Rates of Cardiovascular Disease Following Smoking Cessation in Patients with HIV Infection: Results from the D:A:D Study

On behalf of the D:A:D study group
Background (1)

• Rates of tobacco smoking in HIV-positive patients are very high across virtually all populations in developed countries
• In the era of cART increased risk of smoking associated disease (e.g., cardiovascular disease, pulmonary disease and non-AIDS malignancies) and death
• Smoking tobacco is independently associated with mortality and morbidity in HIV-positive patients
• Despite this evidence rates of smoking remain high in HIV-positive patients
Background (2)

- In HIV-negative smokers there is a substantial reduction in coronary heart disease within one to two years of stopping smoking.
- Clinical benefits from stopping smoking have not previously been reported in an HIV-positive population.
- If similar evidence could be found among HIV-positive smokers, this might provide further incentive for quitting.
Objective

- To estimate the rates of cardiovascular disease events and mortality after stopping smoking among patients in the D:A:D study
Methods (1)

- The D:A:D study is a prospective, multi-national observational study formed by the collaboration of 11 cohorts of HIV-infected patients.

- 33,308 HIV-positive patients are followed in 212 clinics in Europe, the US and Australia

- Primary objective: to establish whether the use of cART is associated with an increased risk of CVD

- Secondary objectives: diabetes-mellitus, stroke and invasive cardiovascular procedures; non-AIDS cancers, renal failure and liver failure
Methods (2)

- All D:A:D patients who report smoking status at baseline, and no prior CVD, were included.
- *Current* (yes/no) and *ever* (yes/no) smoking status is collected at each visit.
- Duration of stopping smoking determined only for current smokers at baseline:
  - Calculated from the mid-point between the last visit where patients reported being a current smoker to the first visit s/he reported being a non-smoker.
  - Patients who reported that they re-started smoking were assumed to do so at the mid-point of the respective visits.
Endpoints

- Myocardial infarction (MI): fatal and non-fatal cases
- Coronary heart disease (CHD): MI plus invasive coronary artery procedure (including coronary artery by-pass or angioplasty), or death from other CHD
- Cardiovascular disease (CVD): CHD plus carotid artery endarterectomy, or stroke
- All-cause mortality
Statistical Methods

• Event rates were calculated for never smokers, ex-smokers at D:A:D study entry, current smokers, and smokers who stopped during D:A:D follow-up

• Incidence rate ratios (IRR) were determined using Poisson regression adjusted for:
  • age, sex, cohort, calendar year, family history of CVD, diabetes, and time-updated lipids and blood pressure assessments, antiretroviral treatment
  • Mortality endpoint also adjusted for: HCV, HBV, mode of HIV exposure, ethnicity and incidence of CVD during follow-up
## Results (1)

<table>
<thead>
<tr>
<th>Smoking status at baseline</th>
<th>Reported stopping smoking during D:A:D follow-up&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never smoked (n=8920)</strong></td>
<td><strong>Ex-smoker (n=6265)</strong></td>
</tr>
<tr>
<td>Age (years)</td>
<td>38 (33, 46)</td>
</tr>
<tr>
<td>Female</td>
<td>35.2%</td>
</tr>
<tr>
<td>Transmission group</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>45.1%</td>
</tr>
<tr>
<td>Homosexual</td>
<td>41.8%</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>5.0%</td>
</tr>
<tr>
<td>White</td>
<td>47.9%</td>
</tr>
<tr>
<td>HCV Positive</td>
<td>8.4%</td>
</tr>
<tr>
<td>HBV Positive</td>
<td>14.3%</td>
</tr>
<tr>
<td>CD4 count</td>
<td>406 (255, 591)</td>
</tr>
<tr>
<td>Viral load &gt;50 copies/ml</td>
<td>62.9%</td>
</tr>
<tr>
<td>cART exposure (years)</td>
<td>1.5 (0, 3.0)</td>
</tr>
<tr>
<td>PI exposure (years)</td>
<td>1.0 (0, 2.7)</td>
</tr>
</tbody>
</table>

1. Characteristics at first attempt to stop smoking. Figures are medians (inter quartile ranges) unless otherwise specified.
## Results (2)

**Smoking status at baseline**

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Never Smoked (n=8920)</th>
<th>Ex-smoker (n=6265)</th>
<th>Current Smoker (n=11951)</th>
<th>Reported smoking during D:A:D follow-up (^1) (n=8197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>120 (115, 130)</td>
<td>120 (110, 130)</td>
<td>120 (110, 130)</td>
<td>120 (110, 130)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80 (70, 84)</td>
<td>80 (70, 82)</td>
<td>80 (70, 80)</td>
<td>80 (70, 80)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.0 (4.2, 6.0)</td>
<td>5.0 (4.2, 6.0)</td>
<td>4.9 (4.0, 5.8)</td>
<td>5.0 (4.2, 5.8)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.2 (0.9, 1.4)</td>
<td>1.1 (0.9, 1.4)</td>
<td>1.1 (0.9, 1.4)</td>
<td>1.2 (0.9, 1.4)</td>
</tr>
<tr>
<td>Cholesterol:HDL ratio</td>
<td>4.4 (3.4, 5.7)</td>
<td>4.6 (3.4, 6.0)</td>
<td>4.4 (3.4, 5.7)</td>
<td>4.3 (3.3, 5.6)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.5 (1.0, 2.6)</td>
<td>1.6 (1.1, 2.7)</td>
<td>1.6, (1.1, 2.6)</td>
<td>1.7 (1.1, 2.7)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>23.5 (21.5, 25.8)</td>
<td>23.0 (21.1, 25.2)</td>
<td>22.5 (20.7, 24.6)</td>
<td>22.8 (20.9, 25.0)</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>6.4%</td>
<td>7.9%</td>
<td>9.7%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.2%</td>
<td>3.1%</td>
<td>1.9%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

\(^1\) Characteristics at first attempt to stop smoking. Figures are medians (inter quartile ranges) unless otherwise specified.
Myocardial Infarction

![Graph showing the incidence rate ratio (IRR) for myocardial infarction across different smoking statuses and durations.]

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

- Never smoked
- Previous
- Current

Baseline status

- 1.60

Stopped smoking during follow-up

- < 1 yr: 2.93
- 1-2 yrs: 2.48
- 2-3 yrs: 1.90
- 3+ yrs: 1.83

Adjusted for: age, sex, cohort, calendar year, antiretroviral treatment, family history of CVD, diabetes, and time-updated lipids and blood pressure assessments.
Cardiovascular disease

<table>
<thead>
<tr>
<th>Smoking History</th>
<th>IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous</td>
<td>1.38</td>
</tr>
<tr>
<td>Current</td>
<td>2.19</td>
</tr>
</tbody>
</table>

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

Adjusted for: age, sex, cohort, calendar year, antiretroviral treatment, family history of CVD, diabetes, and time-updated lipids and blood pressure assessments, HCV, HBV, mode of HIV exposure, ethnicity and incidence of CVD during follow-up
Mortality (>50 years)

Adjusted for: age, sex, cohort, calendar year, antiretroviral treatment, family history of CVD, diabetes, and time-updated lipids and blood pressure assessments, HCV, HBV, mode of HIV exposure, ethnicity and incidence of CVD during follow-up
Limitations

- Smoking data collected as Yes/No at each visit, no start/stop dates; no pack/years
  - *Akin to measurement error, though difficult to see how this might generate an association*

- Patients with smoking status reported at baseline but not during follow-up
  - *Sensitivity analysis excluding these patients reached similar conclusions*

- Difficult to establish cause and effect when assessing mortality
  - *Future analyses of other serious non-AIDS events might help*
Conclusion

- The risk of CVD events in HIV-positive patients decreased with increasing time since stopping smoking
- However, we did not see this in terms of mortality
- Smoking cessation efforts should be a priority in the management of HIV-positive patients
- Further research needed regarding smoking cessation in this population:
  - Clinical research
  - Behavioural research
Acknowledgements

- **Cohort PI's:** W E-Sadr * (CPCRA), G Calvo * (BASS), F Dabis * (Aquitaine), O Kirk * (EuroSida), M Law * (AHOD), A d’Arminio Monforte * (ICONA), L Morfeldt * (HivBIVUS), C Pradier * (Nice), P Reiss * (ATHENA), R Weber * (SHCS), S De Wit * (Brussels)
- **Cohort coordinators and data-managers:** S Zaheri, L Gras (ATHENA), M Bruyand, S Geffard, (Aquitaine), K Petoumenos, S Marashi Pour (AHOD), S Mateu, F Torres (BASS), M Delforge (Brussels), G Bartsch, G Thompsen (CPCRA), J Kjær (EuroSIDA), I Fanti (ICONA), E Fontas, C Caissotti (Nice), A Sundström, G Thulin (HivBIVUS), M Rickenbach (SHCS)
- **Statisticians:** CA Sabin*, AN Phillips*, Alim Kamara
- **Community representative:** S Collins *
- **D:A:D coordinating office:** SW Worm N Friis-Møller, R Brandt, JD Lundgren *¢
- **Steering Committee:** Members indicated w/*; ¢ chair;
  Additional members: S Storfer *, G Pearce*, B Rode *
- **Funding:** ‘Oversight Committee for The Evaluation of Metabolic Complications of HAART’ with representatives from academia, patient community, FDA, EMEA and a consortium of "Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Hoffmann-La Roche and Tibotec"