Author’s response to reviews

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

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Author’s response to reviews:

OUR RESPONSE INCLUDES FORMATTED PARTS. WE HAVE UPLOADED A WORD FILE CONTAINING THE RESPONSE

Walter Dehority, MD, MSc
Editor, BMC Pediatrics

July 30, 2019
Dear Walter Dehoriity, MD

I would like to thank you for the reviewers’ comments about our original research article entitled “Impact of antiretroviral treatment on height evolution of HIV infected children”.

Please find attached the revised manuscript, and find below our response to each of the specific comments in the order that they were provided (the reviewer’s comments are in italics).

Reviewer 1: Paige Williams, PhD

GENERAL

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 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.

Major comments:

Comment 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.

Response:

Thank you for this comment. Using the same methods, we fitted a model for each sex, then
plotted the VPC. We agree that the advantage of fitting a model for each sex is that the VPC
shows that the effect on pubertal growth appears earlier in girls.

Therefore, we have modified (underlined) the following sentences in the Methods and Results
sections:

- Page 7, line 120

“Parameters were estimated separately for males and females by computing the maximum
likelihood estimator of the parameters ...”

- Page 14, line 221-224

“The Supplemental Tables 1 and 2 provide the estimated values of the model parameters
separately for males and females. There was a good estimation of the parameters were
accurately estimated, as shown by the precision of these parameters (small relative standard
errors) [see Supplemental Table 1 and 2 in Additional file 1].”

Comment 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.
Response:

We agree that the abstract was unclear. We meant “final height predicted by the model” for the 477 children participating in the analysis, whether or not the actual adult height was available. In the text, in the first part of the results, we described the data set and mentioned that actual data on final height was available only in 48 children. We have clarified the manuscript accordingly, replacing:

Page 3, line 60-65:

“A model with 4 components, birth length and 3 exponential functions of age accounting for the 3 growth phases was developed. The height-growth velocity was inversely associated with the age at ART initiation. Final adult height was significantly lower in female children and in those who had experienced at least one AIDS-defining event.”

with:

“A model with 4 components, birth length and 3 exponential functions of age accounting for the 3 growth phases was developed and showed that the height-growth velocity was inversely associated with the age at ART initiation, the adult height was significantly lower in those who had experienced at least one AIDS-defining event while, as expected, the model found that adult height in females was lower than in males.”

Comment 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).

Response:

We agree. This was not mentioned in the Abstract and we have modified page 4, line 65 the following sentence (underlined):

“Age at ART initiation, type of ART regimen, CDC stage, CD4 percentages, and HIV-RNA load were not associated with the final height.”

Comment 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".

Response:

We agree with the reviewer and we have added the manuscript accordingly in page 4, line 69 as follows:

“Conclusions: The younger the children at ART initiation, the greater the effect on height-growth velocity, supporting the World Health Organization’s recommendation to start ART as early as possible. However, final adult height was not linked to age at ART initiation.”

Comment 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.

Response:

We agree with the reviewer. We have reviewed the suggested papers and revised the introduction according to current literature in page 5, line 78-81 as follows (underlined):

“Results of the few several studies analyzing the effect of ART on height-for-age z-score (HAZ), …”

The papers of additional literature review were cited in introduction section page 5 and added an entry in our reference list as follows.

- line 74-75

“HIV infection in children has been associated with growth delays in terms of weight (wasting and underweight) and height (stunting) [1-9]”
"Antiretroviral treatments (ART) have been shown to have a positive impact on the evolution of the anthropometric parameters [8-13]
"

"but studies have mostly focused on the improvement of the weight-for-age z-score (WAZ) [9, 14-18]"

We also added the additional citation in discussion section in page 16 and added an entry in our reference list as follows.

"This is consistent with previous studies [8, 41-47], indicating that ART initiation at an early age significantly increased the height-growth velocity."

"Height-growth velocity did not differ according to the initial ART regimen, even if it was a dual NRTI regimen as compared to a triple combination. Other studies did not find any difference of HAZ [8, 11] and weight-growth velocity [41, 48] according to the type of ART regimen."

References


Comment 6: Methods, p.7:

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.

Response:

We agree with the reviewer. We have corrected in page 7, line 126-130 the following sentence (underlined):

"Likelihood ratio test (LRT) including the log-likelihood, Akaike information criterion (AIC) and The Bayesian information criterion (BIC) were used to test different hypotheses regarding the final model, covariate effect(s) on parameter(s) was used to select the best model. It is based on both the likelihood function and the number of model parameters and is more conservative than the Akaike Information Criterion."

Comment 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.

Response:

We agree with the reviewer. We have corrected this in page 8, line 146-152 as follows (underlined):

“The covariates of interest were: sex, ART regimen (dual nucleoside reverse transcriptase inhibitor (NRTI)-, NNRTI- or protease inhibitor (PI)-based), CD4 percentage, HIV-RNA load and CDC stage at ART initiation (baseline) and the occurrence of AIDS-defining events. The effect of each covariate was systematically tested via the LRT. A covariate was finally retained if i) its effect was biologically plausible, ii) a reduction in AIC/BIC value criterions was observed (LRT) and iii) it produced a reduction in the variability of the parameter, as assessed by the associated inter-subject variability.

Comment 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.

Response:
We have corrected this error page 10, line 176-178 as follows (underlined):

“Of note, stunted children were significantly older at ART initiation, more often on NNRTI, in CDC stage B or C, with lower CD4 percentages and wasting more likely to be underweight (Table 1).”

Comment 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).

Response:

We have added the number of male and female among those HIV-infected children who had measured after 18 years in page 11, line 187-188 as follows (underlined):

“Forty-eight HIV-infected children (16 males and 32 females) had height measurements after 18 years.”

Comment 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?

Response:

This is because the model estimated the maximum final adult height (HTmax), while in the description of the data (beginning of the Results section) we reported the median final height of the 48 children with available measurement after 18 years of age. The predicted maximum height cannot be compared with the observed median height.

Comment 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?

Response:

We agreed with the reviewer. The small number of children with height measures after 18 years of age was a limitation.

We have clarified this limitation in page 18 as follows:

“There were some limitations in our study. Since females generally attain their final adult height at a younger age than males (around 15 years in females as compared to around 18 years in males). The small number of children with height measures after 18 years of age was a limitation. Indeed, 87 females had been measured after 15 years but only 16 males after 18 years, which impacted the precision of predictions beyond this age.”

Comment 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.

Response:

We have added a Supplemental Table 4 showing the results of LRT, AIC, and BIC which supported the model fit for final height accounted for covariates and we have inserted these results as follows:

“Type of ART regimen, CDC stage, CD4%, and HIV-RNA load at baseline were not associated with the maximum height [see Supplemental Table 4].”

Minor comments:

Comment 13:

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".

Response:
We have corrected the manuscript accordingly.

Reviewer 2: Vu Linh Dang, PhD

Dear authors,

It has been a pleasure to read your manuscript, there are certain strong points of the manuscript especially the numbers of patients involved, which is 477 children that not many papers could have been accessed to that amount of data. However, there are certain points that could be taken into consideration:

Comment 14:

The cohort of patients are quite similar in HIV viral load and many papers have been shown the strong association between HIV viral load and relative height, more over this is the crucial marker for the monitoring of disease progression and treatment response. Given that this marker is similar to most of the patients at the time of diagnosis, so that it is understandable that this marker did not play any role in model. However, if the original cohort is not representative of the HIV pediatrics population then the model cannot be applicable.

Response:

We agree that a limitation of the model used in this analysis is that it does not take into account the sequence of events occurring during the follow up. However, the results provide valuable
information on the role of baseline factors. Our objective was limited to the description of patterns of height evolution and identified predictors of catch-up growth in HIV-infected children on ART. HIV-RNA load at baseline was taken into account as covariate. This has been added in the Discussion

“Since changes in CD4 percentage and HIV-RNA load as well as in treatment may be related to the height velocity or final height, it could be more accurate to develop more complex models including time-dependent variables.”

Comment 15:
During the time followed up, patients would have changed the treatment regimen several times, so that ART regimen should be analyzed in more appropriate way.
Response:
This comment has been addressed with the previous one, please see our response to the previous comment.

Comment 16:
Most of the covariates of interest should be monitored periodically so that the model could represent better the changes of relative height in relation to these covariates, otherwise the baseline levels could not represent the whole changes during the treatment response.
Response:
In our study, we found that CD4 percentages at baseline were different between severity of stunting among children at baseline. Therefore, we suspected that CD4 percentages at baseline might affect height velocity or final height.

We agreed with the reviewer that the changes in CD4 percentage and HIV-RNA load might be related with the height velocity or final height.
This has been addressed with the previous two comments and a sentence has been added to the Discussion (see response to Comment 14).

Comment 17:
There have been lost of follow-up in substantial numbers of children

Response:

We respectfully disagree. Actually, among 477 children there were only 92 (19%) children lost to follow-up over a median follow-up duration of 6.3 years (IQR, 3.0 to 8.3). We believe that this was a strength of this paper as acknowledged by Reviewer 1.

Comment 18:

The model should be represented the changes of other markers in association to the HAZ of HIV infected patients, however, this model has not been fully identify this association and it is difficult to have the application in clinic.

Response:

This comment is similar to Comment 14, please see our response to this comment.

Reviewer 3: Rajeev Malhotra, PhD

The manuscript is well written and strengthen the effect of ART on height evolution of HIV infected children. My concerns are as follows.

Comment 19:

Is there any difference between the baseline characteristics between those who completed the study and those who died, lost to follow-up and shifted to the other hospitals.

Response:

Thank you for this comment. After we have read, as suggested in Comment 27, a recent paper on this topic, we have now compared the baseline characteristics between these groups of children.
Age, CD4 percentage, HIV-RNA load, CDC HIV classification stage, HAZ, WAZ, and WHZ were different between children who died, lost to follow-up, and referred compared to those who completed the study.

<table>
<thead>
<tr>
<th>N (%) or median [IQR]</th>
<th>Follow-up status</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death/LTFU/ Refer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=222)</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td>(n=255)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>101 (46%)</td>
<td>105 (41%)</td>
<td>0.342a</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.9 [2.0-10.1]</td>
<td>5.8 [1.6-9.3]</td>
<td>0.064b</td>
</tr>
<tr>
<td>ART regimen</td>
<td></td>
<td>0.391a</td>
</tr>
<tr>
<td>Dual NRTI-based regimen</td>
<td>21 (9.5%)</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>PI-based regimen</td>
<td>22 (9.9%)</td>
<td>35 (14%)</td>
</tr>
<tr>
<td>NNRTI-based regimen</td>
<td>179 (80.6%)</td>
<td>200 (78%)</td>
</tr>
<tr>
<td>CD4 percentage</td>
<td></td>
<td>0.534b</td>
</tr>
<tr>
<td>8 [2-18]</td>
<td>9 [2-17]</td>
<td></td>
</tr>
<tr>
<td>HIV-RNA load (log10copies/mL)</td>
<td>5.12 [4.64-5.60]</td>
<td>5.23 [4.75-5.73]</td>
</tr>
<tr>
<td>CDC HIV classification stage</td>
<td></td>
<td>0.489a</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 (18%)</td>
<td>47 (18%)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>63 (28%)</td>
<td>73 (29%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 (31%)</td>
<td>64 (25%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 (23%)</td>
<td>71 (28%)</td>
<td></td>
</tr>
<tr>
<td>Height-for-age z-score</td>
<td></td>
<td>0.002a</td>
</tr>
<tr>
<td>&lt;-3 SD</td>
<td>34 (15%)</td>
<td>16 (6%)</td>
</tr>
<tr>
<td>-3 to &lt;-2 SD</td>
<td>41 (18%)</td>
<td>34 (13%)</td>
</tr>
<tr>
<td>-2 to &lt;-1 SD</td>
<td>50 (23%)</td>
<td>75 (30%)</td>
</tr>
<tr>
<td>≥1 SD</td>
<td>97 (44%)</td>
<td>130 (51%)</td>
</tr>
<tr>
<td>Weight-for-age z-score</td>
<td></td>
<td>0.079a</td>
</tr>
</tbody>
</table>
<-3 SD    7 (3%)  6 (2%)
-3 to <-2 SD 20 (9%)     19 (7%)
-2 to <-1 SD 80 (36%)    68 (27%)
≥1 SD      115 (52%)    162 (64%)

Weight-for-height z-score 0.079a
<-3 SD    5 (2%)  1 (1%)
-3 to <-2 SD 11 (5%)     5 (2%)
-2 to <-1 SD 27 (12%)    31 (12%)
≥-1 SD     179 (81%)    218 (85%)

CDC, Centers for Disease Control and Prevention; IQR, interquartile range; n, number of children in category; LTFU, Loss to follow-up

a Chi-square test
b Kruskal-Wallis test

This information has been added as Supplemental Table 3 and, page 10, line 184-186 we have specified:

“We found that HAZ at baseline was significantly different between children who died, lost to follow-up, and referred compared to those who completed the study. [see Supplemental Table 3].” in Additional file 2

Comment 20:

It would be better to explain model equation 1 with a practical real data of single child growth and explain how the HT can be predicted based on the model estimated parameters in the appendix. This would help the reader to understand the model in more effective way.

Response:

We selected 4 children by random to compared data observed and data predicted using the model equation 1 and added the following table at the end of Supplemental Table 2:
<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>ADEs</th>
<th>Age at ART initiation (months)</th>
<th>Age at last height measurement (months)</th>
<th>Observed height (cm)</th>
<th>Predicted height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>No</td>
<td>63.179</td>
<td>172.682</td>
<td>162</td>
<td>156.194</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>Yes</td>
<td>9.692</td>
<td>149.257</td>
<td>137</td>
<td>134.827</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>No</td>
<td>120.739</td>
<td>172.485</td>
<td>158.9</td>
<td>155.208</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>Yes</td>
<td>139.203</td>
<td>211.023</td>
<td>150</td>
<td>151.124</td>
</tr>
</tbody>
</table>

For example, the calculation for case 1 was as follows:

\[
HT_a = 0.557 \times (1 - \exp(-0.693 \times 172.268 / (50.8 \times 0.713))) \quad \text{with } t = 172.268 \text{ months}
\]

\[
HT_b = 0.274 \times (1 - \exp(-0.693 \times (98.768)/(75.3 \times 1))) \quad \text{with } t = 172.268 - 73.5 = 98.768 \text{ months}
\]

\[
HT_c = 0.169 \times (1 - \exp(-0.693 \times (28.868)/(15.7 \times 1))) \quad \text{with } t = 172.268 - 143.4 = 28.868 \text{ months}
\]

\[
HT = 54.7 + (178 - 54.7) \times (0.537 + 0.164 + 0.123) = 156.194
\]

Comment 21:

In Page 15- the author reported short length at birth (51.4 versus 54.2) but in supplement table 1 it is 51.4 versus 55.9 cm

Response:

It was a typo error. The valid value is according to the value in supplement table (51.4 versus 55.9 cm). However, the model was separated in to 2 models for male and female according to the comment from reviewer 1. The results of the separated model were replaced in page 15, line 225-228 as follows:

“The models showed a significant association between a final adult height (HTmax) and the occurrence of ADEs both in male (178 versus 169 cm in those without and with ADEs, p<0.01)
and female (165 versus 159 cm, p<0.01) [see Supplemental Table 1 and 2].” See Additional file 1

Comment 22:
Model need more explanation covering the following points:

a. How the author derived the equation 1?
b. How the phases were decided?

Response:
We have added the detail about concept how the equation 1 and the 3 phases of exponential function were derived in method section in page 7, line 116-120 as follows:

“Firstly, a height versus age scatter plot was drawn. As expected, the curve was non-linear. Thereafter, a log(Height) versus age showed that the curve could be roughly described by 3 successive straight segments defining 3 growth phases. A sum of 3 exponential functions was then used for describing growth as a function of age.”

c. Reason for choosing 50% time duration of HTa, HTb, HTc.

Response:
We defined A50a, A50b and A50c as the time durations in each phase for which 50% of HTa, HTb or HTc, respectively, were reached, in analogy to the time needed for plasma concentration to be halved (after one elimination half-life) in pharmacokinetic models.

d. The implication of b1, b2, b3 parameters estimated in the model (See Supplemental Table 1)

Response:
We have clarified the formula of HTa, HTb, and HTc with implication of b1, b2, b3 at the end of Supplemental Table 2 as follows (underlined):

A model including exponential functions of age corresponding to 3 phases (a, b and c) fitted the observations (Equation 1):
HT = HTbirth + (HTmax – HTbirth)*(HTa + HTb + HTc) \hspace{1cm} (1)
a) from birth to age A1
HTa = fa*(1 – exp(-0.693*t/(A50a*b1))) \hspace{1cm} with \ t = \text{age}
b) from age A1 to age A2
HTb = fb*(1 – exp(-0.693*t/(A50b*b2))) \hspace{1cm} with \ t = \text{age} – A1
c) above age A2
HTc = fc*(1 – exp(-0.693*t/(A50c*b3))) \hspace{1cm} with \ t = \text{age} – A2

where HTbirth is the birth length; HTmax the maximum (adult) height; fa, fb and fc the fractions of adult height gained at each phase; A50a, A50b and A50c the time durations in each phase for which 50% of HTa, HTb or HTc are reached; and, A1 the age bounds between phases 1 and 2, and A2 between 2 and 3.

Adding the age at ART initiation, AgeART, improved the fit, showing an inverse association between height-growth velocity and age at ART initiation (if AgeART is higher, the A50a, A50b or A50c parameters decrease by a b1, b2 or b3 fraction), i.e. the older the child at ART initiation, the slower the growth.

The final model was

if (AgeART <A1)\hspace{1cm} b1 \text{ estimated (if not) } b1 = 1
if (AgeART >A1 and Age(ART) <A2)\hspace{1cm} b2 \text{ estimated (if not) } b2 = 1
if (AgeART >A2)\hspace{1cm} b3 \text{ estimated (if not) } b3 = 1

e. Compare the non-linear mixed model with linear or quadratic time mixed effect models to show former is better fit.

Response:

we did not develop models using linear or quadratic mixed effect models because the distribution of data was strongly suggesting that exponential functions would best describe the growth.
Comment 23:

It seems from Figure 2, individual parameters model provided better prediction than the population parameters. Has internal prediction power of these two was compared?

Response:

We cannot compare Figure 2 (a) and (b) because (a) shows predictions made using population parameters and (b) using individual parameters. Since we have now a model for each sex, please note that Figure 2 was changed to be 2 (a) and 2 (b) for population and individual parameters among males and 2 (c) and 2 (d) among females.

Comment 24:

Author stated all children born with HIV were included it means all the children were perinatally infected. Endocrine disease effects the growth velocity apart from the HIV infection. Are these patients included or excluded.

Response:

There was only one child (ID63) with endocrine disease in this study. We have added the limitation in page 18, line 287-288 as follows:

“Finally, there was one girl with endocrine disorder which could impact her growth. However, her growth curve was not affected by her disorder.”

Comment 25:

Author reported no significance of age at ART initiation on final height but in model results author reported inverse association between height-growth velocity and age at ART initiation. The terms early ART initiation and age at initiation seems confusing and need clarification.

Response:
We have clarified this in the conclusion section in page 18, line 291-293, as follows (underlined):

“Our results show the beneficial effect of early age at ART initiation on the height-growth velocity but regardless of age at ART initiation and initial ART regimen, children were able to catch up in terms of final adult height.”

Comment 26:
Report the proportion of stunting (z-score <-2 SD) at last follow-up visit those started ART <=6.2 years and > 6.2 years of age.
Response:
We have added the proportion of stunting at last follow-up separated by age at ART initiation in results section in page 11, line 191-193 as follows (underlined):

“Finally, the proportion of stunted children decreased from 49% at ART initiation to 26% at last visit. The proportions of stunting were 25% (59/239) in children who started ART ≤6.2 years of age and 28% (66/238) in those who started after (p-value=0.012).”

<table>
<thead>
<tr>
<th>Stunting at last follow-up visit</th>
<th>All (n=477)</th>
<th>Age at ART initiation p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤6.2 years (n=239)</td>
<td>&gt;6.2 years (n=238)</td>
</tr>
<tr>
<td>No</td>
<td>352 (74%)</td>
<td>59 (25%)</td>
</tr>
<tr>
<td>Yes</td>
<td>125 (26%)</td>
<td>180 (75%)</td>
</tr>
</tbody>
</table>

a Chi-square test

Comment 27:
The authors may refer to a recent published study from India on effect of antiretroviral therapy on growth parameters of children with HIV infection in The paediatric Infectious Disease Journal

Response:
Thank you for the suggestion. The paper was cited in page 5, line 75-77 and added an entry in our reference list.
“Antiretroviral treatments (ART) have been shown to have a positive impact on the evolution of the anthropometric parameters [8-13]”