Clinical Infectious Diseases

MAJOR ARTICLE

CD4/CD8 Ratio Outcome According to the Class of the Third Active Drug in Antiretroviral Therapy (ART) Regimens: Results From the Quebec Human Immunodeficiency Virus (HIV) Cohort Study

Mohamed N'dongo Sangaré,[1] Jean-Guy Baril,[2,3,4] Alexandra de Pokomandy,[5,6] Marina Klein,[5] Réjean Thomas,[7] Cécile Tremblay,[3,4,8,9] Costa Pexos,[5] Madeleine Durand,[8] Seerat Chawla,[6] Louise Laporte,[10] and Helen Trottier[10,11]

[1]Université du Québec en Abitibi-Témiscamingue, Rouyn-Noranda, Canada; [2]Clinique de Médecine Urbaine du Quartier Latin, Montreal, Canada; [3]Faculty of Medicine, Université de Montréal, Montreal, Canada; [4]Centre Hospitalier de l'Université de Montréal, Montreal, Canada; [5]Chronic Viral Illness Service, McGill University Health Centre, Montreal, Canada; [6]Department of Family Medicine, McGill University, Montreal, Canada; [7]Clinique Médicale L'Actuel, Montreal, Canada; [8]Department of Microbiology, Infectious Diseases, and Immunology, Université de Montréal, Montreal, Canada; [9]Department of Microbiology and Immunology, Centre Hospitalier de l'Université de Montréal, Montreal, Canada; [10]Sainte Justine University Hospital Center, Montreal, Canada; and [11]Department of Social and Preventive Medicine, Université de Montréal, Montreal, Canada

Background. The impact of different therapeutic classes of drugs in antiretroviral therapy (ART) regimens on the CD4/CD8 ratio is not well documented in people treated for HIV. The objective of this study was to analyze the long-term effect of exposure to integrase strand transfer inhibitor (INSTI) on CD4/CD8 ratio compared with nonnucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) among ART-treated persons with HIV (PLHIV).

Methods. Data from the Quebec HIV Cohort collected from 31 August 2017 were used. Our analysis included all patients in the cohort who received a first or subsequent ART regimen composed of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a third active drug of a different class (NNRTI, PI, or INSTI) for at least 16 weeks. Marginal structural Cox models were constructed to estimate the effect of different therapeutic classes on the CD4/CD8 ratio outcome.

Results. Among the 3907 eligible patients, 972 (24.9%), 1996 (51.1%), and 939 (24.0%) were exposed to an ART regimen whose third active agent was an NNRTI, PI, or INSTI, respectively. The total follow-up time was 13 640.24 person-years. The weighted hazard ratio for the association between the third active class and CD4/CD8 ratio ≥1 was .56 (95% confidence interval [CI]: .48–.65) for patients exposed to NNRTI + 2 NRTIs and .41 (95% CI: .35–.47) for those exposed to PI + 2 NRTIs, compared with those exposed INSTI + 2 NRTIs.

Conclusions. For people treated for HIV, INSTI-based ART appears to be associated with a higher CD4/CD8 ratio than NNRTI and PI-based ART.

Keywords. CD4/CD8 ratio; PLHIV; INSTIs; NNRTIs; PIs.

Different inflammatory markers have been associated with human immunodeficiency virus (HIV) infection in persons with HIV (PLHIV) including an inversion of the CD4/CD8 ratio [1–3]. A value below the critical threshold of 1 for this inflammatory marker has been associated with increased morbidity and mortality among PLHIV [2–8], including a greater risk of non-AIDS events [9]. Some studies have shown that a low CD4/CD8 ratio was associated with the risk of developing certain chronic diseases, such as kidney disease, vascular disease [10], and some cancers, such as lung cancer, non-Hodgkin lymphoma, Kaposi sarcoma, and anal cancer [11–14], even among PLHIV with viral load (VL) suppression [15]. The CD4/CD8 ratio can therefore be a useful clinical indicator during the chronic phase of HIV infection [1, 16, 17]. Antiretroviral therapy (ART) generally leads to an increase in the CD4/CD8 ratio [2, 9]. However, a persistence of the CD4/CD8 ratio below 1 can be observed despite viral suppression on ART [18, 19]. This immune alteration might be a sign of immune activation and immunosenescence [3, 5, 17, 20, 21], which is associated with an increase in bioinflammatory markers during HIV infection. The mechanisms of action may be related to endothelial damage that occurs during viral replication [22–24] or persistence of viral replication marked by an increase in quiescent virus reservoirs [25]. Normalization of the CD4/CD8 ratio has been associated with a reduction in the virus reservoir [26].

Following initiation of ART, normalization of the CD4/CD8 ratio (>1) may be associated with the therapeutic classes of

Received 23 August 2022; editorial decision 24 January 2023; published online 1 February 2023

Correspondence: M. N. Sangaré, Département des sciences de la santé, Université du Québec en Abitibi-Témiscamingue, 445 Bd de l'Université, Rouyn-Noranda, QC, Canada J9X 5E4 (mohamedndongo.sangare@uqat.ca).

Clinical Infectious Diseases®

https://doi.org/10.1093/cid/ciad056

antiretrovirals and the delay in initiation of ART [27, 28]. Previous literature has shown that some therapeutic classes with lipid-lowering properties can be better than others at reducing inflammatory markers [29–31]. The use of integrase strand transfer inhibitor (INSTI)–based ART in treatment-naive patients has specifically been shown to provide a better long-term effect on the CD4/CD8 ratio [28, 32–34]. These studies suggest a beneficial role of INSTIs for the normalization of the CD4/CD8 ratio compared with other antiretroviral classes such as protease inhibitors (PIs). To our knowledge, Masiá et al [35] is the only study that included some ART-treated patients not on their first regimen. This study showed a better effect of INSTIs compared with nonnucleoside reverse transcriptase inhibitors (NNRTIs). The objective of our study was to analyze the long-term effect of INSTIs on CD4/CD8 ratio outcome compared with both NNRTIs and PIs when given as a first or subsequent treatment for HIV.

METHODS

Data Source

We used data from the Quebec HIV Cohort, from which data have been published previously [36, 37]. This is an observational cohort including data prospectively collected from patients' files of PLHIV followed in 4 sites specialized in HIV care in Montreal: 2 community clinics, Clinique Médicale l'Actuel (CMA) and Clinique de Médecine Urbaine du Quartier Latin (CMUQL), and 2 hospital clinics, Centre Hospitalier de l'Université de Montréal (CHUM) and McGill University Health Center (MUHC). The clinical databases from each center were merged to create the Quebec HIV Cohort, which includes 10 219 patients with 5844 PLHIV actively followed as of 31 August 2017 [38]. The Quebec HIV Cohort Study was approved by the Research Ethics Boards (REBs) of the MUHC, CHUM, CMA, and CMUQL. This specific study was approved by the REB of the MUHC.

Patient Selection

In our observational cohort, all patients who started their first or subsequent ART regimen from or after 1 January 2006 that consisted of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a third agent from a different class for at least 16 weeks and who had a baseline CD4/CD8 ratio measurement were included. Figure 1 details the selection of PLHIV from the cohort for our analysis. The NRTIs included in the regimen of PLHIV were abacavir/lamivudine, tenofovir disoproxil/emtricitabine, and tenofovir disoproxil/lamivudine.

Exposure and Outcome

Patients were compared according to the classes of the third drug included in their regimen: an NNRTI, a PI, or an INSTI. Exposure was therefore categorized into the following 3 groups: NNRTI + 2 NRTIs, PI + 2 NRTIs, and INSTI + 2 NRTIs. Antiretroviral therapy discontinuation of fewer than 15 days was not considered and drug changes within the same class were allowed.

The outcome of interest was the incidence of a CD4/CD8 ratio of 1 or greater during follow-up. The incidence of a CD4/CD8 ratio above 0.3, 0.5, 0.8, and 1.2 was also analyzed.

Other Variables

The following variables were considered in our analysis: age at inclusion (continuous), VL at inclusion (<50, 50–10 000, and >10 000 copies/mL), CD4 count at inclusion (<200, 200–350, and >350 cells/mm^3), CD8 count at inclusion (<800 and >800 cells/mm^3), delay in first ART treatment initiation (continuous), anti–hepatitis C virus antibodies before inclusion (yes or no), hepatitis B surface antigen before inclusion (yes or no), CD4 nadir before inclusion (<200, 200–350 and >350 cells/mm^3), treatment changes before inclusion (yes or no), ART duration before inclusion (continuous), time since HIV diagnosis at inclusion (continuous), previously documented virologic failure before inclusion (yes or no), CD4/CD8 ratio at inclusion (<1 and >1), cytomegalovirus (CMV) serostatus before inclusion (yes or no), previous exposure to mono-/dual NRTI therapy before inclusion (yes or no), year of inclusion (2006–2009, 2010–2013, and 2014–2017), and risk factors for HIV acquisition. We defined previously documented virologic failure as 1 VL value greater than 200 copies/mL after 6 months of therapy, VL greater than 50 copies/mL at discontinuation of treatment, or 2 consecutive VL values greater than 50 copies/mL after having reached suppressive viremia. Previous exposure to mono-/dual NRTI therapy was defined as exposure to 1 or 2 NRTIs for at least 1 month.

Statistical Analysis

A survival analysis was conducted to analyze the incidence of CD4/CD8 ratio outcome according to exposure. Time zero was defined as the date of inclusion (1 January 2006, or the earliest subsequent date where the inclusion criteria were met). An explanatory Kaplan–Meier curve with log-rank test was used to compare the cumulative incidence of CD4/CD8 ratio outcome between the 3 groups. The observations were censored at the end of therapy, at the change of the therapeutic class including the addition of a fourth antiretroviral drug (ARV), or at the end of follow-up.

A marginal structural Cox model analysis was performed to estimate the effect of the therapeutic class on the CD4/CD8 ratio. The database was discretized into 5-month intervals. Inverse probability of treatment and censoring stabilized weights (IPTW and IPCW) was then performed using a logistic regression model to estimate the probability of being on INSTI + 2 NRTIs and the probability of not being censored at each follow-up visit. All covariables described above were

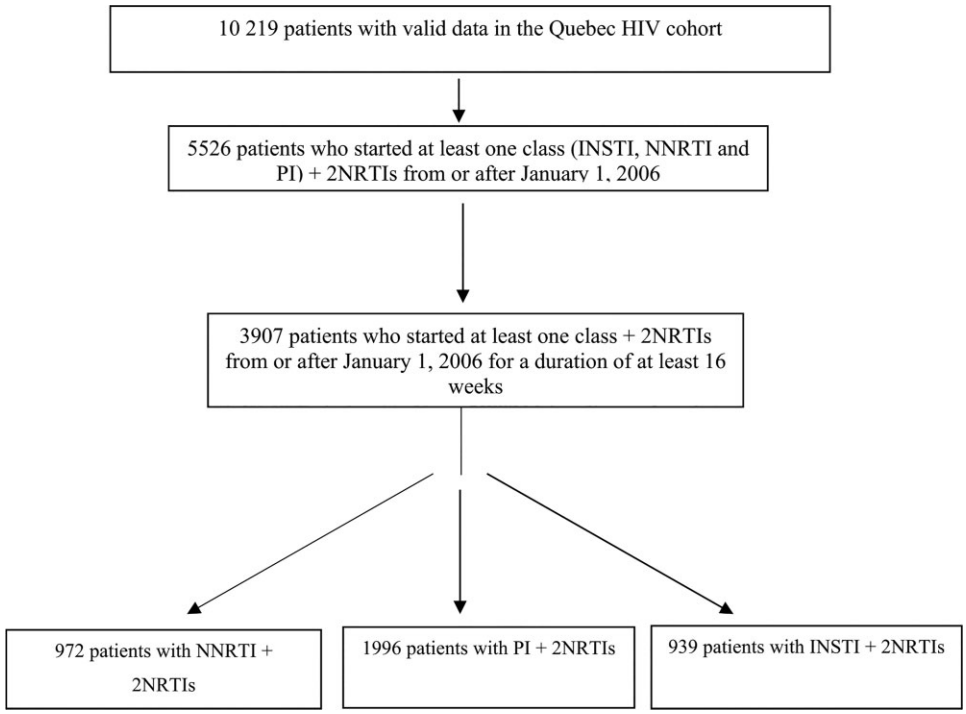

Figure 1. Flowchart of persons with HIV included in our analysis. Abbreviations: HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

considered in the model. Variables with a correlation coefficient of 0.30 or greater were removed from the logistic regression model for the estimation of exposure and censorship weights. The choice of the correlated variables to include in the logistic regression model was made based on clinical relevance. CD4 count, CD8 count, and VL variables (continuous) were considered time-dependent variables. Missing values for hepatitis serologies were considered negative for the analyses. Sensitivity analyses have shown that considering missing values for CMV serostatus as positive or negative had no impact on the adjusted hazard ratios (HRs) obtained. Missing values for CMV serostatus were therefore considered as negative in the analyses. Missing CD4 count, CD8 count, and VL values were replaced by the most recent previous values.

After the calculation of the censor weight, a 1% truncation was performed on stabilized censor weight because of the high weights. A pooled logistic regression conditional model was made to estimate the HR in the marginal structural Cox model. Patients receiving INSTI + 2 NRTIs were used as the reference group.

Sensitivity analyses were carried out with the same methods restricting the analysis to treatment-naive patients receiving a first treatment only and to patients receiving a second or subsequent regimen only. Models were built independently for these 2 populations. In the analysis restricted to treatment-naive patients receiving a first treatment, the following variables were not considered in the models: treatment changes before inclusion and ART duration before inclusion. STATA version 14 (StataCorp, College Station, TX, USA) was used to perform the statistical analyses.

RESULTS

Among the 3907 eligible patients, 972 (24.9%), 1996 (51.1%), and 939 (24.0%) were exposed to NNRTI + 2 NRTIs, PI + 2 NRTIs, and INSTI + 2 NRTIs, respectively. The INSTIs at inclusion were raltegravir (37.6%), elvitegravir (19.4%), and dolutegravir (43%).

The total follow-up time after inclusion was 13 640.24 person-years and 1790 of 3907 PLHIV reached a CD4/CD8 ratio of 1 or greater (13.1%; 95% confidence interval [CI]: 12.5%–13.7%) after a median duration (25%–75%) of 4.4 years (2.1–7.4). In our study, the median (25%–75%) follow-up time was 5.8 years (3.1–8.4), 4.5 years (2.0–7.4), and 2.9 years (1.7–5.3), respectively, for patients exposed to NNRTI + 2 NRTIs, PI + 2 NRTIs, and INSTI + 2 NRTIs.

Patient characteristics are summarized in Table 1. Mean (standard deviation [SD]) age was 42.9 (10.4) years, 42.5 (9.9) years, and 42.6 (11.6) years for patients exposed to NNRTI + 2 NRTIs, PI + 2 NRTIs, and INSTI + 2 NRTIs, respectively. Mean (SD) time since diagnosis at inclusion was 6.1 (6.1), 6.7 (6.3), and 5.5 (7.0) years for patients exposed to NNRTI + 2

Table 1. Characteristics of Eligible Patients

Variables	NNRTI (n = 972)	PI (n = 1996)	INSTI (n = 939)
Age at inclusion (in years)			
Mean (SD)	42.9 (10.4)	42.5 (9.9)	42.6 (11.6)
Sex			
Male	851 (87.5)	1610 (80.7%)	827 (88.1%)
Risk factor for HIV acquisition			
MSM	628 (64.6%)	1201 (60.2%)	658 (70.1%)
Bisexual	21 (2.2%)	67 (3.4%)	25 (2.7%)
Heterosexual	187 (19.2%)	480 (24.1%)	132 (14.1%)
From endemic countries	144 (14.8%)	291 (14.6%)	67 (7.1%)
Vertical transmission	9 (0.9%)	10 (0.5%)	4 (0.4%)
Delay in ART treatment initiation (in years)			
Mean (SD)	2.0 (4.0)	2.0 (3.7)	2.2 (4.8)
ART duration before inclusion (in years)			
Mean (SD)	4.3 (4.8)	5.0 (5.3)	3.6 (5.5)
Time since diagnosis at inclusion (in years)			
Mean (SD)	6.1 (6.1)	6.7 (6.3)	5.5 (7.0)
Treatment changes before inclusion[a]			
Yes	332 (34.2%)	873 (43.7%)	174 (18.5%)
Viral load (copies/mL) at inclusion			
<50	305 (31.4%)	499 (25.0%)	212 (22.6%)
50–10 000	293 (30.1%)	623 (31.2%)	297 (31.6%)
>10 000	306 (31.5%)	752 (37.7%)	400 (42.6%)
Missing data	68 (7.0%)	122 (6.1%)	30 (3.2%)
Median (25%–75%)	444.0 (49.5–25 731.5)	774.5 (49.5–59 764.0)	3170.0 (97.0–59 358.0)
CD4 count at inclusion (cells/mm^3)			
<200	148 (15.2%)	507 (25.4%)	131 (14.0%)
200–350	289 (29.7%)	582 (29.2%)	237 (25.2%)
>350	465 (47.8%)	778 (38.9%)	532 (56.7%)
Missing data	70 (7.3%)	129 (6.5%)	39 (4.1%)
Median (25%–75%)	360.0 (246.0–540.0)	309.0 (190.0–480.0)	400.0 (270.0–580.0)
CD8 count at inclusion (cells/mm^3)			
<800	354 (36.4%)	785 (39.3%)	348 (37.1%)
≥800	425 (43.7%)	914 (45.8%)	402 (42.8%)
Missing data	193 (19.9%)	297 (14.9%)	189 (20.1%)
Median (25%–75%)	860.0 (610.0–1146.0)	850.0 (582.0–1200.0)	840.0 (600.0–1184.0)
CD4/CD8 ratio at inclusion			
<1	694 (71.4%)	1602 (80.3%)	678 (72.2%)
>1	85 (8.7%)	96 (4.8%)	71 (7.6%)
Missing data	193 (19.9%)	298 (14.9%)	190 (20.2%)
Median (25%–75%)	0.4 (0.2–0.7)	0.3 (0.2–0.5)	0.4 (0.3–0.7)
CD4 nadir before inclusion (cells/mm^3)			
<200	190 (19.6%)	611 (30.6%)	161 (17.1%)
200–350	325 (33.4%)	643 (32.2%)	270 (28.7%)
>350	387 (39.8%)	613 (30.7%)	469 (49.9%)
Missing data	70 (7.2%)	129 (6.5%)	39 (4.3%)
Median (25%–75%)	320.0 (220.0–480.0)	270.0 (170.0–401.0)	364.0 (245.5–500.0)
Hepatitis B before inclusion			
Positive for HBsAg	55 (5.7%)	94 (4.7%)	22 (2.3%)
Negative for HBsAg	710 (73.0%)	1471 (73.7%)	747 (79.6%)
Not documented	207 (21.3%)	431 (21.6%)	170 (18.1%)
Hepatitis C before inclusion			
Positive for anti-HCV	50 (5.1%)	212 (10.6%)	41 (4.4%)
Negative for anti-HCV	519 (53.4%)	979 (49.1%)	587 (62.5%)
Not documented	403 (41.5%)	805 (40.3%)	311 (33.1%)

Table 1. Continued

Variables	NNRTI (n = 972)	PI (n = 1996)	INSTI (n = 939)
Cytomegalovirus serostatus			
Positive	196 (20.2%)	423 (21.2%)	134 (14.3%)
Negative	54 (5.6%)	113 (5.7%)	125 (13.3%)
Not documented	722 (74.2%)	1460 (73.1%)	680 (72.4%)
Previous exposure to mono-/dual NRTI therapy before inclusion			
Yes	53 (5.5%)	291 (14.6%)	57 (6.1%)
Previously documented virologic failure before inclusion			
Yes	21 (2.2%)	166 (8.3%)	21 (2.2%)
Years of inclusion			
2006–2009	618 (63.6%)	1519 (76.1%)	201 (21.4%)
2010–2013	296 (30.4%)	432 (21.6%)	362 (38.5%)
2014–2017	58 (6.0%)	45 (2.3%)	376 (40.1%)

Data are presented as n (%) unless otherwise indicated. N = 3907. Abbreviations: ART, antiretroviral therapy; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; HBsAg, hepatitis B surface antigen; HVC, hepatitis C virus; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

[a]Treatment changes before inclusion were considered as any changes of antiretroviral drug in the regimen. The only exception for ignoring a change was a change between emtricitabine and lamivudine.

NRTIs, PI + 2 NRTIs, and INSTI + 2 NRTIs, respectively. Median (25%–75%) CD4 nadir before inclusion was 320.0 cells/mm^3 (220.0–480.0) in the NNRTI + 2 NRTIs group, 364.0 (245.5–500.0) in the INSTI + 2 NRTIs group, and 270.0 (170.0–401.0) in the PI + 2 NRTIs group.

Patient characteristics for treatment-naive patients receiving a first treatment only as well as those for patients receiving a second or subsequent treatment only are presented in Supplementary Tables 1 and 2.

Figure 2 shows the cumulative incidence of CD4/CD8 outcome using 5 different cutoff values (≥0.3, ≥0.5, ≥0.8, ≥1, or ≥1.2). For the CD4/CD8 ratio of 1 or greater, the cumulative incidence was 13.6% (95% CI: 12.4–14.8%) for those exposed to NNRTIs (n = 529), 10.4% (95% CI: 9.7–11.2%) for those exposed to PIs (n = 767), and 20.3% (95% CI: 18.6–22.2%) for those exposed to INSTIs (n = 494) (all $P = .00001$). Results were similar with CD4/CD8 ratios of 0.3, 0.5, 0.8, and 1.2.

The results from the marginal structural Cox model in Table 2 show that a better CD4/CD8 ratio outcome was reached for patients exposed to an INSTI compared with those exposed to an NNRTI or a PI. Using the CD4/CD8 ratio of 1 or greater, the weighted HRs were .56 (95% CI: .48–.65) for patients exposed to NNRTI + 2 NRTIs and .41 (95% CI: .35–.47) for those exposed to PI + 2 NRTIs, compared with the patients exposed to INSTI + 2 NRTIs. The nonoverlapping CIs of the HRs also suggested that NNRTIs were better than PIs for the normalization of the CD4/CD8 ratio. The results were similar using the CD4/CD8 ratio cutoffs of 0.3, 0.5, 0.8, and 1.2.

When the analysis was restricted to treatment-naive patients receiving their first treatment (n = 1041), the weighteds HR for the CD4/CD8 ratio of 1 or greater were .60 (95% CI: .47–.77) for patients exposed to NNRTI + 2 NRTIs and .41 (95% CI: .32–.51) for those exposed to PI + 2 NRTIs compared with those exposed to INSTI + 2 NRTIs (Table 3). Table 4 presents the analyses restricted to patients on a second or subsequent treatment. Weighted HRs for a CD4/CD8 ratio of 1 or greater were .78 (95% CI: .66–.92) for patients exposed to NNRTI + 2 NRTIs and .57 (95% CI: .49–.67) for those exposed to PI + 2 NRTIs compared with those exposed to INSTI + 2 NRTIs.

DISCUSSION

Our study including patients on their first or subsequent HIV treatment showed that an INSTI-based regimen seems to be better than NNRTI- and PI-based ART for the normalization of the CD4/CD8 ratio. The majority of previous studies investigating the impact of therapeutic classes on the CD4/CD8 ratio were done among treatment-naive patients receiving their first treatment regimen. In such a cohort study including 1876 patients on NNRTIs, 1804 on PIs, and 291 on INSTIs, Herrera et al [34] showed that the CD4/CD8 ratio after 48 weeks after ART initiation was higher among patients exposed to NNRTIs compared with PIs (adjusted odd ratio [aOR] = 1.50; 95% CI: 1.15–1.93). This study also found an increase in the normalization of the CD4/CD8 ratio (≥1) in patients on INSTIs compared with those on PIs (aOR = 1.7; 95% CI: 1.1–3.0). The beneficial effect of NNRTIs was mainly explained by a decrease in CD8 count ($P = .025$) and not by the CD4 count, which was not statistically different between NNRTIs and PIs ($P = .702$). The Nice cohort consisting of 567 treatment-naive PLHIV also found a higher number of patients with a CD4/CD8 ratio of 1 or greater on regimens containing INSTIs compared with those on regimens without INSTIs (OR = 7.67; 95% CI: 2.54–23.2). In this study, 8% (45/567) of patients started a regimen containing INSTIs, and after 1 year following ART initiation, 22.2% (10/45) had normalized their CD4/CD8 ratio (≥1) [33]. In the STARTMRK

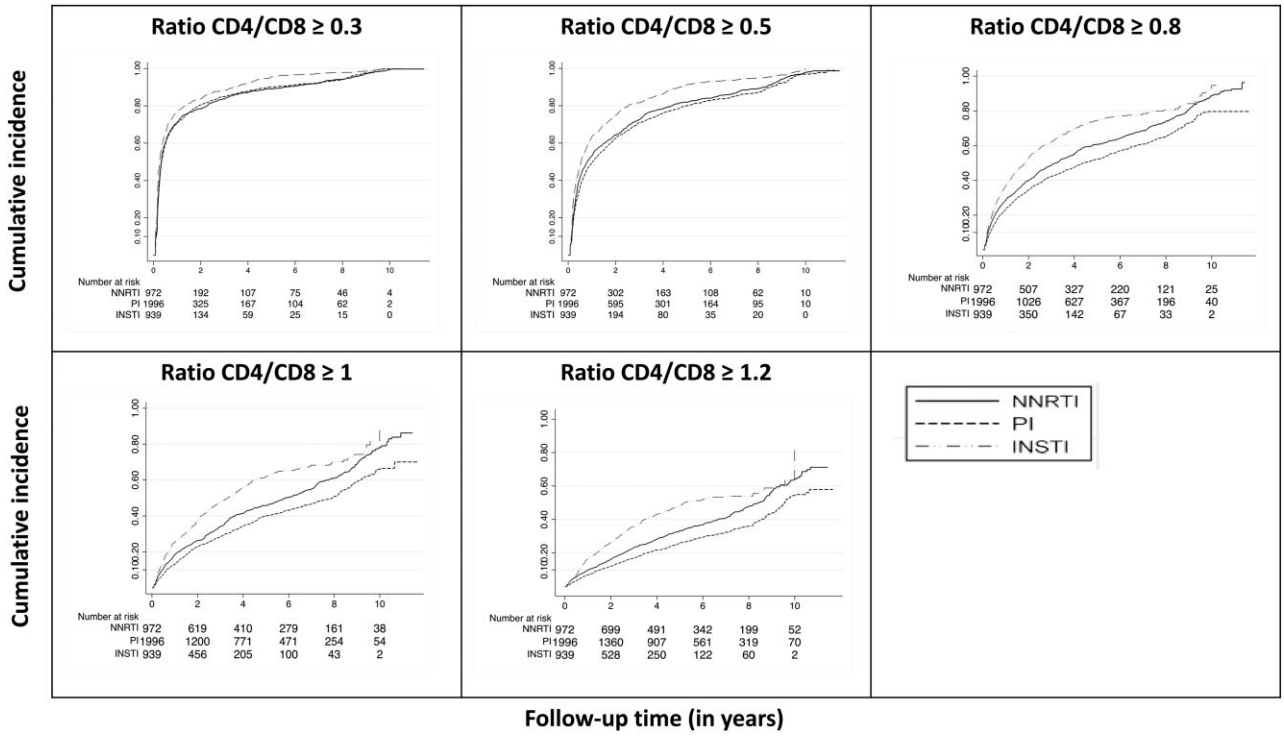

Figure 2. Unadjusted cumulative incidence of the normalization of the CD4/CD8 ratio according to the class of drugs in the triple antiretroviral therapy presented according to the use of different cutoffs of the ratio. Log-rank test (testing the difference in the unadjusted curves), $P = .00001$ for the 5 cutoffs of CD4/CD8 ratio. Abbreviations: INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2. Marginal Structural Cox Model Estimates for the Effect of the Third Active Class in Antiretroviral Therapy on CD4/CD8 Ratio

ART Class	Person-years	Incident Number	Crude HR (95% CI)	IPTW[a] IPCW Weighted Marginal Structural Model, HR (95% CI)
Ratio CD4/CD8 ≥0.3				
INSTI + 2 NRTIs	890.1	902	1 (reference)	1 (reference)
NNRTI + 2 NRTIs	1329.6	929	.58 (.52–.65)	.59 (.49–.70)
PI + 2 NRTIs	2352.5	1819	.59 (.53–.66)	.57 (.48–.67)
Ratio CD4/CD8 ≥0.5				
INSTI + 2 NRTIs	1229.7	827	1 (reference)	1 (reference)
NNRTI + 2 NRTIs	1919.0	848	.58 (.52–.65)	.60 (.51–.70)
PI + 2 NRTIs	3730.3	1561	.50 (.44–.55)	.49 (.42–.57)
Ratio CD4/CD8 ≥0.8				
INSTI + 2 NRTIs	1957.62	622	1 (reference)	1 (reference)
NNRTI + 2 NRTIs	3194.11	665	.55 (.48–.62)	.58 (.51–.67)
PI + 2 NRTIs	6216.74	1032	.41 (.36–.46)	.42 (.36–.48)
Ratio CD4/CD8 ≥1				
INSTI + 2 NRTIs	2425.42	494	1 (reference)	1 (reference)
NNRTI + 2 NRTIs	3873.01	529	.53 (.47–.61)	.56 (.48–.65)
PI + 2 NRTIs	7341.80	767	.40 (.35–.46)	.41 (.35–.47)
Ratio CD4/CD8 ≥1.2				
INSTI + 2 NRTIs	2794.23	370	1 (reference)	1 (reference)
NNRTI + 2 NRTIs	4456.06	393	.67 (.58–.77)	.66 (.56–.77)
PI + 2 NRTIs	8310.32	525	.47 (.41–.54)	.44 (.38–.51)

N = 3907. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; IPCW, inverse probability of censoring weights; IPTW, inverse probability of treatment weights; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Weighted variables: age (continuous), delay in ART treatment initiation (continuous), nadir CD4 (<200, 200–350 and >350 cells/mm^3), treatment changes before inclusion (yes or no), previously documented virologic failure before inclusion (yes or no), hepatitis C before inclusion (yes or no), cytomegalovirus serostatus before inclusion (yes or no), and year of inclusion (2006–2009, 2010–2013, and 2014–2017). CD4, CD8, and viral load variables (continuous) were considered time-dependent variables during follow-up.

Table 3. Marginal Structural Cox Model Estimates for the Effect of the Third Active Class in Antiretroviral Therapy on CD4/CD8 Ratio Among Treatment-Naive Patients Receiving a First Treatment Only

ART Class	Person-years	Incident Number	Crude HR (95% CI)	IPTW[a] IPCW Weighted Marginal Structural Model, HR (95% CI)
Ratio CD4/CD8 ≥0.3				
INSTI + 2 NRTIs	230.3	349	1 (reference)	1 (reference)
NNRTI + 2 NRTIs	313.5	243	.48 (.39–.59)	.52 (.36–.75)
PI + 2 NRTIs	427.9	388	.55 (.46–.66)	.57 (.40–.80)
Ratio CD4/CD8 ≥0.5				
INSTI + 2 NRTIs	326.9	321	1 (reference)	1 (reference)
NNRTI + 2 NRTIs	454.2	222	.48 (.39–.58)	0.51 (.37–.69)
PI + 2 NRTIs	730.0	333	.44 (.36–.52)	.43 (.32–.58)
Ratio CD/CD8 ≥0.8				
INSTIs + 2 NRTIs	545.1	257	1 (reference)	1 (reference)
NNRTIs + 2 NRTIs	695.8	180	.55 (.45–.67)	.56 (.44–.72)
PIs + 2 NRTIs	1210.6	222	.37 (.31–.45)	.38 (.30–.47)
Ratio CD4/CD8 ≥1				
INSTIs + 2 NRTIs	696.2	204	1 (reference)	1 (reference)
NNRTIs + 2 NRTIs	833.3	142	.59 (.47–.74)	.60 (.47–.77)
PIs + 2 NRTIs	1386.5	166	.40 (.32–.50)	.41 (.32–.51)
Ratio CD4/CD8 ≥1.2				
INSTIs + 2 NRTIs	815.9	159	1 (reference)	1 (reference)
NNRTIs + 2 NRTIs	960.4	109	.59 (.46–.76)	.61 (.47–.79)
PIs + 2 NRTIs	1569.54	111	.36 (.28–.46)	.39 (.30–.50)

N = 1041. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; IPCW, inverse probability of censoring weights; IPTW, inverse probability of treatment weights; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Weighted variables: age (continuous), delay in ART treatment initiation (continuous), and nadir CD4 (<200, 200–350 and >350 cells/mm^3). CD4, CD8, and viral load variables (continuous) were considered time-dependent during follow-up.

Table 4. Marginal Structural Cox Model Estimates for the Effect of the Third Active Class in Antiretroviral Therapy (ART) on CD4/CD8 Ratio Among Treatment-Experienced Patients Receiving a Second or Subsequent ART Regimen

ART Class	Person-years	Incident Number	Crude HR (95% CI)	IPTW[a] IPCW Weighted Marginal Structural Model, HR (95% CI)
Ratio CD4/CD8 ≥0.3				
INSTI + 2 NRTIs	659.9	553	1 (reference)	1 (reference)
NNRTI + 2 NRTIs	1016.2	686	.79 (.69–.89)	.78 (.64–.95)
PI + 2 NRTIs	1924.6	1431	.86 (.77–.96)	.80 (.67–.95)
Ratio CD4/CD8 ≥0.5				
INSTI + 2 NRTIs	902.7	506	1 (reference)	1 (reference)
NNRTI + 2 NRTIs	1464.8	626	.75 (.65–.85)	.73 (.61–.87)
PI + 2 NRTIs	3000.3	1228	.70 (.63–.79)	.64 (.55–.75)
Ratio CD/CD8 ≥0.8				
INSTIs + 2 NRTIs	1412.5	365	1 (reference)	1 (reference)
NNRTIs + 2 NRTIs	2498.3	485	.75 (.65–.87)	.77 (.65–.90)
PIs + 2 NRTIs	5006.1	810	.62 (.54–.70)	.57 (.49–.67)
Ratio CD4/CD8 ≥1				
INSTIs + 2 NRTIs	1729.2	290	1 (reference)	1 (reference)
NNRTIs + 2 NRTIs	3039.7	387	.77 (.65–.91)	.78 (.66–.92)
PIs + 2 NRTIs	5955.2	601	.59 (.51–.69)	.57 (.49–.67)
Ratio CD4/CD8 ≥1.2				
INSTIs + 2 NRTIs	1978.3	211	1 (reference)	1 (reference)
NNRTIs + 2 NRTIs	3495.6	284	.76 (.64–.92)	.78 (.65–.95)
PIs + 2 NRTIs	6740.7	414	.57 (.48–.67)	.56 (.47–.68)

N = 2866. Abbreviations: CI, confidence interval; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; IPCW, inverse probability of censoring weights; IPTW, inverse probability of treatment weights; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Weighted variables: age (continuous), delay in ART treatment initiation (continuous), nadir CD4 (<200, 200–350 and >350 cells/mm^3), and cytomegalovirus serostatus before inclusion (yes or no). CD4, CD8, and viral load variables (continuous) were considered time-dependent during follow-up.

study, which included 563 treatment-naive patients, the authors similarly concluded that raltegravir, an INSTI, was associated with a higher probability to reach a CD4/CD8 ratio greater than 0.4 compared with efavirenz (NNRTI) ($P = .02$) [28]. Studies comparing the 3 therapeutic classes have also been carried out. In a population of treatment-naive patients contributing to 37 149 person-years, Serrano-Villar et al [32] showed a greater increase in CD4/CD8 ratio of 1 or greater with INSTIs compared with NNRTIs (adjusted coefficient: −.70; 95% CI: −.08, −0.06) and PIs (adjusted coefficient: −.08; 95% CI: −.09, −.08). In this study, 2820 (41.4%) patients were on an NNRTI, 1574 (23.1%) were on a PI, and 2410 (35.5%) were on an INSTI. The authors of this study did not, however, find a statistically significant difference between the type of INSTIs (dolutegravir, elvitegravir, and raltegravir). In our study, we observed a difference on CD4/CD8 ratio recovery according to the type of INSTI. When restricting our analysis to patients with INSTI-based ART (n = 939) and categorizing the treatment group by the type of INSTI (raltegravir, elvitegravir, or dolutegravir), we observed a similar impact of elvitegravir compared with dolutegravir (weighted HR = 1.03; 95% CI: .74–1.43) but a lower efficacy for raltegravir compared with dolutegravir (weighted HR = .52; 95% CI: .17–.68) (data not shown).

To our knowledge, the study of Masiá et al [35] is the only study to include PLHIV treated with a first or subsequent ART regimen. In this prospective cohort study including virologically stable PLHIV (HIV-RNA < 400 copies/mL) with a median (quartiles 25%–75%) follow-up time of 90 months (44–139 months), a better mean increase in the CD4/CD8 ratio was observed among patients on NNRTIs compared with PIs (adjusted coefficient: −.0912; 95% CI: −.1604, −.0219). However, there was no statistically significant difference found when comparing NNRTIs with INSTIs (adjusted coefficient: −.0968; 95% CI: −.2359, .0423). In this study, 1068 ART regimens from 570 patients were included (<50% were initial regimens in treatment-naive patients), of whom 52.25% (558), 41.10% (439), and 6.65% (71) were treated with PIs, NNRTIs, and INSTIs, respectively. In our study with PLHIV treated with a first (n = 1041) or a subsequent ART regimen (n = 2866), we did find that INSTIs were better than both NNRTIs and PIs for the normalization of the CD4/CD8 ratio globally and in both groups of first and subsequent treatment. Although NNRTIs were better than PIs for CD4/CD8 ratio normalization, they did not reach the levels of normalization achieved with INSTIs.

In our study, the effect of INSTI-based ART on CD4/CD8 ratio recovery appears to be explained more strongly by a greater increase in CD4 rather than a decrease in CD8. For the association between ARVs and CD4 (≥350 cells/mm^3), the weighted HRs were .38 (95% CI: .20–.72) for patients exposed to NNRTI + 2 NRTIs and .44 (95% CI: .23–.83) for those exposed to PI + 2 NRTIs compared with the patients exposed to INSTI + 2 NRTIs. For the association between ARVs and CD8 (≤500 cells/μL), the weighted HRs were 1.25 (95% CI: .45–3.46) for patients exposed to NNRTI + 2 NRTIs and 1.67 (95% CI: .65–4.24) for those exposed to PI + 2 NRTIs compared with the patients exposed to INSTI + 2 NRTIs. Results were similar when the CD8 variable was dichotomized using a cutoff of 1000 cells/μL.

Our study has several strengths. First, the data came from a multicenter cohort study with a large sample size and long follow-up period. The mean duration of follow-up time of patients included in our study was 4.8 (SD = 3.0) years. We also used a structural marginal model with longitudinal data using the Target Trials approach [39]. This approach allowed us to define causal effects between the time-dependent exposure and the outcomes including time-dependent confounding factors that are potentially influenced by the previous exposure such as CD4 count and VL. Causal inference must satisfy 4 presuppositions to be valid, including positivity, which was validated by a verification of stabilized weight of our sample. The average stabilized weights (maximum stabilized weight) among the entire population were 1.01 (3.00), 1.02 (3.3), 0.96 (2.97), 0.92 (2.58), and 0.89 (2.63) for the models with CD4/CD8 ratios of 0.3, 0.5, 0.8, 1, and 1.2, respectively. These results were similar for the analyses restricted to patients receiving a first treatment or to those receiving subsequent treatments. Consistency was validated using the Target Trials approach with a well-defined exposure [39]. Non-interference was archived by the fact that the exposure of 1 patient in 1 group does not affect the counterfactual result of another patient. Finally, most potential confounding factors known in the literature were considered, although we recognize that we could not adjust for adherence to ART and intravenous drug user status, and the absence of unmeasured confounders cannot be guaranteed. Residual confounding is also possible because of missing data for variables such as CMV serostatus.

Conclusions

Our study showed that INSTI-based ART seems better than NNRTI- and PI-based regimens for normalizing the CD4/CD8 ratio, a potential marker of reduced immune activation, among ART-treated PLHIV. Integrase strand transfer inhibitors are newer therapeutic agents that have demonstrated their virological efficacy with a higher genetic barrier to resistance among both treatment-naive patients receiving a first treatment and ART-treated PLHIV. Due to the association between a persistently low CD4/CD8 ratio and morbidity among PLHIV, it is important to determine the role of therapeutic classes in normalizing the CD4/CD8 ratio.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors,

so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. All authors of this research paper have directly contributed to the conception and design (H. T., M. N. S., J.-G. B., A. d. P., R. T., M. K., C. T., M. D.), or acquisition of data (M. N. S., J.-G. B., A. d. P., R. T., M. K., C. P., L. L., S. C., M. D., H. T.), or data management, analysis, and interpretation (M. N. S., H. T., J.-G. B., A. d. P.) of the study. M. N. S., H. T., J.-G. B., and A. d. P. wrote the first draft of the manuscript. All authors have subsequently read, revised, and approved the version that was submitted.

Acknowledgments. The authors are grateful to Anne-Fanny Vassal and Maliheh Vaziri (Clinique Médicale l'Actuel), Joseph Niyibizi (Sainte-Justine Hospital), Tudor Luncean and Stéphanie Matte (Centre Hospitalier de l'Université de Montréal), Jessica Lumia and Leo Wong (McGill University Health Center), and all other contributing research staff for their help in collecting and managing data in all sites.

Financial support. Funding for the Quebec HIV Cohort was provided by the Fonds de la Recherche du Québec en Santé (FRQS) Réseau SIDA et maladies infectieuses I. A. d. P. and M. D. hold salary awards (clinician researcher scholar) from the FLQS.

Potential conflicts of interest. H. T. has received unrestricted grants from ViiV Healthcare, Merck, and Gilead Sciences and occasional lecture fees from Merck. J.-G. B. has received honoraria for consulting for ViiV Healthcare, Merck, and Gilead Sciences and for participation as a speaker at conferences from Merck and Gilead Sciences unrelated to this work. His institution (Clinique de Médecine Urbaine du Quartier Latin [CMUQL]) has received research grants from GlaxoSmithKline, Merck, and Gilead Sciences. A. d. P.'s institution participates in several pharmaceutical clinical trials for HIV antiretrovirals and hepatitis C virus treatments in which she is the site principal investigator (ViiV Healthcare, Janssen, Merck, Gilead Sciences), and has received honoraria for consulting in advisory board meetings for ViiV Healthcare and Merck. R. T. has received honoraria for consulting for ViiV Healthcare, Merck, and Gilead Sciences, and for participation as a speaker at conferences from Merck and Gilead Sciences. His institution (Clinique Médicale l'Actuel [CMA]) has received research grants from GlaxoSmithKline, Gilead Sciences, Merck, and Janssen. S. C. reports grants or contracts from Canadian Institutes of Health Research (CIHR) Canada Graduate Scholarship—Master's (CGSM). C. T. reports grants or contracts from Merck, CIHR, Gilead, and the National Institutes of Health (NIH); consulting fees from Merck, GlaxoSmithKline, Medicago, Gilead, AstraZeneca, and Moderna; and payment or honoraria for manuscript writing or education event lectures for Merck, GlaxoSmithKline, AstraZeneca, Gilead, Pfizer, and Sanofi. Additionally, C. T. reports support for meetings and/or travel from Moderna and participation on a Data Safety Monitoring or Advisory Board for Colcorona, Dalcor, and Hesperidin. M. K. reports consulting fees from ViiV Healthcare, AbbVie, and Merck, as well as grants or contracts from ViiV Healthcare, AbbVie, Merck, and Gilead for an investigator-initiated study. M. D. reports operating grants from CIHR through the Public Health Agency of Canada and serves as the co-lead for the clinical management core of CIHR HIV Clinical Trial Network. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Sainz T, Serrano-Villar S, Díaz L, et al. The CD4/CD8 ratio as a marker T-cell activation, senescence and activation/exhaustion in treated HIV-infected children and young adults. AIDS **2013**; 27:1513–6.
2. Leung V, Gillis J, Raboud J, et al. Predictors of CD4:cD8 ratio normalization and its effect on health outcomes in the era of combination antiretroviral therapy. PLoS One **2013**; 8:e77665.
3. Serrano-Villar S, Sainz T, Lee SA, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. PLoS Pathog **2014**; 10:e1004078.
4. Zaaqoq AM, Khasawneh FA, Smalligan RD. Cardiovascular complications of HIV-associated immune dysfunction. Cardiol Res Pract **2015**; 2015:302638.
5. Deeks SG. HIV Infection, inflammation, immunosenescence, and aging. Annu Rev Med **2011**; 62:141–55.
6. Clifford GM, Rickenbach M, Lise M, et al. Hodgkin lymphoma in the Swiss HIV cohort study. Blood **2009**; 113:5737–42.
7. Serrano-Villar S, Pérez-Elías MJ, Dronda F, et al. Increased risk of serious non-AIDS-related events in HIV-infected subjects on antiretroviral therapy associated with a low CD4/CD8 ratio. PLoS One **2014**; 9:e85798.
8. Bernal E, Serrano J, Perez A, et al. The CD4:CD8 ratio is associated with IMT progression in HIV-infected patients on antiretroviral treatment. J Int AIDS Soc **2014**; 17(4 Suppl 3):19723.
9. Mussini C, Lorenzini P, Cozzi-Lepri A, et al. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: an observational cohort study. Lancet HIV **2015**; 2:e98–106.
10. Torti C, Prosperi M, Motta D, et al. Factors influencing the normalization of CD4+ T-cell count, percentage and CD4+/CD8+ T-cell ratio in HIV-infected patients on long-term suppressive antiretroviral therapy. Clin Microbiol Infect **2012**; 18:449–58.
11. Castilho JL, Bian A, Jenkins C, et al. Increased cancer risk with lower CD4/CD8 ratio among adults with HIV in NA-ACCORD. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 8–11 March 2020; Boston, Massachusetts.
12. Moeng LR, Byrne M, Monroe A, et al. Association of nadir CD4/CD8 with CVD and non-AIDS–defining cancers in the DC Cohort. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 6–11 March 2021; virtual.
13. Achenbach CJ, Joyce B, Hou L, et al. CD4/CD8 ratio as a predictor of HIV-associated cancers in CNICS. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 4–7 March 2019; Seattle, Washington.
14. Serrano-Villar S, Wu K, Hunt PW, et al. Predictive value of the CD8 counts and CD4/CD8 ratio at two years of successful art. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 8–11 March 2020; Boston, Massachusetts.
15. Novak RM, Armon C, Buchacz K, Li J, Ward D, Palella FJ. Aging, trends in CD4/CD8 ratio, and clinical outcomes with HIV suppression. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 8–11 March 2020; Boston, Massachusetts.
16. Friis-Møller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients–association with antiretroviral therapy. Results from the DAD study. AIDS **2003**; 17:1179–93.
17. Serrano-Villar S, Sainz T, Moreno S. Monitoring the CD4/CD8 ratio: a promising indicator of disease progression in HIV-infected individuals? Future Med **2015**; 10:1–4.
18. Saracino A, Bruno G, Scudeller L, et al. Chronic inflammation in a long-term cohort of HIV-infected patients according to the normalization of the CD4:CD8 ratio. AIDS Res Hum Retroviruses **2014**; 30:1178–84.
19. Autran B, Carcelaint G, Li TS, et al. Restoration of the immune system with antiretroviral therapy. Immunol Lett **1999**; 66(1–3):207–11.
20. Serrano-Villar S, Moreno S, Fuentes-Ferrer M, et al. The CD4:CD8 ratio is associated with markers of age-associated disease in virally suppressed HIV-infected patients with immunological recovery. HIV Med **2014**; 15:40–9.
21. Zheng L, Taiwo B, Gandhi RT, et al. Factors associated with CD8+ T-cell activation in HIV-1-infected patients on long-term antiretroviral therapy. J Acquir Immune Defic Syndr **2014**; 67:153–60.
22. Aziz N, Nishanian P, Fahey JL. Levels of cytokines and immune activation markers in plasma in human immunodeficiency virus infection: quality control procedures. Clin Diagn Lab Immunol **1998**; 5:755–61.
23. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med **2006**; 12:1365–71.
24. Kurz K, Teerlink T, Sarcletti M, Weiss G, Zangerle R, Fuchs D. Plasma concentrations of the cardiovascular risk factor asymmetric dimethylarginine (ADMA) are increased in patients with HIV-1 infection and correlate with immune activation markers. Pharmacol Res **2009**; 60:508–14.
25. Serrano-Villar S, Gutiérrez C, Vallejo A, et al. The CD4/CD8 ratio in HIV-infected subjects is independently associated with T-cell activation despite long-term viral suppression. J Infect **2013**; 66:57–66.
26. Ananworanich J, Sacdalan CP, Pinyakorn S, et al. Virological and immunological characteristics of HIV-infected individuals at the earliest stage of infection. J Virus Erad **2016**; 2:43–8.
27. Ndumbi P, Falutz J, Pant Pai N, Tsoukas CM. Delay in cART initiation results in persistent immune dysregulation and poor recovery of T-cell phenotype despite a decade of successful HIV suppression. PLoS One **2014**; 9:e94018.

28. Serrano-Villar S, Zhou Y, Rodgers AJ, Moreno S. Different impact of raltegravir versus efavirenz on CD4/CD8 ratio recovery in HIV-infected patients. J Antimicrob Chemother **2017**; 72:235–9.
29. Martínez E, D'Albuquerque PM, Llibre JM, et al. Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir. AIDS **2012**; 26:2315–26.
30. Asundi A, Robles Y, Starr T, et al. Immunological and neurometabolite changes associated with switch from efavirenz to an integrase inhibitor. J Acquir Immune Defic Syndr **2019**; 81:585–93.
31. Fabbiani M, Borghetti A, Squillace N, et al. Integrase inhibitors use and cytomegalovirus infection predict immune recovery in people living with HIV starting first-line therapy. J Acquir Immune Defic Syndr **2021**; 86:119–27.
32. Serrano-Villar S, Martínez-Sanz J, Ron R, et al. Effects of first-line antiretroviral therapy on the CD4/CD8 ratio and CD8 cell counts in CoRIS: a prospective multicentre cohort study. Lancet HIV **2020**; 7:e565–e73.
33. De Salvador-Guillouët F, Sakarovitch C, Durant J, et al. Antiretroviral regimens and CD4/CD8 ratio normalization in HIV-infected patients during the initial year of treatment: a cohort study. PLoS One **2015**; 10:e0140519.
34. Herrera S, Fernandez-Felix BM, Hunt PW, et al. Impact of first-line antiretroviral therapy regimens on the restoration of the CD4/CD8 ratio in the CNICS cohort. J Antimicrob Chemother **2020**; 75:1604–10.
35. Masiá M, Padilla S, Barber X, et al. Comparative impact of suppressive antiretroviral regimens on the CD4/CD8 T-cell ratio: a cohort study. Medicine (Baltimore) **2016**; 95:e3108.
36. Sangaré MN, Baril JG, de Pokomandy A, et al. Impact of previous HIV resistance and virologic failures on virologic outcome following a switch to dolutegravir with 2 NRTIs among people living with HIV. Medicine (Baltimore) **2020**; 99:e23335.
37. Sangaré MN, Baril JG, de Pokomandy A, et al. Treatment switch to dolutegravir with 2 nucleoside reverse-transcriptase inhibitors (NRTI) in comparison to continuation with protease inhibitor/ritonavir among patients with human immunodeficiency virus at risk for prior NRTI resistance: a cohort analysis of real-world data. Open Forum Infect Dis **2020**; 7:ofaa404.
38. Thomas R, Machouf N, Dufresne S, et al. La Cohorte De Montréal—Registre De Données Communes Vih. **2011**. https://www.reseausidami.quebec/cohortes-et-banques-de-recherche/cohorte-vih-du-quebec/. Accessed March 2022.
39. Hernán MA, Robins JM. Using Big Data to emulate a target trial when a randomized trial is not available. Am J Epidemiol **2016**; 183:758–64.