because we did not observe any decrease in the plasma 16S rDNA between enrollment and intensification start (data not shown). Additional work is needed to clarify the mechanism responsible for the effect of maraviroc on the plasma load of bacterial compounds and the versatile effect of maraviroc on T-cell and monocyte activation. Apart from technical issues, the latter might depend on the baseline level of immune activation, as suggested by Hunt et al.[1] Of note, in their study, the preintensification duration of treatment was 4 times shorter, and the percentage of HLA-DR$^+$ CD38$^+$CD8$^+$ T cells at week 0 was 50% higher than in our study.

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Acknowledgments: The authors are grateful to all of the investigators who participated in the MARIMUNO assay.

Contribution: C.P. and B.A. were in charge of the immunological part of the study; J.-P.L. quantified 16S rDNA; C.B., J.G., C.L.-C., L.C., and J.R. were in charge of the study in their clinical centers; S.T. was the project manager; P.F. performed the statistical analysis; and P.C. was the principal investigator of this substudy of the MARIMUNO-ANRS 145 study and wrote the manuscript.

Conflict-of-interest disclosure: C.P., J.R., and P.C. have received honoraria for lectures from ViiV Healthcare. J.R. and P.C. have been advisory board members for ViiV Healthcare. P.C. received a research grant from ViiV Healthcare. J.G. has received honoraria and support for travel expenses from ViiV Healthcare. The remaining authors declare no competing financial interests.

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Response

Maraviroc intensification and microbial translocation

In response to our recently published trial,[1] Psomas et al present new microbial translocation data from another recently published uncontrolled trial of maraviroc intensification in HIV-infected individuals with incomplete CD4$^+$ T-cell recovery.[2] They observed significant reductions in plasma 16S ribosomal DNA levels, which is consistent with the significant reductions in plasma lipopolysaccharide (LPS) levels observed in our trial.[1] Although both of these observations support the hypothesis that maraviroc decreases microbial translocation, it is important to emphasize that the plasma LPS declines observed in the maraviroc arm of our trial were not significantly different than those observed in the placebo arm. To date, no randomized controlled trial has proven that maraviroc decreases microbial translocation. Indeed, in another uncontrolled trial of maraviroc intensification, plasma LPS levels actually increased.[3] We highlighted the reduction in plasma LPS levels in the maraviroc arm of our study because it occurred despite a tendency for neutrophil counts and soluble markers of monocyte activation to increase. We thus speculated that an increase in monocyte, macrophage, and neutrophil activation might contribute to increased clearance of microbial products. We recognize that

this is a hypothesis that has yet to be proven, but it remains a viable potential explanation for the immunologic changes we observed.

Psomas et al also highlight the different conclusions reached by our trials regarding the effects of maraviroc intensification on changes in T-cell activation and monocyte activation. As discussed in our recent paper,[1] we agree that technical issues and differences in patient populations may have contributed to the reductions in T-cell activation observed in several uncontrolled trials of maraviroc intensification.[2-4] Psomas et al discount the possibility that increased adherence to the background antiretroviral therapy regimen could have contributed to the decreased T-cell activation levels or plasma 16S ribosomal DNA levels observed in their study because levels did not significantly change between enrollment and the start of study medication, but adherence typically improves when trial subjects start taking a study medication, particularly when they know that pills are being counted. This appeared to be the case in the placebo arms of our trial and another recent placebo-controlled treatment intensification study.[1,5] This is one of the reasons why double-blind randomized placebo-controlled trials are the gold standard for evidence in clinical research. We agree that further research will be necessary to understand many of the unexpected effects of maraviroc intensification on the immune system in treated HIV infection, but strongly suggest that this work be conducted in the context of adequately powered randomized controlled trials so that observed effects can be clearly attributed to the intervention.

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Acknowledgments: The original study was funded by investigator-initiated research grants from Pfizer, Inc, and the American Foundation for AIDS Research (amfAR, http://www.amfar.org/, 107170-44-RGRL). Additional support was provided from the National Institutes of Health (P30 AI27763 and UL1 RR024131). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Contribution: P.W.H. wrote the first draft of the manuscript; and M.M.L. and S.G.D. assisted with the interpretation, discussion, and editing of the letter.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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To the editor:

MYD88 (L265P) mutation is an independent risk factor for progression in patients with IgM monoclonal gammopathy of undetermined significance

MYD88 (L265P) is a recurrent somatic mutation in Waldenström macroglobulinemia (WM).[1-4] By means of allele-specific polymerase chain reaction (AS-PCR), the *MYD88* mutation is detectable in almost all patients with WM and in roughly half the patients with IgM monoclonal gammopathy of undetermined significance (IgM-MGUS).[2,3,5]

IgM-MGUS patients have a probability of progression to WM or to other lymphoproliferative disorders (LPD) of ~1.5% per year, and the initial concentration of the serum monoclonal (M) protein is the main predictor of progression.[6]

In a case-control study of 77 IgM-MGUS patients, we previously demonstrated that the *MYD88* mutation was associated with higher disease burden and with a higher risk of progression to WM or to other LPD.[2]

We have now analyzed by AS-PCR bone marrow samples, collected at the time of diagnosis, of 136 consecutive IgM-MGUS patients, with the aim to confirm the prognostic role of the *MYD88* mutation in a longitudinal study and to evaluate the effect of the *MYD88* mutation and of the other potential risk factors in multivariate analysis.

Genomic DNA was extracted from bone marrow mononuclear cells (n = 92) or archival Giemsa-stained slides (n = 44). AS-PCR was performed as previously described.[2] Sensitivity of AS-PCR was 0.1%. Cumulative probability of progression was calculated using the Kaplan-Meier product-limit method. The effects of potential risk factors on progression rates were examined in a Cox proportional hazards model.

The *MYD88* (L265P) mutation was detected in 71 of 136 patients (52%). Patients were followed for a total of 469 person-years (median, 34 months). During follow-up, 11 of them (8%) progressed to WM (n = 9) or to marginal zone lymphoma (n = 2). Eight of 9 patients who progressed to WM and 1 of 2 patients who progressed to marginal zone lymphoma carried the *MYD88* (L265P) mutation at the time of diagnosis of IgM-MGUS. The other 2 patients were *MYD88* wild type at diagnosis as well as at progression.

In a competing-risk model considering death for any cause as a competing event, the 5- and 10-year cumulative incidence of progression was respectively 15% and 45% in patients with the *MYD88* mutation compared with 2% and 14% in patients with *MYD88* wild