Author’s response to reviews

Title: Growth patterns among HIV-exposed infants receiving nevirapine prophylaxis in Pune, India

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Dear Editor,

Thank you for having our manuscript entitled “Growth patterns among HIV-exposed infants receiving nevirapine prophylaxis in Pune, India” peer-reviewed. We appreciate the excellent and detailed comments given by Dr. Nachman and Dr. Swaminathan.

We have addressed each of the comments / suggested revisions provided by the two reviewers and below are our responses:

Reviewer 1 – Sharon Nachman

1. I understand that few of the infected babies were started on HAART during the first year of life, even though they were identified as HIV+. “Only 16 HIV-infected infants were on HAART during the follow-up period”, of the 93 who were infected. Do the authors think that their data would be different now as many of these babies are treated early on and cART is available in the public sector?

Response: We are unsure whether the data would be different now. Based on NACO annual report for 2010-11, there are 79,719 children registered for ART, of which 33,058 (41.5%) were ever started on ART, and only 22,837 (28.6%) are alive and on ART. Although availability of cART has improved, the average age at which HIV-infected infants present for care in India is typically 6 years and many infants with perinatally acquired HIV infection remain undiagnosed and uninitiated on treatment (Padmapriyadarsini et al, 2009). Currently very few infants less than 1 year of age are on HAART in India despite the new guidelines. At the BJ Medical Center ART Center in Pune, where our research was conducted, we have 15 infants (about 15% of children under 5) that are currently on HAART. Therefore, we think that monitoring growth and nutritional status remains an important strategy for identifying infants in need of targeted intervention whether in terms of nutrition and/or antiretroviral therapy. In addition, our data remain highly relevant with respective to HIV-exposed, uninfected children.

2. Despite the finding of a significant difference in hemoglobin of 10.1 in the moms of the babies identified as HIV+ to 10.8 in those babies who were not infected, I am not sure how critical or clinically relevant it is. Would the study team think that clinicians would use that as a guide with
moms when discussing possible outcomes?

Response: Maternal hemoglobin level remains a critical predictor of gestational weight gain (Young et al. 2012) and subsequent infant outcomes. It is routine practice to measure maternal hemoglobin levels during antenatal visits, and our data reinforce the need for women with lower hemoglobin levels to be identified during pregnancy and more closely monitored and managed to prevent adverse outcomes for both maternal and infant health irrespective of the HIV status.

3. Clearly stunting was seen early in the infected cohort (but really only 28 infants were infected in utero and appearance of stunting at that age should be used as a reflection of that early infection). It is the stunting that occurs in a non-stunted baby after 1 month that should trigger an urgent HIV test.

Response: Both stunting and underweight manifested early in the infected cohort, and since stunting is an indicator of chronic growth failure, we agree that manifestation of stunting among those non-stunted within 6 weeks should trigger an HIV test underscoring the importance of growth monitoring of all HIV-exposed infants.

4. In the discussion the authors comment that “SWEN exposure was associated with lower risk of wasting in HIV-exposed, uninfected infants”, underscoring that it was its use and prevention of HIV infection that really protected these infants from stunting. They go on to suggest that maternal factors such as education may be as important as CD4 or viral load. The authors correctly point out that Maternal education is not only a good measure of their knowledge of health-related issues, prenatal and postnatal infant care, infant feeding practices, and better sanitary habits, but it also impacts health-seeking behavior, income generating capacity, and ability to make autonomous decisions. Perhaps putting these two sections together in the discussion will help the clinician with their patients.

Response: We agree with the suggestion that the association between SWEN exposure and lower risk of wasting in HIV-exposed, uninfected infants could primarily be because SWEN was instrumental in protecting infants from getting HIV infection, thereby lowering the risk of wasting. Although this explanation is plausible, there could be alternate explanations as suggested the second reviewer that SWEN may have effects on absorption /prevention of GI infections. There is paucity of data with regard to the mechanisms by which SWEN has an impact on growth indices. Ascertaining the level of maternal education at first antenatal clinic contact in conjunction with measuring levels of malnutrition and anemia would be helpful to clinicians in providing adequate information and care to HIV-infected pregnant women and subsequently ensuring positive outcomes for infants.

5. Do the authors think that the HIV+ moms who were sicker had inadequate milk for breastfeeding (not supply, but quality)? Especially if these moms had lower CD4, higher viral load and a higher likelihood of their babies getting infected?

Response: It is quite likely that HIV-infected mothers who are sicker were also malnourished. Unfortunately, we have not evaluated the quality of breast milk and therefore cannot address this issue adequately.

6. Overall this is an interesting snapshot of the SWEN era study (2002-2007), but its current clinical relevance today is not as clear.

Response: In India, the proportion of total institutional deliveries according to District Level Household Survey (DLHS III) conducted in 2007-2008 was only 47% overall and 63.8% in
Maharashtra (Ministry of Health and Family Welfare Annual Report 2011-12, Chapter 4) and often pregnant women are not HIV screened. There is wide disparity not only in HIV screening of pregnant women but also in antenatal prophylaxis of those found to be HIV-infected. Additionally, infants born to mothers who delivered in non-institutional settings may not receive HIV screening unless they present with symptoms and HIV infection is suspected (Seth et al, 2012). Most symptomatic children may present with diarrhea, sepsis or pneumonia which also commonly occur during infancy. Without early diagnosis and treatment, HIV-infected infants in the first year of life remain at high risk of morbidity and mortality. Therefore, we believe that our data remain relevant especially in the Indian context.

Reviewer 2 – Soumya Swaminathan

1. The role of Nevirapine in protecting against under-nutrition is less clear, however, and the authors have been unable to provide a good explanation for the observed effect, especially in the uninfected babies. This could have been a coincidence or Nevirapine may have effects on absorption/prevention of GI infections that are not well known.

Response: We agree with the reviewer that it could be a coincidence or that NVP may have an impact on absorption/prevention of GI infections. Interestingly as we describe in our discussion, Palumbo et al (NEJM) found that NVP based HAART was associated with better growth parameters compared to PI-based HAART in young HIV-infected children who were randomized to receive either regimen. Therefore this finding that longer NVP exposure may have some improved effects on growth needs further study to determine if there is a biologically plausible explanation for these observed findings in two different studies of two different populations of children.

2. Page 2 Result section 6th line -please clarify which of these groups had the “worst” outcomes “In utero HIV infection had the worst growth outcomes. Infants infected at birth had the worst growth outcomes during the follow-up period.”

Response: In the Results section of the abstract, the sentence “In utero HIV infection had the worst growth outcomes” has been deleted, and we have revised the following sentence “Infants infected at birth had the worst growth outcomes during the follow-up period” to “Infants infected in utero had the worst growth outcomes during the follow-up period.”

3. Page 9 Results section 10th line-discrepancy from Table 1 Both cohorts had a similar median duration of breastfeeding (99 days vs. 98 days) and proportion breastfed for 1-4 months (81% vs. 79%). A significantly higher proportion of infants in the infected cohort were hospitalized for illnesses during the follow-up period compared to those in the uninfected infants (37% vs. 18%, p<0.0001).

Response: The sentence beginning with “Both cohorts had a similar median duration of breastfeeding (99 days vs. 98 days)…” has been corrected to “Both cohorts had a similar median duration of breastfeeding (98 days vs. 98 days)…” as per values in Table 1.

4. It is mentioned that only 16 HIV-infected infants were on HAART during the follow-up period. However, there is no mention regarding its time of initiation and its influence on growth patterns.

Response: Of the 16 infants on HAART, we did not have the date of initiation for one infant, 2
infants began HAART early before 3 months, 6 infants began HAART between 6 and 8 months, 5 infants between 9 and 12 months and 2 infants after 12 months. We did not look into the influence of HAART on the growth patterns since the sample size was so small and we did not believe we can draw any meaningful conclusions from analyzing these data.

5. In Table 1 the unit of infant gestational age (weeks) is not mentioned.

**Response:** The unit for infant gestational age “in Weeks” has been added in Table 1

6. Hospitalization Total does not match with HIV infected and uninfected. (It should be 156 total hospitalization and not 1546). Height for age score has to be changed to Length for age score as throughout the text LAZ is used and not HAZ. In the footnotes it is mentioned that comparison of median values are based on Pearsons X2 test but it should be Mann Whitney test

**Response:** The typo on Table 1 for “Hospitalization, Total” has been corrected to 156 and “Height for age score” has been changed to “Length for Age”. In the footnote for table 1, the following sentence has been changed to “…comparison of median values are based on Mann Whitney test.”.

7. Discretionary Revision: Table 3 can be deleted as findings are mentioned in the text. In Table S1-S3 mean scores can be included.

**Response:** Thanks for your comment. We have moved Table 3 to a supplementary table S7 as we do not fully describe the comparisons in the text. We have added the mean scores to Tables S1-S3, and included some of the references suggested by the reviewer.

We hope that these responses and revision are acceptable for the manuscript to be published. Please contact me if you have any questions.

Sincerely yours,

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