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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

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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 focussed on exposure to stavudine and zidovudine. For completeness, the same analyses were performed for the other NRTIs (abacavir, didanosine and lamivudine), for which there was sufficient exposure in the DAD 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; 1st 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 PIs and non-nucleoside reverse transcriptase inhibitors in use over the study period)

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Table 1

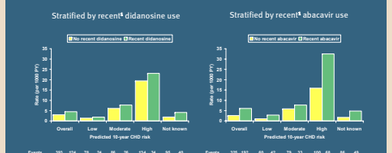
Cardiovascular risk profile at time of MI

	All	Recent[1] didanosine	Recent[1] abacavir	ART no recent[1] ddI /ABC	No MI
N	517 *	124 **	192 **	237	32830
Age (% male)	49 (92%)	50 (94%)	48 (92%)	50 (90%)	43 (74%)
BMI≥26 kg/m² (%)	18%	15%	15%	18%	17%
CVD Own history	9%	9%	10%	8%	1%
Family	14%	15%	11%	14%	8%
Smoking Curr	42%	43%	46%	40%	28%
Ex	30%	29%	32%	30%	29%
Hypertension (%)	40%	38%	41%	42%	18%
Total cholesterol (mM)	5.7	5.6	5.7	5.7	4.8
HDL cholesterol (mM)	1.1	1.1	1.0	1.1	1.2
Diabetes (%)	16%	19%	16%	15%	5%
10 y CHD risk Low	22%	20%	23%	21%	53%
Moderate	26%	27%	22%	30%	13%
High	23%	21%	28%	21%	4%
Unknown	29%	32%	27%	28%	30%

[1]Recent =still using or stopped within last 6 months
*: 8 (2%) MIs in patients not yet started ART; **: 43 patients on abacavir + didanosine – included in both columns

Figure 1

Rates of MI for recent[1] use of didanosine and of abacavir by predicted 10-year coronary heart disease (CHD) risk



[1]Recent =still using or stopped within last 6 months

Table 2

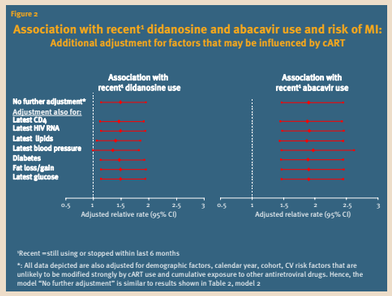
Rates of MI by use of various NRTIs

NRTI's	Model 1: Cumulative use only Rel. rate [95% CI];p-value	Model 2: Cum. + recent[1] use Rel. rate [95% CI];p-value	Model 3: Cum., recent[1] + past[2] use Rel. rate [95% CI];p-value
Zidovudine			
Cumulative use (per year)	1.03 [0.99, 1.08]; p=0.14	1.04 [0.99, 1.09]; p=0.08	1.04 [0.99, 1.09]; p=0.15
Any recent[1] use	-	0.97 [0.76, 1.25]; p=0.82	1.22 [0.82, 1.82]; p=0.33
Any past[2] use	-	-	1.29 [0.89, 1.85]; p=0.18
Didanosine			
Cumulative use (per year)	1.06 [1.01, 1.12]; p=0.03	1.01 [0.95, 1.08]; p=0.78	1.00 [0.93, 1.07]; p=0.91
Any recent[1] use	-	1.63 [1.14, 1.95]; p=0.003	1.53 [1.10, 2.13]; p=0.01
Any past[2] use	-	-	1.08 [0.84, 1.39]; p=0.54
Stavudine			
Cumulative use (per year)	1.04 [0.99, 1.10]; p=0.11	1.05 [0.98, 1.13]; p=0.15	1.02 [0.95, 1.09]; p=0.60
Any recent[1] use	-	1.00 [0.76, 1.31]; p=0.98	1.22 [0.84, 1.77]; p=0.30
Any past[2] use	-	-	1.24 [0.93, 1.66]; p=0.14
Lamivudine			
Cumulative use (per year)	1.03 [0.98, 1.08]; p=0.28	1.00 [0.94, 1.07]; p=0.91	0.99 [0.93, 1.06]; p=0.80
Any recent[1] use	-	1.25 [0.96, 1.62]; p=0.10	1.62 [1.02, 2.80]; p=0.04
Any past[2] use	-	-	1.45 [0.88, 2.40]; p=0.15
Abacavir			
Cumulative use (per year)	1.14 [1.08, 1.21]; p=0.0001	1.01 [0.93, 1.09]; p=0.80	1.02 [0.92, 1.08]; p=0.91
Any recent[1] use	-	1.90 [1.47, 2.45]; p=0.0001	1.94 [1.48, 2.55]; p=0.0001
Any past[2] use	-	-	1.29 [0.94, 1.77]; p=0.12

[1]Recent =still using or stopped within last 6 months; [2]Past = last used more than 6 months ago

Figure 2

Association with recent[1] didanosine and abacavir use and risk of MI: Additional adjustment for factors that may be influenced by cART



[1]Recent =still using or stopped within last 6 months
*: All data depicted are also adjusted for demographic factors, calendar year, cohort, CV risk factors that are unlikely to be modified strongly by cART use and cumulative exposure to other antiretroviral drugs. Hence, the model "No further adjustment" is similar to results shown in Table 2, model 2

Table 3

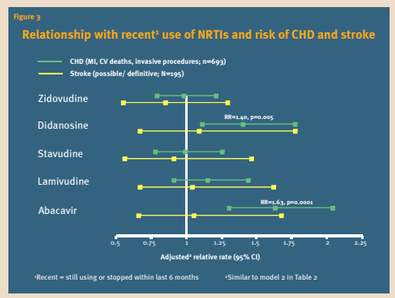
Characteristics of patients under follow-up[1] with recent[2] exposure to each NRTI

	Zidovudine		Didanosine		Stavudine		Lamivudine		Abacavir	
	Recent use	No recent use	Recent use	No recent use	Recent use	No recent use	Recent use	No recent use	Recent use	No recent use
MI events	214	303	124	393	134	383	377	140	192	325
Total person-years	62357	95556	27728	130184	36056	121856	102423	55490	31331	126581
Event rate (95% CI) /1000 person-years	3.4 (3.0, 3.9)	3.2 (2.8, 3.5)	4.5 (3.7, 5.3)	3.0 (2.7, 3.3)	3.7 (3.1, 4.4)	3.1 (2.8, 3.5)	3.7 (3.3, 4.1)	2.5 (2.1, 2.9)	6.1 (5.3, 7.0)	2.6 (2.3, 2.9)
Male sex (%)	74.5	74.1	74.9	74.1	76.0	73.7	75.2	72.5	76.8	73.6
Age 345 (male) or 255 (female) (%)	32.3	29.9	30.7	30.9	28.7	31.5	33.2	26.5	36.2	29.5
BMI≥26 kg/mm²(%)	20.2	18.2	15.4	19.8	15.1	20.2	19.1	18.9	17.7	19.3
Current/ex-smoker (%)	57.2	57.3	58.8	56.9	58.1	57.0	57.5	56.8	56.9	57.3
CVD Own history (%) Family	2.1 8.2	1.9 7.8	1.7 7.9	2.0 8.0	2.0 6.8	1.9 8.3	2.2 7.9	1.6 8.0	2.7 8.6	1.8 7.8
Diabetes (%)	4.3	4.7	5.4	4.4	5.2	4.4	4.9	3.9	5.8	4.3
Hypertension (%)	14.4	14.6	14.6	14.6	13.6	14.9	15.5	12.9	17.2	13.9
Any dyslipidaemia (%)	45.0	47.7	52.9	45.3	54.0	44.5	48.6	43.0	53.0	45.1
Moderate/high predicted 10-year CHD risk (%)	16.4	16.5	17.5	16.3	17.2	16.3	17.6	14.4	20.4	15.5

[1]Unless otherwise stated, cell entries are the proportion of follow-up time of patients in the cohort falling into each category; among patients with recent use of both didanosine and abacavir, the event rate was 7.9 (4.3 [14.5]7 per 1000 PY.
[2]Recent = still using or stopped within last 6 months

Figure 3

Relationship with recent[1] use of NRTIs and risk of CHD and stroke



[1]Recent = still using or stopped within last 6 months [2]Similar to model 2 in Table 2

RESULTS

- Neither cumulative nor recent use of the two thymidine analogues or lamivudine was associated with risk of MI (**Table 2, Model 1 & 2**)
- Cumulative use of abacavir and didanosine were 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 2**). 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 1**) into the main regression model (**Table 2, Model 2**), the MI rate was increased by 119% (2.19 [1.64, 2.92]; p=0.0001) in those with a moderate 10-year CHD risk and by 222% (3.22 [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 risks of MI associated with recent abacavir and didanosine use were seen regardless of duration of use and remained after adjustment for HIV-RNA levels, CD_4 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 1**)
- 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 no 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 was generally little difference between those with and without recent use.
- As patients with a higher underlying risk of CVD may be initially placed on abacavir, 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 ratio. 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 CHD 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 an 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 - in 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

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