Title: Standardized definitions of in utero HIV and antiretroviral drug exposure among children

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Key words: HIV, antiretroviral, in utero, pregnancy, definition

Running title: In utero HIV & antiretroviral exposure definitions

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Key points: In countries with high HIV prevalence, 20-30% of pregnant women have HIV and receive antiretrovirals. The proposed definitions offer a uniform approach to facilitate consistent description and estimation of effects of in utero HIV and antiretroviral exposure on child health outcomes.

Abstract:

In countries with high HIV prevalence, up to 30% of pregnant women are living with HIV, with fetal exposure to both HIV and antiretroviral therapy during pregnancy. Additionally, pregnant women without HIV but at high risk of HIV acquisition are increasingly receiving HIV pre-exposure antiretroviral prophylaxis. Investments are being made to establish and follow cohorts of children to evaluate the long-term effects of in utero HIV and antiretroviral exposure. Agreement on a key set of definitions for relevant exposures and outcomes is important both for interpreting individual study results and for comparisons across cohorts. Harmonized definitions of in utero HIV and antiretroviral drug (maternal treatment or pre-exposure prophylaxis) exposure will also facilitate improved classification of these exposures in future observational studies and clinical trials. The proposed definitions offer a uniform approach to facilitate the consistent description and estimation of effects of HIV and antiretroviral exposures on key child health outcomes.

The case for harmonized definitions of in utero HIV and antiretroviral drug exposure in children

In high-HIV prevalence countries, specifically in southern Africa, up to 30% of pregnant women live with HIV[1]. Most women with HIV now appropriately receive lifelong antiretroviral therapy (ART) including whilst pregnant and breastfeeding, and their children are exposed to both HIV and antiretroviral drugs in utero[2]. Annually, over 1 million infants are born HIV-uninfected after in utero exposure to HIV and maternal antiretrovirals[3]. In 2020, an estimated 15.4 million children aged 0-14 years globally were HIV-exposed and uninfected; and by 2018 estimates 71% had also been exposed in utero to antiretrovirals[4,5]. Furthermore, prevailing HIV prevention policies promoting use of pre-exposure antiretroviral prophylaxis (PrEP) for individuals at high risk of HIV acquisition, including pregnant and breastfeeding women, will result in an emerging population of children with antiretroviral exposure in the absence of HIV exposure[6].

Collectively, observational research from the last two decades has fallen short of clarifying whether the large population of children who are HIV-exposed but uninfected (HEU) are achieving equivalent survival, health and developmental outcomes as children who are HIV- and antiretroviral drug-unexposed and HIV-uninfected. Overall, data suggest that children who are HEU may experience a greater burden of infectious morbidity and a greater risk of mortality than children who are HIV-unexposed and uninfected (HUU)[7–12]. Concerns have been raised regarding poorer growth outcomes and greater neurodevelopmental deficits following in utero HIV and antiretroviral exposure, although evidence is inconclusive[13,14]. The numerous interconnected pathways, whether biological, socioeconomic or structural, that may be driving differences between children who are HEU and HUU have been challenging to isolate and measure with research approaches used to date[15]. Understanding the mechanisms underlying the health disparities occurring in children who are HEU has been hindered by i) study-specific definitions for exposures and outcomes making comparison of findings challenging; ii) studies identifying signals of concern in children who are HEU but often without appropriate comparison to children who are HUU; iii) studies underpowered to adequately interrogate confounders, mediators or specific sub-groups at greater risk within the heterogenous population of children who are HEU; and iv) retrospective secondary analysis of data where the primary purpose of the study did not have a specific scientific objective to evaluate outcomes of children who are HEU.

In the universal ART era, the bar has been raised to achieve equivalent life expectancy and quality of life for adults with and without HIV. This standard should be no different for children born to women with and without HIV, wherever they live. With expanding access to maternal ART resulting in improved maternal health and survival in combination with safer breastfeeding, it is imperative to reframe the research approach of evaluating differences in outcomes to one that can conclusively evaluate whether children who are HEU are achieving health and developmental outcomes equivalent to their peers who are HUU. From recent work that has more carefully considered the heterogeneity in risk factors among women with HIV and how these may be contributing to, rather than confounding, the disparities in outcomes for their children, it is clear that many children who are HEU are achieving health and developmental outcomes comparable to children who are HUU, while sub-groups at greater risk of adverse outcomes exist[16–19]. Efforts to confidently evaluate equivalence or conduct sub-group analyses require substantially larger sample sizes than seen in recent years. Importantly, robust comparison and generalizability of findings across diverse settings require more consistent classification of exposures and measurement of outcomes. Investments are being made to establish larger cohorts of children who are HEU for long-term follow-up. These investments will benefit from agreement on the definitions of a key set of relevant exposures and outcomes, irrespective of the primary scientific aims of the individual studies[20]. Similarly, while preliminary reports on PrEP use in pregnancy have found this preventive strategy to be safe for mothers and their infants, the evidence is limited by selection bias and small numbers [21,22]. Studies evaluating PrEP exposure during pregnancy and breastfeeding could be strengthened through these same harmonized approaches[21].

The Brighton Collaboration and affiliated Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project have set an example of developing standardized case definitions and data collection guidelines for adverse events following immunization through an established process[23,24]. Standardized outcome definitions are one tool employed by the Brighton Collaboration and the GAIA project to achieve their objectives of improved comparability of data, maximized research utility from all studies by harmonization of methods and promotion of scientific progress by increasing analytic power and options through data pooling[23,24].

The DECIPHER Project

The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Program of the International AIDS Society established the CIPHER Cohort Collaboration in 2013 as a network of observational pediatric and adolescent HIV cohorts to answer key questions related to children and adolescents living with HIV that could not be answered by individual cohorts[25]. In 2017, the CIPHER Cohort Collaboration recognized the emerging scientific gap and growing importance to robustly evaluate outcomes in children who are HEU, including those with in utero exposure to antiretroviralss. To this end, the DECIPHER (Data Evaluation and CIPHER Preparation for an HIV Exposed Uninfected Child Cohort) Project was initiated to lay the foundation for establishing cohort collaborations that could identify subtle but possibly meaningful effects of HIV and antiretroviral exposures on children who are HEU that individual studies have limited power to confidently identify or evaluate. The DECIPHER Project Team includes voluntary representatives with a wide range of expertise from eight cohort networks or program partners (Baylor International Pediatric AIDS Initiative at Texas Children's Hospital; European Pregnancy and Paediatric HIV Cohort Collaboration; Elizabeth Glaser Pediatric AIDS Foundation; International Maternal Pediatric Adolescent AIDS Clinical Trials Group; International epidemiology Databases to Evaluate AIDS [IeDEA]; ICAP at Columbia University; Pediatric HIV/AIDS Cohort Study) working in more than 30 countries across the world. The DECIPHER Project drew on the experience of the CIPHER Cohort Collaboration in pooling data from diverse cohorts of children and adolescents with HIV, as well as the Brighton Collaboration and GAIA approaches. The initial step was to prioritize key exposure and outcome variables for standardization to facilitate improved classification in future observational studies and clinical trials including children or adolescents who are HEU. The first of these harmonized definitions, for in utero HIV and antiretroviral exposures, are presented and discussed here.

Definition development process

General considerations for definition development

The DECIPHER Project's primary focus centered on the development of harmonized definitions and tools amenable to uptake in future prospective research in diverse settings, with priority given to feasibility and applicability in low- and middle-income countries (LMICs). Although not designed for program surveillance and monitoring systems, the DECIPHER definitions could be used in these contexts and for retrospective

application to existing cohort and clinical trial data. Furthermore, the definitions have been designed for exposure and outcome classification in research contexts but not for diagnosis or clinical management where there are different considerations for appropriate clinical care. The hierarchical format to the certainty of the variable classification, adopted from the Brighton Collaboration approach, does not imply potential causality between factors, but rather acknowledges the depth of information available with which to classify the exposure or outcome that in turn determines the level of certainty of classification.

The DECIPHER Project Team prioritized variables for harmonization based jointly on the frequency and public health importance of exposures and outcomes. For the first phase of the project the following were prioritized: in utero HIV and antiretroviral exposures, postnatal antiretroviral exposure (through maternal ART or PrEP via breastfeeding or direct administration of infant antiretroviral prophylaxis), adverse birth outcomes and neonatal morbidity and mortality. Post-neonatal under-5-year all-cause mortality and infectious morbidity outcome definition harmonization is already being undertaken by the INFORM-HIV Free (A harmonized Infrastructure For Monitoring outcomes of the HIV Free generation) Project and standardization of childhood neurodevelopment measurement tools by the WHO and partners[26,27].

To arrive at this first set of definitions, a scoping literature review was conducted to identify how studies had previously defined or classified infants and children according to the presence or absence of in utero HIV or antiretroviral exposures. Using scientific and technical expertise of the project team during seven teleconferences and one in-person meeting, draft definitions were proposed and revised until agreement on separate sets of definitions for in utero HIV exposure and in utero antiretroviral exposure was reached.

In utero HIV exposure definitions

Correct classification of the presence or absence of in utero HIV exposure and exclusion of HIV infection are central to correctly determining associations between HIV exposure and outcomes in the absence of HIV infection in the child. Children can be misclassified as HEU when they are actually HIV-infected but child HIV infection has been missed. Alternatively, children can be misclassified as HUU when they are actually HIV-exposed but maternal HIV infection has been missed. The possibility of missing HIV infection in children who are classified as HEU is influenced primarily by three factors: i) early postnatal testing during the window

period of nucleic acid test positivity following intrapartum HIV transmission; ii) the impact of maternal ART via breastmilk or of infant antiretroviral prophylaxis that may reduce the infant's viral load to below the limit of detection for diagnostic testing resulting in a false negative nucleic acid test in an infant actually infected with HIV; iii) ongoing exposure to HIV via breastmilk and the accompanying risk of postnatal HIV acquisition. These factors have been taken into consideration in classifying a child as HEU (Table 1 section A, Supplementary Figures A (algorithm) & B (selected illustrated examples)). Any negative HIV test, whether antibody- or nucleic acid-based, is sufficient to exclude HIV infection at that particular time-point in children older than 6 weeks of age. The possibility of missing HIV exposure, i.e., maternal HIV infection in children classified as HUU, is influenced primarily by the timing of maternal HIV testing and the possibility of maternal HIV acquisition following negative test results earlier in pregnancy (Table 1 section B, Supplementary Figures C (algorithm) & D (selected illustrated examples)). This has relevance for studies in lower HIV prevalence settings where repeated maternal HIV testing might not be clinically justified or cost-effective due to the low risk of HIV acquisition. However, promotion of the proposed DECIPHER definitions provides motivation for prospectively designed studies interested in achieving high certainty of a child's HIV exposure status, including those with a control group of children who are HUU, to incorporate repeat testing of mothers at delivery or later to exclude maternal HIV infection. An additional element for consideration in the classification of children as HUU with high certainty is exclusion of child HIV infection in this group. Although non-vertical transmission is rare, cases and localized outbreaks continue to be documented, and high certainty that a child is HUU, under the proposed definition, requires the exclusion of HIV infection in the child rather than assuming this based on absence of maternal HIV infection[28–30]. Direct confirmation of child HIV status also has relevance for long-term cohorts as children age into adolescence and early adulthood and may become increasingly at risk for horizontal HIV acquisition.

Preliminary relevance and feasibility of the definitions for in utero HIV exposure were evaluated in two ways. Following review of the literature, 16 published observational cohorts including children who were HEU and children who were HUU were identified from across LMIC and high-income country settings[31]. The DECIPHER definitions for classifying children as HEU and HUU were applied at the study level using the information available in published methods of these cohorts. Five studies met moderate and 11 studies met high certainty criteria for classification of children as HEU. For classification of children as HUU, 4 studies met

low, 11 studies met moderate and 1 study met high certainty criteria. The definitions for children who are HEU were also retrospectively applied at the individual level to the data available on births from 2015-2017 in the Surveillance Monitoring for ART Toxicities (SMARTT) study conducted by the Pediatric HIV/AIDS Cohort Study (PHACS) network. In this cohort, 29% met low, 2% moderate and 69% met high certainty criteria[28].

In utero antiretroviral exposure definitions

Greater precision and consistency in defining and classifying in utero antiretroviral exposure, either due to maternal ART or to maternal PrEP, are essential to advancing understanding of the possible effects of these exposures. Therapeutic and prophylactic options for HIV management and prevention may expand beyond antiretrovirals alone and other modalities may need to be considered in the future. For pragmatic purposes, only in utero exposures to maternal ART or antiretroviral PrEP are considered here.

To reduce complexity, a single set of definitions was designed that apply either to fetal exposure to maternal ART or to maternal antiretroviral PrEP. Certainty of the type (Table 2 section A and Supplementary Figure E (algorithm)) and timing (Table 2 section B and Supplementary Figures F (algorithm) & G (selected illustrated examples)) of in utero antiretroviral exposure are defined separately. The definitions do not incorporate duration of antiretroviral exposure during pregnancy, although investigators could choose to collect and analyze this information. Differences in risks of adverse birth outcomes and infectious morbidities may be associated with timing of initiation of maternal ART, either preconception or during pregnancy[32,33]. Thus, timing of in utero antiretroviral exposure is categorized either as starting preconception or starting during pregnancy. Antiretroviral exposure initiated during pregnancy can be further categorized by weeks (high certainty) or trimesters (moderate certainty) of gestation at initiation. In the absence of any information on the type or timing of antiretrovirals taken during pregnancy, in utero antiretroviral exposure is unclassifiable. Unless there is documentation of maternal antiretroviral interruption, for the purpose of these definitions it is assumed that antiretrovirals are taken consistently as prescribed from the date of most recent initiation. As pregnancy represents a particularly high-risk period for maternal HIV acquisition and onward vertical transmission, it is assumed that unless otherwise documented PrEP was taken continuously during pregnancy[34]. Assessing how exposure would vary depending on adherence, changing pregnancy physiology or interactions with other medications is beyond the scope of this project.

Gestational age assessments are essential to distinguish antiretroviral exposures initiated close to conception from those initiated during pregnancy. The GAIA Preterm Birth Working Group's levels of certainty of gestational age assessment were adopted with some minor modifications to inform in utero antiretroviral exposure timing definitions (Table 3)[35]. Use of gestational age assessment methods included in GAIA levels 1 (highest level of certainty) through 3A permits gestational age estimation to a specific number of weeks. This was deemed adequate to differentiate preconception from pregnancy-initiated antiretrovirals with high certainty, as well as to classify gestational week of initiation during pregnancy with high certainty. GAIA gestational age assessment level 3B was adapted for the DECIPHER definitions to include unknown last menstrual period (LMP) dates and a definition of LMP has been added (Table 3).

Guidance for application of the definitions

We anticipate that many well-designed and well-implemented studies may not reach high levels of certainty in classifying all DECIPHER-defined exposures. This may occur in low HIV prevalence settings where frequent maternal and child HIV testing are not routinely indicated due to the much lower risks of HIV acquisition. It could also occur in high prevalence settings where accurate gestational age determination, required for antiretroviral exposure timing definitions, is challenging due to limited resources or high rates of first antenatal care presentation during the second half of pregnancy. Classification of HIV or antiretroviral exposure as less than high certainty does not indicate that the study is of low or questionable quality, but rather provides transparency around where misclassification may occur and informs how study findings are interpreted.

We propose that studies applying the DECIPHER definitions for in utero HIV and antiretroviral exposures summarize the certainty of classifications when presenting study results in a simple tabular format similar to the example given in Table 4 or in a simple text summary similar to the following: "*In our cohort, 48%, 40% and 4% of the children were classified as HEU with high, moderate or low certainty respectively, and 0%, 96% and 4% of the children were classified as HUU with high, moderate or low certainty, respectively. HIV exposure status could not be classified in 8% of children. Among children who were HEU, maternal ART type was known with high, moderate or no certainty in 36%, 52% and 12% respectively. Maternal ART timing was known to be preconception with high or moderate certainty in 80% and 8%, respectively, and maternal ART was known to*

be pregnancy-initiated with high or moderate certainty in 25% and 75%, respectively. *In 12%, there was insufficient information to classify timing of maternal ART initiation."*

Conclusions

We are of the view that the evolving state of the HIV epidemic requires investment in systematic data collection and monitoring systems from which data-driven interventions can be designed to improve the survival, health and wellbeing of children who are HEU. Through a shared understanding and common vocabulary to define in utero HIV and antiretroviral exposures, we can optimize the quality and utility of smaller studies by improving data collection while simultaneously setting the stage for more rigorous scientific analyses. The potential value of these standardized definitions will only be realized following broad endorsement by researchers with wide dissemination, practical application, continuous collaboration and refinement. Future iterations could explore extending the HIV and antiretroviral exposure definitions to include the intensity or duration of both in utero and postnatal exposures to better understand their impacts on child health outcomes. Ensuring that children who are HEU achieve comparable survival, growth and neurodevelopmental outcomes as children who are HUU supports the premise that the highest attainable standard of health is a fundamental right of every human being, while simultaneously addressing the significant impacts that disparities could present on human capital in high HIV prevalence settings. The proposed harmonized DECIPHER Project definitions offer a uniform approach to facilitate the precise and consistent description and estimation of effects of HIV and antiretroviral exposures on key child health outcomes.

Funding:

This work was supported by the International AIDS Society [grant numbers C3P2 2017 to MAD, 2017/518-SLO to ALS]; Fogarty International Center of the National Institutes of Health [grant number 1K43TW010683 to ALS]; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development of the National Institutes of Health [grant number 1R21HD093531 to KMP; grant numbers 5U01HD052102 and 5P01HD103133 to PLW and EGC]; EPPICC is supported by the Penta Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the International AIDS

Society or the National Institutes of Health. CIPHER is made possible through unrestricted educational grants from ViiV Healthcare and Janssen.

Conflict of interest: The authors declare no conflicts in relation to this work.

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Table 1: Levels of certainty to classify children as in utero HIV-exposed and uninfected (HEU) and HIV-unexposed and uninfected (HUU) at the time of specified study outcome evaluation

A. Classification of children who are HEU
Mother known to have HIV Classifying a child as HEU with any level of certainty requires that the *mother is known to have HIV* by at least one of the following scenarios: 1. Documented positive maternal HIV status determined according to local diagnostic testing algorithms during pregnancy with this child or earlier 2. Evidence of > 1 month of ART received during pregnancy with this child or earlier 3. Registered in any HIV care or ART program during pregnancy with this child or earlier 4. Child (in study) < 24 months of age with positive HIV antibody test and negative HIV nucleic acid test *If the child's mother is not known to have HIV according to at least one of criteria 1-4 above, refer to Section B (Classification of children who are HUU)*
Child is HEU – high certainty Child of a mother known to have HIV (according to criteria 1-4 above for Mother known to have HIV) AND Child *tested HIV-negative* (antibody or nucleic acid test) *at ≥ 6 weeks of age* AND Timing of HIV-negative test met at least one of the following scenarios: 1. The test was performed **at the same time or after study outcome measurement** [no breastfeeding or ARV prophylaxis information required] 2. If the last test is performed **before study outcome measurement** a. In the absence of breastfeeding and child ARV prophylaxis, child tested HIV-negative at least once at ≥ 6 weeks of age b. If child was breastfed without extended ARV prophylaxis, child tested HIV-negative ≥ 6 weeks after end of breastfeeding c. If child received ARV prophylaxis but was never breastfed, child tested HIV-negative ≥ 4 weeks after ARV prophylaxis completion d. If child was breastfed with extended ARV prophylaxis, child tested HIV-negative ≥ 6 weeks after end of breastfeeding AND at ≥ 4 weeks after ARV prophylaxis completion
Child is HEU – moderate certainty Child of a mother known to have HIV (according to criteria 1-4 above for Mother known to have HIV) AND Child *tested HIV-negative* by either antibody or nucleic acid test at least once at ≥ 6 weeks of age, but timing of last test does not meet criteria for high certainty
Child is HEU – low certainty Child of a mother known to have HIV (according to criteria 1-4 above for Mother known to have HIV) AND Child tested *HIV-negative* by nucleic acid test at < 6 weeks of age and never tested again at ≥ 6 weeks of age
Child is HIV exposed - no certainty that child is HIV-uninfected Child of a mother known to have HIV (according to criteria 1-3 above for Mother known to have HIV) AND Child either 1. Never tested for HIV

OR 2. Tested HIV antibody-positive at < 24 months of age but never received confirmatory nucleic acid test and was never started on antiretroviral therapy
B. Classification of children who are HUU
Section B applies to children whose mothers do not meet criteria for "Mother known to have HIV" in Section A above
Child is HUU – high certainty Child of a *mother who tested HIV-negative* by any test type under at least one of the following scenarios 1. At or after the time of study outcome measurement [no breastfeeding information required] 2. In the absence of any breastfeeding, mother tested HIV-negative at the end of pregnancy or later 3. In the presence of any breastfeeding, mother tested HIV-negative at the end of breastfeeding or later AND Child *tested HIV-negative* by any test type at least once at any time
Child is HUU – moderate certainty Child of a *mother who tested HIV-negative* by any test type more than once during pregnancy or breastfeeding, but the timing of the mother's last test does not meet criteria for high certainty OR Child whose mother's test meets high certainty but child has never tested for HIV
Child is HUU – low certainty Child whose *mother tested HIV-negative* only once during pregnancy or breastfeeding, but the timing of the mother's last test does not meet criteria for high certainty
Unclassified In the absence of any information about maternal HIV status the child is **Unclassified**

ARV – antiretroviral; ART – antiretroviral therapy; HEU – HIV exposed uninfected; HUU – HIV unexposed uninfected

Table 2: Levels of certainty to classify ARV (maternal ART or maternal PrEP) exposure type and timing

A. Classification of ARV Exposure Type
Type: high certainty Name of each individual ARV known
Type: moderate certainty Known to be on regimen according to program-specific guidelines OR Classes of all drugs known but individual ARVs not specified
Type: no certainty Mother known to be on ART/PrEP but no or incomplete information about which ARV classes or whether program-specific guidelines were used
B. Classification of ARV Exposure Timing
Timing: Preconception ARV – high certainty Maternal ART/PrEP started preconception according to at least one of the following scenarios: 1. Maternal ART/PrEP start date known to be ≥ 42 weeks (or 294 days) prior to end of pregnancy date [no gestational age information required] 2. Maternal ART/PrEP start date known to be before documented first date of last menstrual period 3. Maternal ART/PreP start date known to be before negative pregnancy test (quantitative or qualitative beta-HCG) 4. Maternal ART/PrEP start date known to be before estimated date of conception according to gestational age known by certainty level 1-3A[a] AND No evidence of maternal ART/PrEP interruption ± 8 weeks of the expected date of conception
Timing: Preconception ARV – moderate certainty Maternal ART/PrEP started preconception according to at least one of the following scenarios (and doesn't meet criteria for high certainty): 1. Maternal ART/PrEP start date known to be > 37 and < 42 weeks (or 259-293 days) prior to the pregnancy end date [no gestational age information available] 2. Maternal ART/PrEP start date before estimated date of conception according to gestational age known by certainty level 3B[a] AND No evidence of maternal ART/PrEP interruption ± 8 weeks of the expected date of conception
Timing: Pregnancy-initiated ARV – high certainty Maternal ART/PrEP start date known exactly as day/month/year AND Start date on or after estimated date of conception according to gestational age estimated by certainty level 1-3A[a]
Timing: Pregnancy-initiated ARV – moderate certainty Maternal ART/PrEP start date not known exactly but rather known by trimester of gestation (i.e., first, second or third trimester) OR Start date on or after estimated date of conception according to gestational age estimated by certainty level 3B[a]
Timing: No certainty

Maternal ART/PrEP known to be received during pregnancy but timing of ART/PrEP initiation does not meet criteria for high or moderate certainty of preconception or pregnancy-initiated ARV

ARV – antiretroviral; ART – antiretroviral therapy; PrEP – pre-exposure antiretroviral prophylaxis

[a] See Table 3 - Certainty of Gestational Age Assessments

Table 3: Certainty of gestational age assessment methods [35]

Level 1	Certain[a] LMP or intrauterine insemination date or embryo transfer date WITH confirmatory 1st trimester ultrasound (≤$13^{6/7}$ weeks) [Use LMP if within 7 days of ultrasound gestation at ≤$13^{6/7}$, if not default to ultrasound gestational age assessment] OR 1st trimester ultrasound (≤13 6/7 weeks) WITH uncertain or no LMP
Level 2A	Certain[a] LMP WITH 2nd trimester ultrasound ($14^{0/7}$ - $27^{6/7}$ weeks) [Use LMP if within 14 days of ultrasound gestation at ≤$26^{0/7}$ weeks or within 21 days of ultrasound gestation $26^{0/7}$ - $27^{6/7}$ weeks, if not default to ultrasound gestational age assessment] OR Certain LMP WITH first trimester bimanual examination
Level 2B	Uncertain or no LMP WITH 2nd trimester ultrasound ($14^{0/7}$ - $27^{6/7}$ weeks). [Use LMP if the discrepancy between LMP and 2nd trimester ultrasound is ≤10 days, if not default to ultrasound gestational age assessment]
Level 3A	Certain[a] LMP WITH 3rd trimester ultrasound ≥$28^{0/7}$ weeks. [Use LMP if within 21 days of ultrasound gestation, if not default to ultrasound gestational age assessment] OR Certain[a] LMP WITH confirmatory 2nd trimester symphysis fundal height measurement OR Certain[a] LMP WITH birth weight OR Uncertain/no LMP WITH 1st trimester bimanual examination OR Uncertain/no LMP WITH 3rd trimester ultrasound [Use ultrasound established gestational age]
Level 3B	Uncertain/no LMP WITH symphysis fundal height measurement OR Uncertain/no LMP WITH new born physical assessment OR Uncertain/no LMP WITH birth weight

LMP – last menstrual period

[a] Certain LMP defined as the first date of LMP in dd/mm/yyyy format that is either reported by the woman as being accurate or specifically documented in the medical record as a "certain" or "sure" (or analogous) LMP.

Table 4: Example summary table of levels of certainty for in utero HIV and ARV exposures in a hypothetical cohort of 1000 children born to women with HIV and women without HIV

	High Certainty N (row %)	Moderate Certainty N (row %)	Low Certainty N (row %)	No Certainty N (row %)
In utero HIV exposure (Total N = 1000)	240 (24%)	680 (68%)	40 (4%)	40 (4%)
Children HUU (N=500)	0 (0%)	480 (96%)	20 (4%)	40 (8%)
Children HEU (N=500)	240 (48%)	200 (40%)	20 (4%)	
In utero ARV exposure (Total N = 500 children HEU)				
Maternal ART type (N=500)	180 (36%)	260 (52%)	NA	60 (12%)
Maternal ART timing: preconception (N=300)	240 (80%)	24 (8%)	NA	36 (12%)
Maternal ART timing: pregnancy-initiated (N=200)	50 (25%)	150 (75%)	NA	

ARV – antiretroviral; ART – antiretroviral therapy; HEU – HIV-exposed uninfected; HUU – HIV-unexposed uninfected