Effects of Maraviroc versus Efavirenz in Combination with Zidovudine-Lamivudine on the CD4/CD8 Ratio in Treatment-Naive HIV-Infected Individuals

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ABSTRACT

A low CD4/CD8 ratio during treated HIV infection reflects heightened immune activation and predicts death. The effects of different antiretroviral therapy regimens on CD4/CD8 ratio recovery remains unclear. We performed a post hoc analysis of the MERIT study, a randomized, double-blind trial of maraviroc versus efavirenz in combination with zidovudine-lamivudine in treatment-naive HIV-infected individuals. We found higher rates of CD4/CD8 ratio normalization with efavirenz, which was driven by a greater CD8+ T-cell decline.

KEYWORDS

HIV, antiretroviral therapy, CD4/CD8 ratio, T cells, T-cell activation, efavirenz, maraviroc

Despite the unquestionable success of antiretroviral therapy (ART), HIV infection is still associated with an increased risk of death (1). A salient predictor of clinical progression is the activation of innate and adaptive immunity, as reflected by increased levels of markers of inflammation, coagulation, bacterial translocation, monocyte and macrophage activation, T-cell activation and T-cell senescence (2, 3). While these pathways are linked with the development of comorbidities during ART, a number of issues, including technical difficulties, economic constraints, and high intra- and inter-individual variability, preclude their clinical use. The CD4/CD8 ratio has been demonstrated to correlate well with some of these pathways (4, 5) and has been shown to predict morbidity and death during ART (6, 7) despite adequate CD4+ recovery.

Although definitive evidence is lacking, the CCR5 antagonist maraviroc has been regarded as an antiretroviral agent with immunomodulatory properties, given its abilities to affect activation in peripheral blood and the gut mucosa (8), to improve HIV-associated neurocognitive disorder symptoms (9), and even to reactivate latent HIV (10). We hypothesized that first-line maraviroc-based therapy would result in a greater CD4/CD8 ratio recovery than nonnucleoside reverse transcriptase inhibitor-based therapy. For this purpose, we used the final 5-year data from a randomized, double blind, multicenter phase Ib/II (MERIT) study of treatment-naive patients.

The MERIT study (ClinicalTrials.gov no. NCT0098293 and NCT03178084) is a randomized, double-blind, multicenter, phase Ib/II clinical trial originally planned for 96 weeks but then extended to another 3 years of an open-label phase. The study design and details have been described elsewhere (11, 12). Briefly, treatment-naive R5 HIV-1 affected patients without baseline genotypic resistance to efavirenz, zidovudine, or lamivudine and with a minimum plasma HIV-1 RNA level of 2,000 copies/ml were considered eligible to receive maraviroc at 300 mg once a day (q.d.), maraviroc at 300...
mg twice a day (b.i.d.), or efavirenz at 600 mg four times a day (q.d.) combined with zidovudine and lamivudine at 300 and 150 mg b.i.d. Treatment with maraviroc q.d. was discontinued in all of the patients included in this arm at week 16 for failure to meet the previously established efficacy criteria. Blinding was maintained for the first 96 weeks of the study, and then it was continued with a nominal 3-year open-label phase.

**Ethics.** The protocol was approved by the appropriate review committee at each site and executed in accordance with good clinical practice guidelines. All participants provided written informed consent. This substudy was approved by the ethics committee of the Hospital Universitario Ramón y Cajal (approval no. 107/17).

**Statistical methods.** The study sponsor shared the data with the investigators via the ClinicalStudyDataRequest.com consortium and had no role in the study design or analysis. Only patients treated with maraviroc at 300 mg b.i.d. or efavirenz at 600 mg q.d. in the MERIT study were included in this intention-to-treat post hoc analysis, since the maraviroc q.d. arm was abandoned at week 16. We aimed to assess the time to CD4/CD8 normalization at different cutoffs (>0.4 and >1.0). The rationale for this categorization was that (i) values of <1.0 correlate with immunosenescence in the general population (13) and HIV-infected individuals above this cutoff show levels of immunoactivation and immunosenescence similar to those of healthy controls (13) and (ii) a value of <0.4 (in a range of 0.3 and 0.5) appears to be the best cutoff to predict adverse outcomes in ART-treated HIV patients (5–7, 14).

For these cutoffs, we used Kaplan-Meier curves to calculate the time to and the rate of CD4/CD8 normalization and cumulative probabilities. Cox proportional-hazard models with Breslow methods for ties were used to compare the times to CD4/CD8 normalization by treatment arms. Then, we used generalized estimating equations (GEE) with an exchangeable correlation structure to compare longitudinal changes in the CD4/CD8 ratio taking into account repeated-measures and within-subject correlations, adjusting for the effects of age, sex, baseline CD4$^+$ and CD8$^-$ cell counts, and hepatitis C virus (HCV) serostatus. Interaction terms (time-versus-treatment arm) were created to assess whether these changes over time differed significantly between the two study arms. Continuous variables were log transformed when necessary to satisfy model assumptions. All statistical analyses were conducted with Stata v. 14.0 (StataCorp LP, College Station, TX, USA).

**Characteristics of the study population and duration of follow-up.** A total of 721 subjects were included in this subanalysis, 361 treated with efavirenz and 360 treated with maraviroc at 300 mg b.i.d. Patients were representative of a medium-aged (37 ± 9.6 years) population with a higher prevalence of men (71.4%) and with baseline median CD4$^+$ counts of 251.5 (range, 183 to 324) cells/mm$^3$. One hundred eighty-one patients on maraviroc b.i.d. and 168 patients on efavirenz completed the 96-week blinded period and entered the open-label phase. The study population was comparable in both arms with respect to demographic and immunovirological parameters without statistically significant differences in the assessed parameters, as has been previously described (15, 16), with a median CD4/CD8 ratio of 0.3 (interquartile range, 0.2 to 0.4) in both groups. The study disposition has been previously published (15). The total duration of therapy (overall sum of all of the patients’ treatment durations) was 1,243.3 years (median of 5.1 years per patient) in the maraviroc b.i.d. arm and 1,204.1 years (median of 3.9 years) in the efavirenz q.d. arm.

**Changes in CD4/CD8 ratio normalization per treatment arm.** Using Kaplan-Meier methods, the median time to a CD4/CD8 cutoff of >0.4 was 10 (range, 0 to 37) weeks for efavirenz versus 14 (range, 0 to 47) weeks for maraviroc (log rank test $P = 0.009$). Similar findings were observed for the time to CD4/CD8 normalization at a cutoff of >1.0, with a median of 151 (range, 53 to 274) weeks for efavirenz versus 209 (range, 61 to 278) weeks for maraviroc (log rank test $P < 0.001$). Figure 1 shows Kaplan-Meier survival plots of estimated overall 5-year CD4/CD8 normalization at cutoffs of >0.4 and >1.0.
We explored the cumulative probabilities of CD4/CD8 ratio normalization in proportional-hazards models. The probability of normalizing the ratio above 0.4 over time was 25% higher with efavirenz than with maraviroc (hazard rate \( HR = 1.25, P = 0.020 \)) (see Table S1 in the supplemental material). Similar results were obtained after adjustment for age, sex, the baseline CD4 count, the baseline CD8 count, and HCV serostatus, with an adjusted probability of normalizing the ratio 24% lower with maraviroc than with efavirenz (HR \( = 1.30, P = 0.007 \)). For CD4/CD8 normalization at a cutoff of 1, we found a 42% greater probability of normalizing the ratio over time with efavirenz than with maraviroc (HR \( = 1.42, P = 0.010 \)), which remained statistically significant in the adjusted model (HR \( = 1.43, P = 0.009 \)) (Table S2).

The linear CD4/CD8 ratio trajectories in the treatment arms were compared by using GEE, observing overall statistically significant changes (\( P < 0.001 \)) (Table S3). The overall longitudinal changes in the CD4/CD8 ratio are represented in Fig. 2, which illustrates that differences were already apparent within the first year of the follow-up. Finally, using GEE modeling, we examined whether the overall CD4/CD8 ratio increase was driven by increases in CD4\(^+\) T-cell counts, decreases in CD8\(^-\) T-cell counts, or both (Table S3). While no statistically significant CD4\(^+\) T-cell count changes between treatment arms were found, the CD8\(^+\) counts showed a marked and significant decrease in

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**Fig 1** Kaplan-Meier analysis for the comparison of time to CD4/CD8 normalization at cutoffs of 0.4 (a) and 1.0 (b).
the efavirenz arm, indicating that the better CD4/CD8 ratio recovery observed in the efavirenz arm was driven by a CD8⁺ T-cell count decline, rather than by a CD4⁺ T-cell count increase.

Discussion. In this post hoc analysis of a randomized, double-blind phase IIb/III clinical trial with a 5-year follow-up, efavirenz-based first-line ART was found to be more efficacious at improving the CD4/CD8 ratio than was maraviroc-based ART. Against our research hypothesis, patients treated with maraviroc showed slower CD4/CD8 ratio recovery and lesser CD8⁺ T-cell count declines. Some, but not all, studies of maraviroc intensification have shown a reduction of immune activation (17–20). In a substudy of the MERIT trial involving 57 subjects, there was an earlier decrease in the marker of percent CD4⁺ CD38⁺ T cells and a smaller proportion of patients with high-sensitivity C-reactive protein levels of >2 µg/ml, a threshold indicating low-grade inflammation. A recent comparison of maraviroc and tenofovir, each combined with boosted darunavir or emtricitabine, highlighted a greater capacity of maraviroc to increase the CD4/CD8 ratio after 48 weeks, although subjects treated with maraviroc showed smaller CD8⁺ T-cell count declines (21). We and others have shown that maraviroc exerts unique effects on the gut mucosa, implicating maturation and activation, likely explained via CCR5 signaling, increases in circulating CCR5 ligands, and higher drug concentrations in the gut tissue than with efavirenz (8, 22). Although unexpected, mechanistically, our results could be explained by the paradoxical increases in mucosal CD8⁺ T-cell activation that we (22) and others (8) have observed under maraviroc intensification, given the strong correlation between the CD4/CD8 ratio and CD8⁺ T-cell activation in the gut and blood (5, 22). It should be noted, however, that other studies have failed to demonstrate the putative beneficial effects of maraviroc on immunoactivation and inflammation (23–25), T-cell recovery (15, 26), or the development of immune reconstitution inflammatory syndrome (26).

Emerging data suggest that chronic inflammation, a hallmark of treated HIV infection, might be affected by the ART regimen selected (27–29). Given the correlation of the CD4/CD8 ratio with markers of activation of both the innate and adaptive immunity (5), we performed a subanalysis of the STARTMRK study. We observed a statistically significantly higher rate of CD4/CD8 ratio normalization with raltegravir than with efavirenz. In contrast to the present study, the differences between regimens were smaller and were explained by a greater CD4⁺ T-cell count increase in the raltegravir arm, without differences in the CD8⁺ T-cell count dynamics. To the best of our knowledge, this is the first report highlighting differential effects of two first-line ART regimens on CD8⁺ T-cell counts. Higher levels of circulating CD8⁺ T cells have been associated with adverse outcomes and seem to capture the spectrum of non-AIDS conditions linked with chronic immune activation that is captured by the CD4/CD8 ratio (5, 7, 30).

Maraviroc is now prescribed only in certain situations, so it is unlikely that these results affect clinical decisions. Moreover, zidovudine is a first-generation nucleoside
reverse transcriptase inhibitor (NRTI) associated with bone marrow toxicity, which could have affected CD4/CD8 ratio dynamics. Given the lack of interaction of zidovudine with efavirenz or maraviroc and the randomized study design, it is unlikely that this effect has influenced our findings. Another important limitation of our work is that current NRTI backbone regimens in most countries no longer include zidovudine, which raises the question of whether similar findings would have been obtained with modern NRTIs.

There is now increasing awareness that ART might not be able to fully normalize health, and clinical research is shifting from strategies aimed at suppressing HIV replication and increasing CD4⁺ T-cell counts to evaluation of the impact of therapies designed to mitigate persistent immune defects. Our data highlight the need to evaluate new outcomes in ART trials, as a clear impact of surrogate markers linked with the risk of non-AIDS events such as the CD4/CD8 ratio might have been overlooked and should influence the positioning of ART regimens in clinical guidelines. The small variation in the effect of the treatment arm on the CD4/CD8 ratio after adjustment by factors known to influence the CD4/CD8 ratio indicates that the drug class used might affect this biomarker of clinical progression.

In conclusion, our data show, for the first time, distinct effects of two first-line ART regimens on CD8⁺ T-cell count dynamics and, secondarily, on the rates of CD4/CD8 ratio normalization at clinically meaningful cutoffs. These outcomes have been largely overlooked in clinical trials. Our findings provide a rationale for comparing the effects of different ART regimens on immune activation and for considering the CD8⁺ T-cell count and the CD4/CD8 ratio as outcomes in future studies.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01763-17.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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REFERENCES

sets, heightened CD8+ T-cell activation, and increased risk of non-AIDS morbidity and mortality. PLoS Pathog 10:e1004078. https://doi.org/10.1371/journal.ppat.1004078


