In March 2008, the D:A:D Study published results demonstrating an increased risk of myocardial infarction (MI) in those receiving abacavir (ABC) [2]; 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 lack of a similar increase in risk among those at moderate and high CVD risk 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 was less likely to be prescribed to those at high CVD risk (i.e. 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-March 2008), CVD risk, and 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/was not suppressed (>1000 copies/ml) and not 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 discontinuation) and MI, 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, lipid, blood pressure, use of anti-hypertensive drugs or ACE inhibitors, glucose, CVD risk, weight loss/gain and creatinine, all time-updated covariates.

**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 drops, were greater in those at moderate or high CVD risk.
- Treatment discontinuations: There was some evidence that ART-naive 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 II(b)).
- 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 II(b)). No such associations were seen pre-March 2008.

**Association between current use of ABC and MI risk**

- By 1st February 2015, 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 [0.19-0.23] among those not currently receiving ABC.
- Current ABC use was associated with a 98% increase in MI rate (adjusted rate ratio [aRR] 1.98 (1.72-2.26)), with no difference in the pre- (1.97 (1.68-2.33)) and post- (1.97 (1.49-2.52)) 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 (i.e. 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**
