

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

Writing group: CA Sabin¹, S Worm², R Weber³, P Reiss⁴, W El-Sadr⁵, R Thiebaut⁶, S De Wit⁷, M Law⁸, A D'Arminio Monforte⁹, N Friis-Møller^{2,10}, O Kirk^{2,10}, C Pradier¹¹, S Collins¹², I Weller¹³, AN Phillips¹, JD Lundgren² on behalf of the D:A:D study group*

¹Royal Free and Univ. College, London; ²Copenhagen HIV Programme (CHIP), Univ. Copenhagen, Denmark; ³Swiss HIV Cohort Study (SHCS), Univ. Zürich, Switzerland; ⁴ATHENA Cohort, Academic Medical Ctr, Amsterdam, The Netherlands; ⁵CPCRA, Columbia Univ., NY, USA; ⁶Aquitaine Cohort, Univ. Bordeaux, France; ⁷Saint-Pierre Cohort, Brussels, Belgium; ⁸AHOD Cohort, Univ N South Wales, Australia; ⁹ICONA Cohort, Italy; ¹⁰EuroSIDA cohort at; ¹¹Nice Cohort, France; ¹²EATG & e-Base, London, UK; ¹³UCL, London, UK

Jens D. Lundgren, MD
Centre for Viral Diseases/KMA & Copenhagen HIV Programme
Rigshospitalet & University of Copenhagen
Panum Institute (Bldg 21.1)
2200 Copenhagen, Denmark
Phone +45 3545 5757
Fax: +45 3545 5758
jdl@cphiv.dk

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)

ACKNOWLEDGEMENTS

Cohort PI's: W El-Sadr⁵ (CPCRA), G Calvo⁶ (BASS), F Dabis⁶ (Aquitaine), O Kirk¹⁰ (EuroSIDA), M Law⁸ (AHOD), A d'Arminio Monforte⁹ (ICONA), L Morfeldt¹¹ (HivBIVUS), C Pradier¹¹ (Nice), P Reiss⁴ (ATHENA), R Weber³ (SHCS), S De Wit⁷ (St-Pierre)
Cohort coordinators and datamanagers: S Zaheri, L Gras (ATHENA), R Thiebaut, E Balestre (Aquitaine), K Petoumenos (AHOD), S Mateu, F Torres (BASS), B Pöll (St-Pierre), G Bartsch, G Thompson (CPCRA), J Kjer (EuroSIDA), P Pezzotti (ICONA), E Fontas, C Caisotti (Nice), A Sundström, G Thulin (HivBIVUS), M Rickenbach, O Keiser (SHCS)
Statisticians: CA Sabin, AN Phillips¹
Community representative: S Collins¹²
DAD coordinating office: N Friis-Møller, S Worm, A Sawitz, JD Lundgren*
Steering Committee: Members indicated w/; * chair. Additional members: S Storer⁸, F Rousseau⁹, I Weller¹³
Funding: The D:A:D study is funded by the "HAART Oversight Committee" - an European Medicines Evaluation Agency (EMA) initiative supported by: Abbott Laboratories, AIDS Treatment Activists Collation (ATAC), Boehringer-Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb, European AIDS Treatment Group (EATG), Food and Drug Administration (FDA), F. Hoffmann-La Roche Ltd, Gilead Sciences Inc., GlaxoSmithKline, Merck & Co Inc and Pfizer Inc.

Table 1 Cardiovascular risk profile at time of MI

	All	Recent didanosine	Recent abacavir	ART no recent 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/m ² (%)	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%
10y CHD risk					
Low	24%	20%	21%	21%	53%
Moderate	26%	27%	27%	30%	13%
High	23%	21%	28%	21%	4%
Unknown	27%	32%	27%	28%	30%

* Recent = still using or stopped within last 6 months
 ** 12% MI in patients not yet started ART; 43 patients on abacavir + didanosine - included in both columns

Table 2 Rates of MI by use of various NRTIs

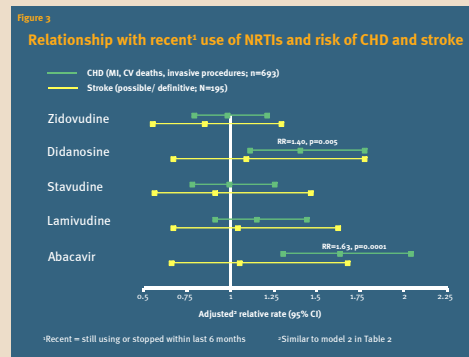
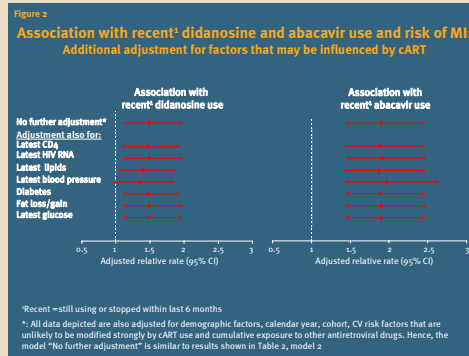
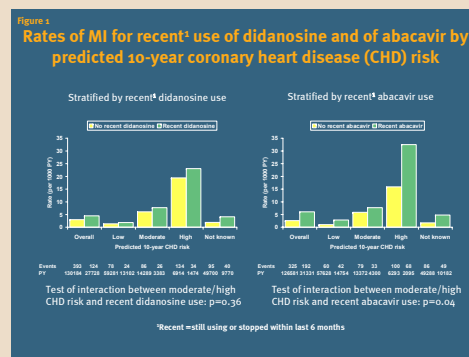
NRTI's	Model 1		Model 2		Model 3	
	Cumulative use only Rel. rate (95% CI)-p-value	Cum. + recent use Rel. rate (95% CI)-p-value	Cum. + recent use Rel. rate (95% CI)-p-value	Cum. + recent use Rel. rate (95% CI)-p-value	Cum. + recent use Rel. rate (95% CI)-p-value	Cum. + recent use Rel. rate (95% CI)-p-value
Zidovudine						
Cumulative use (per year)	1.05 [0.99, 1.08]; p=0.14	1.04 [0.99, 1.08]; p=0.08	1.06 [0.99, 1.09]; p=0.05	1.06 [0.99, 1.09]; p=0.05	1.06 [0.99, 1.09]; p=0.05	1.06 [0.99, 1.09]; p=0.05
Any recent use	-	0.97 [0.85, 1.09]; p=0.82	1.22 [0.82, 1.81]; p=0.33	1.22 [0.82, 1.81]; p=0.33	1.22 [0.82, 1.81]; p=0.33	1.22 [0.82, 1.81]; p=0.33
Any past use	-	-	1.29 [0.89, 1.88]; p=0.18	1.29 [0.89, 1.88]; p=0.18	1.29 [0.89, 1.88]; p=0.18	1.29 [0.89, 1.88]; p=0.18
Didanosine						
Cumulative use (per year)	1.06 [1.01, 1.12]; p=0.03	1.05 [0.99, 1.08]; p=0.08	1.06 [0.99, 1.09]; p=0.05	1.06 [0.99, 1.09]; p=0.05	1.06 [0.99, 1.09]; p=0.05	1.06 [0.99, 1.09]; p=0.05
Any recent use	-	1.49 [1.34, 1.65]; p=0.003	1.53 [1.36, 2.33]; p=0.001	1.53 [1.36, 2.33]; p=0.001	1.53 [1.36, 2.33]; p=0.001	1.53 [1.36, 2.33]; p=0.001
Any past use	-	-	1.08 [0.84, 1.39]; p=0.34	1.08 [0.84, 1.39]; p=0.34	1.08 [0.84, 1.39]; p=0.34	1.08 [0.84, 1.39]; p=0.34
Stavudine						
Cumulative use (per year)	1.04 [0.99, 1.10]; p=0.01	1.05 [0.98, 1.13]; p=0.05	1.02 [0.96, 1.09]; p=0.09	1.02 [0.96, 1.09]; p=0.09	1.02 [0.96, 1.09]; p=0.09	1.02 [0.96, 1.09]; p=0.09
Any recent use	-	1.00 [0.85, 1.17]; p=0.98	1.22 [0.84, 1.77]; p=0.30	1.22 [0.84, 1.77]; p=0.30	1.22 [0.84, 1.77]; p=0.30	1.22 [0.84, 1.77]; p=0.30
Any past use	-	-	1.24 [0.93, 1.64]; p=0.14	1.24 [0.93, 1.64]; p=0.14	1.24 [0.93, 1.64]; p=0.14	1.24 [0.93, 1.64]; p=0.14
Lamivudine						
Cumulative use (per year)	1.03 [0.98, 1.08]; p=0.08	1.00 [0.94, 1.07]; p=0.93	0.99 [0.93, 1.04]; p=0.80	0.99 [0.93, 1.04]; p=0.80	0.99 [0.93, 1.04]; p=0.80	0.99 [0.93, 1.04]; p=0.80
Any recent use	-	1.25 [0.96, 1.62]; p=0.09	1.60 [1.19, 2.16]; p=0.001	1.60 [1.19, 2.16]; p=0.001	1.60 [1.19, 2.16]; p=0.001	1.60 [1.19, 2.16]; p=0.001
Any past use	-	-	1.45 [0.88, 2.40]; p=0.15	1.45 [0.88, 2.40]; p=0.15	1.45 [0.88, 2.40]; p=0.15	1.45 [0.88, 2.40]; p=0.15
Abacavir						
Cumulative use (per year)	1.14 [1.08, 1.20]; p=0.0005	1.03 [0.99, 1.08]; p=0.08	1.00 [0.93, 1.08]; p=0.93	1.00 [0.93, 1.08]; p=0.93	1.00 [0.93, 1.08]; p=0.93	1.00 [0.93, 1.08]; p=0.93
Any recent use	-	1.99 [1.41, 2.80]; p=0.0001	1.94 [1.48, 2.58]; p=0.0001	1.94 [1.48, 2.58]; p=0.0001	1.94 [1.48, 2.58]; p=0.0001	1.94 [1.48, 2.58]; p=0.0001
Any past use	-	-	1.29 [0.94, 1.77]; p=0.12	1.29 [0.94, 1.77]; p=0.12	1.29 [0.94, 1.77]; p=0.12	1.29 [0.94, 1.77]; p=0.12

Recent = still using or stopped within last 6 months; *Past = last used more than 6 months ago

Table 3 Characteristics of patients under follow-up¹ with recent² 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	114	393	124	399	124	383	377	140	192	235
Total person-years	62357	95556	27748	139884	34956	128156	102423	55509	31331	126581
Event rate (95% CI)	3.4	3.2	4.5	3.0	3.7	3.2	3.7	3.2	3.2	4.1
/1000 person-years	(3.0, 3.9)	(2.8, 3.5)	(3.7, 5.3)	(2.7, 3.3)	(3.1, 4.4)	(2.8, 3.5)	(3.3, 4.0)	(3.1, 3.9)	(3.0, 3.7)	(3.3, 3.9)
Male sex (%)	74.5	74.1	74.9	74.1	76.0	73.7	75.2	72.5	76.8	73.6
Age ≥65 (male) or ≥55 (female) (%)	32.3	29.9	30.7	30.9	28.7	31.5	33.2	26.5	36.2	29.5
BMI>26 kg/m ² (%)	30.2	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 (%)	2.1	1.9	1.7	2.0	2.0	1.9	2.2	1.6	2.7	1.8
Family (%)	8.2	7.8	7.9	8.0	6.8	8.3	7.9	8.0	8.6	7.8
Diabetes (%)	4.3	4.7	5.4	4.4	5.2	4.4	4.9	3.9	5.8	4.3
Hypertension (%)	14.6	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

¹Unless 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 (4.3-14.7) per 1000 PY.
²Recent = still using or stopped within last 6 months.



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, 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 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

Download poster at: www.cphiv.dk

