Association between modifiable and non-modifiable risk factors and specific causes of death in the HAART era:

Results from the D:A:D study


on behalf of D:A:D Study Group
Although dramatic reductions in death rates have been seen amongst HIV-infected individuals in recent years, they remain higher than those observed in the general population.

Additionally, there is still limited evidence on the extent to which modification of some risk factors could further reduce death rates in this population.

Thus, we investigated the specific causes of death, and aimed to identify potentially modifiable risk factors associated with these.
All participants in the D:A:D study, a collaboration of 11 cohorts from Europe, USA and Australia, were included.

Individuals were prospectively followed from study entry until last follow-up or date of death.

Database used for analysis closed February 2007.

Causes of death were assigned according to the underlying cause determined by CoDe system (http://www.cphiv.dk)
Factors associated with specific causes of death were identified using Poisson regression:

- **Non-modifiable risk factors:** Age, gender
- **Modifiable non-HIV-specific risk factors:** Smoking status, BMI, diabetes, HBV status, HCV status, hypertension *
- **Modifiable HIV-specific risk factors:** Current CD4 and HIV-RNA

All results presented are adjusted for above risk factors, as well as race, HIV risk, calendar year and ART use.

Hypertension, current CD4 and current HIV-RNA lagged by 3 months.

*Receipt of anti-hypertensives, SBP>140 mmHg or DBP>90 mmHg*
<table>
<thead>
<tr>
<th>Study Entry Characteristics (1)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of participants</strong></td>
<td>33,347 (100)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24,692 (74)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14,890 (45)</td>
</tr>
<tr>
<td>Black African</td>
<td>3,470 (10)</td>
</tr>
<tr>
<td>Prohibited/Other</td>
<td>14,987 (45)</td>
</tr>
<tr>
<td><strong>Risk for HIV Transmission</strong></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>14,376 (43)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>10,047 (30)</td>
</tr>
<tr>
<td>IDU</td>
<td>5,951 (18)</td>
</tr>
<tr>
<td>Other</td>
<td>2,973 (9)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>11,316 (34)</td>
</tr>
<tr>
<td>Ex</td>
<td>5,617 (17)</td>
</tr>
<tr>
<td>Never</td>
<td>8,754 (26)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7,660 (23)</td>
</tr>
<tr>
<td><strong>HCV antibody</strong></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6,606 (20)</td>
</tr>
<tr>
<td><strong>HBV surface antigen</strong></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>4,755 (14)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>952 (3)</td>
</tr>
</tbody>
</table>
## Study Entry Characteristics (2)

<table>
<thead>
<tr>
<th>% with measurement</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>100</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>86</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>55</td>
</tr>
<tr>
<td>HIV-RNA viral load (log copies/ml)</td>
<td>96</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)</td>
<td>97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number exposed (%)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative ART exposure (years)</td>
<td>24,391 (73)</td>
</tr>
<tr>
<td>Cumulative HAART exposure (years)</td>
<td>22,562 (68)</td>
</tr>
<tr>
<td>Cumulative PI exposure (years)</td>
<td>19,332 (58)</td>
</tr>
<tr>
<td>Cumulative NNRTI exposure (years)</td>
<td>11,063 (33)</td>
</tr>
<tr>
<td>Cumulative NRTI exposure (years)</td>
<td>24,299 (73)</td>
</tr>
</tbody>
</table>
• There were 2,192 deaths over 158,959 person-years

Death Rate = 13.8 per 1000 person-years
(95% CI 13.2-14.4)
Causes of death

- AIDS-related (32%)
- Liver-related (14%)
- Non-AIDS Cancers (12%)
- CVD-related (11%)
- Non-Natural (9%)
- Bacterial infection (7%)
- Lactic Acidosis/Pancreatitis (1%)
- Renal (1%)
- Other/Unknown (13%)

D:A:D
Non-modifiable risk factors
Age and Gender

Adjusted rate ratio (95% CI)

- Overall
- AIDS
- Liver
- CVD
- Non-AIDS Malignancies

D:A:D
Age and Gender

Adjusted rate ratio (95% CI)

Overall  
AIDS  
Liver  
CVD  
Non-AIDS Malignancies

Age
Per 10 years older

Gender
Male vs. Female
Modifiable non-HIV-specific factors
Smoking Status

Adjusted rate ratio (95% CI)

Overall  
AIDS  
Liver  
CVD  
Non-AIDS Malignancies

Current  Ex smoker  Unknown  Never (ref.)
Smoking Status

Adjusted rate ratio (95% CI)

Overall  AIDS  Liver  CVD  Non-AIDS Malignancies

D:A:D

Current  Ex smoker  Unknown  Never (ref.)
Body Mass Index (kg/m²)

Adjustment rate ratio (95% CI)

Overall  | AIDS  | Liver  | CVD   | Non-AIDS malignancies

<18  | 1     | 10    | 0.1   | <18 (ref.)
18-25 | 1     | 10    | 0.1   | 18-25
26-30 | 0.5   | 5     | 0.5   | 26-30
30+   | 0.5   | 5     | 0.5   | 30+

D:A:D
Body Mass Index (kg/m²)

<table>
<thead>
<tr>
<th>Category</th>
<th>&lt;18</th>
<th>18-25 (ref.)</th>
<th>26-30</th>
<th>30+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-AIDS malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted rate ratio (95% CI)

D:A:D
Body Mass Index (kg/m²)

<table>
<thead>
<tr>
<th>Adjusted rate ratio (95% CI)</th>
<th>Overall</th>
<th>AIDS</th>
<th>Liver</th>
<th>CVD</th>
<th>Non-AIDS malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>18-25 (ref.)</td>
<td></td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>26-30</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30+</td>
<td></td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Hypertension and Diabetes

Adjusted rate ratio (95% CI)

Overall
AIDS
Liver
CVD
Non-AIDS Malignancies

Hypertensive
Yes vs. No

Diabetic
Yes vs. No
Hypertension and Diabetes

Adjusted rate ratio (95% CI)

Overall
AIDS
Liver
CVD
Non-AIDS Malignancies

Hypertensive
Yes vs. No

Diabetic
Yes vs. No
Modifiable HIV-specific risk factors
CD4 and HIV-RNA status

<table>
<thead>
<tr>
<th>CD4 HIV-RNA (log copies/ml) and ART status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted rate ratio (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
</tr>
</tbody>
</table>

- Per 100
- <2.6 on
- >2.6 on
- <4 off
- 4-5 off
- >5 off
CD4 and HIV-RNA status

Adjusted rate ratio (95% CI)

Overall, AIDS, Liver, CVD, Non-AIDS Malignancies

Per 100
<2.6 on
>2.6 on
<4 off
4-5 off
>5 off

CD4, HIV-RNA (log copies/ml) and ART status
CD4 and HIV-RNA status

Adjusted rate ratio (95% CI)

Overall  AIDS  Liver  CVD  Non-AIDS Malignancies

Per 100  <2.6 on  >2.6 on  <4 off  4-5 off  >5 off

CD4  HIV-RNA (log copies/ml) and ART status
CD4 and HIV-RNA status

- Adjusted rate ratio (95% CI)
  - Overall
  - AIDS
  - Liver
  - CVD
  - Non-AIDS Malignancies

Per 100

<2.6 on
2.6 on
<4 off
4-5 off
>5 off

CD4
HIV-RNA (log copies/ml) and ART status
CD4 and HIV-RNA status

Adjusted rate ratio (95% CI)

Overall  AIDS  Liver  CVD  Non-AIDS Malignancies

Per 100  <2.6 on  >2.6 on  <4 off  4-5 off  >5 off

CD4  HIV-RNA (log copies/ml) and ART status
Summary (1)

- This study reiterates the importance of addressing traditional, non-HIV specific, risk factors in order to further reduce death rates in HIV-positive populations.

- Additionally, high CD4 cell counts and control of HIV replication is associated with reduced risk of death for some specific non-AIDS related causes.

- Further reductions in mortality in HIV-infected populations may only be possible if these factors are appropriately addressed.
Summary (2)

• Large cohort collaborations with systematic ascertainment enable us to investigate factors associated with specific causes of death

• However, even in this study with 160,000 person-years, there is still limited power for some specific causes (e.g. renal disease)

• Although we see an association between the CD4 count/HIV-RNA level and non-AIDS mortality, there is currently no evidence that modifying these markers will reduce the risk of non-AIDS mortality
D:A:D Study Group

- **Cohort PIs:** W El-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)

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- **Statisticians:** C Sabin*, A Phillips*, A Kamara, C Smith

- **Community representative:** S Collins*

- **DAD coordinating office:** SW Worm, N Friis-Møller, A Sawitz, J Lundgren*¢

- **Steering Committee:** Members indicated with *; ¢ chair; Additional members: S Storfer*, D Pizzuti*, I Weller*

- **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, Roche and Tibotec