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Abacavir (ABC) use and risk of recurrent myocardial infarction (MI)

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INTRODUCTION

- Previous analyses of the D:A:D Study, published in 2008, have demonstrated that current exposure to ABC is associated with an increased risk of MI[1,2]. However, associations between exposure to the drug and the risk of a subsequent MI in persons who have already experienced an MI have not yet been investigated.
- Our objective was to describe associations between ABC use and subsequent MI among people having experienced at least one MI during prospective D:A:D follow-up.

METHODS

- We considered the rate of recurrent MI among D:A:D participants who had experienced an MI during study follow-up and who remained under follow-up at 28 days post-MI
- Follow-up was considered from 28 days post-MI to the date of next new (recurrent) MI, death, 1st February 2014 or 6 months after last clinic visit
- Poisson regression models considered associations between recurrent MI and exposure to ABC before and after adjusting for calendar year and age (both time-updated)
- Three different exposures to ABC were considered:
  - Use at the time of initial MI (time-fixed);
  - Current, post-MI use (time-updated); and
  - Cumulative use (time-updated, including exposure both pre- and post-MI)

RESULTS

- 816 people who developed an MI during prospective follow-up remained alive and under follow-up for at least 28 days.
- Included individuals were largely male (91.4%), infected with HIV through sex between men (59.6%) and had a median age of 51 years (inter-quartile range [IQR] 44-58) at initial MI. 80.1% of participants were current/ex-smokers (**Table 1**).
- Median CD4 count at initial MI was 503 (IQR 340-728) cells/mm^3. Most people (793, 97.2%) had received antiretroviral therapy (ART), with 719 (88.1%) receiving ART at the time of MI; 544 people (66.8%) had an HIV RNA <50 copies/ml.
- 415 (50.9%) people had received ABC prior to initial MI for a median of 3.1 years (IQR 0.1-13.9) and 277 (34.0%) were still on ABC at the time of initial MI. Of these, 204 (73.7%) subsequently stopped using the drug after their initial MI (**Table 2**). Of the 139 people who, after their initial MI, either started ABC for the first time or restarted ABC after a previous use, 120 (86.3%) did so prior to the publication of the D:A:D study findings in 2008 demonstrating an association between ABC and MI.

Table 1

Demographic and CVD-related characteristics of people experiencing an MI during prospective D:A:D follow-up

Total number of persons		816	(100.0)
Male gender, n (%)		746	(91.4)
Median (IQR) age (years) at MI		51	(44, 58)
Mode of infection, n (%)	Men having sex with men	486	(59.6)
	Injection drug use	109	(13.4)
	Heterosexual	175	(21.5)
	Other/not known	46	(5.6)
Race, n (%)	White	459	(56.3)
	Black African	24	(2.9)
	Other	13	(1.6)
	Not known	320	(39.2)
Year of MI	1999-2001	95	(11.6)
	2002-2004	203	(24.9)
	2005-2007	200	(24.5)
	2008-2010	178	(21.8)
	2011-2013	140	(17.2)
Hepatitis C virus infection, n (%)		165	(20.2)
Active hepatitis B virus infection, n (%)		30	(3.7)
Smoking, n (%)	Current smoker	464	(56.9)
	Ex-smoker	189	(23.2)
Diabetes, n (%)		113	(13.9)
Dyslipidaemia[1], n (%)		525	(64.3)
Hypertension[2], n (%)		341	(41.8)
Family history of MI, n (%)		124	(19.3)
Previous MI before D:A:D entry, n (%)		60	(7.4)
10-year Framingham risk, n (%)	Low (<10%)	195	(23.9)
	Moderate (10-20%)	263	(32.2)
	High (>20%)	228	(27.9)
	Not known	130	(15.9)
ART exposure			
Any ART	Ever received, n (%)	793	(97.2)
ABC	Ever received, n (%)	415	(50.9)
	Median (IQR) years	3.1	(0.0, 13.9)
	On at the time of MI, n (%)	277	(34.0)
PIs	Ever received, n (%)	695	(85.2)
	Median (IQR) years	4.6	(0.0, 17.7)
NNRTIs	Ever received, n (%)	571	(70.0)
	Median (IQR) years	2.8	(0.0, 17.7)

[1]Defined as total cholesterol ≥6.2mmol/l, HDL-cholesterol ≤0.9 mmol/l, triglyceride ≥2.3 mmol/l and/or use of lipid-lowering agents;
[2]Defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg and/or use of anti-hypertensive agents or ACE inhibitors.

Table 2

Changes to ABC use after the initial MI during the study

ABC use at time of initial MI	Action	N (%)
On ABC at time of initial MI (n=277)	Remained on ABC	73 (26.3)
	Stopped ABC	204 (73.7)
	Restarted ABC	56/204 (27.5)
Never received ABC prior to initial MI (n=401)	Started ABC	63 (15.7)
Previous use of ABC but not on it at time of initial MI (n=138)	Restarted ABC	20 (14.5)

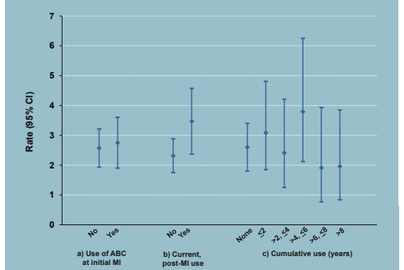
- People with an MI were followed for a median of 4.2 (range 0.1-13.2) years after their MI (total person-years of follow-up (PYFU): 3863). Over this time, there were 102 recurrent MIs, giving a rate of 2.64/1000 PYFU (95% Confidence Interval [CI] 2.13-3.15).
- Rates of recurrent MI were 2.75 (1.90-3.60) and 2.57 (1.93-3.21)/1000 PYFU in those who were and were not on ABC at initial MI. Rates were 3.47 (2.37-4.57) and 2.31 (1.75-2.88)/1000 PYFU in those who were/were not currently receiving ABC post-MI (**Figure 1**).
- Whilst neither cumulative exposure to ABC nor receipt of ABC at initial MI were significantly associated with recurrent MI risk, current post-MI exposure was associated with an increased risk (**Figure 1**). With the exception of age, there were no significant associations between demographic or lifestyle factors and recurrent MI. Earlier calendar year was, however, associated with an increased risk (**Table 3**).
- The association between recent ABC use and recurrent MI risk was similar after controlling for age (adjusted relative hazard: 1.51 [95% CI 1.01, 2.25], p=0.04), but was attenuated after controlling for calendar year (1.19 [0.79, 1.79], p=0.40).

CONCLUSIONS

- Whilst we found some evidence that use of ABC post-MI was also associated with an elevated risk of a recurrent MI, this effect was attenuated after adjusting for calendar year.
- This suggests that the apparent increased risk may be explained by greater use of ABC in those with an initial MI in the earlier years of the study, although our findings should be interpreted cautiously given the collinearity between current ABC use and calendar year.

Figure 1

Incidence of recurrent MI (/100 PYFU, with 95% CIs) stratified by a) use of ABC at time of initial MI, b) current, post-MI use of ABC and cumulative use of ABC



Unadjusted RH (95% CI)	1.07 (0.72, 1.59) p=0.74	1.50 (1.00, 2.24) p=0.05	0.88 /5 years (0.65, 1.19) p=0.41

Table 3

Results from univariable analyses of associations between non-ABC factors and recurrent MI

Factor		Relative Rate (RR)	95% CI	p-value
Year	1999-2001	12.32	(5.17, 29.37)	0.0001
	2002-2004	4.91	(2.53, 9.54)	0.0001
	2005-2007	3.74	(1.98, 7.04)	0.0001
	2008-2010	2.34	(1.23, 4.46)	0.01
	2011-2013	1	-	-
Gender	Male	0.98	(0.48, 2.03)	0.97
	Female	1	-	-
Age (/5 years older)		1.02	(1.00, 1.04)	0.06
Smoking	Current	0.93	(0.49, 1.76)	0.83
	Ex-	1.13	(0.60, 2.15)	0.71
	Never	1	-	-
	Unknown	0.89	(0.29, 2.77)	0.85
Ethnicity	White	1	-	-
	Non-white	0.75	(0.50, 1.12)	0.16
Mode of infection	MSM	1	-	-
	IDU	0.55	(0.26, 1.14)	0.11
	Heterosexual	0.83	(0.49, 1.38)	0.47
	Other/unknown	3.03	(1.67, 5.51)	0.0003
Dyslipidaemia		0.76	(0.43, 1.37)	0.36
Body mass index	<18	1.21	(0.49, 3.01)	0.68
	≥18, <26	1	-	-
	≥26, <30	0.83	(0.47, 1.45)	0.51
	>30	0.86	(0.35, 2.14)	0.75
	Not known	2.81	(1.48, 5.32)	0.002
Diabetes		1.34	(0.82, 2.18)	0.24
Hypertension		0.74	(0.46, 1.19)	0.21

* Gender, ethnic group, mode of acquisition and receipt of ABC at the time of MI were treated as fixed covariates; calendar year, age, smoking status, dyslipidaemia, BMI, diabetes, hypertension, cumulative and recent exposure to ABC were all considered as time-updated covariates.

REFERENCES

1. The D:A:D Study Group. Lancet 2008; 371:1417-26.
2. Sabin C et al. Poster 957c. 15th Conference on Retroviruses and Opportunistic Infections, Feb 3-6, 2008, Boston.

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