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Comparative Impact of Suppressive Antiretroviral Regimens on the CD4/CD8 T-Cell Ratio

A Cohort Study

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Abstract: Although different factors have been implicated in the CD4/CD8 T-cell ratio recovery in HIV-infected patients who receive effective antiretroviral therapy (ART), limited information exists on the influence of the regimen composition.

A longitudinal study carried out in a prospective, single-center cohort of HIV-infected patients. ART regimens including non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), or integrase strand transfer inhibitors (INSTI) from patients who achieved long-term (≥6-month duration) virological suppression (HIV-RNA < 400 copies/mL) from January 1998 to June 2014 were analyzed. The impact of ART composition on the changes of the CD4/CD8 T-cell ratio was modeled using a mixed linear approach with adjustment for possible confounders.

A total of 1068 ART regimens from 570 patients were analyzed. Mean (SD) age of the patients was 42.15 (10.68) years and 276 (48.42%) had hepatitis C virus (HCV) coinfection. Five hundred fifty-eight (52.25%) regimens were PI-based, 439 (40.10%) NNRTI-based, and 71 (6.65%) INSTI-based; 487 (45.60%) were initial regimens, 476 (44.57%) simplification, and 105 (9.83%) salvage regimens. Median (IQR) number of regimens was 1 (1–2) per patient, of 29 (14–58) months duration, and 4 (3–7) CD4/CD8 measurements per regimen. The median baseline CD4/CD8 ratio was 0.42, 0.50, and 0.54, respectively, with the PI-, NNRTI-, and INSTI-based regimens ($P = 0.0073$). Overall median (IQR) increase of CD4/CD8 ratio was 0.0245 (−0.0352–0.0690) per year, and a CD4/CD8 ratio ≥1 was achieved in 19.35% of the cases with PI-based, 25.97% with NNRTI-based, and 22.54% with INSTI-based regimens ($P = 0.1406$). In the adjusted model, the mean CD4/CD8 T-cell ratio increase was higher with NNRTI-based regimens compared for PI-based (estimated coefficient for PI [95% CI], −0.0912 [−0.1604 to −0.0219], $P = 0.009$). Also, a higher CD4/CD8 baseline ratio was associated with higher CD4/CD8 increase in the adjusted model ($P = 0.001$); by contrast, higher age ($P = 0.020$) and simplification of ART regimen ($P = 0.003$) had a negative impact on the CD4/CD8 ratio.

Antiretroviral regimen composition has a differential impact on the CD4/CD8 T-cell ratio; NNRTI-based regimens are associated with enhanced CD4/CD8 T-cell ratio recovery compared to PI-based antiretroviral regimens.

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Abbreviations: ART = effective antiretroviral therapy, HCV = hepatitis C virus, INSTI = integrase strand transfer inhibitors, IQR = interquartile range, NNRTI = non-nucleoside reverse transcriptase inhibitors, PI = protease inhibitors, SD = standard deviation.

INTRODUCTION

HIV infection is characterized by progressive depletion of CD4+ T-cells because of reduced production and increased destruction, and a marked activation and expansion of the CD8+ T-cell compartment. Effective antiretroviral therapy (ART) suppresses HIV replication allowing progressive CD4+ T-cell recovery that is usually accompanied by persistent expansion of CD8+ T-cells. As a consequence, there is an incomplete restoration of the CD4/CD8 T-cell ratio, which very often remains inverted.[1,2] Low CD4/CD8 ratios have been associated with T-cell activation and immune senescence,[3,4] and with higher morbidity and mortality, mainly in relation with a more frequent occurrence of non-AIDS events.[5,6]

Factors associated with the CD4/CD8 T-cell ratio improvement remain to be well characterized. Most studies have centred on the predictors of the ratio normalization. Demographic factors, including female sex or HIV transmission risk group other than men who have sex with men, HIV-associated factors, such as a higher baseline CD4+ T-cell count, lower CD8+ T-cell count, or recent HIV seroconversion, and absence of coinfections such as hepatitis C virus (HCV) or cytomegalovirus, have been associated with higher likelihood of normalization of the CD4/CD8 T-cell ratio.[6–11] ART-related factors, including early initiation and longer duration of HIV RNA suppression, have also been implicated in the normalization of the ratio,[8,10] but limited data exist on the differential effects of the antiretroviral drug classes on the CD4/CD8 T-cell ratio changes. Because of their different mechanisms of action and toxicity profile, the diverse antiretroviral classes might have a dissimilar impact on the CD4/CD8 T-cell ratio, independently of the virological outcome of the patients. Although ART containing tenofovir/emtricitabine was included among the factors associated with normalization of the

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CD4/CD8 ratio in a study,[7] no investigation has focused on the influence of the different antiretroviral regimens on the CD4/CD8 T-cell ratio dynamics.

We aimed to compare the impact of the antiretroviral regimen composition on the CD4/CD8 T-cell ratio evolution in virologically suppressed HIV-infected patients, specifically to assess the contribution of the ''third drug'' antiretroviral families, namely, non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), and integrase strand transfer inhibitors (INSTI).

METHODS

Study Population

The study was carried out in a prospective cohort of adult HIV-infected patients cared for in the outpatients clinic of Elche University Hospital in Spain. Antiretroviral regimens consisting of 2 nucleoside/nucleotide analogs plus a ''third agent,'' specifically an NNRTI, a PI, or an INSTI, of adult (>17 years) patients achieving long-term (≥6-month duration) virological suppression (HIV-RNA < 400 copies/mL) in the next visit after the first 6 months from ART initiation, were included in the analysis. The cut-off point of <400 copies/mL to define virological suppression was chosen to avoid exclusion of patients because of the occurrence of ''blips,'' defined as transient increases in plasma HIV-RNA, typically <400 copies/mL, which are not predictive of virologic failure (https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0).
Exclusion criteria were antiretroviral regimens with only 1 follow-up visit, and those in which data about the CD4/CD8 cell ratio or the regimen composition were missing. The cohort was launched in January 1998, and patients have been gradually included since then. Follow-up time for each individual regimen analyzed started at the time when the regimen was prescribed. The study was censored on June 01, 2014, or when virological failure, defined as an HIV-RNA >400 copies/mL, treatment change for any cause, death, or lost to follow-up occurred. Each regimen change occurring within the same patient was included in the analysis when its composition met the prespecified inclusion criteria. The study was approved by the local Ethics Committee (Comité Ético del Hospital General Universitario de Elche), and all included patients signed an informed consent.

Demographic and clinical data from patients were obtained at the baseline visit and subsequently updated in the follow-up visits. Laboratory tests, including CD4+ and CD8+ cell counts/percentage and HIV viral load determinations, were performed on each clinical visit every 3 to 6 months, in accordance with local standard-of-care. The normalization of the CD4/CD8 ratio was defined as a ratio of ≥1.0 on a minimum of 2 occasions. In addition to their composition, antiretroviral regimens were also classified according to type of treatment into 3 categories: ''initial regimen'' in naive patients; ''simplification regimen,'' defined as switching in the setting of viral suppression to reduce pill burden and/or dosing frequency; and ''salvage regimen,'' when the regimen was changed due to virologic failure. Infection with hepatitis C virus (HCV) was defined with a positive serology plus a positive HCV RNA by a polymerase chain reaction. Patients who received therapy for HCV and achieved sustained virological response were considered to be HCV negative from the end of the anti-HCV therapy.

Statistical Analyses

Baseline characteristics, which included socio-demographic, clinical and laboratory measures, were summarized using frequency and percentages for categorical variables and by medians with inter-quartile ranges (IQR) for continuous variables, unless otherwise indicated. Linear mixed effects modeling was the primary statistical analysis to assess the impact of the antiretroviral regimen composition on the CD4/CD8 T-cell ratio. This allowed each patient to have his/her specific constant variation around the group means. In the first step of modeling, the evolution of CD4/CD8 T-cell ratio by treatment regimen (NNRTI- vs PI- vs INSTI-based) was estimated. The model was adjusted for possible confounders, including age, sex, HIV transmission category, HCV coinfection, baseline CD4/CD8 T-cell ratio, regimen duration, follow-up time, and ART modality (naive vs simplification vs salvage regimen). P values < 0.05 were considered statistically significant. Statistical analyses of the data were performed in R, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org/).

RESULTS

Characteristics of the Regimens Included

Of 2357 regimens based on PIs, NNRTIs, and INSTIs, 377 were excluded because of missing data about the CD4/CD8 ratio, 293 because of <6 months duration, 268 because of only 1 visit after initiation, and 351 because of no virological suppression according to the pre-specified criteria. The analysis included 1068 ART regimens from 570 patients. Baseline characteristics of the patients are shown in Table 1. Mean (SD) age of the patients was 42.15 (10.68) years, 441 (77.37%) were male, 253 (44.39%) had acquired the infection by sexual transmission. There was a high frequency of HCV coinfection, which occurred in 276 (48.42%) patients, with no differences between antiretroviral regimens. Eighty-seven (31.52%) patients received therapy for HCV infection during follow-up; of them, 5 patients received monotherapy with standard interferon; 71 pegylated interferon + ribavirin; and 11 received pegylated interferon + ribavirin + telaprevir.

Five hundred fifty-eight (52.25%) regimens were PI-based, 439 (40.10%) NNRTI-based, and 71 (6.65%) INSTI-based. Among PI-based regimens, the most frequent drugs included were atazanavir/ritonavir in 31.59% of cases and lopinavir/ritonavir in 29.80% of cases. The most frequent NNRTI was efavirenz in 66.97% cases followed by nevirapine in 26.88%. INSTI-based regimens consisted mainly of raltegravir in 91.55% cases. There were significant differences between regimens in the age of patients, with an older age among those receiving INSTI-based regimens ($P < 0.0001$), and in the transmission category, with a higher frequency of injecting drug users among PI users ($P < 0.0001$). Four hundred eighty-seven (45.60%) were initial regimens in naive patients, 476 (44.57%) simplification, and 105 (9.83%) salvage regimens. Of PI-based regimens, 262 (46.95%) were initial regimens in naive patients and 228 (40.86%) simplification regimens; 203 (46.24%) NNRTI-based regimens were initial regimens in naive patients and simplification regimens; 22 (30.99%) INSTI-based regimens were initial and 45 (63.38%) were simplification regimens ($P = 0.0012$). Median (IQR) total number of regimens was 1 (1-2) per patient, with a maximum of 7 in the PI-based regimens, 6 in the NNRTI-based, and 2 in the INSTI-based regimens ($P = 0.0011$). Median (IQR) duration of the regimens was 29 (14–58) months, there were 4 (3–7) visits per regimen, and median follow-up duration was 90 (44–139) months, with no significant differences in relation to regimen composition.

TABLE 1. Characteristics of the Patients and Antiretroviral Regimens Included in the Study

Variable	Patients Included n = 570	PI-Based Regimen n = 558 (52.25%)	NNRTI-Based Regimen n = 439 (41.10%)	INSTI-Based Regimen n = 71 (6.65%)	P^*
Age, y, mean (SD)	42.15 (10.68)	42.08 (9.72)	43.19 (11.55)	45.88 (9.22)	<0.0001
Sex (male)	441 (77.37)	415 (74.37)	336 (76.54)	53 (74.65)	0.7279
HIV transmission category					<0.0001
IDU	257 (45.08)	286 (51.25)	171 (38.95)	22 (30.99)	
MSM	127 (22.28)	99 (17.74)	104 (23.69)	17 (23.94)	
Heterosexual	126 (22.11)	113 (20.25)	126 (28.70)	16 (22.54)	
Other/unknown	60 (10.53)	60 (10.75)	38 (8.66)	16 (22.54)	
Hepatitis C coinfection	276 (48.42)	254 (45.52)	231 (52.62)	31 (43.66)	0.0763
Follow-up duration, months	90 (44–139)	82 (42–132)	98 (49–149)	80 (49–138)	0.1610
Antiretroviral drugs included in the regimens		IDV/r (8.98)	EFV (66.97)	RTG (91.55)	
		LPV/r (29.80)	NVP (26.88)	DTG (8.45)	
		ATV/r (31.59)	ETV (3.42)		
		DRV/r (12.93)	RPV (2.73)		
		Other (16.69)			
Visits per regimen	4 (3–7)	4 (2–7)	5 (3–7)	5 (3–7)	0.2190
Antiretroviral regimens per patient, median (range)	1 (1–7)	1 (1–7)	2 (1–6)	1 (1–2)	0.0011
Antiretroviral regimen duration, months	29 (14–58)	28 (13–53)	29 (15–69)	41 (23–59)	0.0670
ART modality					0.0012
Naive	487 (45.60)	262 (46.95)	203 (46.24)	22 (30.99)	
Simplification	476 (44.57)	228 (40.86)	203 (46.24)	45 (63.38)	
Salvage	105 (9.83)	68 (12.19)	33 (7.52)	4 (5.63)	
Baseline CD4/CD8 cell ratio		0.42 (0.25–0.70)	0.50 (0.30–0.80)	0.54 (0.28–0.77)	0.0073
Baseline CD4+		369 (220–589.5)	384 (237.5–618)	474 (260–720)	0.0962

Continuous variables are expressed in median (Q25–Q75), except age (median, SD). Categorical variables are expressed in no. (%).

ART = antiretroviral therapy, ATV = atazanavir, DRV = darunavir, EFV = efavirenz, ETV = etravirine, IDU = injecting drug user, IDV/r = indinavir/ritonavir, INSTI = integrase strand transfer inhibitor, LPV = lopinavir, MSM = men who have sex with men, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RPV = rilpivirine, SD = standard deviation.

* Chi-squared test was used for categorical variables, and the Kruskal–Wallis test for continuous variables.

Evolution of CD4/CD8 Ratio

Baseline CD4+ and CD4/CD8 T-cell ratio measurements by ''third antiretroviral drug'' are shown in Table 1. The median (IQR) baseline CD4/CD8 T-cell ratio was 0.42 (0.25–0.70), 0.50 (0.30–0.80), and 0.54 (0.28–0.77), respectively, with PI-based, NNRTI-based and INSTI-based regimens ($P = 0.0073$). There were no significant differences between regimens in the baseline CD4+ and CD8+ T-cells ($P = 0.0962$ and $P = 0.0623$, respectively). The median CD4/CD8 T-cell ratio on the last measurement was lower among patients receiving PI-based regimens ($P = 0.0005$), and median CD8+ T-cells were also higher in those patients ($P = 0.0028$).

CD4/CD8 T-cell ratio changes over time by ''third antiretroviral drug'' (PIs, NNRTIs, and INSTIs) antiretroviral regimen are shown in Figure 1. Overall unadjusted median (IQR) increase in the CD4/CD8 T-cell ratio was 0.0245 (−0.0352 to 0.0690) per year. The magnitude of increase in the CD4/CD8 ratio was higher with NNRTI-based regimens, although differences were not statistically significant: median (IQR) increase was 0.0376 (−0.0066 to 0.0837) with NNRTI-based regimens; 0.0146 (−0.0352 to 0.0511) with PI-based regimens; and 0.0240 (−0.0201 to 0.0663) with INSTI-based regimens ($P = 0.5585$). Wilcoxon tests showed a significant change from the first to the last CD4/CD8 T-cell ratio measurement in the 3 regimens ($P < 0.0001$ for PI-based and NNRTI-based regimens and $P = 0.0112$ for INSTI-based regimens). A CD4/CD8 T-cell ratio ≥1 was achieved with 238 (22.28%) regimens during follow-up, with 19.35% PI-based regimens, 22.54% INSTI-based regimens, and 25.97% NNRTI-based regimens ($P = 0.1406$).

Predictors of CD4/CD8 Ratio Evolution

Table 2 includes univariate and multivariate mixed models showing the factors associated with CD4/CD8 T-cell ratio evolution. In the adjusted model, mean CD4/CD8 T-cell ratio increase was higher with NNRTI-based regimens compared with PI-based regimens (adjusted estimated coefficient −0.0912; 95% CI, −0.1604 to −0.0219; $P = 0.009$), with no significant differences between INSTI-based and NNRTI-based regimens (−0.0968; 95% CI, −0.2359 to 0.0423; $P = 0.0172$). A higher baseline CD4/CD8 ratio was also associated with higher CD4/CD8 ratio increase (adjusted estimated coefficient [95% CI], 0.7088 [0.6746–0.7428] per unit, $P = 0.001$). By contrast, higher age (adjusted estimated coefficient [95% CI], −0.0427 [−0.0767 to −0.0087] per year, $P = 0.020$) and simplification of ART regimen (adjusted estimated coefficient [95% CI], −0.1086 [−0.1822 to −0.0349], $P = 0.003$) were associated with a negative effect on the CD4/CD8 T-cell ratio.

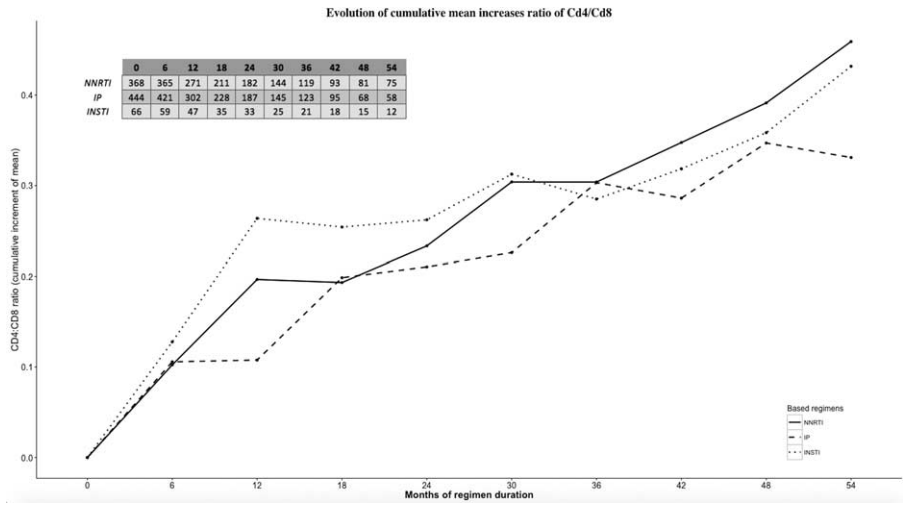

FIGURE 1. Evolution of cumulative mean increase in the CD4/CD8 T-cell ratio.

DISCUSSION

The results of this long-term follow-up study show that, in relation to the ''third antiretroviral drug'' (an NNRTI, PI, or INSTI) used, antiretroviral regimens may have a different effect on the CD4/CD8 T-cell ratio evolution. NNRTI-based regimens were associated with a higher increase in the CD4/CD8 T-cell ratio compared to PI-based regimens. Additional factors linked with the antiretroviral regimen were also found to be associated with the CD4/CD8 ratio, like a decrease with simplification therapy compared to initial regimens. The higher CD4/CD8 baseline T-cell ratio was also associated with greater CD4/CD8 gain in our study; by contrast, older age had a negative effect on the CD4/CD8 T-cell ratio.

Effective ART allows progressive CD4+ T-cell recovery; however, the CD4/CD8 T-cell ratio remains frequently inverted because of persistently elevated CD8+ T-cells.[2–4,8] Although the reasons for this CD8+ T-cell expansion in the presence of effective ART remain to be fully elucidated, potential contributory factors may include: (1) residual HIV replication; (2) persistent inflammation and immune activation linked with the presence of additional co-pathogens such as HCV, cytomegalovirus, herpesviruses, or the translocation of lipopolysaccharide

TABLE 2. Predictors of CD4/CD8 T Cell Ratio Changes Using a Linear Mixed Effects Model

Variable	Unadjusted Estimated Coefficient (95% CI)	*P*	Adjusted Estimated Coefficient (95% CI)	*P**
Age, per year	0.0012 (−0.0037 to 0.0061)	0.630	−0.0427 (−0.0767 to −0.0087)	0.020
Sex (male)	0.2743 (0.1532 to 0.3953)	0.001	0.0762 (−0.0025 to 0.1551)	0.070
Hepatitis C coinfection	0.0100 (−0.0919 to 0.1119)	0.860	0.0470 (−0.0173 to 0.1113)	0.160
HIV transmission risk (IDU)		0.006		0.200
Sexual	0.1427 (−0.0369 to 0.2484)		0.0458 (−0.0215 to 0.1131)	
Baseline CD4+/CD8+ T-cell ratio	0.7159 (0.6855 to 0.7464)	0.001	0.7088 (0.6746 to 0.7428)	0.001
ART regimen duration, per month	0.0791 (0.0259 to 0.1324)	0.008	0.0303 (−0.0034 to 0.0640)	0.080
ART regimen composition (NNRTI)		0.001		0.030
PI-based	−0.2036 (−0.3121 to −0.0951)		−0.0912 (−0.1604 to −0.0219)†	
INSTI-based	0.0195 (−0.1949 to 0.2338)		−0.0968 (−0.2359 to 0.0423)‡	
ART modality (naive)		0.001		0.003
Salvage	−0.0839 (−0.2678 to 0.0999)		0.0692 (−0.0517 to 0.1901)§	
Simplification	0.3610 (0.2534 to 0.4687)		−0.1086 (−0.1822 to −0.0349)‖	

Reference categories within each variable are shown in brackets in the first column.

ART = antiretroviral therapy, CI = confidence interval, IDU = injecting drug user, INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor.

* Adjusted for age, sex, HIV transmission category, hepatitis C virus coinfection, baseline CD4/CD8 T-cell ratio, regimen duration, follow-up time, and ART modality (naive vs simplification vs salvage regimen).

† P = 0.009.

‡ P = 0.172.

§ P = 0.262.

‖ P = 0.003.

across a damaged gut mucosa; (3) loss of T regulatory cells and other immunoregulatory cells; and (4) the intrinsic properties of CD8+ T-cells, consisting of faster reconstitution than that of CD4+ cells and durable persistence without additional divisions.[4,12–19]

Large clinical trials and cohort studies analyzing the virological and immunological effects of the antiretroviral regimen composition have usually focused on CD4+ T-cells;[20–23] however, limited data exist assessing the influence of the regimen composition on the CD4/CD8 T-cell ratio increase. Furthermore, studies addressing the factors associated with the CD4/CD8 ratio have usually analyzed the normalization of the ratio, an endpoint which usually occurs in a low proportion of patients. Because of the high frequency of altered CD4/CD8 T-cell ratio among HIV patients despite effective ART and, importantly, of its association with adverse clinical outcomes, mainly with non-AIDS events development,[5,6] the differential effects of the antiretroviral families on the CD4/CD8 dynamics may be of interest for clinicians, particularly in virologically suppressed patients with persistent low CD4/CD8 T-cell ratio. This long-term study evaluates the effects of suppressive antiretroviral regimens based on NNRTIs and INSTI and includes regimens of up to 5-year duration, mainly those based on NNRTI, PIs, and INSTIs, which allowed a thorough and consistent assessment of their influence on the immune recovery. We found that NNRTI-based regimens resulted in a higher CD4/CD8 T-cell ratio increase, followed by INSTI and PI-based regimens. Immune reconstitution has been described to occur to a similar degree with NNRTIs and PIs in small studies of short-term, usually 1-year follow-up duration,[21–23] although regimens containing PIs have also been associated with higher CD4+ T-cell recovery.[20,24] By contrast, PIs have shown to induce oxidative stress and a proinflammatory response in experimental studies[25–28] and to be associated with increased serum markers of inflammation and immune activation in clinical studies.[29–32] This proinflammatory state induced by PIs might be associated with higher CD8+ T-cells expansion persistence resulting in a lower CD4/CD8 T-cell ratio. In addition, low-level HIV-1 viremia has been observed to occur more frequently with PIs than with NNRTIs, probably in relation with a less willingness to switch PI-based regimens in this scenario due to their higher genetic barrier.[33–34] Persistent residual viremia might therefore be another factor contributing to increased CD8+ T-cell levels in these patients. In our study, INSTI occupied an intermediate position between NNRTIs and PIs regarding their effects on the CD4/CD8 T-cell ratio. Integrase inhibitors have been associated with a favorable effect on inflammation and immune activation biomarkers compared to other antiretroviral classes,[35–37] which could be potentially associated with a larger reduction of CD8+ T-cells. The number of regimens including this class of antiretrovirals was much lower than those including NNRTIs or PIs in our study, and the majority were simplification regimens; results should therefore be interpreted accordingly.

We also found that initial regimens were associated with a higher CD4/CD8 T-cell ratio recovery compared to simplification ART. Successful treatment for HIV infection has been shown to be accompanied by a rebound in the number of $CD4^+$ T-cells, which is more pronounced early after ART initiation. The release of CD4+ cells that were trapped in the lymph nodes because of the presence of high amounts of HIV antigen has been implicated in the rapid increase of CD4+ T-cells after starting ART, due to recirculation of those cells.[38] Also, the intense reduction of inflammation and immune activation occurring in viremic patients after beginning ART[32] might be accompanied by a higher reduction of CD8+ T-cells and, consequently, higher increase of the ratio in naive patients who initiate ART than in stable patients who simplify their treatment. In addition to ART-associated factors, our study revealed additional established factors associated with changes in the CD4/CD8 ratio, including a lower recovery in association with older age, and higher recovery with higher CD4/CD8 baseline ratio and, close to significance, with longer regimen duration.[8,9] Those findings support the consistency of our results.

Limitations of our study include those inherent to retrospective studies, such as existing unmeasured confounding factors. For example, we did not control for other factors potentially influencing the CD4/CD8 T-cell ratio, like malignancy or prior chemotherapy. We were not able to individually assess the effects of every third antiretroviral agent in the CD4/CD8 T-cell ratio because of insufficient sample size. As previously stated, there was a lower representativeness of INSTI-based regimens, which should be taken into account when interpreting the results obtained with this antiretroviral class. Strengths include the large number of CD4/CD8 determinations analyzed for each regimen and the long-term follow-up of the cohort, which guarantee the robustness of the results obtained and the generalizability of the results.

In conclusion, suppressive antiretroviral regimens differ in their effects on the CD4/CD8 T-cell ratio, and PI-based regimens might be associated with a lower CD4/CD8 T-cell ratio increase. Higher experience is needed with INSTIs to elucidate their effect on the CD4/CD8 T-cell ratio changes.

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