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Effects of first-line antiretroviral therapy on the CD4/CD8 ratio and CD8 cell counts in CoRIS: a prospective multicentre cohort study.

Serrano-Villar S, et al. Lancet HIV 2020; 7: e565-73

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Metodología

- Estudio prospectivo de la cohorte CORIS de 13026 personas que inician TAR registradas en 45 hospitales españoles.
- Se seleccionaron los pacientes que habían iniciado TAR triple con inhibidores de la integrasa, de la proteasa o no nucleósidos de la transcriptasa inversa en el período 2004-2018, que habían alcanzado supresión viral en la semana 48 de tratamiento y que tenían datos del cociente CD4/CD8.
- Se utilizaron modelos lineales mixtos de parcelas divididas (0-1 año, 1-4 años y 4-8 año tras inicio de TAR) para comparar cambios longitudinales en el cociente CD4/CD8 entre los tres grupos de TAR. Estos modelos se ajustaron por potenciales factores confusores como sexo, país de origen, modo de transmisión, año de inclusión en la cohorte, nivel de estudios, CV basal, estadio SIDA y nadir de CD4.
- Se utilizaron modelos de riesgos proporcionales de Cox para comparar los tiempos hasta la normalización del cociente CD4/CD8 entre las diferentes pautas de TAR con puntos de corte de 0,4, 1 y 1,5. Los modelos se ajustaron por los mismos factores descritos anteriormente y se realizaron modelos adicionales incluyendo el acme del recuento de CD8, el tiempo desde el diagnóstico VIH al inicio del TAR, el tiempo desde el inicio del TAR a la supresión virológica y la pareja de análogos.

Resultados

- Se analizaron 37680 observaciones de 6804 individuos con una mediana de seguimiento 49 meses, que supusieron 37149 personas-año de seguimiento.

Resultados

	NNRTI group (n=2820)	Protease inhibitor group (n=1574)	INSTI group (n=2410)	All (n=6804)
Age, years	36 (28-43)	38 (31-45)	36 (29-43)	36 (30-44)
Sex				
Male	2467 (87%)	1202 (76%)	2132 (88%)	5801 (85%)
Female	353 (13%)	372 (24%)	278 (12%)	1003 (15%)
Mode of transmission				
MSM	1852 (66%)	747 (47%)	1679 (70%)	4278 (63%)
Heterosexual	740 (26%)	601 (38%)	561 (23%)	1902 (28%)
IDU	137 (5%)	157 (10%)	46 (2%)	340 (5%)
Other	36 (1%)	19 (1%)	18 (1%)	73 (1%)
Unknown	55 (2%)	50 (3%)	106 (4%)	211 (3%)
Origin				
Spain	1561 (55%)	905 (57%)	1396 (58%)	3862 (57%)
Western Europe	593 (21%)	226 (14%)	310 (13%)	1129 (17%)
Eastern Europe	65 (2%)	33 (2%)	41 (2%)	139 (2%)
Sub-Saharan Africa	85 (3%)	98 (6%)	72 (3%)	255 (4%)
Northern Africa	39 (1%)	19 (1%)	29 (1%)	87 (1%)
Latin America	459 (16%)	283 (18%)	525 (22%)	1267 (19%)
Other	8 (0.2%)	7 (0.4%)	9 (0.3%)	24 (0.4%)
Unknown	10 (0.3%)	3 (0.2%)	28 (1%)	41 (1%)
Calendar period				
2004-09	1190 (42%)	696 (44%)	91 (4%)	1977 (29%)
2010-14	1407 (50%)	649 (41%)	591 (25%)	2647 (39%)
2015-18	223 (8%)	229 (15%)	1728 (72%)	2180 (32%)
Education level				
No studies	68 (2%)	67 (4%)	37 (2%)	172 (3%)

(Table 1 continues on next page)

Table 1: Population baseline characteristics according to the ART regimen.

Data are number (%) or median (IQR). All individuals received two nucleoside reverse transcriptase inhibitors in combination with either an INSTI, protease inhibitor, or NNRTI. ART=antiretroviral therapy. IDU=injecting drug use. INSTI=integrase strand transfer inhibitor. MSM=men who have sex with men. NNRTI=non-nucleoside reverse transcriptase inhibitor.

	NNRTI group (n=2820)	Protease inhibitor group (n=1574)	INSTI group (n=2410)	All (n=6804)
(Continued from previous page)				
Primary (6-12 years old)	317 (11%)	214 (14%)	216 (9%)	747 (11%)
Secondary (12-16 years old)	422 (15%)	283 (18%)	301 (12%)	1006 (15%)
High school (16-18 years old)	849 (30%)	406 (26%)	677 (28%)	1932 (28%)
University	720 (25%)	289 (18%)	661 (27%)	1670 (24%)
Other	42 (1%)	39 (2%)	36 (1%)	117 (2%)
Unknown	402 (14%)	776 (48%)	482 (20%)	1160 (17%)
AIDS diagnosis	299 (11%)	351 (22%)	275 (11%)	925 (14%)
AIDS-related death	12 (0.4%)	13 (1%)	10 (0.4%)	35 (0.5%)
All-cause death	69 (3%)	75 (5%)	23 (1%)	166 (2%)
Median time to virological suppression, weeks (IQR)	20 (13-30)	23 (14-34)	12 (6-24)	18 (10-29)
Virological failure	146 (5%)	123 (8%)	81 (3%)	350 (5%)
Time to virological failure in patients with virological failure, weeks	218 (136-313)	229 (139-348)	117 (77-156)	200 (123-315)
Duration on first-line ART, months	28 (10-52)	21 (7-45)	12 (5-22)	18 (7-39)
Maximum HIV-1 RNA, copies per mL	73 931 (27 358-18 6600)	10 8594 (35 962-32 9000)	77 103 (20 720-22 1000)	81 755 (26 825-22 8000)
Number of HIV-1 RNA quantifications	17 (11-24)	17 (10-26)	7 (4-11)	13 (7-21)
Follow-up from ART initiation, months	63 (41-96)	65 (38-104)	19 (9-34)	44 (19-80)
Nadir CD4 count, cells per μ L	300 (200-408)	219 (85-338)	378 (225-512)	304 (178-438)
Nadir CD4/CD8 ratio	0.33 (0.21-0.50)	0.25 (0.13-0.42)	0.39 (0.22-0.59)	0.33 (0.19-0.52)
Acme CD8 count, cells per μ L	1143 (784-1603)	929 (589-1409)	1050 (723-1484)	1066 (714-1516)
Baseline CD4/CD8 ratio	0.37 (0.24-0.58)	0.29 (0.15-0.49)	0.43 (0.25-0.66)	0.38 (0.22-0.60)
Baseline CD4 count, cells per μ L	358 (244-506)	270 (117-423)	424 (254-603)	356 (218-527)
Baseline CD8 count, cells per μ L	917 (656-1275)	815 (544-1172)	929 (656-1290)	899 (627-1257)

Resultados

	Coefficient (95% CI)	p value
Overall period		
INSTI	0 (ref)	..
NNRTI	-0.07 (-0.08 to -0.06)	<0.0001
Protease inhibitor	-0.08 (-0.09 to -0.08)	<0.0001
Sensitivity analyses		
Excluding patients with virological failure		
NNRTI	-0.08 (-0.09 to -0.07)	<0.0001
Protease inhibitor	-0.08 (-0.09 to -0.08)	<0.0001
Excluding patients with low level viraemia		
NNRTI	-0.07 (-0.08 to -0.06)	<0.0001
Protease inhibitor	-0.08 (-0.09 to -0.08)	<0.0001
Excluding patients with blips		
NNRTI	-0.08 (-0.08 to -0.07)	<0.0001
Protease inhibitor	-0.09 (-0.09 to -0.08)	<0.0001
Nadir CD4 cell count		
<200 cells per μ L		
NNRTI	-0.04 (-0.05 to -0.03)	<0.0001
Protease inhibitor	-0.04 (-0.05 to -0.03)	<0.0001
200-500 cells per μ L		
NNRTI	-0.09 (-0.10 to -0.08)	<0.0001
Protease inhibitor	-0.08 (-0.09 to -0.07)	<0.0001
>500 cells per μ L		
NNRTI	-0.08 (-0.10 to -0.06)	<0.0001
Protease inhibitor	-0.12 (-0.15 to -0.10)	<0.0001

	Coefficient (95% CI)	p value
Calendar period at cohort entry		
2004-09		
NNRTI	-0.04 (-0.05 to -0.02)	<0.0001
Protease inhibitor	-0.04 (-0.06 to -0.03)	<0.0001
2010-14		
NNRTI	-0.03 (-0.04 to -0.02)	<0.0001
Protease inhibitor	-0.03 (-0.04 to -0.02)	<0.0001
2015-19		
NNRTI	-0.04 (-0.06 to -0.02)	<0.0001
Protease inhibitor	-0.04 (-0.07 to -0.01)	0.003
Treatment periods		
First year of ART		
NNRTI	-0.03 (-0.05 to -0.13)	0.001
Protease inhibitor	-0.06 (-0.08 to -0.04)	<0.0001
1-4 years of ART		
NNRTI	-0.003 (-0.015 to 0.10)	0.693
Protease inhibitor	-0.007 (-0.020 to 0.007)	0.324
4-8 years of ART		
NNRTI	-0.02 (-0.07 to 0.4)	0.581
Protease inhibitor	-0.02 (-0.08 to 0.04)	0.487

Table 2: Comparison of CD4/CD8 ratio trajectories between treatment groups using adjusted multilevel mixed-effects models.

The coefficients represent the estimates of the interaction terms (time per treatment group) assuming a linear relationship between the CD4/CD8 ratio and time in a linear mixed model comprising the full period (2004-19). The coefficients for the intercept and the treatment group are provided in the appendix (p 3). All individuals received two nucleoside reverse transcriptase inhibitors in combination with either an INSTI, protease inhibitor, or NNRTI. Models adjusted for sex, country of origin, mode of transmission, calendar year, educational level, baseline HIV RNA, presence of AIDS, and pre-ART nadir CD4 cell count. Additional models including the acme CD8 cell count, time from HIV diagnosis to ART initiation, time from ART initiation to virological suppression, and backbone nucleoside reverse transcriptase inhibitors because covariates did not yield different results. ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Resultados

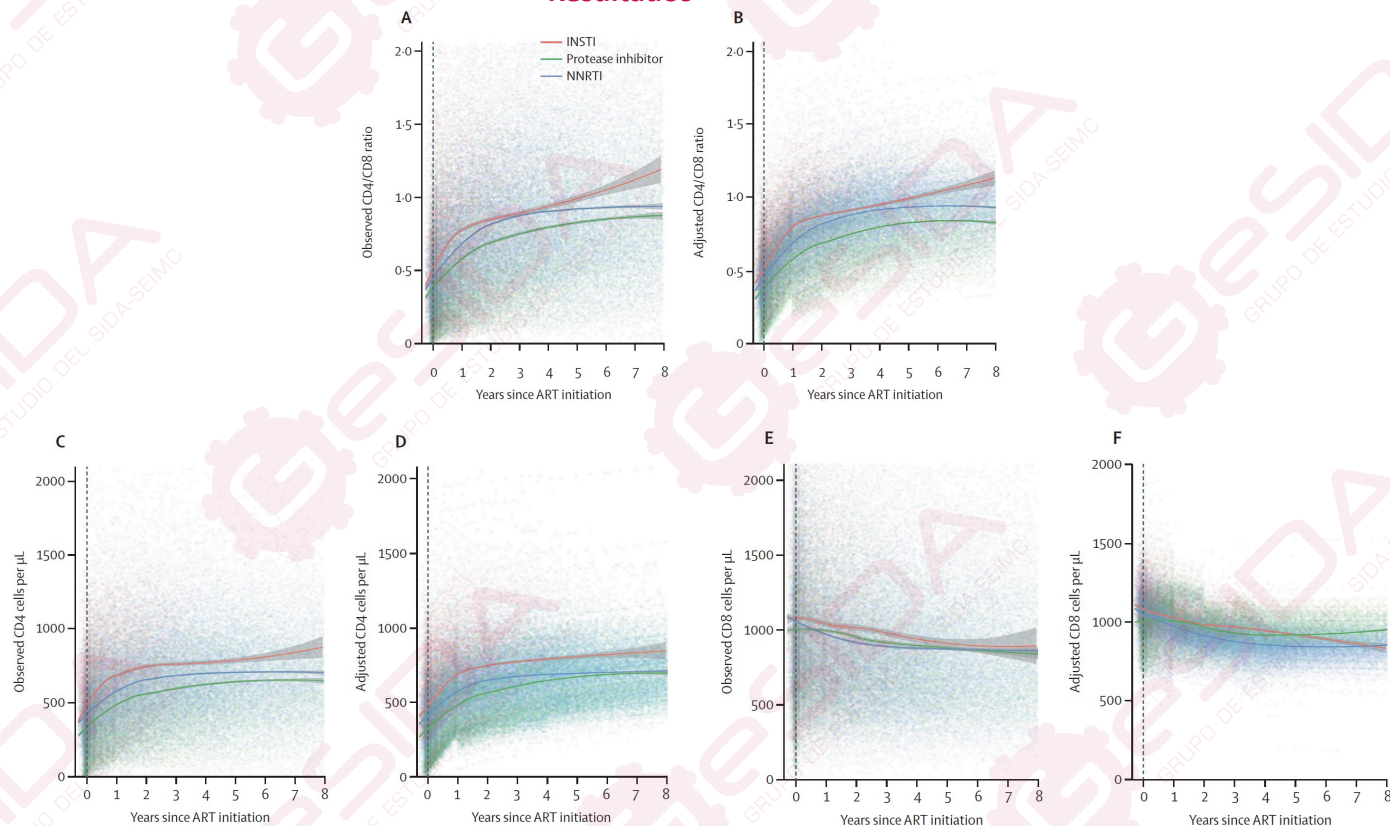


Figure 1: Effects of NNRTI-based, protease inhibitor-based, and INSTI-based ART on CD4/CD8 ratio and CD4 and CD8 cell count changes. All individuals received two nucleoside reverse transcriptase inhibitors in combination with either an INSTI, protease inhibitor, or NNRTI. (A) Observed trajectory of CD4/CD8 ratio. (B) Adjusted trajectory of CD4/CD8 ratio. Overall changes INSTI vs NNRTI $p < 0.0001$ and INSTI vs protease inhibitors $p < 0.0001$. (C) Observed trajectory of CD4 cell count. (D) Adjusted trajectory of CD4 cell count. Overall changes INSTI vs NNRTI $p < 0.0001$ and INSTI vs protease inhibitors $p < 0.0001$. (E) Observed trajectory of CD8 cell count. (F) Adjusted trajectory of CD8 cell count. Overall changes INSTI vs NNRTI $p < 0.0001$ and INSTI vs protease inhibitors $p < 0.0001$. The adjusted trajectories represent the values predicted in piecewise linear mixed models at intervals between years 0–1 years, 1–2 years, 3–4 years, and 4–8 years, adjusted for sex, country of origin, mode of transmission, year of entry in the cohort, educational level, baseline HIV RNA, presence of AIDS, and pre-ART nadir CD4 cell count. Lines represent observed and predicted mean values, shaded areas the 95% CIs, and dots the individual observations. The p values shown in the adjusted trajectories represent the between-group comparison of CD4/CD8 ratio trajectories from baseline through year 8. Piecewise comparisons for the periods 0–1 years, 1–4 years, and 4–8 years are provided in table 2 and the appendix (p 3). ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Resultados

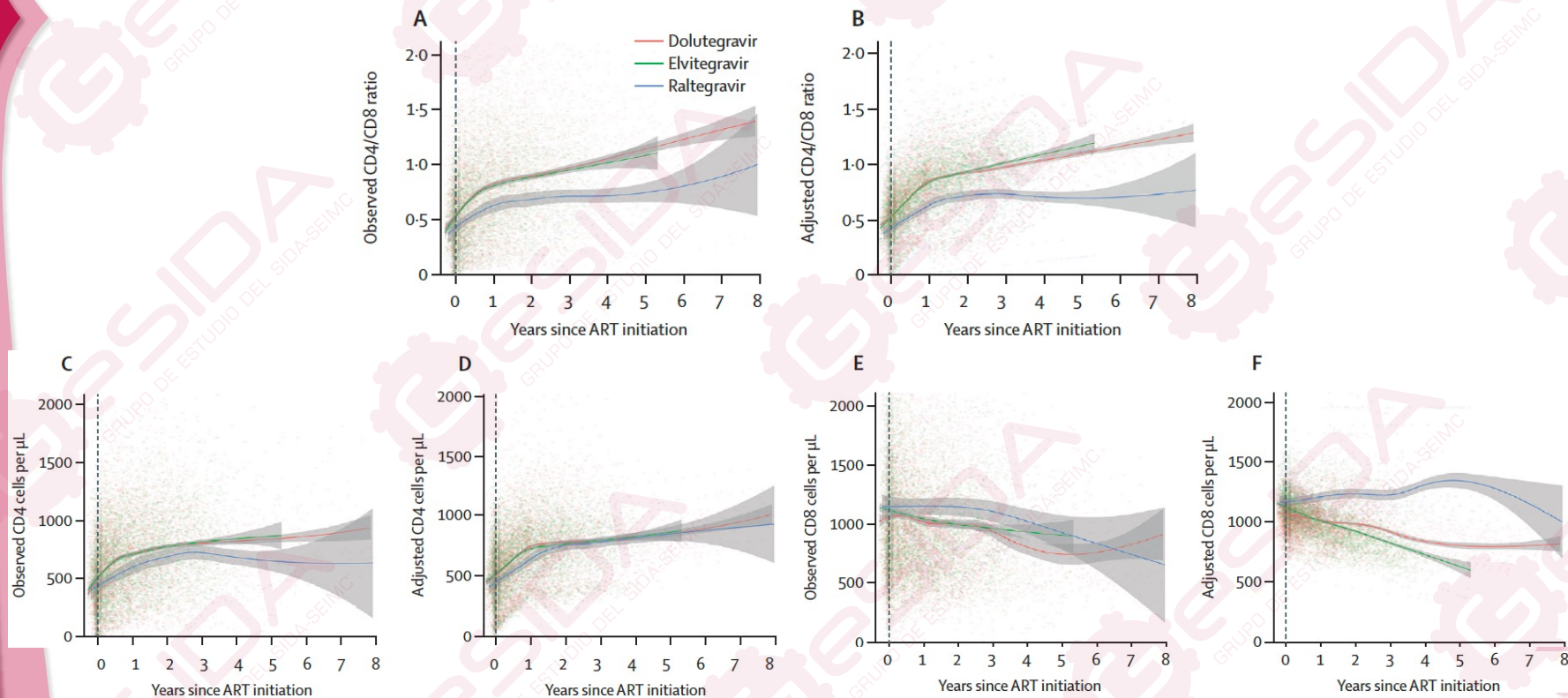


Figure 2: Effects of raltegravir-based, dolutegravir-based, and elvitegravir-based ART on CD4/CD8 ratio, CD4 cell and CD8 cell count changes. All individuals received two nucleoside reverse transcriptase inhibitors in combination with either an INSTI, protease inhibitor, or NNRTI. (A) Observed trajectory of CD4/CD8 T cell ratio. (B) Adjusted trajectory of CD4/CD8 T cell ratio. Overall changes raltegravir vs dolutegravir $p < 0.0001$ and raltegravir vs elvitegravir $p < 0.0001$. (C) Observed trajectory of CD4 cell count. (D) Adjusted trajectory of CD4 cell count. Overall changes raltegravir vs dolutegravir $p < 0.0001$ and raltegravir vs elvitegravir $p < 0.0001$. (E) Observed trajectory of CD8 cell count. (F) Adjusted trajectory of CD8 cell count. Overall changes raltegravir vs dolutegravir $p = 0.0015$ and raltegravir vs elvitegravir $p < 0.0001$. The adjusted trajectories represent the values predicted in linear mixed models, adjusted for sex, country of origin, mode of transmission, calendar year, educational level, baseline HIV RNA, presence of AIDS, and preART nadir CD4 cell counts. Lines represented observed and predicted mean values, shaded areas the 95% CIs, and dots the individual observations. The p values shown in the adjusted trajectories represent the between-group comparison of CD4/CD8 ratio trajectories from baseline through year 8. The adjusted coefficients by INSTI according to duration on first-line ART and nadir CD4 cell count are shown in the appendix (p 5). ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Resultados

	Adjusted hazard ratio (95% CI)	p value
0.4		
INSTI	1 (ref)	..
NNRTI	1.06 (0.95-1.18)	0.321
Protease inhibitor	1.03 (0.92-1.16)	0.571
1.0		
INSTI	1 (ref)	..
NNRTI	0.80 (0.72-0.89)	<0.0001
Protease inhibitor	0.79 (0.69-0.90)	<0.0001
1.5		
INSTI	1 (ref)	..
NNRTI	0.79 (0.65-0.95)	0.011
Protease inhibitor	0.78 (0.63-0.97)	0.024

Table 3: Cox proportional-hazard model for CD4/CD8 normalisation by treatment group for each cutoff point.

All individuals received two nucleoside reverse transcriptase inhibitors in combination with the investigated treatments. Adjusted for sex, country of origin, mode of transmission, calendar year, educational level, baseline HIV RNA, presence of AIDS, preART nadir CD4, and acme CD8 count. ART=antiretroviral therapy. HR=hazard ratio. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Resultados

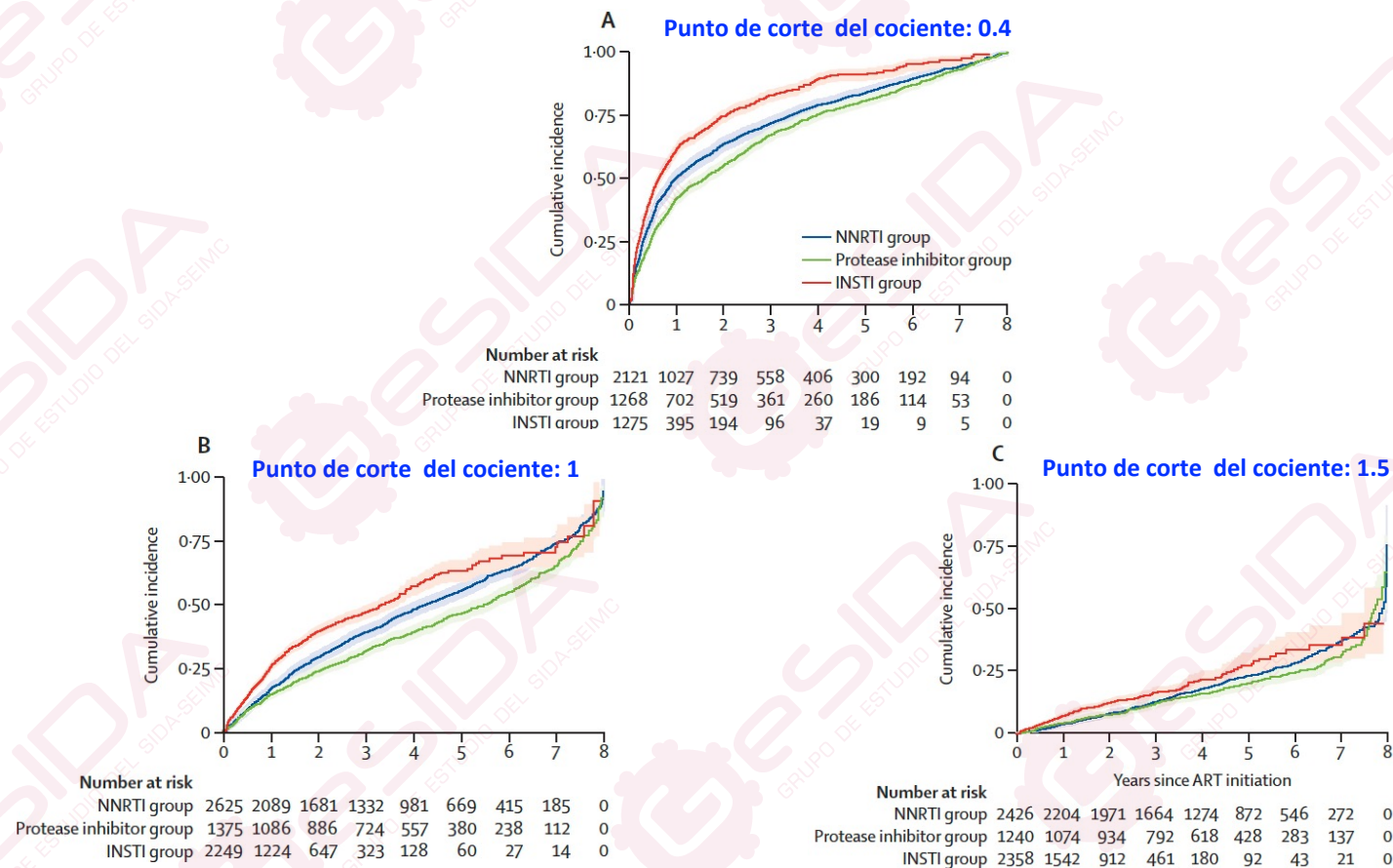


Figure 3: Kaplan-Meier survival estimates for CD4/CD8 ratio normalisation. (A) CD4/CD8 normalisation at cutoff ≥ 0.4 . (B) CD4/CD8 normalisation at cutoff ≥ 1 . (C) CD4/CD8 normalisation at cutoff ≥ 1.5 . All individuals received two nucleoside reverse transcriptase inhibitors in combination with either an INSTI, protease inhibitor, or NNRTI. Shaded areas are 95% CI. ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

¿Por qué he elegido este artículo?

Compara el efecto del tercer fármaco de la 1ª pauta de TAR sobre la evolución del cociente CD4/CD8, reconocido marcador de inmunosenescencia asociado a mayor riesgo de morbimortalidad.

¿Cambia este artículo mi práctica clínica habitual? ¿Por qué?

Refuerza la importancia de monitorizar la evolución del cociente CD4/CD8 como parte de la evaluación de la respuesta a las diferentes pautas de TAR.

**En caso de que no cambie mi práctica clínica habitual,
¿qué implicaciones prácticas puede tener este artículo?**

La evaluación del cociente CD4/CD8 se irá incorporando en la mayoría de los ensayos clínicos y estudios observacionales como marcador del efecto de las diferentes pautas de TAR sobre la morbilidad asociada a la inmunosenescencia e inmunoadactivación.

¿Qué aporta de nuevo este artículo con respecto a lo ya publicado sobre este tema?

Primer estudio de cohortes prospectivo que demuestra el beneficio de los inhibidores de la integrasa sobre los inhibidores de proteasa e inhibidores de la TI no nucleósidos sobre el cociente CD4/CD8

¿Existe alguna limitación que en mi opinión comprometa la validez interna o externa del estudio?

- Factores de confusión no controlados inherentes a todo estudio observacional.
- Posible influencia de diferencias en adherencia a TAR en los grupos comparados (p.e. mayor representación de HSH en pacientes tratados con INI).
- No se hizo ajuste por estado serológico frente a citomegalovirus.
- Pequeño tamaño muestral en la comparación entre fármacos de la misma clase.

Resumen

El tratamiento antirretroviral de inicio con inhibidores de la integrasa normaliza antes el cociente CD4 / CD8 que los inhibidores de la TI no nucleósidos y que los inhibidores de la proteasa.



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