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Differential CD4+ cell count increase and CD4+ :CD8+ ratio normalization with maraviroc compared with tenofovir

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Abstract

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Author contributions

All authors played a role in editing the manuscript and approving the text as submitted.
BT and TB and were responsible for study conceptualization and design.
EC and HR performed the statistical analyses.
AL, JP, and JM performed the laboratory assays.
EC and BT wrote the manuscript.
EC, AL, TB, HR, PM, IO, MNW, JM, KK, JE, CF, JP, and BO revised the manuscript critically for important intellectual content, and approved the final version.
EC, HR, AL, and BT take responsibility for the integrity of the data and the accuracy of the data analysis.

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Objective—Studies exploring the immunologic effects of maraviroc (MVC) have produced mixed results; hence it remains unclear whether MVC has unique immunologic effects in comparison to other antiretroviral drugs. We sought to determine whether MVC has differential effects compared to tenofovir disoproxil fumarate (TDF) during initial antiretroviral therapy.

Design—Prospective study in AIDS Clinical Trials Group A5303, a double-blind, placebo-controlled trial (N=262) of MVC versus TDF, each combined with boosted darunavir and emtricitabine

Methods—A total of 31 cellular and soluble biomarkers were assayed at weeks 0 and 48. Polychromatic flow cytometry was performed on cryopreserved peripheral blood mononuclear cells (PBMC). Soluble markers were assayed in plasma using ELISA kits. Analyses were as-treated.

Results—Analyses included 230 participants (119 in MVC arm and 111 in TDF arm). Over 48 weeks of treatment, no significant differences were detected in declines in markers of inflammation and activation with MVC versus TDF. A greater $CD4^+$ T-cell count increase (median +234 cells/μl vs. +188 cells/μl, p=0.036), a smaller $CD8^+$ T-cell count decrease (−6 cells/μl vs. −109 cells/μl, p=0.008) and a smaller $CD4^+$:$CD8^+$ ratio increase (0.26 vs. 0.39, p=0.003) occurred with MVC. Among participants with baseline $CD4^+$:$CD8^+$ ratio<1, smaller proportion of MVC group normalized to ratio >1 at week 48 (15% and 36%, p<0.001).

Conclusions—MVC resulted in less improvement in $CD4^+$:$CD8^+$ ratio driven by greater increase in $CD4^+$ count but smaller decline in $CD8^+$ count. Changes in soluble or cellular biomarkers of inflammation and immune activation were not different between MVC and TDF.

Keywords

HIV; maraviroc; tenofovir; inflammation; CD4 Lymphocyte count; CD4-CD8 ratio

Introduction

HIV-induced immune dysfunction is not completely restored by ART [1]. Elevated soluble markers of inflammation and coagulation during ART predict non-AIDS events [2]. T-cell populations may also remain numerically abnormal and $CD4^+$:$CD8^+$ T-cell ratio often fails to normalize to >1 despite viral suppression [3]. The likelihood of attaining $CD4^+$:$CD8^+$ T-cell ratio >1 may be influenced by the ART regimen [4], and a low ratio independently predicts non-AIDS defining events and death [3, 5]. Studies exploring the immunologic effects of maraviroc (MVC) have produced mixed results, hence it remains unclear whether MVC has unique immunologic effects in comparison to other antiretroviral drugs [6, 7, 8].

We recently reported less bone loss in 48 weeks of an initial MVC-containing regimen compared to a tenofovir disoproxil fumarate (TDF)-containing combination in AIDS Clinical Trials Group (ACTG) study A5303 [9]. Virologic efficacy was not different between the two arms [9]. Here, we present the immunology results. The immunology objective of A5303 was to determine whether the effects of MVC on inflammation, immune activation and T-cell reconstitution in the context of initial ART could be differentiated from the effects of TDF.

Methods

ACTG A5303 was a phase II, prospective, double-blind, placebo-controlled, multicenter, 48-week study of an experimental regimen (MVC arm: darunavir /ritonavir [DRV/r] 800/100 mg + emtricitabine [FTC] 200mg + MVC 150mg QD) compared to a standard of care regimen (TDF arm: DRV/r 800/100 mg+ FTC 200mg + TDF 300mg QD) in antiretroviral (ARV)-naive adults infected with C-C chemokine receptor type 5 (CCR5)-tropic HIV-1. HIV-1 tropism was determined using Trofile (Monogram Biosciences, San Francisco, California, USA). Eligibility required HIV-1 RNA > 1,000 copies/mL and no evidence of active hepatitis B. Randomization was stratified by plasma HIV-1 RNA < or ≥ 100,000 copies/mL and age < or ≥ 30 years. Details for the study designs were described in the primary manuscript [9]. The Institutional Review Board of each study site approved the protocol. Each participant provided a written informed consent (Clinicaltrials.gov identifier NCT01400412). The study enrolled 262 participants in the United States.

Polychromatic flow cytometry was performed in batch on week 0 and 48 cryopreserved peripheral blood mononuclear cells (PBMCs) from each participant. In brief, cellswere stained for viability with Aqua Live/Dead (Life Technologies, Eugene, Oregon, USA) followed by cell staining using fluorochrome-conjugated monoclonal antibodies (BD Biosciences, San Jose, California, USA; BioLegend, San Diego, California, USA; eBiosciences, Inc., San Diego, California, USA). PBMC were stained for T-cell subsets (CD3/CD4, CD3/CD8) and associated markers of immune activation (CD38/HLA-DR), senescence (CD57/CD28), and T-regulatory (CD25/FOXP3) cells. In a separate tube, PBMC were stained for markers of monocyte subsets (CD14/CD16/CCR2/CX3CR1), B cells (CD19/FcRL4), and natural killer (NK) cell subsets (CD56/CD16). All tubes were fixed in 1% formaldehyde and analyzed within 24 h on an LSRFortessa flow cytometer (BD Biosciences) using BD FACSDiva software v7.0. Analysis of flow cytometry data was performed using FlowJo software (FlowJo, LLC, Ashland, Oregon, USA).

Frozen\thawed week 0 and 48 EDTA plasma samples were analyzed using ELISA kits for quantification of soluble (s) CD14, sCD163, interferon gamma induced protein (IP)-10, soluble tumor necrosis factor receptor (sTNFR) II, and high-sensitivity interleukin (IL)-6 (all Quantikine; R & D Systems, Inc., Minneapolis, Minnesota, USA). D-dimer was measured in citrate plasma using an ELISA kit from Diagnostica Stago, Inc. (Parsippany, New Jersey, USA). All ELISAs were run according to the manufacturers' protocols.

Statistical analyses

All analyses were as-treated and included only participants who remained on their randomized MVC or TDF component by week 48 without an interruption in treatment of more than 10 weeks with available data for both baseline and week 48. Participants with missing data due to insufficient blood samples, data errors, or lab errors were further excluded from the analyses.

Wilcoxon signed rank tests were used to test for within treatment arm changes greater than zero; 95% confidence intervals (CI) for median changes within treatment arm were estimated using distribution-free method via percentiles. Stratified Wilcoxon rank sum tests

were used to test for treatment arm differences, stratified by the age stratum (<30 vs. ≥ 30 years). Among participants with inverted $CD4^+$:$CD8^+$ ratio (ratio < 1) at baseline, treatment arm differences in $CD4^+$:$CD8^+$ ratio normalization (ratio >1) [4] over 48 weeks were assessed with Fisher's tests. In addition, proportions of participants with $CD4^+$:$CD8^+$ ratio >0.4 [5] were also evaluated with Fisher's test. Changes in soluble biomarkers and $CD4^+$ / $CD8^+$ counts were assessed on the absolute changes from baseline to week 48, whereas changes in percentage expression for cellular biomarkers were assessed as percentage change (i.e. 100% x (week 48 – week 0) / week 0).

All statistical tests were two-sided and presented with nominal p-values. To account for the large number of soluble and cellular markers tested, p-values for treatment arm comparisons for these markers were conservatively interpreted at the 0.5% nominal level of significance; conclusions regarding p-values between 0.05 and 0.005 were tempered. Given the prior data with MVC with respect to changes in $CD4^+$ T-cell count changes, inferences regarding $CD4^+$, $CD8^+$, and their ratio were interpreted at a conventional 5% level. Analyses were conducted using SAS statistical software 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Results

A total of 230 participants were in the as-treated population (119 in the MVC arm and 111 in the TDF arm). There were 9% female; 44% White, 31% Black, 22% Hispanic. The median age at baseline was 33 years, median VL was 4.5 $\log_{10}$ copies/mL and median $CD4^+$ count was 390 cells/μl.

$CD4^+$ and $CD8^+$ T-cell Counts

A greater $CD4^+$ T-cell count increase from baseline to week 48 was observed in the MVC arm (median change 234 cells/μl [Q1, Q3: 131, 327]) than in the TDF group (188 cells/μl [94, 304]; p=0.036). While significant within arm decreases in CD8 T-cell count were observed over 48 weeks in TDF arm (median change −109 cells/μl [−340, 59]; p<0.001), these were not apparent with MVC (−6 cells/μl [−252, 175]; p=0.51); between arm comparison (p=0.008). In turn, a smaller increase in $CD4^+$:$CD8^+$ ratio from baseline to week 48 was observed in the MVC arm than in the TDF arm (p=0.003); median (Q1, Q3) change 0.26 (0.13, 0.43) in the MVC arm compared with 0.39 (0.21, 0.54) in the TDF arm (Table 1).

Among 215 participants with $CD4^+$:$CD8^+$ ratio<1 at baseline (n=110 in MVC, n=105 in TDF), 15% and 36% of the participants in the MVC arm and TDF arm respectively had normalized $CD4^+$:$CD8^+$ ratio (ratio >1) at week 48 (p<0.001). Using a $CD4^+$:CD8 ratio cut-off of 0.4, there was no significant difference between the two arms (p=0.93): 90% and 88% on MVC versus TDF arm with ratio >0.4 at week 48.

Soluble biomarkers

With the exception of IL-6 and sCD14, significant declines in all soluble biomarkers from baseline to week 48 in both treatment arms were apparent (p<0.001). For IL-6 and sCD14, declines were apparent in the MVC arm (p=0.007 and 0.001, respectively) but not the TDF

arm (p=0.12 and 0.41, respectively). Differences between the two treatment arms were not apparent in any of these soluble biomarkers (p>0.10) (Table 1).

Cellular biomarkers (CD4 and CD8 subsets, monocytes, B cells and NK cells)

Although significant within-group changes in a range of the CD4, CD8, or monocyte subsets examined were apparent, there was no evidence of differences between MVC and TDF arms (p>0.05) (Table 2). Of note, while the treatment arm difference in %increase in %CD56HI/CD16-(NK cells) approached our conservative threshold for statistical significance (p=0.007; median %change 4% [−23%, 64%] in the MVC arm compared to 30% [−2%, 89%] in the TDF arm the magnitude of these increases on an absolute scale were small (median absolute change 0.2% vs. 1.0%).

Discussion

In this randomized trial, initiating ART with a MVC-containing regimen resulted in significant declines in all soluble markers (IL-6, IP-10, sTNF-rII, sCD14, d-dimer, and sCD163) from weeks 0 to 48. Significant declines in the soluble biomarkers occurred in the TDF arm with the exception of IL-6 and sCD14. Overall, no significant differences were detected between MVC and TDF in the decline in any soluble marker in our study. Changes from baseline to week 48 in cellular markers of T-cell activation and senescence, and in monocyte, B cell and NK cell populations were also not different between MVC and TDF. We saw a treatment arm difference in %CD56HI/CD16-(natural killer cells) that was marginally significant, but the magnitudes of the increases were too small to be considered clinically meaningful. Given the comparable virologic efficacy of the MVC and TDF regimens in our study [9], the immunologic changes in both arms were likely driven mainly by suppression of viral replication. Of note, ACTG A5260s also found no significant decline in IL-6 and sCD14 levels among participants who received TDF/FTC plus DRV/r, although both markers declined significantly in the TDF/FTC plus raltegravir arm of the study [10].

Our results demonstrate that MVC produces a greater numerical increase in $CD4^+$ T-cells than TDF in initial ART (difference in median increase of 46 cells/μl), consistent with the greater improvement reported with MVC relative to efavirenz [11]. Meta regression of data from 17 clinical trials involving treatment-experienced participants also demonstrated that MVC use was associated with an additional gain of 30 $CD4^+$ T-cells/μl at 24 weeks [12]. An effect of MVC on $CD4^+$T-cell counts was previously demonstrated even when virologic suppression was not achieved [13].

$CD8^+$ T-cell count decreased significantly in the TDF arm but not the MVC arm. A potential explanation for this is that $CD8^+$ T cells are more likely to express CCR5 than $CD4^+$ T cells in circulation [6]; hence, CCR5 blockage may preferentially prevent trafficking of $CD8^+$ cells out of circulation, and result in a differential expansion of $CD8^+$ T cells. Consistent with this, although the $CD4^+$: $CD8^+$ T-cell ratio increased in both arms, the improvement was significantly smaller in the MVC arm. Further, among study participants with an inverted $CD4^+$: $CD8^+$ ratio (ratio <1) at baseline, normalization to a ratio greater than 1 occurred less frequently in the MVC arm. Although the clinical implications of these findings are uncertain, inversion of the $CD4^+$: $CD8^+$ ratio is a hallmark of

immunosenescence and an independent predictor of mortality [14]. Nevertheless, our findings on $CD4^+$:$CD8^+$ T-cell repopulation should be interpreted with caution since participants were followed for 48 weeks only and there is no evidence that MVC increases long-term morbidity or mortality. Using a $CD4^+$:$CD8^+$ ratio cut-off of 0.4 at week 48, which has been linked with risk of non-AIDS events during ART [3,5], we found no significant difference between MVC and TDF. Some investigators recently reported a strong association between use of an integrase strand transfer inhibitor in initial ART and normalization of $CD4^+$:$CD8^+$ T-cell ratio [4]. Future studies should delineate further how contemporary ART regimens differ in their effects on the $CD4^+$:$CD8^+$ T-cell ratio and also define the clinical consequences.

In summary, the randomized, placebo controlled A5303 clinical trial showed similar changes in markers of inflammation and activation in the first 48 weeks of MVC- or TDF-containing ART. The regimens differentiated with respect to CD4 and CD8 numerical reconstitution with higher $CD4^+$T-cell gain recorded in with MVC while normalization of $CD4^+$:$CD8^+$ ratio to >1 occurred more frequently with TDF.

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Appendix: Study Sites participated in ACTG A5303

- Massachusetts General Hospital
- Brigham and Women's Hospital
- Johns Hopkins University
- University of California, Los Aangeles CARE Center
- University of California, San Diego Antiviral Research Center
- University of California, San Francisco HIV/AIDS
- University of Miami, AIDS Clinical Research Unit
- Georgetown University
- University of Southern California
- University of Washington AIDS
- Washington University in St Louis
- Ohio State University
- University of Cincinnati
- Case Western University
- MetroHealth
- Northwestern University
- Rush University
- The Miriam Hospital
- University of North Carolina, Chapel Hill
- University of North Carolina, Greensboro
- Vanderbilt University
- IHV Baltimore Treatment
- Puerto Rico AIDS Clinical Trials Unit
- The Ponce de Leon Center, Emory University
- University of Colorado Hospital
- University of Pennsylvania
- Columbia Physicians and Surgeons
- Trinity Health and Wellness Center
- Houston AIDS Research Team
- Cooper University Hospital

- University of Rochester, Adult HIV Therapeutics
- University of Alabama
- University of South Florida
- Children’s National Medical Center
- St. Jude Children’s Research Hospital
- Texas Children’s Hospital
- University of Colorado, Denver

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Table 1

Summary of soluble biomarkers and CD4/CD8 counts change from baseline to week 48 by treatment arm

Marker	Treatment Arm	N	Baseline Median (Q1, Q3)	Absolute Change Median (Q1, Q3)	95% CI for Change Median	p-value (within group)[a]	p-value (between group)[b]
IL-6 [pg/mL]	MVC	116	1.48 (0.98, 2.42)	−0.21 (−0.91, 0.25)	(−0.31, −0.03)	0.007	0.50
	TDF	107	1.77 (1.14, 2.49)	−0.12 (−0.83, 0.42)	(−0.33, 0.08)	0.12	
Ip-10 [pg/mL]	MVC	116	363 (235, 564)	−198 (−366, −91)	(−243, −148)	<0.001	0.75
	TDF	107	354 (244, 551)	−170 (−310, −97)	(−232, −138)	<0.001	
sTNF-rII [pg/mL]	MVC	115	3619 (2826, 4409)	−1108 (−1658, −597)	(−1389, −876)	<0.001	0.54
	TDF	102	3751 (3146, 4301)	−1198 (−1875, −641)	(−1431, −1042)	<0.001	
sCD14 [pg/mL]	MVC	116	17779 (15464, 23281)	−1178 (−3478, 1032)	(−1558, −149)	0.001	0.17
	TDF	107	18526 (15511, 29902)	−103 (−2991, 2627)	(−1714, 1037)	0.41	
D-dimer [ng/mL]	MVC	115	266 (162, 429)	−82 (−210, −1)	(−133, −51)	<0.001	0.65
	TDF	106	231 (146, 434)	−61 (−211, −7)	(−94, −40)	<0.001	
sCD163 [ng/mL]	MVC	116	810 (579, 1145)	−250 (−469, −129)	(−309, −216)	<0.001	0.87
	TDF	107	850 (652, 1064)	−258 (−458, −136)	(−325, −209)	<0.001	
CD4 Count [cells/μl]	MVC	117	385 (295, 493)	234 (131, 327)	(195, 262)	<0.001	0.036
	TDF	111	391 (279, 518)	188 (94, 304)	(147, 226)	<0.001	
CD8 Count [cells/μl]	MVC	117	867 (686, 1141)	−6 (−252, 175)	(−38, 61)	0.51	0.008
	TDF	111	863 (575, 1227)	−109 (−340, 59)	(−173, −56)	<0.001	
CD4:CD8 Ratio	MVC	117	0.43 (0.32, 0.60)	0.26 (0.13, 0.43)	(0.21, 0.34)	<0.001	0.003
	TDF	111	0.48 (0.30, 0.68)	0.39 (0.21, 0.54)	(0.31, 0.43)	<0.001	

[a] Wilcoxon signed rank p-value evaluating the within treatment group changes from baseline.

[b] Stratified Wilcoxon rank sum p-value evaluating the difference in changes from baseline between the two treatment groups, stratified by age (<30 and ≥30 years).

CI, confidence interval; IP-10, induced protein 10; MVC, maraviroc; TDF, tenofovir disoproxil fumarate; sTNF-rII, soluble tumor necrosis factor receptor II.

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Table 2

Summary of cellular biomarkers percentage change from baseline to week 48 by treatment arm

Marker	Treatment Arm	N	Baseline Median (Q1, Q3)	%Change Median (Q1, Q3)[a]	95% CI for %Change Median[a]	p-value (within group)[b]	p-value (between group)[c]
Percent CD38+/HLA−DR+(CD4+) [%]	MVC	115	6.0 (3.8, 10.1)	−52.1 (−60.8, −34.4)	(−56.0, −46.5)	<0.001	0.81
	TDF	108	6.1 (3.9, 10.0)	−48.6 (−65.3, −31.0)	(−55.1, −42.1)	<0.001	
Percent CD28−/CD57+(CD4+) [%]	MVC	115	5.5 (2.6, 10.8)	−14.7 (−46.5, 20.0)	(−27.0, −3.9)	0.047	0.53
	TDF	108	6.9 (2.5, 11.8)	−26.6 (−44.7, 18.6)	(−32.0, −17.3)	0.032	
Percent CD57+(CD4+) [%]	MVC	115	11.8 (8.1, 18.0)	−5.7 (−24.9, 17.8)	(−13.9, 4.4)	0.23	0.35
	TDF	108	13.4 (8.7, 20.3)	−11.0 (−28.0, 14.5)	(−17.1, −3.4)	0.015	
Percent CD28+(CD4+) [%]	MVC	115	87.5 (81.6, 93.0)	0.3 (−6.2, 4.9)	(−1.2, 1.6)	0.70	0.23
	TDF	108	87.4 (79.5, 93.2)	2.1 (−4.0, 7.0)	(−0.1, 3.2)	0.057	
Percent Treg+(CD4+) [%]	MVC	115	9.6 (7.8, 12.3)	−13.7 (−26.7, 2.6)	(−20.5, −7.1)	<0.001	0.10
	TDF	108	9.8 (7.9, 12.4)	−9.0 (−21.9, 7.8)	(−14.6, −3.1)	0.002	
Percent CD4 [%]	MVC	115	36.2 (26.6, 45.3)	21.9 (7.8, 42.0)	(15.2, 30.3)	<0.001	0.91
	TDF	108	39.4 (27.4, 46.6)	20.2 (7.6, 46.7)	(13.9, 29.0)	<0.001	
Percent CD38+/HLA−DR+(CD8+) [%]	MVC	115	22.0 (14.4, 29.8)	−59.5 (−70.5, −43.5)	(−63.1, −54.4)	<0.001	0.26
	TDF	108	20.3 (14.7, 31.0)	−60.9 (−71.3, −49.4)	(−66.0, −57.4)	<0.001	
Percent CD28−/CD57+(CD8+) [%]	MVC	115	47.2 (38.6, 55.2)	−5.5 (−19.8, 11.2)	(−8.7, 0.0)	0.052	0.97
	TDF	108	47.8 (39.4, 55.9)	−4.7 (−18.5, 9.9)	(−11.4, 1.9)	0.080	
Percent CD57+(CD8+) [%]	MVC	115	60.1 (50.7, 68.6)	−3.5 (−16.9, 6.5)	(−9.3, −1.5)	0.003	0.78
	TDF	108	60.9 (51.0, 68.8)	−4.6 (−18.4, 6.6)	(−9.5, −0.5)	0.004	
Percent CD28+(CD8+) [%]	MVC	115	40.0 (31.2, 49.4)	11.9 (−6.0, 37.0)	(6.1, 19.1)	<0.001	0.63

Marker	Treatment Arm	N	Baseline Median (Q1, Q3)	%Change Median (Q1, Q3)[a]	95% CI for %Change Median[a]	p-value (within group)[b]	p-value (between group)[c]
	TDF	108	39.4 (32.8, 50.6)	14.0 (−2.6, 38.4)	(9.7, 23.0)	<0.001	
Percent CD8 [%]	MVC	115	56.6 (46.1, 66.1)	−11.5 (−21.8, −3.5)	(−16.4, −8.8)	<0.001	0.44
	TDF	108	50.7 (44.8, 65.8)	−13.4 (−22.8, −5.9)	(−17.3, −10.0)	<0.001	
Percent CD14++CD16− (total monocytes) [%]	MVC	115	86.9 (80.1, 92.0)	1.0 (−1.8, 7.4)	(−0.0, 3.2)	0.003	0.16
	TDF	109	85.2 (79.1, 91.4)	3.5 (−1.8, 9.6)	(2.3, 5.3)	<0.001	
Percent CD14++CD16+(total monocytes) [%]	MVC	115	6.2 (4.1, 9.3)	−31.5 (−55.1, 1.1)	(−39.6, −19.7)	<0.001	0.075
	TDF	109	7.3 (3.9, 10.6)	−41.9 (−58.4, −17.7)	(−50.5, −33.6)	<0.001	
Percent CD14+CD16++(total monocytes) [%]	MVC	115	6.5 (3.3, 11.5)	−0.4 (−40.4, 72.6)	(−12.1, 22.4)	0.048	0.57
	TDF	109	6.5 (3.9, 10.1)	−5.7 (−36.7, 56.3)	(−20.0, 17.3)	0.26	
Percent CCR2+(CD14++CD16+) [%]	MVC	115	46.4 (32.8, 58.8)	−14.6 (−31.2, 16.6)	(−20.7, −3.3)	0.10	0.67
	TDF	109	48.0 (35.9, 62.7)	−8.9 (−32.4, 19.6)	(−14.4, 0.0)	0.16	
Percent CX3CR1+(CD14++CD16+) [%]	MVC	115	52.1 (40.4, 65.2)	12.0 (−14.2, 31.6)	(0.5, 19.3)	0.021	0.66
	TDF	109	51.8 (36.5, 62.8)	6.9 (−13.1, 36.9)	(0.4, 16.0)	0.007	
Percent Total CD19+ [%]	MVC	115	6.1 (4.0, 8.8)	9.8 (−18.7, 40.7)	(1.2, 22.9)	0.001	0.73
	TDF	109	5.4 (3.5, 8.5)	5.5 (−19.1, 44.3)	(−4.5, 21.6)	0.017	
Percent FcRL4+(CD19+) [%]	MVC	115	5.9 (4.6, 8.1)	−36.9 (−55.4, −15.8)	(−44.6, −31.0)	<0.001	0.31
	TDF	109	5.7 (4.2, 8.1)	−35.0 (−53.6, −11.0)	(−42.4, −25.9)	<0.001	
Percent CD56HI/CD16− (NK cells) [%]	MVC	115	3.8 (2.3, 6.5)	4.2 (−23.2, 64.0)	(−7.5, 25.4)	0.006	0.007
	TDF	109	3.7 (2.3, 6.7)	29.6 (−1.8, 88.5)	(20.6, 46.4)	<0.001	
Percent CD56dim/CD16− (NK cells) [%]	MVC	115	5.6 (3.7, 9.3)	−1.6 (−38.7, 45.4)	(−14.2, 14.0)	0.44	0.57
	TDF	109	5.8 (3.6, 8.8)	6.2 (−32.1, 57.6)	(−12.2, 18.5)	0.092	
Percent CD56+/CD16+(NK cells) [%]	MVC	115	64.3 (48.1, 74.6)	9.9 (−0.2, 21.6)	(5.6, 12.3)	<0.001	0.66

Marker	Treatment Arm	N	Baseline Median (Q1, Q3)	%Change Median (Q1, Q3)[a]	95% CI for %Change Median[a]	p-value (within group)[b]	p-value (between group)[c]
	TDF	109	62.0 (49.7, 73.3)	6.4 (−2.2, 29.4)	(3.8, 11.5)	<0.001	
Percent CD56−/CD16+(NK cells) [%]	MVC	115	20.1 (14.0, 37.7)	−25.3 (−38.9, −3.9)	(−30.3, −18.1)	<0.001	0.77
	TDF	109	23.5 (13.0, 32.8)	−25.8 (−44.9, 1.0)	(−32.0, −19.6)	<0.001	

[a] Percentage change from week 0 to week 48 (%), defined as ((w48-w0)/w0) x100%

[b] Wilcoxon signed rank p-value evaluating the within treatment group percentage changes from baseline.

[c] Stratified Wilcoxon rank sum p-value evaluating the difference in percentage changes from baseline between the two treatment groups, stratified by age (<30 and ≥30 years).

CI, confidence interval; MVC, maraviroc; TDF, tenofovir disoproxil fumarate; NK, natural killer.