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

Gabriel L Ekali,[1,2,3] Julie Jesson,[3] Pascal B Enok,[4] Valériane Leroy[5]

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[1]Biotechnology Center, Universite de Yaounde I, Yaounde, Cameroon
[2]National AIDS Control Committee, Cameroon
[3]Inserm UMR 1027, Universite Toulouse III Paul Sabatier, Toulouse, France
[4]Department of Preventive Medicine, University of Montreal, Montreal, Canada
[5]Universite Toulouse III Paul Sabatier, Toulouse, France

Correspondence to
Dr Gabriel L Ekali;
eloni2000@yahoo.com

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 the 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 problem of growth impairment in HEU infants and so shed more light on our understanding of the higher morbidity and mortality in this growing population.

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Strengths and limitations of the study

- 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.

BACKGROUND

One of the major strategies of reducing new paediatric HIV infections is by preventing mother-to-child transmission (MTCT) of the virus. This transmission can occur in utero, during delivery or breastfeeding (BF).[1] In the absence of any intervention, MTCT of HIV can be as high as 45%.[2] However, with antiretroviral therapy (ART), the rate of MTCT can be reduced to <2%.[3] With widespread access to ART, the Joint United Nations Programme on HIV/AIDS (UNAIDS) report that new paediatric HIV infections have declined by 47% between 2010 and 2016, whereas coverage of antiretroviral medicines provided to pregnant women living with HIV to prevent transmission to their children rose from 47% to 76% during the same period.[4]

As MTCT rates drop, the proportion of children who are exposed in utero to HIV and ART and are born uninfected with the virus (HEU) is increasing worldwide, especially in sub-Saharan Africa where the greatest burden of the HIV pandemic is found. Indeed, HEU children constitute about 30% of the Southern African paediatric population.[5] Even though HEU children are not infected with HIV, a growing body of literature shows evidence of higher morbidity and mortality compared with HIV/ART unexposed uninfected

(HUU) children. Higher frequency of hospitalisations, more severe respiratory tract infections especially from encapsulated bacteria as well as diarrhoeal diseases have been described.[5 6] Children exposed to maternal HIV and ART have a modest but significant impairment of development and a higher risk of growth impairment.[7] Growth failure, reflected by restricted linear growth and weight gain, have been reported among HEU children. A number of recent reviews have dwelt on summarising the available evidence of higher morbidity, mortality, immune dysfunction and its possible role in the higher susceptibility of HEU to diseases.[5–9] However, the spectrum of growth disorders found in this growing population and its possible association and role to the higher susceptibility to infectious diseases they experience is yet to be documented. This is important as it is known that impaired growth clinically represents an altered nutritional status, which is significantly associated with mortality in infancy. Indeed, nutrition-related factors contribute to about 45% of deaths in children under 5 years of age in low-income and middle-income countries, translating into the loss of approximately 3 million young lives annually.[10] Furthermore, restricted linear growth in early life also affects the quality of life an individual as it is associated with cognitive impairment[11] and lower lifetime earnings.[12] In addition, appropriate comparisons of HEU and HUU infants were rare before the antiretroviral era. With increasing ART access, it is methodologically challenging to disentangle effects of HIV exposure from those associated with ART exposure, particularly in regions where malnutrition and comorbidities are common and could increase the potential effects of these exposures.

In view of the recent reports of altered linear growth and weight gain among HEU infants, the main goal of this paper is to review and summarise evidence on the effects of perinatal/postnatal exposure to HIV and ART on growth outcomes in HEU children until 60 months of age and in later life.

Review question

What is the effect of in utero/postnatal exposure to HIV and ART on growth outcomes (stunting, wasting and underweight) until 60 months of age in HEU compared with HUU children as documented in studies reported between 1 January 1989 and 1 December 2018.

Specific objectives

To answer this review question, a systematic review and meta-analysis of the existing evidence will be conducted, the objectives of which will be to determine:

1. The effect of HIV and ART exposure on underweight (weight-for-age <2 SD) until 60 months of age in the global HEU population compared with HUU children.
2. The effect of HIV and ART exposure on stunting (height/length-for-age <2 SD) until 60 months of age in the global HEU population compared with HUU children.
3. The effect of HIV and ART exposure on wasting (weight-for-height/length <2 SD) 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[13] 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.

Table 1 Search strategy for the review of the impact of in utero exposure to HIV and ART on growth in HIV-exposed uninfected infants

Search	Search terms
#1	HIV OR HIV-1 OR HIV-2 OR HIV1 OR HIV2 OR HIV infect* OR human immune*
#2	HIV-exposed uninfected OR HIV exposed uninfected OR HEU OR HIV-EU OR HIV-unexposed OR HIV unexposed OR HUU OR HU OR HIV-UE OR HIV-uninfected OR HIV uninfected
#3	Children OR child OR infant OR infants OR pediatric OR pediatrics OR paediatric OR paediatrics
#4	Growth OR development OR stunting OR malnutrition OR wasting OR underweight OR weight OR length OR height OR BMI OR head circumference OR growth faltering OR Growth velocity
#5	Limits: from 1 January 1989 to 1 December 2017
#6	#1 AND #2 AND #3 AND #4 AND #5

ART, antiretroviral therapy; BMI, body mass index; HEU, HIV-exposed uninfected.; HUU, HIV unexposed uninfected.

- Growth velocity.
- Prevalence of stunting, 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[14] (online supplementary file 2), whereas for intervention studies, the Effective Public Health Practice (EPHPP) tool[15] (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 $I^2=100*(Q-df)/Q$ Q (with Q being 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 ≥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-height outcomes report first and weight-for-age being less discriminant.[16]

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,[18] 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 sheding 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.

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REFERENCES

1. Mofenson LM. Mother-child HIV-1 transmission: timing and determinants. *Obstet Gynecol Clin North Am* 1997;24:759.
2. Lehman DA, Farquhar C. Biological mechanisms of vertical human immunodeficiency virus (HIV-1) transmission. *Rev Med Virol* 2007;17:381–403.
3. Brocklehurst P. Interventions for reducing the risk of mother-to-child transmission of HIV Infection. *Cochrane Database Syst Rev* 2002;1:CD000102.
4. UNAIDS. UNAIDS data 2017. http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf (Accessed 29th Jan 2018).
5. Slogrove AL, Goetghebuer T, Cotton MF, *et al*. Pattern of infectious morbidity in HIV-exposed uninfected infants and children. *Front Immunol* 2016;7:164.
6. Brennan AT, Bonawitz R, Gill CJ, *et al*. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. *AIDS* 2016;30:2351–60.
7. Desmonde S, Goetghebuer T, Thorne C, *et al*. Health and survival of HIV perinatally exposed but uninfected children born to HIV-infected mothers. *Curr Opin HIV AIDS* 2016;11:465–76.
8. Abu-Raya B, Kollmann TR, Marchant A, *et al*. The immune system of HIV-Exposed uninfected infants. *Front Immunol* 2016;7:383.
9. Ruck C, Reikie BA, Marchant A, *et al*. Linking susceptibility to infectious diseases to immune system abnormalities among HIV-exposed uninfected infants. *Front Immunol* 2016;7:310.
10. WHO Media Center. Children: reducing child mortality Fact sheet. http://www.who.int/mediacentre/factsheets/fs178/en/ (Accessed on 2nd Feb 2018).
11. Sudfeld CR, McCoy DC, Danaei G, *et al*. Linear growth and child development in low- and middle-income countries: a meta-analysis. *Pediatrics* 2015;135:e1266–e1275.
12. Adair LS, Fall CH, Osmond C, *et al*. Associations of linear growth and relative weight gain during early life with adult health and human

capital in countries of low and middle income: findings from five birth cohort studies. *Lancet* 2013;382:525–34.
13. Centers for Reviews and Dissemination. CRD's guidance for undertaking reviews in healthcare. Centers for Reviews and Dissemination. 2009 http://www.york.ac.uk/crd/SysRev/!SSL!/WebHelp/SysRev3.htm (Accessed 2nd Feb 2018).
14. National Heart, Lung and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (Accessed 2nd Feb 2018).
15. Effective Public Health Practice Project. Quality assessment tool for quantitative studies. http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf (Accessed 2nd Feb 2018).
16. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
17. WHO. Global database on child growth and malnutrition. 1997 http://apps.who.int/iris/bitstream/handle/10665/63750/WHO_NUT_97.4.pdf;jsessionid=3467A6BA2F61719518EEF6309CE1ACD7?sequence=1 (Accessed 24th Sep 2019).
18. Waterlow JC, Buzina R, Keller W, *et al*. The presentation and use of height and weight data for comparing the nutritional status of groups of children under the age of 10 years. *Bull World Health Organ* 1977;55:489–98.
19. WHO. WHO Anthro for personal computers, version Software for assessing growth and development of the world's children. 2007 http://www.who.int/childgrowth/software/en/