Author's response to reviews

Title: Effectiveness of two antifolate prophylactic strategies against malaria in HIV positive pregnant women in Bangui, Central African Republic: study protocol for a randomized controlled trial (MACOMBA)

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Author's response to reviews: see over
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The Editor

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Dear Editor

We thank you for the reviews of our manuscript: ‘Comparative Study of Effectiveness of Two Antifolates Prophylactic Strategies against Malaria in HIV Positive Pregnant Women in Bangui, Central African Republic (MACOMBA study protocol): a randomized open label control trial’ by Alexandre Manirakiza, Abdoulaye Sepou, Eugène Serdouma, Samuel Gondjé, Ghislain GB Bata, Sandrine Moussa, Aude Boulay, Jean-Methode Moyen, Olga Sakanga, Lénaig Le-Fouler, Mirdad Kazanji and Muriel Vray

We have taken account of all the comments and questions in revising the manuscript (highlighted text in the manuscript), which is attached. We also revised written English.

Best regards

Alexandre Manirakiza, MD, PhD
1. The study design is adequate to test the hypothesis for this study which is very relevant in the light of the ever increasing resistance to SP and the added burden of malaria among HIV infected pregnant women. This design also addresses the information gap related to the outcomes of CTM use in pregnancy in a randomized clinical trial as most reports provided so far on this subject are derived from studies not primarily designed to explore the effects of CTM on malaria in HIV infected women. The antimalarial effects have been documented but not in this vulnerable target population.

2. The details provided in the protocol are sufficient to allow replication of the work or comparison with related analyses.

2.1 However, with regards to participant information (the study population), the last statement ‘Women who already know their HIV status can also be included if their CD4 count is >350 and they have no opportunistic diseases (WHO stage 2, 3 and 4’, there is need to further clarify this statement as to whether the women will be re-tested and CD4 count checked at this stage of inclusion in the study or whether, the previous information shall form basis for recruitment (minor essential revision).

Authors’ response: Women who already know their HIV status can also be included if their CD4+ count is > 350 and they have no opportunistic diseases (WHO stage 2, 3 or 4). These women will not be re-tested for HIV, but their CD4+ count will be checked at this stage of inclusion in the study.

2.2 As regards to the eligibility criteria, the protocol is silent concerning the women who will be found to have malaria parasites (asymptomatic and symptomatic) at recruitment and yet they fulfill all other inclusion criteria, are these women going to be treated before inclusion? Or will they be excluded, treated and later perhaps re-considered for inclusion when they are no longer parasitaemic? -(Major compulsory revision)

Authors’ response: A woman who fulfills all the inclusion criteria but is found to have symptomatic malaria parasites at recruitment will be treated for the malaria episode and will not be included in the study. She will be reconsidered for inclusion later, when she is no longer parasitaemic. All women with asymptomatic malaria parasites at baseline will
be included and randomized to either SP-IPT or co-trimoxazole group. If symptomatic malaria or persistence of asymptomatic malaria parasitaemia is seen 8 days later, the woman will be given curative treatment, as stated above (Figure 1).

2.3 The background information/relevance (rationale) did not reflect the current prevalence of malaria in the study area, to provide the burden of disease among the study population. This information is essential. Additionally, perhaps this information could help clarify whether; there would be a number of potential study participants with parasitaemia or symptomatic malaria at the time of recruitment as indicated in the item 2.2 above. (Major compulsory revision)

Authors’ response: The current prevalence of malaria among women at first presentation to an antenatal clinic in Bangui is estimated to be 23%

2.4 Under recruitment and randomization: perhaps further details on exactly how the randomization is being carried out will make this section clearer. It is mentioned that randomization will be centralized and stratified according to maternity clinic and gravidity. The actual process of how this will proceed is not entirely clear.(Discretionary revision)

Authors’ response: For each maternity clinic, two random lists for SP-IPT and co-trimoxazole in a ratio 1:1 will be generated for primigravidae and multigravidae, with the R software (version 2.14.1). Once a pregnant woman is confirmed to be eligible for the study, the field investigator will telephone the coordination staff at the Institut Pasteur of Bangui to indicate the gravid rank, and the staff will assign women to a treatment arm according to the randomization list, respecting the chronological order of inclusion.