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Growth, Neurodevelopment and Birth Defects of Human Immunodeficiency Virus Exposed and Uninfected Children: A Systematic Review

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Growth, Neurodevelopment and Birth Defects of Human Immunodeficiency Virus Exposed and Uninfected Children: A Systematic Review

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Abstract

Human Immunodeficiency Virus (HIV) infection is a widespread disease that afflicts millions of people worldwide including 1,7 million children.[1] This number has been declining due to prevention of mother-to-child transmission (MTCT) through antiretroviral (ARV) treatment. This resulted in an increasing number of HIV uninfected children exposed *in utero* to the virus and ARV. These interactions which may influence these children's health and development are a matter of current scientific research.

This study aims to do a systematic review of literature in the search engine PubMed published between the beginning of January 2010 and the end of March 2020 regarding Growth, Neurodevelopment and Birth Defects among HIV exposed uninfected (HEU) children. The articles were included if they compared HEU children against standard values or HIV unexposed uninfected (HUU) children.

Birth defects had a prevalence from 4,5% to 6,8% in HEU children. Highly active ARV (HAART) or protease inhibitor (PI) regimens were associated with higher risk for birth defects.

Z-scores at birth were generally lower in HEU children when compared to HUU children. Zidovudine exposure was associated with higher scores than triple ARV exposure.

The analyses regarding preschool age z-scores are contradictory, however it was found that in most studies HEU children had lower weight-for-age z-score (WAZ) and were more often underweight than HUU children. Length-for-age z-score (LAZ) were either similar between the two groups or HEU children had lower scores. Both groups were similarly stunted, wasted, and had similar weight-for-length z-score (WLZ).

Numerous confounders influenced z-scores, some were consensual such as male sex and having siblings which were associated with lower WAZ and LAZ scores, but others such as feeding methods had contradictory results. Lower maternal education and lower birth weight were linked to an increase risk of underweight and stunting. Low birth weight was also related to an increased risk of wasting and lower WLZ scores. Regarding ARV exposure several studies agreed that the type of regimen the mother was under did not influence WAZ and LAZ/HAZ trajectory as well as risk of stunting or wasting.

The majority of the studies found similar neurodevelopment between HEU and HUU children. Lower maternal education was frequently discovered as a risk for lower neurodevelopment scores while lower maternal CD4+ count was not associated with neurodevelopment scores. Type of ARV regimen was either not associated or associated with higher neurodevelopment scores.

The literature reviewed does not present conclusive evidence associating adverse results with HIV or ARV exposure, even though some studies are conflicting. Most of the literature do not

follow the children into adolescence. As the number of HEU children is rising, it is crucial to evaluate their long-term development. Studies with longer follow-ups of these patients are needed.

Keywords: “HIV”, “HIV exposed uninfected”, “Children”, “Growth”, “Neurodevelopment”, “Birth Defects”

Resumo

A infeção pelo Vírus da Imunodeficiência Humana (VIH) é uma doença globalizada que atinge milhões de pessoas em todo o mundo, incluindo 1,7 milhões de crianças.[1] Este número tem vindo a diminuir devido à prevenção da transmissão de mãe para filho (MTCT) através de tratamentos com antirretrovirais (ARV). Isto resultou num aumento do número de crianças não infetadas pelo VIH mas expostas *in utero* ao vírus e a ARV. Existe um interesse científico crescente para compreender de que forma estas interações podem influenciar a saúde e o desenvolvimento destas crianças.

Este estudo pretende fazer uma revisão sistemática da literatura publicada no motor de busca PubMed entre o início de janeiro de 2010 e o final de março de 2020 sobre Crescimento, Neurodesenvolvimento e Defeitos Congénitos em crianças expostas, não infetadas por VIH (HEU). Os artigos foram incluídos caso comparassem crianças HEU com valores-padrão ou crianças não expostas nem infetadas por VIH (HUU).

Defeitos congénitos apresentaram-se com uma prevalência entre 4,5% e 6,8% em crianças HEU. Regimes com ARV com alta eficácia (HAART) ou com inibidores da protéase (PI) foram associados a um risco aumentado para defeitos congénitos.

Os z-scores à nascença foram geralmente mais baixos nas crianças HEU do que nas crianças HUU. A exposição zidovudine foi associada a pontuações mais elevadas do que a exposição a terapia tripla com ARV.

Estudos relativos aos z-scores em idade pré-escolar não são consensuais, contudo verificou-se que, na maioria deles, as crianças HEU tinham menor "weight-for-age z-score" (WAZ) e tinham mais frequentemente baixo peso que as crianças HUU. Os resultados da "length-for-age z-score" (LAZ) eram semelhantes entre os dois grupos ou as crianças HEU tinham resultados mais baixos. Ambos os grupos apresentavam resultados semelhantes relativamente à baixa estatura, "wasting" e "weight-for-length z-score" (WLZ).

Numerosos confundidores influenciaram as z-scores, alguns eram consensuais como sexo masculino e ter irmãos que estavam associados a pontuações WAZ e LAZ mais baixas, mas outros, como a alimentação, tinham resultados contraditórios. Menor educação materna e menor peso à nascença foram associados a um risco aumentado de baixo peso e baixa estatura. O baixo peso à nascença foi também associado a um risco acrescido de "wasting" e menores valores de WLZ. Relativamente à exposição a ARV, vários estudos concordaram que o tipo de regime a que a mãe esteve exposta não influenciavam a trajetória de WAZ e LAZ/HAZ, assim como o risco de baixa estatura or "wasting".

A maioria dos estudos demonstraram que o neurodesenvolvimento das crianças HEU e HUU era semelhante. Baixa educação materna foi frequentemente apresentada como um risco

para níveis inferiores de neurodesenvolvimento enquanto que níveis mais baixos de CD4+ maternos não foram associados ao neurodesenvolvimento. O tipo de regime ARV ora não estava associado ao neurodesenvolvimento ora estava associado a valores mais elevados.

A revisão da literatura não apresenta provas conclusivas de resultados adversos associados à exposição ao VIH ou ARV, embora alguns estudos sejam contraditórios. A maioria da literatura não acompanha as crianças até à adolescência. Uma vez que o número de crianças HEU está a aumentar, é fundamental estudar o seu desenvolvimento a longo prazo. São necessários estudos com seguimento mais prolongado destes doentes.

Palavras-chave: *"HIV", "HIV exposed uninfected", "Children", "Growth", "Neurodevelopment", "Birth Defects"*

List of Abbreviations

AIDS – Acquired Immune Deficiency Syndrome
ARV – Antiretroviral
ASQ – Ages and Stages Questionnaire
ATV – Atazanavir
BMI-for-age – Body Mass Index-for-Age Z-scores
BSID – Bayley Scales of Infant Development
CDI – MacArthur-Bates Communicative Development Inventory Test
EFV – Efavirenz
HAART – Highly Active Antiretroviral Therapy
HEU – HIV Exposed Uninfected
HIV – Human Immunodeficiency Virus
HUU – HIV Unexposed Uninfected
IPV – Intimate Partner Violence
IQ – Intelligence Quotient
KABC-II – Kaufman Assessment Battery for Children second edition
LAZ/HAZ – Length/Height-for-Age Z-score
LLE – Late Language Emergence
LPV/r – Lopinavir + Ritonavir
MSEL – Mullen Scales of Early Learning
MTCT – Mother-to-Child Transmission
NNRTI – Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI – Nucleoside Reverse Transcriptase Inhibitors
PACTG 219/219C – Paediatric AIDS Clinical Trails Group
PI – Proteinase Inhibitors
SMARTT – Surveillance Monitoring for ART Toxicities
TDF – Tenofovir Disoproxil Fumarate
UNAIDS – Join United Nations Programme on HIV/AIDS
WAZ – Weight-for-Age Z-score
WHO – World Health Organization
WLZ/WHZ – Weight-for-Length/Height Z-score
ZDV – Zidovudine
3TC – Lamivudine

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Introduction

Since 1980, the Human Immunodeficiency Virus (HIV) infection and Acquired Immune Deficiency Syndrome (AIDS) have been an important public health issue. Several strategies have been implemented in order to decrease the number of new infections, which cause a decrease of new infections from around 2,8 million in 2000 to 1,7 million in 2018/2019 worldwide according to The Join United Nations Programme on HIV/AIDS (UNAIDS).[1,2]

Paediatric HIV infection incidence rates benefited greatly of such programmes, showing a decrease of 290 000 new cases per year in the last 19 years. An one important milestone was the prevention of mother-to-child transmission (MTCT) which, according to the "HIV/AIDS *Surveillance in Europe 2019 – 2018 data."* report, accounted to a decrease of 38% of paediatric cases from this mode of transmission from 2009 to 2018 (Figure 1).[2,3]

Vertical transmission can occur during pregnancy, delivery or in the post-partum period through breastfeeding; therefore, the prevention for MTCT needed to address all three to be successful. The eviction of breastfeeding and programmed caesarean sections helped decrease the prevalence of transmission, but the major strategy was the implementation of antiretroviral (ARV) treatment in pregnant women and women trying to conceive. [4]

As the implementation of ARV regimens in pregnancy has increased, a new population of HIV exposed but uninfected (HEU) children must be considered (Figure 2). New questions and concerns have arisen regarding the possible consequences of the exposure of HEU children to the virus and to ARV during pregnancy, especially since it is known that many ARV drugs cross the placenta and some have demonstrated mutagenic and carcinogenic effects in animal studies.[5,6,7] In order to take better care of mothers and to minimize the influence of *in utero* ARV in the foetuses, a growing amount of literature involving multiple domains such as birth defects, premature delivery, low birth weight (<2500g) and growth, neurodevelopment, morbidity and mortality, mental health disorders, mitochondrial toxicity, immunologic and hematologic abnormalities in HEU children, have been published.[8-14]

The published results have been contradictory since the analysis of HIV and ARV effects are difficult to assess due to different moments of diagnosis and initiation of the ARV, the adherence to the treatment and the diverse types of ARV on the market. Other factors contributing for these discrepancies might be the difficulty in adjusting for potential confounders such as socioeconomic status, ethnicity, alcohol, tobacco, and illicit drug use, maternal or obstetric comorbidities, maternal viral load and $CD4^+$-lymphocyte count. An example of the influence of some of these factors is demonstrated in a study carried out in Mukuru Slum, Kenya, which shown that not only the HIV exposure was associated to high risk of wasting, stunting and underweight, but also household composition, food aid and use of food supplements.[15]

This study aims to perform a systematic review of studies published after January 2010, focused on the analyses of the differences between the growth and neurodevelopment of HUE children and their HIV unexposed and uninfected (HUU) comparisons or equivalent, as well as the prevalence and type of birth defects. When available it is also important to consider the possibility of these alterations being connected to a specific ARV or category of ARV or any other variable such as maternal viral load.

Methodology

A structured PubMed search was performed throughout March and April of 2020. The search terms employed included “HEU” and “Birth Defects”, “Growth” or “Neurodevelopment”; “ARV” or “HIV Exposed Uninfected” and “Children” and “Birth Defects”, “Growth” or “Neurodevelopment”; “ARV” or “HAART” and “Exposed Uninfected Children”. 561 articles met the search criteria. Only original articles written in English or Portuguese published between 1 January 2010 and 1 April 2020 were included; duplicates were excluded.

Titles and abstracts were screened and analysed to capture potentially relevant studies containing references to HEU children exposed to ARV in utero, regardless of their ARV exposure postpartum, and their growth, neurodevelopment and/or presence of birth defects as a standalone or when compared with controlled groups of HUU children or any kind of standardised measure such as the World Health Organization Child Growth Standards. Publications comparing HEU children with infected children and children with unclear infection status were excluded, while publications comparing infected children with HEU and HUU children were accepted. Regarding the growth analysis, it was only considered manuscripts who used weight-for-age (WAZ), length/height-for-age (LAZ/HAZ) and weight-for-length/height (WLZ/WHZ) until 5 years old or Body Mass Index-for-age (BMI-for-age) z-scores according to the World Health Organization (WHO) Child Growth Standards. Studies addressing the presence of birth defects in HEU children were included when the HIV status was clear. This group of papers also needed to fulfil the Metropolitan Atlanta Congenital Defects Program modified to the Antiretroviral Pregnancy Registry criteria to have the most uniform results and minimize bias. Any articles where the entire population had a significant confounding factor, such as cytomegalovirus infection, were excluded. The remaining 97, were read in full to evaluate their eligibility. From the retrieved reference lists, additional researching was performed, allowing to scan for relevant publications initially missed by the structured search.

Additionally, reports and fact sheets from international organizations were also considered, such as WHO and UNAIDS, regarding HIV MTCT, HIV infection treatment in women trying to conceive, pregnant women or post-partum, epidemiology or targets regarding the transmission of the virus. The data was collected from the more recent reports available on the 1st April 2020.

Development

Birth Defects

The period in which a pregnant woman is exposed to a drug is instrumental to predict if there is a possibility of birth defects. Teratogenic risk is greatest during organogenesis, from the 18th to the 60th day after conception. However, even though the risk for profound structural abnormalities is less frequent in later exposure, ARV can, at any time, prove to be teratogenic, with central nervous system abnormalities being the most likely.[16]

Dolutegravir was not a first line drug for pregnant women according to the 2016 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection due to lack of evidence of its security. In 2019 a paper showed an association between dolutegravir and neural tube defects. However, it was not conclusive since HIV infected mothers exposed to dolutegravir also had other risk factors for neural tube defects such as a lack of folic acid supplementation. In the 2019 updated guidelines it remains as an alternative. Most recent data has shown a smaller prevalence of neural tube defects than the initial study, however it is still higher than other ARV. [17,18,19]

In a study conducted by *Williams et al.,* it was reported an overall prevalence birth defects in HEU children of 6,78 per 100 live births within Surveillance Monitoring for ART Toxicities (SMARTT) population[20], which is higher than in prior studies, including the Paediatric AIDS Clinical Trails Group (PACTG 219/219C), with a report of 5,4%[21], the International Maternal Paediatric Adolescent AIDS Clinical Trials Group protocol P1025 with 6%[22], and within the ANRS CO1/CO11 cohort with a 4,5% report of birth defects among HEU children[23]. (Table I)

Specific Birth Defects

Regarding affected systems, abnormalities in the musculoskeletal and cardiovascular systems were the defects more often found in the SMARTT population. The presence of musculoskeletal and skin defects was significantly associated with first-trimester exposure to atazanavir (ATV), to didanosine plus stavudine and ritonavir as a booster of ATV (Figure 3). This study was the first to associate ATV and musculoskeletal and skin abnormalities.[20] As for the cardiovascular defects, *Watts et al.* identified two cases of cardiomyopathy and a case of septal hypertrophy, which may be indicative of cardiomyopathy, among the HEU infants.[24] These findings support the importance of analysing birth defects in HEU children separated from HIV infected children since HIV infection alone is a known risk factor for cardiomyopathy in infants.[25]

Williams et al. also found male genital anomalies, like hypospadias and cryptorchidism, associated with first-trimester exposure to zidovudine (ZDV) and lamivudine (3TC). However, an

increased risk for birth defects was also observed in later trimester when used by themselves or combined.[20]

Confounders for Birth Defects

When accounting for potential confounding factors, demographic and socioeconomic characteristics in the SMARTT cohort showed no significant differences in the prevalence of birth defects, as well as higher maternal viral load (>1000 copies/mL), tobacco, alcohol, or any other drug. There was a higher number of children with birth defects being born by caesarean section and more cases of preterm deliveries; however, the increase in caesarean sections was expected since it might be the preferred option when a birth defects is suspected.[20]

ARV Influence in Birth Defects

When evaluated according to the exposure of ARV classes, children exposed to highly active ARV therapy (HAART), defined as those containing 3 or more ARVs from 2 or more drug classes, and to Proteinase Inhibitors (PI), in the SMARTT population, had higher prevalence of birth defects, 8,1% and 8,5% respectively, while unexposed children had a prevalence of 5,8%. In the nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) groups, only the association of didanosine with stavudine showed a higher prevalence with 8-fold higher odds.[20]

Focusing on the individual ARV therapy children exposed to ATV, lopinavir and ritonavir, when used as a booster (>99% of use), exhibited significantly higher birth defects when compared with the unexposed children with prevalence of 11.7% vs 6.2%, 9.4% vs 6.3% and 9.3% vs 5.8%. Combination of ATV plus ritonavir, Tenofovir Disoproxil Fumarate (TDF) or emtricitabine were associated with an increased risk of birth defects, whereas the association with ZDV or 3TC was not significant. Furthermore, the exposure to Lopinavir + Ritonavir (LPV/r) in the first trimester led to higher birth defects when compared to children unexposed to LPV/r in the first trimester, without any specific defect associated.[20]

Growth

The z-scores were considered according to WHO guidelines. They also defined other concepts which are important to understand in the context of this article. Underweight when weight-for-age z-score is less than 2 standard deviations of median; Stunting when height-for-age z-score is less than 2 standard deviations of median; Wasting when weight-for-height z-score less than 2 standard deviations of median. [26]

These concepts are important when evaluating growth patterns, considering that they reflect the children's wellbeing. Wasting and underweight indicate recent or acute nutrition shortages whilst stunting reflects chronic growth impairment.[27] A child's health can also be indirectly assessed through LAZ and WAZ scores. Lower LAZ and WAZ indicates poor health which may be addressed with early interventions, whereas higher WAZ are associated with greater chance of survival.[27,28]

At Birth

WAZ

HEU children had a statistically significant lower mean WAZ value at birth than HUU children.[29,30] Contradictory results were found by *Le Roux et al.,* with HEU and HUU children having not only similar birth WAZ results, as well as having results close to 0, meaning that they are close to the standard population mean WAZ values.[31] (Table II)

Term HEU children had higher WAZ at birth than preterm infants; female newborns had higher risk of having lower WAZ than males.[32] Analysing maternal factors, it was found that HEU newborns had lower mean birth WAZ when mothers had lower $CD4^+$ count and, these differences were significant when the $CD4^+$ count were <200 cells/mm^3.[28,32] Lower birth WAZ scores were also associated with reduce levels of third trimester vitamin D and older maternal age. [32,33]

Morden et al. found that at birth, HEU newborns from mothers with exposure to any ARV had higher birth WAZ than those not exposed, while in a Brazilian study, it was concluded that HEU children not exposed to ARV or with exposure after the first trimester had higher WAZ scores than those with exposure in the beginning of the pregnancy. These differences continued significant even after adjustment for confouders.[32,34]

In Botswana studies, comparing two different regimens, it was shown that HEU children exposed to HAART were significantly lighter than those from mothers under ZDV.[28,35] TDF concentrations in meconium were not associated with differences in WAZ.[36]

In Nigeria, the proportion of underweight HEU children at birth was 2,9%, which was not statistically significant when compared to the HUU group (0%).[29] Nevertheless a Danish cohort

found statistical significance, HEU newborns were more frequently underweight than the HUU comparison group.[30]

LAZ

HEU children had a statistically significant lower mean LAZ value at birth than HUU children.[29,30]

HEU newborns with low birth weight were found to have lower LAZ results at birth and low maternal vitamin D levels were also associated with lower birth LAZ.[33,37]

The exposure to ARV did not significantly interfere with LAZ scores at birth.[34] New-borns exposed to *in utero* ZDV were bigger than those exposed to HAART; however, in adjusted models this significant difference only prevailed for children from mothers with $CD4^+$ count $\geq$ 200 cells/mm^3.[28] *In utero* exposure to TDF was associated with LAZ scores, being similar to the WHO refence scores.[38] Correspondingly different TDF meconium concentrations were not associated with differences in LAZ.[36]

Moseholm et al. found no differences in the proportion of stunting between HEU and HUU newborns.[30] In a Nigerian study, it was demonstrated that stunting at birth was more prevalent in HEU than HUU newborns, with proportions of 32% and 17,9% respectively, this study had a higher incidence of stunting than a Kenyan study (13% of HEU).[29,39]

WLZ and BMI-for-age

HEU children did not have statistically significant different mean WLZ, BMI-for-age and wasting at birth than HUU Nigerian children.[29]

ZDV exposed newborns had higher birth WLZ, specially within mothers with $CD4^+$ count $\geq$ 200 cells/mm^3 whereas TDF meconium concentrations did not influence birth WLZ. [28,36]

Preschool-aged children

WAZ

Multiple investigations have shown statistical differences in WAZ mean between the HEU and the HUU children, with the exposed children having lower values[27,29,40,41,42] Nonetheless, no significant differences between HEU and HUU infants WAZ scores have also been found. [30,43,44] Contradictory results were found among 9 to 12-month-old Ethiopian infants, in which HEU children had significantly higher WAZ than the HUU comparison group.[45] (Table III)

It was also observed that both HUU and HEU groups had lower WAZ scores at 12 and 24 months when compared to the WHO population references, probably due to endemic child

undernutrition.[27,35] While there was another study who found normal mean z-scores which were attributed to the efficacy of nutrition intervention in Jamaica.[8]

WAZ values in HEU children were found to have a slightly descendent pattern up to 24 months of age.[46] The evolution of the WAZ from 1 to 6 weeks showed small differences between HEU and HUU infants and was similar from 6 to 16 weeks.[41] One study revealed that, at 6 weeks, WAZ scores had increased in both HEU and HUU infants, with the first scoring consistently lower than their HUU counterparts; the follow-up period also revealed that at 12 months old, both groups had WAZ scores above the standard mean.[31](Figure 4A) In HEU infants, although the WAZ values remained stable between 2 and 6 months, they started to improve after 10 months.[8]

Analysing risk factors, who may influence WAZ results, in several studies it was found that HEU children from mothers with lower education, lower maternal BMI 1-month postpartum, lower maternal height, low birth weight and small for gestational age, breastfeeding and longer breastfeeding practices, male sex and having two or more siblings had lower WAZ scores, as well as HEU children from anaemic mothers with haemoglobin levels lower than 10g/dl during pregnancy and preterm infants.[30,31,35,37,45] Maternal vitamin D in the last trimester did not influence WAZ score.[33]

Moreover, weight gain velocities were associated to different confounders. HEU children with lower birth WAZ presented a catch-up since they had a significant faster growth velocity than those born with a normal weight.[32] In contrast children from mothers with 2 or more children had higher birth WAZ, but had a significant slower increased in WAZ until around 6 months.[32] Other factors associated with faster increase in WAZ was formula feeding instead of breastfeeding and being female.[32,45] Contrasting results were found regarding feeding since *Li et al.* discovered that formula and breastfeeding did not influence HEU infants' WAZ trajectory and *Muhangi et al.* found no interaction between breastfeeding duration and growth.[37,44]

Additionally, children in a study with dietary supplements, had a smaller decline in the WAZ trajectory than the control group between 6 and 12 months.[47] Maternal age and antenatal maternal $CD4^+$ count were also not linked to growth in the first 6 months of life.[32]

Adjusted models revealed that even though newborns exposed to HAART had lower WAZ z-scores at birth, they had faster weight gain in the first 2 months of life than the ZDV group. For the next 3 months they had parallel rates of weight gain for age.[28] A different paper from the same author shows that ZDV exposed children has having higher mean WAZ compared to triple ARV exposed infants at 24 months whilst having similar growth trajectory.[35] (Figure 5A) Nevertheless *Morden et al.* found ARV regimen was not linked to differences in WAZ scores in the first 6 months of life.[32] PI containing regimens were associated with lower WAZ z-scores.[30] Adjusted analyses

revealed significant differences in WAZ scores between infants exposed early in pregnancy and infants exposed later.[34]

Supporting the previously mentioned, the following regimens TDF, Abacavir plus ZDV plus 3TC, LPV/r with ZDV plus 3TC and Nevirapine with ZDV plus 3TC were also not associated with differences in WAZ scores.[34,35] Similar results were identified at 9 months by *Pintye et al.*; however, unadjusted models at 6 weeks show WAZ was lower among HEU infants exposed to TDF *in utero* compared to those exposed to other ARV.[48]

By 24 months *Lane et al.* found that 4,1% of HEU children were underweight.[46] At 6 weeks postpartum, HEU infants had greater odds of being underweight than HUU infants.[49] Similarly, other studies found that the HEU group had significant higher proportion of underweight children that the HUU group.[29,30,44] However, another study with a longer follow-up showed that HEU and a HUU children with less than 5 years had no differences in risk for underweight.[40] This was also found by *König et al.* and *Blakstad et al.*.[45,50]

Coloured nonblack race, birth by caesarean section, low birth weight, early weaning, diarrheal episodes in the first 6 weeks of life or malaria in infancy, maternal tuberculosis infection during pregnancy, lower maternal education and poorer households were associated with increased odds of underweight.[44,45,49] Nevertheless variables that decreased the risk of underweight were also found, such as breastfeeding, greater maternal height, higher birth WAZ, 5 or more antenatal appointments, as well as higher frequency of infants postnatal follow-up and male sex; however, male sex had conflicting results since other studies associated it with an increased risk.[37,44,45,49,51] Not only breastfeeding improved children's weight, but also lipid-based supplement and nutritional education from 6 to 12 months allowed that at 12 months infants under the intervention had a 67,3% lower underweight prevalence comparing to a HEU historical control even thought at 6 months there were no differences between the two.[47] (Figure 6A)

There were no significant different proportions of underweight infants at 6 weeks and at 9 months when compared to the exposure to TDF.[48]

LAZ/HAZ

Amongst HEU and HUU children, no significant LAZ differences were found.[30,43,44,45] However, this was not supported by others studies in which HEU children had significant lower LAZ/HAZ than the HUU group.[27,29,41,42,52] (Table IV)

Both HUU and HEU African children were found to have lower LAZ scores at 12 and 24 months when compared to the WHO population references.[27] In a different African study, the same was found at 6 moths. Nevertheless, LAZ had different evolutions for HEU and HUU children. At 9 months HEU children continued to have LAZ scores below the refences while HUU children had an

increased in LAZ scores to above 0. After 9 months both groups exhibited a decrease in growth, with HEU children having significant lower LAZ results when compared to the HUU children.[31] (Figure 4B) A Kenyan study observed a decline of 0,55 in LAZ amongst HEU infants during the first 12 months of life, which is lower than other studies in sub-Saharan Africa.[39]

Multiparous mothers, lower maternal BMI 1-month postpartum, low maternal height, maternal unemployment and male sex were risk factors for lower LAZ results, as well as maternal vitamin D deficiency (<20ng/mL) in the third trimester at 12 months.[33,35,38] Viral load at ARV initiation, low socioeconomic status, low birth weight, small for gestational age and gestational age were also associated with infant LAZ.[30,31,38] Feeding practices may have an impact in LAZ since children in a supplement intervention study had a smaller declined in LAZ trajectory than the control group and another article who shows that never breastfed HEU children or breastfed for less than 3 months had higher LAZ scores even though they had a greater decline in LAZ in the first 6 months of life. [47,53] (Figure 7) However, different results have already been seen with neither breastfeeding nor formula feeding influencing HEU infants growth, as well as the duration of breastfeeding.[31,37,39] There were as well confounders not associated with LAZ scores alterations such as early infant diarrhoea and hospitalization.[39]

Some similar factors, male sex, and some different factors, not being an only child, no maternal education, early infant pneumonia, socioeconomic status, sanitation, low birthweight and stunting at birth, were associated with a decreased in LAZ score.[39,45] Furthermore, there were also factors associated with less LAZ deterioration, such as mother education above primary education and maternal height.[39]

LAZ has been reported to be below 0 at 24 months regardless of ARV exposure, with i*n utero* exposure to HAART leading to lower LAZ scores during the first 24 months of life than exposure to ZDV. From 6 to 24 months (end of follow-up), both groups saw a similar decreased in mean LAZ, coincident with breastfeeding cessation.[35] (Figure 5B) A different article considering these two treatment plans, observed the same trend but only within the first 2 months of life.[28] Additionally, mothers with PI treatments had children with lower LAZ.[30]

A follow-up with a longevity of 2 years demonstrated that LAZ evolution was less beneficial to children exposed to ARV since the first trimester of pregnancy.[34]

Concerning exposure to TDF or association of ARV as Abacavir plus ZDV plus 3TC or LPV/r with ZDV plus 3TC or Nevirapine with ZDV plus 3TC, the exposure did not significantly influence LAZ scores in diverse age points.[34,35,38,48]

There was no statistically significant difference in the proportion of stunting between HEU and HUU group around 12 months.[44,45,50]

The same was not seen in a Botswana study in which both unadjusted and adjusted models disclosed that stunting was significantly more frequent in HEU children under one and between 2 and 5 years old, from 1-2 years HUU toddles had an increased prevalence of stunting, coincident with the usual timing of breastfeeding cessation.[30] Statistically significant differences in the proportion of stunting, with HEU children been more frequently stunted than HUU children, was also found in other studies, in low-resource areas.[27,29,31]

HEU children were twice as likely to have low birth weight compared to HUU children, which was strongly associated with stunting. [40,44] Being male, having siblings, smaller household, younger mothers, lower maternal education and repeated episodes of malaria were also associated with greater risk of being stunted.[44,45,53] Duration of breastfeeding was controversial, with one paper reporting it to be inversely associated with stunting incidence and other showing unaltered risk of stunting with different duration of exclusive breastfeeding and with never breastfed children.[40,53] Reduced risk of stunting was associated with the unavailability of running water, lipid-based supplements and nutritional education.[45,47] (Figure 6B)

In utero exposure to ZDV, triple ARV and TDF were not significantly associated with differences in stunting.[35,48,53] Short ARV exposures did not influence the proportion of stunting.[53]

WLZ/WHZ and BMI-for-age

Although both HUU and HEU African children were found to have lower WAZ and LAZ scores at 12 and 24 months when compared to the WHO population references, they did not had lower mean WLZ scores.[27] No significant differences between HEU and HUU children's WLZ/WHZ were found in other investigations.[27,29,30,40,43,44] (Table V)

Nonetheless, a South African study found that at 6 weeks HEU infants had lower WLZ than HUU infants. However WLZ increased overtime, especially among HEU children, until the differences became negligible and comparable results were found using BMI-for-age.[31] (Figure 4C) Similarly, there was a cohort in which HEU children until they were 16 weeks old, had lower BMI-for-age z-score than HUU children; after that age there were no significant differences.[41]

Moreover, differences between HEU and HUU Chinese children's WLZ/WHZ results were found at any age until 18 months old, except in the 9 and the 18-month-old marks.[42]

Male infants were more likely to have the highest WLZ values, whist infants born with low birth WAZ and children with longer illness periods had an increased prospect of having the lowest WLZ.[46] Maternal vitamin D in the last trimester did not influence WLZ score while being small for gestation age and breastfed for a long time was linked to lower WLZ among HEU children.[31,33] Higher WLZ scores was associated among HEU children with full-term pregnancies until 6 months of age.[30]

No differences were also found amongst HEU infants when attending to the beginning of *in utero* exposure to ARV, as well as children not exposed to ARV.[34] A study found that in the 2 first months of life, infants exposed to HAART had a faster growth in WLZ z-score than those exposed to ZDV. However, from the third month until the sixth this difference declined since HAART children had a more significant increase in LAZ than WAZ. Within this period, growth patterns from the two groups were significantly distinct with ZDV exposed children having always a lower mean WLZ score.[28] The exposure to TDF did not influence WLZ among HEU infants.[34,48]

There was no significant differences found in the risk of wasting amongst HEU and HUU children.[40,50] A Rwanda study demonstrated that only 0,7% of HEU children was wasted at 24 months.[46] When analysing potential confounders, it was discovered that by 24 months children breastfed and children formula fed had a similar rate of wasting.[51] Meanwhile, low birth weight, low maternal income, child's history of diarrhoea and higher number of children in the household had an increased risk of wasting.[44,51] Also regarding infant nutrition, there is a study which supplemented HEU infants from 6 to 12 months with daily ration of lipid-based supplement and other complement intervention, such as nutritional education, found that at 12 months infants under the intervention had a 69,7% lower wasting prevalence comparing to a historical control even though at 6 months there were no differences between the two.[47] (Figure 6C)

Exposure to different ARV treatments, ZDV or HAART was not linked to wasting.[28,35] (Figure 5C) Also not associated with wasting at 6 weeks and 9 months was *in utero* exposure to TDF.[48]

School-aged children

WAZ

HEU children with around 7,5 years were found to have lower WAZ than their HUU comparisons; however, the differences were not statistically significant.[41] (Table VI)

HAZ

HEU and HUU children had similar mean HAZ z-scores, with -0,36 vs -0,34, respectively.[54] The lack of differences in HAZ amongst HEU and HUU school aged children was also discovered in another study.[41]

BMI-for-age

In all analyses from a Zambian study, the only difference found between HEU and HUU children's BMI was 16 cases of overweight (BMI-for-age z-score>2) children in the HUU group.[54] Nevertheless, another study found lower BMI-for-age among 7,5 years old HEU children compared

to the HUU children with an increased difference since 18 months, this was the only score in this study to be statistically influenced by the duration of breastfeeding.[41]

Neurodevelopment

From all the studies analysed regarding neurodevelopment in HEU children only 5 had results from children above 5 years of age, probably in an attempt to evaluate the critical years of early childhood development which according to The United Nations International Children's Emergency Fund, are the first 8 years of a child's life. This period is crucial for an optimal cognitive, social, physical, and emotional development and it is affected by numerous conditions.[55]

The Bayley Scales of Infant Development (BSID) first, second or third editions (BSID-I; BSID-II; BSID-III) were the most common tools used to assess the neurodevelopment in children.

Williams et al. used the first two editions to analyse children up to 3 years old of the PACTG 219/219C cohort, applying the result closest to 24 months of age. The mean value of the general mental function skills and motor skills within the HEU was of 87,7 and 92,9, respectively, which is significantly lower than the United States' mean of 100. When using models adjusted for cofounders, both means increased to, 94,8 and 93,9 respectively, without reaching the standard value.[56] Comparable results were found by *Kerr et al.* who discovered both a lower verbal intelligence quotient (IQ) and full-scale IQ (verbal plus performance IQ) in HEU children when compared to HUU children, a Uganda-based analyses found similar results.[14,52](Figure 8) A 2018 meta-analyses also disclosed that HEU children had lower cognitive and motor scores (BSID-I and II) when compared to HUU children.[57] (Table VII)

More recent studies, which used the third edition of the BSID or other scales, did not recreate these findings. A Botswana investigation in 24 month old children demonstrates no clinically important differences in neurodevelopment between the HEU and the HUU children.[58] Similar results were also found in other researches with children within 6 to 36 months[59-66] in North American and South African infants and toddlers, 3 and 5 years old Canadian children [67] and 7-11 year-old children from South Africa, Uganda, Malawi and Zimbabwe[68,69].

Applying adjusted models *Chaudhury et al.* encountered significantly higher BSID-III scores were associated with mother's age, education, income and breastfeeding.[58] Global mean scores were also significantly higher among girls, children with normal birth weight and those with highly educated primary caregivers, while depressive symptoms, psychological Intimate Partner Violence (IPV) during pregnancy, viral load close to birth, lower $CD4^+$ count at delivery, socioeconomic status or whether the child's caregiver was a parent, did not influence the child's development.[14,60,61,70-73]

Cognitive Development and Confounders

Lower scores in at least 1 domain of the BSID were linked to lower-quality housing, food insecurity, maternal depression, lack of social support, stigma and alcohol use, with the latter being significantly linked with worse results in cognitive and expressive language.[58] (Table VIII)

In an evaluation done to 5-year old HEU children, 24% of them were classified as having low cognitive scores.[74] In an Uganda study, that compared the HEU and the HUU children, it was also determined that HEU children had significantly lower cognitive scores than HUU.[52] Adverse cognitive outcomes were more likely in children from younger mothers, from low income household, with low education, lower maternal cognitive ability, in households with fewer people, low birth weight, preterm birth, HIV exposure, child malnutrition and physical IPV.[50,58,59,68,72,75] However, no significant associations were found within children who were underweight, wasted or stunted among 1-year old South African children.[60,61] Third trimester vitamin D levels were also not associated with alterations in cognitive scores, or any other BSID-III domain.[33]

Motor Development and Confounders

In a Tanzanian study, delivery characteristics were analysed, determining that HEU children born in hospitals had higher cognitive and fine motor scores, while the exposure to oxytocin led to lower fine motor scores.[50] (Table IX) Another risk factor found for poorer motor skills was postnatal hospitalization in Neonatal Intensive Care Units and prematurity.[67,70]

Lower levels of motor development were also associated with lower maternal education and prematurity, which was also presented as a risk factor for lower levels of adaptive behaviour development.[50,59,76]

Behaviour/Social Development and Confounders

Adaptive Behaviour Composite and Socialization subtests of the Wechsler Preschool and Primary Scale of Intelligence 3rd edition had significantly lower scores at 3,5 years of age than expected for the age though these deviations were not observed at the age of 5,5.[67] (Table X) (Figure 9) Other studies regarding behaviour analysis did not presented differences between HEU and HUU children and, higher proportions of behaviour problems were associated with stunting regardless of HIV exposure.[14,65]

In one of these papers, attention problems were also investigated which revealed a superior proportion of HEU versus HUU children suffered from attention deficits (6,1% HEU vs 0,9% HUU children); this difference did not persist when adjusted for sociodemographic problems.[14]

Regarding personal/social subscale of the Griffiths Mental Development Scale the HEU children had significantly lower scores than HUU children.[64] Social withdrawal was compared among HEU and a HUU children using the Alarm Distress Baby Scale, which exhibited no significant differences between the two. Furthermore, the children that did exhibited social withdrawn had lower language BSID-III scores and were associated with stunting at 12 monts.[61]

Language Development and Confounders

Lower overall language scores was found in HEU children as well as lower vocabulary and grammar scores were discovered; no association has been established regarding speech impairment.[74] (Table XI) Nevertheless a study using the Mullen Scales of Early Learning (MSEL) scale encounter no differences in receptive language between the HUU and HEU children cohort.[78]

Expressive and receptive language domains were found to have worse outcomes among HEU children exclusively breastfed, delivered preterm, from depressed mothers and from smaller households, while HEU girls had higher scores.[50,60,66] However, a study carried out among Botswana HEU children, reported breastfeeding as a protective factor for adverse outcomes not only in language, but in the cognitive domain as well.[70] Alcohol exposure showed no significant repercussions on language. Additionally, there is a study who found no association with any domain as well as no association between tobacco and poorer results in any subtest.[65,66,77]

The discovery of low birth weight, maternal age, education and income association with BSID-III language and cognitive domains support the findings of the previous studies.[56,59,70,79]

Neurodevelopment Progression

Regarding the evolution of the neurodevelopment, *Wedderburn et al.* concluded that at 24 months, the cognitive, expressive and receptive language outcomes reported lower mean scores in the HEU children group versus the HUU children group, even though there were no differences at 6 months.[66] Additionally a Kenyan study concluded that subtle differences in language development may only become detectable at an older age and a Zambian investigation showed an increase odds of developmental delays of 8% per every month the child was older, reassuring the need of follow-up during childhood and adolescence.[71,80] Furthermore, a serial assessment of South African children at 12 and at 30-42 months demonstrated that they had a significant decline in the cognitive domain regardless of HIV exposure.[65] The evolution of Canadian HEU children between 3 and 5 years exhibited lower verbal IQ and significant improvements in the Adaptive Behaviour Composite and Communication scores.[67] (Figure 9) Lastly in a school aged cohort, HEU children had a significantly lower likelihood of completing higher levels of schooling, 15,4%, versus the 49,5% of HUU children, which agrees with another school aged study in which HEU children were identified has having below average cognitive scores and academic outcomes.[79,81] These findings were not replicated by *Debeaudrap et al.* and *Nicholson et al.* in their studies, which presented HEU and HUU children with similar levels of education.[54,82] HEU girls had twice the odds of repeating a grade than the HUU girls in adjusted and unadjusted models and boys with HIV positive mothers were also associated with grade repetition, but with less significance; this sex-specific difference is most likely explained by social bias rather than biological basis.[83]

Neurodevelopment Delays

Although the exposure to HIV and ARV seems reassuring, delays in some domains were uncovered. In a study performed with children between 12 and 18 months, *Le Roux et al.* discovered that the risk for any impairment in cognitive and motor domains was increased twice-fold in the HEU children when compared to HUU children, whereas the risk for language delay was similar. While the risks remain in the cognitive domain in adjusted models, the motor domain difference was attenuated.[63] (Figure 10) Also, within this cohort a very small number of children was found to have severe delay across all categories with no difference between the two groups. Increase gestational age was a protective factor for cognitive delays, with preterm children having increased odds of motor delay of 16-fold in the HEU children while in HUU children the odds of delay were around 5-fold.[63] Meanwhile, a South African research exposed no statistically significant differences regarding cognitive or motor developmental delays (HEU children with 11% and HUU children with 9%), but accounted more frequent expressive and receptive language delays within the HEU group (receptive language 14% vs 7% and expressive language 11% vs 6%).[66] Language delays, as well as motor delays, were also more often found among HEU Uganda children than their HUU counterparts.[52] Moreover, *Rice et al.* found that at 5 years old a third of the HEU children had language impairments.[74]

A distinct investigation from the same author, using the MacArthur-Bates Communicative Development Inventory Test (CDI), evaluated late language emergence among 12-month HEU children. Within their cohort, 26% was diagnosed with late language emergence (LLE) (defined as ranking lower than the 10th percentile in at least one domain) and 6% were classified with severe late language emergence. At 24 months with the use of Communication scale of the Ages and Stages Questionnaire (ASQ), they categorized 23% of the HEU children with LLE and 14% with severe LLE.[77] Data regarding developmental delays is conflicting, as multiple papers identified no such delays within the HEU groups.[60,71]

Adjusted models revealed that self-reported illicit drugs use, $CD4^+$ count and maternal history of tuberculosis were not associated with developmental delays and increase gestational age was associated with lower incidence of motor and cognitive delays, but not language delay. [62,56] Amongst the full term HEU children increase levels of maternal viral load, despite viral suppression at delivery, maternal age, socioeconomic status, IPV and maternal alcohol use were associated with higher odds of motor and expressive language delays; the cognitive domain was unaffected.[62] Concerning LLE at 12 months boys had higher odds of LLE than girls and children with caregivers with verbal IQ < 85 had more than twice the odds of developing LLE.[77] Also, multilingual exposure, neonatal combination ARV prophylaxis and low $CD4^+$ count peripartum were associated, in adjusted and unadjusted models, with higher odds of LLE. At 24 month, the difference between the sexes

prevailed and low $CD4^+$ count during pregnancy and caregiver's health problems were also associated with increase odds of LLE.[77]

ARV Influence in Neurodevelopment

When analysing ARV exposure amongst American HEU children with less than 3 years, similar developmental results were shown regardless of the regimens the mother was under.[56] Similarly, American cohorts and a Botswana study discovered no developmental differences between HEU children exposed to any type of combination ARV or to ARV monotherapy, as well as between HEU children exposed and unexposed to ARV.[59,65,70,79](Figure 11) However, the longer the child was exposed to the ARV, the higher scores were obtain in the general mental function and, this was not replicated in an American study.[56,59,79]

Likewise, a longitudinal investigation in Uganda and Malawi found no differences in the MSEL scores based on ARV exposure at age 12 and 24 months. It also concluded that, at 48 months, children with mothers using triple ARV ante and post-partum had slightly higher MSEL scores than children of those using the therapy inconsistently. Additionally children whose mothers were consistent with the triple treatment had similar scores to HUU children.[73] However, a distinct Uganda study, also using the MSEL score, determined that HEU children exposed to ARV had higher overall mean scores than ARV unexposed HEU children at 6 months; at 12 months this difference was no longer found.[52] (Figure 8)

The Kaufman Assessment Battery for Children second edition (KABC-II) mental processing index score also had parallel results amongst the HEU children regardless of the ARV exposure.[73] The only affected domain in the KABC-II was learning, which was lower in children from mothers with triple ARV therapy followed by infant nevirapine and in ZDV followed by maternal triple ARV at 48 months, compared with HUU children. These differences did not persist in adjusted models.[73] The use of the CDI and the ASQ test exhibited similar results, with exposure to combined ARV or a specific ARV class being irrelevant for the incidence of LLE.[77] Complementary South African investigations analysing triple ARV exposure and HIV unexposed mothers found that language impairments were higher in the HEU children with mothers treated with triple ARV when compared to HUU children and that the moment in which the ARV was initiated did not influence BSID-III scores, which is contradictory to what was previously observed by *Williams et al*..[56,60,66]

Children with ARV exposure did not present higher incidence of impairment, having a percentage of mental impairment of 13% and motor impairment of 10%.[56] Fine motor scores were also found to have lower scores in infants of mothers who were under combined ARV treatment instead of ZDV monotherapy, being the only affected domain.[61]

PI-based regimens were associated with higher performance IQ, visuomotor integration and communications scores when comparing to those exposed to NNRTI-based regimens.[67] Triple NRTI regimens were not associated with an increased risk for speech impairment at age 5, though they added risk for language impairment at 3 years in otherwise unimpaired children.[74] Additionally, a study focused on HEU children exposed to triple NRTI regimens vs dual NRTI plus PI, it was shown that at 24 months of age there were no significant differences between the neurodevelopment of the two groups.[84]

Finally, concerning the exposure to a specific ARV, *Cassidy et al.* discovered that HEU children exposed to Efavirenz (EFV) were more often preterm and had older mothers, with higher $CD4^+$ count and lower socioeconomic status and were less often breastfed than unexposed. The mean scores of these children in the receptive language domain in the BSID-III and the locomotor and personal-social scales of the Development Milestones Checklist were significantly worse, as well as in the Profile of Social Emotional Development in adjusted analyses. In contrast the BSID-III gross motor domain score and the language Development Milestones Checklist were significantly higher. The cognitive domain did not differ in between both groups.[85] In the adjusted analyses the gross motor domain and the personal-social scale differences were not significant. The results were unchanged when adjusted for low birth weight and/or preterm and height-for-age. Adjusting for weight-for-height the receptive language domain no longer had significantly differences between the two groups.[85]

In one investigation, pregnant women at 32 weeks were analysed in order to detect not only EFV but also TDF serum levels. These measurements revealed that mothers with detectable serum ARV had children with lower cognitive scores than HEU children with mothers presenting undetectable ARV. The remaining domains were not affected.[72]

Analyses of the SMARTT data of one and two-year-olds exposed to regimens with ATV as having a significantly lower scores in language development; however, a more recent study with the same cohort found no association between language and ATV.[59,77,79] Although, another investigation, analysing ATV exposed mothers, showed that meconium ATV concentration did not influence BSID-III or CDI scores.[86] *In utero* exposure to ATV and saquinavir were associated with increase odds of LLE at 12 months; at 24 months no significant associations were found between LLE and specific ARV or ARV class.[77] However, an American investigation did not find a significant association between the exposure of ATV plus ritonavir and TDF plus ATV plus ritonavir to the results of BSID-III, CDI and LLE risk.[86] Other investigations associated TDF exposure with reduced risk for language impairments at age 5, while being associated with an increased risk for primary speech impairment at age 3, as well as lower odds of grammar impairment and social–emotional performance, alongside didanosine.[74,79] Didanosine, by itself and associated to stavudine, was

associated with neurodevelopment delay while stavudine alone was associated with language impairment.[87] In two of these investigations adjusted analyses showed an association between the use of ZDV and higher odds of language impairment.[74,79] Nonetheless, *in utero* or peri partum ZDV exposure was not associated with cognitive delays or behaviour disorders.[75]

Regarding the beginning and duration of ARV, early-exposure to EFV was associated with worse mean scores for the BSID-III receptive and expressive language scores.[85] In adjusted analyses, only the expressive language scale differences were observed while, children with longer exposure to ATV had higher BSID-III language results and CDI Phrases Understood domain.[85,86]

Conclusion

Birth Defects studies, unlike growth and neurodevelopment, are predominantly conducted in high resources areas, leaving places, such as Sub-Saharan Africa, under-studied, even though it is one of the regions with the highest prevalence of HIV, especially among young women, with around 6000 new cases per week.[2] These women are also exposed to other factors that might increase the risk of birth defects, such as micronutrient deficiency, like folate acid, co-infections and malnutrition. Although this article broadened the inclusion criteria for literature about birth defects in HEU children, the results were still scarce since most studies only approach the mother's exposure to HIV and ARV, ignoring the HIV status of the child. An example of this, is the *Zash et al.* manuscript, which was very influential in international guidelines due to correlations found between neural-tube defects and dolutegravir.[19]

Reporting and analysing ARV exposure and outcomes are crucial and, even though the Antiretroviral Pregnancy Registry[88] was not use in this study, since it does not differentiate the HEU children from the infected children, it is a valuable resource to elaborate systematic evaluation of birth defects caused by ARV in pregnant women with HIV. In addition to the United States of America's registry, WHO has created a registry for resources limited areas to try and limit the lack of information.[89]

One of the strengths of this work regarding to birth defects is that, every study included used the Antiretroviral Pregnancy Registry modified Metropolitan Atlanta Congenital Defects Program criteria to diagnose the abnormalities.

HEU children are more likely to have mothers with alcohol use, to be from ethnic minorities, with low-incomes, to experience IPV, to be from an unplanned pregnancy and to live in smaller spaces with less access to electricity and water and greater food insecurity. [14,27,29,31,58,61,63,65,76,82,90] All these factors may influence all aspects of a child's development.

Growth among HEU children was similar to HUU children in eleven studies[8,27,29-31,40,41,43-45,54] and lower in 9[27,29,30,31,35,40,41,42,52]. However, the analyses regarding growth mostly include preschool age children which might overlook problems during puberty. This is a particularly important period since it is a fast-growing phase which is more susceptible to impairments.

Even though this study only analysed weight, length/height and weight for length/height z-scores, there are other variables that can be measure or calculated which are equally as important to fully characterise these children, such as head circumference and biceps skinfold. These would enable a more accurate description of the child's health and might help in the discovery of potential confounders and consequences of ARV exposure.

The current literature presents very contrasting results. However, in many of the analysed studies, there was no specific ARV that appeared to have important consequences in growth.[28,32,34,35,38,48]

The majority of the studies analysing neurodevelopment did not find an association between HIV exposure and lower global neurodevelopment scores with only 3 studies[14,52,57] finding lower scores in HEU children. Four studies found lower scores in HEU children in cognitive, motor and language areas.[52,63,66,74] Children born from HIV infected mothers are also significantly less likely to have the same level of education as those born from HIV uninfected mothers, which means they need appropriate support. An Uganda-based investigation studying quality of caregiving showed that women with higher levels of social support and infants living in environments with more stimulation had better general neurodevelopment scores.[52] It was also shown that long follow-ups are needed since some delays, especially in language, can only detected in older children.[71,80]

Even though the use of the BSID-III scale was very frequent, which is a positive aspect of this work since it allows to make comparisons between different investigations, its use is not universal. The upside of choosing scales is that although they were used in multiple different countries, they are adapted to the specific languages and cultures, meaning that they provide more precise results and enable comparisons regardless of where they were applied. However, not all studies used scales entirely adjusted for their countries; the use of American-based scores employed in less developed communities can lead to lower mean scores. For more accurate results, it would be important to define scales to use, which could be validated for each specific language and culture.

To conclude, there were no definite evidence linking HIV or ARV exposure to birth defects, growth or neurodevelopment problems. Long-term effects of in utero exposure to HIV and ARV must continue to be studied. Studies with longer follow-up periods must be done, to allow for the analysis of HEU children into adolescence and adulthood. This cohorts should be analysed in a global and uniform approach with adequate HUU comparisons to minimize bias.

Additionally, an important question to address regarding all the previously mentioned topics, is what might be the pathways and mechanisms that could explain the presence of the differences between HEU and HUU children or within the HEU group since this would allow for targeted therapies and preventive interventions.

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Appendix

Table I: Summary of the studies analysed regarding birth defects

Reference	Author	Year	Country	Key Outcomes
20	Williams P. *et al.*	2015	United States of America	• Prevalence of 6,78% of birth defects - 72 musculoskeletal and 55 cardiovascular defects • Higher risk for birth defects with exposure to HAART, PI, ATV and ritonavir as a booster. - no individual NRTI was associated with defects • Highest risk for skin and musculoskeletal defects with first trimester exposure to ATV • Higher risk for genital defects in male children with first trimester exposure to ZDV and 3TC. • No cofounder factors were found to influence birth defects.
21	Brogly S. *et al.*	2010	United States of America	• Prevalence of 5,4% of birth defects in HEU children.
22	Knapp K. *et al.*	2012	International	• Prevalence of 6% of birth defects in HEU children.
23	Sibiude J. *et al.*	2014	France	• Prevalence of 4,5% of birth defects in HEU children.
24	Watts D. *et al.*	2011	International	• Two cases or cardiac defects among HEU children.

Table II - Summary of the studies analysed regarding WAZ, LAZ, WLZ and BMI-for-age at birth

Reference	Author	Year	Country	Key Outcomes
28	Powis K. *et al.*	2011	Botswana	• Lower $CD4^+$ count was associated with lower WAZ • ZDV exposed children had higher WAZ than those exposed to HAART • ZDV exposed children had higher LAZ than those exposed to HAART - In adjusted models this difference was only found when maternal $CD4^+$ count $\geq$ 200 cells/mm^3 • ZDV was associated with higher WLZ
29	Jumare J. *et al.*	2019	Nigeria	• HEU children were born with lower WAZ and LAZ than HUU children • HEU and HUU children were similarly underweight - 2,9% of HEU vs 0% of HUU • HEU children were more often stunted than HUU children - 32% of HEU vs 17,9% of HUU • HEU and HUU children had similar WLZ, BMI-for-age and wasted proportion
30	Moseholm E. *et al.*	2019	Denmark	• HEU children were born with lower WAZ and were more often underweight than HUU children • HEU children were born with lower LAZ and were just as stunted as HUU children
31	Le Roux S. *et al.*	2019	South Africa	• HEU and HUU children had similar birth WAZ
32	Morden E. *et al.*	2016	South Africa	• Preterm, female sex, lower $CD4^+$ count and older maternal age were linked to lower WAZ • ARV exposure was associated with higher WAZ

33	Sudfeld C. *et al.*	2019	United States of America	• Low maternal vitamin D in the 3rd trimester was associated with lower WAZ and LAZ
34	Hofer C. *et al.*	2016	Brazil	• Unexposure to ARV or exposure after the 1st trimester were associated with higher WAZ than when exposure started in the beginning of the pregnancy - ARV exposure did not influence LAZ
35	Powis K. *et al.*	2016	Botswana	• HEU children exposed to ZDV had higher WAZ than those exposed to triple ARV
36	Himes S. *et al.*	2015	United States of America	• TDF meconium concentrations was not associated with WAZ, LAZ or WLZ
37	Li B. *et al.*	2019	China	• HEU children with low birth weight were associated with lower LAZ
38	Le Roux S. *et al.*	2017	South Africa	• HEU children exposed to TDF had similar LAZ scores to the standard scores
39	Deichsel E. *et al.*	2019	Kenya	• 13% of HEU children were stunted

Table III - Summary of the studies analysed regarding WAZ in preschool age children

Reference	Author	Year	Country	Key Outcomes
27	Aizire J. *et al.*	2020	Uganda and Malawi	• HEU children had lower WAZ than HUU children – Both groups had scores lower than the standard
28	Powis K. *et al.*	2011	Botswana	• ZDV exposed children had slower weight growth than those exposed to HAART until 2 months – From 2 to 5 months they had similar rates
29	Jumare J. *et al.*	2019	Nigeria	• HEU children had lower WAZ than HUU children • HEU children were more often underweight than HUU children
30	Moseholm E. *et al.*	2019	Denmark	• HEU and HUU children had similar WAZ • PI regimens were associated with lower WAZ • HEU children were more often underweight than HUU children
31	Le Roux S. *et al.*	2019	South Africa	• WAZ increased in HEU and HUU children until the age of 6 weeks – At 12 months both groups had WAZ scores above the standard • Small for gestational age, breastfeeding and longer breastfeeding practices were associated with lower WAZ
32	Morden E. *et al.*	2016	South Africa	• HEU children with lower birth WAZ had faster growth than those with normal weight • Female sex and formula feeding were associated with a faster WAZ trajectory – Maternal age and $CD4^+$ count did not influence WAZ trajectory • Type of ARV regimen was not associated with WAZ
34	Hofer C. *et al.*	2016	Brazil	• Duration of ARV exposure was associated with WAZ • Type of ARV did not influence WAZ trajectory
35	Powis K. *et al.*	2016	Botswana	• HEU and HUU children had lower WAZ scores than the standard

				• Lower maternal BMI 1-month postpartum, lower maternal height, male sex and having two or more siblings were associated with lower WAZ • ZDV exposed children had higher WAZ than those exposed to triple ARV - They had similar weight growth trajectory • Type of ARV did not influence WAZ trajectory
37	Li B. *et al.*	2019	China	• Preterm HEU children and those from anaemic mothers were associated with lower WAZ • Formula and breastfeeding did not influence WAZ trajectory in HEU children • Higher frequency of infants postnatal follow-up and male sex were associated with decrease odds of being underweight
40	Sudfeld C. *et al.*	2016	Botswana	• HEU children had lower WAZ than HUU children • HEU and HUU children had similar risk of underweight until the age of 5 years
41	Rosala-Hallas A. *et al.*	2017	Zambia	• HEU children had lower WAZ than HUU children • WAZ evolution was slightly different between HEU and HUU children from 1 to 6 weeks - It was similar from 6 to 16 weeks
42	Chen J. *et al.*	2019	China	• HEU children had lower WAZ than HUU children
43	Ramokolo V. *et al.*	2014	South Africa	• HEU and HUU children had similar WAZ
44	Muhangi L. *et al.*	2013	Uganda	• HEU and HUU children had similar WAZ • The duration of breastfeeding was not associated with weight growth • HEU children were more often underweight than HUU children • Male sex, low birth weight, early weaning and malaria during infancy were associated with increase odds of being underweight
45	König W. *et al.*	2017	Ethiopia	• HEU children had higher WAZ than HUU children from 9 to 12 months

				• Lower education, male sex and having two or more siblings were associated with lower WAZ • Female sex was associated with a faster WAZ trajectory • HEU and HUU children had similar risk of underweight • Lower maternal education and male sex were associated with increase odds of being underweight
46	Lane C. *et al.*	2019	Rwanda	• HEU children had decedent WAZ scores until the age of 24 months • 4,1% of HEU children were underweight at 24 months
47	Heidkamo R. *et al.*	2012	Haiti	• Dietary supplements and nutritional education were associated with smaller decline in WAZ trajectory and lower prevalence of underweight
48	Pintye J. *et al.*	2015	Kenya	• TDF exposed children had lower WAZ than those exposed to other regimens at 6 weeks • TDF exposure did not influence the risk of underweight at 6 weeks and 9 months
49	Ramokolo V. *et al.*	2017	South Africa	• HEU children were more often underweight than HUU children • Coloured nonblack race, birth by caesarean section, diarrhoea in the first 6 weeks of life, maternal history of tuberculosis, lower maternal education and poorer households were associated with increase odds of being underweight • Breastfeeding and 5 or more antenatal appointments were associated with decrease odds of being underweight
50	Blakstad M. *et al.*	2019	Tanzania	• HEU and HUU children had similar risk of underweight
51	McGrath C. *et al.*	2012	Kenya	• Higher birth WAZ and greater maternal height were associated with decrease odds of being underweight

Table IV - Summary of the studies analysed regarding LAZ/HAZ in preschool age children

Reference	Author	Year	Country	Key Outcomes
27	Aizire J. *et al.*	2020	Uganda and Malawi	• HEU children had lower LAZ/HAZ than HUU children – Both groups had LAZ scores under the standard at 12 and 24 months • HEU children were more often stunted than HUU children
29	Jumare J. *et al.*	2019	Nigeria	• HEU children had lower LAZ/HAZ and were more often stunted than HUU children
30	Moseholm E. *et al.*	2019	Denmark	• HEU and HUU children had similar LAZ • PI exposure was associated with lower LAZ scores • HEU children with <1year or with 2-5 years were more frequently stunted than HUU children – From 1-2 years HUU children had a higher prevalence of stunting
31	Le Roux S. *et al.*	2019	South Africa	• HEU and HUU children had LAZ scores under the standard at 6 months – At 9 months HUU children had scores above the standard – After 9 months they had descendent trajectory; HEU children had lower LAZ • Feeding modality and duration of breastfeeding were not associated with HEU children's growth • HEU children were more often stunted than HUU children
34	Hofer C. *et al.*	2016	Brazil	• First trimester ARV exposure was associated with worst LAZ trajectory for the 1st two years of life • Type of ARV did not influence LAZ/HAZ trajectory
35	Powis K. *et al.*	2016	Botswana	• Bellow standard LAZ scores regardless of ARV regimen at 24 months – HAART exposed children had lower LAZ scores than those exposed to ZDV – Both groups had similar LAZ decline between 6 and 24 months

				• Multiparous mothers, lower maternal BMI 1-month postpartum, lower maternal height, maternal unemployment and male sex were associated with lower LAZ at 24 months • Type of ARV did not influence LAZ/HAZ trajectory or stunting risk
37	Li B. *et al.*	2019	China	• Feeding modality and duration of breastfeeding were not associated with HEU children's growth
38	Le Roux S. *et al.*	2017	South Africa	• Maternal height and viral load at ARV initiation was associated with lower LAZ • Type of ARV did not influence LAZ/HAZ trajectory
39	Deichsel E. *et al.*	2019	Kenya	• HEU children had a decline of 0,55 in LAZ in the 1st year of life • Early infant diarrhoea and hospitalization were not associated with LAZ scores • Feeding modality and duration of breastfeeding were not associated with HEU children's growth • Early infant pneumonia, socioeconomic status, sanitation, low birthweight and stunting at birth were associated with lower LAZ scores – Higher maternal education and height were associated with less LAZ decline
40	Sudfeld C. *et al.*	2016	Botswana	• Low birth weight and lower breastfeeding duration were associated with higher risk of stunting
41	Rosala-Hallas A. *et al.*	2017	Zambia	• HEU children had lower LAZ/HAZ than HUU children
42	Chen J. *et al.*	2019	China	• HEU children had lower LAZ/HAZ than HUU children
43	Ramokolo V. *et al.*	2014	South Africa	• HEU and HUU children had similar LAZ
44	Muhangi L. *et al.*	2013	Uganda	• HEU and HUU children had similar LAZ and stunting risk • Low birth weight, male sex, younger mothers, lower maternal education and repeated episodes of malaria were associated with greater risk of stunting
45	König W. *et al.*	2017	Ethiopia	• HEU and HUU children had similar LAZ and stunting risk

				• Male sex, having sibilings, no maternal education were associated with lower LAZ scores • Male sex, having siblings, smaller household and no maternal education were associated with greater risk of stunting
47	Heidkamo R. *et al.*	2012	Haiti	• Dietary supplements and nutritional education were associated with smaller decline in LAZ trajectory and lower prevalence of stunting
48	Pintye J. *et al.*	2015	Kenya	• Type of ARV did not influence LAZ/HAZ trajectory or stunting risk
50	Blakstad M. *et al.*	2019	Tanzania	• HEU and HUU children had similar risk of stunting
52	Familiar I. *et al.*	2018	Uganda	• HEU children had lower LAZ/HAZ than HUU children
53	Bork K. *et al.*	2017	Burkina Faso, Kenya, and South Africa	• HEU children never breastfed or breastfed for <3 months had higher LAZ scores – They had a greater decline in LAZ until the age of 6 months • Breastfeeding duration was not associated with risk of stunting • Male sex was associated with greater risk of stunting • Short ARV exposures and ARV type did not influence the proportion of stunting

Table V - Summary of the studies analysed regarding WLZ/WHZ and BMI-for-age in preschool age children

Reference	Author	Year	Country	Key Outcomes
27	Aizire J. *et al.*	2020	Uganda and Malawi	• HEU and HUU children had similar WLZ/WHZ – Both groups had similar scores to the standard
28	Powis K. *et al.*	2011	Botswana	• HAART exposure was associated with faster growth in WLZ than those exposed to ZDV until age 3 months – Between 3-6 months the differences decline but ZDV exposed children had lower WLZ • Type of ARV exposure did not influence risk of wasting
29	Jumare J. *et al.*	2019	Nigeria	• HEU and HUU children had similar WLZ/WHZ
30	Moseholm E. *et al.*	2019	Denmark	• HEU and HUU children had similar WLZ/WHZ • Full-term was associated with higher WLZ until age 6 months
31	Le Roux S. *et al.*	2019	South Africa	• HEU children had lower WLZ than HUU children at 6 weeks – WLZ increased overtime until the differences became negligible • Small for gestational age and longer breastfeeding were associated with lower WLZ
34	Hofer C. *et al.*	2016	Brazil	• Duration of ARV exposure or exposure to TDF did not influence WLZ
35	Powis K. *et al.*	2016	Botswana	• Type of ARV exposure did not influence risk of wasting
40	Sudfeld C. *et al.*	2016	Botswana	• HEU and HUU children had similar WLZ/WHZ and wasting risk
41	Rosala-Hallas A. *et al.*	2017	Zambia	• HEU children had lower BMI-for-age than HUU children until age 16 weeks – After 16 weeks there were no differences

43	Ramokolo V. *et al.*	2014	South Africa	• HEU and HUU children had similar WLZ/WHZ
44	Muhangi L. *et al.*	2013	Uganda	• HEU and HUU children had similar WLZ/WHZ • Low birth weight, low maternal income and higher number of children in the household were associated with an increased risk of wasting
46	Lane C. *et al.*	2019	Rwanda	• Low birth WAZ and longer periods of illness were associated with lower WLZ • Male sex was associated with higher WLZ • 0,7% of HEU children were wasted at 24 months old
47	Heidkamo R. *et al.*	2012	Haiti	• Dietary supplements and nutritional education were associated with lower wasting prevalence
48	Pintye J. *et al.*	2015	Kenya	• TDF exposure did not influence WLZ or wasting risk
50	Blakstad M. *et al.*	2019	Tanzania	• HEU and HUU children had similar risk of wasting
51	McGrath C. *et al.*	2012	Kenya	• Breast or formula feeding did not influence the prevalence of wasting at 24 months • Child's history of diarrhoea was associated with an increased risk of wasting

Table VI - Summary of the studies analysed regarding WAZ, HAZ and BMI-for-age in school age children

Reference	Author	Year	Country	Key Outcomes
41	Rosala-Hallas A. *et al.*	2017	Zambia	• 7,5-year-old HEU children had lower WAZ than HUU comparison - The differences were not statistically significant • HEU and HUU children had similar HAZ scores • HEU children had lower BMI-for-age at 7,5 years old than HUU children - Difference present since 18 months old - It was influenced by breastfeeding duration
54	Nicholson L. *et al.*	2015	Zambia	• HEU and HUU children had similar HAZ scores • 16 overweight HUU children vs 0 overweight HEU children - No other differences were found between HEU and HUU children's BMI

Table VII - Summary of the studies analysed regarding global neurodevelopment

Reference	Author	Year	Country	Developmental Scale	Key Outcomes
14	Kerr S. *et al.*	2014	Thailand and Cambodia	WISC-III, WPPSI-III and Child Behaviour Checklist	• HEU children had lower scores than HUU children • Higher parental education associated with higher full-scale IQ • Lower income and parent as a caregiver did not influence
52	Familiar I. *et al.*	2018	Uganda	MSEL	• HEU children had lower scores than HUU children
56	Williams P. *et al.*	2010	United States of America	BSID-I and BSID-II	• HEU children had lower BSID-III scores than the standard • ARV exposure was associated with higher BSID scores – the type of therapy did not influence • Illicit drug use was not associated with developmental delays
58	Chaudhury S. *et al.*	2017	Botswana	BSID-III	• HEU and HUU children had similar BSID-III scores • Mother's age, education, income and breastfeeding were associated with higher BSID-III scores
59	Sirois P. *et al.*	2013	United States of America	BSID-III	• HIV and ARV were not associated with neurodevelopment
60	Strehlau R. *et al.*	2020	South Africa	BSID-III	• HEU and HUU children had similar BSID-III scores
61	Springer P. *et al.*	2018	South Africa	BSID-III and Alarm Distress Baby Scale	• HEU and HUU children had similar BSID-III scores • Lower maternal CD4+ count did not influence BSID-III scores
62	Le Roux S. *et al.*	2019	South Africa	BSID-III	• HEU and HUU children had similar BSID-III scores

					• $CD4^+$ count and maternal history of tuberculosis were not associated with developmental delays
63	Le Roux S. *et al.*	2018	South Africa	BSID-III	• HEU and HUU children had similar BSID-III scores • Preterm was associated with risk of delays
64	Springer P. *et al.*	2012	South Africa	Griffiths Mental Developmental Scales	• HEU and HUU children had similar neurodevelopment scores in all but one domain
65	Springer P. *et al.*	2019	South Africa	BSID-III and Strengths and Difficulties questionnaire	• HIV and ARV were not associated with neurodevelopment • Alcohol and tobacco exposure were not associated with BSDI-III scores
66	Wedderburn C. *et al.*	2019	South Africa	BSID-III	• HEU and HUU children had similar BSID-III scores
67	Smith M. *et al.*	2017	Canada	WPPS-I and WPPS-II	• HEU and HUU children had similar neurodevelopment results
68	Rochat T. *et al.*	2016	South Africa	KABC-II	• HEU and HUU children had similar neurodevelopment results
69	Boivin M. *et al.*	2018	South Africa, Uganda, Malawi and Zimbabwe	KABC-II	• HEU and HUU children had similar neurodevelopment results
70	Chaudhury S. *et al.*	2018	Botswana	BSID-III and Development Milestones Checklist	• Viral load and lower $CD4^+$ count were not associated with neurodevelopment • Triple ARV and ZDV monotherapy did not influence BSID-III scores • Breastfeeding was a protective factor against lower scores
73	Boivin M. *et al.*	2019	Uganda and Malawi	MSEL and KABC-II	• HEU children had similar scores regardless of the type of ARV • HEU children from mothers with consistent triple ARV had similar scores to HUU children

75	Reliquet V. *et al.*	2017	France	"Questionnaire"	• ZDV was associated with higher WPPSI-IIII scores
79	Nozyce M. *et al.*	2014	United States of America	WPPSI-III, Wechsler Abbreviated Scale of Intelligence and Wechsler Individual Achievement Test	• HEU children had below average academic outcomes • ARV was not associated with neurodevelopment
81	Brahmbhatt H. *et al.*	2017	Uganda	KABC-II	• 15,4% of HEU children completed higher levels of school – vs 49,5% of HUU children
83	Mitchell J. *et al.*	2016	South Africa	KABC-II	• HIV exposure was associated with grade repetition
85	Cassidy A. *et al.*	2019	Botswana	BSID-III and Development Milestones Checklist	• HEU children exposed to EFV were more often preterm
86	Himes S. *et al.*	2015	United Sates of America	CDI and BSID-III	• CDI and BSID-III results were not influenced by ATV meconium concentration or ATV+ritonavir or TDF+ATV+ritonavir
87	Williams P. *et al.*	2016	United Sates of America	-	• Didanosine and didanosine+stavudine were associated with developmental delays

Table VIII - Summary of the studies analysed regarding cognitive development

Reference	Author	Year	Country	Developmental Scale	Key Outcomes
50	Blakstad M. *et al.*	2019	Tanzania	BSID-III	• Born in a hospital was associated with higher cognitive scores • Lower maternal education and smaller households were associated with lower cognitive scores
52	Familiar I. *et al.*	2018	Uganda	MSEL	• HEU children had lower cognitive scores than HUU children
57	McHenry M. *et al.*	2018	International	BSID-I and BSID-II	• HIV and ARV were associated with lower cognitive scores
58	Chaudhury S. *et al.*	2017	Botswana	BSID-III	• Alcohol use, younger mothers and low income were associated with lower cognitive scores
59	Sirois P. *et al.*	2013	United States of America	BSID-III	• Prematurity was associated with lower cognitive scores
60	Strehlau R. *et al.*	2020	South Africa	BSID-III	• Underweight, wasting and stunting did not influence cognitive scores
61	Springer P. *et al.*	2018	South Africa	BSID-III and Alarm Distress Baby Scale	• Underweight, wasting and stunting did not influence cognitive scores
62	Le Roux S. *et al.*	2019	South Africa	BSID-III	• Increase gestational age was associated with lower incidence of cognitive delays
63	Le Roux S. *et al.*	2018	South Africa	BSID-III	• HEU children had higher risk for cognitive delays than HUU children • Increase gestational age was protective for cognitive delays

65	Springer P. *et al.*	2019	South Africa	BSID-III and Strengths and Difficulties questionnaire	• Decline in cognitive scores regardless of HIV exposure
66	Wedderburn C. *et al.*	2019	South Africa	BSID-III	• HEU and HUU children had no differences in cognitive scores at 6 months – At 24 months HEU children had lower scores • HEU and HUU children had similar incidence of cognitive delays
68	Rochat T. *et al.*	2016	South Africa	KABC-II	• Lower maternal cognitive ability was associated with lower cognitive scores
70	Chaudhury S. *et al.*	2018	Botswana	BSID-III and Development Milestones Checklist	• Breastfeeding in HEU children was protective against lower cognitive scores
72	Alcaide M. *et al.*	2019	South Africa	BSID-III	• Cognitive delays were associated with antenatal physical intimate partner violence, but not psychological • Children from mothers with detectable serum ARV at 32 weeks of gestation had lower cognitive scores • Maternal detectable serum ARV was associated with lower cognitive scores
75	Reliquet V. *et al.*	2017	France	"Questionnaire "	• ZDV was not associated with cognitive delays
85	Cassidy A. *et al.*	2019	Botswana	BSID-III and Development Milestones Checklist	• EFV exposure did not influence cognitive scores

Table IX - Summary of the studies analysed regarding motor development

Reference	Author	Year	Country	Developmental Scale	Key Outcomes
14	Kerr S. *et al.*	2014	Thailand and Cambodia	WISC-III, WPPSI-III and Child Behaviour Checklist	• HEU and HUU children had no differences in performance IQ
50	Blakstad M. *et al.*	2019	Tanzania	BSID-III	• Born in a hospital was associated with higher fine motor scores • Oxytocin exposure and lower maternal education were associated with lower motor scores
52	Familiar I. *et al.*	2018	Uganda	MSEL	• HEU children had lower MSEL gross motor scores than HUU children • HEU children had more often motor delays than HUU children
56	Williams P. *et al.*	2010	United States of America	BSID-I and BSID-II	• HEU children had lower motor scores than the standard • ARV did not influence the incidence of motor impairments
57	McHenry M. *et al.*	2018	International	BSID-I and BSID-II	• HIV and ARV exposure were associated with lower motor BSID scores
59	Sirois P. *et al.*	2013	United States of America	BSID-III	• Lower maternal education and prematurity were associated with lower motor scores
61	Springer P. *et al.*	2018	South Africa	BSID-III and Alarm Distress Baby Scale	• Combined ARV exposed children had lower fine motor scores than single ZDV exposed children
62	Le Roux S. *et al.*	2019	South Africa	BSID-III	• Higher maternal viral load, maternal age, socioeconomic status, IPV and maternal alcohol use were associated with higher odds of motor delays

					• Increase gestational age was associated with lower incidence of cognitive delays
63	Le Roux S. *et al.*	2018	South Africa	BSID-III	• HEU children had higher risk for motor delays
66	Wedderburn C. *et al.*	2019	South Africa	BSID-III	• HEU and HUU children had similar incidence of motor delays
67	Smith M. *et al.*	2017	Canada	WPPS-I and WPPS-II	• Hospitalization in a Neonatal Intensive Care Unit was associated with lower motor scores • PI regimens were associated with higher performance IQ and visuomotor integration scores than NNRTI regimens
70	Chaudhury S. *et al.*	2018	Botswana	BSID-III and Development Milestones Checklist	• Prematurity was associated with lower motor scores
76	Wu J. *et al.*	2018	China	BSID-III	• Lower maternal education was associated with lower motor scores
85	Cassidy A. *et al.*	2019	Botswana	BSID-III and Development Milestones Checklist	• EFV exposed children had worse locomotor scores and higher gross motor scores

Table X - Summary of the studies analysed regarding behaviour/social development

Reference	Author	Year	Country	Developmental Scale	Key Outcomes
14	Kerr S. *et al.*	2014	Thailand and Cambodia	WISC-III, WPPSI-III and Child Behaviour Checklist	• HEU and HUU children had similar behaviour scores • HEU children had more attention problems than HUU children when not adjusting for sociodemographic problems
59	Sirois P. *et al.*	2013	United States of America	BSID-III	• Prematurity and lower maternal education were associated with lower behaviour scores
61	Springer P. *et al.*	2018	South Africa	BSID-III and Alarm Distress Baby Scale	• Social withdrawal was similar in HEU and HUU children
64	Springer P. *et al.*	2012	South Africa	Griffiths Mental Developmental Scales	• HEU children had lower personal/social scores than HUU children
65	Springer P. *et al.*	2019	South Africa	BSID-III and Strengths and Difficulties questionnaire	• HEU and HUU children had similar behaviour scores • Stunting was associated with behaviour problems
67	Smith M. *et al.*	2017	Canada	WPPS-I and WPPS-II	• Adaptive Behaviour Composite and Socialization scores of HEU children were lower than expected at 3,5 years - Alterations were not found at 5,5 years
75	Reliquet V. *et al.*	2017	France	"Questionnaire "	• ZDV was not associated with behaviour disorders
76	Wu J. *et al.*	2018	China	BSID-III	• Lower maternal education was associated with lower behaviour scores

85	Cassidy A. *et al.*	2019	Botswana	BSID-III and Development Milestones Checklist	• EFV exposed children had worse personal-social scores

Table XI - Summary of the studies analysed regarding language development

Reference	Author	Year	Country	Developmental Scale	Key Outcomes
14	Kerr S. *et al.*	2014	Thailand and Cambodia	WISC-III, WPPSI-III and Child Behaviour Checklist	• HEU children had lower verbal IQ than the HUU children
50	Blakstad M. *et al.*	2019	Tanzania	BSID-III	• Smaller households was associated with lower language scores
52	Familiar I. *et al.*	2018	Uganda	MSEL	• HEU children had more often language delays than HUU children
56	Williams P. *et al.*	2010	United States of America	BSID-I and BSID-II	• ARV did not influence the incidence of language impairments
58	Chaudhury S. *et al.*	2017	Botswana	BSID-III	• Alcohol use was associated with lower expressive language scores
59	Sirois P. *et al.*	2013	United States of America	BSID-III	• ATV was associated with lower language scores
60	Strehlau R. *et al.*	2020	South Africa	BSID-III	• Female sex was associated with higher language scores • Triple ARV exposed HEU children had more often language impairments than HUU children
62	Le Roux S. *et al.*	2019	South Africa	BSID-III	• Higher maternal viral load, maternal age, socioeconomic status, IPV and maternal alcohol use were associated with higher odds of expressive language delays
63	Le Roux S. *et al.*	2018	South Africa	BSID-III	• HEU and HUU children had similar risk for language delays

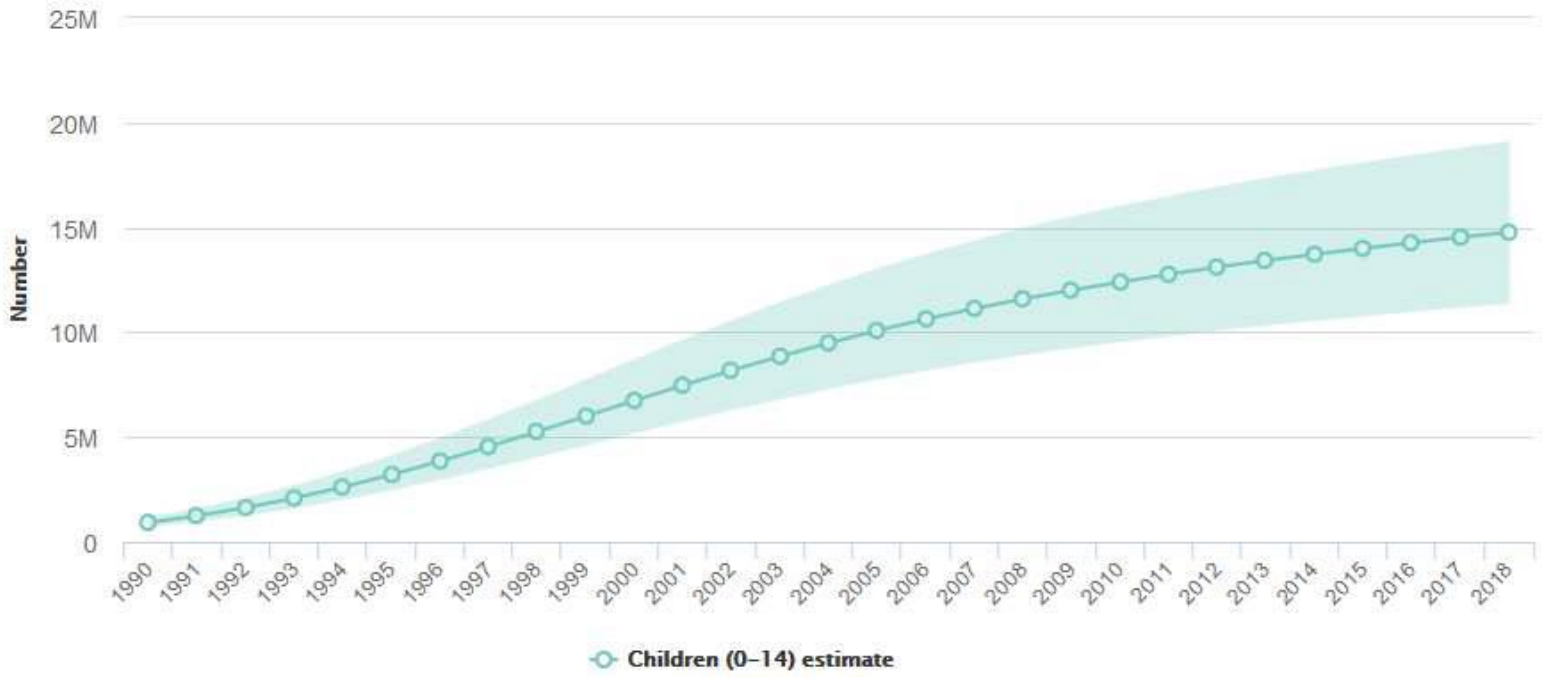
66	Wedderburn C. *et al.*	2019	South Africa	BSID-III	• HEU and HUU children had no differences in expressive and receptive language scores at 6 months - At 24 months HEU children had lower scores • HEU children had more often language delays than HUU children • Alcohol exposure was not associated with language • Exclusively breastfed, preterm and mothers depression were associated with lower language scores • Female sex was associated with higher language scores • Triple ARV exposed HEU children had more often language impairments than HUU children
67	Smith M. *et al.*	2017	Canada	WPPS-I and WPPS-II	• Verbal IQ declined in HEU children between 3 and 5 years • PI regimens were associated with higher communication scores than NNRTI regimens
70	Chaudhury S. *et al.*	2018	Botswana	BSID-III and Development Milestones Checklist	• Breastfeeding in HEU children was protective against lower language scores

74	Rice M. *et al.*	2018	United States of America	Test of Language Development, Peabody Picture Vocabulary Test, WPPSI-III and BSID-III	• HEU children had lower grammar, vocabulary and overall language scores
					  - One third had language impairments
					• Triple NRTI were associated with language impairment at age 3
					  - No association with speech impairment at age 5
					• ZDV was associated with higher odds of language impairment
					• TDF and didanosine were associated with lower odds of language and grammar impairment

77	Rice M. *et al.*	2013	United States of America	CDI and ASQ	• At 12 months 26% of HEU children had late language emergence - 23% at 24 months old • Late language emergence was more likely in boys, multilingual exposure, neonatal ARV prophylaxis, in children from mothers with verbal IQ <85 and low $CD4^+$-lymphocyte count peripartum • Type of ARV did not influence language emergence at 24 months - ATV and saquinavir influence language scores
78	Boivin M. *et al.*	2016	Uganda and Malawi	MSEL	• HEU and HUU children had no differences in receptive language scores
79	Nozyce M. *et al.*	2014	United States of America	WPPSI-III, Wechsler Abbreviated Scale of Intelligence and Wechsler Individual Achievement Test	• ZDV was associated with higher odds of language impairment • ATV did not influence language scores
80	Abubakar A. *et al.*	2013	Kenya	ASQ	• Language differences may only be noticeable at older ages
85	Cassidy A. *et al.*	2019	Botswana	BSID-III and Development Milestones Checklist	• EFV exposed children had worse language BSID-III scores and higher language Development Milestones Checklist - Early-exposure to was associated with lower language scores
86	Himes S. *et al.*	2015	United Sates of America	CDI and BSID-III	• ATV+ritonavir and TDF+ATV+ritonavir were not associated with language emergence • Higher ATV meconium concentration was associated with lower risk for late language emergence

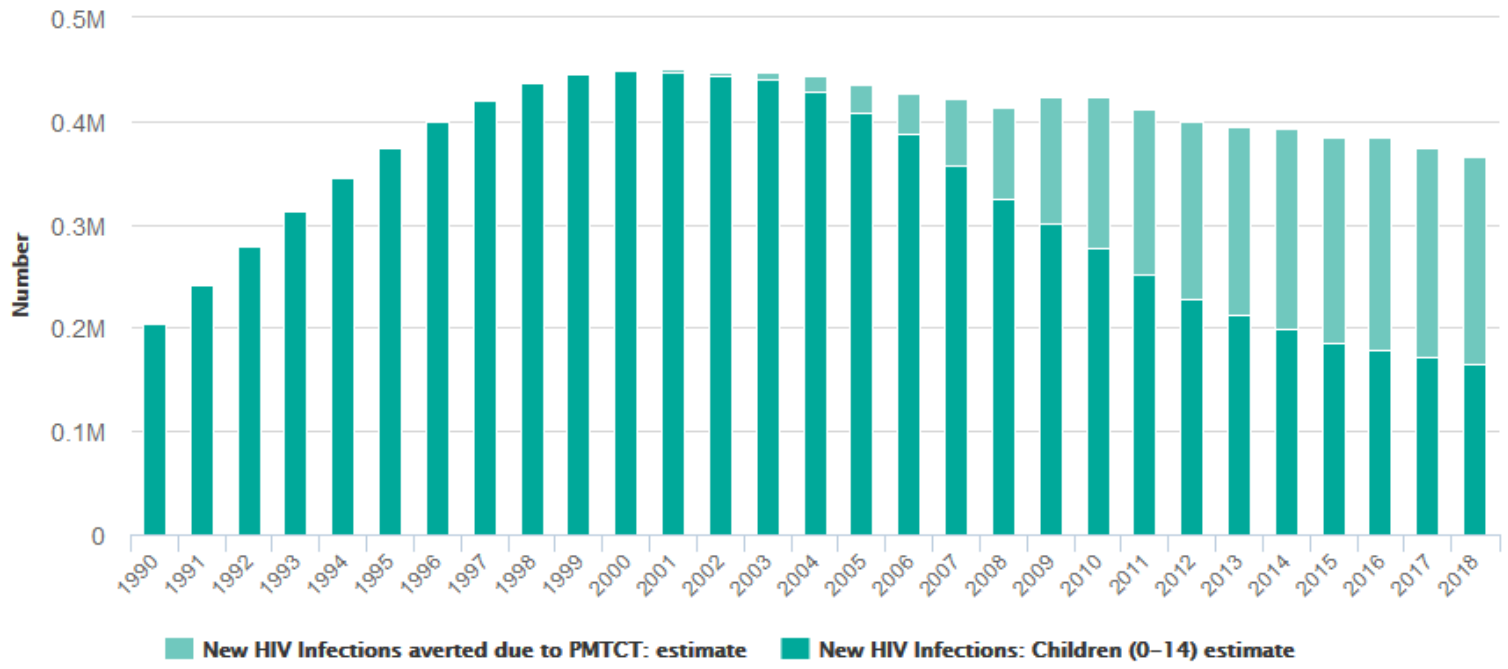
					• Longer ATV exposure was associated with higher language scores
87	Williams P. *et al.*	2016	United Sates of America	-	• Stavudine was associated with language impairment

Figure 1: Number of children exposed uninfected to HIV



Source: UNAIDS 2019 estimates

Figure 2: New HIV paediatric infections and new HIV infections averted due to MTCT prevention



Source: UNAIDS 2019 estimates; Global AIDS Monitoring 2019

Figure 3: Birth Defect according to ARV exposure

Table 3. Analyses Conducted by Type of Anomaly

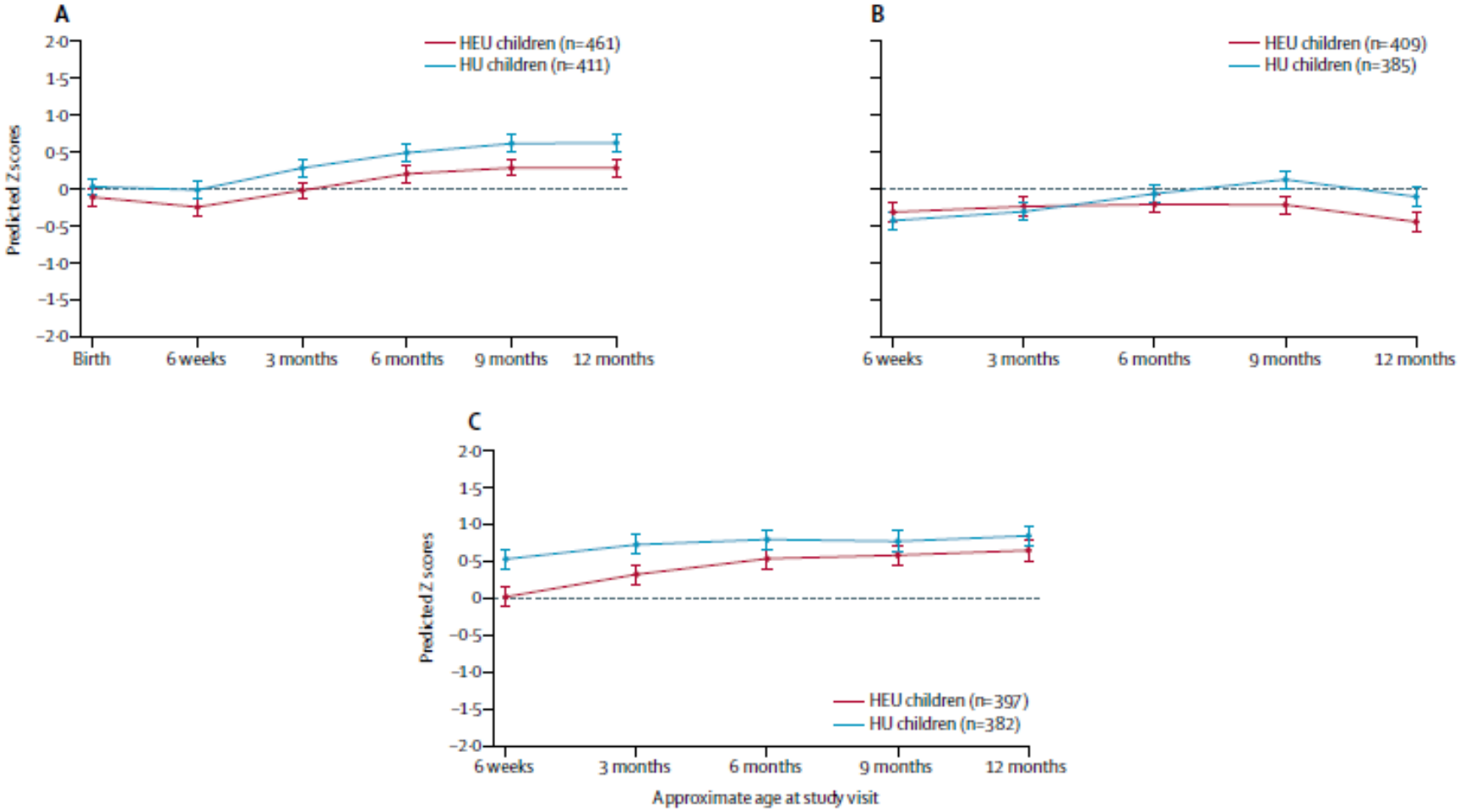
Type of Anomaly	Defect Rate, No./Total No. (%)		Odds Ratio (95% CI)	
	Exposed	Unexposed	Unadjusted Model	Adjusted Model[a]
Atazanavir sulfate				
Cardiovascular	7/222 (3.2)	33/2295 (1.4)	2.23 (0.98-5.11)	2.02 (0.88-4.64)
Musculoskeletal	11/222 (5.0)	46/2295 (2.0)	2.55 (1.30-5.00)	2.57 (1.30-5.08)
Skin	3/222 (1.4)	6/2296 (0.3)	5.23 (1.30-21.04)	6.01 (1.43-25.33)
Ritonavir when used as a booster				
Cardiovascular	16/635 (2.5)	24/1882 (1.3)	2.00 (1.06-3.79)	1.83 (0.96-3.49)
Musculoskeletal	22/635 (3.5)	35/1882 (1.9)	1.89 (1.10-3.25)	1.79 (1.02-3.14)
Lopinavir				
Cardiovascular	6/341 (1.8)	34/2176 (1.6)	1.13 (0.47-2.71)	0.79 (0.40-2.34)
Musculoskeletal	11/341 (3.2)	46/2176 (2.1)	1.54 (0.79-3.01)	1.40 (0.70-2.83)
Zidovudine				
Male genital	8/726 (1.1)	6/1791 (0.3)	3.31 (1.15-9.59)	3.18 (1.10-9.22)
Lamivudine				
Male genital	8/797 (1.0)	6/1720 (0.3)	2.90 (1.00-8.38)	2.77 (0.96-8.03)
Didanosine plus stavudine				
Cardiovascular	0/7	40/2510 (1.6)	NA	NA
Musculoskeletal	1/7 (14.3)	56/2510 (2.2)	7.30 (0.86-61.68)	8.29 (0.96-71.83)

Abbreviation: NA, not applicable.

[a] Models adjusted for any anomaly (low maternal CD4 count [<250 cells/mm^3] early in pregnancy and birth cohort), cardiovascular anomaly (birth cohort), musculoskeletal anomaly (low maternal CD4 count early in pregnancy and first-trimester maternal alcohol consumption), skin anomaly (low maternal CD4 count early in pregnancy), and male genital anomaly (maternal age >35 years at delivery).

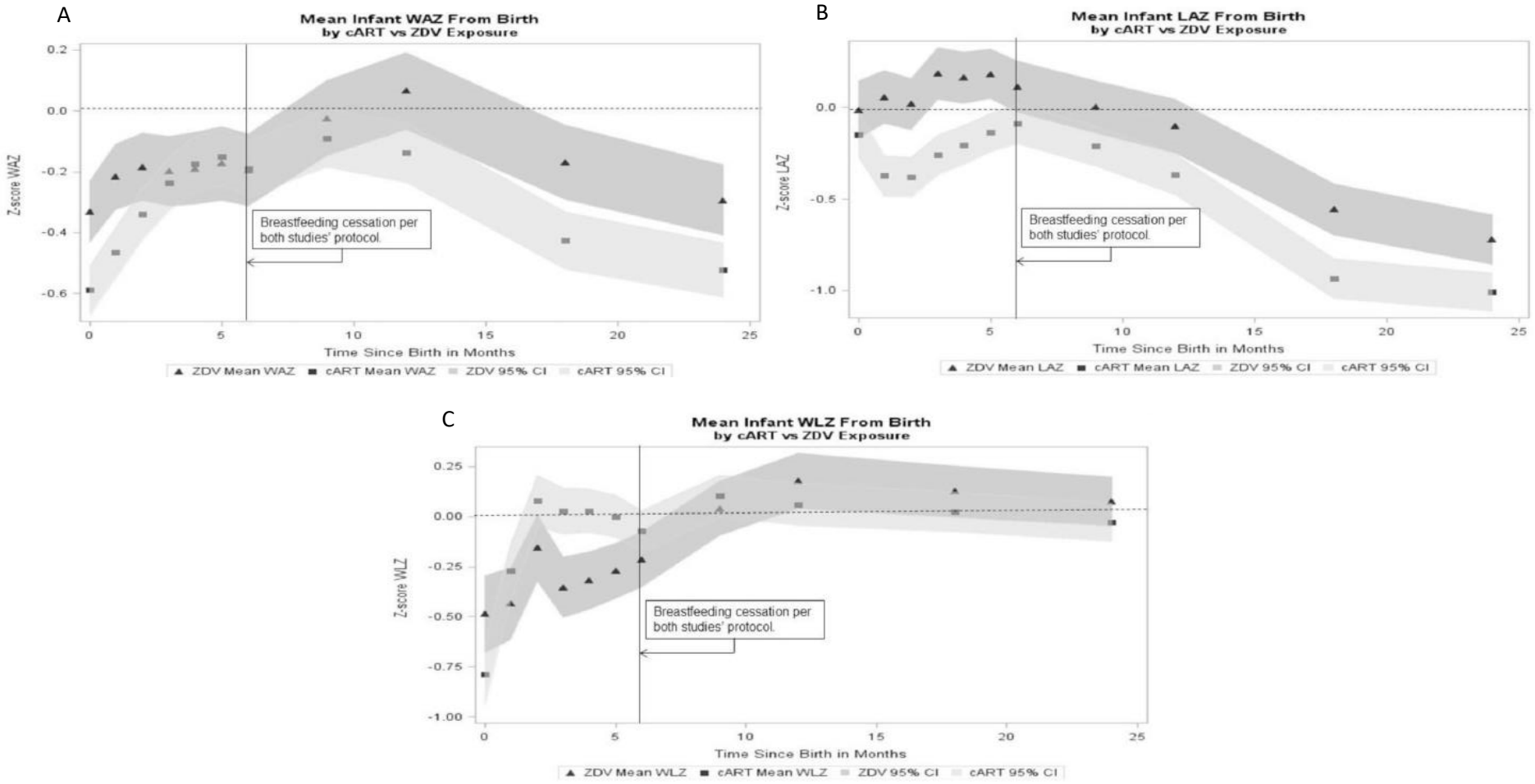
Source: Williams P, Crain M, Yildirim C, *et al.* 'Congenital Anomalies and in Utero Antiretroviral Exposure in Human Immunodeficiency Virus-Exposed Uninfected Infants'. JAMA Pediatrics 169, no. 1 (January 2015): 48–55.

Figure 4: WAZ (A), LAZ (B) and WLZ (C) from birth to 12 months comparing growth trajectories of HEU and HUU children



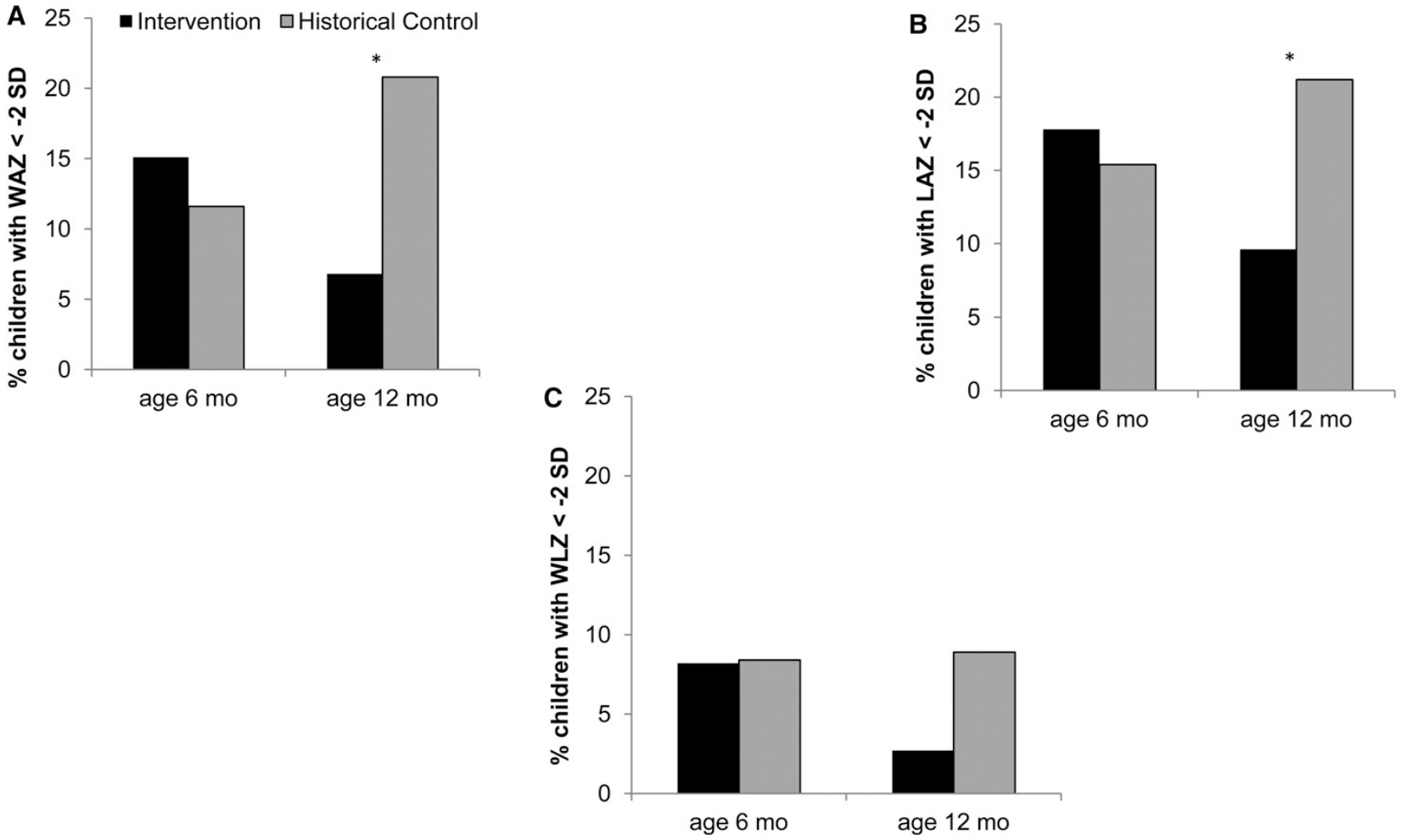
Source: Le Roux S, Abrams E, Donald K, *et al.* 'Growth Trajectories of Breastfed HIV-Exposed Uninfected and HIV-Unexposed Children under Conditions of Universal Maternal Antiretroviral Therapy: A Prospective Study'. The Lancet. Child & Adolescent Health 3, no. 4 (April 2019): 234–44.

Figure 5: WAZ (A), LAZ (B) and WLZ (C) from birth to 24 months by exposure to ZDV or to HAART



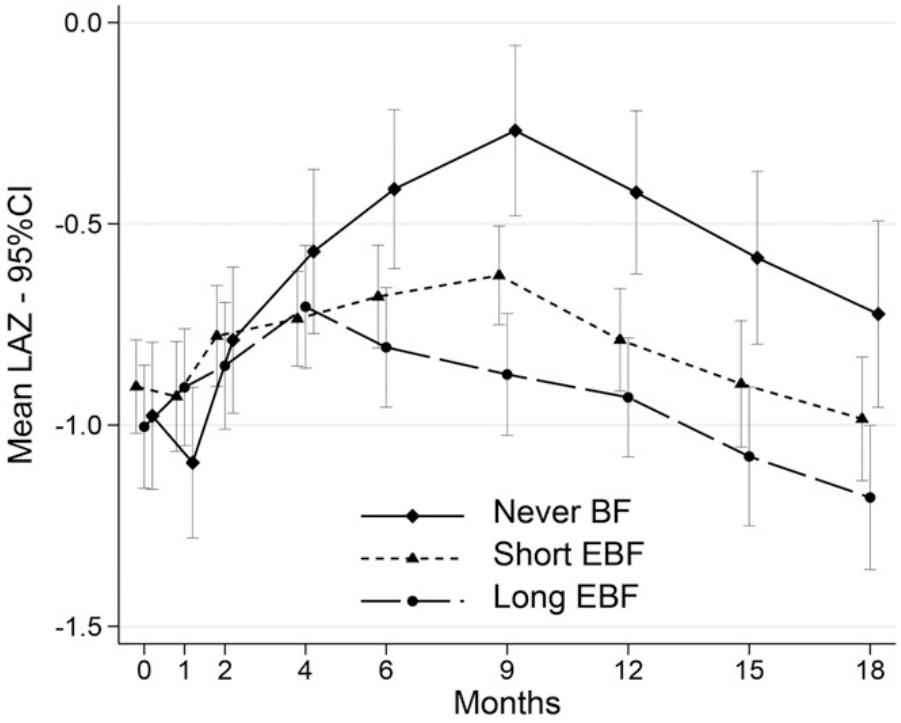
Source: Powis K, Smeaton L, Hughes M, *et al.* 'In-Utero Triple Antiretroviral Exposure Associated with Decreased Growth among HIV-Exposed Uninfected Infants in Botswana'. AIDS (London, England) 30, no. 2 (January 2016): 211–20.

Figure 6: Prevalence of underweight (A), stunting (B) and wasting (C) in HEU children vs historical control groups at 6 and 12 months



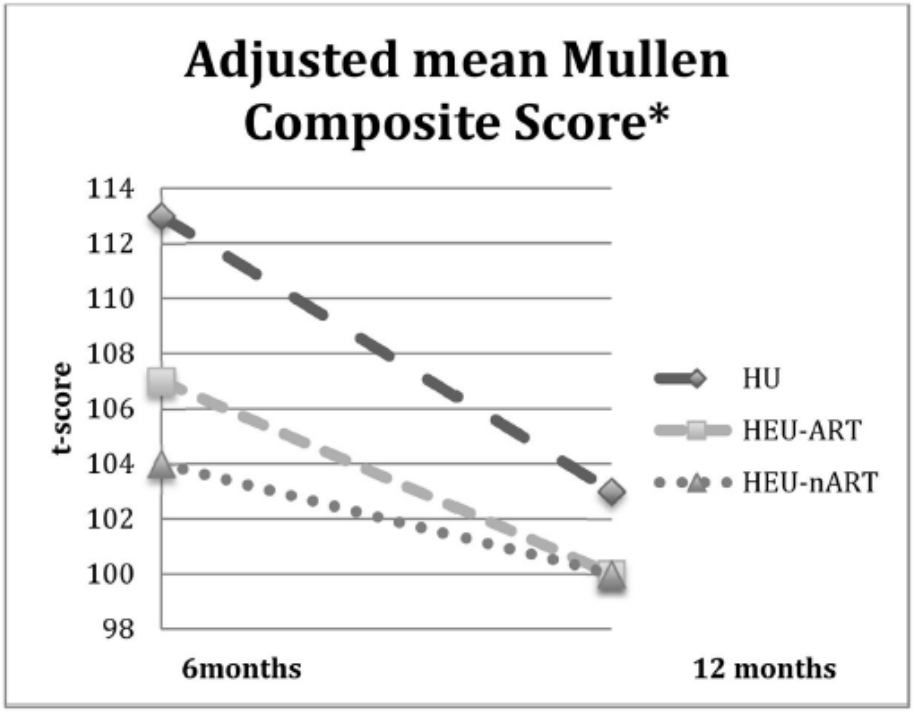
Source: Heidkamp R, Stoltzfus R, Fitzgerald D, Pape J. 'Growth in Late Infancy among HIV-Exposed Children in Urban Haiti Is Associated with Participation in a Clinic-Based Infant Feeding Support Intervention'. The Journal of Nutrition 142, no. 4 (April 2012): 774–80.

Figure 7: LAZ scores according to feeding practices in HEU children from birth to 18 months



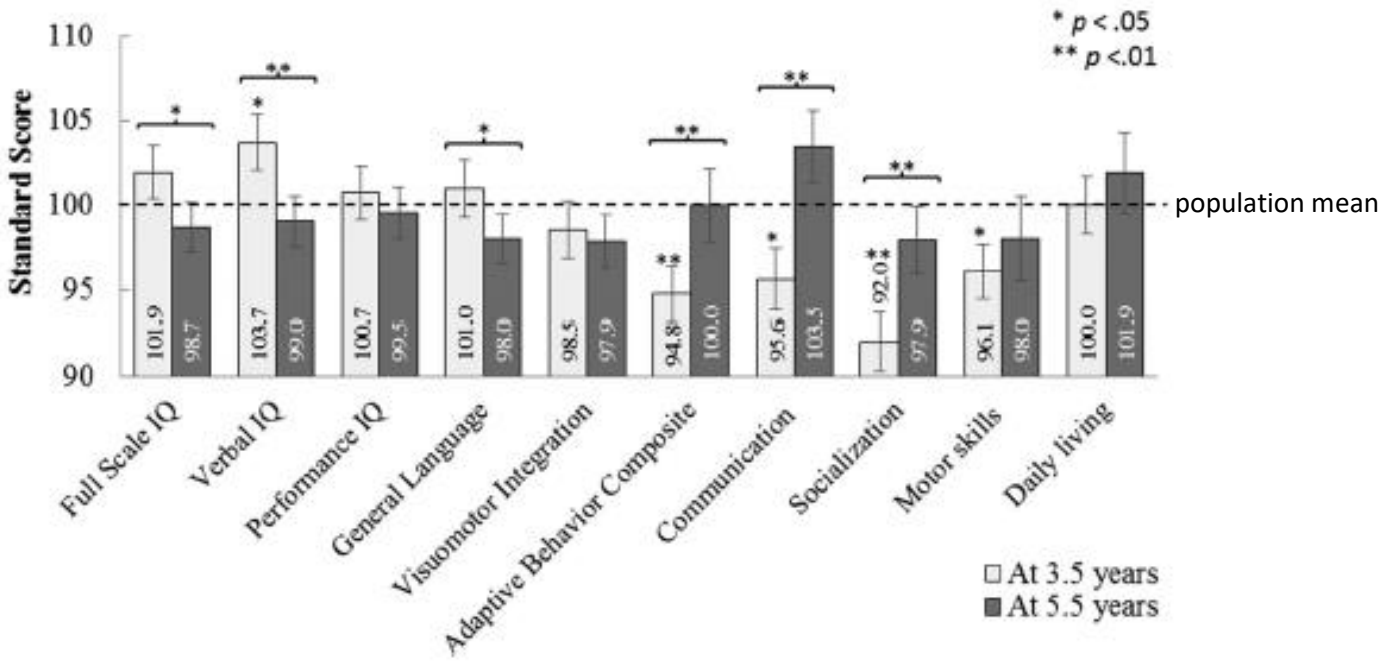
Source: Bork K, Cames C, Newell M, *et al.* 'Formula-Feeding of HIV-Exposed Uninfected African Children Is Associated with Faster Growth in Length during the First 6 Months of Life in the Kesho Bora Study'. The Journal of Nutrition 147, no. 3 (2017): 453–61.

Figure 8: Adjusted MSEL scores overtime amongst HUU children, HEU children exposed to ARV and HEU children unexposed to ARV



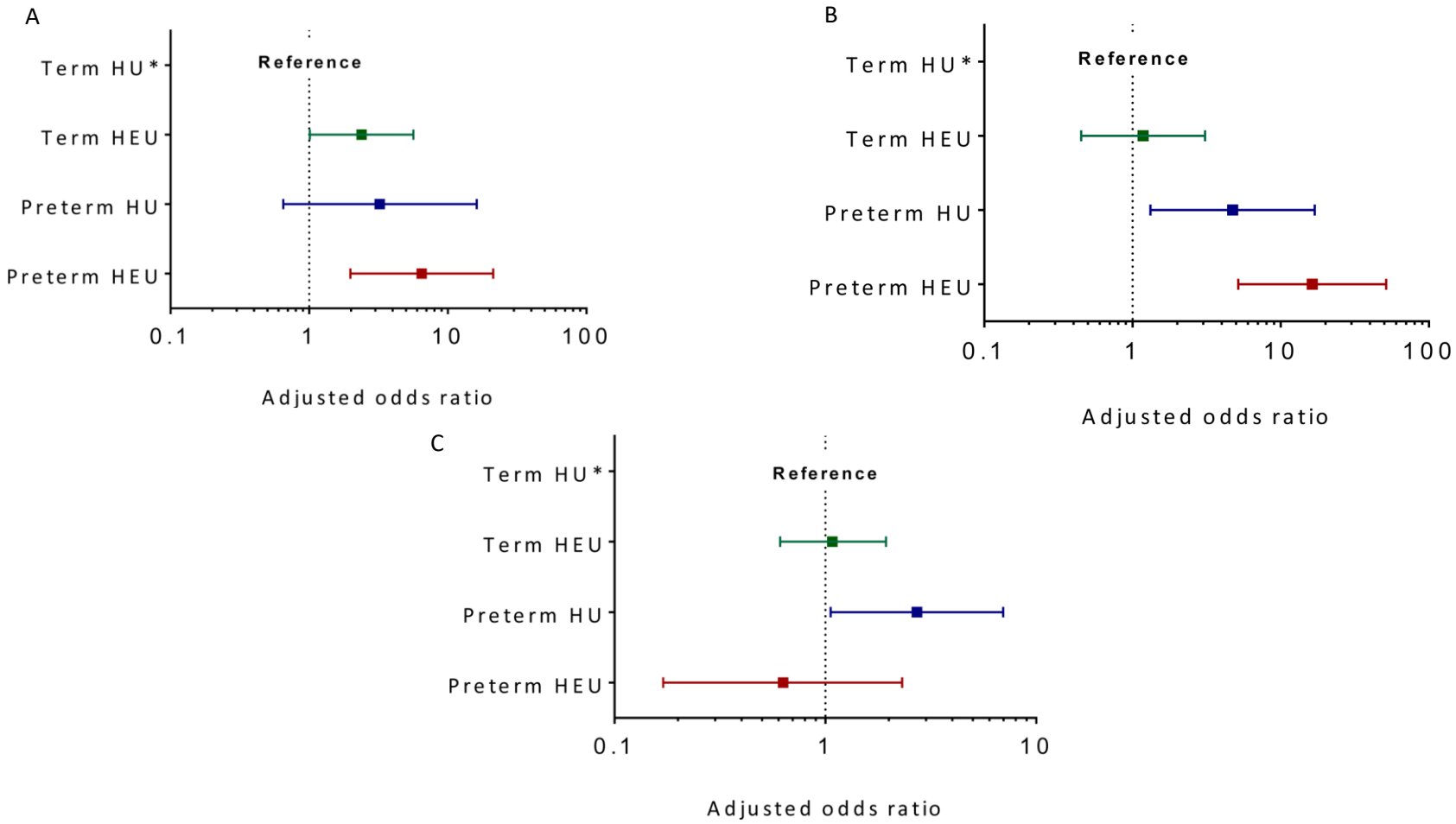
Source: Familiar I, Collins S, Sikorskii A, *et al.* 'Quality of Caregiving Is Positively Associated With Neurodevelopment During the First Year of Life Among HIV-Exposed Uninfected Children in Uganda'. Journal of Acquired Immune Deficiency Syndromes (1999) 77, no. 3 (01 2018): 235–42.

Figure 9: Neurodevelopmental assessment at 3,5 years old and follow-up at 5,5 years old



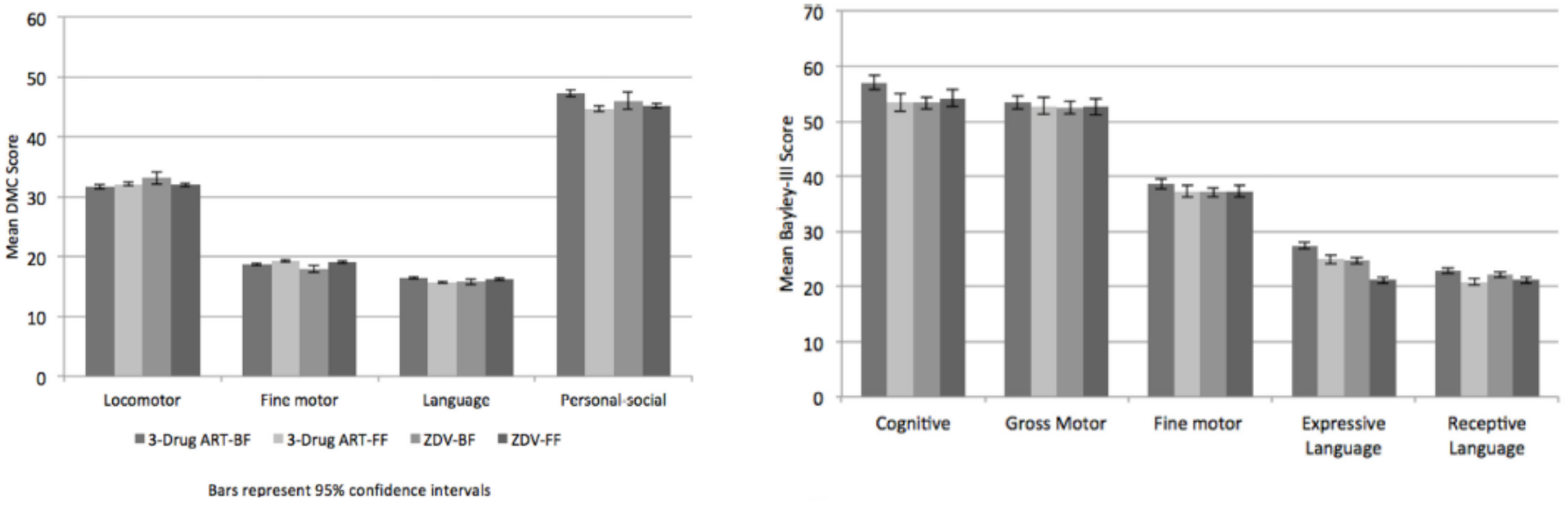
Source: Smith M, Puka K, Sehra R, Read S, Bitnun A. 'Longitudinal Development of Cognitive, Visuomotor and Adaptive Behavior Skills in HIV Uninfected Children, Aged 3-5 Years of Age, Exposed Pre- and Perinatally to Anti-Retroviral Medications'. AIDS Care 29, no. 10 (2017): 1302–8.

Figure 10: Adjusted models for Cognitive (A), Motor (B) and Language (C) delays in HEU and HUU children by preterm delivery using HUU term children as reference



Source: Le Roux S, Donald K, Brittain K, *et al.* 'Neurodevelopment of Breastfed HIV-Exposed Uninfected and HIV-Unexposed Children in South Africa'. AIDS (London, England) 32, no. 13 (24 2018): 1781–91.

Figure 11: BSID-III and Development Milestones Checklist scores at 24 months according to ARV exposure and feeding practices amongst HEU Botswana children



Source: Chaudhury S, Mayondi G, Williams P, *et al.* 'In-Utero Exposure to Antiretrovirals and Neurodevelopment among HIV-Exposed-Uninfected Children in Botswana'. AIDS (London, England) 32, no. 9 (01 2018): 1173–83.