Is there continued evidence for an association between abacavir and myocardial infarction risk?

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Background

- In March 2008, the D:A:D Study published results demonstrating an increased risk of myocardial infarction (MI) in those receiving abacavir (ABC) [1]; associations from subsequent publications have been inconsistent [2-5] although such an association is supported by mechanistic studies [6,7].
- The initial analyses had adjusted for all known confounders (including renal dysfunction), and the reversibility of the association and the lack of a similar association with tenofovir both argued against confounding as an explanation. However, one of the criticisms of the analysis was that it was impossible to remove the effects of unmeasured confounders which may have been present as ABC had been preferentially prescribed to those at higher cardiovascular disease (CVD) risk.
- We describe changes to the use of ABC since publication of the study findings, and investigate whether the association between ABC and MI remains present in data collected *after* this time, when ABC would be less likely to be prescribed to those at high CVD risk (ie. any confounding, if present, would be expected to act in the opposite direction).

Methods

- The D:A:D Study is a prospective cohort collaboration of >49,000 HIV-positive persons from 11 cohorts in Europe, Australia, and the United States.
- Associations between a person's 10-year CVD risk, calculated using the Framingham equation and classified as low (<10%), moderate (10-20%), high (>20%) or unknown, and initiation or discontinuation of ABC were assessed as follows:

  Initiation of ABC in persons initiating ART for the first time: Logistic regression models were used to assess associations between the calendar period (pre-/post-March 2008), CVD risk, and whether the initial ART regimen included ABC.

  Discontinuation of ABC in persons receiving an ABC-containing regimen: Poisson regression was used to describe associations between the calendar period, CVD risk and the rate of ABC discontinuation. Analyses were performed separately for those with suppressed/low (≤1000 copies/ml) and non-suppressed (>1000 copies/ml) viral load.
- Poisson regression was used to assess the association between current use of ABC (with a 6-month lag to allow for recent discontinuation) and MI risk, adjusting for use of other ART drugs and known confounders. Participants were followed from study entry until the first of an MI, death, 1st February 2013 or 6 months after the person's last clinic visit.
- For all analyses, interaction tests were performed to assess whether associations had changed over the two calendar periods.
- Sensitivity analyses considered whether the associations between ABC and MI remained after adjustment for factors potentially on the causal pathway, including diabetes, lipids, blood pressure, use of anti-hypertensive drugs or ACE inhibitors, glucose, CVD risk, weight loss/gain and creatinine, all as time-updated covariates.

Figure 1: Use of ABC in the D:A:D cohort over time, overall and stratified by CVD disease risk

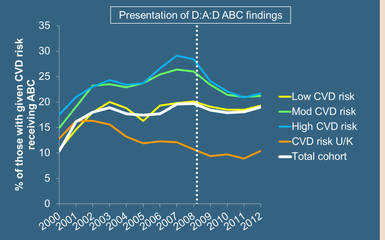


Table 1: Associations between Framingham risk and (i) initiations and (ii) discontinuations of ABC*

(i) ABC initiation

Framingham risk group	ABC initiations/total ART initiations (%)	aOR (95% CI)
Pre-March 2008		
Low/unknown	1251/9213 (13.6)	1
Moderate/High	111/648 (17.1)	1.14 (0.90, 1.44)
Post-March 2008		
Low/unknown	326/4282 (7.6)	1
Moderate/High	33/622 (5.3)	0.74 (0.48, 1.13)
Interaction *P*-value		0.007

(ii) ABC discontinuation

Framingham risk group	Disconts/PYRS	Rate (95% CI)/100 PYRS	aRR (95% CI)
Suppressed/low viral load			
Pre-March 2008			
Low/unknown	2045/16506	12.4 (11.9, 12.9)	1
Moderate/High	562/5465	10.3 (9.4, 11.1)	1.04 (0.93, 1.16)
Post-March 2008			
Low/unknown	1403/13950	10.1 (9.5, 10.6)	1
Moderate/High	880/6560	13.4 (12.5, 14.3)	1.49 (1.34, 1.65)
Interaction *P*-value			0.0001
Non-suppressed viral load			
Pre-March 2008			
Low/unknown	2966/7766	38.2 (36.8, 39.6)	1
Moderate /High	662/2041	32.4 (29.9, 34.9)	0.99 (0.90, 1.09)
Post-March 2008			
Low/unknown	622/2297	27.1 (25.0, 29.2)	1
Moderate/High	236/921	25.6 (22.4, 28.9)	1.23 (1.02, 1.48)
Interaction *P*-value			0.07

*Models adjusted for age, gender, body mass index, family history of CVD, mode of acquisition of HIV, ethnicity, previous CVD event and the CD4 count; analyses of discontinuation in those with a non-suppressed viral load also included adjustment for the viral load at switch

Results

Changes in the use of ABC over time

- Use of ABC increased from 10% of the cohort in 2000 to 20% of the cohort in 2008, before stabilising at around 18-19% (**Figure 1**).
- When the study group was stratified by CVD risk, increases in use of ABC pre-March 2008, and subsequent decreases, were greatest in those at moderate and high CVD risk.
- *Treatment initiations:* There was some evidence that ART-naïve people at moderate/high CVD risk post March 2008 were less likely to initiate ABC than those at low/unknown CVD risk; in contrast, in the pre-March 2008 period those with moderate/high CVD risk were, if anything, *more* likely to initiate ABC (**Table 1(i)**).
- *Treatment discontinuations:* Post-March 2008, those on ABC who were at moderate/high CVD risk were more likely to discontinue ABC than those at low/unknown CVD risk, regardless of the individual's viral load at the time of discontinuation (**Table 1(ii)**); no such associations were seen pre-March 2008.

Association between current use of ABC and MI risk

- By 1st February 2013, 941 MI events had occurred in 367,559 PYRS (rate 0.26 [95% CI 0.24-0.27] /100 PYRS). The rate of MI was 0.47 [0.42-0.52] among those currently receiving ABC and 0.21 [0.19-0.22] among those not currently receiving ABC.
- Current ABC use was associated with a 98% increase in MI rate (adjusted rate ratio (aRR) 1.98 [1.72-2.29]), with no difference in the pre- (1.97 [1.68-2.33]) and post- (1.97 [1.43-2.72]) March 2008 periods (*P*-value for interaction=0.74) (**Figure 2**). Results were unchanged after stratifying by Framingham risk group, and after further adjusting for factors potentially on the causal pathway, including renal function, dyslipidaemia and hypertension (**Table 2**).

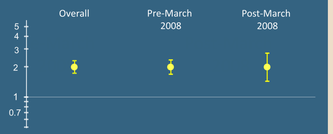
Conclusion

- It is clear that there has been some channelling of ABC away from those at higher risk of CVD since 2008 – despite this, we continue to observe a strong association between current ABC use and MI risk.
- Confounding cannot be ruled out in any cohort study. However, as any channelling bias would now be expected to act in the opposite direction to that prior to March 2008 (ie. we would expect it to result in an artificially low rate of MI in those initiated on ABC after March 2008), our findings argue against channelling bias as an explanation for our findings.

References

[1]Sabin CA et al. *Lancet* 2008;371:1417-26; [2]Lang S et al. *Arch Int Med* 2010;170:1228-38; [3]Choi AI et al. *AIDS* 2011;25:1289-98; [4]Obel N et al. *HIV Med* 2010;11:130-6; [5]Ding X et al. *JAIDS* 2012;61:441-7; [6]Baum PD et al. *AIDS* 2011;25:2243-48; [7]Satchell CS et al. *J Infect Dis* 2011;204:1202-10.

Figure 2: Adjusted relative rate (RR) for MI in those currently receiving ABC*, overall and stratified by calendar period



	Overall	Pre-March 2008	Post-March 2008
Not currently on ABC			
Events / PYRS	600 / 295642	425 / 169417	175 / 126225
Rate (95% CI) /100 PYRS	0.20 (0.19, 0.22)	0.25 (0.23, 0.28)	0.14 (0.12, 0.16)
Currently on ABC			
Events / PYRS	341 / 71917	247 / 40833	94 / 31084
Rate (95% CI) /100 PYRS	0.47 (0.42, 0.52)	0.61 (0.53, 0.68)	0.30 (0.24, 0.36)

*Models adjusted for age, gender, body mass index, family history of CVD, mode of acquisition of HIV, ethnicity, smoking status, previous CVD event, and clinical cohort

Table 2: Associations between current use of ABC and MI rate after a) stratifying by Framingham risk score, and b) adjusting for factors potentially on the causal pathway[2]

Sensitivity analysis	Pre-March 2008 RR (95% CI)	Post-March 2008 RR (95% CI)	*P*-value (interaction between ABC use and calendar period)
a) Stratified by Framingham risk[1]			
Low	2.48 (1.74, 3.52)	2.11 (1.12, 3.98)	0.78
Moderate	1.69 (1.21, 2.35)	2.19 (1.25, 3.84)	0.68
High	1.51(1.12, 2.05)	1.65 (0.93, 2.92)	0.16
b) Further adjustment for factors on causal pathway[2]	1.88 (1.55, 2.28)	2.03 (1.46, 2.84)	0.61

[1]All models adjusted for the factors listed in Table 2; [2]Models additionally adjusted for diabetes mellitus, total and HDL cholesterol, triglycerides, systolic/diastolic blood pressure, the use of anti-hypertensive drugs or ACE inhibitors, glucose, CVD risk, weight loss/gain and creatinine measurements.

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