A Pilot Trial of Adding Maraviroc to Suppressive Antiretroviral Therapy for Suboptimal CD4\(^+\) T-Cell Recovery Despite Sustained Virologic Suppression: ACTG A5256

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Background. Despite viral suppression, antiretroviral therapy (ART) does not restore CD4\(^+\) T-cell counts in many patients infected with human immunodeficiency virus type 1 (HIV-1).

Methods. In a single-arm pilot trial involving ART recipients with suppressed plasma levels of HIV-1 RNA for at least 48 weeks and stable suboptimal CD4\(^+\) T-cell recovery, subjects added maraviroc, a CCR5 antagonist, to their existing ART for 24 weeks. After stopping maraviroc, they were followed for an additional 24 weeks. A Wilcoxon signed-rank test was used to evaluate whether maraviroc was associated with an increase of at least 20 cells/\(\mu\)L in the CD4\(^+\) T-cell count.

Results. A total of 34 subjects were enrolled. The median age was 50 years, and the median baseline CD4\(^+\) T-cell count was 153 cells/\(\mu\)L. The median increase in CD4\(^+\) T-cell count from baseline to week 22/24 was 12 cells/\(\mu\)L (90% confidence interval, 1–22). A CD4\(^+\) T-cell count increase of at least 20 cells/\(\mu\)L was not detected (\(P= .97\)). Markers of immune activation and apoptosis decreased during maraviroc intensification; this decline partially reversed after discontinuing maraviroc.

Conclusions. Adding maraviroc to suppressive ART for 24 weeks was not associated with an increase in CD4\(^+\) T-cell counts of at least 20 cells/\(\mu\)L. Further studies of CCR5 antagonists in the dampening of immune activation associated with HIV infection are warranted.

Clinical Trials Registration. NCT 00709111.
with a CD4+ T-cell count of >200 cells/µL, even after control for plasma HIV-1 RNA level [3]. Moreover, recent studies have established that CD4+ T-cell count is related to overall mortality and incidence of non–AIDS-defining cancer, even among subjects with a CD4+ T-cell count of >350 cells/µL [4, 5].

A meta-regression of phase 2 and 3 clinical trials of investigational ART agents found that the increase in CD4+ T-cell count in groups using a CCR5 antagonist was 30 cells/µL higher than that in groups not using a CCR5 antagonist, after control for differing rates of virologic suppression [6]. Similarly, greater recovery in CD4+ T-cell count was observed in a phase 3 trial comparing combination regimens with maraviroc, a CCR5 antagonist, or with efavirenz, a nonnucleoside reverse-transcriptase inhibitor (NNRTI), for initial ART of HIV-1 infection, or with efavirenz, a nonnucleoside reverse-transcriptase inhibitor (NNRTI), for initial ART of HIV-1 infection [7]. While maraviroc did not meet prespecified criteria in that study for a noninferiority comparison with efavirenz, subjects receiving maraviroc had a significantly greater increase in CD4+ T-cell count 48 weeks after randomization as compared to those receiving efavirenz (change from baseline, +170 vs +144 cells/µL; difference, 26 cells/µL [95% CI, 7–46]) [7].

Given the potential benefit of maraviroc on CD4+ T-cell recovery, we designed and conducted AIDS Clinical Trials Group (ACTG) protocol A5256, a single-arm, multicenter, open-label clinical trial designed to test the hypothesis that adding the CCR5 inhibitor maraviroc will result in a CD4+ T-cell count increase of at least 20 cells/µL over 24 weeks in ART recipients with a rigorously defined suboptimal CD4+ T-cell recovery despite sustained virologic suppression.

**METHODS**

Institutional review board approval was obtained at each participating clinical site. All subjects provided written informed consent, and the human-experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of this research.

**Study Participants**

Participants were enrolled at 29 clinical trials units. Eligible participants were HIV-1–infected males and females aged ≥16 years who had been receiving a stable ART regimen for at least 48 weeks, had had a plasma HIV-1 RNA load below the limit of detection of the assay for at least 48 weeks, and had had stable but suboptimal CD4+ T-cell recovery over the previous year (defined as a CD4+ T-cell count of <250 cells/µL and a calculated slope of the annual change in CD4+ T-cell count ranging from −20 to +20 cells/µL during the year before enrollment). Study exclusions were an uncontrolled medical condition or recent AIDS-defining illness, current receipt of immunomodulatory agents, current pregnancy or breastfeeding, or prior exposure to a CCR5 antagonist.

**Study Design**

ACTG A5256 was a 48-week, single-arm, open-label clinical trial in which HIV-1–infected participants with suboptimal CD4+ T-cell recovery added maraviroc (Pfizer) to their existing ART regimen for 24 weeks and then discontinued maraviroc and were followed for an additional 24 weeks. The study was designed to enroll 32 patients. The maraviroc dose was 150–600 mg twice daily, depending on pharmacokinetic interactions with prestudy medications, as specified in the package insert. Participants with virologic failure (defined as 2 consecutive measurements of HIV-1 RNA levels at or above the limit of detection of the assay used at local sites) discontinued maraviroc.

Participants had 2 baseline assessments prior to starting maraviroc. Participants were seen at 4, 8, 12, 16, 22, and 24 weeks after starting maraviroc, and then at weeks 36, 46, and 48 (12, 22, and 24 weeks after maraviroc discontinuation).

**Immunologic Analyses**

Participants had CD4+ and CD8+ T-cell counts assessed by flow cytometry at the local-site laboratories at each visit. To determine the potential mechanisms of CD4+ T-cell change with maraviroc use, we also measured the following changes in CD4+ and CD8+ T-cell subsets (defined below): activation, senescence, proliferation, and apoptosis. At the 2 baseline visits and at weeks 12, 22, 24, 36, 46, and 48 after study entry, participant blood samples were collected in sodium-heparinized vacuum-tainer tubes (BD) and shipped at ambient temperature overnight to a central processing laboratory, where peripheral blood mononuclear cells (PBMCs) were isolated via density gradient centrifugation. PBMCs were washed and analyzed for markers of T cell activation, maturation, proliferation, apoptosis, and memory/naive subsets by polychromatic cytometry. In brief, cells were pretreated with human Fc block (Miltenyi Biotec) prior to staining with fluorochrome-conjugated monoclonal antibodies to CD3, CD4, CD8, CD45RA, CCR7, HLA DR, CD38, and CD57. For intracellular Ki67, Bcl-2, and caspase-3 detection, cells were fixed and permeabilized, using the BD Cytofix/Cytoperm kit (BD Biosciences), and then stained with the appropriate fluorochrome-conjugated antibodies. After staining, cells were washed, fixed in 2% formaldehyde, and acquired within 24 hours on an LSR2 flow cytometer (BD), using FACS Diva software, v.6.1.1. Analysis of immune activation (CD38+/HLA DR+), senescence (CD57+), proliferation (Ki67+), apoptosis (Bcl-2− and caspase-3−), and memory/naive subsets (naive: CCR7+/CD45RA-; central memory: CCR7+/CD45RA-; effector memory: CCR7+/CD45RA+; and terminal effectors expressing CD45RA [T EMRA]: CCR7+/CD45RA+) was performed after stringent gating on singlet CD3+/CD4+ or CD3+/CD8+ T cells, using FlowJo software, v.8.8.6 (Tree Star).

**Coreceptor Tropism on Proviral DNA**

DNA was extracted from cryopreserved cell pellets obtained from participants prior to receiving maraviroc and used as
transfection into 293T cells with an HIV plasmid (pNL4-3.Luc. R-E-) containing a nonfunctional env. The coreceptor used by the viral quasi-species was determined by infection of U87.CD4. CCR5 and U87.CD4.CXCR4 cells, with viral entry indicated by expression of the luciferase gene and ablation of the signal in the presence of the specific coreceptor inhibitor.

### Biomarker Analysis

Plasma samples were analyzed for biomarkers, using a multiplexing sandwich enzyme-linked immunosorbent assay system based on chemiluminescent or fluorescent detection of analytes whose respective capture-antibodies are spotted in arrays within each well of a 96-well microplate (Aushon Biosystems, Billerica, MA). The analytes included a marker of gut microbial translocation (soluble CD14 [sCD14]) and inflammatory markers associated with atherosclerosis (D-dimer, high-sensitivity C-reactive protein, interleukin 6, soluble intercellular cell adhesion molecule 1, monocyte chemoattractant protein 1, monocyte chemoattractant protein 2, plasma P-selectin, soluble tumor necrosis factor receptor type II, matrix metalloproteinase 9, and plasma CD40 ligand).

### Statistical Analyses

The primary end point was the change in CD4\(^+\) T-cell count from the average of the 2 baseline assessments (before entry and entry) to the average of the week 22 and 24 assessments. The study was designed to have 80% power to show that the addition of maraviroc was associated with a CD4\(^+\) T-cell count increase of at least 20 cells/µL over 24 weeks, using a 1-sided Wilcoxon signed-rank test. This assumed an underlying change in CD4\(^+\) T-cell count induced by maraviroc of 50 cells/µL, a SD of 60 cells/µL around the mean change in CD4\(^+\) T-cell count, a loss to follow-up or premature maraviroc discontinuation rate of 10%, and a 1-sided type 1 error of 0.05. The estimated median change in CD4\(^+\) T-cell count and accompanying exact Hahn and Meeker 90% confidence intervals (CIs) are presented. The before-and-after treatment slopes and the difference between them are summarized across the population by using generalized estimating equations.

Secondary objectives were to investigate the persistence of the increase in CD4\(^+\) T-cell count after maraviroc receipt, the mechanisms by which maraviroc influences the CD4\(^+\) T-cell responses (immunologic markers for activation, proliferation, senescence, and apoptosis), the effect of maraviroc on gut microbial translocation and inflammatory markers associated with atherosclerosis, and the relationship of viral coreceptor tropism to study outcomes. Given the exploratory nature of our secondary objectives, formal hypothesis testing was not planned; rather, median distributional shifts were estimated with 90% exact Hahn and Meeker CIs.

### RESULTS

#### Baseline Characteristics and Subject Disposition

Thirty-four participants were enrolled from 14 January through 4 May 2009. Participants included 32 men (94%), 24 non-Hispanic whites (71%), 6 non-Hispanic blacks (18%), and 4 Hispanics (12%), with a median age of 50 years. The median duration of HIV-1 RNA suppression prior to study entry was 3 years. At baseline, the median CD4\(^+\) and CD8\(^+\) T-cell counts were 153 cells/µL (interquartile range [IQR], 119–203) and 559 cells/µL (IQR, 416–872), respectively. The background ART included ritonavir-boosted protease inhibitor/nucleoside reverse-transcriptase inhibitors (NRTIs) in 22 (65%), NNRTI/NRTI regimens in 9 (26%), and ritelgravir-containing regimens in 3 (9%). Five (15%) had chronic hepatitis B virus infection, and 2 (6%) had hepatitis C virus infection.

Sixty-one participants gave informed consent for this study, and 27 did not satisfy eligibility criteria. The most common reasons for not entering the protocol were not having a stable CD4\(^+\) T-cell count slope, having a screening CD4\(^+\) T-cell count of ≥250 cells/mm\(^3\), and having a plasma HIV-1 RNA load above the assay limit. Of 34 participants enrolled, 2 (6%) experienced virologic failure at study entry despite having virologic suppression prior to entry and were excluded from the analysis per protocol. One completed follow-up, and one left the study at 12 weeks. One additional subject was unable to attend clinic visits after 22 weeks of follow-up.

#### CD4\(^+\)/CD8\(^+\) T-Cell Count Changes

Figure 1A shows the change in CD4\(^+\) T-cell count from baseline over time. Of the 32 participants with evaluable data on changes in CD4\(^+\) T-cell count from baseline to week 22/24 during maraviroc therapy, a CD4\(^+\) T-cell count increase of at least 20 cells/µL was not detected (P = .97); the estimated median increase was 12 cells/µL (90% CI, 1–22). Only 2 participants had an increase of ≥50 cells/µL. The estimated rate of change in the CD4\(^+\) T-cell count following maraviroc initiation was +24.7 cells/µL per year, for an estimated difference of +25.2 cells/µL per year (90% CI, +2.1 to +48.3) from the period before maraviroc receipt. The median change in CD4\(^+\) T-cell count after maraviroc discontinuation (from week 22/24 to week 46/48) was +7 cells/µL (90% CI, −5 to +18).

The estimated median change in CD8\(^+\) T-cell counts from baseline to week 22/24 was +59 cells/µL (90% CI, +6 to +95), and the estimated median change from week 22/24 to week 46/48 was −30 cells/µL (90% CI, −91 to +23). Figure 1B shows the change in CD8\(^+\) T-cell count from baseline over time.
Markers of Immune Activation, T-Cell Subsets, Proliferation, Apoptosis, and Senescence

The median changes (90% CIs) in the frequency of proliferation, activation, apoptotic, and senescent T-cell subsets are shown in Figures 2 and 3. On average, a decrease in the percentage of naive (ie, CD45RA+/CCR7+) CD4+ and CD8+ T cells was observed (median change, $-1.3\%$ and $-3.3\%$, respectively) during 24 weeks of maraviroc administration; upon maraviroc discontinuation, these changes partially reversed (median change, $+2.1\%$ and $+1.1\%$, respectively).

We observed a reduction in the percentage of various activated T-cell subsets during maraviroc intensification, including CD38+, CD38+/HLA-DR+, and Ki67+ CD4+ and CD8+ T cells (Figures 2A and 3A). These changes were partially reversed after discontinuation of maraviroc (Figures 2B and 3B).

Coreceptor Tropism

We attempted HIV-1 proviral DNA coreceptor tropism testing on samples from 29 of 32 participants in the primary analysis (3 had no samples available). Of the 18 participants with available results (samples for 11 were not able to be amplified), 11 (61%) had CCR5-tropic virus, 5 (28%) had dual-tropic/mixed infections, and 2 (11%) had CXCR4-tropic virus.

The study end points did not vary appreciably when comparing individuals with CCR5-tropic virus to those with dual-tropic/mixed infections or CXCR4-tropic virus ($P > .3$, by the exact Wilcoxon rank-sum test).

Biomarker Analysis

The changes in plasma biomarkers are shown in Table 1. There was a median change from baseline to week 22/24 in D-dimer of $+0.09 \mu g/mL$ (90% CI, $+0.06$ to $+0.13$), with a median baseline value of $+0.33 \mu g/mL$. In a post hoc analysis, we...
performed D-dimer testing on stored specimens, using a different assay (Asserachrom D-Dimer, Diagnostica Stago; Asnières, France). These results showed a median change from baseline to week 22/24 in D-dimer of +0.007 µg/mL (90% CI, −0.001 to +.024), with a median baseline value of +0.13 µg/mL. There were no other appreciable changes in plasma biomarkers or sCD14 resulting from maraviroc administration.

Virologic Outcomes
Two participants experienced confirmed virologic failure while receiving maraviroc; both had a detectable HIV-1 RNA load at their entry visit, just prior to initiation of maraviroc. Two participants experienced confirmed virologic failure with their initial rise at visit week 24, when maraviroc was discontinued. The initial rise and confirmation values were 101 and 62 copies/mL and 88,780 and 340 copies/mL, respectively, for these 2 participants. Furthermore, 2 participants had unconfirmed elevations in plasma HIV-1 RNA at the final study visit with values of 99 copies/mL and 174 copies/mL, respectively.

Safety Analyses
After exclusion of a case of hyperbilirubinemia due to atazanavir, there were 4 participants who reported a grade 3 sign, symptom, or laboratory abnormality (ie, hypoalbuminemia, hypocalcemia, hyperglycemia, and bradycardia) that occurred during maraviroc administration and 1 participant who reported a grade 3 event (ie, dyspnea) that occurred after maraviroc discontinuation. There were no grade 4 events reported among study participants, and no one discontinued maraviroc because of adverse events.

DISCUSSION
In a population with suboptimal CD4+ T-cell counts after a median of 3 years of virologic suppression, adding maraviroc did not lead to an appreciable increase in CD4+ T-cell counts. Our data showed a detectable increase in CD4+ T-cell counts, but we felt the observed effect was not large enough to merit further study of this agent to improve CD4+ T-cell counts in patients with suboptimal recovery. There are no accepted therapies for increasing CD4+ T-cell counts other than suppressive ART. Interleukin 2 increased CD4+ T-cell counts but did not reduce AIDS-defining events or overall mortality [9].

Suboptimal CD4+ T-cell responses have been associated with a variety of factors, including older age and lower thymic
function [10], nadir CD4+ T-cell counts of <200 cells/µL [11], some ART drugs (eg, zidovudine [12] and the combination of didanosine and tenofovir [13]), CD4+ T-cell hyperactivation [14], and increased cell death by apoptosis [15, 16]. In randomized treatment trials, a suboptimal increase in CD4+ T-cell count in the setting of virologic suppression has been associated with older age, female sex, a higher CD4+ naive T-cell level, a higher CD4+ naive/memory T-cell ratio, a lower CD8+ memory T-cell level, and a higher proportion of activated CD4+ and CD8+ T cells [17–19].

Although the hypothesized increase in CD4+ T cells was not found, we did observe decreases in the frequency of activated CD4+ and CD8+ T cells, as well as improved markers of T-cell apoptosis in both CD4+ and CD8+ T cells. Moreover, these changes generally reversed after discontinuing maraviroc, which supports but not establish a causal effect. The β-chemokines CCL3, CCL4, and CCL5 bind to CCR5 on T cells and trigger their activation through a pathway mediated by nuclear factor of activated T cells [20]. Maraviroc inhibits the binding of β-chemokines to CCR5, and this may explain the decreases in levels of immune activation seen in this study.

Adding maraviroc was also associated with decreased peripheral blood naive and central memory CD4+/CD8+ T cells and increased effector memory and TEMRA CD4+/CD8+ T cells. This may reflect redistribution of these T-cell subsets between the peripheral blood and tissue compartments. CCR5–β-chemokine interaction also modulates the chemotaxis of CCR5+ cells along a chemokine concentration gradient, allowing for directed migration of immune cells between different tissue compartments [21–23]. Maraviroc may also influence this process [24]. On the basis of HIV-1 proviral DNA tropism testing, we did not detect differences between these changes in participants harboring CCR5-tropic virus as compared to those with CXCR4-tropic, dual-tropic, or mixed infections, suggesting viral tropism may not affect the immunologic effects of maraviroc.

In contrast to A5256, a small, randomized, placebo-controlled trial of maraviroc in a similar population found that the percentage of CD38+/HLA-DR+ CD8+ T cells increased slightly in the maraviroc group, compared with a decrease in the placebo group [25]. The differing results between studies were driven by the large decrease in CD38-expressing T cells
Table 1. Change in Levels of Plasma Biomarkers During and After Maraviroc Treatment Among Individuals With Suppressed Plasma Levels of Human Immunodeficiency Virus Type 1 RNA for ≥48 Weeks and Stable Suboptimal CD4+ T-Cell Recovery During Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline Level (n = 32)</th>
<th>From Baseline to Wk 22/24 (n = 32)</th>
<th>From Wk 22/24 to Wk 46/48 (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/mL)</td>
<td>8</td>
<td>0.7 (−.9 to +1.6)</td>
<td>−0.5 (−2.1 to +0.6)</td>
</tr>
<tr>
<td>MCP-1 (pg/mL)</td>
<td>447.2</td>
<td>+44.6 (−39.6 to +103.1)</td>
<td>+7.7 (−18.5 to +43.2)</td>
</tr>
<tr>
<td>MCP-2 (pg/mL)</td>
<td>16.8</td>
<td>−1.4 (−2.4 to +2.2)</td>
<td>+0.2 (−2.3 to +1.8)</td>
</tr>
<tr>
<td>sTNF-RII (ng/mL)</td>
<td>1</td>
<td>+0.2 (+1.0 to +3.0)</td>
<td>0 (0 to +1.0)</td>
</tr>
<tr>
<td>hs-CRP (mg/dL)</td>
<td>0.1</td>
<td>0 (0 to +0.1)</td>
<td>0 (0 to +0.1)</td>
</tr>
<tr>
<td>sICAM-1 (ng/mL)</td>
<td>470.1</td>
<td>−25.7 (−59.3 to +23.5)</td>
<td>−32.4 (−46.3 to +6.8)</td>
</tr>
<tr>
<td>CD40L (pg/mL)</td>
<td>113.4</td>
<td>−0.4 (−45.6 to +43.1)</td>
<td>+34.9 (0 to +66.7)</td>
</tr>
<tr>
<td>sCD14 (μg/mL)</td>
<td>2.1</td>
<td>0 (−1.0 to +2.0)</td>
<td>−0.2 (−4.0 to +1.0)</td>
</tr>
<tr>
<td>MMP-9 (ng/mL)</td>
<td>171.1</td>
<td>−12.5 (−48.1 to +4.0)</td>
<td>+12.8 (−14.9 to +29.5)</td>
</tr>
<tr>
<td>P-selectin (ng/mL)</td>
<td>189.8</td>
<td>−11.7 (−66.2 to +30.5)</td>
<td>−17.3 (−62.1 to +5.2)</td>
</tr>
<tr>
<td>D-dimer (μg/mL)</td>
<td>0.3</td>
<td>+0.09 (−.06 to +.13)</td>
<td>−0.02 (−.03 to +.01)</td>
</tr>
</tbody>
</table>

Maraviroc was received from baseline to week 24.
Abbreviations: CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein 1; MCP-2, monocyte chemoattractant protein 2; MMP-9, matrix metalloproteinase 9; sCD14, soluble CD14; sICAM-1, soluble intercellular cell adhesion molecule 1; sTNF-RII, soluble tumor necrosis factor receptor type II.

in A5256. Immunophenotyping was performed on fresh cells in A5256, whereas in the study by Hunt et al, cryopreserved cells were used. We repeated immunophenotyping by using cryopreserved cells from 17 A5256 participants with available samples. We found that CD38 expression was lower in cryopreserved cells as compared to fresh cells at baseline, with no appreciable difference at week 24. Consequently, the observed changes from baseline to week 24 in cryopreserved cells were not consistent with a decrease in immune activation. A number of confounding factors, such as different sample processing, shipping season, and underlying levels of activation, could have contributed to the discrepant results observed with cryopreserved cells. Ultimately, to fully explain these differences and understand the optimal processing conditions for immunophenotyping, further independent study under controlled conditions is required. An additional randomized clinical trial [26] and single-arm trial [27] involving patients with poor CD4+ T-cell recovery found declines in immune activation markers after the addition of maraviroc to a suppressive regimen, although these changes were not different than those for placebo for the randomized clinical trial.

An increase in CD8+ T-cell counts was observed in this study. A similar effect has been seen in other maraviroc clinical trials [28]. The clinical significance of this finding is unknown. Plasma D-dimer levels showed an unexpected increase after the addition of maraviroc; however, when D-dimer levels were restested post hoc using a different assay, we did not find an appreciable increase in D-dimer levels.

The persistently elevated levels of activation and inflammation in HIV-1–infected persons treated with ART may explain the greater prevalence of cardiovascular, hepatic, and renal diseases, neurocognitive dysfunction, and non–AIDS-related malignancies in this population [29–34]. Currently, there are no accepted therapies other than suppressive ART to reduce immune activation. The mechanism by which maraviroc may reduce immune activation is unclear. CCR5 binding by β-chemokines promotes T-cell activation and proliferation. CCR5 antagonists may downmodulate T-cell activation by preventing this interaction.

There are several limitations to this study. This was a single-arm trial that was designed to detect a relatively robust increase in CD4+ T-cell counts. A larger randomized trial would be needed to demonstrate a smaller effect on CD4+ T-cell increase. Because we did not have a control group, the changes in immune activation markers may have been due to factors other than maraviroc. Immunophenotyping was performed in real time, and laboratory characteristics or interpretation may have changed over time. The study did not directly evaluate gut-associated lymphoid tissue, which is a major locus of ongoing immune activation. Finally, the prognostic value of the immune activation markers CD38 and CD38+HLA-DR+ was established originally in untreated HIV-1 infection [35]. Less is known about the relationship of these markers to long-term outcomes for those with sustained virologic suppression on ART.

In summary, the addition of maraviroc was not associated with a clinically significant increase in CD4+ T-cell counts in our trial. Our study does not support the strategy of adding maraviroc to increase CD4+ T-cell counts. We did find a decrease in markers of immune activation and reduced T-cell apoptosis. However, further studies are needed to confirm this...
effect. There is growing evidence linking immune activation and end-organ disease. However, much work is needed to define the key components in the cascade of events resulting in immune activation in HIV-1-infected patients. Ultimately, large-scale clinical trials with morbidity and mortality outcomes will be needed before novel therapies targeting immune activation can be recommended for clinical practice.

Notes

Acknowledgments. ACTG A5256 Team Members other than the co-authors are as follows: Beatrice Kallungal (clinical trials specialist), Jennifer Janik (data manager), Debra Meres (study pharmacist), Todd Strober and Christina Megill (field representatives), Daniel Eggers (laboratory technologist), Dennis Pontani (industry representative), Amy Jennings (laboratory data coordinator), and Kate Savage and Kirsten Brady (Rush University Immunology Laboratory). Enrolling research sites were as follows: Weill-Cornell Medical College (Glenn Sturge and Luis Lopez-Detres), University of Pittsburgh (Deborah McMahon and Sally McNulty), University of Cincinnati (Jaime Robertson and Jenifer Baer), Peabody Health Center (M. Keith Rawlings and Michelle Ukwu), Massachusetts General Hospital (Theresa Flynn and Amy Srolla), Boston Medical Center (Jon D. Fuller, and Betsy Adams), Johns Hopkins University (Ilene Wiggins and Andrea Weiss), New York University/New York City Health and Hospitals Corporation at Bellevue Hospital Center (Judith Aberg and Karen Cavanagh), Stanford University (Deborah Slamowitz and Sandra Valle), University of California–Los Angeles (Vanessa Cahuahuria), University of California–San Diego (Linda Meixner and Dee Dee Pacheco), University of California–San Francisco (Annie Luetkemeyer and Jay Dwyer), University of Miami (Margaret A. Fischl and Hector Bolivar), Georgetown University (Princy N. Kumar and Joseph G. Timpone), University of Rochester (Jane Reid and Amneris Luque), Rochester–AIDS Care (Christine Hurley and Roberto Corales), Duke University Medical Center (Charles Hicks and Joan Riddle), Washington University School of Medicine (Judy Frain and Teresa Spitz), The Ohio State University (Michael F. Para and Kathy J. Watson), Case Western (Barbara Philpotts and Dawn Antosh), Northwestern University (Babafemi Taiwo and Margarita Aguilar), University of North Carolina (David Curtin and Susan Pedersen), Vanderbilt University (Brenda R. Jackson and Husamettin Erdem), Institute of Human Virology (William A. Blattner and Charles E. Davis, Jr.), University of Alabama (Elizabeth Lindsey and Tamara James), Emory University (Melody Palmore and Ericka R. Patrick), University of Pennsylvania (Pablo Tesfa and Kathryn Maffei), and University of Texas–Houston (Roberto C. Arduino and Francisco E. Mora). We thank the patients for volunteering to participate.

Financial support. National Institute of Allergy and Infectious Diseases (grant U01 AI032847 to the AIDS Clinical Trials Group; Virology Support Laboratory subcontract 204VC009 to the University of Pittsburgh; grant AI068634 to the Statistical and Data Analysis Center; grants AI069418, AI069419, AI069423, AI069432, AI069439, AI069447, AI069452, AI069465, AI069471, AI069472, AI069474, AI069477, AI069484, AI069494, AI069495, AI069501, AI069502, AI069503, AI069511, AI069532, and AI069536 to participating clinical trial units; grants AI045008, AI050409, AI050410, AI060354, and AI082151 to the Centers for AIDS Research; grant K24 AI51666 to R.M. G.; and grant R01 AI066992-04A1 to R.T.G.); National Center for Research Resources (grants RR023561, RR024160, RR 025747, RR024975, and RR024996 to the Clinical and Translational Science Centers); National Library of Medicine (grant G88LM008830-01 to R.T.G.); and Pfizer Investigator-Initiated Research Grant (funds for assays and supply of maraviroc).

Potential conflicts of interest. T. J. W. has served as an ad hoc consultant to Pfizer and Quest Diagnostics and as site principal investigator for research grants (to Weill Cornell Medical College) for Tibotec and GlaxoSmithKline. R. T. G. has received grant support from Tibotec and Gilead Sciences. A. L. receives research grants from Merck and Tobira and has served as a consultant to Merck. J. S. C. has served as the principal investigator for research grants (to UCLA) for Merck and Tibotec. J. W. M. is a consultant for Gilead Sciences, Merck, and RFS Pharma and owns share options in RFS Pharma. R. M. G. served as an ad hoc consultant for Bristol-Myers, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, ViV, and Virostatics and as site principal investigator for research grants (to Weill Cornell Medical College) for Merck, Pfizer, and ViV. A. R. T. has served as an ad hoc consultant to Johnson & Johnson and as principal investigator for research grants from Abbott and Gilead Sciences. All other authors report no potential conflicts.

All authors have submitted the ICJME Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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