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


On behalf of the D:A:D Study Group
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)
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).
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).
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.
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
Relationships between exposure to individuals drugs and incidence of DM

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- Adjusted for age, sex, BMI, race, smoking status, calendar year and cohort.
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• Adjusted for age, sex, BMI, race, smoking status calendar year and cohort.
Incidence of DM and exposure to stavudine

![Graph showing incidence of DM (per 1000 PYFU) over exposure to stavudine. The x-axis represents different exposure periods: None, <1 yr, 1-2 yrs, 2-3 yrs, 3-4 yrs, 4-5 yrs, 5-6 yrs, >6 yrs. The y-axis represents the incidence DM (per 1000 PYFU) ranging from 0 to 14. The graph shows an increase in incidence with longer exposure periods.]
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
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
• 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.
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 → this does not exclude a common mechanism underlying the development of both DM and lipodystrophy.
Acknowledgements

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**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”