Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Wedderburn CJ, Weldon E, Bertran-Cobo C, et al. Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis. Lancet Child Adolesc Health 2022; published online April 25. https://doi.org/10.1016/S2352-4642(22)00071-2.
Supplementary Information

Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis

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Protocol deviations:

- Studies including children born before January 2000 or where ART was documented not to be available at the time of the study were excluded. This differed to the original inclusion period of January 1990 for the date of search. We made this change in order to ensure relevance to the current ART era, fitting with the WHO guidelines advocating for PMTCT interventions in the year 2000.
- We were unable to assess vision, hearing, and intellect as outcomes due to a lack of appropriate studies within this age range.
- We used the validated National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart, Lung, and Blood Institute [NHLBI], 2014) to assess risk of bias instead of the originally specified Newcastle-Ottawa Quality Assessment Scale (NOS). We found this tool had many similarities to the NOS but allowed us to better assess the various aspects of bias for all types of studies included in this review.
- We performed formal risk of bias assessment for all Aim 1 outcomes which went forward into meta-analysis. Following review of the papers for Aim 2, we noted we were unable to perform a meta-analysis for the ART analyses due to study heterogeneity and that the risk of bias tool did not adequately focus on additional areas of concern specific to ART analyses. Therefore, instead of performing individual study risk of bias using a formal tool for these papers we describe the overall limitations and risk of bias specific to studies in Aim 2.
- Pre-specified sensitivity analyses included only studies with adequate comparison groups and excluding those with a moderate or high risk of bias. Due to limited numbers of studies fitting these criteria we did not perform subgroup analyses on breastfeeding. Similarly, we originally planned to stratify by region and socioeconomic status. However, given the limited number of studies, and lack of comparable reporting on socioeconomic status, we were only able to perform a sensitivity analysis of the meta-analysis excluding the one study from a high-income country.
S2 Appendix: Electronic search strategy by database

MEDLINE
1. (infant* or newborn* or new-born* or perinat* or neonat* or baby or babies or toddler* or child* or pediatric* or paediatric*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2. exp CHILD, PRESCHOOL/
3. exp INFANT/
4. exp Pediatrics/
5. exp INFANT, NEWBORN/
6. 1 or 2 or 3 or 4 or 5
7. (HIV or HIV-1 or HIV-2 or human immunodeficiency virus or human immune deficiency virus or human immune-deficiency virus or HIV infect* or HIV-infected or living with HIV or HIV-positive or AIDS or Acquired Immunodeficiency Syndrome or Acquired Immune Deficiency Syndrome or HEU or HIV-exposed or HIV-exposed-uninfected or HIV-uninfected or HAART or antiretroviral* or anti-retroviral* or anti-HIV agents or HIV treatment or PMTCT or prevention of mother-to-child transmission).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. exp HIV/ or exp HIV-2/ or exp HIV-1/ or exp HIV INFECTIONS/
9. exp HIV PROTEASE INHIBITORS/ or exp ANTI-HIV AGENTS/ or exp HIV INTEGRASE INHIBITORS/ or exp HIV FUSION INHIBITORS/
10. exp Reverse Transcriptase Inhibitors/
11. exp Anti-Retroviral Agents/ or exp ANTIRETROVIRAL THERAPY, HIGHLY ACTIVE/ or exp Acquired Immunodeficiency Syndrome/
12. 7 or 8 or 9 or 10 or 11
13. (Neurodevelop* or (develop* adj4 child) or neurocog* or cogniti* or communication or language or speech or verbal or motor or neuromotor or locomotor or neuroanatom* or (brain adj4 structure) or (brain adj4 microstructure) or (white adj4 matter) or head circumference or (developmental adj4 delay*) or (developmental adj4 disorder*) or (developmental adj4 disabilit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. exp CHILD DEVELOPMENT DISORDERS, PERVERSIVE/ or exp MUSCULOSKELETAL DEVELOPMENT/ or exp HUMAN DEVELOPMENT/ or exp LANGUAGE DEVELOPMENT DISORDERS/ or exp "MALFORMATIONS OF CORTICAL DEVELOPMENT"/ or exp "MALFORMATIONS OF CORTICAL DEVELOPMENT, GROUP II"/ or exp "GROWTH AND DEVELOPMENT"/ or exp "MALFORMATIONS OF CORTICAL DEVELOPMENT, GROUP I"/ or exp LANGUAGE DEVELOPMENT/ or exp "NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (U.S.)"/ or exp CHILD DEVELOPMENT/
15. exp CHILD BEHAVIOR/ or exp CHILD BEHAVIOR DISORDERS/
16. exp DEVELOPMENTAL DISABILITIES/
17. exp NEUROCOGNITIVE DISORDERS/ or exp NEURODEVELOPMENTAL DISORDERS/ or exp COMMUNICATION DISORDERS/
18. exp CHILD LANGUAGE/
19. exp Prenatal Exposure Delayed Effects/
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 6 and 12 and 20

EMBASE search
1. (infant* or newborn* or new-born* or perinat* or neonat* or baby or babies or toddler* or child* or pediatric* or paediatric*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2. exp preschool child/
3. exp infant/
4. exp pediatrics/
5. exp newborn/
6. 1 or 2 or 3 or 4 or 5
7. (HIV or HIV-1 or HIV-2 or human immunodeficiency virus or human immune deficiency virus or human immune-deficiency virus or HIV infect* or HIV-infected or living with HIV or HIV-positive or AIDS or Acquired Immunodeficiency Syndrome or Acquired Immune Deficiency Syndrome or HEU or HIV-exposed or HIV-exposed-uninfected or HIV-uninfected or HAART or antiretroviral* or anti-retroviral* or anti-HIV agents or HIV treatment or PMTCT or prevention of mother-to-child transmission).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8. exp Human immunodeficiency virus/ or exp Human immunodeficiency virus 2/ or exp Human immunodeficiency virus 1/
9. exp Human immunodeficiency virus infection/ or exp integrase inhibitor/ or exp Human immunodeficiency virus fusion inhibitor/ or exp Human immunodeficiency virus protease inhibitor/ or exp anti human immunodeficiency virus agent/ or exp nonnucleoside reverse transcriptase inhibitor/
10. exp antiretrovirus agent/ or exp highly active antiretroviral therapy/ or exp acquired immune deficiency syndrome/ or exp antiretroviral therapy/
11. 7 or 8 or 9 or 10
12. (Neurodevelop* or (develop* adj4 child) or neurocog* or cogniti* or communication or language or speech or verbal or motor or neuromotor or locomotor or neuroanatom* or (brain adj4 structure) or (brain adj4 microstructure) or (white adj4 matter) or head circumference or (developmental adj4 delay*) or (developmental adj4 disorder*) or (developmental adj4 disability*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
13. exp MUSCULOSKELETAL DEVELOPMENT/ or exp developmental language disorder/ or exp LANGUAGE DEVELOPMENT/ or exp child behavior/ or exp behavior disorder/
14. exp cognition/ or exp DEVELOPMENTAL DISORDER/
15. exp child development/
16. 12 or 13 or 14 or 15
17. 6 and 11 and 16

PubMed search
infan* or newborn* or new-born* or perinat* or neonat* or baby or babies or toddler* or child or children or pediatric* or paediatric*

HIV or HIV-1 or HIV-2 or human immunodeficiency virus or human immune deficiency virus or human immune-deficiency virus or HIV infect* or HIV-infected or “living with HIV” or HIV-positive or AIDS or “Acquired Immunodeficiency Syndrome” or HEU or HIV-exposed or HIV-exposed-uninfected or HIV-uninfected or HAART or antiretroviral* or anti-retroviral* or “anti-HIV agents” or “HIV treatment” or PMTCT or “prevention of mother-to-child transmission”

Neurodevelop* or “child develop***” or neurocog* or cogniti* or communication or language or speech or verbal or motor or neuromotor or locomotor or neuroanatom* or “brain structure” or “brain microstructure” or “white matter” or “head circumference” or “developmental delay***” or “developmental disorder***” or “developmental disability”
1. 1 and 2 and 3

PsycINFO
1. (infan* or newborn* or new-born* or perinat* or neonat* or baby or babies or toddler* or child* or pediatric* or paediatric*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2. exp preschool students/
3. exp pediatrics/
4. 1 or 2 or 3
5. (HIV or HIV-1 or HIV-2 or human immunodeficiency virus or human immune deficiency virus or human immune-deficiency virus or HIV infect* or HIV-infected or living with HIV or HIV-positive or AIDS or Acquired Immunodeficiency Syndrome or Acquired Immune Deficiency Syndrome or HEU or HIV-exposed or HIV-exposed-uninfected or HIV-uninfected or HAART or antiretroviral* or anti-retroviral* or anti-HIV agents or HIV treatment or PMTCT or prevention of mother-to-child
transmission).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6. exp hiv/ or exp aids/
7. exp antiviral drugs/
8. 5 or 6 or 7
9. (Neurodevelop* or (develop* adj4 child) or neurocog* or cogniti* or communication or language or speech or verbal or motor or neuromotor or locomotor or neuroanatom* or (brain adj4 structure) or (brain adj4 microstructure) or (white adj4 matter) or head circumference or (developmental adj4 delay*) or (developmental adj4 disorder*) or (developmental adj4 disabilit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. exp childhood development/ or exp early childhood development/ or exp motor development/ or exp psychomotor development
11. exp brain development/
12. exp neonatal development/
13. exp language development/ or exp cognitive development/ or exp language delay/ or exp language disorders/ or exp speech development/
14. exp behavior problems/ or exp behavior/ or exp behavior disorders/
15. exp developmental disabilities/ or exp delayed development/
16. exp neurodevelopmental disorders/
17. exp Infant Development/
18. 9 or 10 or 11 or 12 or 14 or 15 or 16 or 17
19. 4 and 8 and 18

Global Health
1. (infan* or newborn* or new-born* or perinat* or neonat* or baby or babies or toddler* or child* or pediatric* or paediatric*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2. Exp PRESCHOOL CHILDREN/
3. Exp INFANTS/
4. exp PAEDIATRICS/
5. 1 or 2 or 3 or 4
6. (HIV or HIV-1 or HIV-2 or human immunodeficiency virus or human immune deficiency virus or human immune-deficiency virus or HIV infect* or HIV-infected or living with HIV or HIV-positive or AIDS or Acquired Immunodeficiency Syndrome or Acquired Immune Deficiency Syndrome or HEU or HIV-exposed or HIV-exposed-uninfected or HIV-uninfected or HAART or antiretroviral* or anti-retroviral* or anti-HIV agents or HIV treatment or PMTCT or prevention of mother-to-child transmission).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. exp acquired immune deficiency syndrome/
8. exp human immunodeficiency viruses/ or exp hiv infections/ or exp human immunodeficiency virus 1/ or exp human immunodeficiency virus 2/
9. exp hiv fusion inhibitors/ or exp antiretroviral agents/ or exp hiv integrase inhibitors/ or exp hiv protease inhibitors/
10. exp reverse transcriptase inhibitors/ or exp non-nucleoside reverse transcriptase inhibitors/ or exp nucleoside reverse transcriptase inhibitors/ or exp nucleotide reverse transcriptase inhibitors/
11. exp antiviral agents/
12. 6 or 7 or 8 or 9 or 10 or 11
13. (Neurodevelop* or (develop* adj4 child) or neurocog* or cogniti* or communication or language or speech or verbal or motor or neuromotor or locomotor or neuroanatom* or (brain adj4 structure) or (brain adj4 microstructure) or (white adj4 matter) or head circumference or (developmental adj4 delay*) or (developmental adj4 disorder*) or (developmental adj4 disabilit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. exp child development/
15. exp early childhood development/ or exp infant development/
16. exp pervasive child development disorders/
17. exp development/
18. exp cognitive development/ or exp psychomotor development/ or exp motor development/
19. exp speech development/
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 5 and 12 and 20

Africa-wide information
(infant* or newborn* or new-born* or perinat* or neonat* or baby or babies or toddler* or child* or pediatric* or paediatric*) AND (HIV or HIV-1 or HIV-2 or human immunodeficiency virus or human immune deficiency virus or human immune-deficiency virus or HIV infect* or HIV-infected or living with HIV or HIV-positive or AIDS or Acquired Immunodeficiency Syndrome or Acquired Immune Deficiency Syndrome or HEU or HIV-exposed or HIV-exposed-uninfected or HIV-uninfected or HAART or antiretroviral* or anti-retroviral* or anti-HIV agents or HIV treatment or PMTCT or prevention of mother-to-child transmission) AND (Neurodevelop* or (develop* N4 child) or neurocog* or cogniti* or communication or language or speech or verbal or motor or neuromotor or locomotor or neuroanatom* or (brain N4 structure) or (brain N4 microstructure) or (white N4 matter) or head circumference or (developmental N4 delay*) or (developmental N4 disorder*) or (developmental N4 disabilit*))
### S3 Appendix: PECO inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| **Population**     |                    |
| • Children aged 0 to 5 years | • Studies of children >5 years that did not include younger children* |
| • Born after January 2000 (WHO first issued recommendations for antiretroviral drugs in 2000) | • Children born before the year 2000 |
| **Exposure**       |                    |
| • HIV exposure without HIV infection. HEU children were defined as children born to mothers with HIV infection with appropriate reporting confirming that children were not infected | • No documentation of maternal and child HIV infection status |
| • ART exposure was defined as exposure to any maternal antiretroviral drugs during pregnancy | • Children with HIV infection |
|                    | • Studies where ART was noted to be unavailable at the time of the study |
|                    | • Studies of HEU children where the primary scientific question related to other exposures and relevant data could not be extracted (e.g. nutritional deficiencies or other infections) |
| **Control**        |                    |
| • Children born to HIV-uninfected mothers (Aim 1) AND/OR | • Studies without either of these control groups |
| • HEU children exposed to different maternal ART regimens, classes or drugs or no treatment (Aim 2) | |
| **Outcomes**       |                    |
| Primary:           | Other outcomes     |
| • Cognitive development, receptive language, expressive language, fine motor, gross motor (as recommended for children 0-5 years corresponding to developmental areas in the ICD-10 and -11 Delayed Milestones definitions) | |
| Secondary:         |                    |
| • Social-emotional and adaptive behaviour (defined as daily living skills that enable everyday function appropriate to the relevant age group) | |
| • Measured using validated instruments. | |
| **Study type**     |                    |
| • All primary data study designs | Conference and poster abstracts |
| • Reviews and meta-analyses were hand-searched for additional primary studies | Languages other than English and Spanish |
| • Academic publications | |
| • English or Spanish language | |

*Studies were included if they had stratified analyses of the population of interest and the majority of children fulfilled the inclusion criteria. If the age range extended through 5 years, studies were included if the median age was <5 years.*
S4 Appendix: Quality assessment tool

NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies criteria

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?
5. (5.a) Was a sample size justification, power description, or variance and effect estimates provided?
   (5.b) Was sample size ≥ 50 per group?*
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? For the purposes of this review we assessed whether studies examined results by maternal CD4, viral load or ART.**
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? For the purposes of this review we assessed for valid HIV testing of mothers of HEU and HU children for ascertainment of exposure.***
10. Was the exposure(s) assessed more than once over time? For the purposes of this review we assessed valid HIV testing of HIV-exposed children and that children with HIV were excluded.***
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Risk of bias rating: Yes; No; CD, cannot determine; NA, not applicable; NR, not reported

Overall Study Quality rating: Good, Fair, Poor

* Question five was specifically adapted for this review per Carbia et al., 2018;
**Question eight was adapted for this review to assess if studies examined results by maternal CD4/viral load/ART to lend credibility to the hypothesis of causality between exposure and outcome;
***Given the importance of accurately assessing HIV exposure and avoidance of child HIV infection we adapted questions nine and ten to assess whether mothers of both HEU and HU children received valid HIV testing and that children who were HIV-exposed received valid HIV testing.
| No. | Year | Author | Title | Journal | Exclusion criteria |
|-----|------|--------|-------|---------|-------------------|
| 1   | 2009 | Abubakar, A. et al | The role of weight for age and disease stage in poor psychomotor outcome of HIV-infected children in Kilifi, Kenya | Dev Med Child Neurolog | No ART exposure – ART not routinely available at the time of the study |
| 2   | 2013 | Abubakar, A. et al | The performance of children prematurely exposed to HIV on the A-not-B task in Kilifi, Kenya: A preliminary study | Int J Environ Res Public Health | No ART exposure – ART not routinely available at the time of the study |
| 3   | 2014 | Abubakar, A. | Biomedical risk, psychosocial influences, and developmental outcomes: lessons from the pediatric HIV population in Africa | New directions for child and adolescent development | Review article; no new data. |
| 4   | 2016 | Ackermann, C. et al | Early antiretroviral therapy in HIV-infected children is associated with diffuse white matter structural abnormality and corpus callosum sparing | American Journal of Neuroradiology | No HEU group (parallel vaccine study included HEU and HIV children combined in this paper); Age >5 years (control group mean 5.7 years) |
| 5   | 2020 | Ackermann, C. et al | Diffusion tensor imaging point to ongoing functional impairment in HIV-infected children at age 5, undetectable using standard neurodevelopmental assessments | AIDS Research and Therapy | No distinct HEU group (control group of 11 from parallel vaccine study which included 9 HEU and 2 HIV combined in this paper); Age >5 years included (control group mean 5.6 years) |
| 6   | 2019 | Ajayi, OR. et al | Association of anthropometric status and residential locality factors with cognitive scores of 4-6-year-old children in Kwazulu-Natal, South Africa | South African Journal of Clinical Nutrition | No HEU group; Age >5 years (4-6 years) and no stratification |
| 7   | 2016 | Alcock, K.J. et al | The effect of prenatal HIV exposure on language functioning in Kenyan children: establishing an evaluative framework | BMC Res Notes | No ART exposure – ART not routinely available at the time of the study |
| 8   | 2013 | Andronikou, S. | Corpus callosum thickness on MRI as a surrogate marker of brain volume in children with HIV and its correlation with developmental scores and clinical parameters | Pediatric Radiology | No HEU group; Conference presentation |
| 9   | 2001 | Bakaki, P. et al | Epidemiologic and clinical features of HIV-infected and HIV-uninfected Ugandan children younger than 18 months | JAIDS | No distinct HEU group - HEU and HIV grouped together as 'HIV-uninfected' |
| 10  | 2016 | Bass, J.K. et al | Association of caregiver quality of care with neurocognitive outcomes in HIV-affected children aged 2-5 years in Uganda | AIDS Care | Cohort outcomes reported in Ruiseñor-Escuerdo et al. |
| 11  | 2019 | Blakstad, M.M. et al | Nutritional, socioeconomic, and delivery characteristics are associated with neurodevelopment in Tanzanian children | Journal of Pediatrics | HEU data reported in Manji KP et al. (NCT00197730 trial) |
| 12  | 2001 | Blanchette, N. et al | Cognitive and motor development in children with vertically transmitted HIV infection | Brain and Cognition | Cohort spanned years <2000 |
| 13  | 2016 | Blokhuis, C. et al | The Eye as a Window to the Brain: Neuroretinal Thickness Is Associated With Microstructural White Matter Injury in HIV-Infected Children | Investigative Ophthalmology & Visual Science | No specified HEU group; Age >5 years (mean 12.1 years) |
| 14  | 2017 | Boateng, G.O. et al | Early childhood learning activities buffer adverse effects of HIV exposure on infant cognitive development: A longitudinal study | PASEB Journal | No specified HEU group - 'HIV-exposed' group analysed which may include HIV-infected children; Poster presentation |
| 15  | 2014 | Boivin, M.J. et al | Bouts of malaria illness as mediated by anemia diminishes cognitive development in very young Ugandan children | American Journal of Tropical Medicine and Hygiene | Conference abstract (paper included in full reviews). No distinct HEU group – ‘HIV-exposed’ group analysed which may include HIV-infected children |
| 16  | 2017 | Boivin, M.J. et al | Effect of caregiver training on neurodevelopment of HIV-exposed uninfected children and caregiver mental health: a Ugandan cluster randomized controlled trial | J Dev Behav Pediatr | Intervention trial. ART exposure not mentioned |
| 17  | 2018 | Boivin, M.J. et al | Neuropsychological performance in African children with HIV enrolled in a multisite antiretroviral clinical trial | AIDS | Age >5 years (5-11 years) |
| 18  | 2018 | Boivin, M., et al | Developmental and cognitive effects of type of antepartum and postpartum ARV exposure for Ugandan and Malawian IMPACT PROMISE HIV-exposed versus unexposed children at age 12, 24 and 48 months | JIAS | Conference presentation, paper included in full texts |
| 19  | 2018 | Boivin, M.J. et al | African multi-site 2-year study of neurocognition in HIV infected/affected children | Topics in Antiviral Medicine (CROI 2018) | Age >5 years (5-11 years) |
| 20  | 2019 | Boivin, M.J. et al | African multi-site 2-year neuropsychological study of school-age children perinatally infected, exposed, and unexposed to human immunodeficiency virus | CID | Age >5 years (5-11 years) |
| 21  | 2020 | Boivin, M.J. et al | Early Childhood Development Caregiver Training and Neurocognition of HIV-exposed Ugandan Siblings | Journal of Developmental & Behavioral Pediatrics | Age >5 years (5-12 years) |
| 22  | 2008 | Botha, J.A.E. | Motor development and growth status of 2 to 6 year old children infected with Human Immunodeficiency Virus [HIV] | NA | Thesis |
| 23  | 2008 | Botha, JAE & Pienaar AE. | The motor development of 2 to 6-year old children infected with HIV | SA Journal for Research in Sport, Physical Education and Recreation | No ART exposure – access to ART was limited at the time of the study |
| 24  | 2011 | Bowes, J. et al | Pervasive developmental disorder in antiretroviral- and HIV-exposed, uninfected children | Canadian Journal of Infectious Diseases | Cohort spanned years <2000 (1997-2010); Conference presentation |
and Medical Microbiology

25 2009 Briand, N. et al No relation between in-uteru exposure to HAART and intrathecal growth retardation AIDS Cohort spanned years <2000 (children born 1990 – 2006); although stratified by year only n=23 have head circumference measured in the >2000 group, <10% of cohort

26 2001 Bruck, L. et al Developmental milestones of vertically HIV infected and seroreverters children: follow up of 83 children Arquivos de neuro-psiquiatria Cohort spanned years <2000 (children born 1995 – 2000)

27 2018 Budd, M.A. et al Blood mitochondrial DNA content in HIV-exposed uninfected children with autism spectrum disorder Viruses Age > 5 years (2-16 years)

28 2003 Bulgheroni, S. et al Longitudinal neuropsychological evaluation of neurologically asymptomatic HIV infected children Psicologia Clinica della Sviluppo Age > 5 years included (4 – 15 years); Italian

29 2015 Buonomo, E., et al Malnutrition decreases the odds of attaining motor milestones in HIV exposed children: results from a paediatric DREAM cohort Epidemiologia e prevenzione HEU group included HIV-infected child

30 2013 Cambrea, S.C. et al Can HIV infection during pregnancy cause an intrathecal growth restriction? BMC Infectious Diseases No distinct HEU group - HEU and HIV-infected children grouped together; Conference presentation

31 2014 Cambrea, S.C. et al Evaluation of anthropometric and virologic data in newborn from HIV positive mothers BMC Infectious Diseases No distinct HEU group - HEU and HIV-infected children grouped together; Conference presentation

32 2009 Carceller, A. et al Lack of effect on prematurity, birth weight, and infant growth from exposure to protease inhibitors in utero and after birth Pharmacotherapy Cohort spanned years <2000 (1997-2005)

33 2020 Chanda, J. et al Effects of improved complementary feeding and improved water, sanitation and hygiene on early child development among HIV-exposed children: sub-study of a cluster randomized trial in rural Zimbabwe BMJ Global Health Main study results presented in Ntzioni, R et al, included

34 2000 Chase, C. et al Early cognitive and motor development among infants born to women infected with human immunodeficiency virus. Pediatrics Cohort spanned years <2000 (children born 1990 onwards)

35 2011 Chaworth-Musters, T. et al Adverse health outcomes in HIV exposed uninfected children (HEU) in British Columbia - CHIR team grant in HIV therapy and aging (CARMA) Canadian Journal of Infectious Diseases and Medical Microbiology Age > 5 years included (mean 5.4 years, range 0.6-19.6 years); Conference presentation

36 2018 Chernoff, M. et al Assessing Psychiatric Symptoms in Young Affected by HIV: Comparing a Brief Self-Administered Rating Scale with a Structured Diagnostic Interview Journal of Clinical Psychology in Medical Settings Age > 5 years (range 6-18 years)

37 2018 Chernoff, M.C. et al Validity of neuropsychological testing in young African children affected by HIV Journal of Pediatric Infectious Diseases Age > 5 years (range 5-11 years)

38 2018 Chhaya, R. et al The feasibility of an automated eye-tracking-modified Fagan test of memory for human faces in younger Ugandan HIV-exposed children Child Neuropsychology Feasibility study for automated eye-tracking. No mention of ART

39 2005 Chiriboga, C.A. et al Incidence and prevalence of HIV encephalopathy in children with HIV infection receiving highly active anti-retroviral therapy (HAART) Journal of Pediatrics No HEU group; Cohort spanned years <2000 (followed up from 1988 onwards)

40 2018 Chingono, R. et al Evaluating the effectiveness of a multi-component intervention on early childhood development in paediatric HIV care and treatment programmes: a randomized controlled trial BMC Pediatrics Trial protocol, no results

41 2019 Christodoulou, J. et al Perinatal maternal depression in rural South Africa: Child outcomes over the first two years Journal of Affective Disorders No HEU group or stratification by HIV status

42 2019 Cockroft, K. and Milligan, R. Working memory structure in atypical development: HIV-infected and HIV-exposed, uninfected school beginners Developmental Neuropsychology Age > 5 years (HEU mean age 7.36 years, SD 0.88)

43 2017 Coelho, A.V. et al Antiretroviral Treatment in HIV-1-Positive Mothers: Neuropsychological Implications in Virus-Free Children International Journal of Molecular Sciences Review

44 2015 Converse, D.G., et al Maternal HIV illness and its impact on children well-being and development in Haiti J Child Fam Stud No neurodevelopment outcomes; focus on caregiver not children; no distinct HEU group

45 2018 Dalili, D. et al Growth and development status in the first two years of uninfected children born from HIV positive mothers Acta Medica Iranica No HIV control group or statistical comparison with normative data

46 2016 Das, P.K. et al Abundance of psychiatric morbidity in perinatally HIV infected children and adolescents with comparison to their HIV negative sibling Neurology Psychiatry and Brain Research Age > 5 years included (stratification at 6 years)

47 2016 Datong, P et al Breast-fed HIV-1 exposed infants play catch up BMC Infectious Diseases Conference Conference abstract; No distinct HEU group – no statement HIV exposed children are all uninfected

48 2000 Davis-McFarland, E. Language and oral-motor development and disorders in infants and young toddlers with human immunodeficiency virus Seminars in speech and language Review of HIV-infected children

49 2018 Debeaudrap, P et al Neurodevelopmental outcomes in HIV-infected and uninfected African children AIDS Age > 5 years (4-9 years, mean HEU 6.2 years, HU 6.2 years)

50 2003 Del Pilar Kafa, M. et al Neurodevelopment in HIV-exposed children Interdisciplinaria Revista de No distinct HEU group – infants born to HIV-infected women analysed which may include HIV-infected children
| Year | Authors                  | Title                                                                 | Journal/Conference                                                                 | Status |
|------|--------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------|
| 2016 | Desmond, S.T. et al      | Health and survival of HIV perinatally exposed but uninfected children born to HIV-infected mothers | Current opinion in HIV and AIDS                                                     | Review |
| 2019 | Donald, K.A. et al       | Risk and protective factors for child development: An observational South African birth cohort | PLOS Medicine                                                                       | HEU outcomes reported in Wedderburn, C.J. et al |
| 2019 | Ekali, G.L. et al        | Effect of in utero exposure to HIV and antiretroviral drugs on growth in HIV-exposed uninfected children: a systematic review and meta-analysis protocol | BMJ Open                                                                            | Review; protocol without results |
| 2016 | Evans, C.V. et al        | Head circumferences of children born to HIV-infected and HIV-uninfected mothers in Zimbabwe during the preantiretroviral therapy era | AIDS                                                                                 | Cohort spanned years <2000 (1997-2000) |
| 2016 | Ezeanama, A.E. et al     | Perinatal HIV Status and Executive Function During School-Age and Adolescence: A Comparative Study of Long-Term Cognitive Capacity Among Children From a High HIV Prevalence Setting | Medicine                                                                            | Age >5 years (cognitive assessment between 6-18 years, school age) |
| 2019 | Ezeanama, A.E. et al     | Serum vitamin D is differentially associated with socioemotional adjustment in early school-aged Ugandan children according to perinatal HIV status and in utero or peripartum antiretroviral exposure history | American Journal of Tropical Medicine                                                | Age >5 years (6-10 years, mean HEU 7.5 years, HUU 7.6 years); conference presentation (full paper checked: Yakah, W., et al Nutrients 2019;11(7):1570) |
| 2020 | Familiar, I. et al       | Association between caregiver depression symptoms and child executive functioning. Results from an observational study carried out in four sub-Saharan countries | AIDS Care                                                                            | Age >5 years (5-11 years; HEU mean 7.3 years, HUU 7.3 years) |
| 2016 | Fasunla, A.J.O.G. et al  | Comparison of hearing status of HIV-exposed and-unexposed newborns and immunovirologic correlates in HIV-exposed newborns | Otalaryngology - Head and Neck Surgery (United States)                              | Conference abstract; No distinct HEU group - 'HIV-exposed' group analysed which may include HIV-infected children |
| 2014 | Fasunla A.J. et al       | Comparison of auditory brainstem response in HIV-1 exposed and unexposed newborns and their correlation with the maternal viral load and CD4 cell counts | AIDS                                                                                 | Paper from above; HEU group not clearly defined; Outcome not included. |
| 2009 | Ferguson, G. et al       | The prevalence of motor delay among HIV infected children living in Cape Town, South Africa | International Journal of Rehabilitation Research                                    | No specified HEU group – reference sample unknown HIV-status |
| 2011 | Ferguson, G. et al       | The motor development of orphaned children with and without HIV: Pilot exploration of foster care and residential placement | Physiotherapy (United Kingdom)                                                      | Conference abstract; No HEU group |
| 2013 | Ferguson, K.T. et al     | Cognitive, motor, and behavioral development of orphans of HIV/AIDS in institutional contexts | Neuropsychology of children in Africa: Perspectives on risk and resilience           | No distinct HEU group (20% of children had been diagnosed with HIV/AIDS) |
| 2009 | Fernández Ibieta, M. et al | Growth of uninfected infants exposed to antiretrovirals born to HIV-infected women | Anales de Pediatría                                                                  | No control group |
| 2000 | Fishkin, P.E. et al      | Brief report: relationship between HIV infection and WPSSI-R performance in preschool-age children | Journal of Pediatric Psychology                                                      | No HEU group; Cohort spanned years <2000 (1999+) |
| 2018 | Fouché, C. et al         | Anthropometric parameters of HIV-infected and HIV-uninfected mothers and their premature infants | Journal of Tropical Pediatrics                                                       | No distinct HEU group - 'HIV-infected mothers and their premature infants analysed which may include HIV-infected children |
| 2019 | Gaulee Pokhrel, K. V. D. et al | Influence of stigma and discrimination on psychosocial health in children affected by AIDS in Nepal: A cross-sectional study | HIV Medicine                                                                         | No distinct HEU group; Age > 5 years (2-14 years); Conference abstract |
| 2020 | Ge, X.M. et al           | Influence on physical development of children aged 18 months from HIV-positive mothers for prevention mother to child transmission of HIV | Zhonghua liu xing bing xue za zhi Anthropometry measures grouped, no head circumference. Language of full-text: Chinese |
| 2018 | Gonzalez, R. et al       | Effects of HIV infection on maternal and neonatal health in southern Mozambique: a prospective cohort study after a decade of antiretroviral drugs roll out | PLoS ONE                                                                             | No distinct HEU group - infants born to HIV-infected women which may include HIV-infected children |
| 2012 | Gompels, U.A. et al      | Human Cytomegalovirus Infant Infection Adversely Affects Growth and Development in Maternally HIV-Exposed and Unexposed Infants in Zambia | CID                                                                                 | No distinct HEU group - separated by maternal HIV status but not combined with child status so HIV-infected children included with HEU group |
| 2011 | Griner, R. et al         | In utero and postnatal exposure to antiretrovirals among HIV-exposed but uninfected children in the United States | AIDS Patient Care STDs                                                                | Cohort spanned years <2000 (1995 to 2009); No neurodevelopmental outcomes |
| 2008 | Grosch-Woerner, I. et al | Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women | HIV Medicine                                                                         | Cohort spanned years <2000 (1995-2001) |
| 2005 | Hankin, C. et al         | Does exposure to antiretroviral therapy affect growth in the first 18 months of life in uninfected children born to HIV-infected women? | JAIDS                                                                                | Cohort spanned years <2000 (1985+) |
| 2018 | Heffron, R. et al        | Pregnancy outcomes and infant growth among babies with intrauterine exposure to tenofovir-based preexposure prophylaxis for HIV prevention | AIDS                                                                                 | No HEU children |
| 2016 | Hermetet-Lindsay, K.D.   | Contributions of disease severity, psychosocial factors, and cognition to behavioral functioning in youth perinatally exposed to HIV | Dissertation Abstracts                                                              | Age includes >5 years (school age: mean 10.9 years); Dissertation |

11
75 2013 Herrero, D. et al Motor development of infants exposed to maternal human immunodeficiency virus (HIV) but not infected International Archives of Medicine No HEU control group or statistical comparison with normative data.

76 2015 Hines, S.K. et al Meconium atazanavir concentrations and early language outcomes in HIV-exposed, uninfected infants with prenatal atazanavir exposure JAIDS No control group. Focus on meconium concentrations.

77 2008 Hochhauser, C.J. et al The impact of environmental risk factors on HIV-associated cognitive decline in children AIDS Care No HEU group; Cohort spanned years <2000 (1993-onwards); Age >5 years (1-13 years)

78 2001 Holditch-Davis, D. et l Parental caregiving and developmental outcomes of infants of mothers with HIV Nursing research Cohort spanned years <2000 (children born before year 2000). No distinct HEU group

79 2011 Hutchings, J. Developmental delay in HIV-exposed infants attending Newlands Clinic in Harare, Zimbabwe NA Dissertation

80 2014 Hutchings, J. & Poterton, J Developmental delay in HIV-exposed infants in Harare, Zimbabwe Vulnerable children and youth studies No HEU control group or statistical comparison with normative data.

81 2019 Iloghalu, E.I. et al Effect of maternal HIV infection on treatment with HAART on neonatal birth weight and other anthropometry: A cohort study of HIV sero-positive children in Enugu, South-East Nigeria Journal of Clinical and Diagnostic Research No distinct HEU group - infants born to HIV sero-positive women which may include HIV-infected children

82 2017 Ilohi, K.K. et al Neurocognitive function of school-aged HIV-infected children in Enugu, Nigeria Journal of Tropical Pediatrics No specified HEU group; Age>5 years (6-15 years)

83 2018 Jacobson, D. et al Alcohol use among HIV-infected pregnant women and child outcomes in the Pediatric HIV AIDS Cohort study (PHACS) Alcoholism: Clinical and Experimental Research Conference presentation; substance use confounder; age range for neurodevelopment evaluations not clear (children followed up until age 18)

84 2017 Jankiewicz, M. et al White matter abnormalities in children with HIV infection and exposure Frontiers in Neuroanatomy Age (follow up >5 years; mean age 7.3 years)

85 2020 Jantarabenjakul W. et al Behavioral problems in perinatally HIV-infected young children with early antiretroviral therapy and HIV-exposed uninfected young children: prevalence and associated factors AIDS Care Neurodevelopmental outcomes reported in other paper (Jantarabenjakul W. et al., 2019)

86 2019 Jantarabenjakul W. et al Low risk of neurodevelopmental impairment among perinatally acquired HIV-infected preschool children who received early antiretroviral treatment in Thailand JIAS No HEU control group or statistical comparison with normative data

87 2015 Jao, J. et al Growth patterns in the first year of life differ in infants born to perinatally vs. non-perinatally HIV-infected women AIDS No neurodevelopmental outcomes or OFC

88 2020 Jao, J. et al Neurodevelopment of HIV-exposed uninfected infants born to women with perinatally acquired HIV in the United States J Acquir Immune Defic Syndr Comparison of perinatally versus non-perinatally acquired HIV in mothers. SMARTT cohort and neurodevelopmental outcomes reported in included papers

89 2011 Jelsma, J. et al The motor development of orphaned children with and without HIV: Pilot exploration of foster care and residential placement BMC Pediatrics No HEU group

90 2016 Kaaya, S. et al Association of maternal depression and infant nutritional status among women living with HIV in Tanzania Maternal & child nutrition No neurodevelopmental outcomes; 20% infants of unknown HIV status; cohort spanned years <2000 (1995 – 1997)

91 2016 Kakkar, F.W. et al Safety of combination antiretroviral prophylaxis in high-risk HIV-exposed newborns: A retrospective review of the Canadian experience JIAS No distinct HEU group - ‘high-risk HIV-exposed’ group analysed which may include HIV-infected children

92 2012 Kapetanovic, S. et al T-cell activation and neurodevelopmental outcomes in perinatally HIV-infected children AIDS No HEU group

93 2004 Keller, M.A. et al Altered neurematabolite development in HIV-infected children: Correlation with neuropsychological tests Neurology No specified HEU group; Age >5 years (range 6-16 years)

94 2014 Kerr, S.J. et al Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV AIDS Care Age includes >5 years and no subanalysis (1-12 years, mean 7.6 years)

95 2000 Knight, W.G. et al Brief report: Effects of pediatric HIV infection on mental and psychomotor development Journal of Pediatric Psychology Cohort spanned years <2000

96 2018 Knox, J. et al Screening for developmental disabilities in HIV positive and HIV negative children in South Africa: Results from the Asenze Study PLoS One No distinct HEU group - separated by child HIV status but not the combined HEU v. HUU groupings – ‘HIV-negative group contains HEU and HU children

97 2004 Kullgren, K.A. et al Prediction of cognitive, adaptive, and behavioral functioning in preschool and school-age children with HIV Children's Health Care No HEU group; Age >5 years (3 to 16 years and no stratification)

98 2014 Kuona, P. et al Growth and development of the HIV exposed uninfected children below 5 years in developing countries: focus on nutritional challenges, mortality and neurocognitive function. (Special issue on malnutrition.) Food and Nutrition Sciences Review

99 2000 Layton, T. et al Language development and assessment in children with human immunodeficiency virus: 3 to 6 years Seminars in speech and language Review

100 2012 Le Doare, K. et al Neurodevelopment in children born to HIV-infected mothers by infection and treatment status Pediatrics Review

101 2018 Le Roux, S.M. et al HIV viremia in pregnancy and neurodevelopment of HIV-exposed uninfected children Topics in Antiviral Medicine Conference presentation
| Year | Authors | Title | Journal | References |
|------|---------|-------|---------|------------|
| 2018 | Le Roux, S.M. et al | HIV viremia during pregnancy and neurodevelopment of HIV-exposed uninfected children in the context of universal antiretroviral therapy and breastfeeding | BMC Pregnancy and Childbirth | Language of full-text: Chinese; No distinct HEU group - 'HIV-infected versus normal children' |
| 2018 | Et al | Physical development of HIV-exposed infants in Kunming city: a cohort study | Maternal and Child Health Care of China | Language of full-text: Chinese; No developmental outcomes |
| 2018 | Lin, XY. et al | Physical and psychological health among children affected by HIV/AIDS: Difference in groups and caring arrangements | Chinese Journal of Clinical Psychology | No HEU group - only HIV status of mother described |
| 2018 | Lindsey, J.C. et al | Neurodevelopmental functioning in HIV-infected infants and young children before and after the introduction of protease inhibitor-based highly active antiretroviral therapy | Pediatrics | Cohort spanned years <2000 (1993 onwards); cohort demographics grouped by year of birth but not development |
| 2018 | Linn, K. et al | HIV-Related Cognitive Impairment of Orphans in Myanmar with Vertically Transmitted HIV Taking Antiretroviral Therapy | Pediatric Neurology | No distinct HEU group - 'HIV-infected versus HIV-negative children in orphanages' |
| 2018 | Liotta, G. | Growth indices in breastfed infants pre and postnatally exposed to tenofovir compared with tenofovir-unexposed infants | AIDS | No neurodevelopmental outcomes |
| 2018 | Lipman, T.H. et al | Assessment of growth and immunologic function in HIV-infected and exposed children | Journal of the Association of Nurses in AIDS Care | No neurodevelopmental outcomes; Includes children <5 years (0-14 years) |
| 2018 | Lous, K.A. et al | Correlates of emotional and behavioural problems in children with perinatally acquired HIV in Cape Town, South Africa | AIDS Care | No HEU group; Age includes >5 years (6-16 years) |
| 2018 | Macmillan, C. et al | Head growth and neurodevelopment of infants born to HIV-1-infected drug-using women | Neurology | Cohort spanned years <2000; Focused on opiates and cocaine |
| 2018 | Malee, K.M. et al | Mental health functioning among children and adolescents with perinatal HIV infection and perinatal HIV exposure | AIDS Care | Age >5 years (7-16yrs) |
| 2018 | Malee, K.M. et al | Brain and Cognitive Development Among U.S. Youth With Perinatally Acquired Human Immunodeficiency Virus Infection | Journal of the Pediatric Infectious Diseases Society | Review |
| 2018 | Manfredi, A.K. et al | Newborn hearing screening in infants born to HIV-seropositive mothers | J Soc Bras Fonoaudiol | No distinct HEU group - 'HIV-exposed' group analysed which may include HIV-infected children |
| 2018 | Manji, K.P. et al | Effect of multivitamin supplementation on the neurodevelopment of HIV-exposed Tanzanian infants: a randomized, double-blind, placebo-controlled clinical trial | J Tropical Pediatrics | Focus on multivitamin supplementation |
| 2018 | Manno, D. et al | Rich micronutrient fortification of locally produced infant food does not improve mental and motor development of Zambian infants: a randomised controlled trial | British Journal of Nutrition | No distinct HEU group - separated by child HIV status and maternal HIV status but not the combined HEU v. HIV groupings |
| 2018 | Marques, K.C. et al | Motor coordination of children and adolescents with human immunodeficiency virus | Ciência & Saúde | Language: Portuguese; Age > 5 years |
| 2018 | Martinez, P.C. et al | Intellectual quotient score comparison between HIV-infected and HIV exposed children at the Peruvian national institute of child health, Lima Peru | Retrovirology (Conference) | Age >5 years (3-7 years and no stratification); Conference presentation |
| 2018 | McDonald, C. et al | Morbidity and undernutrition are associated with impaired neurodevelopment among HIV-exposed infants in Tanzania | FASEB Journal, Conference: Experimental Biology | Conference abstract of 2013 McDonald et al paper; Insufficient information for HEU analysis |
| 2018 | McDonald, C. et al | Effect of multiple micronutrient supplementation on the neurodevelopment of HIV-exposed Tanzanian infants | FASEB Journal, Conference: Experimental Biology | Conference abstract of 2014 Manji et al paper. |
| 2018 | McDonald, C. et al | Stunting and wasting are associated with poorer psychomotor and mental development in HIV-exposed Tanzanian infants | Journal of Nutrition | Cohort spanned years <2000 (pregnant women recruited 1995 to 1997) |
| 2018 | McGrath, N et al | Effect of maternal multivitamin supplementation on the mental and psychomotor development of children who are born to HIV-1-infected mothers in Tanzania | Pediatrics | Cohort spanned years <2000 (pregnant women recruited 1995 to 1997); Not analysed by HEU status |
| 2018 | McGrath, N et al | The timing of mother-to-child transmission of human immunodeficiency virus infection and the neurodevelopment of children in Tanzania | PIDIJ | Cohort spanned years <2000 (pregnant women recruited 1995 to 1997) |
| 2018 | Mchery, M.S. et al | Neurodevelopment in Young Children Born to HIV-Infected Mothers: A Meta-analysis | Pediatrics | Review |
| 2018 | Mchery, M.S. et al | In utero exposure to HIV and/or antiretroviral therapy: a systematic review of preclinical and clinical evidence of cognitive outcomes | JIAS | Review |
127 2019 McHenry, M.S. et al Interventions for developmental delays in children born to HIV-infected mothers: a systematic review AIDS Care Review

128 2018 McHenry, M.S. et al Early childhood development in children born to HIV-infected mothers: perspectives from Kenyan clinical providers and caregivers Glob Pediatr Health No neurodevelopmental outcomes measured

129 2018 Mebrahtu, H. et al Postpartum maternal mental health is associated with cognitive development of HIV-exposed infants in Zimbabwe: a cross-sectional study AIDS Care No ART exposure documented. Children with HIV included in the analysis

130 2019 Mebrahtu, H. et al Effects of parenting classes and economic strengthening for caregivers on the cognition of HIV-exposed infants: a pragmatic cluster randomized controlled trial in rural Zimbabwe BMJ Global Health Developmental outcomes not assessed by HEU status; same trial [CHIDO] as included Mebrahtu et al 2018 paper

131 2019 Mebrahtu, H. et al The impact of common mental disorders among caregivers living with HIV on child cognitive development in Zimbabwe AIDS Care Developmental outcomes not assessed by HEU status; same trial [CHIDO] as included Mebrahtu et al 2018 paper

132 2018 Mellins, C.A. et al Screening for mental health among young South African children: the use of the Strengths and Difficulties Questionnaire (SDQ) Global Social Welfare Developmental outcomes not assessed by HEU status

133 2017 Milligan, R. et al Working memory profiles in HIV-exposed, uninfected and HIV-infected children: A comparison with neurotypical controls Frontiers in Human Neuroscience Age >5 years (mean age HEU group 88.28 months)

134 2019 Moraka, N.O. et al Child HIV exposure and CMV seroprevalence in Botswana: No associations with 24-month growth and neurodevelopmental outcomes Open Forum Infectious Diseases Analysis by CMV status and not HEU status; Children from the Tshipidi study included in Chaudhury et al paper

135 2013 Muhangi, L. et al Maternal HIV infection and other factors associated with growth outcomes of HIV-uninfected infants in Entebbe, Uganda Public Health Nutrition No neurodevelopmental outcomes

136 2019 Mukherjee, S.B. et al Development, cognition, adaptive function and maladaptive behavior in HIV-infected and HIV-exposed uninfected children aged 2-9 years Indian Pediatrics Age includes >5 years (2-9 years; HEU group mean 6.1 years) and no stratification

137 2017 Munoz, M et al Community-Based Needs Assessment of Neurodevelopment, Caregiver, and Home Environment Factors in Young Children Affected by HIV in Lima, Peru Journal of the International Association of Providers of AIDS Care 7 HEU children only and no HEU group analysis (only child and maternal status analysed separately)

138 2018 Murthy, V. et al A study of neuropsychological profile of human immunodeficiency virus-positive children and adolescents on antiretroviral therapy Indian Journal of Psychiatry No specified HEU group; Age >5 years (8-15 years)

139 2017 Nachega, J.B. et al No evidence of neurodevelopmental delay in HEU infants exposed to cART in utero and breastfeeding JAIDS Review

140 2014 Ngoma, M. et al No evidence of neurodevelopmental delay in HEU infants exposed to cART in utero and breastfeeding Topics in Antiviral Medicine Conference presentation; duplicate of Ngoma et al 2014 paper included in analysis

141 2014 Ngoma, M. et al Zambian HIV-Exposed Uninfected (HEU) infants exposed to HAART during pregnancy and one year of breastfeeding show no evidence of neurodevelopmental delay compared to HIV-Exposed Uninfected (HU) infants from the same community Canadian Journal of Infectious Diseases and Medical Microbiology Conference presentation; duplicate of Ngoma et al 2014 paper included in analysis

142 2012 Nielsen-Saines, K. et al Infant outcomes after maternal antiretroviral exposure in resource-limited settings Pediatrics Included children with HIV in the analysis

143 2019 Obiagwu, P.N Gross motor developmental delay in human immunodeficiency virus-infected children under 2 years of age Annals of African Medicine No HEU group (children were tested for HIV but mothers were only tested if children were HIV-infected)

144 2019 Onyango-Makumbi, C. Extended prophylaxis with nevirapine does not affect growth in HIV-exposed infants JAIDS No maternal ART exposure comparison group (compared postnatal prophylaxis regimen)

145 2019 Pamplona, M.C.C.A. et al Influence of exposure and vertical transmission of HIV-1 on the neuropsychomotor development in children' Revista da Sociedade Brasileira de Medicina Tropical No distinct HEU group (children born to mothers with HIV-1 infection compared to those born to mothers without HIV-1 infection, at least one HIV-infected child included in exposed group)

146 2010 Patel, D. et al Breastfeeding, HIV status and weights in South African children: a comparison of HIV-exposed and unexposed children AIDS No neurodevelopmental outcomes

147 2005 Paul, M.E. et al Morbidity and mortality during the first two years of life among uninfected children born to human immunodeficiency virus type 1-infected women: the women and infants transmission study PIDJ Cohort spanned years <2000 (enrolled by 1999)

148 2018 Paul, R. et al Cognition, emotional health, and immunological markers in children with long-term nonprogressive HIV JAIDS Age >5 years (HEU median 6.8 [5.0-9.8]; HUU 7.4 [5.3 – 9.8])

149 2015 Perez, E.M. et al Massage therapy improves the development of HIV-exposed infants living in a low socio-economic, peri-urban community of South Africa Infant Behavior & Development No HU control group or statistical comparison with normative data. Intervention study

14
| ID | Year | Authors | Title |
|----|------|---------|-------|
| 150 | 2017 | Pham, A. et al | Prenatal anti-retroviral exposure: An exploratory study of neurodevelopmental outcome in non-infected 5-years-old children |
| 151 | 2018 | Phillips, N.J. et al | HIV-associated cognitive disorders in perinatally infected children and adolescents: a novel composite cognitive domains score |
| 152 | 2016 | Pierre, R.B. et al | Infectious disease morbidity and growth among young HIV-exposed uninfected children in Jamaica |
| 153 | 2018 | Piske, M. et al | Developmental outcomes and ARV exposure in HIV-exposed uninfected children |
| 154 | 2018 | Piske, M. et al | Neurodevelopmental outcomes and in-utero antiretroviral exposure in HIV-exposed uninfected children |
| 155 | 2007 | Potterton, J.L. | A longitudinal study of neurodevelopmental delay in HIV infected children |
| 156 | 2001 | Potterton, J.L. & Eales, C.J. | Prevalence of developmental delay in infants who are HIV positive |
| 157 | 2016 | Powis, K.M. et al | In-utero triple antiretroviral exposure associated with decreased growth among HIV-exposed uninfected infants in Botswana |
| 158 | 2011 | Powis, K.M. et al | Effects of in utero antiretroviral exposure on longitudinal growth of HIV-exposed uninfected infants in Botswana |
| 159 | 2018 | Purswani, M. et al | Birth prevalence of congenital cytomegalovirus infection and language, hearing and developmental outcomes in a cohort of HIV-exposed, uninfected preschool children |
| 160 | 2019 | Purswani, M. et al | Birth prevalence of congenital cytomegalovirus infection in HIV-exposed uninfected children in the era of combination antiretroviral therapy |
| 161 | 2010 | Puthanakit, T. et al | Poor cognitive functioning of school-aged children in Thailand with perinatally acquired HIV infection taking antiretroviral therapy |
| 162 | 2013 | Puthanakit, T. et al | Cognitive function and neurodevelopmental outcomes in HIV-infected children older than 1 year of age randomized to early versus deferred antiretroviral therapy: The PREDICT neurodevelopmental study |
| 163 | 2013 | Ransom, C.E. et al | Infant growth outcomes after maternal tenofovir disoproxil fumarate use during pregnancy |
| 164 | 2016 | Redmond, S.M. et al | Longitudinal Evaluation of Language Impairment in Youth With Perinatally Acquired Human Immunodeficiency Virus (HIV) and Youth With Perinatal HIV Exposure |
| 165 | 2017 | Reliquest, V. et al | Developmental delay and behavioral disorders in 59 HIV-exposed uninfected infants |
| 166 | 2016 | Rice, M.L. et al | ARV risk for speech and language impairments in HEU children at 3 and 5 years |
| 167 | 2005 | Rocha, C. et al | Neurological findings in a group of children and adolescents exposed and infected by HIV-1. |
| 168 | 2018 | Rodriguez, V.J. et al | Pre- and postnatal exposure to intimate partner violence among South African HIV-infected mothers and infant developmental functioning at 12 months of age |
| 169 | 2018 | Rodriguez, V.J. et al | Infant development and pre- and post-partum depression in rural South African HIV-infected women |
| 170 | 2017 | Rosala-Hallas, A. et al | Growth of HIV-exposed uninfected, compared with HIV-unexposed, Zambian children: a longitudinal analysis from infancy to school age |
| 171 | 2019 | Rotheram-Borus, M. J. et al | Maternal HIV does not affect resiliency among uninfected/HIV exposed South African children from birth to 5 years |
| 172 | 2018 | Rotheram-Fuller, E.J. | Maternal patterns of antenatal and postnatal depressed mood and the impact on child health at 3 years postpartum |
| 173 | 2019 | Ruiseñor-Escudero, H. et al | Building capacity in neurodevelopment assessment of children in sub-Saharan Africa: A quality assurance model to implement standardized neurodevelopmental testing |
| 174 | 2019 | Ruiseñor-Escudero, H. et al | Neurodevelopmental outcomes in preschool children living with HIV-1 subtypes A and D in Uganda |
| 175 | 2016 | Ruskowski, A. et al | The role of maternal vitamin D and iron status on developmental outcomes and head circumference in HIV-exposed uninfected infants |
Motor and cognitive developmental status of children exposed and no exposed to HIV  

Physiotherapy (United Kingdom)
Conference abstract; included paper da Silva et al, 2015

Maternal HIV/AIDS status and neurological outcomes in neonates: A population-based study  

Maternal and Child Health Journal
Cohort spanned years <2000 (1998-2007)

Growth, developmental, and behavioral outcomes of HIV-affected preschool children in Thailand  

Journal of the Medical Association of Thailand
Population spanned years <2000 (children born 1998-2000)

Growth and neurodevelopmental status in HIV infected children  

Iranian Journal of Pediatrics
No HEU group

The relationship between pediatric HIV infection, CD4 percentage, HAART, and WISC-III performance  

Dissertation Abstracts International Section A:
Dissertation abstract; Insufficient information

Neurodevelopment and growth of institutionalized children with vertically transmitted human immunodeficiency virus  

Vulnerable Children and Youth Studies
No HEU group (HIV-uninfected children, but no indication of maternal HIV status)

A systematic review of psychological functioning of children exposed to HIV: using evidence to plan for tomorrow's HIV needs  

AIDS and behavior
Review

Cognitive and physical development in HIV-positive children in South Africa and Malawi: A community-based follow-up comparison study  

Child: Care, Health and Development
Age includes >5 years (4-13 years) and no sub-analysis

Cognitive, neurological and adaptive behaviour functioning among children with perinatally-acquired HIV infection in India  

JIAS
No distinct HEU group; Age includes >5 years (4-15 years); Conference abstract;

Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11)  

PLoS Medicine
No HEU group analysis;
Cohort spanned years <2000 (1994-2010).

Concurrent validity between instruments of assessment of motor development in infants exposed to HIV  

Infant Behavior and Development
No distinct HEU group – infants exposed to HIV which may include HIV-infected children

Child development in HIV-positive and HIV-affected children in South Africa and Malawi-What role for community organisations?  

Children and Youth Services Review
No specific HEU group analysis;
Age > 5 years (4-13 years)

Neurological and neurocognitive function of HIV-infected children commenced on antiretroviral therapy  

South African Journal of Child Health
No HEU group

Neurocognitive development in young HIV-Exposed uninfected children exposed pre-or perinatally to antiretroviral medications  

Canadian Journal of Infectious Diseases and Medical Microbiology
Conference abstract; appears to be overlap with 2017 paper included in full text reviews

Neurocognitive outcomes in pre-school and early school-age HIV-exposed uninfected children exposed pre-or perinatally to antiretroviral medications  

Canadian Journal of Infectious Diseases and Medical Microbiology
Conference abstract; appears to be overlap with 2017 paper included in full text reviews

Mental functioning of children with HIV infection: The preschool and early school-age years  

Dissertation Abstracts International
Age >5 years included (3-7 years);
Dissertation

Effects of perinatal HIV infection and associated risk factors on cognitive development among young children  

Pediatrics
Cohort spanned years <2000 (1990-2000 births);
Age >5 years (3-7 years)

Predicting long-term outcomes for children affected by HIV and AIDS: Perspectives from the scientific study of children's development  

AIDS
Review

HIV-associated neurodevelopmental delay: prevalence, predictors and persistence in relation to antiretroviral therapy initiation and viral suppression  

Child: care, health and development
No HEU group

Neurodevelopmental assessment of HIV-exposed uninfected and early-treated HIV-infected children: study protocol  

BMC research notes
Protocol; no results

Interventions addressing neurodevelopmental delay in young children infected with or exposed to HIV: A scoping review  

Rehabilitation Oncology
Review

A description of early neurodevelopment in a cohort of HIV-exposed uninfected children  

AIDS Care
No HIV control group or statistical comparison with normative data.

Third trimester vitamin D status is associated with birth outcomes and linear growth of HIV-exposed uninfected infants in the United States  

JAIDS
Focus on vitamin D exposure

Neurological profile and neurodevelopment of 88 children infected with HIV and 84 seroreverter children followed from 1995 to 2002  

Brazilian Journal of Infectious Diseases
Cohort spanned years <2000 (1995-2002) with no stratification

Cerebral MR imaging in uninfected children born to HIV-seropositive mothers and perinatally exposed to zidovudine  

American Journal of Neuroradiology
Cohort spanned years <2000

Blood lead levels and neurodevelopmental function in perinatally HIV-exposed, uninfected children in a U.S.-based longitudinal cohort study  

AIDS Research and Human Retroviruses
Focus on lead exposure
| Year | Authors | Title | Journal or Conference | Notes |
|------|---------|-------|-----------------------|-------|
| 2020 | Thomaidis, L. et al | Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: A case-control study | BMC Pediatrics | No HEU group; Age >5 years (range 3-18 years) |
| 2001 | Thompson, W.S. et al | Language, memory, and cognitive performance in minority children infected with HIV (immune deficiency) | Dissertation Abstracts International | Dissertation; Age >5 years (school age); No distinct HEU group (uninfected siblings and peers) |
| 2018 | Tomlinson, M. et al | Antenatal depressed mood and child cognitive and physical growth at 18-months in South Africa: a cluster randomized controlled trial of home visiting by community health workers | Epidemiology and psychiatric sciences | No distinct HEU group |
| 2015 | Torre, P. Iii et al | Hearing assessment data in HIV-infected and uninfected children of Cape Town, South Africa | AIDS Care | Age includes >5 years (4-14 years) and no sub-analysis |
| 2015 | Torre, P. Iii et al | Distortion product otoacoustic emission data in perinatally HIV-infected and HIV-exposed but uninfected children and adolescents in the Pediatric HIV/AIDS Cohort Study | Pediatric Infect Dis J | Age > 5 years (7-16 years) |
| 2012 | Torre, P. Iii et al | Hearing loss in perinatally HIV-infected and HIV-exposed but uninfected children and adolescents | Pediatric Infect Dis J | Age >5 years (7-16yrs) |
| 2008 | Urban, M.F. et al | Growth of infants born to HIV-infected women when fed a biochemically acidified starter formula with and without probiotics | S Afr J Clin Nutr | Trial confounded outcome |
| 2016 | Van Dalen, Y.W. et al | Neurometabolite Alterations Associated With Cognitive Performance in Perinatally HIV-Infected Children | Medicine | No specified HEU group; Age >5 years (8-18 years) |
| 2019 | Van den Hof, M. et al | Lower IQ and poorer cognitive profiles in treated perinatally HIV-infected children is irrespective of having a background of international adoption | PLOS ONE | No specified HEU group; Age >5 years (mean 10.45 years) |
| 2020 | Van den Hof, M. et al | Neurocognitive development in perinatally human immunodeficiency virus-infected adolescents on long-term treatment, compared to healthy matched controls: a longitudinal study | CID | No specified HEU group; Age >5 years (8-18 years) |
| 2016 | Van Dyke, R.B. et al | The PHACS SMARTT study: Assessment of the safety of in utero exposure to antiretroviral drugs | Frontiers in Immunology | Review of SMARTT outcomes |
| 2019 | Vannappagari, V. et al | Pregnancy and neonatal outcomes following prenatal exposure to dolutegravir | JHIDS | No neurodevelopmental outcomes, reports birth defects |
| 2017 | Van Wyhe, K.S. et al | Cross-cultural assessment of HIV-associated cognitive impairment using the Kaufman assessment battery for children: a systematic review | JIAS | Review |
| 2018 | Visser, M.J. et al | A comparative study of the psychological problems of HIV-infected and HIV-uninfected children in a South African sample | AIDS Care | No HEU group; age >5 years (6-12 years) |
| 2003 | Von Giesen, H.J. et al | Delayed motor learning and psychomotor slowing in HIV-infected children | Neuropediatrics | No specified HEU group; Age >5 years (8-16 years) |
| 2018 | Wesevich, A. et al | PMTCT option b+ efavirenz and tenofovir exposure through breastfeeding and bayleys neurodevelopmental scores in Malawian infants | Pediatrics | No specified HEU group - infants born to HIV-positive mothers which may include HIV-infected children; Conference presentation |
| 2019 | White, M. & Connor, K.L. | Determining how in utero HIV exposure, with or without infection, influences neurodevelopment in infants before age three: Findings from an evidenced-based review of observational and experimental studies | Reproductive Sciences Supplement | Review; Conference presentation |
| 2019 | White, M. et al | Does the early nutritional environment and in utero HIV exposure, without infection, impact infant development? | Reproductive Sciences Supplement | Conference presentation; no HEU and neurodevelopment analysis results |
| 2012 | Whitehead, N. | The neurodevelopment of HIV positive infants on HAART compared to HIV exposed but uninfected infants | NA | Thesis. |
| 2014 | Whitehead, N et al | The neurodevelopment of HIV-infected infants on HAART compared to HIV-exposed but uninfected infants | AIDS Care | No HEU control group or statistical comparison with normative data. |
| 2010 | Williams, P.L. et al | Neurodevelopment and in utero antiretroviral exposure of HIV-exposed uninfected infants | Pediatrics | Cohort spanned years <2000 (1993-2006) |
| 2012 | Williams, P.L. et al | A trigger-based design for evaluating the safety of in utero antiretroviral exposure in uninfected children of human immunodeficiency virus-infected mothers | American Journal of Epidemiology | Methods paper, no neurodevelopmental results |
| 2016 | Williams, P.L. et al | Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design | AIDS | Age >5 years included. |
| 2019 | Williams, P.L. et al | Associations of maternal ARV use with microcephaly in HIV-exposed uninfected children | Open Forum Infectious Diseases | Conference presentation, paper included in full text |
| 2017 | Yadav, S.K. et al | Altered structural brain changes and neurocognitive performance in pediatric HIV | NeuroImage | No HEU group; Age >5 years (controls mean 11.2 years) |
| 2019 | Yang, L. et al | Child development in HIV exposed, uninfected children: Challenges with accessing services | Paediatrics and Child Health | Conference abstract; insufficient information on developmental outcomes |
## S6 Appendix: List of included studies and relevant articles

| Study name (where available) | Country | HEU v. HU articles | ART analysis articles | Secondary outcomes articles |
|------------------------------|---------|--------------------|-----------------------|-----------------------------|
| 1. -                         | Canada  | Alimenti et al., 2006 |                       |                             |
| 2. Malaria RCT               | Uganda  | Boivin et al., 2016   |                       |                             |
| 3. PROMISE                   | Malawi & Uganda | Boivin et al., 2019 | Boivin et al., 2019 | Aizire et al., 2020        |
| 4. Rakai Community Cohort Study (RCCS); Nevirapine (NVP) Prevention of Mother to Child HIV Transmission (PMTCT) study | Uganda | Brahmbhatt et al., 2014 |                       |                             |
| 5. Tshipidi                  | Botswana | Chaudhury et al., 2017 | Chaudhury et al., 2018 |                             |
| 6. PreNAPS PostNAPS          | Uganda  | Familiar et al., 2018 | Familiar et al., 2018 |                             |
| 7. Aluvia                    | Zambia  | Ngoma et al., 2014   |                       |                             |
| 8. SHINE                     | Zimbabwe | Ntozini et al., 2020 |                       |                             |
| 9. HIVNET 012 clinical trial | Zimbabwe | Kandawasvika et al., 2011 |                       |                             |
| 10. -                        | Malawi  | Landes et al., 2012  |                       |                             |
| 11. CHER                     | South Africa | Laughton et al., 2012 | Laughton et al., 2012 |                             |
| 12. MCH-ART                  | South Africa | Le Roux et al., 2018   | Le Roux et al., 2019 (also HU2) |                             |
| 13. Aluvia                   | Zambia  | Ngoma et al., 2014   |                       |                             |
| 14. SHINE                    | Zimbabwe | Ntozini et al., 2020 |                       |                             |
| 15. SMARTT                   | USA & Puerto Rico | Siros et al., 2013 | Caniglia et al., 2016 |                             |
| 16. MIHS                     | South Africa | Springer et al., 2012 | Springer et al., 2018 |                             |
| 17. -                        | Malawi  | Struyf et al., 2019  | Springer et al., 2018 |                             |
| 18. -                        | DRC     | Van Rie et al., 2008 | Van Rie et al., 2009 |                             |
| 19. DCHS                     | South Africa | Wedderburn et al., 2019 |                       | Donald et al., 2017 |
| 20. -                        | China   | Wu et al., 2019     |                       |                             |
| 21. PMTCT RCT                | South Africa | Alcaide et al., 2019 |                       |                             |
| 22. Mepeu                    | Botswana | Cassidy et al., 2019 (also Tshipidi and Mma Bana) |                       |                             |
| 23. Mma Bana                 | Botswana | Kacanek et al., 2018 (also Cassidy et al., 2019) |                       |                             |
| 24. -                        | India   | Rajan et al., 2017   |                       |                             |
| 25. -                        | Canada  | Smith et al., 2017   |                       |                             |
| 26. -                        | Nigeria | Jumare et al., 2019  |                       |                             |
| 27. CIGNIS                    | Zambia  | Filteau et al., 2011 |                       |                             |
| 28. -                        | USA     | Neri et al., 2013    |                       |                             |
| 29. Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) study | Latin America and Caribbean | Caniglia et al., 2016 |                             |
| 30. -                        | Kenya   | Puntye et al., 2015  |                       |                             |
## S7 Appendix: Characteristics of studies examining neurodevelopment of HEU children compared to HU children

| Author, year of publication, study | Country (time period) | Study design | Child age | N participants | Study design | HIV test in HEU children (age) | Maternal ART (%) | ART regimen | Infant PNP (duration) | Breastfeeding | Tool | Confounders included in adjusted analysis |
|-----------------------------------|----------------------|--------------|-----------|----------------|--------------|-------------------------------|------------------|-------------|---------------------|---------------|------|------------------------------------------|
| Alimenti et al., 2006 | Canada (2003 – 2004) | CS | 18 – 36m | 39 | 24 | PCR (twice <6m) & Ab confirming seroreversion (6m) | 100% | Triple therapy (quadruple in 3) | AZT at delivery | AZT (neonatal period) | ND | BSID-II VABS | Maternal substance use. |
| Boivin et al., 2016 | Uganda (2010 – 2013) | Cohort / RCT | 2yr | 143 | 325 | PCR at enrolment and (6w after cessation BF) | 100% | Triple therapy | NVP (6wks) | NVP | 100%; Duration HEU=HU | MSEL | Malaria, anaemia, age, WAZ, breastfeeding days, trial arm, sex, SES, observation days prior to randomization. Note RCT malaria intervention trial. |
| Boivin et al., 2019 | Malawi and Uganda (2013 – 2014) | Cohort / RCT | 12, 24, 48, and 60m | 405 | 456 | PCR (12m, 24m) | 54% | Triple therapy AZT | NVP (50%) No maternal AZT | HEU 73-83%, HU 95% (12m; Duration HEU=HU) | MSEL | HEU and HU children matched for age, sex, SES. Data collection site. |
| Brahmbhatt et al., 2014 | Uganda (not reported) | Cohort | 0 to 6yr (median 36.1m HEU 57.5m HU) | 105 | 108 | PCR (<18m), EIA (>18 m) | ND | NVP | NVP (% ND) | ND | MSEL | Child age, weight and height. |
| Chaudhury et al., 2017 | Botswana (2010 – 2012) | Cohort | 2yr (22-29 m) | 313 (BSID) | 357 (BSID) | PCR (<18m), ELISA (18m) | 36% | Triple therapy AZT | NVP (single dose) and AZT (1m) | HEU 9% HU 99.5% HEU=HU | BSID-III - adapted | DMC | Maternal age, income, education, and depression, household access to water, sanitation and electricity, food insecurity, housing type, cooking method. Prematurity & birthweight examined in sensitivity analyses. |
| Da Silva et al., 2017 | Brazil (timeframe ND) | CS | 4, 8, 12 & 18m | 40 (10/age) | 40 (10/age) | PCR (16m) | 100% | Not specified | Not specified (6wks) | Interrupted | BSID-III – |
| Familiar et al., 2018 | Uganda (2012 – 2015) | LG | 6 & 12m | 75 complete data (79 total) | 140 complete data (149 total) | DBS PCR | 76% | Triple therapy | ND | 100% | MSEL | Child sex, maternal age, education level, marital status, asset index, employment status, social support and depression, HOME score. HAZ mediator. |
| Gomez et al., 2009 | Colombia (not reported) | LG | 0 – 24 m (3, 6, 9, 12 , 18 and 24m) | 23 | 20 | ELISA (18m) | 100% | Triple therapy | ND | ND | BSID-II DDST – |
| Kandawasvika et al., 2011 | Zimbabwe (2002 – 2004) | Cohort | 3 to 12m (3m assessments) | 188 | 287 | PCR (<15m), AB (>15m) | In labour % ND | NVP | NVP | ND | 99% | BINS – |
| Landes et al., 2012 | Malawi (2008) | Cohort | 20m | 128 | 200 | Health passport, offered rapid testing | –10% –70% | Triple therapy NVP | NVP (66%) | HEU & HU=90% Duration HEU=HU | Milestones – |
| Laughton et al., 2012  | South Africa (2005 – 2006) | Cohort | 11m (10-16m) 11.5m HEU 11.5m HU | 28 | 34 | HEU: PCR at baseline and 1 month after PCV 3rd dose (12-24 wks), ART/PMTCT prophylaxis - personal correspondence NVP and AZT (7 days) (%ND) | ND | ART/PMTCT prophylaxis - personal correspondence NVP and AZT (7 days) (%ND) | ND | GMDS – |
| Laughton et al., 2018 | South Africa (2005 – 2013) | Cohort | 11 to 60m (11, 20, 30, 42, 60 m) | 34 | 39 | HEU: PCR at baseline and 1 month after PCV 3rd dose (12-24 wks), HEU | 85% | NVP and AZT (85%) | ND | NVP and AZT (85%) | ND | GMDS – |
| Le Roux et al., 2018 | South Africa (2013 – 2016) | Cohort | 13m (IQR 12-14) | 215 | 306 | PCR (12m) | 100% | Triple therapy (TFD+FTC+ EFV) | NVP +/- AZT | 100% (duration HEU=HU) | BSID-III (no receptive language) OFC | Gestation, sex, SGA, Maternal education, intimate partner violence, Risky drinking, breastfeeding duration, housing, maternal age, employment; planned pregnancy, postpartum depression |
| Ngoma et al., 2014 | Zambia (2011 – 2013) | Double cohort | 15 to 36m | Mean HEU 22.4m HU 28.1 | 97 | 103 | RNA PCR on DBS; Controls had serology performed. | 100% | Triple therapy (ZDV+3TC+ LPV/r) | NVP in labour | NVP (48b) and AZT (1wks) | 100% (duration HEU=HU) | FSDOQ (CAT/CLAMS) | Child age and birthweight, maternal education, monthly income. |
et al, 2020\textsuperscript{17}

Zimbabwe

2016 – 2017

RCT

24m

205

1175

PCR / Rapid (18m)

86%

ART (majority TDF-based triple therapy)

Unknown

ND

100%

MDAT CDI A-not-B

(1): Child age, sex and month of birth, trial arm, study nurse.

(2): Maternal education, household wealth, maternal age, parity.



et al, 2013\textsuperscript{18}

USA & Puerto Rico

2007 – 2011

Cohort

12.7m

(9 to 15m)

374

49

ND in paper; study design on clinicaltrials.gov

97%

Triple therapy

Other

None

AZT (8w)

97%

ND

BSID-III

–

et al

2008

Van Rie

et al

2012\textsuperscript{19}

South Africa

2009

(Pilot study)

CS

17 to 19m

17

20

PCR (2, 6 & 12wks)

94%

ART / PMTCT prophylaxis

ND

HEU 0%,

HU 100%

GMDS OFC

–

et al

2018\textsuperscript{20}

South Africa

2012 – 2013

Nested cohort

12m

(11-14)

58

38

ELISA with PCR if positive (12m)

50%

cART

AZT

monotherapy

NVP and AZT (1wks)

HEU 12%,

HU 66% at 6m

BSID-III

ADDB OFC

–

et al

2020\textsuperscript{21}

South Africa

2012 – 2013

Cohort

3yrs

(30-42 m)

32

27

ELISA with PCR if positive (12m)

41%

cART

AZT

NVP and AZT (1wks)

HEU 9%,

HU 67% at 6m

BSID-III

SDQ OFC

Stunting, maternal education.

et al, 2019\textsuperscript{22}

Malawi

2008 – 2011

Cohort

15wks to

24m (BSID at

15w; 6, 9, 12, 15, 18 and 24m)

289

170

PCR (6w and follow up visit), Ab (>15m) also for

HU. Note 21/289 seroconverted and

were censored from analysis

29.5%

NVP only

NVP (90%)

ND

BSID-III

–

Cognitive only

Van Rie et al, 2008\textsuperscript{23}

Democratic Republic of Congo (DRC)

2004-2005

CS

18m to 72m

(HEU median 33.4 m; HU median 45.6m)

35

90

HIV-1-infected children who were orphans of maternal AIDS / whose

mothers had symptomatic AIDS

ND

Unclear but ART was available at the
time

ND

ND

BSID

(18-29m)

PDMS SONR

(30-72m)

RITLS

(18-36m)

et al, 2009\textsuperscript{24}

Democratic Republic of Congo (DRC)

2004 – 2005

Cohort

18m to 71m

35

90

At above: ELISA available.

ND

Unclear but ART was available at the
time

ND

ND

BSID-III

PDMS SONR

–

Wedderburn et al, 2019\textsuperscript{25}

South Africa

2012 – 2015

Cohort

6m

2yrs

61

168

199

PCR at 6 weeks, PCR / Ab (9m/18m)

88%

Triple therapy

AZT

NVP 87%

NVP+AZT 13%

HEU 14%,

HU 18% at 6m.

Duration

HEU=HU

BSID-III

Child age and sex, maternal age and education,

household income.

Sensitivity analysis premature, depression, breastfeeding.

Wu et al, 2019\textsuperscript{26}

China

2010 – 2013

CS

6m to 3yr in five age bands

250

(50/age)

250

(50/age)

PCR (6wks)

100%

Triple therapy

AZT or NVP

(4 to 6w)

(100%)

ND but guidelines

HEU FF (~97.9%)

BSID-III

HIV and HEU children matched for child gender,

age, maternal age and residency. Neonatal jaundice,

child anaemia, low birthweight, prematurity and malnutrition, maternal education and smoking.

Abbreviations | ND: not documented; HEU: children who are HIV-exposed and uninfected; HU: children who are HIV-unexposed; CS: cross-sectional study; LG: longitudinal study; RCT: randomized controlled trial; DRC: Democratic Republic of Congo; yr: year; m: month; wks: weeks; ART: antiretroviral treatment; PNP: postnatal prophylaxis; AZT: zidovudine; 3TC: lamivudine; NVP: nevirapine; LPV/r: lopinavir/ritonavir; TDF: tenofovir; FTC: emtricitabine; EFV: efavirenz; cART: combination ART; PMTCT: prevention of mother-to-child transmission; Ab: HIV antibody test; PCR: HIV polymerase chain reaction test; DBS: Dried blood spot; FF: formula feeding; OFC: occipitofrontal circumference; HCAZ: head circumference-for-age; NP: neonatal period; WAZ: weight for age; SES: socioeconomic status; SGA: small for gestational age; STI: sexually transmitted infection; All assessment tool abbreviations are listed in S8 Appendix.
## S8 Appendix: Child development tools used across included studies highlighting those in the meta-analysis

| Tool                                                                 | Abbreviation | Scales                                                                 | Domains included in meta-analysis                                                                 |
|----------------------------------------------------------------------|--------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| A-not-B task                                                         | A-not-B      | Object permanence; early executive                                   |                                                                                                  |
| Alarm Distress Baby Scale                                           | ADDB         | Socioemotional state                                                 |                                                                                                  |
| Ages & Stages Questionnaire                                         | ASQ          | Cognitive, language, motor,                                          |                                                                                                  |
| Bayley Infant Neurodevelopmental Screener                           | BINS         | Risk for developmental delay                                          |                                                                                                  |
| Bayley Scales of Infant & Toddler Development, 2nd edition          | BSID-II      | Mental & psychomotor development                                      |                                                                                                  |
| Bayley Scales of Infant & Toddler Development, 3rd edition          | BSID-III     | Cognitive, receptive language, expressive language, fine motor,      | Cognitive, receptive language, expressive language, fine motor, gross motor, social-emotional,    |
|                                                                     |              | gross motor, social-emotional,                                        |                                                                                                  |
| Beery-Buktenica developmental tests of Visual Motor Integration     | VMI          | Visual perception, motor, and hand-eye coordination                   |                                                                                                  |
| Capute Scales Clinical Adaptive Test: Cognitive Adaptive Test        | CAT          | Cognition, visual-motor                                              |                                                                                                  |
| Capute Clinical Linguistic and Auditory Milestone Scales            | CLAMS        | Language and nonverbal problem-solving skills                         |                                                                                                  |
| Denver Developmental Screening Test                                 | DDST         | Gross motor, language, fine motor, adaptive, and personal-social,    |                                                                                                  |
| Development Assessment Scale for Indian Infants                     | DASII        | Motor and mental scales                                              |                                                                                                  |
| Developmental Milestones Checklist                                  | DMC          | Locomotor, fine motor, language, personal-social                      |                                                                                                  |
| Dubowitz Neonatal Neurobehavioral Tool                              | DNNT         | Neurobehaviour and neurological                                       |                                                                                                  |
| Full-Scale Developmental Quotient                                   | FSDQ         | Cognition, Language, Social                                           |                                                                                                  |
| Goldman-Fristoe Test of Articulation                                | GFTA         | Language                                                              |                                                                                                  |
| Griffiths Mental Development Scales                                 | GMDS         | Locomotor, personal-social, hearing & language, eye & hand coordination, performance |                                                                                                  |
| Head circumference-for-age z score or Occipital frontal circumference| HCAZ or OFC  |                                                                      |                                                                                                  |
| Kaufman Assessment Battery for Children, 2nd edition                | KABC-II      | Simultaneous, sequential, learning, planning, knowledge               |                                                                                                  |
| MacArthur-Bates Communicative Developmental Inventories             | CDI          | Language by parent report                                             | CDI vocabulary used for expressive language per correspondence with expert                         |
| Malawi Developmental Assessment Tool                                | MDAT         | Total score, gross motor, fine motor, language, social               | Total score, gross motor, fine motor, language - MDAT language used for receptive language per correspondence with expert; total score used to represent cognitive development |
| Mullen Scales of Early Learning                                     | MSEL         | Visual reception, fine motor, gross motor, receptive and expressive    | Fine motor, gross motor, receptive and expressive language, composite - Early learning composite used to represent cognitive development |
|                                                                     |              | language, composite                                                  |                                                                                                  |
| Peabody Developmental Motor Scales                                  | PDMS         | Motor                                                                 |                                                                                                  |
| Peabody Picture Vocabulary Test                                     | PPVT         | Language                                                              |                                                                                                  |
| Personal, social and emotional development                          | PSED         | Social-emotional development                                          |                                                                                                  |
| Rossetti Infant-Toddler Language Scale                              | RITLS        | Language                                                              |                                                                                                  |
| Strengths and Difficulties Questionnaire                            | SDQ          | Socio-emotional                                                       |                                                                                                  |
| Snijders-Oomen Nonverbal Intelligence Test                          | SONR         | Intelligence                                                          |                                                                                                  |
| Test of early language development                                  | TELD         | Receptive and expressive language                                     |                                                                                                  |
| Vineland Adaptive Behaviour Scales                                   | VABS         | Daily living, socialization, communication, motor                     |                                                                                                  |
| WHO Milestones Chart                                                | Milestones   | Motor, language                                                       |                                                                                                  |
| Wechsler Preschool and Primary Scales of Intelligence               | WPPSI        | Verbal IQ, Performance IQ, Full Scale IQ and General Language         |                                                                                                  |
Appendix: Quality assessment and risk of bias of studies comparing HEU and HU children

| Study authors          | Year   | 1. Objective stated | 2. Study population defined and representative* | 3. Participation rate is >50%* | 4. Control subjects are from the same community* | 5a. Sample size calculation | 5b. Sample size >50 subjects per group | 6. Exposure is measured before outcome# | 7. Timeframe is sufficient to see the exposure effects# | 8. Additional analyses performed (ART/VL/CD4) | 9. A valid HIV test is used in mothers | 10. A valid HIV test is used in children | 11. Valid neurodevelopment tests are used in children** | 12. Assessors are blinded to child HIV exposure status** | 13. Lost to follow up is <20%^ | 14. Potential confounders adjusted for (or matched)# | Quality assessment |
|------------------------|--------|---------------------|-----------------------------------------------|-------------------------------|-----------------------------------------------|------------------------------|-------------------------------------------|---------------------------------------------|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------------------------------|-----------------------------------|------------------------------------------|
| Alimenti et al.        | 2006   | ✓                   | ✓                                             | ✓                             | X                                             | ✓                            | ✓                                         | X                                           | X                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | X                                               | FAIR |
| Boivin et al.          | 2016   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| Boivin et al.          | 2019   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | GOOD |
| Brahmbhatt et al.      | 2014   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | GOOD |
| Chaudhary et al.       | 2017   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| da Silva et al.        | 2017   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | POOR |
| Familiar et al.        | 2018   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | GOOD |
| Gomez et al.           | 2009   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | POOR |
| Kandawasvika et al.    | 2011   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| Landes et al.          | 2012   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | POOR |
| Laughton et al.        | 2012   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| Laughton et al.        | 2018   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| le Roux et al.         | 2018   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | GOOD |
| Ngoma et al.           | 2014   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| Ntozini et al.         | 2020   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | GOOD |
| Sirois et al.          | 2013   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | GOOD |
| Springer et al.        | 2012   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| Springer et al.        | 2018   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| Springer et al.        | 2020   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| Struyf et al.          | 2019   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |
| van Rie et al.         | 2008   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | NOT APPLICABLE |
| van Rie et al.         | 2009   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | NOT APPLICABLE |
| Wedderburn et al.      | 2019   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | GOOD |
| Wu et al.              | 2019   | ✓                   | ✓                                             | ✓                             | ✓                                             | ✓                            | ✓                                         | ✓                                           | ✓                                          | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | ✓                                             | FAIR |

✓ Yes; X No; ✂ Not reported / Not documented / Cannot determine; NA: not applicable; ART: antiretroviral therapy; VL: viral load; CD4: CD4 cell count.

Types of bias: *Selection bias; **Information bias; *Attrition bias; #Confounding
## S10 Appendix: Characteristics of studies of HEU children comparing different maternal ART regimens

| Author, year of publication | Country (time period) | Study design | Child age | Tool | Last HIV test (age) | Maternal ART regimen | Maternal ART regimen | Maternal ART regimen/control | Infant PNP (duration) | Breast-feeding | Confounders included in adjusted analysis |
|-----------------------------|-----------------------|--------------|-----------|------|---------------------|----------------------|----------------------|--------------------------|------------------------|--------------|-----------------------------------------|
| Alcaide et al., 2019*       | South Africa (2015 – 2018) | CS           | 9 to 20 m | BSID-III | PCR from DBS (12m) | Triple therapy, EFV/TDF/FTC detectable at 32 weeks' gestation (66) | Triple therapy, EFV/TDF/FTC undetectable (14) | - | ND | ND | Intimate partner violence, maternal depression. |
| Boivin et al., 2019*        | Malawi and Uganda (2013 – 2014) | Cohort/RCT | 12m, 2, 4 & 5yr | MSEL | PCR (12, 24 m) | Group 1 & 2 Antenatal triple ART (PI-based) + postnatal triple ART or infant NVP (93 / 103) | Groups 3 & 4 Antenatal AZT monotherapy + postnatal triple ART or infant NVP (88 / 80) | HU (374) | See groups | Yes | Data collection site. 
Note: PI-based regimen: LPV/r + 3TC + AZT or LPV/r + FTC + TDF |
| Caniglia et al., 2016* SMARTT | USA & Puerto Rico (2006 – 2013) | Cohort | 9 to 15m | BSID-III | OFC | ART: ATV-based 1st trimester 2nd/3rd trimester | ART: no ATV 1st trimester 2nd/3rd trimester | - | ND | ND | Maternal education, CD4, HIV RNA, year, illicit substances, alcohol, tobacco, race, ethnicity, primary language, household income, age, Full Scale IQ, STI, LBW, GA. |
| Cassidy et al., 2019* Tshipidi plus (Mpepu; Mma Bana; Tshipidi) | Botswana (2016 – 2017) | Cohort | 2yr | BSID-III | DMC | Per individual cohort | Triple therapy, EFV/TDF/FTC (126) | Triple therapy, non-EFV multiple (367) | - | ND | ND | Child age, sex, feeding method, in utero ART initial exposure timing, maternal age, employment, income, marital status, indoor faucet, electricity, indoor toilet. Sensitivity analyses: Preterm birth, LBW. |
| Chaudhury et al., 2018* Mma Bana | Botswana (2006 – 2008) | Cohort & RCT | 2yr | BSID-III | DMC | PCR at birth, 1, 6, 12 months, ELISA (>18mo) | ART: multiple regimens (382) | AZT monotherapy (210) | - | NVP (single dose) and AZT (1m) | ART 71.5% AZT 8.1% | Maternal age, education, income, CD4 cell count, year of neurodevelopmental testing. Sensitivity analysis restricted to formula fed infants from one cohort. Prematurity & birthweight examined in sensitivity analyses. |
| Familiar et al., 2018* Tshipidi | Uganda (2012 – 2015) | Cohort | 6 & 12m | MSEL | DBS PCR | ART: multiple regimens (57) | No therapy (18) | HU (140) | Not specified | Yes | Child age and sex, maternal age, education level, marital status, HOME, SES, social support and depression. |
| Kacanek et al., 2018* Mma Bana | Botswana (2006 – 2008) | CS/RCT | 2yr | BSID-III | DMC | Per study: birth, 1m, 6m PCR | Triple NRTI ABC/AZT/3TC (101) | Dual NRTI+PI LVP/r / AZT/3TC (96) | - | NVP (single dose) and AZT (1m) | Yes | Low maternal body mass index at follow-up, child age, access to electricity in the home; GA at enrolment. Randomised from 26-34w gestation. |
| Rajan et al., 2017* | India (2013 – 2015) | Cohort | 6-18 m (assessed at enrolment, 3m, 6m) | DASH | PCR (6 wks, 6 m, and 12 wks after breast feeding); Serology at 18 m | ART (31) | No ART (10) | - | NVP (single dose n=80), NVP (6 wks, n=30), none (n=3) | ND | - |
Abbreviations | ND: not documented; HEU: children who are HIV-exposed and uninfected; HU: children who are HIV-unexposed; CS: cross-sectional study; LG: longitudinal study; RCT: randomized controlled trial; yr: year; m: months; wks: weeks; PCR: HIV polymerase chain reaction test; DBS: Dried blood spot; ART: antiretroviral treatment; PNP: postnatal prophylaxis; AZT: zidovudine; 3TC: lamivudine; NVP: nevirapine; LPV/r: lopinavir/ritonavir; TDF: tenofovir; FTC: emtricitabine; EFV: efavirenz; ATV: atazanavir; ABC: abacavir; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; cART: combination ART; PMTCT: prevention of mother-to-child transmission; FF: formula feeding; NP: neonatal period; WAZ: weight for age; LBW: low birth weight; SES: socioeconomic status; GA: Gestational age; STI: sexually transmitted infection; All assessment tool abbreviations are listed in S8 Appendix.

*Also in HEU v. HU analysis
## S11 Appendix: Characteristics of studies examining head circumference and neuroimaging

| Author, year of publication | Country (time period) | Study design | Child age | N HEU | N HU | HIV test in HEU children (age) | Maternal ART (%) | Maternal ART regimen | Infant PNP (duration) | Breast-feeding status | Confounders included in adjusted analysis |
|----------------------------|-----------------------|--------------|-----------|-------|------|-------------------------------|-----------------|---------------------|----------------------|----------------------|------------------------------------------|
| Aim 1: HEU children versus HU children - Head circumference |
| Donald et al., 2017**6 | South Africa (2012 – 2015) | Cohort | Neonatal period | 131 | 536 | PCR at 6 weeks, PCR/Ab (9m/18m) | 100% | Triple ART or AZT monotherapy | NPV or NVP + AZT | ND | Socioeconomic status, depression, smoking, alcohol use in interaction variables (HIV by alcohol use and HIV by smoking status). |
| Le Roux et al., 2019**7 | South Africa (2013 – 2016) | Cohort | Birth to 1yr (0, 3m, 6m, 9m, 12m) | 461 | 411 | PCR at 6 weeks and 48 weeks. | 100% | Triple therapy | ND | Yes | Age-adjusted, sex-adjusted and gestation-adjusted z-scores. Socioeconomic factors, risky drinking, intimate partner violence, recent childhood illness, and infant feeding) with and without adjustment for birth outcomes. |
| Jumare et al., 2019**8 | Nigeria (2013 – 2017) | Cohort | Birth to 18m | 297 | 103 | PCR at birth, 3-4wks, 6wks, 1yr or 6wks postbreastfeeding | 100% | Triple therapy | NVP (6w) | Yes | WHO standard z-scores. Maternal education, marital status, breastfeeding, prematurity, maternal weight and baseline Z-score. |
| Gomez et al., 2009**10 | Colombia (not reported) | LG | Birth to 2yrs (0, 3, 6m, 9m, 12m, 18m, 2y) | 23 | 20 | ELISA (18m) | 100% | Triple therapy, multiple | ND | ND | - |
| Filleau et al., 2011**11 | Zambia (2005 – 2009) | RCT | 6m to 2 yrs | 125 | 382 | Ab testing at 18m | ND | NVP | NVP | HEU 42%, HU 97% | - (Only baseline characteristics included here) |
| Neri et al., 2013**16 | USA (2006 – 2009) | LG | 2w to 2yrs (mean age 10m) | 111 (82 in matched group) | 82 | PCR first 6 m, Ab after 12m | 90% | Triple therapy | AZT (6w) | ND | Age, sex, race. |
| Springer et al., 2018**20 | South Africa (2012 – 2013) | Cohort | 12m (11-14) | 58 | 38 | ELISA with PCR if positive (12m) | 50% | cART | AZT | ND | HEU no (12%), HU yes (66% at 6 months) |
| Aizire et al., 2020**21 | Malawi and Uganda (2013 – 2014) | Cohort | 1 to 2yrs (1yr, 2yr) | 471 | 462 | Documentation of uninfected status | 54% | Triple therapy | AZT | NVP in some | HEU Yes, HU Yes. HU>HEU |
| Laughton et al., 2012**13 | South Africa (2005 – 2006) | Cohort | 11m (10-16m) 11.5m HEU 11.5m HU) | 28 | 34 | HEU: PCR at baseline and 1 month after PCV 3rd dose (12-24wks). | ND | NVP and AZT | ND. Likely NVP and AZT | ND | Breastfeeding status, maternal age, electricity/gas use and tap-water use. |
| Springer et al., 2012**19 | South Africa (2009) | CS | 17 to 19m | 17 | 20 | PCR (2, 6 & 12wks) | 94% | PMTCT prophylaxis or cARV | ND | HEU no, HU yes |
| Springer et al., 2020**21 | South Africa (2012 – 2013) | Cohort | 2 to 3yr (30 to 42m) | 32 | 27 | ELISA with PCR if positive (12m) | 40.6% | cART | AZT | HEU low (9%), HU (67%) at 6 months | - |
### Aim 1: HEU children versus HU children - Neuroimaging

| Tran et al., 2016<sup>52</sup> | South Africa (2012 – 2015) | Cohort | Neonatal period | 15 | 22 | PCR at 6 weeks, PCR/Ab (9m/18m) | 100% | Triple ART | NVP / NVP & AZT | ND | Neonatal postnatal age and infant sex. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| DCHS South Africa (2012 – 2015) Cohort | Neonatal period | 15 | 22 | PCR at 6 weeks, PCR/Ab (9m/18m) | 100% | Triple ART | NVP / NVP & AZT | ND | Neonatal postnatal age and infant sex. |

### Aim 2: ART analyses - Head circumference

| Spaulding et al., 2016<sup>63</sup> | Latin America and Caribbean (2002 – 2009) | Cohort | Birth to 6m (0-3m, 6m) | 1400 Multiple ART | 67% | PI + 2 NRTIs | AZT | ND; likely none |
|---|---|---|---|---|---|---|---|---|
| Latin America and Caribbean (2002 – 2009) Cohort | Birth to 6m (0-3m, 6m) | 1400 Multiple ART | 67% | PI + 2 NRTIs | AZT | ND; likely none |

| Pintye et al., 2015<sup>44</sup> | Kenya (2013) | CS | 6w and 9m | TDF+ 51 TDF- 104 PCR testing | 100% | Triple therapy, multiple | ND | Yes |
|---|---|---|---|---|---|---|---|---|
| Kenya (2013) CS | 6w and 9m | TDF+ 51 TDF- 104 PCR testing | 100% | Triple therapy, multiple | ND | Yes |

| Siberry et al., 2012<sup>55</sup> SMARTT | USA (2005-2010) | Cohort | Birth and 1yr | TDF+ 274 209 TDF- 416 361 | 100% | Triple therapy, multiple | ND | No |
|---|---|---|---|---|---|---|---|---|
| USA (2005-2010) Cohort | Birth and 1yr | TDF+ 274 209 TDF- 416 361 | 100% | Triple therapy, multiple | ND | No |

| Caniglia et al., 2016<sup>56</sup> SMARTT | USA & Puerto Rico (2006 – 2013) | Cohort | 1yr | ART: ATV+ 480 297 ART: ATV+ 601 393 | ND | 100% | ART, multiple | ND | ND |
|---|---|---|---|---|---|---|---|---|---|
| USA & Puerto Rico (2006 – 2013) Cohort | 1yr | ART: ATV+ 480 297 ART: ATV+ 601 393 | ND | 100% | ART, multiple | ND | ND |

| Jacobson et al., 2017<sup>56</sup> SMARTT | USA & Puerto Rico (2007 – 2011) | Cohort | 2yr | 509 Multiple ART | 100% | Triple therapy, multiple | ND | ND |
|---|---|---|---|---|---|---|---|---|
| USA & Puerto Rico (2007 – 2011) Cohort | 2yr | 509 Multiple ART | 100% | Triple therapy, multiple | ND | ND |

| Williams et al., 2020<sup>77</sup> SMARTT | USA & Puerto Rico (2007 – 2017) | Cohort | Birth to 5yrs | 3055 Multiple ART | 141 2842 | EFV+ non-EFV+ Multiple combinations assessed | ND | ND |
|---|---|---|---|---|---|---|---|---|
| USA & Puerto Rico (2007 – 2017) Cohort | Birth to 5yrs | 3055 Multiple ART | 141 2842 | EFV+ non-EFV+ Multiple combinations assessed | ND | ND |

**Abbreviations** | ART: antiretroviral treatment; AZT: zidovudine; EFV: efavirenz; TDF: tenofovir; NVP: nevirapine; 3TC: lamivudine; FTC: emtricitabine; cART: combination ART; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; BF: breastfeeding; NP: neonatal period; PNP: postnatal prophylaxis; HEU: Children who are HIV-exposed and uninfected; HU: Children who are HIV-unexposed; CS: cross-sectional study; LG: longitudinal study; RCT: randomized controlled trial; HCAZ: head-circumference-for-age z-score; ND: not documented
References:

1. WHO. New data on the prevention of mother-to-child transmission of HIV and their policy implications: conclusions and recommendations: WHO Technical consultation on behalf of the UNFPA/UNICEF/WHO/UNAIDS Inter-Agency Task Team on Mother-to-Child Transmission of HIV. Geneva, 2001.

2. Villagomez AN, Munoz FM, Peterson RL, et al. Neurodevelopmental delay: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2019; 37(52): 7623-41.

3. Alimenti A, Forbes JC, Oberlander TF, et al. A prospective controlled study of neurodevelopment in HIV-uninfected children exposed to combination antiretroviral drugs in pregnancy. *Pediatrics* 2006; 118(4): e1139-45.

4. Boivin MJ, Sikorskii A, Familiar-Lopez I, et al. Malaria illness mediated by anaemia lessens cognitive development in younger Ugandan children. *Malar J* 2016; 15: 210.

5. Boivin MJ, Maliwichi-Senganimalanje L, Ogwang LW, et al. Neurodevelopmental effects of ante-partum and post-partum antiretroviral exposure in HIV-exposed and uninfected children versus HIV-unexposed and uninfected children in Uganda and Malawi: a prospective cohort study. *The lancet HIV* 2019; 6(8): e518-e30.

6. Brahmbhatt H, Boivin M, Ssemija V, et al. Neurodevelopmental benefits of antiretroviral therapy in Ugandan children aged 0-6 years with HIV. *Journal of acquired immune deficiency syndromes* 2014; 67(3): 316-22.

7. Chaudhury S, Williams PL, Mayondi GK, et al. Neurodevelopment of HIV-Exposed and HIV-Unexposed Uninfected Children at 24 Months. *Pediatrics* 2017; 140(4).

8. da Silva KM, de Sa CD, Carvalho R. Evaluation of motor and cognitive development among infants exposed to HIV. *Early Hum Dev* 2017; 105: 7-10.

9. Familiar I, Collins SM, Sikorskii A, et al. Quality of Caregiving is Positively Associated With Neurodevelopment During the First Year of Life Among HIV-Exposed Uninfected Children in Uganda. *Journal of acquired immune deficiency syndromes* 2018; 77(3): 235-42.

10. Gomez C, Archila ME, Rugeles C, Carrizosa J, Rugeles MT, Cornejo JW. [A prospective study of neurodevelopment of uninfected children born to human immunodeficiency virus type 1 positive mothers]. *Revista de neurologia* 2009; 48(6): 287-91.

11. Kandawasvika QQ, Ogundipe E, Gumbo FZ, Kurewa EN, Mapingure MP, Stray-Pedersen B. Neurodevelopmental impairment among infants born to mothers infected with human immunodeficiency virus and uninfected mothers from three peri-urban mothers primary care clinics in Harare, Zimbabwe. *Developmental medicine and child neurology* 2011; 53(11): 1046-52.

12. Landes M, van Lettow M, Chan AK, Mayuni I, Schouten EJ, Bedell RA. Mortality and health outcomes of HIV-exposed and unexposed children in a PMTCT cohort in Malawi. *PloS one* 2012; 7(10): e47337.

13. Laughton B, Cornell M, Grove D, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. *Aids* 2012; 26(13): 1685-90.

14. Laughton B, Cornell M, Kidd M, et al. Five year neurodevelopment outcomes of perinatally HIV-infected children on early limited or deferred continuous antiretroviral therapy. *Journal of the International AIDS Society* 2018; 21(5): e25106.

15. le Roux SM, Donald KA, Brittain K, et al. Neurodevelopment of breastfed HIV-exposed uninfected and HIV-unexposed children in South Africa. *Aids* 2018; 32(13): 1781-91.

16. Ngoma MS, Hunter JA, Harper JA, et al. Cognitive and language outcomes in HIV-uninfected infants exposed to combined antiretroviral therapy in utero and through extended breast-feeding. *Aids* 2014; 28 Suppl 3: S323-30.

17. Ntozini R, Chandna J, Evans C, et al. Early child development in children who are HIV-exposed uninfected compared to children who are HIV-unexposed: observational sub-study of a cluster-randomized trial in rural Zimbabwe. *Journal of the International AIDS Society* 2020; 23(5): e25456.

18. Sirois PA, Hsiao Y, Williams PL, et al. Safety of perinatal exposure to antiretroviral medications: developmental outcomes in infants. *The Pediatric infectious disease journal* 2013; 32(6): 648-55.

19. Springer P, Laughton B, Tomlinson M, Harvey J, Esser M. Neurodevelopmental status of HIV-exposed but uninfected children: A pilot study. *SAJCH South African Journal of Child Health* 2012; 6(2): 51-5.

20. Springer PE, Slogrove AL, Laughton B, et al. Neurodevelopmental outcome of HIV-exposed but uninfected infants in the Mother and Infants Health Study, Cape Town, South Africa. *Tropical medicine & international health* 2018; 23(1): 69-78.

21. Springer PE, Slogrove AL, Kidd M, et al. Neurodevelopmental and behavioural outcomes of HIV-exposed uninfected and HIV-unexposed children at 2-3 years of age in Cape Town, South Africa. *AIDS care* 2020; 32(4): 411-9.

22. Struyf T, Dube Q, Cromwell EA, Sheahan AD, Heyderman RS, Van Rie A. The effect of HIV infection and exposure on cognitive development in the first two years of life in Malawi. *European journal of paediatric neurology* 2020; 25: 157-64.
23. Van Rie A, Mupuala A, Dow A. Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in Kinshasa, Democratic Republic of the Congo. *Pediatrics* 2006; **122**(1): e123-8.
24. Van Rie A, Dow A, Mupuala A, Stewart P. Neurodevelopmental trajectory of HIV-infected children accessing care in Kinshasa, Democratic Republic of Congo. *Journal of acquired immune deficiency syndromes* 2009; **52**(5): 636-42.
25. Wedderburn CJ, Yeung S, Rehan AM, et al. Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort study. *Lancet Child Adolesc Health* 2019; **3**(11): 803-13.
26. Wu J, Li J, Li Y, et al. Neurodevelopmental outcomes in young children born to HIV-positive mothers in rural Yunnan, China. *Pediatr Int* 2018; **60**(7): 618-25.
27. Alcaide ML, Rodriguez VJ, Abbamonte JM, et al. Maternal Factors Associated With Infant Neurodevelopment in HIV-Exposed Uninfected Infants. *Open forum infectious diseases* 2019; **6**(10): ofz351.
28. Caniglia EC, Patel K, Huo Y, et al. Atazanavir exposure in utero and neurodevelopment in infants: a comparative safety study. *Aids* 2016; **30**(8): 1267-78.
29. Cassidy AR, Williams PL, Leidner J, et al. In Utero Efavirenz Exposure and Neurodevelopmental Outcomes in HIV-exposed Uninfected Children in Botswana. *The Pediatric infectious disease journal* 2019; **38**(8): 828-34.
30. Chaudhury S, Mayondi GK, Williams PL, et al. In-utero exposure to antiretrovirals and neurodevelopment among HIV-exposed-uninfected children in Botswana. *Aids* 2018; **32**(9): 1173-83.
31. Kacanek D, Williams PL, Mayondi G, et al. Pediatric Neurodevelopmental Functioning After In Utero Exposure to Triple-NRTI vs. Dual-NRTI + PI ART in a Randomized Trial, Botswana. *Journal of acquired immune deficiency syndromes* 2018; **79**(3): e93-e100.
32. Rajan R, Seth A, Mukherjee SB, Chandra J. Development assessment of HIV exposed children aged 6-18 months: a cohort study from North India. *AIDS care* 2017; **29**(11): 1404-9.
33. Rice ML, Zeldow B, Siberry GK, et al. Evaluation of risk for late language emergence after in utero antiretroviral drug exposure in HIV-exposed uninfected infants. *The Pediatric infectious disease journal* 2013; **32**(10): e406-13.
34. Rice ML, Russell JS, Frederick T, et al. Risk for Speech and Language Impairments in Preschool Age HIV-exposed Uninfected Children With In Utero Combination Antiretroviral Exposure. *The Pediatric infectious disease journal* 2018; **37**(7): 678-85.
35. Smith ML, Puka K, Sehra R, Read SE, Bitmum A. Longitudinal development of cognitive, visuomotor and adaptive behavior skills in HIV uninfected children, aged 3-5 years of age, exposed pre- and perinatally to anti-retroviral medications. *Aids care* 2017; **29**(10): 1302-8.
36. Donald KAM, Fernandez A, Claborn K, et al. The developmental effects of HIV and alcohol: a comparison of gestational outcomes among babies from South African communities with high prevalence of HIV and alcohol use. *AIDS research and therapy* 2017; **14**(1): 28.
37. le Roux SM, Abrams EJ, Donald KA, et al. Growth trajectories of breastfed HIV-exposed uninfected and HIV-unexposed children under conditions of universal maternal antiretroviral therapy: a prospective study. *Lancet Child Adolesc Health* 2019; **3**(4): 234-44.
38. Jumare J, Datong P, Osawe S, Okolo F, Inyang B, Abimiku A. Compromised growth among HIV exposed compared to unexposed children in Nigeria. *Journal of acquired immune deficiency syndromes* 2019; **81**(Supplement 1): 68.
39. Filteau S, Baisley K, Chisenga M, Kasonka L, Gibson RS, Team CS. Provision of micronutrient-fortified food from 6 months of age does not permit HIV-exposed uninfected Zambian children to catch up in growth to HIV-unexposed children: a randomized controlled trial. *Journal of acquired immune deficiency syndromes* 2011; **56**(2): 166-75.
40. Neri D, Somarrriba GA, Schaefer NN, et al. Growth and body composition of uninfected children exposed to human immunodeficiency virus: comparison with a contemporary cohort and United States National Standards. *The Journal of pediatrics* 2013; **163**(1): 249-54 e1-2.
41. Aizire J, Sikorskii A, Ogwang LW, et al. Decreased growth among antiretroviral drug and HIV-exposed uninfected versus unexposed children in Malawi and Uganda. *Aids* 2020; **34**(2): 215-25.
42. Tran LT, Roos A, Fouche JP, et al. White Matter Microstructural Integrity and Neurobehavioral Outcome of HIV-Exposed Uninfected Neonates. *Medicine (Baltimore)* 2016; **95**(4): e2577.
43. Spaulding AB, Yu Q, Civitello L, et al. Neurologic Outcomes in HIV-Exposed/Uninfected Infants Exposed to Antiretroviral Drugs During Pregnancy in Latin America and the Caribbean. *AIDS research and human retroviruses* 2016; **32**(4): 349-56.
44. Pintye J, Langat A, Singa B, et al. Maternal Tenofovir Disoproxil Fumarate Use in Pregnancy and Growth Outcomes among HIV-Exposed Uninfected Infants in Kenya. *Infect Dis Obstet Gynecol* 2015; **2015**(276851): 276851.
45. Siberry GK, Williams PL, Mendez H, et al. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. *Aids* 2012; **26**(9): 1151-9.
46. Jacobson DL, Kunjal P, Williams PL, et al. Growth at 2 years of age in HIV-exposed uninfected children in the United States by trimester of maternal antiretroviral initiation. *Pediatric Infectious Disease Journal* 2017; 36(2): 189-97.

47. Williams PL, Yildirim C, Chadwick EG, et al. Association of maternal antiretroviral use with microcephaly in children who are HIV-exposed but uninfected (SMARTT): a prospective cohort study. *The Lancet HIV* 2020; 7(1): e49-e58.