Do Thymidine Analogues, Abacavir, Didanosine and Lamivudine Contribute to the Risk of Myocardial Infarction (MI)?

Recent Use of Abacavir and Didanosine, but not of Thymidine Analogues, Is Associated with Risk of Myocardial Infarction

**Background**
- Attention has focused mainly on the role of protease inhibitors (PIs) and risk of myocardial infarction (MI) and less on drugs from the nucleoside reverse transcriptase inhibitor (NRTI) class. However, PIs are usually prescribed in combination with drugs from the NRTI class.
- Despite the known association of the two thymidine analogues within the NRTI class (zidovudine and stavudine) with dyslipidaemia and insulin resistance, the question of whether they may also be associated with an increased risk of MI remains unanswered.
- The primary hypothesis focused on exposure to stavudine and zidovudine. For completeness, the same analyses were performed for the other NRTIs (abacavir, didanosine and lamivudine), and there was sufficient exposure in the D:A:D cohort.

**Methods**
- D:A:D is a prospective study of 33,347 patients from 212 clinics participating in 11 existing cohorts in Europe, Australia, and the USA.
- During 157,912 person-years (PY) of prospective follow-up 517 patients developed a MI (Table 1).
- Follow-up was considered from the time of entry in D:A:D until the earliest of: new onset MI; first February 2007; death; or 6 months after last clinic visit.
- 10 year predicted coronary heart disease (CHD) risk was derived from the Framingham equation (Anderson et al., Circulation, 1991; for calculation see: www.cphiv.dk/tools.aspx).
- Poisson regression assessed the impact of cumulative, recent (still using or stopped within last 6 months) and past (last used 6 months ago) use of the five NRTIs after adjustment for demographic factors (age, sex, HIV risk and ethnicity), calendar year, cohort, following CV risk factors that are not modified greatly by ART (smoking status, family history of CV disease, previous CV event, body mass index), and cumulative exposure to other antiretroviral drugs (tenofovir, the main PI's and non-nucleoside reverse transcriptase inhibitors in use over the study period).

**Results**
- Neither cumulative nor recent use of the two thymidine analogues or lamivudine was associated with risk of MI (Table 2, Model 3).
- Cumulative use of abacavir and didanosine was each associated with an excess risk of MI (Table 2, Model 1).
- In another model including recent use, recent use of abacavir and didanosine predicted risk of MI but not cumulative use (Table 2, Model 3).
- In a third model, recent, but not past, use of abacavir and didanosine predicted risk of MI (Table 2, model 3).
- After incorporation of the predicted 10-year CHD risk (Figure 2) into the regression model (Table 2, Model 2), the MI rate was increased by 19% (95% CI: 2.27, 2.79), p=0.0001 in those with a moderate-high 10-year CHD risk and by 22% (95% CI: 2.27, 4.57), p=0.0001 in those with a high 10-year CHD risk, when compared to those with a low 10-year CHD risk.
- In this model, recent use of both abacavir and didanosine remained significantly associated with an increased MI risk. There was a significant interaction between the predicted 10-year CHD risk and recent use of abacavir (p=0.04) but not with recent use of didanosine.
- The risk of MI associated with recent abacavir and didanosine use were seen regardless of duration of use and remained after adjustment for HIV RNA levels, CD4 count, dyslipidaemia and other metabolic factors (Figure 2).
- At MI diagnosis, the cardiovascular risk profile was similar irrespective of type of ARV regimen used when the event occurred (Table 2).
- Patients with recent exposure to abacavir were more likely to be male, older and to have diabetes, hypertension, dyslipidaemia or a family history of CVD than those with recent exposure to abacavir, but were less likely to be smokers or to have a high BMI (Table 3).
- Patients with recent exposure to didanosine did not differ greatly from those without recent exposure to this drug. For other NRTIs there were general little difference between those with and without recent use.
- As patients with a higher underlying risk of CVD may be initially placed on, we explored whether our findings could be explained by "channelling bias". However, in the main model (Table 2), the factors displayed in Table 3 are adjusted for with little resulting change in rate ratios. Additionally, the MI risk remained high as long as patients were receiving these drugs, but then decreased after their cessation (Table 2, model 3).
- Had the drugs merely served as surrogates for a high underlying cardiovascular risk, this increased risk would have been expected to remain even after discontinuation of the drugs. Finally, the effect was specific for MI and other outcomes related to CVD but not for stroke (Figure 3), which shares many risk factors with MI and might to some extent be expected to be affected by the same bias. Hence, preferential use of abacavir and didanosine in patients with a priori elevated CV risk appears not to explain the findings.

**Conclusions**
- Contrary to our hypothesis, use of thymidine analogues were not associated with risk of MI.
- Unexpectedly, recent use of abacavir and didanosine were associated with increased risk of MI, by 90% and 49%, respectively.
- The excess risks of MI associated with abacavir and didanosine use were most pronounced – in absolute terms - patients with high underlying cardiovascular risk
- Although it is impossible to rule out bias as an explanation, if these associations are causal, the unknown biological mechanism(s) appears reversible upon cessation of these drugs.