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 the remaining comments from Reviewer #1. All edits to the manuscript are listed in boldface text both below as well as in the revised manuscript.

Thank you for your consideration of this manuscript.

Sincerely,

Kathleen Doherty, BA
Reviewer # 1:

Item 3/4 on initial review: It is great to see the sensitivity analyses about the analysis assumptions. The authors still need to provide a justification for their assumption that the coefficient of variation should be half the population value. In the Excel tool it is stated that this assumption is required so that the weight distribution for HIV-infected children will be narrower than for the general population, but this will be the case anyway if one assumes the coefficient of variation is fixed but the average is reduced. The authors must have had some motivation for this decision. If this decision was based on published research, please provide the citation. If the decision was based on unpublished information (e.g. programmatic experience of the authors, personal communications, etc), this can be fine, but just needs to be explained. On the sensitivity analyses themselves, it is unconventional that both values used in the sensitivity analysis for $S_{hiv}$ ($S_{hiv} = S$ and $S_{hiv} = S/\sqrt{2}$) are larger than the value used in the main analysis ($S_{hiv} = S/2$). I also note that $S$ is used to describe the variance in some locations and the coefficient of variation in others, including in the edits made in response to the initial review. The variance and the coefficient of variation are different quantities, with the coefficient of variation equal to the square root of the variance divided by the mean. I am not sure if this is the source of the issues discussed above, but is makes it unclear how these quantities are being used in the analysis. Please review to make sure the correct term is being used in the text (and correct value in calculations).

All other changes: look great. In particular, the Excel tool now looks very clear.

We had originally assumed that the weight distribution of HIV-infected children would be both shifted to the left and narrower than that of the general population. Although several studies have reported that the average HIV-infected child is of lower weight than a child of the general population, there are no available data on the coefficient of variation of the weight distribution for HIV-infected children. We originally chose to reduce the coefficient of variation of the general population by 50%, due to the assumption that the weight distribution would be narrower than that of the general population. The reviewer is correct to note that the weight distribution will become narrower by just reducing the average. Due to the lack of published data to inform this assumption, at the reviewer's request, we have changed the coefficient of variation to that of the general population ($S_{HIV} = S$). We have noted this change in the manuscript, as well as noting that this represents an assumption, and have updated results in Tables 4, 5, 6.

Methods Section, Page 8, Paragraph 4:

Although few data are 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 ($S_{HIV}$) was equal to that of the general population.

Sensitivity analyses were redone on the modified results with the new coefficient of variation. We have now included sensitivity analyses on the coefficient of variation in both directions of the base case assumption ($S_{HIV} = \frac{1}{2}*S$ and $S_{HIV} = 2*S$). The manuscript text has been modified to reflect these changes and the new results.
Methods, Page 8, Paragraph 4:

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 coefficient of variation (double and half $S_{HIV}$). These parameters can also be modified by use 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 9.7%. 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 coefficient of variation of the weight distribution among HIV-infected children ($S_{HIV}$) also demonstrated minimal change in monthly drug costs estimates. First, assuming that $S_{HIV}$ was equal to half the coefficient of variation of the general population, we found that monthly drug costs changed by 4.2%, on average. Second, assuming $S_{HIV}$ was double the coefficient of variation of the general population, we found that monthly drug costs changed on average by 6.4%.

We also thank the reviewer for pointing out our inconsistency between variance and coefficient of variation. Here, we are referring to the coefficient of variation of the weight distribution of HIV-infected children. We have made these corrections throughout the manuscript.