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Epigenetic age acceleration changes 2 years after antiretroviral therapy initiation in adults with HIV: a substudy of the NEAT001/ANRS143 randomised trial

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Envejecimiento

- Situación fisiopatológica de pérdida funcional, morbilidad y mortalidad
- Biomarcadores
 - Acortamiento de los telómeros
 - Envejecimiento epigenético: biomarcadores basados en el estudio de la metilación del ADN combinado con algoritmos matemáticos
 - Relojes epigenéticos: reloj de Hovart, reloj de Hannum, Pheno Age y Grim Age
 - Mayor aproximación a edad biológica: predice morbilidad y mortalidad asociada a la edad

Envejecimiento y VIH

RESEARCH ARTICLE

Acceleration of Age-Associated Methylation Patterns in HIV-1-Infected Adults

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MÉTODO

- Sobre muestras de 168 pacientes del estudio NEAT001/ANRS143, comparaba DRVr/RAL frente DRVr/TDF/FTC se realizan la estimación de envejecimiento epigenético con estas escalas antes y dos años después de inicio de TAR.
- Se comparan con muestras de 44 pacientes sanos (anónimas)
- Subgrupos CD4 y CV

	All participants (n=168)	Ritonavir-boosted dolutegravir plus raltegravir group (n=84)	Ritonavir-boosted dolutegravir plus tenofovir disoproxil fumarate and emtricitabine group (n=84)
Age, years*	38.1 (30.5-46.5)	39.5 (30.7-46.3)	37.4 (29.9-46.5)
Sex			
Female	20 (12%)	11 (13%)	9 (11%)
Male	148 (88%)	73 (87%)	75 (89%)
Ethnicity			
White	138 (82%)	70 (83%)	68 (81%)
Black	22 (13%)	11 (13%)	11 (13%)
Asian	2 (1%)	2 (2%)	0
Other	6 (4%)	1 (1%)	5 (6%)
Tobacco use*			
Currently smoking	59 (35%)	26 (31%)	33 (39%)
Stopped smoking	18 (11%)	8 (10%)	10 (12%)
Never smoked	91 (54%)	50 (60%)	41 (49%)
Alcohol use*			
Current drinker†	13 (8%)	3 (4%)	10 (12%)
Ex-drinker†	1 (1%)	1 (1%)	0
Non-drinker or moderate drinker‡	154 (92%)	80 (95%)	74 (88%)
Body-mass index, kg/m ² **	23.8 (22-26.3)	24.2 (22.0-27.2)	23.1 (21.9-25.7)
Statin treatment*	13 (8%)	8 (10%)	5 (6%)
Time since HIV diagnosis, years	1.2 (0.4-2.5)	1.2 (0.4-2.5)	1.2 (0.3-2.5)
Method of HIV infection			
Same-sexual activity	118 (70%)	56 (67%)	62 (74%)
Heterosexual sexual activity	41 (24%)	22 (26%)	19 (23%)
Injection drug use	1 (1%)	0	1 (1%)
Other	8 (5%)	6 (7%)	2 (2%)
CD4 count, cells per µL			
Baseline	346.0 (254.3-412.3)	347.8 (268.5-419.0)	344.3 (243.8-403.6)
Week 96	557.3 (430.0-688.0)	561.0 (453.0-695.0)	544.0 (434.0-687.0)
CD8 count, cells per µL			
Baseline	865.0 (641.6-1159.0)	879.0 (650.0-1256.0)	840.0 (624.0-1079.0)
Week 96	768.0 (529.0-971.0)	807.0 (545.0-1002.0)	728.5 (504.0-960.0)
CD4 to CD8 ratio			
Baseline	0.37 (0.35-0.51)	0.37 (0.34-0.48)	0.38 (0.26-0.52)
Week 96	0.74 (0.55-1.06)	0.75 (0.58-1.06)	0.73 (0.53-1.07)
Nadir CD4 count, cells per µL	305.5 (235.8-360.5)	332.5 (244.0-368.5)	296.3 (222.8-353.0)
Log HIV viral load, copies per mL at baseline	4.7 (4.3-5.1)	4.6 (4.1-5.2)	4.7 (4.4-5.1)
HIV RNA, 50^3 copies per mL at week 96	159 (95%)	82 (98%)	77 (92%)

Data are median (IQR) or n (%). *Baseline characteristics. †More than four alcoholic drinks for men and three for women in a single day, and more than 4 drinks for men and seven for women per week. ‡Meet criteria for non-drinker or moderate drinker but have met criteria for current drinker in the past. §Up to four alcoholic drinks for men and three for women in a single day, and a maximum of 14 drinks for men and seven for women per week.

Table: Characteristics of participants with HIV

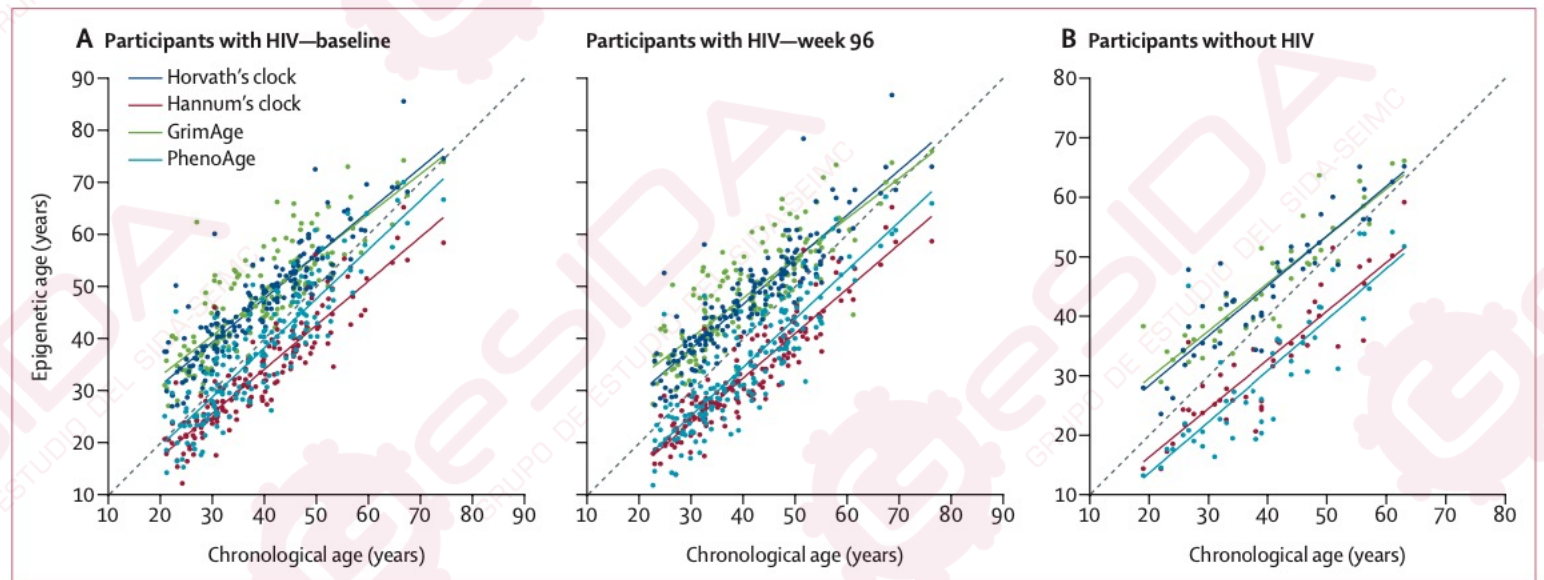


Figure 1: Correlations between estimators of epigenetic age and chronological age in whole blood samples from 168 participants with HIV At baseline and 2 years after antiretroviral therapy initiation (week 96; A) and in 44 participants without HIV (B). Chronological age versus epigenetic age according to Horvath's clock, Hannum's clock, GrimAge, and PhenoAge. Grey dashed lines indicate $y=x$.

TAR y envejecimiento acelerado

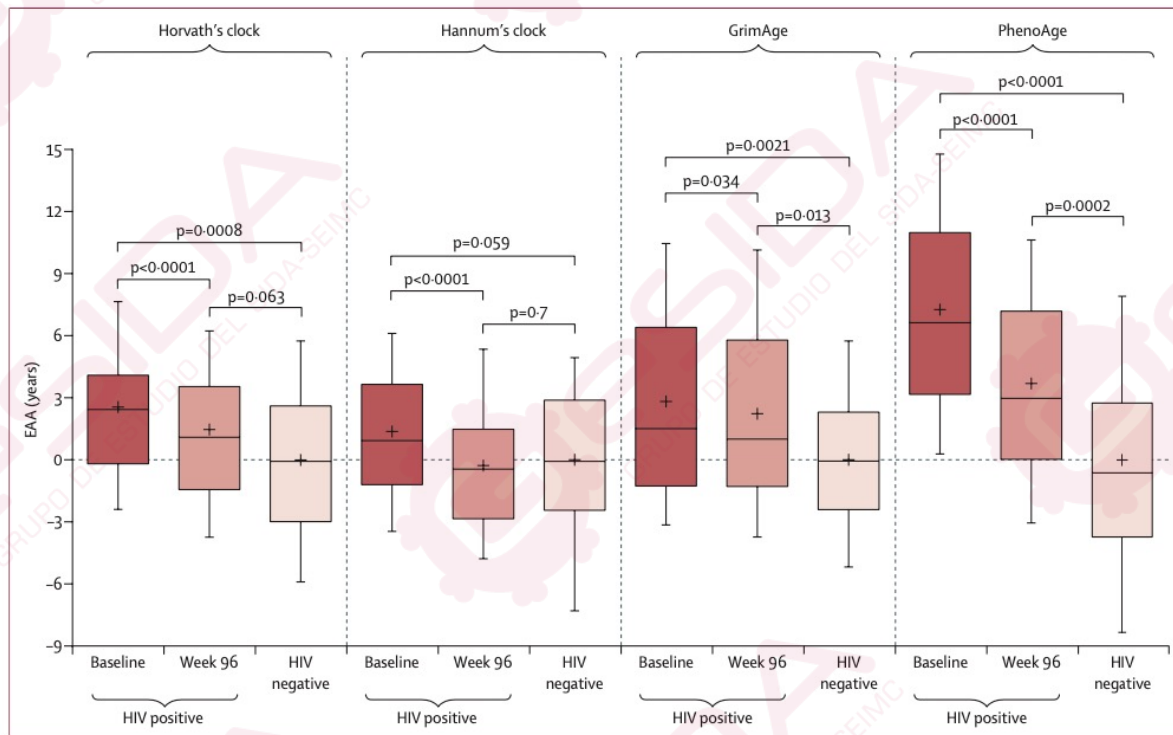


Figure 2: Epigenetic age acceleration in ART-naive participants with HIV before and 2 years after ART initiation
EAA according to Horvath's clock, Hannum's clock, GrimAge, and PhenoAge in 168 ART-naive participants with HIV at baseline and 2 years after ART initiation (W96), and in 44 HIV-uninfected participants. Boxes show medians and IQRs; whiskers correspond to 10th and 90th percentiles. The + symbol indicates the mean. ART=antiretroviral therapy. BL=baseline. EAA=epigenetic age acceleration.

- VIH sin tratamiento: mayor edad epigenética, que personas no infectadas
- El TAR, independientemente de la combinación usada (DRVr/RAL ó DRVr/TDF/FTC), disminuyó la aceleración de la edad epigenética a los 2 años

Subgrupos desfavorables

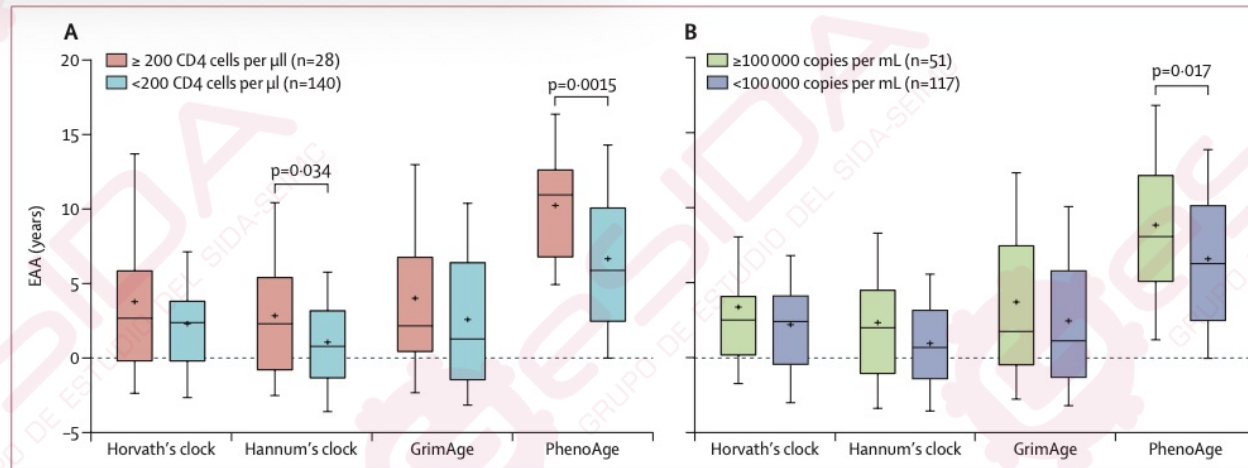


Figure 3: EAA according to baseline CD4 counts (A) and baseline viral load (B) in participants with untreated HIV infection
EAA according to Horvath's clock, Hannum's clock, GrimAge, and PhenoAge in ART-naive participants with HIV. Boxes show medians and IQRs; whiskers correspond to 10th and 90th percentiles. The + symbol indicates the mean. ART=antiretroviral therapy. EAA=epigenetic age acceleration.

- Aceleración de la edad epigenética es mayor en < 200 CD4 y en > 100.000 copias
- Peor si disregulación inmune. Cociente CD4/CD8 más desfavorable
- El efecto del TAR fue mayor en estos grupos

Conclusiones

- TAR: Reversión parcial del envejecimiento acelerado
- Mayor en pacientes con peor situación inmunoviológica y de disregulación inmune
- Utilidad de nuevas herramientas de valoración de la edad epigenética: Grim Age y Pheno Age

Limitaciones y preguntas

- Grupo control no VIH con bajo tamaño muestral y sólo datos de edad y sexo
- Ajuste por otras comorbilidades
- Ajuste por poblaciones celulares
- Este efecto se mantiene en otras pauta de TAR

Muchas gracias por la atención

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