Impact of individual antiretroviral drugs on the risk of myocardial infarction in HIV-infected patients: a case-control study nested within the FHDH ANRS Cohort CO4

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FHDH ANRS CO4: MI Case Control Study

- Nested, case-control study to evaluate association between risk of MI and
  - Cumulative exposure to specific NRTIs
  - Recent (current or within last 6 months) and past exposure (>6 months ago) to specific NRTIs
  - Cumulative to specific NNRTIs
  - Cumulative exposure to specific Pis

- 74 958 HIV-infected patients followed between 2000 and 2006
  - Cases: 289 Patients with a first definite or probable MI or possible death from MI prospectively reported between January, 2000 and December, 2006.
  - The diagnosis of MI was confirmed by a cardiologist, blind to the antiretroviral treatment (ART) history, who was provided with cardiac signs and symptoms, troponin and/or creatine-kinase levels, and electrocardiographic findings
  - Matched Controls: For each MI case, up to 5 controls with no history of MI matched for age, sex and clinical center, followed at time of the corresponding case MI
  - Incidence 1.24/1000 P-Y (SMR 1.50 [1.34-1.68]) (Lang S et al; AIDS 2010; 24(8): 1228-1230)

- Data collected for cases and controls
  - Cardiovascular risk factors and treatments
  - HIV history and treatment checked

Characteristics of patients at the index date - I

	Cases n = 289	Controls n = 884	P value of univariate conditional logistic regression
General characteristics			
Sex, male	257 (89)	788 (89)	..
Age, years	47 (41-54)	46 (40-54)	..
BMI ≥ 30 kg/m2	10 (4)	39 (4)	0.805[#]
Current smoker*	186 (64)	356 (40)	<0.028[#]
Smoking cessation ≤ 3 years	24 (8)	32 (4)	

Characteristics of patients at the index date - II

	Cases n = 289	Controls n = 884	P value of univariate conditional logistic regression
Cardiovascular disease			
Family history of premature CAD*	53 (18)	59 (7)	<0.001#
Hypertension or hypertension treatment*	59 (20)	103 (12)	0.001#
Current cocaine and/or intravenous drug use	38 (13)	83 (9)	0.041
Diabetes or treatment*	45 (16)	91 (10)	0.036#
Glycaemia, mmol/L	5.3 (4.9-6.0)	5.1 (4.7-5.7)	0.120
Latest lipid measurements, use of lipid-lowering medication			
Hypercholesterolemia or treatment*	150 (52)	288 (33)	<0.001#
Hypertriglyceridemia*	164 (57)	423 (48)	0.075#
Total cholesterol, mmol/L	5.4 (4.5-6.6)	5.3 (4.4-6.1)	0.001
LDL cholesterol, mmol/L	3.3 (2.4-4.2)	3.2 (2.4-4.0)	0.429
HDL cholesterol, mmol/L	1.0 (0.8-1.3)	1.1 (0.9-1.4)	0.023
Triglycerides, mmol/L	1.9 (1.3-3.3)	1.7 (1.1-2.5)	<0.001
Number of cardiovascular risk factors**			<0.001
None	5 (2)	170 (19)	
One or two	171 (59)	553 (63)	
Three or more	113 (39)	161 (18)	

Characteristics of patients at the index date - III

	Cases n = 289	Controls n = 884	P value of univariate conditional logistic regression
Characteristics linked with HIV infection			
Plasma HIV-1 RNA	127 (50-3900)	50 (50-1368)	0.015
Plasma HIV-1 RNA ≤ 50 copies/ml	125 (43)	457 (52)	0.006
CD4 cell nadir, cells/mm^3	135 (41-238)	177 (68-309)	0.001
CD4 cells count, cells/mm^3	427 (256-638)	451 (291-634)	0.476
CD4/CD8 cells ratio ≥ 1*	19 (7)	116 (13)	0.001#
CD8 cells count, cells/mm^3	1049 (710-1372)	929 (639-1246)	0.589
Delay HIV diagnosis / index date	10.1 (6.4-14.6)	8.9 (4.8-13.3)	0.001
AIDS prior index date	126 (44)	289 (33)	0.001
No treatment before index date	11 (4)	55 (6)	0.132
No treatment at index date	15 (5)	61 (7)	<0.001
Time under ART, years	6.6 (3.9-8.9)	7.0 (4.1-10.1)	0.003
Number of different therapeutic line	5 (2-8)	4 (2-7)	<0.001
Number of different ARV	7 (5-10)	6 (4-8)	<0.001
First ART after inclusion in the cohort	210 (73)	677 (77)	0.321

Treatment history

	Cases n = 289		Controls n = 884	
	cases exposed n and %	Cumulative exposure*	controls exposed n and %	Cumulative exposure*
NRTI				
Abacavir	127 (43.9)	1.43 (0.35 Ğ 3.02)	283 (32.0)	1.77 (0.53 Ğ 3.64)
Didanosine	186 (56.1)	2.06 (0.85 Ğ 3.75)	505 (57.1)	2.20 (0.94 Ğ 4.00)
Lamivudine	269 (93.1)	3.72 (2.23 Ğ 5.19)	774 (87.6)	3.55 (1.94 Ğ 5.35)
Stavudine	199 (68.9)	3.15 (1.68 Ğ 4.58)	519 (58.7)	3.02 (1.62 Ğ 4.38)
Tenofovir	65 (22.5)	1.34 (0.55 Ğ 2.17)	173 (19.6)	1.00 (0.53 Ğ 1.91)
Zalcitabine	92 (31.8)	1.02 (0.53 Ğ 1.84)	222 (25.1)	0.91 (0.52 Ğ 1.84)
Zidovudine	256 (88.6)	2.65 (1.55 Ğ 4.70)	742 (83.9)	2.77 (1.38 Ğ 4.83)
Any thymidine analogue	276 (95.5)	5.15 (3.27 Ğ 7.36)	810 (91.6)	4.89 (3.01 Ğ 6.80)
NNRTI				
Efavirenz	109 (37.7)	1.42 (0.61 Ğ 2.52)	295 (33.4)	1.69 (0.72 Ğ 3.01)
Nevirapine	111 (38.4)	1.14 (0.66 Ğ 2.40)	269 (30.4)	1.49 (0.67 Ğ 3.13)
PI				
Amprenavir/fosAmp+/-r	46 (15.9)	1.28 (0.64 Ğ 2.69)	71 (8.0)	0.80 (0.45 Ğ 1.49)
Amprenavir/fosAmp/r	38 (13.1)	1.20 (0.51 Ğ 3.03)	61 (6.9)	0.69 (0.37 Ğ 1.59)
Amprenavir/fosAmp	20 (6.9)	0.85 (0.25 Ğ 1.34)	17 (1.9)	0.64 (0.42 Ğ 0.90)
Indinavir+/-r	146 (50.5)	1.77 (0.85 Ğ 2.97)	351 (39.7)	1.79 (0.73 Ğ 3.16)
Indinavir/r	39 (13.5)	0.95 (0.30 Ğ 1.40)	98 (11.1)	0.61 (0.34 Ğ 1.24)
Indinavir	130 (45.0)	1.66 (076 Ğ 2.89)	312 (35.3)	1.78 (0.90 Ğ 3.08)
Lopinavir/r	94 (32.5)	1.62 (0.65 Ğ 2.78)	196 (22.2)	1.09 (0.45 Ğ 2.11)
Nelfinavir	131 (45.3)	1.29 (0.81 Ğ 2.44)	322 (36.4)	1.52 (0.83 Ğ 2.49)
Saquinavir+/-r	92 (31.8)	1.31 (0.65 Ğ 2.15)	232 (26.2)	1.46 (0.79 Ğ 2.33)
Saquinavir/r	51 (17.6)	1.61 (0.62 Ğ 2.46)	125 (14.1)	1.33 (0.79 Ğ 2.40)
Saquinavir	60 (20.8)	0.84 (0.45 Ğ 1.30)	146 (16.5)	1.00 (0.66 Ğ 1.69)
Any PIs except saquinavir	239 (82.7)	3.27 (1.56 Ğ 5.05)	625 (70.7)	2.84 (1.46 Ğ 4.44)

Exposure to abacavir and other NRTIs and risk of MI, FHDH Study

	N exposed	N exposed cases	Univariate model OR [95% CI]	Model 1: cumulative exposure only OR [95% CI]
Abacavir, cumul expo	410	127	1.05 (0.96 - 1.15)	0.97 (0.86 - 1.10)
Didanosine, cumul expo	691	186	1.02 (0.95 – 1.09)	0.91 (0.82 – 1.01)
Lamivudine, cumul expo	1043	269	1.06 (1.00 – 1.13)	0.96 (0.86 – 1.08)
Stavudine, cumul expo	718	199	1.09 (1.02 – 1.16)	1.11 (0.99 – 1.24)
Tenofovir, cumul expo	238	65	1.19 (0.99 – 1.44)	1.01 (0.79 – 1.30)
Zalcitabine, cumul expo	314	92	1.08 (0.94 – 1.24)	0.99 (0.82 – 1.21)
Zidovudine, cumul expo	998	256	1.03 (0.98 – 1.08)	1.09 (1.00 – 1.19)

This is different from D:A:D

Without D:A:D, we would have found no association

Adjusted for hypertension, smoking, family history of premature CAD, use of cocaine and/or IV drug use, plasma HIV-1 RNA level, CD4/CD8 cells ratio, exposure to emtricitabine, atazanavir, ritonavir and tipranavir and other ARVs

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The impact of cardiovascular risk factors on the likelihood of receiving tenofovir and abacavir is big

Adjusted for hypertension, smoking, family history of premature CAD, use of cocaine and/or IV drug use, plasma HIV-1 RNA level, CD4/CD8 cells ratio, exposure to emtricitabine, atazanavir, ritonavir and tipranavir and other ARVs

Exposure to NNRTIs and PIs and risk of MI

	N exposed	N exposed cases	Univariate model OR [95% CI]	Final model OR [95% CI]
NNRTI				
Efavirenz, cumul expo	404	109	1.00 (0.90 – 1.10)	1.01 (0.87 – 1.17)
Nevirapine, cumul expo	380	111	1.00 (0.90 – 1.10)	1.00 (0.87 – 1.14)
PI				
Ampr/fos+/-r cumul expo	117	46	1.41 (1.17 – 1.69)	1.53 (1.21 – 1.94)
Indinavir+/-r, cumul expo	497	146	1.10 (1.01 – 1.19)	1.07 (0.94 – 1.20)
Lopinavir/r, cumul expo	290	94	1.35 (1.17 – 1.55)	1.33 (1.09 – 1.61)
Nelfinavir, cumul expo	453	131	1.08 (0.98 – 1.19)	1.10 (0.97 – 1.26)
Saqui+/-r, cumul expo	324	92	1.02 (0.91 – 1.13)	0.93 (0.80 – 1.09)

No such impact for NNRTIs and PIs

Adjusted for hypertension, smoking, family history of premature CAD, use of cocaine and/or IV drug use, plasma HIV-1 RNA level, CD4/CD8 cells ratio, exposure to emtricitabine, atazanavir, ritonavir and tipranavir and other ARVs

Exposure to abacavir and other NRTIs and risk of MI

	N exposed	N exposed cases	Univariate model OR [95% CI]	Final model OR [95% CI]
Abacavir				
No exposure	763	162	1	1
Exposure < 1y, current	72	31	2.76 (1.67 – 4.55)	2.01 (1.11 – 3.64)
Exposure > 1y, current	218	57	1.34 (0.94 – 1.93)	1.05 (0.65 – 1.69)
Exposure < 1y, past	76	24	1.66 (0.99 – 2.79)	1.31 (0.68 – 2.51)
Exposure > 1y, past	44	15	1.94 (1.00 – 3.79)	1.48 (0.62 – 3.49)
Didanosine, cumul expo	691	186	1.02 (0.95 – 1.09)	0.91 (0.82 – 1.01)
Lamivudine, cumul expo	1043	269	1.06 (1.00 – 1.13)	0.96 (0.85 – 1.07)
Stavudine, cumul expo	718	199	1.09 (1.02 – 1.16)	1.11 (0.99 – 1.24)
Tenofovir, cumul expo	238	65	1.19 (0.99 – 1.44)	1.00 (0.77 – 1.28)
Zalcitabine, cumul expo	314	92	1.08 (0.94 – 1.24)	0.98 (0.81 – 1.20)
Zidovudine, cumul expo	998	256	1.03 (0.98 – 1.08)	1.09 (1.00 – 1.19)

Adjusted for hypertension, smoking, family history of premature CAD, use of cocaine and/or IV drug use, plasma HIV-1 RNA level, CD4/CD8 cells ratio, exposure to emtricitabine, atazanavir, ritonavir and tipranavir and other ARVs

Sensitivity analyses

Analyses in patients naïve at enrolment in the cohort

- At enrolment in the cohort, 76 % of patients had never received ART (210 cases and 677 controls)
- The analyses restricted to cases and their matched controls naïve at enrolment included 61% of the full sample (207 cases and 510 controls)
- For short term/recent abacavir, the univariate OR was estimated as 3.77 (95% CI, 1.86-7.64) and the adjusted OR as 1.79 (95% CI, 0.74-4.27)
- Other results were robust

Characteristics 31 cases with recent exposure to abacavir versus the other cases

	Cases Recent exposure to ABC (n = 31)	Others Cases (n = 258)
Cardiovascular disease		
Hypertension, n (%)	4 (13%)	55 (21%)
Family history of CHD, n (%)	7 (23%)	46 (18%)
Diabetes or treatment, n (%)	3 (10%)	42 (16%)
Glycaemia, mmol/L (IQR)	5.0 (4.6 – 6.2)	5.3 (4.9 – 6.0)
Cocaine and/or intravenous drug use, n (%)	9 (29%)	29 (11%)
Latest lipid measurements, use of lipid-lowering treatment		
Hypercholesterolemia or treatment, n (%)	13 (42%)	137 (53%)
Hypertriglyceridemia or treatment, n (%)	19 (61%)	186 (72%)
Total cholesterol, mmol/L (IQR)	5.2 (4.4 – 6.0)	5.5 (4.5 – 6.7)
LDL cholesterol, mmol/L (IQR)	3.1 (2.6 – 3.9)	3.4 (2.4 – 4.3)
HDL cholesterol, mmol/L (IQR)	1.0 (0.8 – 1.0)	0.9 (0.8 – 1.3)
Triglycerides, mmol/L (IQR)	1.8 (1.2 – 3.2)	1.9 (1.3 – 3.3)
Number of cardiovascular risk factors		
0, n (%)	1 (3%)	4 (2%)
1-2 n, (%)	19 (61%)	152 (59%)
≥ 3 n, (%)	11 (36%)	102 (40%)

	All n= 954	Cases n= 250	Univariate Model	Final Model*
	N exposed	N exposed		
NRTI				
Abacavir				
No exposure	612	141	1	1
Short term, recent	57	22	2.00 (1.13-3.54)	1.27 (0.64-2.49)
Long term, recent	184	52	1.36 (0.92-2.01)	0.95 (0.56-1.63)
Short term, past	64	21	1.60 (0.91-2.83)	1.09 (0.52-2.29)
Long term, past	37	14	1.97 (0.95-4.05)	1.24 (0.48-3.22)
Didanosine, cumulative exposure	564	164	1.03 (0.95-1.10)	0.89 (0.79-1.00)
Lamivudine, cumulative exposure	845	232	1.07 (1.00-1.15)	0.98 (0.86-1.12)
Stavudine, cumulative exposure	577	174	1.11 (1.04-1.19)	1.11 (0.98-1.26)
Tenofovir, cumulative exposure	191	56	1.23 (1.01-1.50)	1.01 (0.77-1.32)
Zalcitabine, cumulative exposure	247	77	1.10 (0.95-1.27)	0.97 (0.78-1.20)
Zidovudine, cumulative exposure	812	220	1.04 (0.98-1.09)	1.10 (1.00-1.21)
NNRTI				
Efavirenz, cumulative exposure	330	98	1.02 (0.91-1.14)	1.01 (0.86-1.20)
Nevirapine, cumulative exposure	314	99	1.03 (0.92-1.14)	0.99 (0.86-1.15)
PI				
Amprenavir/fosAmp+/-r, cumulative exposure	105	43	1.48 (1.19-1.84)	1.63 (1.21-2.19)
Indinavir+/-r, cumulative exposure	410	125	1.08 (0.99-1.19)	1.06 (0.93-1.22)
Lopinavir/r, cumulative exposure	248	86	1.34 (1.16-1.55)	1.29 (1.05-1.59)
Nelfinavir, cumulative exposure	370	117	1.10 (0.99-1.23)	1.12 (0.97-1.30)
Saquinavir+/-r, cumulative exposure	265	80	1.03 (0.92-1.16)	0.97 (0.83-1.14)

PIs impact not explained completely by their impact on lipid or diabetes

Study	Risk
D:A:D NEJM 2007	1.16 (1.10-1.23) ↓ 1.10 (1.04-1.18)
FHDH ANRS CO4 Arch Int Med 2010. In press	1.15 (1.06-1.26) ↓ 1.12 (1.02-1.23)

Nor by boosting with ritonavir

Interpretation - I

- Most PIs so far studied have been found to increase the risk of MI, and this increase is not solely mediated by an effect on lipid metabolism
- The ten years odds ratio of the risk of MI was estimated as 4 for exposure to PIs except saquinavir
- To translate this result in practical terms for a given patient, one can calculate the number of patients to treat for ten years with a PI to observe an additional MI (NNH, number needed to harm)
  - For a patient whose risk is the risk observed in the French HIV-infected patients in this study, that is 1.24 per 1000 per year (1.2 per 100 after 10 years), the NNH is estimated as 29
  - If one considers a patient whose ten year risk using the Framingham equation is 20%, the NNH is estimated as 3, meaning that for 3 patients treated with a PI for ten year, there will be an additional MI
- This means that long-term exposure to this drug class should be avoided if virologically possible, in patients with multiple cardiovascular risk factors
- There are currently no datasets, including our own, in which exposure to atazanavir +/-r or darunavir+/-r is sufficient to conclude on these two newer PIs

Interpretation - II

- We found no association between NNRTI exposure and the risk of MI, and this result also appears to be robust
- The results for NRTIs are more complex and more likely to be affected by residual confounding
- While cumulative exposure to thymidine analogues appeared to increase the risk of MI (OR 1.09 (1.00-1.19)) per year, the observed association with short-term/recent exposure to abacavir disappeared when restricting the analysis to non-users of cocaine or intravenous drugs
- Taken together, these elements suggest that the relationship between exposure to abacavir and the risk of MI cannot be considered as causal