Effect of in utero exposure to HIV and antiretroviral drugs on growth in HIV-exposed uninfected children: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction HIV-exposed uninfected (HEU) children have higher morbidity and mortality compared with HIV unexposed uninfected children. Despite the fact that malnutrition contributes to about half of all infant deaths below 5 years of age in low-income and middle-income countries and that growth impairment has been reported in the HEU population, the spectrum of growth disorders associated with HIV and antiretroviral therapy (ART) exposure during in utero and perinatal periods is yet to comprehensively summarised among the global HEU population. This protocol for a systematic review and meta-analysis aims to critically synthesise data concerning the prevalence of underweight, stunting and wasting at different ages in the global HEU population.

Methods and analysis Medline, EMBASE, Cochrane Library, TOXLINE, WHO Global Index Medicus and the Web of Science will be searched for relevant articles published between 1 January 1989 and 1 December 2017 without language restriction. In addition, conference abstracts and reference lists of eligible papers and relevant review articles will be screened. Authors will screen and select studies, extract data, assess the risk of bias as well as studies individually for heterogeneity. Study-specific estimates will be pooled through a random-effects meta-analysis model for studies that are clinically homogeneous while funnel plots and Egger’s test will be used to detect publication bias. Results will be presented by ART availability period, country income levels and mode of breastfeeding.

Ethics and dissemination Ethical approval will not be required for this study because it will be based on published data. The final report of this study will be published in a peer-reviewed journal and presented at scientific conferences. This review will summarise the evidence and quantify the growth outcomes of HIV-exposed uninfected infants compared with an appropriate control group of HIV-unexposed uninfected children.

One of the limitations of the current review could be insufficient data to quantify the growth outcomes of interest. To our knowledge, this will be the first study to summarise the effect of HIV and antiretroviral therapy (ART) exposure on the growth of HIV-exposed uninfected infants compared with an appropriate control group of HIV-unexposed uninfected children. This review will cover both the era before widespread combination ART and the era after widespread access to combination ART so as to investigate whether any differences in growth outcomes exist between these two eras.
1. The effect of HIV and ART exposure on underweight (weight-for-age <2SD) until 60 months of age in the global HEU population compared with HUU children.

2. Studies whose data will not be sufficient to calculate the appropriate measures of effect.

3. The effect of HIV and ART exposure on wasting (weight-for-height/length <2SD) until 60 months of age in the global HEU population compared with HUU children.

**METHODS AND ANALYSIS**

**Design**

This will be a systematic review and meta-analysis of the published literature. The Centre for Reviews and Dissemination guidelines will be used for the methodology of this review and the review will be registered in the PROSPERO International Prospective Register of systematic reviews.

**Inclusion criteria**

1. Type of studies: all observational cohort studies and randomised controlled trials that have data on any growth parameter of interest, either as main or secondary outcomes. Only comparative studies with HEU and HUU children will be included in the meta-analysis.

2. Type of participants: adequately defined HEU (children exposed in utero to HIV and combination ART of any class, who are declared HIV negative by either DNA PCR between 6 weeks and 18 months OR appropriate HIV serological tests above 18 months) and HUU children (children born of mothers with documented HIV-negative serological test), aged 0–5 years. All ART exposure will be considered.

3. Outcome measures: prevalence of, stunting, wasting and underweight; growth velocity or studies that have enough data to compute the outcomes of interest at yearly time intervals, available from 12 to 60 months.

4. Type and period of publications: published studies and conference abstracts from 1 January 1989 to 1 December 2017.

For studies with several publications of their findings over time, we will retain in the review the one that has the best quality and the most appropriate regarding our objective. For the meta-analysis, studies with a documented measure of the effect of in utero/postnatal HIV and ART exposure on growth comparing HEU and HUU groups will be included. For studies without reported measures of effect, these will be computed if the provided data are adequate.

**Exclusion criteria**

We will exclude:

1. Type of studies: unpublished manuscripts, case reviews, policy reports, commentaries and editorials.

2. Studies whose data will not be sufficient to calculate the appropriate measures of effect.

**Outcome measures**

The following measures will be considered at different age points (6, 9, 12, 18, 24, 36, 48 and 60 months)

- Height-for-age.
- Weight-for-height/length.
- Weight-for-age.
Prevalence of stunting, wasting and underweight at each age point.

Growth velocity.

Prevalence of wasting and underweight at each age point.

**Search strategy to identify relevant studies**

**Databases**

An exhaustive literature search will be carried out in Medline, EMBASE, Cochrane Library, TOXLINE, WHO Global Index Medicus and the Web of Science to identify relevant articles published on growth in HIV-exposed uninfected infants between 1 January 1989 and 1 December 2017. The proceedings of the following conferences will also be searched: International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; International AIDS Conference; Conference of Retroviruses and Opportunistic Infections. The search strategy that will be used for online databases is presented in table 1.

**Searching other sources**

The list of references of eligible articles as well as relevant review articles will also be manually searched.

**Selecting studies for inclusion in the review**

All articles returned by the search will be saved to the Endnote version X4 software which will be used to remove duplicates. The titles and abstracts of the articles remaining after exclusion of duplicates will be reviewed to identify potentially relevant papers according to the inclusion and exclusion criteria. Two investigators will independently review retrieved the full text of all identified papers for eligibility and then retain those that are eligible by consensus. Any disagreement between investigators will be settled by a third reviewer. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be used to detail the number of articles identified, screened, included and excluded (online supplementary file 1).

**Data extraction and management**

A tool for data abstraction will be developed and the following data will be extracted:

1. Details about the author: name and journal.
2. Characteristics of the study: design, country, period when the study was conducted, year of publication, duration of follow-up, sample size and study endpoints.
3. Characteristics of participants: Age, sex, class of maternal ART, term of delivery, low birth-weight, mode of infant feeding (no BF, mixed feeding, exclusive BF), duration of BF, cotrimoxazole prophylaxis and growth references used.
4. Outcome measures at different time points: weight-for-age, length-for-age, weight-for-length, BMI for age and growth velocity.

Two investigators will independently extract data and any disagreements will be reconciled through discussion or by a third investigator as necessary.

**Assessing the methodological quality of included studies and risk of bias**

The quality assessment tool for Observational Cohort and Cross-sectional studies of the National Heart, Lung and Blood Institute (NHLBI) will be used to assess the quality of observational cohort studies (online supplementary file 2), whereas for intervention studies, the Effective Public Health Practice (EPHPP) tool (online supplementary file 3) will be used by two investigators independently. Agreement between the two investigators will be measured by Cohen’s kappa statistic. For the NHLBI tool, the score will be graded as good, fair and poor whereas for the EPHPP tool, it will be graded as strong, moderate and weak.

**Data synthesis and analysis**

Prevalences of underweight, stunting and wasting in the HEU and HUU groups will be recalculated based on the information provided by individual studies and ORs will be computed at each age point. The exposure variable will be HIV and combination ART exposure in utero and the outcome variable will be the different measures of growth: length/height-for-age, weight-for-height, then weight-for-age. We will use the statistic $I^2 = \frac{100\times(Q-df)}{Q}$, where $Q$ is the statistic of the Cochran heterogeneity Q-test and df the number of df corresponding to the number of studies minus one, which makes it possible to capture the proportion of the total variance observed due to a real difference in the measures of effects between the studies, in order to explore heterogeneity. Unlike the Q-test, this statistic is not influenced by the number of studies. Moreover, a non-significant Q-test does not necessarily imply that there is no heterogeneity between the studies because the power of the test depends on the number of studies. For statistical $I^2$, the values of 0%, 25%, 50% and 75%, respectively, represent the...
following heterogeneity levels: absence, weak, moderate and high. For each risk factor, the combined measure of relative risk will be estimated from a random-effect model if \(I^2 \geq 25\%\) and a fixed-effect model if \(I^2 < 25\%\). If substantial heterogeneity is observed, a meta-regression will be used to identify the characteristics of the studies (eg, study quality, study location, sample size, adjusting of confounders or not, ART agents and regimens, duration and mode of BF, maternal socioeconomic status and so on) that may explain the observed heterogeneity. All data will be analysed using Stata V.14. A forest plot will be presented for each factor studied in the studies found. The qualitative synthesis will be used in cases where data extracted is insufficient to perform quantitative synthesis or when the included studies significantly differ in design, setting and outcome measures.

**Assessment of reporting bias**

To explore a potential publication bias, funnel plots and Egger test will be done and a p value <0.10 will be considered indicative of significant publication bias.

**Presentation and reporting of the results**

The results of this meta-analysis will be presented by HIV and ART exposure status, by pre-ART and post-ART era according to the different classes of ART, by infant feeding mode and, if feasible, by country income level. We will prioritise length/height-for-age, weight-for-age according to the different classes of ART, by infant HIV and ART exposure status, by pre-ART and post-ART setting and outcome measures.

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As National Center for Health Statistics (NCHS)/Centers for Disease Control and Prevention (CDC)/WHO\(^{17}\) growth standards were used before 2005, and WHO child growth standards were used after 2005,\(^ {16}\) this may affect the longitudinal comparisons of the outcomes. Therefore, we will stratify our results according to the different standards. We will carry out a sensitivity analysis to determine whether the low birth weight has an impact on our results. Adherence to ART will be documented if reported by authors of the selected papers and discussed in the qualitative synthesis section of our manuscript.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) will be used for reporting this present protocol (online supplementary file 4).\(^ {19}\) Results of the search method will be presented with a flow chart, detailing the selection process. Causes of exclusion for studies first identified as eligible will be documented.

**Patient and public involvement**

Patients were not involved in the design of this study protocol.

**Potential protocol amendments**

The current protocol as written will not be amended in the course of the study. This is to avoid any outcome reporting bias.

**Ethical considerations and dissemination**

In this study, only published data will be used. No ethical clearance will therefore be needed. The final results will be published in peer-reviewed journals and also presented at conferences.

**CONCLUSION**

A comprehensive summary of the evidence concerning how in utero/postnatal exposure to HIV and ART affect growth is critical to shedding more light on our understanding of why HEU children have higher morbidity and mortality to certain infectious diseases compared with HUU. It is hoped that the results of this review will quantify the problem of growth impairment and draw attention to the necessity to possibly develop appropriate nutritional interventions for this growing population.

**Contributors**

GLE and VL: had the idea; guarantors of the study. GLE designed the protocol, VL, JJ and PBE: critically reviewed intellectual content and revised the methodology of the study. All the authors approved the final version of the manuscript.

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**Competing interests**

None declared.

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