D:A:D

Evaluation of sudden death and non-haemorrhagic stroke and their association with HIV protease inhibitor (PI) usage

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On behalf of the D:A:D study group

Background-I

- Concerns have evolved about potential adverse effects of protease inhibitors (PIs) on cardiac conductivity
  - May manifest as prolongation of Q-T and P-R interval durations on standard electrocardiogram (ECG)
- FDA has issued warnings that some PIs [LPV/r, SQV/r] may have an effect on cardiac electric conductivity*

*U.S. Food and Drug Administration:
i) Labeling changes for Kaletra reflecting new QT/QTC interval and PR interval prolongation information. April 2009
http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/hivandaidsactivities/ucm155697.htm
ii) Invirase (saquinavir): Ongoing safety review of clinical trial data. February 2010
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm201563.htm
www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm230449.htm - 34k - 2010-10-21

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- FDA has issued warnings that some PIs [LPV/r, SQV/r] may have an effect on cardiac electric conductivity
- In SMART**, N=3719 all PI-based regimens (whether boosted or non-boosted) were associated with prolongation of P-R
- Average Q-T was significantly lower for any PI/r group compared to the NNRTI

**Soliman EZ, Lundgren JD et al. On behalf of SMART
Poster H-218, ICCAC 2010, *AIDS in press*

Background-II

- Q-T prolongation may increase risk of sudden death
- It has been suggested that prolonged P-R interval may be a predictor of atrial fibrillation - associated with stroke and mortality*, no causal relationship has been established
- The possible clinical consequences of these ECG abnormalities in HIV-positive persons have not been assessed
    - Neither good ascertainment of ECGs nor good descriptions of ECGs in HIV+
    - Sudden deaths are rare events

*Soliman EZ, Prineas RJ et al. *Stroke* 2009
Scjabel RB, Sullivan LM et al. *Lancet* 2009,
Cheng S, keyes et al. *JAMA* 2009

Hypothesis

- Sudden death and non-haemorrhagic strokes may be rare 'end-stage' outcomes of prolonged Q-T or P-R intervals
- If exposure to PIs (as a class) does indeed cause these ECG abnormalities, we may expect to see an excess risk of sudden deaths/non-haemorrhagic strokes in patients exposed to PIs

Methods

- Centrally validated (with cardiologist input) cases of sudden deaths and non-haemorrhagic strokes were identified using standard case-definitions
- Person-years (PY) calculated from D:A:D entry to first event, death, 6 months after last visit or Feb 2009
- Association between *combined endpoint* and current/recent (any use in previous year) exposure to PIs (+/-ritonavir boosting) investigated using Poisson regression, adjusting for confounders (age, sex, body mass index, family and personal history of CVD)
- Sensitivity analyses assessed associations with *sudden deaths* alone

Results

- 49, 727 patients followed for total of 234,818 PY
- 78 sudden deaths
  - Event rate: 0.34/1000 PY
- 172 non-haemorrhagic strokes
  - Event rate: 0.73/1000 PY
- 250 combined endpoint
  - Event rate: 1.06/1000 PY
- Associations with Bleeds

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- 250 combined endpoint
  - Event rate: 1.06/1000 PY
- Associations with PI class
  - In patients currently/recently exposed to PIs rates of 1.23 /1,000 PY
  - In patients not exposed to PIs rates of 0.92 /1,000 PY

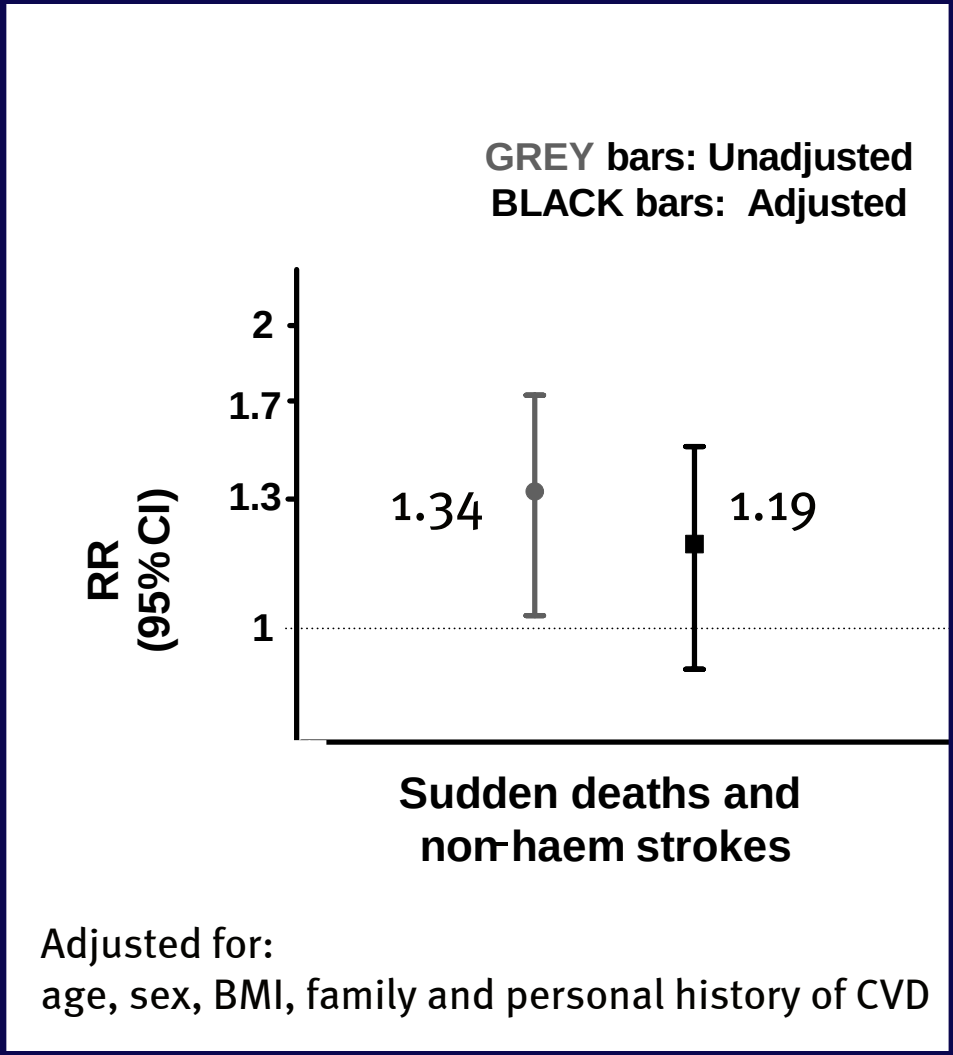
Characteristics at D:A:D entry

		Sudden deaths N=78	Non-haem strokes N=178	DAD overall N=49,737
Age (years)		46	50	38
Gender, (%)	Male	84.6	85.5	73.5
Race, (%)	White	59.0	47.7	50.4
	Black	7.7	11.6	9.8
BMI kg/m2, (%)	26-30	10.3	11.1	11.0
	>30	6.4	5.8	4.0
Lipids (mmol/L),	TG	2.3	1.9	1.5
	CHOL	5.5	5.2	4.8
	HDL	1.1	1.0	0.9
Smoking Status, (%) Current/EX-smoker		35.4/60.3	41.3/58.1	30.0/51
Fam history of CVD, (%)		5.1	7.0	6.2
Previous CVD event, (%)		7.7	9.3	1.5
Diabetes Mellitus, (%)		7.7	14.5	2.6
Anti hyp mediciation, (%)		6.4	12.1	3.5
Lipid lowering drugs, (%)		7.7	7.0	3.5

Characteristics at D:A:D entry

		Sudden deaths N=78	Non-haem strokes N=178	DAD overall N=49,737
Mode of infection, (%)	Homo-sexual	52.6	49.4	43.6
	Hetero-sexual	26.9	15.1	15.3
	IDU	14.1	25.0	32.3
Duration of previous exposure to ART, years	PIs	1.8	1.8	0.0
	NNRTIs	0.0	0.0	0.0
	NRTIs	3.4	3.0	0.7
Log HIV-1 RNA (copies/ml)		3.4	2.5	3.0
CD4 counts (cells/mm3)		307	351	402

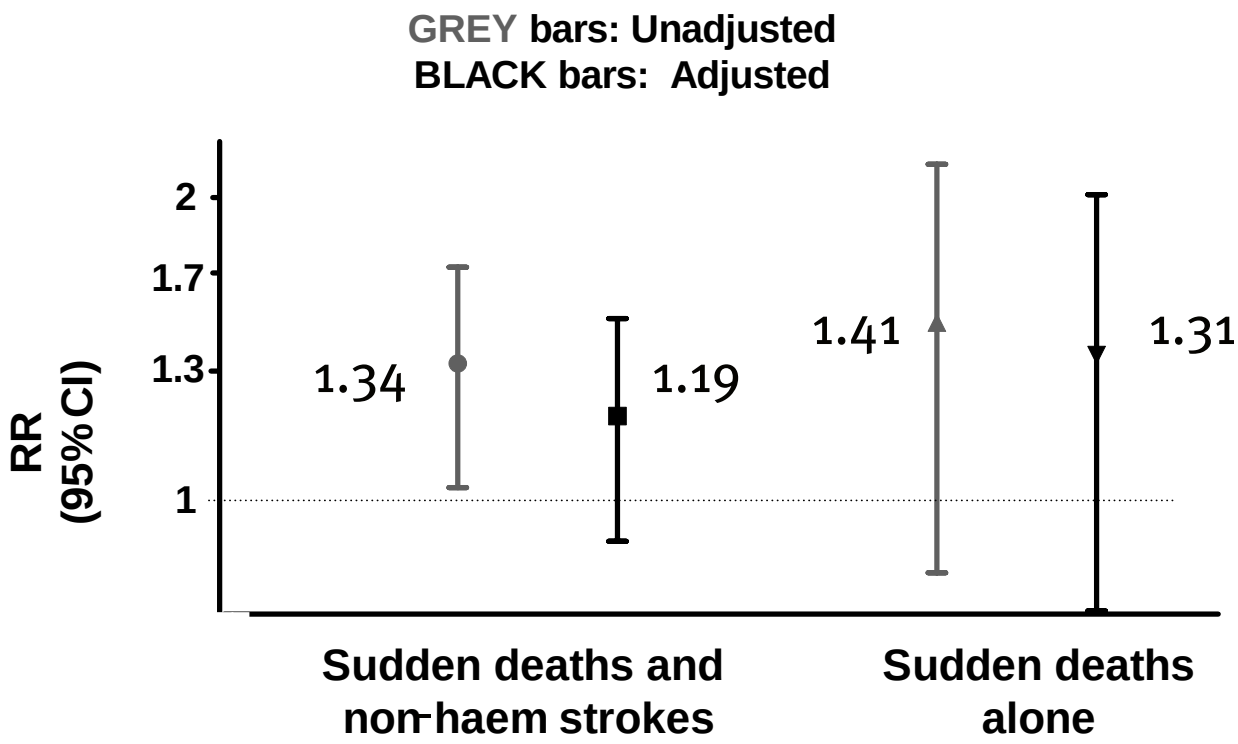
Relative rate of non-haemorrhagic strokes or sudden deaths and current/recent PI exposure (unadjusted and adjusted)



Adjusted for:
age, sex, BMI, family and personal history of CVD

Rates of the CE, currently/recently exposed to PIs 1.23 /1,000 PY

Relative rate of non-haemorrhagic strokes or sudden deaths and current/recent PI exposure (unadjusted and adjusted)



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Limitations

- ECGs are not collected on a routine basis in D:A:D
- Sudden deaths are rare events – our study is only sufficiently powered to detect a strong signal between PIs (as a class) and this outcome
  - It remains possible that one or few individual drugs are associated with a markedly raised risk of sudden death.
- Even if relative rates of sudden death are close to 1, we cannot rule out the possibility that some patients might be adversely affected
- Inability to distinguish sudden death resulting from conduction disturbances caused by genetics, or secondary to ischemic heart disease
- The study has limited information on concomitant cocaine use, methadone or on use of anti-arrythmic drugs

Conclusions

- A small increased risk of sudden death/non-haemorrhagic stroke was observed with PI exposure in univariate analyses
  - this association (including sudden deaths) was not noted after adjustment for potential confounders
- These findings do not support the routine use of ECG monitoring for *all* patients on PIs, however, monitoring might be considered:
  - For patients receiving other drugs with known effects on cardiac conductivity
- In this study, we did not have sufficient power to examine the association between individual PIs and sudden death/non-haemorraghic stroke

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

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