</td>
</tr>
<tr>
<td>1 mth mortality (%)</td>
<td>26.4</td>
<td>24.7</td>
<td>19.8</td>
<td>16.4</td>
<td>8.2</td>
</tr>
</tbody>
</table>

HIV and MI – role of traditional risk factors

Framingham risk assessment may underestimate MI risk in HIV
Observed and predicted MI rates according to ART exposure (D:A:D Study)

HIV and CVD – incidence of MI

CVD risk prediction equations consistently underestimate CVD risk in HIV+ subjects
- Partners Healthcare System HIV longitudinal cohort (n=2270)
- HIV Outpatient Study cohort (n=2392)

Observed vs. Predicted 5-Year CVD Outcomes

HIV & CVD

What are the unmeasured risks?

Cardiovascular events: Do drugs matter?

D:A:D: MI risk is associated with recent and/or cumulative exposure to specific NRTIs and PIs

Platelet dysfunction

May explain reversible increased risk of MI with ABC
Increased platelet reactivity in HIV-infected patients on abacavir-containing ART
Switching from Lamivudine/Abacavir (3TC/ABC) to Emtricitabine/Tenofovir DF (FTC/TDF) Based Regimen (SWIFT) Study

Platelet Biology Sub-study

O’Halloran JA1, Dunne E2, Tinago W1, Denieffe S1, Kenny D2, Mallon PWG1

1HIV Molecular Research Group, School of Medicine and Medical Science, University College Dublin, Dublin, Ireland, 2Cardiovascular Biology Group, Royal College of Surgeons in Ireland, Dublin, Ireland

Aim of SWIFT platelet biology sub-study

To examine changes in markers of platelet function as a sub-study of the SWIFT trial

SWIFT Study design

- ABC/3TC + PI/r for ≥ 3 months HIV RNA <200c/ml ≥ 3 months
- TDF/FTC + PI/r
- ABC/3TC + PI/r
- 1:1 randomisation

SWIFT Study - results

- Significant increase in sGPVI in the TDF/FTC group
  - (+0.57 ng/ml, 95% CI; 0.2 - 0.94), p=0.003
  - Persisted when corrected for age, gender ethnicity, smoking status, history of dyslipidaemia or hypertension, baseline CD4+ T-cell and platelet count and creatinine and change from baseline to week 48 in creatinine


No between-group difference in the change in sP-selectin, sCD40L and vWF to 48 weeks

GPVI and CVD

Imbalance in soluble versus platelet-bound GPVI in both ACS\(^1\) and stroke\(^2,3\)

Dyslipidaemia in HIV UPBEAT

HIV, HDL and monocytes

Monocyte Cholesterol Efflux (MCE) assay

Quantification of MIC/EC standardised for total cell count in HIV neg subjects

MCE = ratio of extracellular to intracellular cholesterol (EC\(_T\): MIC\(_T\))

Additional 24 hr measure with ApoA1 (EC\(_A\): MIC\(_A\)).
Monocyte Cholesterol Efflux (MCE) assay

Untreated HIV associated with enhanced, not inhibited, MCE!

Effect of initiating antiretroviral therapy on markers of monocyte activation, endothelial dysfunction and platelet activation in HIV-1 infection

O’Halloran J et al. CROI 2015; abstract 732

Markers of monocyte activation

- Both sCD14 & sCD163 were significantly higher in untreated HIV+ subjects compared to HIV- controls
- ART initiation resulted in significant reductions in sCD163
- No effect on sCD14 with ART initiation

Markers of endothelial dysfunction

- Pre-ART, higher ICAM-1, VCAM-1 and vWF versus controls
- Significant reductions in all endothelial markers post ART initiation
- Remained higher than control values at week 12
Markers of platelet function

- Pre-ART sGPVI, sCD40L and sP-selectin higher in HIV+ subjects compared with HIV- controls
- All platelet markers significantly reduced with ART, to levels observed in controls

HIV and CVD summary

- Excess risk of CVD in those with HIV, despite effective therapy
- Traditional risk factors do not fully explain excess CV risk
- Drug and HIV-specific effects on vascular function and thrombosis among the potential contributory mechanisms
- Complex interactions between gut, immune activation, coagulation and endothelial dysfunction
- Improve risk assessment – systems biology

Future research to understand risk

**REPRIEVE**

‘Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults’

- NHLBI / NIAID ‘A5332’
- Pitavastatin 4mg vs placebo
- N=6,500, HIV+ on ART, age >40 yrs, ASCVD risk <7.5%
- 1st endpoint time to CVD event
- 2nd endpoints include non-calcified plaque, inflammation (sCD163)

Future research to understand risk

**‘Pharmacokinetic and Clinical Observations in People over Fifty’**

UK and Ireland

The Netherlands

Future research to understand risk

Acknowledgements

HIV Molecular Research Group:
- Dr Eoin Fozney
- Dr Tara McGinty
- Dr Jane O’Halloran
- Dr Elena Alvarz-Barco
- Robert Maughan
- Willard Tinago
- Alan Mackan
- Abbe Flaherty
- Sadbhíh Tennant
- Aoife Lacey
- Joanne Maher
- Maria Byrne

Infectious Diseases MMUH:
- Dr Jack Lambert
- Dr Gerard Sheehan