Reply: Beyond Viral Suppression

To the Editor—We thank our esteemed colleague Professor Georg Behrens for his comment regarding our publication. It was highlighted that the DUALIS study protocol has undergone several revisions throughout the study. All amendments were (1) fully transparent, (2) concordant with all legal regulations, and (3) disclosed to the applicable authorities and institutional review board, and therefore they did not affect the integrity or the design of the trial. However, the differences addressed in the trial registers should not have occurred. Meanwhile, all protocol changes have been processed as protocol amendments, and the ClinicalTrials register (NCT02486133) has been updated.

DUALIS compared a switch to ritonavir-boosted darunavir in combination with dolutegravir (2DR), compared with the continuation of the standard-of-care treatment, consisting of 2 nucleoside reverse-transcriptase inhibitors in combination with ritonavir-boosted darunavir (3DR) in patients who are virologically suppressed and have human immunodeficiency virus (HIV) infection. Changes in the allowed backbones with the addition of emtricitabine (FTC)/tenofovir alafenamide to FTC/tenofovir disoproxil fumarate and abacavir/lamivudine in protocol amendment 2.0 were based on changes in the European (to EACS 8.0; see https://www.eacsociety.org/files/guidelines_8.0-english-revised_20160610.pdf) and national (German–Austrian) antiviral treatment guidelines during the study period; these were intensively discussed during meetings among the investigators. The switch in the backbone treatment in the standard-of-care arm was allowed at any time during the study follow-up period; accordingly, the backbone switch was not considered as treatment failure, as outlined in the main manuscript [1]. The document “Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry” cited in this context is the US Food and Drug Administration guidance for the pharmaceutical industry referring to pivotal trials. Therefore, the guidance is not applicable to DUALIS as an investigator-initiated study comparing licensed HIV agents; nevertheless, for the trial analysis, the study group adhered as close as possible to the referred guidance and stated differences wherever needed.

The aforementioned decision to allow a switch in the backbone during the study period might have impacted the analysis of the secondary outcome parameters. However, this does not hold true for the main outcome of the study, which was designed to show noninferiority of switching to 2DR in comparison to continuation of 3DR. Classifying the backbone switch in the 3DR arm as failure would have resulted in an even greater deviation from the noninferiority margin of −10% of the lower bound of the 95.48% confidence interval of the primary endpoint.

Regarding the missing P values in the abstract and tables, introducing P values is uncommon for non-prespecified endpoints. Therefore, the P value mentioned in Table 3 (referring to events on an event level rather than a patient level) should have been omitted, because statistical testing was not prespecified in this case. Of note, the comparison of discontinuations due to adverse events (2DR: 4.6%, 3DR 0.8%) at patient level did not reach a P level <.05, which was specifically mentioned in the comment. However, the reporting of nonsignificance might have led to misinterpretation.

Finally, questions were raised regarding the conclusions of the trial, as stated in the manuscript. The major hypothesis of the DUALIS trial was the noninferiority of 2DR versus the standard-of-care treatment. Neither benefit nor price or cost-eficacy were prespecified endpoints or the scope of the study, because DUALIS was not designed as an implementation study. Although we value the comments because these are highly important points in clinical HIV care, the main objective of the DUALIS study, as addressed in the main manuscript, was to assess noninferiority in terms of maintaining viral suppression in the 2DR group.

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Potential conflict of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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References
1. Spinner CD, Kümmerle T, Schneider J, et al.; DUALIS Study Group. Efficacy and safety of switching to dolutegravir with boosted darunavir in virologically suppressed adults with HIV-1: a randomized, open-label, multicenter, phase 3, noninferiority trial: the DUALIS study. Open Forum Infect Dis 2020; 7:ofaa356.