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Atazanavir (ATV)-Containing Antiretroviral Treatment is not Associated with an Increased Risk of Cardio- or Cerebro-Vascular Events (CVE) in the D:A:D Study

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BACKGROUND

Prior findings from the D:A:D study suggest that the duration of exposure to protease inhibitor (PI)-containing ART is associated with an increased risk of myocardial infarction (MI) (1). Further analyses suggested that this association was present with some individual PIs (lopinavir and indinavir), but was not present with other PIs (saquinavir or nelfinavir). An association with atazanavir (ATV) usage has not previously been investigated due to the limited follow-up among persons exposed to ATV. However, sufficient person-years of follow-up (PYFU) have now accrued among those exposed to ATV to permit an investigation of the association between ATV and the risk of MI and stroke.

AIM OF THE STUDY

The aims of this analysis are to evaluate whether exposure to ATV-containing ART is associated with an increased risk of cardio-and cerebro-vascular events (CVE) defined as the occurrence of MI and stroke, according to the MONICA study definition (2). Other factors associated with MI and stroke were also investigated, including a possible inverse relationship between bilirubin levels and the risk of MI (such a finding has previously been described in HIV-negative subjects) (3-5).

METHODS

The D:A:D is an observational study of >49,000 HIV-infected patients from 11 cohorts from Europe, Australia, and the United States. The aim of the study is to investigate associations between use of antiretroviral drugs and risk of cardiovascular and other major disease events.

In this analysis we evaluate a possible association between cumulative exposure to ATV and the rate of MI or stroke. Poisson regression was used to investigate the association between cumulative exposure to ATV and MI and stroke after adjusting for known demographic and clinical confounders, cumulative exposure to antiretroviral drugs and recent exposure to nucleoside reverse transcriptase inhibitors. Follow-up started on the date of enrolment in the D:A:D Study and ended at the earliest of: (i) a new MI/stroke, (ii) death, (iii) six months after last clinic visit, or (iv) 1st February 2011. A sensitivity analysis was performed to investigate a potential modifying association with the latest bilirubin level, included as a categorical covariate, based on the inverse association between bilirubin level and risk of MI reported in HIV-negative persons.

References

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Table 1

Cardio- and cerebro-vascular events in the D:A:D Study

Diagnosis	Number (%)
MI	844 (61.3)
Definite	502 (59.4)
Probable	200 (23.7)
Not known	143 (16.9)
Fatal events*	172 (20.4)
Strokes	532 (38.7)
Fatal events*	83 (15.6)
Total	1376 (100)

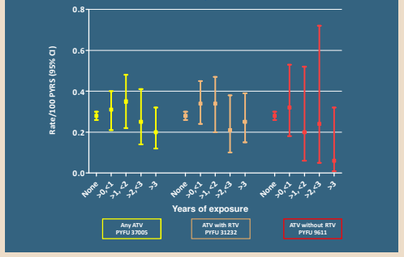
*Fatal events= events where death occurred within 31 days.

Table 2 **Characteristics of patients who are currently receiving or not receiving ATV, expressed as % of total follow-up time**

		Currently on ATV	Not currently on ATV
Total person-years		27125	274782
Gender	female	7181 (26.5)	72352 (26.4)
Risk group	MSM	12299 (45.3)	122709 (44.7)
	IDU	4305 (16.1)	42448 (15.4)
	Heterosexual	8583 (31.6)	89359 (32.5)
	Other/not known	1878 (6.9)	20266 (7.4)
Race	White	14116 (52.0)	140834 (51.0)
	Black	1965 (7.2)	23104 (8.4)
	Other	640 (2.4)	7082 (2.6)
Age (years)	<20	34 (0.1)	670 (0.2)
	20-29	1039 (3.8)	22342 (8.3)
	30-39	5696 (21.0)	88985 (32.1)
	40-49	10990 (44.2)	102344 (37.2)
	50-59	5760 (21.2)	43233 (15.7)
	60-69	2079 (7.7)	14660 (5.4)
	≥70	527 (1.9)	3461 (1.3)
BMI	<18	1053 (3.9)	8579 (3.1)
	≥18 ,<25	18147 (66.9)	188032 (68.4)
	≥25, <30	4425 (16.3)	41204 (15.0)
	≥30	1732 (6.4)	15672 (5.7)
	Not known	1768 (6.5)	21175 (7.7)
Family history	Yes	2521 (9.3)	21349 (7.8)
Smoker	Never smoker	6941 (25.6)	68000 (24.7)
	Current smoker	11199 (41.3)	100038 (36.4)
	Ex smoker	6578 (24.3)	56186 (20.5)
	Not known	2407 (8.9)	43261 (15.7)
Previous CVD event	Yes	826 (3.0)	5479 (2.0)
Diabetes	Yes	1843 (6.8)	12278 (4.5)
Framingham score	Low (<10%)	16345 (60.3)	137111 (49.9)
	Moderate (>10, <20%)	5306 (19.6)	36569 (13.4)
	High (≥20%)	2342 (8.6)	15723 (5.7)
	Not known	3072 (11.3)	87378 (32.0)

Figure 1

MI rate stratified by cumulative exposure to (i) any ATV, (ii) ATV with ritonavir, and (iii) ATV without ritonavir



RESULTS

A total of 844 cases of MI (301,907 PYFU) and 532 strokes (303,118 PYFU) have been reported, with an incidence of 2.80/1000 PYFU (95%CI: 2.61, 2.98) and 1.76/1000 PYFU(95%CI: 1.61, 1.90) respectively. The details of the events are reported in **Table 1**.

Overall, a total of 37,005 PYFU were contributed by individuals exposed to ATV. ATV usage increased from 0.2% of PYFU in 1999/2000 to 16.5% of PYFU in 2010/11. In detail, 31,502 PYFU were contributed by patients exposed to ATV with ritonavir (RTV), and 9,611 by patients exposed to ATV without RTV boosting. Demographic and clinical characteristics of the patients according to ATV usage are shown on **Table 2**.

The rate of MI varied from 2.80 [95% CI: 2.6, 23.0]/1000 PYFU in those with no exposure to ATV to 2.0 [1.2, 3.2]/1000 PYFU in those with >3 years exposure, with the rate of stroke being 1.7 [1.6, 1.9] and 1.7 [1.0, 2.7]/1000 PYFU in these two groups (**Figure 1 and 2**).

Longer exposure to ATV was not associated with an increased risk of either MI or stroke either in univariate or in multivariable analyses (**Table 3**).

After excluding patients from three cohorts that did not provide any bilirubin measurements, there was a total follow-up of 278,845 person-years. Estimates of the rate of MI, stratified by latest bilirubin level in this subgroup of patients are shown in **Table 3**.

Further adjustment for the latest bilirubin level, in the subgroup of cohorts that provide these data, had no impact on the size of the association with either MI or stroke (**Figure 3**).

CONCLUSIONS

ATV was not associated with an increased risk of CVE, suggesting that previously reported associations in the D:A:D Study with lopinavir and indinavir are unlikely to reflect a class-wide association. We found no evidence that these findings were altered by adjustment for the latest bilirubin level, although only limited data were available. Our findings may be strengthened by the inclusion of individuals exposed to ATV for longer periods of time.

Figure 2

Strokes rate stratified by cumulative exposure to (i) any ATV, (ii) ATV with ritonavir, and (iii) ATV without ritonavir

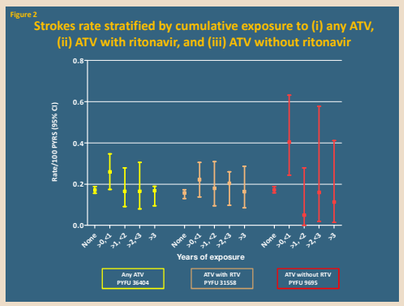


Table 3

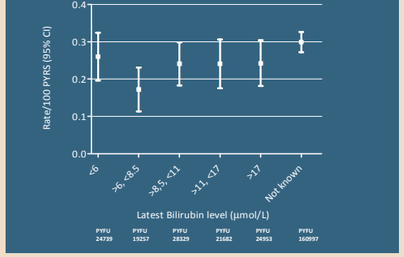
Relative rate (RR) and 95% confidence interval (CI) for association between cumulative exposure to atazanavir (per additional year of exposure) and the rate of myocardial infarction and stroke.
(i) All participating cohorts. (ii) Cohorts providing data on bilirubin levels

	Myocardial infarction			Stroke		
	RR	95% CI	p-value	RR	95% CI	p-value
(i) All cohorts						
Unadjusted	0.96	0.88, 1.04	0.32	1.02	0.98, 1.05	0.74
Adjusted for exposure to antiretroviral drugs, demographic and clinical factors[1]	0.95	0.87, 1.05	0.30	0.90	0.81, 1.01	0.07
(ii) Cohorts providing bilirubin data						
Unadjusted	0.95	0.87, 1.04	0.28	1.02	0.92, 1.14	0.65
Adjusted for exposure to antiretroviral drugs, demographic and clinical factors[2]	0.94	0.86, 1.04	0.24	0.92	0.82, 1.03	0.14
Additionally adjusting for latest bilirubin level	0.95	0.86, 1.05	0.34	0.94	0.83, 1.05	0.27

[1]gender, age, cohort, risk group, ethnicity, BMI, family history, smoking status, previous cardiovascular event and calendar year.
[2]gender, age, BMI, smoking status, previous cardiovascular event, calendar year and hypertension.

Figure 3

MI event rate stratified by latest bilirubin level



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