Reply to Banda et al., “Interpretation of Drug Interactions between Dolutegravir and Artemether-Lumefantrine or Artesunate-Amodiaquine”

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We thank Banda et al. for their interest in our study and for suggesting a procedure for handling biologically implausible concentrations. In the study group that investigated the drug-drug interaction between dolutegravir (DTG) and the artemisinin-containing therapy (ACTs) artemether-lumefantrine (AL), we reported higher DTG concentrations at 24 h postdosing (C_{24}) in the period when DTG was administered alone.

We agree with Banda et al. in their observation that participants do not perfectly adhere to study protocol instructions. We dispensed exact numbers of pills, monitored adherence by pill count, and directly observed the final dose. We investigated the possibility of a dosing error and found nothing to suggest that this had occurred. We recognize that others have reported unexplained peaks in concentration measurements of antiretroviral therapies. For example, Kakuda et al. reported a higher C_{24} in a healthy-volunteer study of a fixed-dose combination of darunavir plus cobicistat than that with darunavir and ritonavir as single agents (1). Unexpected peaks may occur due to enterohepatic circulation and by other mechanisms, including drug formulation and intersubject physiological variability (2). Castellino et al. report that 33% to 48% of the fraction of DTG absorbed in the gastrointestinal tract undergoes enterohepatic recirculation (3).

For these reasons, we felt that the most appropriate approach was to retain all data points in our analyses. However, we have stated (and Banda et al. acknowledge) that the statistical difference that we reported is not clinically significant.

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This is a response to a letter by Banda et al. (<https://doi.org/10.1128/AAC.00576-19>).

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