

HHS Public Access

Author manuscript *AIDS*. Author manuscript; available in PMC 2017 August 24.

Published in final edited form as:

AIDS. 2016 August 24; 30(13): 2091–2097. doi:10.1097/QAD.00000000001181.

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

Ellen S. CHAN¹, Alan L. LANDAY², Todd T. BROWN³, Heather J. RIBAUDO¹, Paria MIRMONSEF², Igho OFOTOKUN⁴, M. Neale WEITZMANN⁵, Jeffrey MARTINSON², Karin L. KLINGMAN⁶, Joseph J. ERON⁷, Carl J. FICHTENBAUM⁸, Jill PLANTS², and Babafemi O. TAIWO⁹

Babafemi O. TAIWO: b-taiwo@northwestern.edu

¹Statistical and Data Analysis Center, Harvard Chan School of Public Health, Boston, MA

²Department of Immunology/Microbiology, Rush University Medical Center, Chicago, IL

³Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University, Baltimore, MD

⁴Division of Infectious Diseases, Emory University, Atlanta, GA

⁵Division of Endocrinology and Metabolism and Lipids, Emory University, Atlanta, GA, and Atlanta VA Medical Center, Decatur, GA

⁶HIV Research Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, MD

⁷Division of Infectious Diseases, University of North Carolina, Chapel Hill, NC

⁸Division of Infectious Diseases, University of Cincinnati, OH

⁹Division of Infectious Diseases, Northwestern University, Chicago, IL

Abstract

CORRESPONDENCE: Ellen S. Chan, M.Sc, Mailing address: Harvard Chan School of Public Health, 651 Huntington Ave, FXB 539, Boston, MA 02115, USA, echan@sdac.harvard.edu, Telephone: 617-432-4879, Fax: 617-432-2832.

PRIOR PRESENTATIONS: This work was presented at the Conference on Retroviruses and Opportunistic Infections 2016 (February 22–25, 2016, Abstract #695LB) in Boston, Massachusetts

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.

CONFLICTS OF INTEREST: B.O.T. has served as a consultant to ViiV, Pfizer, Janssen, GlaxoSmithKline (GSK), and Gilead Sciences, and has received research support to Northwestern University from ViiV Healthcare and Pfizer. C.J.F.'s institution receives research funding from Gilead, Pfizer, BMS, ViiV, Janssen, and Cubist. J.J.E. has served as consultant to Gilead, Merck, BristolMyers Squibb (BMS), ViiV, and Janssen. The University of North Carolina School of Medicine has received research support for projects led by J.J.E. from ViiV, Janssen, and Gilead. A.L.L. has served on the scientific advisory board for Merck and has provided scientific consultation to GSK, BMS, and Tobira. I.O. receives research funding to Emory University from BMS. T.T.B. has served as a consultant for BMS, GSK, Merck, AbbVie, Gilead, ViiV, Theratechnologies, and EMD-Serono and has received research funding from Merck and GSK. All other authors report no potential conflicts.

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, placebocontrolled 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 astreated.

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, 48week 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 cutoff 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/ μ l), 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/ μ l 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.

Acknowledgments

Sources of Funding

This work was supported by [Award Number U01AI068636] from the National Institute of Allergy and Infectious Diseases and supported by National Institute of Mental Health (NIMH), National Institute of Dental and Craniofacial Research (NIDCR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health. This work was also supported by grants from the NIH ([grant numbers AI068634 and AI068636] to the ACTG Statistical Data Analysis Center [to E.S.C. and H.J.R.], [grant number AI068636] to the Rush University Medical Center [to A.L.L., P.M, J.M, and J.P.], and to the research sites that participated in the study [grant numbers UMAI069494, UMAI069432, UM1AI 069471, UM1AI069452, UM1 AI069501, 2UM1AI069432, UL1 TR001082, 1U01AI069477-01, P30AI073961, 5UM1 AI068636, 2UM1AI069503, UM1 AI069471, 2UM1AI069439-08, and UL1 TR000445 from the National Center for Advancing Translational Sciences/NIH, AI69439, UM1 AI069496, 5UM1AI069412, UM1 AI069423, 1UL1TR001111, P30 AI50410, 2UMIA1069423-08, 2UM1AI069418-08, 2P30 AI 50409-10, UL1TR000454, AI069501, 5UM1AI069415-10, 2UM1AI069412-08, AI069424, UL1 RR025780, 2UM1-AI069470-08, UM1AI069472, 2UMAI069432, AI 69501, UM1AI069471, UM1A 068636-09, 5 P30 AI-045008-15, U01AI069447, NO1-HD-3-3345, UMI AI069511, UM1 AI069465, UL1TR001079, UL1 RR024160, and UL1 TR000042]). ViiV, Gilead, and AbbVie provided study drugs. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

We wish to gratefully acknowledge all of the A5303 study participants who have devoted their time and effort to this research endeavor. We also would like to acknowledge the additional members of the A5303 study team who contributed to the study: Denise Barr (clinical trials specialist), Ana I. Martinez (Division of AIDS pharmacist), Robert Kalayjian, Allan Tenorio, and Cara Wilson (investigators), Edward Acosta (pharmacologist), Athe Tsibris (Virologist), Baiba Berzins (field representative), David Rusin (data manager), Amy Gonzales (laboratory data manager), Orlando Roman (community representative), Jaylene Allred and Kimberley Brown (Janssen), Srinivas Rao Valluri (Pfizer), Kathy Melbourne and James Rooney (Gilead), Alex Reinhart (ViiV), Roula Qaqish and John Arkins (AbbVie), and Laura Napolitano, Charles Walworth, and Christos Petropoulos (LabCorp). We gratefully acknowledge the research sites and personnel who participated in this study: Ohio State University (John Davis, Mark Hite); University of California, San Diego Antiviral Research Center (Edward Seefried, Constance Benson); Northwestern University (Nina Lambert, Karen Coleman); University of Alabama (Messer, Tamara James); University of Cincinnati (Amy Dill, Jenifer Baer); University of Colorado Hospital (Christine Griesmer, Cathi Basler); University of Miami (Hector Bolivar, Margaret A. Fischl); Houston AIDS Research Team (Roberto C. Arduino, Aristoteles E. Villamil); Rush University (Beverly Sha, Tondria Green); Vanderbilt University (Brenda Jackson, Fred Nicotera); Washington University in St Louis (GeYoul Kim, Mark Rodrieguez); University of California, San Francisco (Annie Luetkemeyer, Jay Dwyer); The Miriam Hospital (Pamela Poethke, Aadia Rana); University of Carolina, Chapel Hill (Miriam Chicurel-Bayard, Megan Telfer); University of North Carolina at Greensboro research site (Cornelius van Dam, Timothy Lane); Ponce de Leon Center, Emory University (Ighovwerha Ofotokun, Melody Palmore); Case Western University (Patricia Walton, Felicia Williams); Puerto

Rico Clinical Trials Unit (Jorge L. Santana, Olga I. Mendez); University of Pennsylvania (Pablo Tebas, Aleshia Thomas); Massachusetts General Hospital (Teri Flynn, ANP-BC, Amy Sbrolla); University of California, Los Angeles CARE Center (Raphael Landovitz, Vanessa Cajahuaringa); University of Washington AIDS CRS (Shelia Dunaway, Sheryl Storey); Johns Hopkins University (Ilene Wiggins, Andrea Weiss); University of Colorado (Daniel Reirden, Hannah Bernath); Columbia Physicians and Surgeons (Michael Yin, Jolene Noel-Connor); Cooper University Hospital (Rose Kim, Yolanda Smith); Brigham and Women's Hospital (Paul Sax, Cheryl Keenan); Georgetown University (Princy Kumar, Joseph Timpone); University of Southern California (Michael P. Dubé, Bartolo Santos); and University of Rochester (Mary Adams, Christine Hurley).

References

- Wada NI, Jacobson LP, Margolick JB, Breen EC, Macatangay B, Penugonda S, et al. The effects of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS. 2015; 29(4):463–471. [PubMed: 25630041]
- Tenorio A, Zheng Y, Bosch RJ, Krishnan S, Rodriguez B, Hunt PW, et al. Soluble markers of inflammation and coagulation but not T-cell activation predict non-AIDS-defining morbid events during suppressive antiretroviral treatment. Journal Infect Dis. 2014; 210:1248–59. [PubMed: 24795473]
- Mussini C, Lorenzini P, Cozzi-Lepri A, Lapadula G, Marchetti G, Nicastri E, 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(3):e98– 106. [PubMed: 26424550]
- 4. De Salvador-Guillouët F, Sakarovitch C, Durant J, Risso K, Demonchy E, Roger PM, 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(10):e0140519. [PubMed: 26485149]
- Serrano-Villar S, Perez-Elias MJ, Dronda F, Casado JL, Moreno A, Royuela A, 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(1):e85798. [PubMed: 24497929]
- 6. Hunt PW, Shulman NS, Hayes TL, Dahl V, Somsouk M, Funderburg NT, et al. The immunologic effects of maraviroc intensification in treated HIV-infected individuals with incomplete CD4+ T-cell recovery: a randomized trial. Blood. 2013; 121(23):4635–46. [PubMed: 23589670]
- Wilkin TJ, Lalama CM, McKinnon J, Gandhi RT, Lin N, Landay A, et al. A pilot trial of adding maraviroc to suppressive antiretroviral therapy for suboptimal CD4⁺ T-cell recovery despite sustained virologic suppression: ACTG A5256. J Infect Dis. 2012; 206(4):534–42. [PubMed: 22740718]
- Funderburg N, Kalinowska M, Eason J, Goodrich J, Heera J, Mayer H, et al. Effects of maraviroc and efavirenz on markers of immune activation and inflammation and associations with cell rises in HIV-1 infected patients. PLos. 2010; 5(10):e13188.
- Taiwo BO, Chan ES, Fichtenbaum CJ, Ribaudo H, Tsibris A, Klingman KL, et al. Less Bone Loss With Maraviroc- Versus Tenofovir-Containing Antiretroviral Therapy in the AIDS Clinical Trials Group A5303 Study. Clin Infect Dis. 2015; 61(7):1179–88. [PubMed: 26060295]
- Kelesidis T, Tran TT, Stein JH, Brown TT, Moser C, Ribaudo HJ, et al. Changes in Inflammation and Immune Activation With Atazanavir-, Raltegravir-, Darunavir-Based Initial Antiviral Therapy: ACTG 5260s. Clin Infect Dis. 2015; 61(4):651–60. [PubMed: 25904376]
- Cooper DA, Heera J, Ive P, Botes M, Dejesus E, Burnside R, et al. Efficacy and safety of maraviroc vs. efavirenz in treatment-naïve patients with HIV-1: 5-year finding. AIDS. 2014; 28(5):717–25. [PubMed: 24983542]
- Wilkin TJ, Ribaudo HR, Tenorio AR, Gulick RM. The relationship of CCR5 antagonists to CD4+ T-cell gain: a meta-regression of recent clinical trials in treatment-experienced HIV-infected patients. HIV Clin Trials. 2010; 11(6):351–8. [PubMed: 21239363]
- Fätkenheuer G, Nelson M, Lazzarin A, Konourina I, Hoepelman A, Lamprirs H, et al. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. N Engl J Med. 2008; 359(14): 1442–55. [PubMed: 18832245]
- Wikby A, Maxson P, Olsson J, Johansson B, Ferguson FG. Changes in CD8 and CD4 lymphocyte subsets, T cell proliferation responses and non-survival in the very old: the Swedish longitudinal OCTO-immune study. Mech Ageing Dev. 1998; 102(2–3):187–98. [PubMed: 9720651]

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

\rightarrow
<
<u> </u>
t
_
5
U.
_
~
ູ
~
2
nusc
nus
nusc
nuscr

~
Φ
Q
Та

С
t arm
B
÷
Ę.
ЭE
treatm
at
9
₽
>
48 b
∞
4
week
j O
e.
5
0
e from baseline to
e
Ξ.
5
S
)a
from b
Ξ
ō
Ę.
(h)
D
change
la
5
<u> </u>
~
ts
ints ch
ounts
counts
8 counts
8 cour
CD8 counts
/CD8 counts
4/CD8 counts
D4/CD8 counts
CD4/CD8 counts
d CD4/CD8 counts
nd CD4/CD8 counts
and CD4/CD8 counts
s and CD4/CD8 counts
ers and CD4/CD8 counts
kers and CD4/CD8 counts
D4/CD
narkers and CD4/CD
biomarkers and CD4/CD
biomarkers and CD4/CD
biomarkers and CD4/CD
biomarkers and CD4/CD
biomarkers and CD4/CD
biomarkers and CD4/CD
biomarkers and CD4/CD
y of soluble biomarkers and CD4/CD
y of soluble biomarkers and CD4/CD
y of soluble biomarkers and CD4/CD
y of soluble biomarkers and CD4/CD
y of soluble biomarkers and CD4/CD
ummary of soluble biomarkers and CD4/CD
y of soluble biomarkers and CD4/CD

Marker	Treatment Arm	Z	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	

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.

-
_
닱
_
_
-
-
ō
<u> </u>
_
~
~
0
2
_
_
_
ŝ
Š.
õ
č
öŗ
čri
scrip
scrip

Author Manuscript

CHAN et al.

treatment arm
eek 48 by tr
o week .
baseline to wee
ge from b
3
kers percentage chai
ar
ular biom
r of cellular
Summary 6

Marker	Treatment Arm	z	Baseline Median (Q1, Q3)	%Change Median (Q1, Q3) ^d	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

_
—
-
_
0
$\mathbf{}$
~
\leq
-
<u>w</u>
=
_
S
Õ
U
$\mathbf{\sigma}$
<u> </u>

A

Author Manuscript Author Manuscript

	5
	đ
	etween group) ^c
	ñ
	wee
	et

CHAN et al.

The 100 30,0,0,0 100 20,0,0 000 recurc Te, [v] NC 15 $66,0,0$ $-15, -13, -35$ $-16, -8, 3$ 000 044 Freeur CF, [v] 10 $30,0,0$ $134, -28, -59$ $-15, -13, -100$ 000 044 Freeur CF, [v] 10 $30,0,0$ $134, -28, -59$ $-15, -100$ 000 044 Freeur CD (1+CD) (4 ohull monocyol) NC 115 600 $-31, -50$ $-13, -54, -50$ 000 000 Freeur CD (1+CD) (4 ohull monocyol) NC 115 $62, -1, -50$ $-13, -54, -50$ 000 000 Freeur CD (1+CD) (5 (ohull monocyol) NC 115 $62, -1, -50$ $-13, -54, -1, -50$ 000 000 Freeur CD (1+CD) (5 (0hull monocyol) NC 115 $62, -13, -50$ $-13, -54, -23, -50$ 000 000 Freeur CD (1+CD) (5 (0hull monocyol) NC 115 $62, -13, -50$ $-13, -54, -50$ 000 000 Freeur CD (1+CD) (5 (0hull monocyol) NC 115 </th <th>Marker</th> <th>Treatment Arm</th> <th>z</th> <th>Baseline Median (Q1, Q3)</th> <th>%Change Median (Q1, Q3)^d</th> <th>95% CI for %Change Median^a</th> <th>p-value (within group)b</th> <th>p-value (between group)^c</th>	Marker	Treatment Arm	z	Baseline Median (Q1, Q3)	%Change Median (Q1, Q3) ^d	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	
TDF 10s $50.7(44.8, \ -13.4(-22.8, -5.9)$ $(-17.3, -10.0)$ 6001 (es) MVC 115 $86.8(9)$ $1.0(-1.8, 7.4)$ $(-0.0, 3.2)$ 0.003 (es) TDF 109 $85.7(9.1)$ $3.5(-1.8, 9.6)$ $(-3.5, -3.5)$ 0.001 (es) MVC 115 $62.(41, 9.3)$ $-31.5(-55.1, 1.1)$ (-96197) 0.001 (es) MVC 115 $62.(3, 1.0)$ $-31.5(-55.1, 1.1)$ (-96197) 0.001 (es) MVC 115 $62.(3, 1.0)$ $-57(-36.7, 56.3)$ $(-20.1, 7.3)$ 0.001 (es) MVC 115 $63(3, 1.0)$ $-53(3, -14.6)$ 0.26 0.01 (es) MVC 115 $464.(32.8)$ $-14.6(-31.2, 16.6)$ $(-20.7, -3.3)$ 0.001 (es) MVC 115 $464.(32.8)$ $-14.6(-31.2, 16.6)$ $(-20.7, -3.3)$ 0.01 (f) MVC 115 $85(-33, 11.5)$ $-14.6(-31.2, 31.6)$ 0.021 (f) MVC <t< td=""><td>Percent CD8 [%]</td><td>MVC</td><td>115</td><td>56.6 (46.1, 66.1)</td><td>-11.5 (-21.8, -3.5)</td><td>(-16.4, -8.8)</td><td><0.001</td><td>0.44</td></t<>	Percent CD8 [%]	MVC	115	56.6 (46.1, 66.1)	-11.5 (-21.8, -3.5)	(-16.4, -8.8)	<0.001	0.44
(w) MVC 115 $89, 9, 0, 0$ $10(-1.8, 7.4)$ $(-0.0, 3.2)$ 0.003 (w) TDF 109 $82, 1, 0, 0$ $3.5 (-1.8, 9, 6)$ $(2.3, 5.3)$ 0.001 (w) 115 $6.2 (4.1, 9.3)$ $-31.5 (-55.1, 1.1)$ $(-30.6, -19.7)$ 0.001 (w) 115 $6.2 (3.1, 1.5)$ $-410.4, 72.60$ $(-12.1, 22.4)$ 0.016 (w) 115 $6.5 (3.3, 11.5)$ $-04 (-40.4, 72.6)$ $(-20.1, 7.3)$ 0.001 (w) 1106 115 $6.5 (3.3, 11.5)$ $-04 (-40.4, 72.6)$ $(-12.1, 22.4)$ 0.061 (w) 110 115 $6.5 (3.2, 1.15)$ $-0.4 (-40.4, 72.6)$ $(-12.0, 1.2, 3.6)$ 0.01 (w) 111 $464 (2.3.8)$ $-146 (-31.2, 16.6)$ $(-14.4, 0.0)$ 0.16 (w) 115 $464 (2.3.8)$ $-146 (-31.2, 16.6)$ $(-12.0, 2.3.6)$ 0.01 (w) 110 $480 (35.9)$ $-89 (-32.4, 19.6)$ $(-14.4, 0.0)$ 0.16 (w) 110 MVC <t< td=""><td></td><td>TDF</td><td>108</td><td>50.7 (44.8, 65.8)</td><td>-13.4 (-22.8, -5.9)</td><td>(-17.3, -10.0)</td><td><0.001</td><td></td></t<>		TDF	108	50.7 (44.8, 65.8)	-13.4 (-22.8, -5.9)	(-17.3, -10.0)	<0.001	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	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
web MVC I15 $6.2(4,1,9.3)$ $-31.5(-55.1,1.1)$ $(-396, -19.7)$ <0001 mVC 115 $6.2(4,1,9.3)$ $-41.9(-584, -17.7)$ $(-505, -33.6)$ <0001 web TDF 109 $7.3(3,0,10.5)$ $-04(-40,4,72.6)$ $(-121,22.4)$ 0.048 web TDF 109 $6.5(3,3,11.5)$ $-0.4(-312,166)$ $(-200,17.3)$ 0.048 MVC 115 $46.4(32.8)$ $-146(-31.2,166)$ $(-207,-3.3)$ 0.10 MVC 115 $46.4(32.8)$ $-146(-31.2,166)$ $(-207,-3.3)$ 0.10 MVC 115 $46.4(32.8)$ $-146(-31.2,166)$ $(-14.4,00)$ 0.16 MVC 115 $46.4(32.8)$ $-8.9(-32.4,156)$ $(0.4,160)$ 0.021 MVC 115 $52.1(40.4)$ $10.2(-14.2,31.6)$ $(0.4,160)$ 0.01 MVC 115 $52.1(40.4)$ $10.2(-14.2,31.6)$ $(0.4,160)$ 0.01 MVC 115 $52.1(40.4)$ $10.2(-14.2,31.6)$ 0.01		TDF	109	85.2 (79.1, 91.4)	3.5 (-1.8, 9.6)	(2.3, 5.3)	<0.001	
TDF 109 7.3 ($3, 9, 10.6$) -41.9 ($-584, -17.7$) ($-505, -33.6$) -0.001 tes) MVC 115 6.5 ($3.3, 11.5$) -0.4 ($-40.4, 72.6$) ($-12.1, 22.4$) 0.048 tes) TDF 109 6.5 ($3.3, 10.1$) $-5.7 (-36.7, 56.3)$ ($-200, 17.3$) 0.048 MVC 115 $46.4 (32.8)$ $-14.6 (-31.2, 16.6)$ ($-200, 1-3.3$) 0.10 MVC 115 $46.4 (32.8)$ $-8.9 (-32.4, 19.6)$ ($-14.4, 0.0$) 0.16 MVC 115 $52.1 (40.4)$ $12.0 (-14.2, 31.6)$ ($-14.4, 0.0$) 0.16 MVC 115 $52.1 (40.4)$ $12.0 (-14.2, 31.6)$ ($-14.4, 0.0$) 0.021 MVC 115 $52.1 (40.4)$ $12.0 (-14.2, 31.6)$ ($-14.4, 0.0$) 0.021 MVC 115 $52.1 (40.4)$ $12.0 (-14.2, 31.6)$ $(0.4, 16.0)$ 0.001 MVC 115 $52.1 (40.4)$ $12.0 (-14.2, 31.6)$ $(0.4, 16.0)$ 0.001 MVC 115 $51.4 (-3.1, 6)$ $(0.4, 16.0)$ 0.00	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
(w) (15 6.5 (3.3, 11.5) 0.4 (-40.4, 72.6) (-12.1, 22.4) 0.048 TDF 109 6.5 (3.9, 10.1) -5.7 (-36.7, 56.3) (-200, 17.3) 0.26 MVC 115 46.4 (3.28, 38.8) -14.6 (-31.2, 16.6) (-20.7, -3.3) 0.10 MVC 115 46.4 (3.28, 38.8) -8.9 (-32.4, 19.6) (-14.4, 0.0) 0.16 MVC 115 109 480 (35.9) -8.9 (-32.4, 19.6) (-14.4, 0.0) 0.16 MVC 115 52(-19, 14.2, 31.6) (-14.4, 0.0) 0.16 0.021 MVC 115 53(-16, 14.2, 31.6) (-14.4, 0.0) 0.16 0.021 MVC 115 518 (36.5) 6.9 (-13.1, 36.9) (0.4, 16.0) 0.001 MVC 115 6.1 (4.0, 88) 9.8 (-18, 14.3) (-4.5, 21.6) 0.017 MVC 115 6.1 (4.0, 88) 9.8 (-18, 14.3) (-4.5, 21.6) 0.001 MVC 115 6.1 (4.0, 88) 9.8 (-18, 14.3) (-4.5, 21.6) 0.001 MVC 115		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
$ \begin{array}{l l l l l l l l l l l l l l l l l l l $		TDF	109	6.5 (3.9, 10.1)	-5.7 (-36.7, 56.3)	(-20.0, 17.3)	0.26	
TDF109 $480(359, \\ 62.7)$ $-8.9(-324, 19.6)$ $(-144, 0.0)$ 0.16 65.2 62.7 62.1 $0.21(40.4)$ $12.0(-14.2, 31.6)$ 0.021 65.2 65.2 65.2 $0.0(-14.2, 31.6)$ 0.021 $7DF$ 109 $51.8(36.5, \\ 62.8)$ $6.9(-13.1, 36.9)$ $0.041(60)$ 0.007 MVC 115 $61.40.88$ $9.8(-18.7, 40.7)$ $(1.2, 22.9)$ 0.001 MVC 115 $61(4.0, 8.8)$ $9.8(-18.7, 40.7)$ $(1.2, 22.9)$ 0.017 MVC 115 $5.9(4.6, 8.1)$ $-36.9(-55.4, -15.8)$ $(-44.6, -31.0)$ 0.001 MVC 115 $5.9(4.6, 8.1)$ $-36.9(-55.4, -15.8)$ $(-44.6, -31.0)$ 0.001 MVC 115 $5.9(4.6, 8.1)$ $-36.9(-55.4, -15.8)$ $(-44.6, -31.0)$ 0.001 MVC 115 $5.9(4.6, 8.1)$ $-36.9(-55.4, -15.8)$ $(-44.6, -31.0)$ 0.001 MVC 115 $5.9(4.6, 8.1)$ $-36.9(-55.4, -15.8)$ $(-44.6, -31.0)$ 0.001 MVC 115 $5.9(4.6, 8.1)$ $-36.9(-55.4, -15.8)$ $(-44.6, -31.0)$ 0.001 MVC 115 $3.8(2.3, 6.7)$ $-36.9(-55.4, -15.8)$ $(-44.6, -31.0)$ 0.001 MVC 115 $3.8(2.3, 6.7)$ $-36.9(-53.2, 4.10)$ $(-75.25.4)$ 0.001 MVC 119 $3.7(2.3, 6.7)$ $-16.6(-38.7, 4.54)$ $(-14.2, 14.0)$ 0.001 MVC 119 $3.7(2.3, 6.7)$ $-16.6(-38.7, 4.54)$ $(-14.2, 14.0)$ 0.001 MVC 115 $6.$	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
$\%$ MVC 115 $52.1(40.4, \\ 65.2)$ 12.0(-14.2, 31.6) (0.5, 19.3) 0.021 TDF 109 $51.8(36.5, \\ 62.8)$ $6.9(-13.1, 36.9)$ $(0.4, 16.0)$ 0.007 MVC 115 $6.1(4.0, 8.8)$ $9.8(-13.1, 36.9)$ $(0.4, 16.0)$ 0.001 MVC 115 $5.1(4.0, 8.8)$ $9.8(-13.1, 40.7)$ $(1.2, 22.9)$ 0.017 MVC 115 $5.9(4.6, 8.1)$ $-36.9(-55.4, -15.8)$ $(-44.6, -31.0)$ 0.017 MVC 115 $5.9(4.6, 8.1)$ $-36.9(-53.6, -11.0)$ $(-44.6, -31.0)$ 0.001 MVC 115 $5.9(4.6, 8.1)$ $-35.0(-53.6, -11.0)$ $(-42.4, -25.9)$ 0.001 MVC 115 $3.8(2.3, 6.5)$ $4.2(-23.2, 64.0)$ $(-75.2, 5.9)$ -0.001 $\%$ MVC 115 $3.8(2.3, 6.7)$ $2.56(-1.8, 88.5)$ $(-20.6, 46.4)$ -0.001 $\%$ MVC 115 $3.7(2.3, 6.7)$ $2.56(-1.8, 88.5)$ $(-14.2, -25.9)$ -0.001 $\%$ MVC 115 5.6		TDF	109	48.0 (35.9, 62.7)	-8.9 (-32.4, 19.6)	(-14.4, 0.0)	0.16	
TDF109 $518 (36.5, \\ 62.8)$ $69 (-13.1, 36.9)$ $(0.4, 16.0)$ 0.007 MVC115 $6.1 (4.0, 8.8)$ $9.8 (-18.7, 40.7)$ $(1.2, 22.9)$ 0.001 MVC115 $6.1 (3.5, 8.5)$ $5.5 (-19.1, 44.3)$ $(-4.5, 21.6)$ 0.017 MVC115 $5.9 (4.6, 8.1)$ $-36.9 (-55.4, -15.8)$ $(-44.6, -31.0)$ 0.017 MVC115 $5.9 (4.6, 8.1)$ $-36.9 (-55.4, -15.8)$ $(-42.4, -25.9)$ 0.001 MVC115 $3.8 (2.3, 6.5)$ $4.2 (-23.2, 64.0)$ $(-7.5, 25.4)$ 0.001 61 MVC115 $3.8 (2.3, 6.5)$ $4.2 (-23.2, 64.0)$ $(-7.5, 25.4)$ 0.006 961 MVC115 $3.8 (2.3, 6.7)$ $29.6 (-1.8, 88.5)$ $(20.6, 46.4)$ 0.001 961 MVC115 $5.6 (3.7, 9.3)$ $-1.6 (-38.7, 45.4)$ $(-14.2, 14.0)$ 0.44 961 MVC115 $5.6 (3.7, 9.3)$ $-1.6 (-38.7, 45.4)$ $(-12.2, 18.5)$ 0.001 961 MVC115 $5.6 (3.7, 9.3)$ $-1.6 (-38.7, 45.4)$ $(-12.2, 18.5)$ 0.001 961 MVC115 $5.6 (3.7, 9.3)$ $-1.6 (-38.7, 45.4)$ $(-12.2, 18.5)$ 0.001 961 MVC115 $5.6 (3.7, 9.3)$ $-1.6 (-38.7, 45.4)$ $(-12.2, 18.5)$ 0.001 971 199 $-12.2 1.57.6)$ $(-12.2, 18.5)$ 0.001 0.002 971 199 $-12.2 1.60$ $(-12.2, 18.5)$ 0.001	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
$ \begin{array}{llllllllllllllllllllllllllllllllllll$		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
$ \begin{array}{l l l l l l l l l l l l l l l l l l l $		TDF	109	5.4 (3.5, 8.5)	5.5 (-19.1, 44.3)	(-4.5, 21.6)	0.017	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	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	
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	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
%] MVC 115 5.6 ($3.7, 9.3$) -1.6 ($-38.7, 45.4$) ($-14.2, 14.0$) 0.44 TDF 109 5.8 ($3.6, 8.8$) 6.2 ($-32.1, 57.6$) ($-12.2, 18.5$) 0.092 MVC 115 64.3 (48.1 , 9.9 ($-0.2, 21.6$) ($5.6, 12.3$) <0.001		TDF	109	3.7 (2.3, 6.7)	29.6 (-1.8, 88.5)	(20.6,46.4)	<0.001	
TDF1095.8 ($3.6, 8.8$)6.2 ($-32.1, 57.6$)($-12.2, 18.5$)0.092MVC11564.3 (48.1 ,9.9 ($-0.2, 21.6$)($5.6, 12.3$)<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
MVC 115 64.3 (48.1, 9.9 (-0.2, 21.6) (5.6, 12.3) <0.001 74.6)		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

AIDS. Author manuscript; available in PMC 2017 August 24.

Page 12

Marker	Treatment Arm N	Z	Baseline Median (Q1, Q3)	%Change Median (Q1, Q3) ^d	95% CI for %Change Median ^a	p-value (within group) ^b	
	TDF	109	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	115 20.1 (14.0, 37.7)	-25.3 (-38.9, -3.9) (-30.3, -18.1)	(-30.3, -18.1)	<0.001	
	TDF	109	109 23.5 (13.0, 32.8)	-25.8 (-44.9, 1.0) (-32.0, -19.6)	(-32.0, -19.6)	<0.001	
^a Percentage change from week 0 to week 48 (%), defined as ((w48-w0)/w0) x100%	(%), defined as ((w48-	(0M)(0M) x100%				

 $b_{\rm wilcoxon}$ signed rank p-value evaluating the within treatment group percentage changes from baseline.

^cStratified 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.

0.77

p-value (between group) $^{\mathcal{C}}$

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript