Author’s response to reviews

Title: Association of Endogenous Progesterone Levels in Young Women Using Hormonal Contraception with Recent HIV-1 Infection

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We thank the reviewers for their constructive criticisms and have revised the manuscript considerably with particular emphasis on testing the hypothesis that unsuppressed endogenous progesterone levels in women using hormonal contraception may be associated with recently acquired HIV-1 infection. Our responses to reviewer comments are as follows:

1. In the methods, ‘3 monthly intervals’ is confusing. It could be interpreted as being sampled at 3 1-month intervals or at 3-month intervals.

Response: We agree with the suggestion and have changed the phrase to ‘3-month intervals’.

2. Please include the length of follow-up for the women included in this study. Response: We added the following: “The median length of follow-up of women selected for this sub-study was 52 weeks.”

3. Provide the median time to first HIV-positive sample for the sero-converters and median length of for those that remain sero-negative.

Response: We included the following: “The median time to the first HIV positive test since enrolment was 24 weeks (IQR 12-52).” And elsewhere in the manuscript we stated that we also selected women who remained HIV negative at study completion (52 weeks).

4. Provide the breakdown of women who were randomized to use the placebo and the active microbicide gel. Did the active gel impact HIV acquisition in the parent study? Was there a difference in serum progesterone levels between active and placebo among sero-
converters and sero-negative women or those using HC and not using HC? An endogenous progesterone level and sero-conversion may have been masked by microbicide gel use.

Response: Unfortunately, for this sub-study we were not privy to the randomization assignment. We did include the findings of the parent study in the “Methods” section. “The HIV incidence in the MDP 301 trial was reported as 4.5 (95%CI 3.8-5.4) per 100 woman years for the active gel versus 4.3 (95%CI 3.6-5.2) per 100 woman years for placebo. In the latter study, the 0.5% and 0.2% Pro2000 vaginal gel was not efficacious in preventing HIV-1 acquisition.”

Nonetheless, there is no evidence of a topical microbicide altering systemic hormonal levels, particularly progesterone.

5. Reviewer 2 had serious concerns with the study approach, statistics and interpretation of the findings.

Response: We agree with the reviewer and redid the statistical analysis and revised the manuscript considerably while being more cautious with interpreting the findings. Some of our changes include the following:

i) Changed the title of the study from “Endogenous Progesterone Level in Young Women on Hormonal Contraception is not associated with HIV-1 Acquisition” to “Exploring Endogenous Progesterone Levels in Young Women Using Hormonal Contraception and in Association with Recent HIV-1 Infection”.

ii) We revised the tables considerably using a different approach to answering the key question in the study ie. “Is there an association between unsuppressed progesterone level in the presence of hormonal contraception and recently acquired HIV infection”. In Table I, we are reassured that both study groups were comparable and there was a lesser chance of selection bias. We further acknowledge our study limitations particularly the small sample size, and we believe our findings in this “Proof of Concept” warrant similar investigations in larger study cohorts.

iii) Lastly, we have corrected all editorial errors identified by the reviewer.

Once again, thank you for considering this manuscript for the journal and hope our responses meet with your satisfaction. For ease of reference, we have uploaded both a tracked and untracked version of the revised manuscript.