Author’s response to reviews

Title: Estimating age-based antiretroviral therapy costs for HIV-infected children in resource-limited settings based on World Health Organization weight-based dosing recommendations

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Author’s response to reviews: see over
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Dear BMC Health Services Research Editorial Staff,

Thank you for the opportunity to revise our manuscript (MS: 3986096581009760) entitled, “Estimating age-based antiretroviral therapy costs for HIV-infected children in resource-limited settings based on World Health Organization weight-based dosing recommendations.” We have reviewed and responded to each comment from the two reviewers. All edits to the manuscript are listed in boldface text both below as well as in the revised manuscript.

At the Reviewers' request, we have also made the pediatric ARV costing tool (submitted together with our revised manuscript) suitable for posting on our research website (http://web2.research.partners.org/cepac/mainpage.html). If this manuscript is found acceptable for publication, we will add a link to this tool, to make it freely accessible to all interested users.

Thank you very much for your consideration of this manuscript.

Sincerely,

Kathleen Doherty, BA
Editorial Revisions

Please make the following formatting changes during revision of your manuscript. Ensuring that the manuscript meets the journal’s manuscript structure will help to speed the production process if your manuscript is accepted for publication.

1. Box

Unfortunately, we cannot incorporate boxes. Please either change the box to a table and update any references to within the text, or include the information within the manuscript text. You can use indentation to highlight the text.

We have removed the box from the manuscript and have included the information about co-formulation administration in the footnote of Table 1.

2. Tables

Please ensure that the order in which your tables are cited is the same as the order in which they are provided. Every table must be cited in the text, using Arabic numerals. Please do not use ranges when listing tables. Tables must not be subdivided, or contain tables within tables. Please note that we are unable to display vertical lines or text within tables, nor display merged cells: please re-layout your table without these elements. Tables should be formatted using the Table tool in your word processor. Please ensure the table title is above the table and the legend is below the table. For more information, see the instructions for authors on the journal website.

We have removed all merged cells within the tables presented in the manuscript. We have also divided Table 7 into two separate tables to eliminate any subdivisions within a table and have ensured that the table titles and legends appear above and below the tables.

3. Please note that Research article require the following sections:

· Title page
· Abstract
· Keywords
· Background
· Methods
· Results and discussion
· Conclusions
· List of abbreviations used (if any)
· Competing interests
· Authors’ contributions
· Authors’ information
· Acknowledgements
· Endnotes
· References
· Illustrations and figures (if any)
· Tables and captions
· Additional files

Please ensure that these sections are present and clearly labeled as described above. Please do check the instructions for authors on the journal website to ensure that your manuscript follows the correct
structure for this journal and article type, and to ensure that you are aware of additional recommendations for formatting that will facilitate handling of your manuscript.

All relevant sections are included in the attached manuscript in the order listed above. In addition to the requested Abbreviations list, we have also defined all abbreviations at their first appearance in the text.
Reviewer #1

Major Compulsory Revisions
None

Minor Essential Revisions
1. Page 4, paragraph 2: expensive cold-chain systems are mentioned as part of the complications of estimating ART costs for children, yet are not addressed by the approach. It would be useful to reframe this part of the introduction focusing on the problems to which the method provides a solution.

We thank the reviewer for pointing out this inconsistency. We have removed the reference to cold chain storage systems in this paragraph to focus only on issues we address in this manuscript. We have also expanded our discussion of this as a limitation in our analysis:

Discussion, Page 15, Paragraph 2:
These costs do not take into consideration equipment, personnel, overhead, shipping or opportunity costs that may also be involved in the delivery of ART to pediatric patients. We have also excluded the costs of establishing and maintaining a cold chain store needed for drugs that require refrigeration. The costs of these components are infrequently reported, but may be available at the program level and will be important considerations for program planners to include.

2. Page 5, paragraph 1: it is implied that citation 21 examined pediatric HIV treatment costs in South Africa, but this study was conducted in other countries, so I think this needs to be reworded.

We have clarified this point in the text (in the revised manuscript, new reference 22 is the focus of the Reviewer's suggestion).

Background, Page 5, paragraph 2:
Two published studies have also examined pediatric HIV treatment costs. One reports the average cost of HIV treatment care across 43 PEPFAR sites, where 7% of the study population were pediatric patients [22]. Meyer-Rath et al. completed a similar analysis for two dedicated pediatric care sites in South Africa, and further calculated the proportion of total treatment costs pertaining to ART costs [23].

3/4. Page 8, paragraph 3: The authors need to justify the assumption that “the weight distribution for HIV-infected children of a given age will be narrower than for children of the same age in the general population.” At the moment this adjustment is simply stated. In the same section: a couple of assumptions are required to go from weight to age-based dosing. It would be useful to test the sensitivity of the results to these assumptions – e.g. test alternate values for the z-score adjustment and report the impact on final costs. I assume the results will be reasonably robust to these changes, but need to check.

We have conducted a series of sensitivity analyses on both the z-score adjustment and the variance of the weight distribution, and report that they exert only minimal impact on our cost calculations. These are presented in the revised Methods and Results sections:

Methods, Page 8, Paragraph 4:
Although little data is available on how the weight distribution of HIV-infected children compares to the weight distribution of the general population of children the same age, one study found that on average, HIV-infected children are of lower weight [33]. To account for lower weights among HIV-infected children than among the general population, we first shifted
the weight distribution in the growth charts to a -1.5 z-score (Z) and assumed the coefficient of variation of the weight distribution ($S_{\text{HIV}}$) was half that of the general population. To examine the impact of these assumptions, we conducted sensitivity analyses in which we recalculated drug costs after varying both the shifted weight distribution z-score (z-scores of -3 to 0) and the weight distribution variance ($S_{\text{HIV}}$ equal to S (variance of general population) or $S/\sqrt{2}$). These parameters can also be modified by users of the online tool.

Results, Page 12, Paragraph 5:
Sensitivity analyses on weight distributions demonstrated that monthly drug cost estimates were fairly robust to changes in assumptions regarding the weight distribution for HIV-infected children (z-scores). Assuming no change in weight distribution between HIV-infected children and the general population (z-score = 0), monthly drug costs by age changed on average by 7.2%. Monthly drug costs changed substantially from our original estimates (>10%) only when we assumed much lower weights among HIV-infected children (z-score < -3). With improvements in early infant diagnosis and access to antiretroviral therapy (ART), we anticipate that the growth distribution for HIV-infected children will shift toward the WHO growth curves for the general population, and thus drug costs will remain similar to those calculated in this manuscript. Sensitivity analyses on the variance of the weight distribution among HIV-infected children ($S_{\text{HIV}}$) also demonstrated minimal change in monthly drug costs estimates. First, assuming that $S_{\text{HIV}}$ was equal to $S$ (the variance of the general population) divided by the square root of 2, we found that monthly drug costs changed by 4.3%, on average. Second, assuming no difference in the variance between the general population and the HIV-infected population, we found that monthly drug costs changed on average by 5.4%.

5. Comparison to GPRM estimates: the ideal source of validation would be empirical data from a program. I am not exactly sure how the GPRM estimates are calculated, but my strong suspicion is that they are based on a similar calculation to the approach described in this paper, though maybe cruder. There is, as far as I can see, no way would they (GPRM) have the level of reporting data needed to calculate some kind of empirical estimate (and if they were, shouldn’t CE analysts just be using estimates from the GPRM ?). As a consequence, I don’t think the GPRM estimates validate the current approach. It might be reasonable to keep them as some kind of corroboration of the results presented here, but it needs to be clear what they represent. Of note, where a major difference is observed between GPRM estimates and those in this manuscript (i.e. for LPV/r), it would be useful to tease out the cause a bit. I agree with the hypothesis noted in the discussion section (i.e. a difference in prices), but is it possible to confirm this (as far as I remember the price estimates are available in GPRM)?

We agree that the ideal source of validation for our paper would be programmatic data, but we are not aware of published data to describe pediatric antiretroviral drug costs, stratified by patient age or weight. The Global Price Reporting Mechanism (GPRM) database reports average costs for each drug, calculated from volumes of recorded transactions for HIV, tuberculosis, and malaria products purchased in low- and middle-income countries. Therefore, this database likely provides a fairly accurate assessment of the current prices being paid for HIV antiretroviral drugs in resource-limited countries. However, because pediatric prices are only reported for children weighing 10kg, we were not able to extensively validate our methodology for children of lower weights through comparison to the GPRM database. We have described this limitation more fully in the discussion.

Discussion, Page 14, paragraph 2:
In addition, the WHO has compiled average monthly costs for several pediatric and adult drug formulations in their GPRM database based on records of international transactions of HIV, tuberculosis and malaria products purchased in low- and middle-income countries [35], focused on 10-kg children.

We have also expanded the discussion of the differences between GPRM estimates and our calculations of LPV/r costs.

Discussion, Page 14, paragraph 2:
This discrepancy is likely due to the inherent differences in a ceiling price list (used in our analysis for unit cost derivation) and the actual transaction costs found in the GPRM. For example, despite the high cost of liquid LPV/r (80/20mg/ml), many countries and programs may have been able to negotiate its purchase at a lower cost than listed in the CHAI price list because of its key role in pediatric HIV treatment. In addition, the GPRM database shows that prices for LPV/r have fallen substantially over the past five years, from $16.11 to $11.81 per month, demonstrating the rapidly changing economic market for this drug.

6. Page 13, paragraph 2: It is incorrect to state that this approach estimates costs from a healthcare system perspective. This is clear from the very next sentence (regarding the costs not included). This approach estimates the cost of drugs dispensed to patients.

The reviewer is correct to point out that our approach estimates the monthly costs for drug products alone. We have revised this sentence accordingly.

Methods, Page 8, paragraph 1:
This analysis includes only the costs of drug products themselves, and excludes the costs of shipping, or any costs related to the delivery of ART, such as equipment, personnel, overhead, or wasting.

Discussion, Page 15, paragraph 2:
These costs do not take into consideration equipment, personnel, overhead, shipping or opportunity costs that may also be involved in the delivery of ART to pediatric patients. We have also excluded the costs of establishing and maintaining a cold chain store needed for drugs that require refrigeration. The costs of these components are infrequently reported, but may be available at the program level and will be important considerations for program planners to include.

7. I assume the Excel document is intended to be downloadable as a resource for users of this approach? If so, this is great, but there needs to be better documentation – step by step instructions – about how the tool should be used. In similar exercises I have seen a short user manual inserted as the first tab of such a document, but there might be better approaches. It might also be useful to lock cells that the user should not adjust. If this Excel document is not meant to be available for download, please ignore this comment.

The Excel document is intended as a tool available for download, where analysts can update prices and regimen components as needed for their program. We have revised the document to provide more detailed instructions for use. These include:
1. A new first tab, outlining the overall approach to use of the document
2. Detailed instructions on each tab, directing the user to cells that can be modified.
3. New titles and descriptions of the tabs that display output of the tool.
8. A more general concern is that this approach is presented as a method for estimating the costs of pediatric ARVs, as might be useful for program planners and cost-effectiveness analysts, but does not include a number of considerations which will all increase the total cost to the program / health system – shipping, insurance, storage, transport, wastage, shrinkage, expiration, etc – individually these can be minor considerations but they add up. The authors mention these issues in the discussion section but I think it needs to be raised earlier, as I could see the naïve user simply ignoring them. The ideal solution would be to provide some basis for estimating these additional costs, but I realize this may not be easy, and some of these cost will differ substantially by country.

Please see Reviewer #1, Point 6, above.

**Discretionary Revisions**

9. Page 8, last paragraph: I don’t think you need to mention the specific Excel functions you used, though would be worthwhile confirming that this is not one of the functions where Excel is known to give erroneous answers (don’t need to include in text, but should check).

We have removed the mention of the Norm.S.Dist(z,1) Excel function from the Methods section of the paper. This information remains in the caption of Table 4, as well as in the instructions of the Excel-based cost tool, for those with further interest in our methodology of calculating weight-by-age standards. We have also confirmed that this Excel function is not one that is known to give erroneous answers.

10. It would be useful to rework the results section a bit: at the moment it reads like a brief recapitulation of the methods (though I realize is this is somewhat a result of the nature of the analysis).

We elected to structure the Results section in exactly the same format as the Methods section in order to present our approach and findings as clearly as possible to the reader. We agree with the Reviewer that this leads to a slightly redundant format, but hope this concern will be outweighed by the added clarity that this structure provides.

11. Page 12, first paragraph: “uniformly increase” is somewhat unclear. I assume the intended idea is that costs do not increase monotonically. Also, if this is due to a switch away from liquids it might be useful to say that explicitly.

The reviewer is correct to note that monthly costs for a given regimen do not increase monotonically as age and weight increase. This is due to both a switch from pediatric formulations (liquid and tablets) to less costly adult formulations, as well as a change from NVP to EFV at age 3. We have clarified this finding in the manuscript.

Results, Page 13, paragraph 3:

As seen in the Table, monthly regimen costs do not increase **monotonically** as a child grows. **This is due to the switch from more expensive liquid and pediatric tablet formulations to adult tablet doses. In addition, the switch from NVP to EFV at age three also increases overall monthly regimen costs.**

12. Page 14, first paragraph: typo “over a several ages”.

We have corrected this typographical error in the manuscript.
Page 15, first paragraph: “full capacity” this seems not quite right – an underfunded program might hit full capacity very quickly, but I am not sure this is the intended idea. Also in next sentence, perhaps “about” instead of “surrounding”? 

We have made the following clarifications to the text.

Conclusion, Page 17, paragraph 1:

The number of children living with HIV is growing each year, and will likely continue to grow until efforts to prevent perinatal HIV infection reach target goals [37]. Antiretroviral therapy has been shown to drastically reduce morbidity and mortality in children with HIV, yet questions about when to start treatment and what treatment to start remain key issues for policy makers [2, 38].

14. Table 4: it is important to be clear about the content of a table, but the footnote for this table could be more concise (seems to fully reiterate the relevant section of the methods).

Because the full procedure for determining weight-by-age standards was not included in the Methods section of the text, we felt it was important to document the complete methodology in the footnote of Table 4. This was also requested by Reviewer 2 (please see comment #11). If the editors feel it would be more appropriate to include this text in supplemental digital content, we would be happy to move this to an online appendix.

15. It is my understanding that an issue with liquid formulations is the need to dispense ‘whole’ bottles, such that even if the total weight-based dosage for a dispensing period is 185ml, if the bottle contains 240ml then 55ml automatically goes to waste. If this is still true (the authors will likely have a better understanding of the current situation) it could be incorporated into the estimation approach, or otherwise noted in the text.

The reviewer is correct to note that the need to dispense ‘whole’ bottles of liquid drug formations may result in wasting of medications, and therefore an increase in total drug costs. We have clarified this point in the Discussion.

Discussion, Page 15, paragraph 2:

In addition, because entire bottles of liquid formulation must be dispensed monthly, often exceeding the total needed quantity, there will likely be some wastage associated with the distribution of liquid drugs. Our current methodology excludes wastage costs, but these will need to be considered by program planners as well.

16. Occasionally it is mentioned that policy-makers might use this tool. I am not sure that this is the case, and perhaps the intended audience should be restricted to analysts and budget administrators (as the authors mention in the conclusion).

While we hope that this tool will also be helpful for policy makers who are evaluating antiretroviral therapy programs for children, we have removed this reference in the text and have highlighted instead the potential benefits to analysts and budget administrators.

Abstract, Page 3, paragraph 4:

Conclusions: The methodology described here can be used to provide an accurate estimation of pediatric ARV regimen costs for cost-effectiveness analysts to project the optimum packages of care for HIV-infected children, as well as for program administrators and budget analysts who
wish to assess the feasibility of increasing pediatric ART availability in constrained budget environments.

Background, Page 5, paragraph 3:
We hope this approach can be used by investigators seeking to analyze the cost-effectiveness of ART strategies for children, as well as by analysts and program administrators in accurately assessing the costs of potential treatment options for pediatric HIV patients.

Conclusion, Page 17, paragraph 1:
This costing procedure can be modified to reflect ARV prices and available formulations that are most representative for a range of programs and settings, and thus can aid budget analysts in developing more cost-effective recommendations for pediatric ART.
Reviewer #2

This manuscript is very interesting and well written. Information for this paper would be very helpful for pediatricians and policy makers worldwide. There are few comments for your consideration.

Major Compulsory Revisions
None

Minor Essential Revisions
1. Abstract: ART was used at the first time in the last sentence. Please consider to either change to ARV or antiretroviral therapy.

We have now defined the abbreviation "ART" in the first sentence of the abstract.

Abstract, Page 3, paragraph 1
Pediatric antiretroviral therapy (ART) has been shown to substantially reduce morbidity and mortality in HIV-infected infants and children.

2. Background, page 5: The authors mentioned "CHAI" and "PEPFAR" at first time here. Please express its full word after the first abbreviation. In addition, the authors explained more about "CHAI" in the Methods. Maybe, information of "CHAI" can be added more in the Background section.

We have defined the abbreviation "CHAI" where it first appears in the manuscript.

Background, Page 5, paragraph 2:
In 2005, the Clinton Health Access Initiative (CHAI) developed a forecasting tool for pediatric ART which has primarily been used to help countries determine the cost of pediatric treatment targets and as a tool for ARV procurement planning.

3. Methods, page 7: Please add full word of "WHO" after your first abbreviation. In contrast, please remove CHAI's full word if it's already presented in the Background after revision.

We have defined the abbreviation "WHO" at its first appearance in the manuscript.

Methods, Page 7, paragraph 2:
Weight-based doses for each doses for pediatric ARVs were taken from Annex E of the 2010 World Health Organization (WHO) Pediatric Guidelines and Annex 7 of the upcoming WHO 2013 Consolidated Pediatric and Adult Guidelines [7, 28].

We have also changed the mention of the Clinton Health Access Initiative back to CHAI, as it was previously defined as such in the Background section.

Methods, Page 7, paragraph 3
Due to the wide variety of drug prices available to resource-limited countries based on individual agreements with pharmaceutical companies, we used the CHAI May 2012 ceiling price list as the basis for drug cost estimates [24].
4. Methods, page 8: The authors explained how to calculate the monthly cost for each medication by WHO weight band and used "X" in the sentence which made it a bit hard to follow. Please consider to make it in a separate line to show the formula.

We have inserted the formula for monthly cost for each medication as a separate line in the Methods section and have further clarified where the values come from in the sentence below.

Methods, Page 8, Paragraph 2:

3. Calculation of monthly costs for each medication by weight (Table 3). Assuming an average of 30.4 days in a month, we calculate the monthly cost for each medication by WHO weight band as follows:

\[
\text{Monthly cost} = \text{Average dose per day} \times \text{unit cost per drug} \times 30.4 \text{ days per month}
\]

Average daily dose (in mg, ml, tablet, or capsule/day) is found in Table 2 and unit cost (in USD/mg, ml, tablet, or capsule) is found is Table 3 for each of the drugs in this analysis.

5. Methods, page 8: again, please check all abbreviation (for example CDC, LMS) and add their full word after the first abbreviation.

We have defined "CDC" and "LMS" where they first appear in the text.

Methods, Page 8, paragraph 3:

Weight-by-age distributions were obtained from the WHO Child Growth Standards for children <5 years of age and from the Centers for Disease Control and Prevention (CDC) Growth Charts for children ≥5 years [30, 31].

Methods, Page 8, paragraph 3:

Both growth charts contain the Lambda-Mu-Sigma (LMS) parameters (the power in the Box-Cox transformation (L), the median (M), and the generalized coefficient of variation (S)) needed to generate exact percentiles and z-scores by age and gender [32].

6. Methods: in this paper, the only region that was mentioned is Africa. It would be more useful if it is shown in this paper that information from this study can be generalized for any region or country. Please consider some information about recommendation or drug availability in Asia since several resource limited settings are from Asia as well. In addition, please also check if there is any different current recommendation or drug availability that you might need to add in your analysis or not. If not, please state that it is not different among regions. Most of the country in Asia could not access to ABC. Please use information from TApHOD network paper for your information.

We have intended for this methodology to serve as a basis for estimating costs in any resource-limited setting. Although a wide variety of treatment guidelines and drug costs exist between resource limited settings, but we hope that individual programs can adapt our methodology to their individual country settings. We have further emphasized this issue by citing a TApHOD network paper exploring the differences between first- and second- line treatment regimens in Asia and South Africa.

Background, Page 4, paragraph 2:

Although the WHO publishes guidelines on pediatric HIV treatment, differences in first and second line treatment regimens exist between Asian and African care settings [20]. Additionally, discrepancies between preferred regimens exist within individual countries between different programs or clinics.

7. Results, page 12: please use GPRM if you have already abbreviated in the Methods.
All mentions of the Global Price Reporting Mechanism in the manuscript have been updated to ‘GPRM’ following the first use of this abbreviation.

8. All tables: please consider to divide ARV in to NRTI, NNRTI, PI and FDC. But it can remain the same if the authors decided to not change.

Because programs may choose from a variety of individual and co-formulated medications, we felt it was important to show cost results for both individual drug components and available co-formulated regimens. We have re-ordered all of the medications listed in each table to improve clarity (please see Reviewer 2, comment 10, below). If the editors feel it would be helpful, we would be happy to separate each table into sections, including individual NRTIs, individual NNRTIs, individual PIs, and co-formulated combinations. This would likely be most clearly done by including subheadings in each table, however, and the Editor has advised against this (page 2).

9. All tables: please check if there is any abbreviation that needs to be fully defined.

All the abbreviations included in the tables are defined in the footnotes below the corresponding table.

10. All tables: please reorder each drug according to formulation and strength. Now, some ARVs were listed from higher strength to lower strength. The rest was ordered in the opposite way.

We have re-ordered each table to list drugs by formulation and then in descending order by strength. We have chosen to list the liquid form of the drug first, when applicable, followed by the tablet doses. All co-formulations are listed at the bottom of the table.

11. Table 4: the authors added clarification of information under the Table 4. However, it would be nice to move this information to the Methods.

Please see Reviewer 1’s Comments #9 and 14.

12. Table 5: please check all words in "brackets" under "Drug Product" column, for example, liquid adult tab or pedi adult tab. I do not understand these words. But explanation under the table was understandable.

We have reformatted Table 5 to make this point more clear. We have removed all references of “adult and pedi tab” in the table and have instead referred readers directly to the footnote explanation, which the reviewer noted was clearer.

13. Table 7: What is "NR" and "NA"? Please add their full words.

WE have clarified the abbreviations “NR” and “NA” in the footnote to Table 7:

Page 28, Table 7 (footnotes):

NR: not recommended; N/A: not applicable (no cost estimate was available from the GPRM for this formulation)

14. Discussion, page 13 and 14: Please use “GPRM” if it’s already abbreviated.

Please see Reviewer 2, point 8, above.
15. Discussion: it would be very useful if the authors can mention current recommendation from WHO and different practices among each region and how these link to this study.

We have included information about current WHO recommendations on first-line pediatric antiretroviral therapy in the revised manuscript.

Methods, Page 9, paragraph 4:

The WHO 2013 HIV treatment guidelines currently recommend a first-line, PI-based regimen (LPV/r + 3TC + ABC or ZDV) for all HIV-infected children less than three years of age. However, previous WHO guidelines had recommended an NNRTI-based regimen for children who had not been exposed to NNRTIs to prevent mother-to-child transmissions, and in many countries, NNRTI-based regimens remain the most readily available first-line option for children.

In addition, we have added a reference to a TApHOD paper discussing the differences in first- and second-line treatment regimens between programs in South Africa and Asia (please see Reviewer 2, Comment #6 above).

16. It is not clear in this paper about which type of drug is your price reference either “patent” or “generic” ARVs or both. It would be very useful to clarify this information in the Methods.

We have clarified the use of brand-name and patent medication prices in our analysis:

Methods, Page 7, paragraph 3:

These ceiling prices represent the highest level that pharmaceutical companies can charge for these brand-name products in the countries that are members of the CHAI Procurement Consortium, and thus that have access to the reduced costs drug costs negotiated by CHAI. As individual countries or programs may be able to negotiate or obtain access to lower prices for certain formulations, the unit costs shown here should be taken as a maximum estimate of drug costs in resource-limited settings. For the formulations not included in the CHAI 2012 price list, we used the price list from Médecins Sans Frontières (MSF), and chose the price estimate for the generic version of the drug formulation if available [25].