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Journal Name:	International Journal of TROPICAL DISEASE & Health
Manuscript Number:	2013_IJTDH_6085
Title of the Manuscript:	Malarial Morbidity and Postnatal HIV Infection in Breastfeeding HIV-exposed Infants
Type of the Article	Research Paper

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This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	Methods: 1) There is no correspondence between the study design description ("<i>to evaluate the efficacy of daily supplementation with vitamins B, C and E in decreasing the incidence of select childhood morbidities among infants of HIV positive women in Dar es Salaam, Tanzania</i>") and the title of the manuscript as well as what is described in the introduction, in the results and conclusions. Please, comment and take action 2) The setting of the study is not described: which antenatal clinic? In public or private settings? Which laboratory performed the analysis? In which supporting program, if present? Please, specify the study setting. 3) In the section "Standard of care": The described period of enrolment runs from February 2004 to July 2007. Anyway it is then described that mothers were routinely evaluated for ART eligibility only since July 2005. What happened before? Please, specify the ARV prophylaxis regimens given to the patients or the ARV regimens started according to immunological and/or clinical and/or virological features. 4) In the study malaria cases are classified in three groups: clinical malaria, probable malaria and confirmed malaria. In order to better clarify this classification I suggest to categorize the cases of malaria in two groups: confirmed (clinical features+laboratory confirmation) and probable	METHODS: 1. Thank you reviewer # 2 for this comment. It is possible that our presentation might have been confusing. We have modified the text to explicitly inform readers that our study is a nested prospective cohort study that takes advantage of data collected as part of a clinical trial. 2. Thank you for this critique. I have provided additional information as follows: Pregnant women who intended to maintain residence in Dar es Salaam for two or more years post-delivery and who received medical care during pregnancy at either the Makuti or Tama Study Clinics as part of the Muhimbili, Dar es Salaam and Harvard research collaboration project were enrolled in the parent study between February 2004 and July 2007. 3. We state that at the beginning of the study, maternal ART was limited to neivrapine administered prophylactically to prevent HIV MTCT intra-partum or peri-partum. We have specified that mothers were evaluated beginning July 2005 for ART for their own health. 4. Our analytic strategy including 3 case definitions of increasing specificity already provides the information suggested by the reviewer. We prefer to continue with our present approach as it confers the advantage of seeing the relative impact of clinical malaria (the current standard of practice) in relation to more stringent malaria definitions for research purposes – i.e. laboratory confirmed malaria. 5. We disagree with the reviewer regarding whether or not the timing of HIV infection assessment was clearly stated. In fact, we dedicate most of the that paragraph to describe in extensive detail the timing of HIV testing in the parent study and most



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	(only clinical features without laboratory confirmation). 5) In the Outcome section it is not clear the timing schedule of HIV screening: every 6 months? Only at 6 weeks and then at 24 months? Please, clarify and if possible, add a table with this information and the corresponding results (with only the total numbers). Results: 1) I suggest to describe in detail the 91 children who became HIV infected during follow up: the year of diagnosis, how long they were breastfed, which ARV prophylaxis or treatment regimens took mothers, malaria diagnosis and treatment, immunological status of mothers, ARV regimen taken from the newborns 2) In table 2 and 3 no <i>p values</i> are provided to assess statistical significance . Please, complete these results.	importantly for how time at risk for HIV infection was calculated for the present study. Please see below directly from our manuscript “Per protocol of the parent study, real-time HIV tests were done at 6 weeks and 24 months; however, blood samples for future HIV testing were stored every 6 months. Blood samples for children HIV-positive at 24 months were back-tested to estimate the approximate age at HIV infection. For the purpose of this study, children HIV-negative at 6 weeks were at risk of breastfeeding-related postnatal HIV infection only until the end of breastfeeding only.(14) Hence, we limited child malarial morbidity to those diagnoses that occurred during breastfeeding and up to the date of breastfeeding cessation plus an 8-week sero-conversion window to avoid the confusion of temporal sequence between child malarial morbidity and postnatal HIV infection. Per the literature, it may take up to 56 days for HIV antibodies to appear.(22) Because breastfeeding is the primary risk factor for HIV infection for infants HIV-negative at birth, observations were censored for HIV-positive children at either the first HIV-positive blood sample date or the last breastfeeding date plus 56 days, whichever was sooner.” RESULTS: 1. We thank the reviewer for highlighting the importance of these data. We agree with the request to provide this information but respectfully state that this information was already present in our manuscript. Specifically, our results section states thus: “Median breastfeeding duration for children who became postnatally HIV-positive and those persistently HIV-negative through the end of breastfeeding were 4.7 (variance =6.3) and 4.1 months (variance=5.9), respectively.” We also go further to provide details of associations between key child and maternal parameters and infant postnatal HIV-positivity. “There was no relationship between postnatal HIV infection and child micronutrient supplementation (HR=0.98; 95%CI:0.64-1.49) or child baseline CD4%<25 (HR=1.28; 95%CI:0.77-
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		2.14) level. Likewise, there was no association between child postnatal HIV infection risk and the following indicators of maternal health status: maternal malaria, maternal anemia status, or maternal ARV use (Table 3). However, poor maternal immunologic status, as indicated by CD4 T-cell count <350 vs. ≥ 350 cells/μl, was associated with a nearly three times higher risk of postnatal HIV infection. In comparison, current maternal ARV use exhibited a non-statistically protective association with child postnatal HIV infection (Table 3)". 2. The reviewer is correct that we do not provide p-values. We do not provide the confidence intervals we provide allows the reader to assess both statistical significance and the potential range of benefits for reduction in HIV transmission that can be expected with implementation of malaria prevention programs in HIV-exposed infants. Contrary to the reviewers' suggestion, we assess statistical significance by providing the 95% Confidence Intervals. These estimates provide the range of values consistent with our shown average effect at the alpha of 0.05. The exclusion/inclusion of the null value (Hazard Ratio = 1) allows the reader to judge the statistical significance of our results. Presenting the range of values consistent with our average effect informs readers of not only the p-value but allows practitioners, policy makers and others in the position to mitigate malaria risk in HIV-exposed infants to gauge the potentially beneficial impact an intervention might have in their population.
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<u>Minor</u> REVISION comments	Introduction: The Author may consider adding the following recent review reference in the introduction section: Focà et al., Malaria and HIV in Adults: when the parasite runs into the virus. <i>Mediterr J Hematol Infect Dis.</i>2012;4(1); e2012032. Funding source: Please, specify the funder of this study.	1. Again we are grateful for this comment. The citation highlighted by reviewer #2 has now been included in the introduction as reference 5. 2. Funding Source: This work was supported by the National Institute of Child Health and Human Development Grant#: R01HD043688. CD was supported in part by K24 HD058795.
<u>Optional/General</u> comments	This is an interesting study which aims to evaluate the impact of malaria on the risk of HIV sero-conversion in children born from HIV-positive mothers. I therefore suggest to better investigate and describe the statistical and methodological aspects in order to attest the significance of the results.	We thank the reviewer for appreciating the relevance of this study and providing the above comments that have helped to improve the potential impact of this study.