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VIEWPOINTS

Standardized Definitions of In Utero Human Immunodeficiency Virus and Antiretroviral Drug Exposure Among Children

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In countries with high human immunodeficiency virus (HIV) prevalence, up to 30% of pregnant women are living with HIV, with fetal exposure to both HIV and antiretroviral therapy during pregnancy. In addition, pregnant women without HIV but at high risk of HIV acquisition are increasingly receiving HIV preexposure antiretroviral prophylaxis (PrEP). 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 PrEP) 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.

Keywords. HIV; antiretroviral; in utero; pregnancy; definition.

In countries with high prevalence of human immunodeficiency virus (HIV), 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 while pregnant and breastfeeding, and their children are exposed to both HIV and antiretroviral drugs in utero [2]. Annually, >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 but uninfected (HEU), and by 2018 estimates, 71% had also been exposed in utero to antiretrovirals [4, 5]. Furthermore, prevailing HIV prevention policies promoting use of preexposure 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 2 decades has fallen short of clarifying whether the large population of children who are HEU are achieving survival, health, and developmental outcomes equivalent to those of 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 disease and a greater risk of death than children who are HIV unexposed and uninfected (HUU) [7–12]. Concerns have been raised regarding poorer growth outcomes and greater neurodevelopmental deficits after in utero HIV and antiretroviral exposure, although evidence is inconclusive [13, 14]. The numerous interconnected pathways, 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 of the mechanisms underlying the health disparities occurring in children who are HEU has been hindered by (1) study-specific definitions for exposures and outcomes, making comparison of findings challenging; (2) studies identifying signals of concern in children who are HEU but often without appropriate comparison to children who are HUU; (3) studies underpowered to

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adequately interrogate confounders, mediators, or specific subgroups at greater risk within the heterogenous population of children who are HEU; and (4) retrospective secondary analysis of data where the primary purpose of the study was not to evaluate outcomes in 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 or 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 those of their HUU peers. From earlier work that has considered the heterogeneity in risk factors among women with HIV and how these may be contributing to, rather than confounding, the disparities in child outcomes, it is clear that there are subgroups of children who are HEU that are at greater risk of adverse outcomes [16–19].

Efforts to confidently evaluate equivalence or conduct subgroup analyses require substantially larger samples 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 the 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 after immunization through an established process [23, 24]. Standardized outcome definitions are one tool used by the Brighton Collaboration and the GAIA project to achieve their objectives of improving comparability of data, maximizing the research utility of all studies by harmonizing methods, and promoting 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 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 antiretrovirals. 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 7 cohort networks or program partners (Baylor International Pediatric AIDS Initiative at Texas Children's Hospital, the European Pregnancy and Paediatric HIV Cohort Collaboration, the Elizabeth Glaser Pediatric AIDS Foundation, the International Maternal Pediatric Adolescent AIDS Clinical Trials Group, International Epidemiology Databases to Evaluate AIDS, ICAP at Columbia University, and the Pediatric HIV/AIDS Cohort Study) working in >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 who are HEU or adolescents. 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. 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 clinical care requires different considerations. 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 for classifying 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. During the first phase 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. Harmonization of definitions for all-cause mortality and infectious disease outcomes, for children <5 years old, 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 World Health Organization 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 7 teleconferences and 1 in-person meeting, draft definitions were proposed and revised until agreement was reached on separate sets of definitions for in utero HIV and antiretroviral exposure.

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 a child. Children can be misclassified as HEU when they have actually acquired HIV but this has been missed. Alternatively, children can be misclassified as HUU when they are actually HIV exposed but maternal HIV has been missed. The possibility of missing HIV infection in children who are classified as HEU is influenced primarily by 3 factors: (1) early postnatal testing during the window period of nucleic acid test positivity after intrapartum HIV transmission; (2) the impact of maternal ART via breastmilk or of infant antiretroviral prophylaxis, which may reduce the infant's viral load below the limit of detection for diagnostic testing, resulting in a false-negative nucleic acid test in an infant actually infected with HIV; and (3) 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 (Box 1, section A, and Supplementary Figures 1 [algorithm] and 2 [selected illustrated examples]). Any negative HIV test result, whether antibody or nucleic acid based, is sufficient to exclude HIV infection at that particular time point in children >6 weeks of age. To definitively determine the final HIV status of children, infection must be excluded after all breastfeeding and antiretroviral prophylaxis has ceased.

The possibility of missing HIV exposure, that is, 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 (Box 1, section B, and Supplementary Figures 3 [algorithm] and 4 [selected illustrated examples]). This has relevance for studies in settings with lower HIV prevalence, where repeated maternal HIV testing might not be clinically justified or cost-effective owing to the low risk of HIV acquisition. However, promotion of the proposed DECIPHER definitions provides motivation for prospectively designed studies interested in assigning children's HIV exposure status with high certainty, including those with a control group of HUU children, to incorporate repeated testing of mothers at delivery or later to exclude maternal HIV infection. An additional element for consideration in classifying children as HUU with high certainty in this group is exclusion of child HIV infection, which may occur through nonvertical transmission routes or, more commonly, during breastfeeding when maternal HIV has been acquired postnatally. Although nonvertical 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 [28–30]. Direct confirmation of a child's 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.

The preliminary relevance and feasibility of the definitions for in utero HIV exposure were evaluated in 2 ways. After review of the literature, 16 published observational cohorts including children who are HEU and HUU who were identified from across low-to-middle-income 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-certainty and 11 met high-certainty criteria for classification of children as HEU. For classification of children as HUU, 4 studies met low-certainty, 11 met moderate-certainty, and 1 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 to 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-certainty, 2% met moderate-certainty, and 69% met high-certainty criteria [28].

In Utero Antiretroviral Exposure Definitions

Greater precision and consistency in defining and classifying in utero antiretroviral exposure, due to either maternal ART or 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 oral antiretrovirals alone, with other modalities—such as broadly neutralizing antibodies, long-acting injectable antiretroviral formulations, or vaccines—requiring

Box 1. Levels of Certainty for Classifying Children as In Utero Human Immunodeficiency Virus (HIV) Exposed but Uninfected or HIV Unexposed and Uninfected at the Time of 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 any of the following scenarios:

1. Documented positive maternal HIV status determined according to local diagnostic testing algorithms during current pregnancy or earlier
2. Evidence of >1 mo of ART received during current pregnancy or earlier
3. Registration in any HIV care or ART program during current pregnancy or earlier
4. Child (in study) aged <24 mo with positive HIV antibody test and negative HIV nucleic acid test results

Note: If the mother is not known to have HIV according to any of criteria 1–4, refer to section B.

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 age ≥6 wk
AND
Timing of HIV-negative test result met any of the following:

1. Performed at 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 age ≥6 wk
   b. If breastfed without extended ARV prophylaxis, child tested HIV negative ≥6 wk after the end of breastfeeding
   c. If child received ARV prophylaxis but was never breastfed, child tested HIV negative ≥4 wk after completion of ARV prophylaxis
   d. If breastfed with extended ARV prophylaxis, child tested HIV negative ≥6 wk after the end of breastfeeding AND >4 wk after completion of ARV prophylaxis

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 age ≥6 wk, 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 age <6 wk but was never tested again at age ≥6 wk

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. Was never tested for HIV
   OR
2. Tested HIV antibody positive at age <24 mo but never received confirmatory nucleic acid test and was never started on ART

B. CLASSIFICATION OF CHILDREN WHO ARE HUU

Section B applies to children whose mothers do not meet criteria for "Mother known to have HIV" (section A above)

Child is HUU—high certainty

Child of a mother who tested HIV negative by any test type under any 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 within 7 d of the end of pregnancy or later
3. In the presence of any breastfeeding, mother tested HIV negative within 7 d of the end of breastfeeding or later

AND

Child tested HIV negative (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 with the timing of the mother's last test not meeting criteria for high certainty

OR

Child whose mother's HIV test meets high certainty but child has never been tested for HIV

Child is HUU—low certainty

Child whose mother tested HIV negative only once during pregnancy or breastfeeding but with the timing of the mother's last test not meeting criteria for high certainty

Unclassified

In the absence of any information about maternal HIV status, the child is unclassified

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; HEU, HIV exposed but uninfected; HIV, human immunodeficiency virus; HUU, HIV unexposed and uninfected.

future consideration. For pragmatic purposes, only in utero exposures to maternal ART or PrEP taken orally 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 as to the type (Box 2, section A, and Supplementary Figure 5 [algorithm]) and certainty as to the timing (Box 2, section B, and Supplementary Figures 6 [algorithm] and 7 [selected illustrated examples]) of in utero antiretroviral exposure are defined separately. The definitions do not incorporate duration of antiretroviral exposure during pregnancy, although investigators should collect and analyze this information whenever feasible. Differences in risks of adverse birth outcomes and infectious diseases may be associated with the timing of initiation of maternal ART, either before conception or during pregnancy [32, 33]. Thus, the timing of in utero antiretroviral exposure is categorized as starting either before conception or 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. However, investment into dedicated studies designed to evaluate these parameters and how they confound or mediate outcomes in relation to in utero HIV exposure is clearly warranted.

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 1) [35]. The 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.

Box 2. Levels of Certainty for Classifying In Utero Antiretroviral Exposure Type (Maternal Antiretroviral Therapy or Preexposure Prophylaxis) 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 with no/incomplete information about ARV classes or use of program-specific guidelines

B. CLASSIFICATION OF ARV EXPOSURE TIMING[a]

Timing: Preconception ARV—high certainty
Maternal ART/PrEP started before conception according to any of the following scenarios:

1. Maternal ART/PrEP start date known to be ≥42 wk (≥294 d) before the end of pregnancy (no GA 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 result (quantitative or qualitative β–human chorionic gonadotropin)
4. Maternal ART/PrEP start date known to be before estimated date of conception according to GA known by certainty level 1–3A[b]

AND
No evidence of maternal ART/PrEP interruption within 8 wk of the expected date of conception

Timing: Preconception ARV—moderate certainty
Maternal ART/PrEP started before conception according to any of the following scenarios (without meeting criteria for high certainty):

1. Maternal ART/PrEP start date known to be >37 and <42 wk (259–293 d) before pregnancy end date (no GA information available)
2. Maternal ART/PrEP start date before estimated date of conception according to GA known by certainty level 3B[b]

AND
No evidence of maternal ART/PrEP interruption within 8 wk of expected date of conception

Timing: Pregnancy-initiated ARV—high certainty
Maternal ART/PrEP start date known exactly (dd/mm/yyyy format)
AND
Start date on or after estimated date of conception according to GA estimated by certainty level 1–3A[b]

Timing: Pregnancy-initiated ARV—moderate certainty
Maternal ART/PrEP start date not known exactly but known by trimester of gestation (ie, first, second or third trimester)
OR
Start date on or after estimated date of conception according to GA estimated by certainty level 3B[b]

Timing: No certainty
Maternal ART/PrEP known to be received during pregnancy but with timing of ART/PrEP initiation not meeting criteria for high or moderate certainty of preconception or pregnancy-initiated ARV

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; GA, gestational age; PrEP, preexposure antiretroviral prophylaxis.
[a]Whenever feasible, the duration of ARV exposure should also be collected.
[b]See Table 1 (Certainty of Gestational Age Assessments).

Table 1. Certainty of Gestational Age Assessment Methods[a]

Level	Criteria
1	Certain LMP[b] or intrauterine insemination date or embryo transfer date with confirmatory first-trimester US (≤$13^{6/7}$ wk) (Use LMP if within 7 d of US GA at ≤$13^{6/7}$ wk; if not, default to US GA assessment) OR First-trimester US (≤$13^{6/7}$ wk) with uncertain or no LMP
2A	Certain LMP[b] with second-trimester US ($14^{0/7}$–$27^{6/7}$ wk) (Use LMP if within 14 d of US GA at ≤$26^{0/7}$ wk or within 21 d of US GA $26^{0/7}$–$27^{6/7}$ wk; if not, default to US GA assessment) OR Certain LMP with first-trimester bimanual examination
2B	Uncertain or no LMP with second-trimester US ($14^{0/7}$–$27^{6/7}$ wk) (Use LMP if the discrepancy between LMP and second-trimester US is ≤10 d; if not, default to US GA assessment)
3A	Certain LMP[b] with third-trimester US >$28^{0/7}$ wk (Use LMP if within 21 d of US GA; if not, default to US GA assessment) OR Certain LMP[b] with confirmatory second-trimester symphysis fundal height measurement OR Certain LMP[b] with birth weight[c] OR Uncertain/no LMP with first-trimester bimanual examination[c] OR Uncertain/no LMP with third-trimester US (Use US established GA)
3B	Uncertain/no LMP with symphysis fundal height measurement[c] OR Uncertain/no LMP with newborn physical assessment[c] OR Uncertain/no LMP with birth weight[c]

GA indicated as weeks and days in superscript.

Abbreviations: GA, gestational age; LMP, last menstrual period; US, ultrasound.

[a]From Quinn et al [35].

[b]Certain LMP is 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.

[c]Gestational age calculation tools available at www.gestation.net [36].

GAIA gestational age assessment level 3B was adapted for the DECIPHER definitions to include unknown last menstrual period dates, and a definition of last menstrual period has been added (Table 1).

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 high-prevalence settings where frequent maternal and child HIV testing are not routinely indicated, owing 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 owing 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. Although these definitions have been designed for the research context, they may be of value to surveillance programs in determining a minimal set of information required to classify in utero HIV exposure with a minimum of low certainty and antiretroviral exposure type and timing with a minimum of moderate certainty.

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 2 or in a simple text summary similar to the following: "In our cohort, 48%, 40%, 4% and 8% of the children were classified as HEU with high, moderate, low and no certainty, respectively, and 0%, 96%, and 4% were classified as HUU with high, moderate, or low certainty, respectively. 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 before conception 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 well-being of

Table 2. Example Summary Table of Levels of Certainty for In Utero Human Immunodeficiency Virus (HIV) and Antiretroviral Exposures in a Hypothetical Cohort of 1000 Children Born to Women With or Without HIV

	Children, No. (Row %)			
Type and Timing of In Utero Exposure	High Certainty	Moderate Certainty	Low Certainty	No Certainty
HIV exposure (total N = 1000)	240 (24)	680 (68)	40 (4)	40 (4)
Children who are HUU (n = 500)	0 (0)	480 (96)	20 (4)	40 (8)
Children who are HEU (n = 500)	240 (48)	200 (40)	20 (4)	
ARV exposure (total n = 500 HEU children)				
Maternal ART type (n = 500)	180 (36)	260 (52)	NA	60 (12)
Maternal ART timing: before conception (n = 300)	240 (80)	24 (8)	NA	36 (12)
Maternal ART timing: during pregnancy (n = 200)	50 (25)	150 (75)	NA	

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; HEU, HIV exposed but uninfected; HUU, HIV unexposed and uninfected; NA, .

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 after broad endorsement by researchers with wide dissemination, practical application, and 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 survival, growth, and neurodevelopmental outcomes comparable to those in 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.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the International AIDS Society (IAS) or the National Institutes of Health (NIH).

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