D:A:D

Data Collection on Adverse Effects of Antiretroviral Drugs

Relationship between the use of stavudine and new onset diabetes mellitus (DM) : the D:A:D study

S. De Wit, C. Sabin, R. Weber, SW. Worm, P. Reiss,
R Thiebaut, W. El-Sadr, A. D'Arminio Monforte, E Fontas, M. Law,
AN Phillips, N Friis-Møller and JD Lundgren

On behalf of the D:A:D Study Group

Background

- **The causes of insulin resistance and DM among treated HIV-infected patients are multifactorial:**
  - **Established risk factors (e.g. obesity, genetic influences, physical inactivity)**
  - **Drugs used to treat HIV infection**
  - **Lipodystrophy (which may be a consequence of drug treatment)**

D:A:D

Purpose of the study

- **To evaluate whether specific anti-HIV drugs or drug combinations (cART) are associated with the onset of DM.**
- **To evaluate whether known clinical and metabolic risk factors for DM influence or can explain any such associations.**

D:A:D

Methods

- **D:A:D, initiated in 2000, contains data on 33,389 HIV+ve patients from 11 cohorts in Europe, Australia and the US**
- **DM has been collected as a secondary endpoint since the initiation of the study; all prospectively reported cases are validated using the D:A:D case reporting form**
- **New onset DM are defined as :**
  - Fasting plasma glucose >7.0 mmol/L (126 mg/dL), measured on two or more consecutive occasions .
  - In the absence of laboratory data, initiation of anti-diabetic therapy (dietary advice, insulin or oral antidiabetic drugs) .

D:A:D

Statistical methods

Factors associated with new onset DM were identified using Poisson regression models:

1. **Assessment of the univariable relationships between duration of exposure to cART and the rate of new DM.**

2. **Assessment whether the relationship applies to all drugs similarly or is limited to specific drugs, after adjustment for other risk factors for DM and cohort.**

3. **Further adjustment for changes in lipid values (TC, HDL-C, $\log_2$ transformed TG) and lipodystrophy (all as time-updated covariates).**

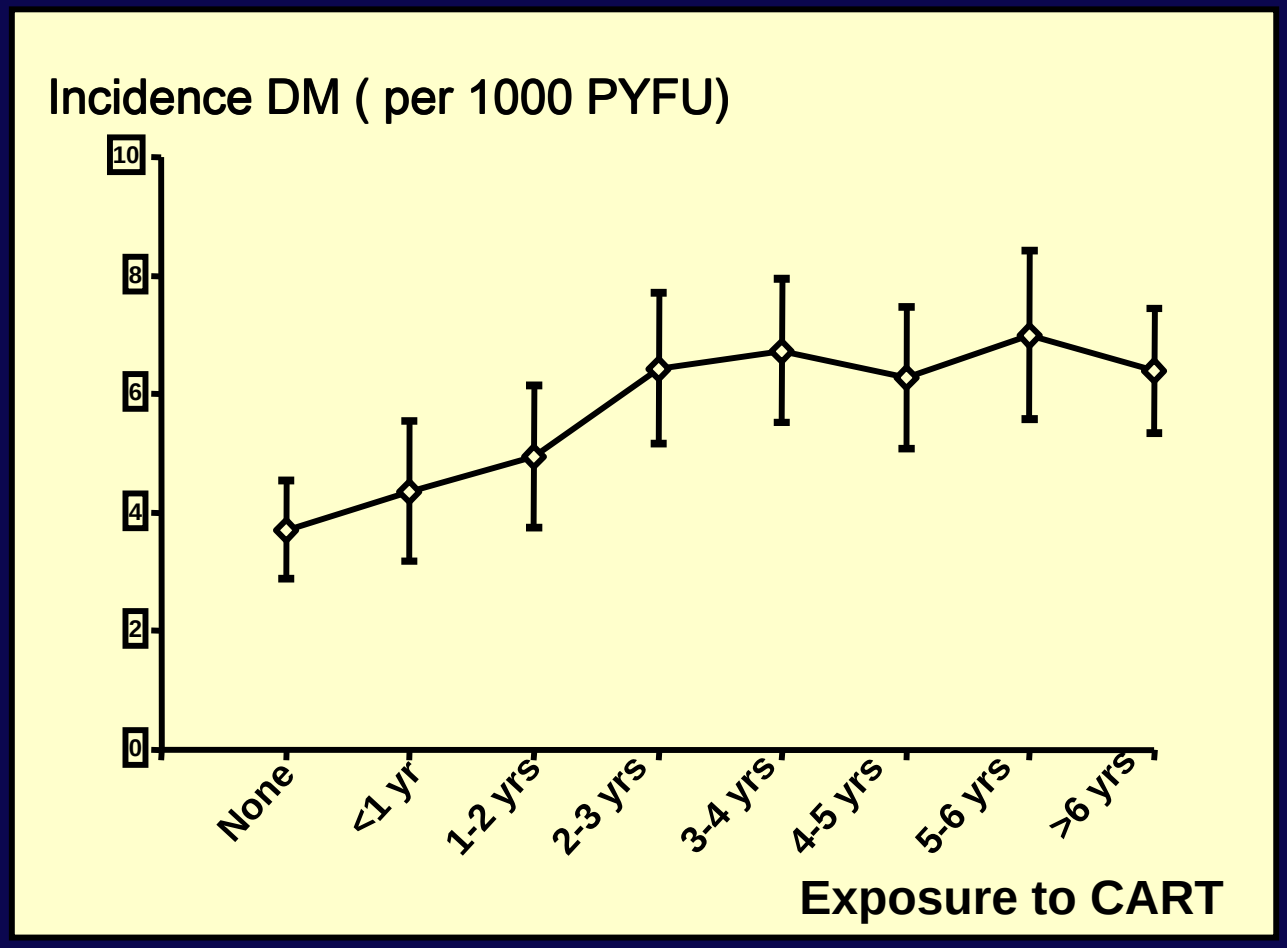
D:A:D

Incidence of DM in D:A:D

- **Overall, 952 of the 33389 (2.85%) of patients had DM at entry to D:A:D. These individuals were excluded from the analysis.**
- **Among the remaining 32437 patients, there were 745 new diagnoses of DM over 130148 person-years**
- **The incidence of DM in D:A:D is 5.72 per 1,000 PYFU**

D:A:D

Incidence of DM and exposure to CART



Unadjusted relative rate per year of exposure to cART :
1.06 [95 % CI 1.03-1.09], p = 0.0001

D:A:D

Relationships between exposure to individuals drugs and incidence of DM

Cumulative exposure to:	Relative rate	95% CI	p-value
Stavudine (per year)	1,19	1.15-1.24	0,0001
Zidovudine (per year)	1,06	1.03-1.10	0,0003
Didanosine (per year)	1,06	1.01-1.11	0,008
Ritonavir (per year)	0,94	0.89-0.99	0,02
Nevirapine (per year)	0,89	0.84-0.95	0,0003

- **Adjusted for age, sex, BMI, race, smoking status , calendar year and cohort.**

D:A:D

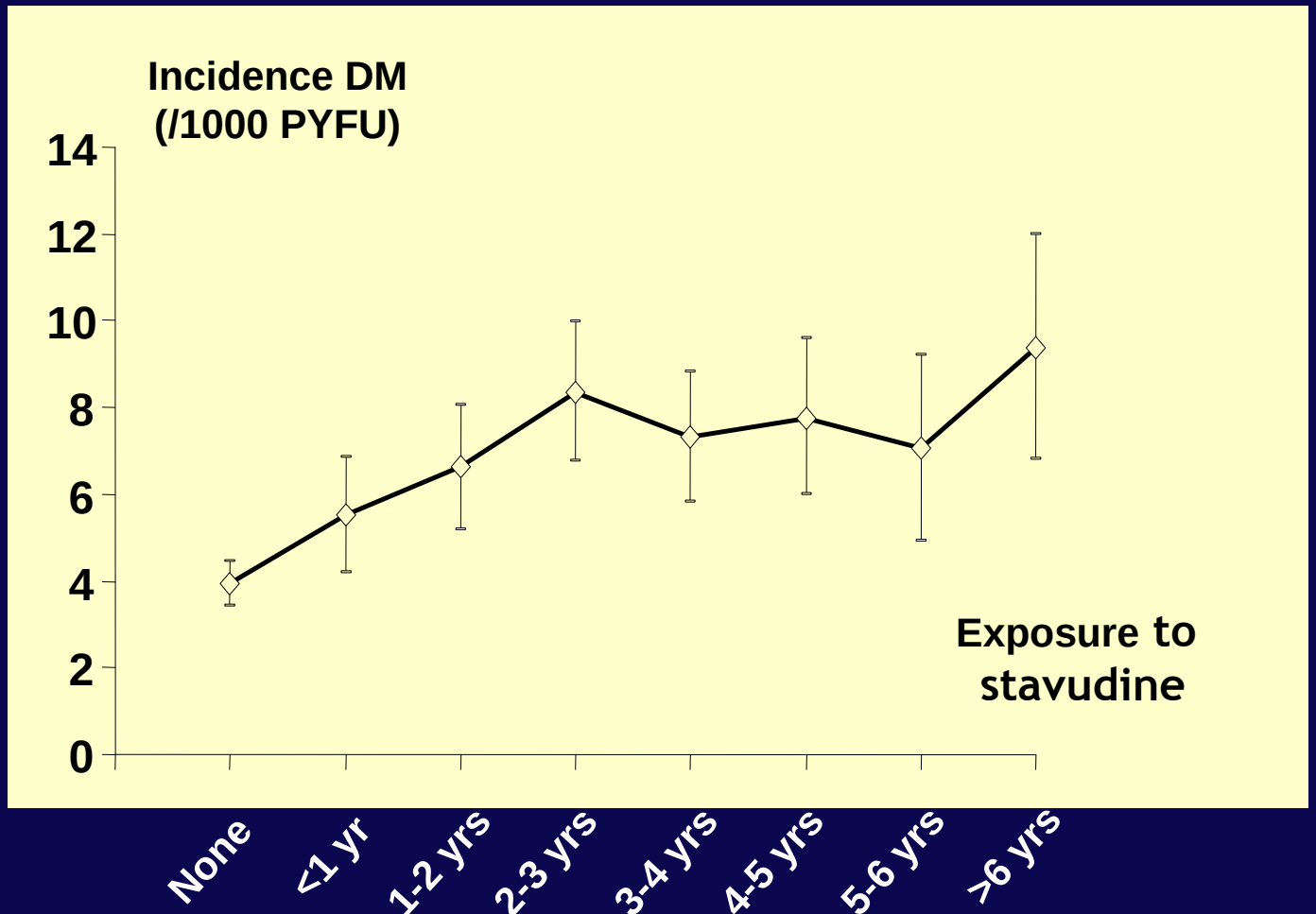
Relationships between exposure to individuals drugs and incidence of DM

Cumulative exposure to:	Relative rate	95% CI	p-value
Stavudine (per year)	1,19	1.15-1.24	0,0001
Zidovudine (per year)	1,06	1.03-1.10	0,0003
Didanosine (per year)	1,06	1.01-1.11	0,008
Ritonavir (per year)	0,94	0.89-0.99	0,02
Nevirapine (per year)	0,89	0.84-0.95	0,0003

- **Adjusted for age, sex, BMI, race, smoking status calendar year and cohort.**

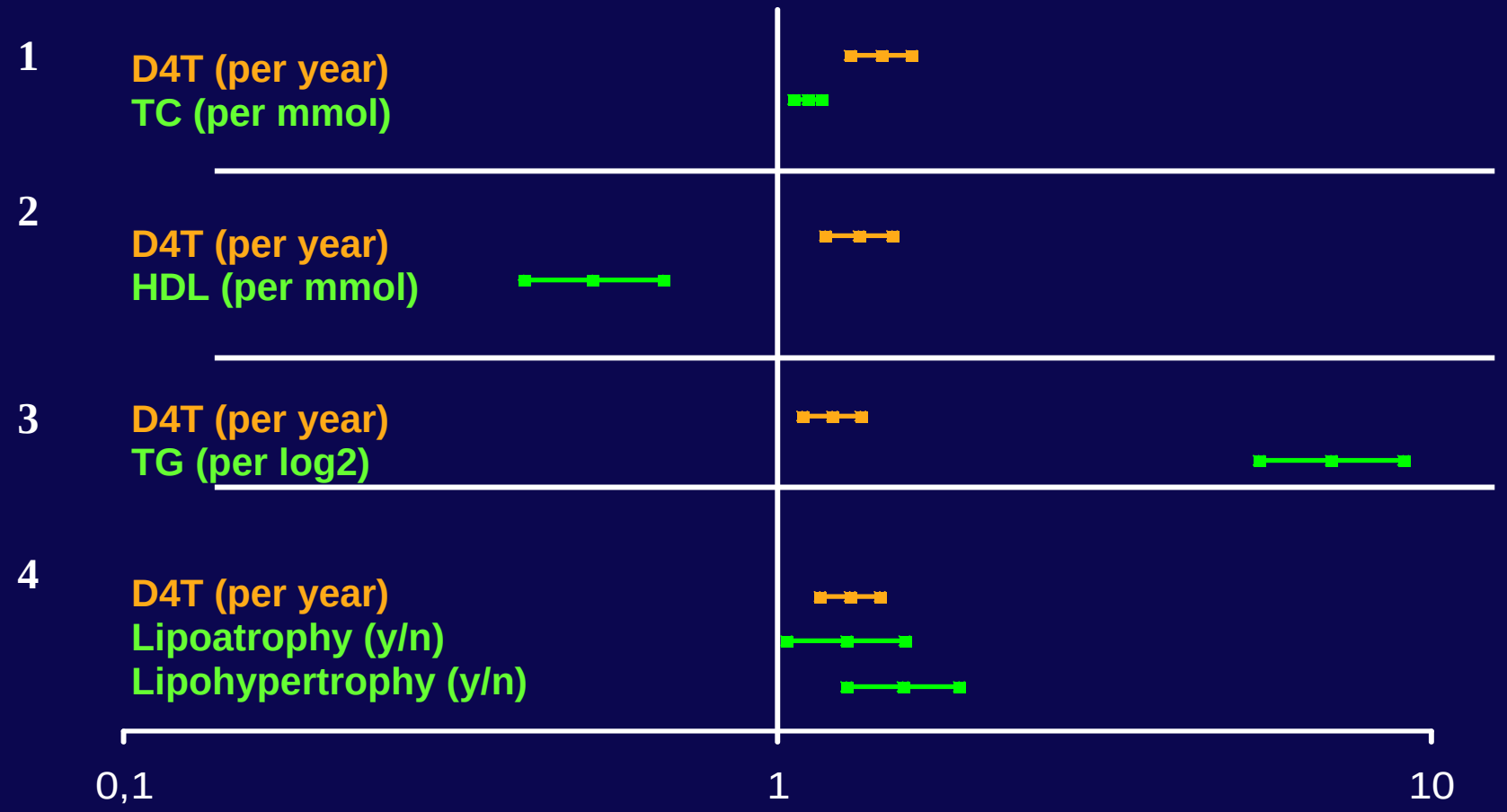
D:A:D

Incidence of DM and exposure to stavudine



D:A:D

Stavudine and risk of DM after adjustment for lipids and lipodystrophy



Adjusted for age, sex, BMI, risk group, race, smoking status, calendar year and cohort

D:A:D

Other risk factors for DM

- Older age, male sex, greater BMI, black race, IDU and earlier calendar year were all associated with an increased risk of DM
- Current smoking status was associated with a marginally non-significant lower risk of new onset DM
- No significant relationship with patient's nadir CD4 count or duration of HIV infection at enrolment in D:A:D

Summary

- The incidence of DM in D:A:D is 5.72 per 1,000 PYFU
- Stavudine is the antiretroviral drug that is the most strongly associated with new onset DM, although weaker relationships also exist with
  - zidovudine and didanosine
  - ritonavir, nevirapine (both apparently protective)
- This relationship remains significant after adjustment for recognized risk factors for DM (age, sex, BMI ...), lipids and lipodystrophy

Discussion (1)

- **Incidence of DM in D:A:D is slightly lower than in other HIV cohorts, possibly due to different socio-demographics and diet.**
- **Although ascertainment bias cannot be ruled out, the prospective follow-up in D:A:D means that it is of less concern.**
- **The relationship between DM and exposure to stavudine is in accordance with the MACS study, which showed an independent effect of stavudine on insulin sensitivity**

D:A:D

Discussion (2)

- **The lack of a relationship between use of PIs and an *increased* risk of DM is intriguing :**
  - **use of more recent PIs could partially explain both the calendar year effect and the weak protective effect of ritonavir.**
  - **DM could represent the “tip of the iceberg” and incidence of glucose intolerance could be higher, and related to PIs**
  - **the PI associated component of insulin resistance may be small in magnitude compared with the lipodystrophy associated component**

Discussion (3)

- **The relationship between DM and both exposure to stavudine and lipodystrophy is striking.**

  Adjustment for lipodystrophy did not modify the relationship between stavudine and DM

  $\rightarrow$ this does not exclude a common mechanism underlying the development of both DM and lipodystrophy.

D:A:D

Acknowledgements

Cohort PI's: W El-Sadr * (CPCRA), G Calvo * (BASS), F Dabis * (Aquitaine), S De Wit * (Brussels), O Kirk * (EuroSida), M Law * (AHOD), A d'Arminio Monforte * (ICONA), L Morfeldt * (HivBIVUS), C Pradier * (Nice), P Reiss * (ATHENA), R Weber * (SHCS)

Cohort coordinators and datamanagers: S Zaheri, L Gras (ATHENA), R Thiébaut, E Balestre (Aquitaine), K Petoumenos (AHOD), S Mateu, F Torres (BASS), B Poll (Brussels), G Bartsch, G Thompsen (CPCRA), J Kjær (EuroSIDA), P Pezzotti (ICONA), E Fontas, C Caissotti (Nice), A Sundström, G Thulin (HivBIVUS), M Rickenbach, O Keiser (SHCS)

Statisticians: CA Sabin, AN Phillips *

Community representative: S Collins *

DAD coordinating office: N Friis-Møller, S Worm, A Sawitz, JD Lundgren *¢

Steering Committee: Members indicated w/*; ¢ chair;

Additional members: E Loeliger *, R Tressler *, 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, and Hoffman-La Roche"