Protocol information:

Mortality and morbidity of HIV-exposed uninfected and HIV-unexposed uninfected children in sub-Saharan Africa: a systematic literature review

Authors
Stanzi le Roux¹ and Kelly Nguyen¹

¹Division of Biostatistics and Epidemiology, School of Public Health & Family Medicine, University of Cape Town

Contact person:
Dr Stanzi le Roux
Division of Biostatistics and Epidemiology
School of Public Health & Family Medicine
University of Cape Town
Cape Town
South Africa

stanzi.leroux@gmail.com
BACKGROUND

With the global expansion of effective strategies to prevent mother-to-child transmission of HIV (PMTCT), large numbers of HIV-exposed but uninfected (HEU) children are born across sub-Saharan Africa annually. In 2012, an estimated 1 million HIV-uninfected children were born to HIV-infected mothers in the region; over 200 000 were born in South Africa, where antiretroviral-based PMTCT coverage exceeded 75%.

Estimating and addressing the health needs of this growing population of children is vital to the successful advancement of child health and survival in Africa.

HEU children may be at increased risk for adverse health outcomes. Historically, HEU children have been reported to have higher risks of mortality and morbidity than expected among HIV-unexposed (HU) children. A number of studies evaluating HEU child health outcomes have reported increased risks of malnutrition, neurodevelopmental delay, hospitalizations, and infectious morbidity including diarrhoea and pneumonia. However, current insights regarding the health of HEU children come predominantly from a previous era of HIV and PMTCT in Africa, where access to lifelong triple drug maternal antiretroviral therapy (ART) was limited and breastfeeding by HIV-infected mothers highly controversial. The available data on child health outcomes for HEU in the context of maternal ART and breastfeeding are limited largely to clinical trial cohorts; the generalizability of these findings are questionable and there are few comparative data on HU child health outcomes.

Attribution of causality in the relationship between maternal HIV exposure and adverse health outcomes in uninfected children is complex. Maternal HIV disease severity and lack of breastfeeding are both well-described independent predictors of childhood morbidity and mortality, therefore associations observed between HIV-exposure and negative child health outcomes may not be directly causal. Where ART is not available, households with HIV-infected caregivers are at increased risk for persistent food insecurity and generally have lower socio-economic status due to loss of income and increased medical costs; both adverse living conditions and early childhood malnutrition increase child mortality and morbidity. Additionally, HIV-infected women may be at high risk of mental illness, substance abuse and/or inter-personal violence, which in turn increases the risk for growth restriction and developmental delay in their offspring. Furthermore, HEU children born to HIV-infected mothers without viral suppression demonstrate a variety of phenotypical immunological differences when compared to HUU children,
and maternal HIV disease progression may alter reduces trans-placental antibody transfer during pregnancy, potentially resulting in earlier infant susceptibility to major childhood illness including measles.36-40

**Several major co-occurring risk factors for child mortality and morbidity will be addressed through universal maternal ART and successful breastfeeding.** Recent advances in PMTCT policies have seen a shift to (a) universal use of antiretroviral therapy (ART) for all HIV-infected pregnant women, and (b) promotion of breastfeeding with maternal ART.41 Since 2013, the World Health Organization recommends the use of antiretroviral therapy for all pregnant HIV-infected women, which should be maintained throughout breastfeeding (“Option B”), and continued for life (“Option B+”). 42 These strategies, implemented in the Western Cape from June 2013 and across South Africa in 2014, are likely to have a substantial impact on the health of HEU children.8,23,30,35,43-46 Moreover effective early use of ART results in maternal viral suppression, with restoration and protection of maternal health. Viral suppression also dramatically reduces the risk of MTCT via breast milk, thus allowing infants to safely benefit from breastfeeding.47 Breastfeeding substantially reduces morbidity and mortality among children globally, and there is a substantial body of literature regarding the benefits of breastfeeding among both HIV-exposed and HIV-unexposed children.8,23,30,35,43-46

For these reasons it is plausible that the increasing availability of ART generally, and to mothers specifically, will significantly improve the antenatal and postnatal socio-economic, nutritional and immunological milieu of HEU children4 and substantially ameliorate the impact of HIV exposure on child health outcomes in low-and middle income (LMIC) settings.8,23,30,35,43-46

**OBJECTIVES**

To describe and evaluate available data on associations between maternal HIV exposure and mortality/morbidity in HIV-uninfected children.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

As the definitive exclusion of HIV infection among children born to HIV-infected women is critical to the question, we will focus on individual level studies, including the following study designs:

1. Cohort analyses of randomized control trial participants
2. Prospective cohort studies
3. Retrospective cohort studies
4. Case-control studies where baseline characteristics were measured before outcomes occurred

Types of participants

HIV-uninfected pre-adolescent children (according to World Health Organization, below 10 years of age). HIV status of children under 15 months should be based on viral assays; studies which relied on clinical diagnoses and/or anti-HIV antibodies in children under 15 months will be excluded.

Context

Exposed (HEU) and control (HU) groups must be from a similar setting or community in sub-Saharan Africa.

Types of exposures

1. Maternal HIV infection as diagnosed before or during the index pregnancy, or during breastfeeding;
   
   and, where data are available:
   
2. Breastfeeding status; and
3. Use of antiretroviral agents

Types of outcome measures

This review will focus on mortality and clinical morbidity, specifically:

1. Primary outcome: Mortality
2. Secondary outcomes: Morbidity (clinical), specifically
   
   a. Hospitalizations and infectious morbidity, specifically
      
      • Diarrhoea
      
      • Pneumonia
   
   b. Child growth, as measured with anthropometry.
   
   c. Early childhood development, as measured with validated developmental tools.

We will not include reports which are limited to laboratory results without clinical outcome data.

Reports that do not prove data separately for HEU and HU children will also be excluded.

Search methods for identification of studies

Electronic searches
The search strategies will be built using a combination of database-specific terms for “HIV” + “mother” + “uninfected” + “child”

Language will be restricted to English, French, Portuguese and German.

We will search the following databases:

1. Journal databases
   - Medline (via Pubmed, appendix 1)
   - EmBase
   - EBSCOhost Research Databases, specifically
     i. PsycINFO
     ii. Global Health
     iii. Health and Psychosocial Instruments
     iv. CINAHL Plus with Full text
     v. Academic Search Premier

2. Conference databases
   
   Conference abstracts will be included in the EBSCOhost search strategy.

Searching other resources

We will review the reference lists of studies that meet our inclusion criteria, and examine the references of any literature reviews we identify during the search.

Data collection and analysis

Selection of studies

We will read the titles and abstracts of all material found during the searches as outlined above, to identify potentially eligible studies. In the event of unclear eligibility based on abstract alone, the full report will be retrieved. All potentially eligible reports will be downloaded in full text, and be screened independently by SLR and KN according to pre-specified, written criteria. Disagreements will be resolved through discussion.

Data extraction and management

Data will be abstracted onto a piloted data abstraction form, including the following:
• Identification details: trial or study number, author(s), published or unpublished, year of publication
• Study specific: study design, setting, dates and duration
• Participants: ages, relevant baseline characteristics, numbers
• Exposure: how and when maternal and infant HIV status was determined; infant feeding choices; maternal and infant use of antiretroviral therapy
• Potential third variables: results of stratified analyses
• Outcomes: details of measurement tools and use of blinding in assessments; summary statistics, measures of association with estimates of precision
• Comparison: how and when maternal HIV infection was excluded for the HIV-unexposed uninfected group of children; sampling method for comparison group

Assessment of risk of bias in included studies

The Newcastle-Ottawa Scale (NOS)\(^\text{48}\) will be used to assess for risk of bias. The scale measures risk of bias in three broad areas of study quality, namely (1) selection of participants (2) comparability of cohorts, and (3) outcome measurement.

Measures of association

We will present the estimates and measures of association used by the authors.

Data synthesis and analysis

We will provide a narrative summary of studies within the pre-specified categories of maternal use of antiretroviral therapy. This broad review will not include a meta-analysis, as we anticipate substantial heterogeneity across study populations and time.

ACKNOWLEDGEMENTS

SLR gratefully acknowledges funding received from the South African Medical Research Council, the Fogarty Foundation (NIH Fogarty International Center Grant #5R25TW009340) and the Office of AIDS Research.

DECLARATIONS OF INTEREST

The authors declare no conflicts of interest.

APPENDICES

1. Pubmed search strategy
((("prevention of mother to child transmission") AND HIV) OR "maternal HIV")
OR ("HIV"[MESH] AND "Pregnancy Complications, Infectious"[Mesh]))
OR (((HIV-exposed) OR HIV-exposed) OR human immunodeficiency virus-exposed))

AND

((((((negative) OR uninfected) OR HIV-free)) AND (((pediatric OR paediatric OR child OR infant OR newborn OR neonate OR children OR infants)) OR ((("Child"[Mesh]) OR "Infant, Newborn"[Mesh])
OR "Infant"[Mesh]))))

1. “Prevention of mother to child transmission” + HIV
2. “Maternal HIV”
4. 1 OR 2 OR 3
5. HIV-1-exposed
6. HIV-exposed
7. Human immunodeficiency virus-exposed
8. 5 OR 6 OR 7
9. 4 OR 8
10. Negative OR uninfected OR HIV-free
11. Pediatric OR paediatric OR child OR children OR infant OR infants OR newborn OR neonate OR newborns OR neonates
13. 11 OR 12
14. 10 + 13
15. 9 + 14

REFERENCES


