CD4/CD8 Recovery And First-line ART: Greatest Improvement With Integrase Inhibitors

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BACKGROUND

- A low CD4/CD8 ratio during antiretroviral therapy (ART) identifies subjects with heightened immunoactivation and immunosenescence, and have been shown to predict morbidity and mortality (Serrano-Villar*, PLoS Pathog* 2014)
- It is unknown whether the different first-line ART regimens have a different impact on the rates of CD4/CD8 ratio normalization.
- We aimed to assess the effects of the INSTI, PI or NNRTI-based first-line ART on long-term CD4/CD8 ratio recovery in a large prospective cohort.

METHODS

- Prospective cohort study in 13,026 HIV-infected individuals registered in the Spanish HIV Research Network (CoRIS) cohort.
- We included subjects who started triple ART and achieved HIV RNA suppression at 48 weeks.
- We used multilevel mixed models with linear splines to compare longitudinal changes in the CD4/CD8 ratio and Cox proportional-hazard models to compare the times to CD4/CD8 normalization by treatment groups (NNRTI, PI, INSTI) at 0.5, 1 and 1.5 cut-offs.
- Analyses were adjusted for sex, country of origin, mode of transmission, calendar year, educational level, baseline HIV RNA, presence of AIDS, pre-ART nadir CD4, acme CD8 count and backbone NRTI.

RESULTS

- A total of 6,804 individuals contributing to 37,149 persons/years and 37,680 observations met the inclusion criteria. The median follow-up was 49 months (IQR 22-89).
- The study sample was representative of a medium-aged population (median age 36 [IQR 30-44] years) with higher representation of men (85.3%), median nadir CD4+ T-cell count of 304 (IQR 178-438) cells/uL, and median baseline CD4/CD8 ratio 0.33 (IQR 0.19-0.52).
- The median time from ART initiation to virologic suppression was 18 (IQR 10-29) months, and first-line regimens included 2,820 subjects starting ART with 2 NRTI+NNRTI (41.5%), 1,574 (23.1%) with 2 NRTI+PI and 2,410 (35.4%) with 2 NRTI+INSTI.

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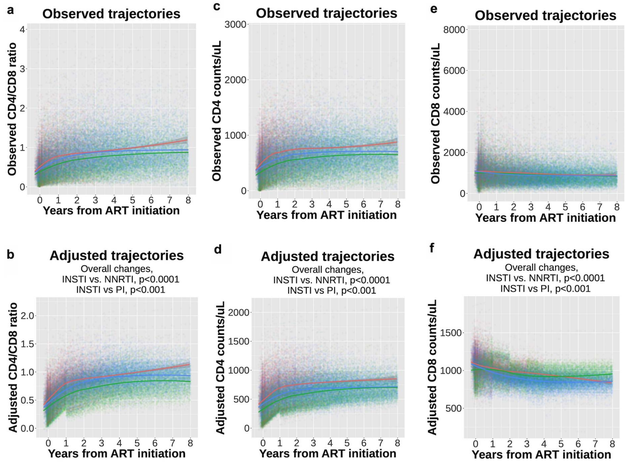
INSTI-based first line ART is associated with a greater CD4/CD8 ratio gain compared to NNRTI and PI-based ART.

Figure 1: Subjects in the INSTI group experience greater CD4/CD8 gain during follow-up than patients in the NNRTI and PI groups.



The observed and adjusted linear trajectories of CD4/CD8 ratio per treatment group significantly differed between groups (p<0.001). The differences were driven by changes in both CD4+ and CD8+ T-cell counts.

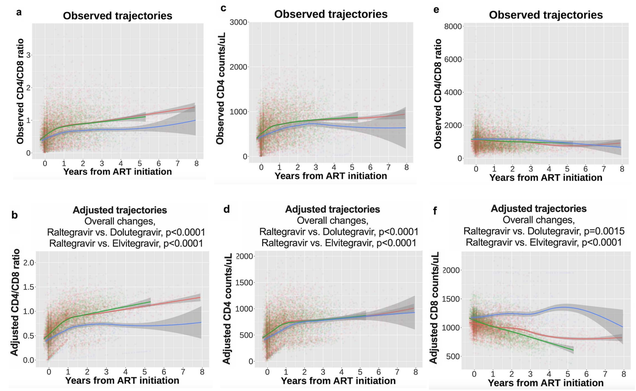
2NRTI+1INSTI
2NRTI+1IP
2NRTI+1NNRTI

Sub-analyses by piecewise indicated that these differences were driven by changes during the first year of ART (**Table 1**) without significant differences in the adjusted CD4/CD8 ratio trajectories after the second year of ART. Hence, a stronger effect of INSTI during the first year of ART determined greater CD4/CD8 ratio values after a similar follow-up.

Table 1

	Coefficient	95% CI	p
First year on ART			
2NRTI + 1NNRTI	-0.03	-0.05, -0.13	0.001
2NRTI + 1PI	-0.06	-0.08, -0.04	<0.001
1-4 years on ART			
2NRTI + 1NNRTI	-0.003	-0.015, 0.10	0.693
2NRTI + 1PI	-0.007	-0.020, 0.007	0.324
4-8 years on ART			
2NRTI + 1NNRTI	-0.02	-0.07, 0.4	0.581
2NRTI + 1PI	-0.02	-0.08, 0.04	0.487
≥ 8 years on ART			
2NRTI + 1NNRTI	-0.51	-7.65, 6.64	0.889
2NRTI + 1PI	-0.52	-7.67, 6.63	0.886

Figure 2: Subanalysis by INSTI group

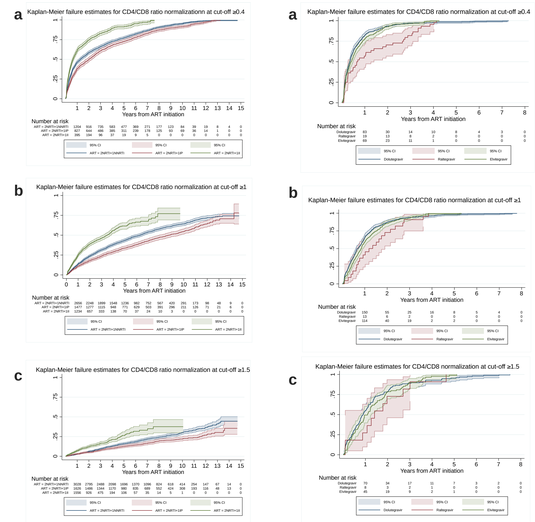


Within INSTI, the greatest CD4/CD8 ratio gain was observed with EVG followed by DTG. This was largely driven by greater declines in CD8+ T-cell counts during the first year of therapy (p<0.001).

DTG
EVG
RAL

Other sensitivity analyses included the CD4 nadir stratum, the calendar year period, and the development of virological failure during follow-up. There were no significant variations with respect to the global primary analysis.

Figure 3: Kaplan-Meier survival plots of estimated overall CD4/CD8 normalization at cut-offs of 0.4, 1.0, and 1.5.



- No differences between treatment groups for times to CD4/CD8 ratio normalization at 0.4 cut-off were detected. However, the NNRTI and PI had lower rates of CD4/CD8 ratio normalization at ≥1 and ≥1.5 cut-offs than INSTI (**Table 2**)
- At year 4, the adjusted mean CD4 count for INSTI, NNRTI and PI was 904, 718 and 696 cells/uL, (p<0.0001), and the adjusted mean CD8 count was 832, 875 and 996 cells/ul, respectively (p<0.0001).

Table 2

Cutoff	ART regimen	aHR	95% CI	p
0.4	2NRTI + 1INSTI (ref.)	-	-	-
	2NRTI + 1NNRTI	1.06	0.95, 1.18	0.321
	2NRTI + 1PI	1.03	0.92, 1.16	0.571
1.0	2NRTI + 1INSTI (ref.)	-	-	-
	2NRTI + 1NNRTI	0.80	0.72, 0.89	<0.001
	2NRTI + 1PI	0.79	0.69, 0.90	<0.001
1.5	2NRTI + 1INSTI (ref.)	-	-	-
	2NRTI + 1NNRTI	0.79	0.65, 0.95	0.011
	2NRTI + 1PI	0.78	0.63, 0.97	0.024

Table 4

Cutoff	ART regimen	aHR*	95% CI	p
0.4	Raltegravir (ref.)	-	-	-
	Dolutegravir	1.09	0.76, 1.57	0.642
	Elvitegravir	1.01	0.65, 1.56	0.957
1.0	Raltegravir (ref.)	-	-	-
	Dolutegravir	1.11	0.69, 1.80	0.661
	Elvitegravir	1.01	0.59, 1.74	0.967
1.5	Raltegravir (ref.)	-	-	-
	Dolutegravir	0.97	0.49, 1.92	0.943
	Elvitegravir	0.98	0.44, 2.18	0.967

Table 3 shows the incidence rates of ratio normalization by treatment group for each cut-off point.

Table 3

Cutoff	ART regimen	Incidence rate (per 1000 person-years)	95% CI
0.4	2NRTI + 1NNRTI	358	344, 374
	2NRTI + 1PI	296	280, 313
	2NRTI + 1INSTI	760	714, 810
1.0	2NRTI + 1NNRTI	113	108, 119
	2NRTI + 1PI	84	79, 91
	2NRTI + 1INSTI	230	215, 246
1.5	2NRTI + 1NNRTI	35	33, 38
	2NRTI + 1PI	26	23, 30
	2NRTI + 1INSTI	63	56, 70

Subanalyses adjusted for backbone NRTIs did not show differences in the rates of CD4/CD8 ratio normalization between raltegravir, dolutegravir and elvitegravir (**Table 4**).

CONCLUSIONS

- This study with prospective design, large sample size, and long follow-up shows that first line ART is associated with a greater CD4/CD8 ratio gain compared to NNRTI and PI-based ART. The INSTI-based ART was associated with higher rates of CD4/CD8 recovery at the threshold for normalization.
- Our findings were independent of the immunovirological covariates analyzed (i.e., CD4 nadir, maximum HIV RNA, and development of virological failure during ART).
- This study in real life indicates that ART initiation with INSTI improves immune recovery with respect to other ART classes, which could affect long-term mortality.

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