Reviewer's report

Title: Impact of antiretroviral treatment on height evolution of HIV infected children

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Reviewer: Paige Williams

Reviewer's report:

The authors of this paper describe development of a non-linear model to evaluate trajectories of growth, specifically height velocity, among children born with perinatally-acquired HIV infection. Their approach was based on maximum likelihood estimation of parameters combined with a MCMC procedure. Various approaches were used to evaluate the goodness of fit of the model. Covariates of interest were taken into account which allowed the investigators to assess the effect of ART regimen and other HIV-disease related measures (CD4 count, viral load, CDC stage) on height trajectories. Once the model was developed, the authors then simulated trajectories and summarize as median, 5th, and 95th percentiles of simulated trends. A large strength of this paper is the rich data source on growth measurements in the 447 children over time, with a median of over 100 measurements per child. However, a major concern I have with the approach as implemented is that it treats sex as a "covariate", rather than developing completely separate trajectory models with different shapes for males and females. Given the well-known differences in timing of pubertal growth spurts, it seems naïve to consider just adjusting for sex. Based on the numbers of males and females and the per-subject number of height measures, there should be adequate support for development of separate models. The pattern over age of height measures should be displayed separately for males and females to allow for their known differences. This approach would also allow the evaluation of whether the effects of HIV-related disease measures differ for the two groups, as has been noted in several past papers. Additional major and minor comments are noted below.

Major comments:
1) Abstract, results: The statement in the results that final adult height was lower in females than males is obvious, since women are known to be shorter than men. This finding is a reflection of the author's strategy that treats sex as an adjustment covariate, rather than developing separate trajectory models for males and females based on their known differences in height velocity patterns over age.

2) Abstract, results: It was unclear which of the comparisons of final adult height formed the basis of the results reported in the abstract. The authors develop a comprehensive non-linear model for final height, but the main text of the paper notes that only 48 children had measurements of height after age 18 and summarize the median final height for males and females in that small subset.

3) Abstract, results: The methods (and background) suggest that one of the main covariates of interest is ART regimen (NRTI, NNRTI, or PI-based), but the results mention nothing about
whether there were any differences in height velocity or final height based on ART regimen. It
would be important to add this to the list of covariates which did not affect either height velocity
or final height if that is the case (in addition to age at any ART initiation).

4) Abstract, conclusion: The conclusions emphasize the finding of an effect of age at ART
initiation on height velocity, but isn't the ultimate outcome the final adult height? It may be
worth adding to the conclusion "however, final adult height was not linked to age at ART
initiation".

5) Introduction: the authors note that only a few studies have evaluated the effect of ART on
height in children with HIV, but then cite about 20 papers that do evaluate this issue. This seems
to be a misrepresentation of this area of literature. In addition, there are several recent papers
which are not included which either provide reviews of this area or are major contributions,
including Shomaker et al (Int J Epi 2017), Williams and Jesson (Curr Opin HIV/AIDS 2018),
Melvin et al (J Ped Inf Dis, S 2017), Boettiger et al (J Adol Health 2016 and PIDJ 2016), and
Jesson et al (PIDJ 2015). The introduction should be revised to reflect more of the current
wealth of literature in this area, while still noting some of the limitations in previous studies.

6) Methods: The authors state that "Likelihood ratio tests (LRT) including the log-
likelihood, Akaike information criteria (AIC) and Bayesian information criterion (BIC) were
used to test different hypotheses regarding the final model, covariate effect(s) on parameters." First,
it's not clear why the phrase "including the log-likelihood" is part of this sentence, since a
LRT would obviously be based on the log-likelihood. But secondly, AIC and BIC are not
equivalent to hypothesis tests - they are measures of goodness of fit which depend on penalty
terms for number of parameters, and may not produce the same decision about the best model as
an LRT.

7) Methods, p.8: On lines 144-146, the authors again equate the reduction in AIC or BIC to
a likelihood ratio test, which is not accurate.

8) Results, p.10: Unclear whether the authors meant a lower CD4 percentage and lower
percentage with wasting, or (more likely), a lower CD4 percentage and a higher percentage with
wasting. Suggest rewording for clarity.

9) Results, p. 10: Since the median adult height is provided separately for girls and boys,
please indicate also the number of boys and girls with measurements after age 18 (among the
n=48).

10) Results, p.15: The final adult height based on the model is stated to be 176cm in males
and 170cm in females without ADEs, and 170cm/164cm in males/females respectively with
ADEs. In each of these subgroups there is about a 6cm difference, whereas the difference in
median adult height noted on p.10 was more than twice as large. Do you have any sense of why
the model results would suggest smaller differences?

11) Since so few of the children (only about 10%) have any measurements after age 18, can
the model predictions be trusted or are they extrapolating beyond the range of data? Since
females generally attain their final adult height at a much younger age than males (around 15 years as compared to around 18 years), are the adult height values estimated for females likely to be more precise?

12) Results/Discussion: It is noted that the model fit for final height was not improved by accounting for any covariates other than sex or children and occurrence of ADEs. However, the results for LRT, AIC, or BIC for other key covariates such as type of ART regimen are never presented, so it is difficult for the reader to draw their own conclusions.

Minor comments:

1) Some wording is awkward and needs to be corrected.
   a. On p.7, lines 119-120, it should say that the SAEM algorithm was "combined with" a MCMC procedure rather than "combined to" a MCMC procedure.
   b. On p.7, also change "Likelihood ratio test (LRT) ..were used" to "A likelihood ratio test (LRT)" or to "Likelihood ratio tests (LRTs)"
   c. In the same sentence, add the word "and" before the phrase "covariate effects on parameters".
   d. On p.7, change "A model…fitted the observations" to "A model…was used to fit the observations".
   e. On p.16, change "other studies did not found any differences" to "other studies did not find any differences".

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

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