Author's response to reviews

Title: Safety and effectiveness of antiretroviral therapies for HIV-infected women and their infants and children: Protocol for a systematic review and network meta-analysis

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This is a thorough and well written protocol. There are only a couple of points where I feel clarification might be needed (described below).

RESPONSE Thank you for your positive feedback and for providing us with useful suggestions for improvement. We have made all of your suggested changes and believe that our protocol is clearer now.

1. Is the study design appropriate?
Yes.
RESPONSE Thank you.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?
Mostly yes. It appears that interventions were restricted to anti-retrovirals approved for use in Canada, but there does not appear to be any restriction by country/setting. Will evidence from low and middle income countries therefore be eligible for inclusion? If so, will country/setting be considered a source of heterogeneity in the analysis?
RESPONSE Thank you for pointing this out. We have added the following to our methods: “All countries and settings are eligible for inclusion” (see line 105). In order to deal with this potential source of heterogeneity, we will explore this via meta-regression if substantial heterogeneity is observed, as outlined on lines 193 to 196: “Meta-regression analysis will explore the influence of important factors such as baseline effect sizes (source of statistical heterogeneity), gestational age...
when antiretroviral therapy was commenced and country/setting of study conduct (sources of clinical heterogeneity), and study quality (source of methodological heterogeneity) on the meta-analysis results”

3. Is the planned statistical analysis appropriate?

The pairwise and network meta-analyses are well described. However, it is not entirely clear how eligible observation evidence (including cohort, case control and registry data) will be incorporated into the analysis. Some elaboration on the anticipated handling of non-trial data in general would be helpful.

RESPONSE Thank you for pointing this out. We have tried to clarify this on lines 231 to 236, as follows: “A sequential approach will be used for the network meta-analysis, first restricted to RCTs (which will be considered the primary analysis that we will base our conclusions on), second adding quasi-experimental data, and then finally incorporating data from observational studies. Such analyses will allow the determination of the contribution of non-randomized studies to the findings from RCTs.”

4. Is the writing acceptable?

Yes.

RESPONSE Thank you.