
Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration

*D:A:D Study Group**

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BASE DEL ESTUDIO

- Evaluar la incidencia de enfermedad cardiovascular en pacientes que reciben tratamiento con fármacos antirretrovirales inhibidores de la transcriptasa inversa análogos de nucleósidos

JUSTIFICACION

- El aumento de la esperanza de vida de las personas infectadas por el virus de la inmunodeficiencia humana (VIH) gracias los tratamientos antirretrovirales ha convertido a la enfermedad cardiovascular en una de las principales preocupaciones en el seguimiento de estos pacientes.
- Estudios recientes señalan un elevado riesgo cardiovascular entre las personas infectadas por el VIH, con aumento de los pacientes que padecen un infarto agudo de miocardio o un ictus cerebral.
- Los fármacos antirretrovirales, aunque mejoran y alargan la vida de las personas infectadas por el VIH, aumentan el riesgo de hipercolesterolemia, dislipemia, hiperglicemia e hipertensión pulmonar.

METODOS: Pacientes

- **Estudio observacional que evalúa la seguridad del tratamiento antirretroviral a largo plazo**
- **Examinan a 33.347 personas infectadas por el VIH de 11 cohortes distintas en Europa, Estados Unidos y Australia**
- **Reclutadas entre diciembre de 1999 y enero de 2005**

RESULTADOS

	Patients with a myocardial infarction				Patients who did not have a myocardial infarction
	All*	Recent use of didanosine†	Recent use of abacavir‡	Antiretroviral-experienced but no recent use of didanosine or abacavir	
General characteristics					
Number of patients	517	124	192	237	32830
Sex (male)	474 (92%)	117 (94%)	177 (92%)	213 (90%)	24218 (74%)
Age (years)	49 (24-92)	50 (30-80)	48 (27-91)	50 (24-92)	43 (12-95)
Body-mass index >76 kg/m ²	97 (18%)	19 (15%)	78 (15%)	43 (18%)	5479 (17%)
Current smoker‡	219 (42%)	53 (43%)	88 (46%)	94 (40%)	9150 (28%)
Ex-smoker	154 (30%)	36 (29%)	61 (32%)	70 (30%)	9441 (29%)
Cardiovascular disease					
In own history	48 (9%)	11 (9%)	20 (10%)	19 (8%)	210 (0.6%)
Family history	70 (14%)	18 (15%)	21 (11%)	34 (14%)	2596 (8%)
Diabetes	84 (16%)	24 (19%)	30 (16%)	36 (15%)	1635 (5%)
Hypertension					
Use of anti-hypertensive medication	166 (32%)	39 (31%)	64 (33%)	77 (32%)	3576 (11%)
Any hypertension	205 (40%)	47 (38%)	78 (41%)	99 (42%)	6016 (18%)
Latest lipid measurements, use of lipid-lowering medication, or lipodystrophy					
Total cholesterol	5.7 (1.4-14.8)	5.6 (2.5-10.4)	5.7 (2.6-14.8)	5.7 (1.4-12.9)	4.8 (1.0-15.6)
HDL cholesterol	1.1 (0.3-3.6)	1.1 (0.3-3.4)	1.0 (0.3-2.7)	1.1 (0.3-13.6)	1.2 (0.1-28.2)
Triglycerides	2.3 (0.4-22.4)	2.5 (0.5-16.4)	2.6 (0.4-22.4)	2.2 (0.6-16.2)	1.6 (0.1-28.2)
Use of lipid-lowering medication	163 (32%)	49 (40%)	66 (34%)	62 (26%)	4051 (12%)
Any dyslipidaemia	379 (73%)	93 (75%)	141 (73%)	173 (73%)	14548 (44%)
Lipodystrophy	205 (40%)	51 (41%)	84 (44%)	88 (37%)	8484 (26%)
Predicted 10-year risk of coronary heart disease					
Low (<10%)	113 (22%)	25 (20%)	44 (23%)	49 (21%)	17454 (53%)
Moderate (10-20%)	134 (26%)	33 (27%)	42 (22%)	72 (30%)	4161 (13%)
High (>20%)	120 (23%)	26 (21%)	54 (28%)	49 (21%)	1308 (4%)
Not known	150 (29%)	40 (32%)	52 (27%)	67 (28%)	9907 (30%)
Dundee categorisation of myocardial infarction					
Definitive	333 (64%)	84 (68%)	128 (67%)	149 (63%)	NA
Possible	113 (22%)	23 (19%)	42 (22%)	53 (22%)	NA
Not known	71 (14%)	17 (14%)	22 (11%)	35 (15%)	NA
Fatal	134 (26%)	27 (22%)	41 (21%)	71 (30%)	NA

Data are n (%) or median (range). NA=not applicable. * Includes eight patients who were antiretroviral-naïve when they had a myocardial infarction. †43 patients had recent use of both didanosine and abacavir at the time of their myocardial infarction; these patients are included in both groups. ‡Percentage based on all patients under follow-up; information on smoking status was available for 426 of those with a myocardial infarction and 24 178 of those who did not.

Table 1: Characteristics of patients at the time of their first myocardial infarction during follow-up (or at last D:A:D follow-up visit for those who did not have a myocardial infarction)

RESULTADOS

	Model 1: cumulative exposure only	Model 2: cumulative and recent exposure	Model 3: cumulative, recent, and past exposure
Zidovudine			
Cumulative exposure (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 exposure	..	0.97 (0.76–1.25); p=0.82	1.22 (0.82–1.81); p=0.33
Past exposure only	1.29 (0.89–1.85); p=0.18
Didanosine			
Cumulative exposure (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 exposure	..	1.49 (1.14–1.95); p=0.003	1.53 (1.10–2.13); p=0.01
Past exposure only	1.08 (0.84–1.39); p=0.54
Stavudine			
Cumulative exposure (per year)	1.04 (0.99–1.10); p=0.11	1.05 (0.98–1.11); p=0.15	1.02 (0.95–1.09); p=0.60
Any recent exposure	..	1.00 (0.76–1.32); p=0.98	1.22 (0.84–1.77); p=0.30
Past exposure only	1.24 (0.93–1.66); p=0.14

Lamivudine			
Cumulative exposure (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 exposure	..	1.25 (0.96–1.62); p=0.10	1.69 (1.02–2.80); p=0.04
Past exposure only	1.45 (0.88–2.40); p=0.15
Abacavir			
Cumulative exposure (per year)	1.14 (1.08–1.21); p=0.0001	1.01 (0.93–1.09); p=0.80	1.00 (0.92–1.08); p=0.91
Any recent exposure	..	1.90 (1.47–2.45); p=0.0001	1.94 (1.48–2.55); p=0.0001
Past exposure only	1.29 (0.94–1.77); p=0.12

Data are relative rate (95% CI), after adjustment for age, sex, risk group, ethnic origin, cohort, body-mass index, family history of cardiovascular disease, smoking status, previous cardiovascular event, calendar year, and cumulative exposure to all other antiretroviral drugs.

Table 2: Rates of myocardial infarction by exposure to various NRTIs

RESULTADOS

	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
Number of myocardial infarctions	214	303	124	393	134	383	377	140	192	325
Total person-years	62 357	95 556	27 728	130 184	36 056	121 856	102 423	55 490	31 331	126 581
Event rate per 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)
Sex (male)	74.5%	74.1%	74.9%	74.1%	76.0%	73.7%	75.2%	72.5%	76.8%	73.6%
Age >45 (men) or >55 (women)	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	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%
History of cardiovascular disease	2.1%	1.9%	1.7%	2.0%	2.0%	1.9%	2.2%	1.6%	2.7%	1.8%
Family history of cardiovascular disease	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%
Use of anti-hypertensive medication	7.7%	7.8%	7.8%	7.8%	7.0%	8.1%	8.5%	6.6%	9.7%	7.3%
Any dyslipidaemia	45.0%	47.7%	52.9%	45.3%	54.0%	44.5%	48.6%	43.0%	53.0%	45.1%
Use of lipid-lowering medication	8.9%	11.3%	13.6%	9.6%	11.0%	10.1%	11.0%	9.2%	14.5%	9.3%
Moderate/high predicted 10-year risk of coronary heart disease†	16.4%	16.5%	17.5%	16.3%	17.2%	16.3%	17.6%	14.4%	20.4%	15.5%

Data are event rate (95% CI) or proportion of follow-up time of patients in the cohort falling into each category, unless otherwise specified. Among patients with recent use of both didanosine and abacavir, the event rate was 7.9 per 1000 person-years (43 events in 5457 person-years). *Percentages based on total person-years; information on smoking status was unavailable for 9809 (16%), 17 094 (18%), 4094 (15%), 22 808 (18%), 5860 (16%), 21 043 (17%), 16 420 (16%), 10 483 (19%), 4740 (15%), and 22 163 (18%) person-years in the ten groups, respectively. †Percentages based on total person-years; information on risk of coronary heart disease was unavailable for 23 093 (37%), 36 377 (38%), 9770 (35%), 49 700 (38%), 14 995 (42%), 44 475 (36%), 37 718 (37%), 21 752 (39%), 10 182 (32%), and 49 288 (39%) person-years in the ten groups, respectively.

Table 3: Characteristics of patients under follow-up* with recent exposure to each NRTI

RESULTADOS

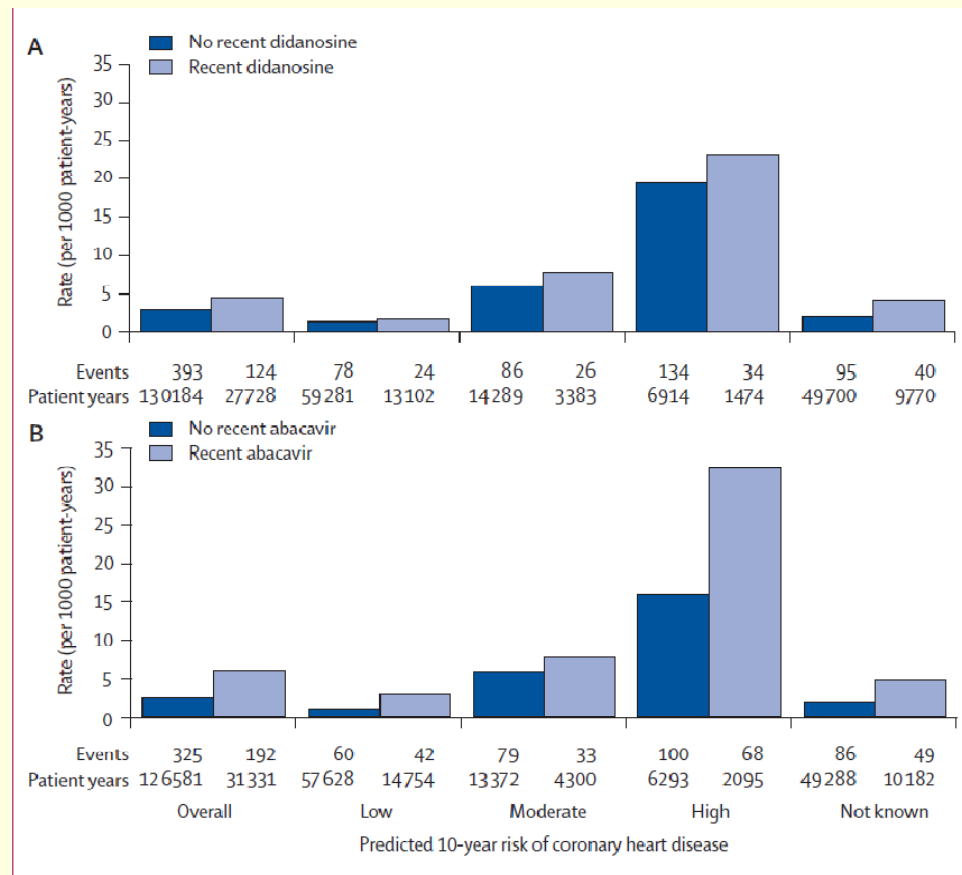


Figure 1: Rates of myocardial infarction, stratified by predicted 10-year risk of coronary heart disease, and recent use of either (A) didanosine or (B) abacavir

RESULTADOS

	First event of myocardial infarction, cardiovascular death, or invasive cardiovascular procedure (693 events)	Possible or definite strokes (196 events*)
Zidovudine		
Cumulative exposure (per year)	1.04 (1.00–1.08); p=0.06	1.07 (0.99–1.19); p=0.10
Any recent exposure	0.98 (0.79–1.21); p=0.83	0.85 (0.55–1.29); p=0.44
Didanosine		
Cumulative exposure (per year)	0.99 (0.94–1.05); p=0.84	0.90 (0.80–1.02); p=0.09
Any recent exposure	1.40 (1.11–1.77); p=0.005	1.09 (0.67–1.77); p=0.74
Stavudine		
Cumulative exposure (per year)	1.04 (0.99–1.10); p=0.13	1.04 (0.94–1.16); p=0.47
Any recent exposure	0.99 (0.78–1.25); p=0.90	0.91 (0.56–1.46); p=0.69
Lamivudine		
Cumulative exposure (per year)	1.01 (0.96–1.06); p=0.74	0.99 (0.89–1.10); p=0.89
Any recent exposure	1.15 (0.91–1.44); p=0.23	1.04 (0.67–1.62); p=0.86
Abacavir		
Cumulative exposure (per year)	1.03 (0.96–1.10); p=0.38	1.06 (0.93–1.21); p=0.40
Any recent exposure	1.63 (1.30–2.04); p=0.0001	1.05 (0.66–1.67); p=0.84

Data are relative rates (95% CI) after adjustment for age, sex, risk group, ethnic origin, cohort, body-mass index, family history of cardiovascular disease, smoking status, previous cardiovascular event, calendar year, and cumulative exposure to all other antiretroviral drugs. *132 (67%) ischaemic, 43 (22%) haemorrhagic, 21 (11%) unknown.

Table 4: Exposure to NRTIs and risk of first myocardial infarction, cardiovascular death, or invasive cardiovascular procedure, and of risk of possible or definite stroke*

CONCLUSIONES

- No encontraron asociaciones entre la tasa de infarto de miocardio en el uso acumulado o reciente de zidovudina, estavudina o lamivudina.
- Por el contrario, el uso reciente, pero no el acumulativo, de abacavir o didanosina sí se asoció con un aumento de la tasa de infarto de miocardio
- Se trata de un estudio de cohortes observacional