Adverse birth outcome case definitions associated with maternal HIV and antiretroviral drug use in pregnancy: a scoping review protocol

Kopano Rebaona Dube,1 Kathleen M Powis,2,3 Michael McCaul,4 Shani Tamlyn de Beer,5,6 Amy L Slogrove

ABSTRACT

Introduction The global antiretroviral therapy era has led to a decline in the number of children newly acquiring HIV and an increase in the number of children who are HIV-exposed and uninfected (HEU). This shift has prompted extensive research focusing on health and survival outcomes of children who are HEU. Study findings, particularly in relation to adverse birth outcomes, have been disparate, inconclusive and have not always been generalisable. Thus, the objectives of this scoping review are (1) to identify and extract definitions used for the adverse birth outcome terms ‘low birth weight’, ‘small for gestational age’, ‘stillbirth’ and ‘preterm birth’; (2) to compare the characteristics of studies from which birth outcome definitions were extracted by (a) temporal periods and (b) study country settings (high-income vs low-income and middle-income countries); (3) to use content analysis to map and describe the temporal and geographic distribution of the definitions used and construct a logical model of their evolution.

Methods and analysis The online databases of PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library and CINHAL/EBSCOhost will be used to identify published and grey literature from 2011 to 2022 to identify definitions for the adverse birth outcome terms ‘low birth weight’, ‘small for gestational age’, ‘stillbirth’ and ‘preterm birth’. A three-step process of (1) duplicate removal, (2) title and abstract screening and (3) full text screening will be used to select included studies. The extracted data will be used to conduct a comparative analysis, content analysis and construct a logic model.

Ethics and dissemination This review will be used to inform a consensus process around the development of harmonised definitions for the specified adverse birth outcomes. Our dissemination plan includes presentations, publications as well as the development of infographics and a resource hub. The study is approved by the Human Research Ethics Committee of Stellenbosch University.

INTRODUCTION

Globally, the majority of pregnant people living with HIV (PPHIV) receive antiretroviral treatment (ART) during pregnancy, with a substantial proportion now on ART at conception.1 2 ART use during pregnancy has increased in recent years in response to evolving global guidelines for both treatment of HIV and prevention of vertical HIV transmission. Prior to 2013 the WHO guidelines recommended initiation of ART based on CD4 cell count or other immunological criteria for all people with HIV including pregnant persons. This meant that only people who had low CD4 counts, or other markers of significant immune compromise were accessing lifelong ART, while guidelines recommended that PPHIV with higher CD4 counts receive short-course mono or dual antiretroviral prophylaxis to prevent vertical HIV transmission. In 2013, WHO recommended that all pregnant and breastfeeding people living with HIV initiate ART irrespective of their clinical or immune status and, for postpartum persons with higher CD4 cell counts, that treatment should at least be continued until there is no longer a risk of perinatal or postnatal HIV transmission (known as the ‘Option B’) or for life (known as the ‘Option B+’).3 In 2016, guidelines extended to recommend universal lifelong ART for all people living with HIV irrespective.
of CD4 or immune status. The evolving implementation of these policies for people of childbearing potential in conjunction with the UNAIDS 90-90-90 strategy has resulted in the decline in the number of infants acquiring HIV. This has been followed by a concomitant increase in the number of infants who have not acquired HIV but have fetal HIV and antiretroviral exposure, estimated at approximately 1 million infants annually. Additionally, in 2015 the WHO recommended pre-exposure antiretroviral prophylaxis (PrEP) for people at substantial risk of HIV acquisition and in 2017 specifically recommended PrEP for pregnant and breastfeeding people in settings of high HIV-incidence. As implementation of these guidelines is taken up by countries, the number of antiretroviral exposed pregnancies will expand even further.

These epidemiological shifts, along with a global commitment to ensure that children everywhere not only survive but thrive, has brought various goals into focus. Among them, complete adherence to ART to ensure parental health which contributes to infant health, as well as the need to optimise policies and programming that continue towards elimination of vertical HIV transmission while ensuring that children with in-utero HIV and antiretroviral drug exposure achieve health and developmental outcomes on course to reach their full individual potential. Subsequently, research and programmatic efforts are increasingly focusing on understanding how to optimise the health and ability to thrive among infants and children who are HIV-exposed and uninfected (HEU). High-quality research evidence plays an important role in guiding the development and implementation of policies as well as identifying the mechanisms that position children who are HEU to thrive.

Several early primary studies observed that maternal HIV disease and combination ART during pregnancy were associated with the adverse birth outcomes of stillbirth, preterm birth and small for gestational age. This is concerning as adverse birth outcomes are associated with increased infant and child mortality and morbidity and have been associated with suboptimal neurodevelopment. To evaluate and appraise existing findings, Wedi et al conducted a systematic review and meta-analysis that investigated the associations between HIV infection in PPLHIV naïve to ART and 11 perinatal outcomes. The authors found that maternal HIV infection without treatment was strongly associated with increased risk of low birth weight, stillbirth, small for gestational age and preterm birth and that advanced maternal HIV disease increased the risk of adverse perinatal outcomes. Uthman and colleagues subsequently summarised data regarding the safety of and adverse birth outcomes associated with ART initiated before versus after conception. Of the 5309 citations identified by Uthman and colleagues, data were extracted from 11 studies and demonstrated preterm birth, very preterm birth and low birth weight were significantly more likely to occur in PPHIV initiating ART before conception compared with PPHIV initiating ART after conception. Despite the variability in definitions, quality and strength of included studies the findings of the reviews consistently demonstrate the association between maternal HIV and ART use in pregnancy and adverse birth outcomes of low birth weight, stillbirth, small for gestational age and preterm birth. However, noteworthy is the number of studies excluded from the analysis due to disparate and often inconclusive findings. This, in part, is attributed to the lack of outcome definitions, heterogeneous outcome definitions, inconsistent use of subgroup classifications (eg, preterm delivery vs very preterm delivery), as well as the use of various population-specific centile charts in place of internationally standardised ones to distinguish between small for gestational age and very small for gestational age. Although there is a considerable amount of information about the adverse birth outcomes associated with maternal HIV and ART use in pregnancy, the heterogeneous definitions likely contribute to disparate findings, precluding the identification of definite conclusions about associations between in utero HIV or antiretroviral exposure and adverse birth outcomes. If adverse birth outcome definitions were standardised, aiding the quality and number of included studies, it would likely strengthen the evidence and enable pooling of data for systematic reviews.

A preliminary search using the terms “low birth weight”, “small for gestational age”, “stillbirth”, or “preterm birth” and “definition” on the sites of several global organisations identified varying definitions for these terms (online supplemental table 1). Noteworthy is that for preterm birth: (1) there is variability in terminology used, organisation A refers to ‘moderate to late preterm’ while organisation C and E refer to ‘moderately preterm’ and ‘late preterm’, respectively. (ii) Five organisations provided subgroup classifications. However, the gestational age cut-offs for the sub-groups ‘very preterm’, ‘moderately preterm’ and ‘late preterm’ birth differed among the organisations. Organisation A refers to very preterm as 28–32 weeks and moderate to late preterm as 32–37 weeks (which are also not mutually exclusive categories), while organisation C refers to very preterm as <32 weeks and moderately preterm as 33–36 weeks (excluding 32 weeks from both categories), whereas organisation E refers to only a single category which is late preterm birth at 34–36 weeks gestation. A similar observation was made when two prominent reviews published in 2016 were compared with each other (table 1).

Review A and B had different terminology or thresholds for subgroup classifications. For example, for small for gestational age, while the cut-offs were the same, review A referred to the more severe subgroup as ‘severely small for gestational age’ while review B referred to it as ‘very small for gestational age’. These discrepancies not only result in the exclusion of studies, but also contribute to misclassification bias, which can compromise the internal validity of the studies.

To maintain maternal confidence in antiretrovirals, improve maternal uptake of ART as well as PrEP, and...
Table 1  Summary of definitions used by two systematic reviews

<table>
<thead>
<tr>
<th>Review</th>
<th>Preterm birth</th>
<th>Small for gestational age</th>
<th>Low birth weight*</th>
<th>Stillbirth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review A</td>
<td>Defined as: Preterm birth (&lt;37 weeks gestation). Very preterm delivery as live birth at &lt;34 weeks’ gestation</td>
<td>Defined as: Small for gestational age, birth weight &lt;10th centile for gestational age. Severe small for gestational age, birth weight &lt;3rd centile for gestational age</td>
<td>Defined as: Low birth weight (&lt;2500g). Very low birth weight (&lt;1500g)</td>
<td>Defined as: Infant born with no signs of life ≥28 weeks’ gestation</td>
</tr>
<tr>
<td>Review B</td>
<td>Defined as: Preterm birth (&lt;37 weeks 0 days gestation), Very preterm birth (&lt;32 weeks 0 days gestation)</td>
<td>Defined as: Small for gestational age (birth weight &lt;10th centile). Very small for gestational age (birth weight &lt;3rd centile)</td>
<td>Defined as: Low birth weight (&lt;2500g). Very low birth weight (&lt;1500g). Term birth with low birth weight (&lt;37 weeks 0 days gestation and &lt;2500g). Preterm low birth weight (&lt;37 weeks 0 days gestation and &lt;2500g)</td>
<td>Defined as: Any third trimester delivery of a stillborn infant with birth weight ≥1000 g or ≥24 weeks 0 days gestation or ≥35 cm body length</td>
</tr>
</tbody>
</table>

*No subgroup classification for extremely low birth weight.

strengthen evidence-based health policy development, research that focuses on the health outcomes of children who are HIV and/or exposed to antiretrovirals needs to be scientifically robust. A preliminary search of PROSPERO, PubMed/MEDLINE, the Cochrane Database of Systematic Reviews and the journal Joanna Briggs Institute (JBI) Evidence Synthesis was conducted, and no planned or current scoping reviews or systematic reviews specifically evaluating the definition of adverse birth outcomes were identified by November 2022.

Our scoping review and appraisal of the existing definitions for the specified adverse birth outcome terms, detailed here, will inform a consensus process by the DECIPHER project (of the CIPHER Programme of the International AIDS Society) team of experts to propose standard terminology and definitions for measurement of adverse birth outcomes in studies of perinatal HIV and antiretroviral exposure. Use of standardised definitions can promote consistency between studies and facilitate data pooling.

REVIEW QUESTION
What definitions and/or subgroup classifications and/or thresholds are used for low birth weight, stillbirth, small for gestational age and preterm birth in primary and secondary research reporting adverse birth outcomes associated with maternal HIV and antiretroviral use in pregnancy?

REVIEW OBJECTIVES
To answer the review question, the objectives of this review are to:

- Identify and extract definitions that are in use for the adverse birth outcome terms ‘low birth weight’, ‘small for gestational age’, ‘stillbirth’ and ‘preterm birth’.
- Compare the characteristics of studies that reported birth outcome definitions by temporal periods and study country setting (high-income vs low-income and middle-income countries).
- Use content analysis to map and describe the temporal and geographic distribution of the definitions used and construct a logic model of their evolution.

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR).

METHODS
We will conduct a scoping review of reported adverse birth outcomes associated with maternal HIV and antiretroviral use in pregnancy specifically low birth weight, stillbirth, small for gestational age and preterm birth to determine case definitions that are in use.

Inclusion and exclusion criteria

Concept
This review will consider case definitions for the terms low birth weight, stillbirth, small for gestational age and preterm birth. If related terms are used for any of these four terms, the alternative terms will be noted together with the specified case definitions.

Context
All the sources of evidence specified below pertaining to any contextual setting are eligible for inclusion. The only restriction to be applied is that definitions should be in the context of HIV and/or maternal and child health.

Types of sources
This scoping review will consider all primary experimental and analytical studies as well as secondary studies in the form of systematic reviews with or without meta-analyses that have evaluated low birth weight, stillbirth, small for gestational age and preterm birth as a primary or
secondary objective associated with HIV or antiretroviral use in pregnancy or exposure to other communicable or non-communicable diseases for inclusion. Conference abstracts and presentations, case reports, case series as well as guidelines will be included while editorials, expert opinions, commentaries and narrative reviews will be excluded. Additionally, sources will be excluded if (1) the adverse birth outcomes that are described do not include terms equal or equivalent to low birth weight and/or, stillbirth and/or, small for gestational age and/or, preterm birth and/or (2) a case definition is not provided anywhere in the text.

Search strategy
The proposed search strategy will be reported in accordance with the PRISMA-ScR checklist. The strategy is aimed at identifying all eligible published and unpublished primary studies, reviews, conference proceedings and trial protocols. An initial search of PubMed/MEDLINE and Cochrane Library will be undertaken to identify articles on the topic. The text words, titles and abstracts as well as index terms and key words used to describe the articles will be used to expand and quality check the full search strategy for PubMed/MEDLINE (see table 2).

To ensure study feasibility, the search will be limited to sources published from January 2011 to July 2022 in English for which the full text or recording, in instances of presentations, can be retrieved. No additional restrictions will be placed on the search. The electronic databases to be searched for the various types of sources stipulated above include PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library and CINHAL/EBSCOhost. The full translated and optimised search strategy that will be used for Scopus, Web of Science, Cochrane Library and CINHAL/EBSCOhost has been included (online supplemental table 2). The reference list of articles that have been selected for full text review will be screened for additional relevant papers. Furthermore, authors will be contacted and/or interlibrary loans sought for full text articles that are not accessible from the selected databases.

Study selection
A three-step process will be followed to select studies that will entail (1) searching and removal of duplicates, (2) title and abstract screening and (3) full text screening. Following the search, all identified records will be collated and uploaded in Covidence (Veritas Health Innovation, Melbourne, Australia) a primary screening and data extraction tool for the management of systematic reviews. Once duplicates are removed, a pilot title and abstract screening phase, using five articles evaluating one or more of the four outcomes, will be conducted to test the predefined inclusion and exclusion criteria. Following the pilot, the relevant adaptations will be made to the criteria. Titles and abstracts will be screened independently in duplicate by two reviewers (KRD and STdB) using the final predefined criteria. The full text and citations of potentially relevant papers will be retrieved, imported into Covidence and reviewed independently and in duplicate to evaluate if they meet inclusion criteria. A third reviewer (ALS) will assess any discrepancies and resolve any disagreements that arise between the reviewers at both screening stages.

Reasons for exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported. The results of the search will be reported in full in the final scoping review and presented using PRISMA-ScR flow diagram.21

Patient and public involvement
None.

Data extraction and analysis
Both qualitative and quantitative approaches as outlined below will be used to analyse the data for each outcome individually to achieve the objectives of the scoping review.

Objective 1: identification and extraction of definitions
Data will be extracted from papers by a single reviewer (KRD) using a modified data extraction tool developed in collaboration with the Data Evaluation and CIPHER.

Table 2 PubMed/MEDLINE search strategy

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<tr>
<th>Database</th>
<th>Search strategy</th>
</tr>
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The search strategy, including all identified keywords and index terms will be adapted and optimised for each information source. The key search terms include but will not be limited to “HIV”, “Antiretroviral Therapy, Highly Active”, “Infant, Low Birth Weight”, “Infant, Small for Gestational Age”, “Stillbirth”, “Premature Birth”, “Adverse pregnancy outcome”, “Adverse birth outcome”, “Preterm deliver” and “Premature deliver”.
Preparation for an HIV Exposed Uninfected Child Cohort (DECIPHER) panel of experts according to selected items from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma) and Consolidated Standards of Reporting Trials (CST). To standardise the extraction process, the data extraction tool will be piloted on five papers evaluating one or more of the four outcomes and assessed for discrepancies by a third reviewer (ALS) prior to the full extraction. The basic publication and study characteristics (such as year of study, publication type, study design, country and setting) as well as key characteristics, including definitions (such as adverse outcome assessed, case definition and methods used for adverse outcome assessment) will be extracted from each study. The third reviewer (ALS) will assess for discrepancies. REDCap will be used to develop the data extraction tool and for data capturing. Logic checks will be built into the tool to ensure that the values that are entered, such as year of study, are within the permitted variable ranges and to guard against errors. All modifications will be detailed in the full scoping review. Data will be imported into STATA V.17 for analysis of objective 2.

Objective 2: comparative analysis

Characteristics of included studies will be compared by the temporal period in which they were conducted (eg, pre-2013 vs 2013 and later) and by country income group (high vs low-income and middle-income) as these factors have relevance to considering applicability and feasibility of definition use going forward. Country income group will be classified according to World Bank Classification. The characteristics to be compared include year of publication, publication type, years of study, study design, region of study, country income group, study setting (eg, clinic), study data sources (eg, clinical records), unit of study (eg, mother), maternal HIV status, outcome assessors’ professional level, and the adverse birth outcome measurement method. Characteristics with categorical variables will be reported as frequency and percentage and compared using the $\chi^2$ test or Fisher’s exact test.

Objective 3: content analysis and logic model construction

Content analysis will be used to analyse the data descriptively using tables and mapping. To map the definitions, the WHO definitions which will be used as the starting framework will be broken up into the root definition and subgroup classification will be presented in columns, while each study will be presented in rows. If studies used modified definitions or subgroup classifications or criteria the modifications will be added as new columns, the letter X will be used to indicate the presence of key words and/or cut-offs, and/or criteria. Colours will be used to code between the differences in key words and/or cut-offs, and/or criteria associated with the WHO or modified definition categories (online supplemental table 3, dummy data).

Data from the content analysis will be used to construct a logic model for each outcome. The logic model will map the sequence of how the definitions evolved or regressed and depict which definitions and accompanying criteria are in use. Two separate logic models will be constructed for high-income and low-income and middle-income settings to allow for comparison of use and evolution of terms in both settings. Narrative summaries will accompany the analysis and images. The tables and figures will be supplemented with additional visualisations such as stacked bar graphs for the most important results. All visuals and narratives will be reported in a manner that answers the review question and accomplishes the objectives.

ETHICS AND DISSEMINATION

This study is approved by the Human Research Ethics Committee of Stellenbosch University (S22/07/138). The results of this proposed review will be used to inform a consensus process to develop harmonised definitions for the specified adverse birth outcomes by a panel of experts for use in future studies of the impact of in utero HIV and antiretroviral drug exposure on these outcomes. We commit to ensuring broad dissemination and access of our research through several knowledge translation strategies. These include but are not limited to publications, presentations, stakeholder engagement meetings as well as housing them in a resource hub.
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