Reviewer’s report

Title: High prevalence of lipoatrophy in pre-pubertal South African children on antiretroviral therapy: A cross-sectional study

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Reviewer: Takara Stanley

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In this manuscript, the authors report phenotyping of 100 HIV-infected children in sub-Saharan Africa with respect to their body composition and medication exposure, with the important result that peripheral and facial lipoatrophy are prevalent and strongly related to cumulative stavudine exposure. This manuscript has important implications, arguing for efforts to move away from stavudine use in children, given its clear association with peripheral fat loss that may be largely irreversible. This study appears to be well-done and is presented in a straightforward manner. It provides a potentially important contribution to both practice and policy-making.

Major Compulsory Revisions: none

Minor Essential Revisions
1. In the abstract results section, the last sentence stating that 80% of children without lipoatrophy were on stavudine is misleading, given that the study found a significant association between stavudine and lipoatrophy. I would suggest removing this sentence from the abstract and saying instead that, in multivariate analysis, cumulative stavudine exposure was the predominant risk factor for LA with OR 1.9 (95% CI…)

2. The statistics section of the methods could use more detail. Which statistical tests were used for between group comparison for normally distributed, non-normal, and categorical data; what kind of modeling (e.g., stepwise, least squares) was used for multivariate modeling, etc.? May want to also clarify that mean±SD is used for normal and median (IQR) for non-normal throughout the paper.

3. In the discussion, p.10, where the results are compared to those of Alam et al., the authors suggest that the higher prevalence of lipoatrophy in the current cohort compared to Alam’s may be because of ethnic differences, and that this may refute the idea that Caucasians are at higher risk. However, the most likely explanation for the higher prevalence found in the current cohort is that a far greater percentage of children in the current cohort were on stavudine. I would remove the statement that “This suggests that immigrant African populations in Europe may be different…” and instead say that differential stavudine exposure likely contributed to different prevalence findings, as the authors argue
elsewhere.

4. In general, I don’t think this section of the discussion is organized optimally – I would suggest reviewing prevalence data found in the 4 previous studies + Alam, then focusing on Alam, then contrasting this with the current study’s relatively higher percentage of LA which is likely due to higher percentage of stavudine use in the current cohort vs. the others which were in “developed” nations.

Discretionary Revisions

1. In the abstract, I would add more numeric results to the Results section. The data on association between stavudine and lipoatrophy are quite impressive and convincing, and it’s a shame to leave them out of the abstract. (See comment 1 above and I’m also referring to the assoc between cumulative stavudine exposure and skinfolds measurements)

2. In the background discussing adverse consequences of lipoatrophy, you may want to also mention that lipoatrophy is associated with (and may play a causal role in) hypertriglyceridemia and overall cardiovascular risk, e.g., Wohl et al., JAIDS 2008, 48(1):44-52, Lake et al., AIDS Care, 2011, 23:929-38.

3. It would be better to provide BMI Z-scores (rather than BMI) in Table 1. In multivariate analyses, since already controlling for age, use of BMI is fine, but for between-group comparison of LA vs. non-LA, Z-scores would be more informative since the children with LA are older. Because the lipoatrophy group is older (and thus Z-score for a given BMI will be lower than in non-LA), and the p-value for absolute BMI is relatively close to significance at 0.2, one might see a significant difference between groups looking at BMI Z-score. If there is still no difference in BMI, I’d be curious to also see ratios from the subset that had DXA regarding lean:total mass and perhaps trunk:total fat – it would be interesting to know what sort of body mass is “making up for” the loss of peripheral fat.

4. I am puzzled by the “proportion recently exposed to stavudine” percentages in the last line of Table 1 – the significance of this is unclear, and it’s also not clear why this is lower in children with LA? Are children with severe LA switched off stavudine?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.