



Neurological development of children who are HIV-exposed and uninfected

GABRIELA TOLEDO¹  | HÉLÈNE C F CÔTÉ^{2,3} | CATHERINE ADLER⁴ | CLAIRE THORNE¹ | TESSA GOETGHEBUER⁴ 

1 UCL Great Ormond Street Institute of Child Health, University College London, London, UK. **2** Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC; **3** Centre for Blood Research, University of British Columbia, Vancouver, BC, Canada. **4** Department of Pediatrics, Centre Hospitalier Universitaire Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium.

Correspondence to Gabriela Toledo, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK. E-mail: gabriela.toledo.19@ucl.ac.uk

PUBLICATION DATA

Accepted for publication 17th April 2021.

Published online

ABBREVIATIONS

ART	Antiretroviral therapy
CHEU	Children who are HIV-exposed and uninfected
CHUU	Children who are HIV-unexposed and uninfected
HIC	High-income country
HIV	Human immunodeficiency virus
LMICs	Low- and middle-income countries
NRTI	Nucleoside reverse transcriptase inhibitor
PVT	Prevention of vertical transmission
SMARTT	Surveillance Monitoring for ART Toxicities
WHO	World Health Organization

Widespread use of antiretroviral drugs for pregnant/breastfeeding females with human immunodeficiency virus (HIV) has led to declining vertical transmission. Despite being HIV-uninfected, the increasing number of children who are HIV-exposed and uninfected (CHEU) often present with developmental alterations. We review seminal and recent evidence on the neurological development of CHEU and associations with early life HIV/antiretroviral exposure. Our conceptual model highlights the numerous exposures and universal risk factors for CHEU developmental disorders. Early studies suggest a significant association between HIV exposure and neurological abnormalities, varying according to the burden of HIV-specific exposures and other risk factors. More recent observations from the modern era are inconsistent, although some studies suggest specific antiretrovirals may adversely affect neurological development of CHEU. As the CHEU population continues to grow, alongside simultaneous increases in types and combinations of antiretrovirals used in pregnancy, long-term monitoring of CHEU is necessary for understanding the effects of HIV/antiretroviral exposure on CHEU developmental outcomes.

BACKGROUND

Human immunodeficiency virus and pregnancy

Globally, approximately 1.3 million females living with human immunodeficiency virus (HIV) become pregnant annually.¹ In the absence of preventive measures for vertical transmission, 40% to 45% of infants born to females living with HIV may be vertically infected.^{2,3} Before 1994, the primary intervention for the prevention of vertical transmission (PVT) was avoidance of breastfeeding.⁴ In 1994, the Pediatric AIDS Clinical Trials Group (PACTG) study demonstrated that zidovudine prophylaxis given to pregnant females living with HIV and during the first 6 weeks of life significantly reduced the risk of vertical transmission.⁵ From 2004 to 2006, the World Health Organization (WHO) recommended combination antiretroviral therapy or antiretroviral prophylaxis for pregnant females living with HIV depending on clinical eligibility criteria.^{6,7} After the advent of evidence regarding the efficacy of antiretroviral therapy (ART) for PVT and the increased risk of infant mortality

associated with suboptimal breastfeeding in resource-limited settings,⁸⁻¹¹ the WHO recommended antiretroviral prophylaxis which allowed for safer and extended breastfeeding in resource-limited settings.³ In 2013, lifelong ART treatment was recommended for all pregnant and lactating females living with HIV, with breastfeeding for at least 12 months in low- and middle-income countries (LMICs) and avoidance of breastfeeding in high-income countries (HICs).¹²

Fetal neurological development

Child development is characterized by various phases including fetal brain development, which begins with neurogenesis, which continues through the first year of life. Migration of microglial cells starts around the fourth week of gestation, establishing a pool of resident immune cells, with synaptogenesis starting around week 12, followed by synapsis pruning. Gliogenesis and myelination start around week 22 and continue after birth until adulthood.¹³

During gestation, fetal neurological development is extremely sensitive to maternal exposures, such as infections, toxins, and illicit drugs, which are associated with a range of developmental disorders, depending on type and timing of exposure.^{14,15}

Children who are HIV-exposed and uninfected: a research priority

In the last two decades, effective PVT strategies have significantly reduced the incidence of perinatal HIV infections, resulting in increasing numbers of children who are HIV-exposed and uninfected (CHEU). With the implementation of maternal lifelong ART, more CHEU are being exposed to antiretroviral drugs.¹ In 2019, approximately 78% of CHEU were antiretroviral-exposed, compared to only 25% in 2010.¹ Currently, the global population of CHEU is estimated at 15.2 million, with over 90% living in sub-Saharan Africa.¹

CHEU have increasingly become a research priority because of their complex and multifactorial exposures associated with worse child health outcomes.¹⁶ In addition to unique HIV-specific exposures, they may also experience universal risk factors for poor development during the 'critical window' for infant growth and development.¹⁷ Before the widespread availability of ART for PVT, it was well recognized that CHEU were more likely to experience adverse birth outcomes,^{18,19} suboptimal growth,^{19,20} and increased infectious morbidity^{19,21,22} and mortality^{23,24} compared to their unexposed counterparts.

In the context of child development, the first study to evaluate CHEU neurological development described eight children presenting with neurological symptoms analogous to mitochondrial dysfunction in France.²⁵ A subsequent prospective cohort study reported a significantly increased incidence of mitochondriopathy at 18 months compared to the general population.²⁶ Alongside these rare disorders, there was also some concern around developmental delay in children HIV-exposed.²⁷⁻³⁰ Recent studies from the universal ART era have described mixed findings on CHEU neurological development,^{28,29,31-34} with some suggesting that poor development persists as a major problem for CHEU in the modern era.^{28,29,31,32}

There is a clear lack of consensus regarding the impact of exposure to maternal HIV/antiretrovirals on child neurological development. Evidently, studying the development of CHEU is challenging, owing to the rapid growth and restructuring of the brain from fetal development to adolescence,^{30,35} changes and variation in the management of HIV in pregnancy, and other potential risk factors. However, as PVT strategies shift towards maternal lifelong treatment, and as more antiretroviral drugs become available, understanding the short- and longer-term effects of HIV and antiretroviral exposure on CHEU development is critical. Our aim is to synthesize the evidence on the neurological development of CHEU and its association with perinatal exposure to maternal HIV/antiretrovirals.

What this paper adds

- Evidence on the neurological development of children who are human immunodeficiency virus (HIV)-exposed and uninfected (CHEU) is synthesized.
- Comparisons are made to children who are HIV-unexposed, across treatment eras and settings, and by antiretroviral drug regimens and drug classes.
- CHEU exposures are complex and include HIV-specific and universal risk factors which may affect development during the early years of life.

METHOD

Ovid Medline, Embase, and Google Scholar online databases were searched for relevant articles or conference abstracts published from January 1999 to September 2020. To be eligible for inclusion in this review, mother and child HIV status had to be reported. Articles that provided empirical data on the neurological development of CHEU (e.g. cognitive, motor, language, socioemotional, behavioural, or growth) were included. Papers were restricted to publications in English-language journals only. Systematic reviews with a meta-analytic component were included in summary tables.

Risk factors and mechanistic pathways underlying CHEU development

Although uninfected, CHEU are still HIV-affected. Separating the effects of HIV/antiretroviral exposure from universal risk factors has been particularly challenging, as HIV-specific exposures may affect development either directly via HIV-specific pathways, or indirectly by universal risk factors (Fig. 1).^{15,36}

HIV-specific exposures

Maternal HIV exposure

Early studies in CHEU suggested HIV may affect early brain growth and development without infection, irrespective of antiretroviral exposure status.^{25,26,37} Fetal immune activation and inflammation³⁸⁻⁴¹ and HIV-specific immune responses have been observed in CHEU,²² suggesting that HIV may modulate immune responses even in the absence of infection. As the immune system plays an important role in homeostasis⁴² and fetal development,⁴³ the dysregulation of immune mechanisms may prime neurotoxicity, influence cell migration, and impact CHEU brain development.^{15,44} Maternal immune activation may be associated with immunological dysregulation in CHEU with atypical white matter alterations.⁴⁵⁻⁴⁷ Advanced maternal HIV disease or detectable HIV viral load have been associated with increased risk of developmental disorders in CHEU.^{31,32,39,48}

Antiretroviral exposure

Although the benefits of antiretrovirals strongly outweigh the risks of infant toxicity, antiretroviral exposure can affect CHEU development by triggering HIV-specific pathways or indirectly by augmenting universal risk factors. For instance, exposure to nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with increased risk of mitochondrial dysfunction and atypical neurological

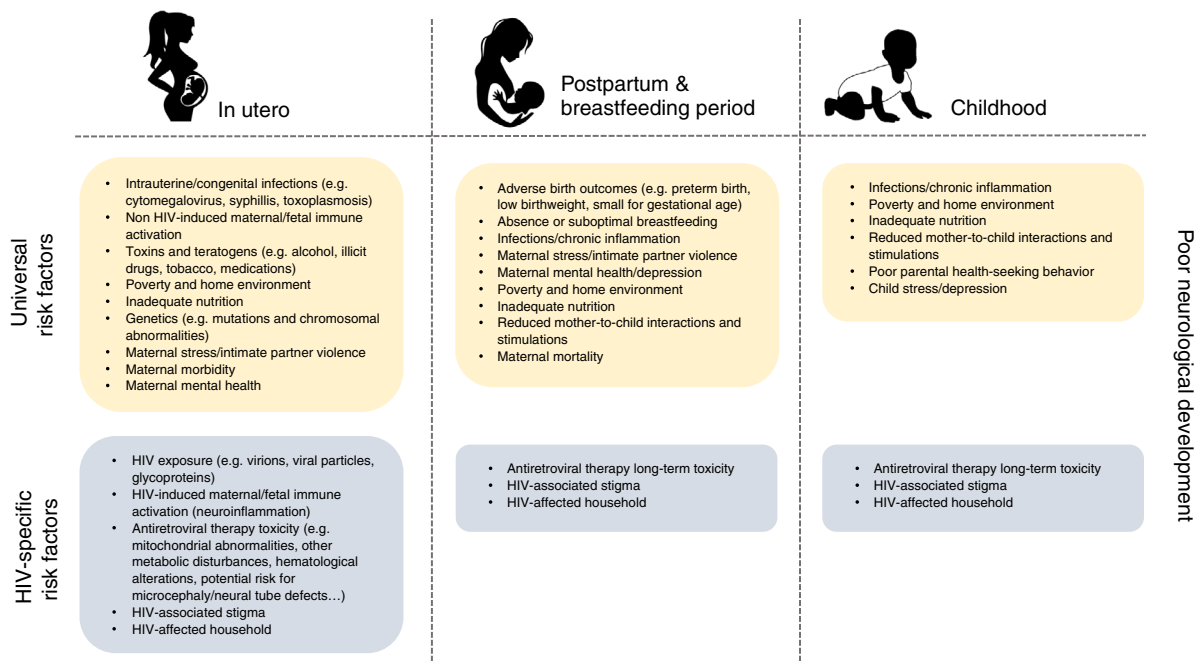


Figure 1: Conceptual framework of human immunodeficiency virus (HIV)-specific exposures and universal risk factors affecting the neurological development of children HIV-exposed and uninfected. [Colour figure can be viewed at wileyonlinelibrary.com]

issues.^{25,26,37} It is also well documented that exposure to specific antiretrovirals may increase the risk of preterm birth in CHEU,⁴⁹⁻⁵¹ which is associated with increased risk of neurodevelopmental disorders.^{41,52-59}

In the context of maternal lifelong ART, it is hypothesized that ART will have a positive impact on CHEU health, by simultaneously addressing some of the co-occurring HIV-specific exposures (e.g. maternal viral load) and universal risk factors (e.g. restoration of maternal health, extended breastfeeding in LMICs, reduced risk of adverse birth outcomes) for poor child development.^{12,23,60}

Universal risk factors

Maternal morbidity and mortality

Maternal physical and mental health have the potential to influence child development. Despite universal access to ART, maternal HIV infection is still associated with increased maternal morbidity and mortality which are linked to poorer CHEU health outcomes.⁶¹ Mothers who are unwell will have reduced mother-to-child interactions from the very first day after birth and may be less able to provide their children with early learning experiences, which shape the neural networks of the developing brain.⁶² This is particularly relevant among mothers with HIV, who may feel hindered in their role as a parent because of the fear of transmitting HIV to their offspring. Maternal depression,^{31,63} stress,^{64,65} and antenatal intimate partner violence³¹ have been identified as risk factors for lower overall performance in neurodevelopmental assessments and delayed cognitive functioning in CHEU. Parental death can negatively affect child development, especially if

a child is institutionalized or has reduced school attendance.⁶⁶

Adverse birth outcomes

CHEU are at increased risk of adverse birth outcomes (i.e. preterm birth, small for gestational age, low birthweight [$<2500\text{g}$])⁴⁹ which are risk factors for poorer neurological development.^{18,55}

Intrauterine/congenital infections and non-HIV induced immune activation

Several intrauterine and congenital infections during pregnancy can adversely affect a developing fetus.^{67,68} CHEU present with an increased risk of congenital infections (new infections or reactivated), including cytomegalovirus, syphilis, and toxoplasmosis.⁶⁹⁻⁷² Other infections or chorioamnionitis may induce preterm labour, which could impact child development.^{15,69} Furthermore, maternal immune activation, which may be triggered by infectious stimuli during pregnancy, has been linked to central nervous system disorders, such as autism spectrum disorder, bipolar disease, and schizophrenia in offspring.⁷³⁻⁷⁵

Toxins and teratogens

In some settings, HIV infection is associated with an augmented risk of maternal substance misuse (including alcohol, illicit drugs, and tobacco)⁷⁶ that can affect neurological development.¹⁴ This can manifest through direct toxicity, exacerbation of inflammatory upregulation, or poorer health-seeking and parenting behaviour.¹⁵

Genetics

Early life biological processes are influenced by the intrauterine environment. HIV infection has been associated with epigenome-wide differential DNA methylation,⁷⁷ which may have long-term consequences on CHEU development.^{68,78}

Childhood illness

CHEU are at increased risk of infectious morbidity,^{36,79–81} manifesting as more frequent hospitalizations and more severe infectious diseases,^{21,36} which can have long-term and cumulative effects on development.

Infant feeding practices

Breastfeeding provides infants with essential nutrition needed to thrive and protection against some life-threatening childhood diseases in the first 12 months of life. It is associated with earlier attainment of child developmental milestones and language,^{82,83} as well as lower risk of neurodevelopmental disorders.^{84–86} Breastfeeding in females living with HIV is discouraged in HICs and strongly encouraged in LMICs, although CHEU may still experience suboptimal breastfeeding practices.¹⁵

Poverty and home environment

Poverty in the context of HIV is complex and is associated with worse child neurological outcomes^{15,87,88} via multifactorial pathways involving food insecurity; access to health care, education, and employment; increased maternal illness; and higher child morbidity. HIV-affected children living in such conditions face some or all of these adversities, which can increase risk of chronic stress and depression,⁶² impact the parent-child relationship, and influence development.

Inadequate nutrition

Food insecurity and HIV infection often coexist.⁶⁴ Maternal food insecurity is a risk factor for adverse birth outcomes, and may result in child nutritional insufficiencies which can hinder optimal growth and development.⁸⁹

Other factors

There may be additional, yet unknown, risk factors for poorer neurological development of CHEU.

Comparison of neurological development in CHEU and children who are HIV-unexposed and uninfected

Studies comparing the developmental outcomes of CHEU and children who are HIV-unexposed and uninfected (CHUU) are critical for understanding the effect HIV/antiretroviral exposure may have on child neurological development (Table S1, online supporting information). Eight observational studies from Asia, Africa, and North America all reported significant differences in various developmental outcomes between CHEU and CHUU. The earliest were two cross-sectional studies conducted in preschool and school-aged children from Thailand and the Democratic

Republic of Congo. They reported significantly lower cognitive functioning and poorer development of motor, mental, and language domains in CHEU compared to CHUU.^{90,91} In one of the largest cohorts to date, Zimbabwean CHEU presented with lower head-circumference-for-age z-scores and higher prevalence of microcephaly than CHUU over the first year of life.⁹² Findings from these early studies highlight the effect of HIV exposure on neurological development without the potential confounding effects of antiretroviral exposure.

Alongside these developmental assessments, two retrospective Canadian studies have observed significantly higher risk of neurodevelopmental disorders in CHEU than CHUU.^{93,94} In a cross-sectional nested case-control study, CHEU diagnosed with autism spectrum disorder had significantly higher leukocyte mitochondrial DNA content than controls, suggesting mitochondrial dysfunction may contribute to autism spectrum disorder risk in CHEU.⁹⁴ In another retrospective cohort study, investigators reported CHEU had a significantly higher risk of preterm birth, presenting disturbance of emotions, hyperkinetic syndrome, autism spectrum disorder, and developmental delays compared to matched controls.⁹³ Numerous other studies have identified increased risk of preterm birth for CHEU,^{18,49,50,95} especially when some antiretroviral regimens are initiated before conception.⁴⁹ This is particularly relevant given the mediating effects of preterm birth and/or low birthweight on neurological development.^{54,55}

Subsequent studies, conducted when antiretrovirals were more readily available, are important for understanding the combined effects of HIV/antiretroviral exposure on neurological development. Findings from three African studies demonstrated persisting risk for developmental delays among CHEU, despite improved access to PVT services.^{28,41,96} In South Africa, a prospective cohort study of breastfed CHEU exposed to maternal ART reported significantly higher odds of any cognitive and motor delay but not language delay in CHEU compared with breastfed CHUU at ages 11 to 18 months.⁴¹ Moreover, they found that CHEU born preterm had a 16-fold increased odds of motor delay when compared to CHUU born at term.⁴¹ Another South African study reported no differences in developmental scores at 6 months, but significantly lower scores on receptive and expressive language domains at 24 months in CHEU compared to CHUU.²⁸ This study also showed that absence of breastfeeding, preterm birth, and maternal depression were risk factors for developmental outcomes in CHEU.²⁸ Findings from a recent cross-sectional Zimbabwean study demonstrated significantly lower developmental scores in CHEU compared to CHUU at 24 months of age, mainly driven by differences in gross motor and language scores.⁹⁶ These findings are also supported by a recent meta-analysis synthesizing data from 12 cohorts using the Bayley Scales of Infant and Toddler Development assessment tool. A Bayesian meta-regression showed that CHEU mean scores for the mental

and psychomotor development index were consistently lower than in CHUU, even after adjusting for confounders, but this difference did not reach statistical significance.²⁹

Other studies have observed no significant differences in developmental outcomes of CHEU and CHUU (Table S1).^{54,76,87,97-99} One of these, conducted when single dose nevirapine was the main PVT strategy, reported no differences for cognitive, personal-social, fine motor-adaptive, and gross motor development between CHEU and CHUU up to 2 years of age in Malawi and Uganda.⁹⁹ In a later prospective study from Canada, CHEU exposed to combination ART performed similarly to CHUU on developmental assessments, after adjusting for maternal substance use during pregnancy.⁷⁶ Subsequently, in a large prospective study conducted in Malawi and Uganda, CHEU whose mothers strictly adhered to their ART antepartum and postpartum performed similarly to CHUU on neurodevelopmental assessments,¹⁰⁰ and, in a smaller cross-sectional study from South Africa, CHEU born at term did not present with any cognitive, language, or motor delays compared to CHUU.³³

CHEU neurodevelopment and ART exposure: differences by setting

As PVT strategies shift from maternal antiretroviral prophylaxis to lifelong ART treatment for females living with HIV, it is critical to understand if CHEU risk for poor developmental outcomes is further impacted by in utero and extended exposure to maternal ART. In this context, it is also important to consider whether the effects of HIV/ART exposure may differ by setting, where the epidemiology of HIV and burden of universal risk factors vary. Eight studies investigating the developmental outcomes of CHEU with ART exposure (i.e. combination ART/triple ART) are summarized in Table S2 (online supporting information).

Among studies conducted in LMICs, a study from South Africa reported that CHEU with in utero ART exposure performed as well as CHEU with single antiretroviral exposure.³³ Consistent with these findings, a study from Malawi and Uganda similarly reported no difference in neurodevelopment of CHEU exposed to zidovudine or nevirapine monotherapy compared to those exposed to ART, although assessment scores were worse for infants whose mothers did not remain on ART.¹⁰⁰ In Mma Bana and Tshipidi studies from Botswana, ART exposure during pregnancy and breastfeeding was not associated with neurological impairment,¹⁰¹ and neurodevelopmental outcomes were similar in ART-exposed and zidovudine-exposed children at 24 months of age.³⁴

Among studies conducted in HICs, a cross-sectional analysis of the Surveillance Monitoring for ART Toxicities (SMARTT) Study reported that antiretroviral exposure was associated with higher motor developmental scores in CHEU with low birthweight but not in CHEU with normal birthweight.¹⁰² In another cross-sectional analysis from

SMARTT, no differences were observed in any developmental domains among CHEU with *in utero* exposure to ART compared to CHEU exposed to one to two antiretrovirals, three NRTIs, or no antiretrovirals during pregnancy, irrespective of timing of initiation.⁵⁴

Although studies on timing of antiretroviral initiation are limited, most suggest no relationship between earlier exposure to antiretrovirals and risk of developmental delays.^{54,103-105} In a prospective study, no association between cumulative duration of prenatal ART exposure and cognitive and academic outcomes was reported.¹⁰⁵ Whereas in the PACTG study, a significant trend of higher mental scores with increasing duration of maternal antiretroviral exposure was noted.¹⁰² In Latin America and the Caribbean, no significant associations between microcephaly or neurological conditions (including mitochondrial disorders) and trimester of ART initiation, maternal HIV viral load, or CD4⁺ cell count during pregnancy were observed.¹⁰⁶

Together, these findings support the safety of ART regimens in the context of child neurological development. However, the current evidence base on CHEU development in the era of lifelong treatment is limited, and more studies are needed to rule out any additional risks associated with exposure to maternal ART.

Comparative safety of antiretrovirals

It is also crucial to understand how exposure to specific antiretrovirals may affect the brain and impact child neurological development. However, investigating specific antiretrovirals is complicated by the fact that maternal ART regimens typically contain three different antiretrovirals belonging to at least two drug classes, and that regimens for PVT and treatments change over time. Observational studies assessing specific antiretroviral drugs or classes in relation to CHEU neurological development are presented in Table S3 (online supporting information).

NRTIs

The brain is a mitochondrial-rich tissue and NRTIs, which are included in most ART regimens, are known to cause mitochondrial toxicity in adults and children living with HIV.^{107,108} NRTIs can also cross the placental barrier and are secreted into breast milk.¹⁰² Earlier studies looking at the neurological development of CHEU established an increased risk of mitochondrial dysfunction in children with exposure to NRTIs, such as lamivudine and/or zidovudine in the third trimester.^{25,26,37} Other early NRTIs such as didanosine and stavudine have also led to mitochondrial DNA depletion,^{107,108} while newer NRTIs may increase the risk of mitochondrial DNA mutations and deletions.¹⁰⁹ Recent paediatric studies reported elevated mitochondrial DNA levels in association with HIV/ART exposure and autism spectrum disorder.¹¹⁰ As mitochondria play a central role in metabolism, steroid synthesis, calcium haemostasis, and apoptosis, it follows that NRTI-induced mitochondrial dysfunction presents a number of

potential mechanistic pathways that could be linked to neurological disorders in CHEU.

The trigger-based design of the SMARTT study identified an increased risk of both neurological cases (defined as febrile or afebrile seizure, microcephaly, or other neurological diagnosis) and neurodevelopmental cases (defined as score >2 standard deviations below population norm on age-specific tests) associated with didanosine use at any time during pregnancy;¹⁰⁴ this association was confirmed in an updated analysis.¹¹¹ The combination of didanosine plus stavudine was also associated with an increased risk of both neurodevelopmental and language delays in CHEU compared to unexposed CHEU,¹⁰⁴ probably due to mitochondrial toxicity and lactic acidosis in pregnant females. This ultimately led to recommendations against using this antiretroviral combination during pregnancy.¹¹²

Non-NRTIs

Historically, there was some concern regarding prenatal use of efavirenz, as early nonhuman primate studies showed neural tube defects with periconception efavirenz use, which led to recommendations against the use of efavirenz during the first trimester of pregnancy in 2005 and 2006.¹¹³ However, subsequent systematic reviews concluded that exposure to efavirenz during the first trimester did not significantly increase risk of birth abnormalities in humans.⁵⁶ Findings from the Tsepamo Study and the European Pregnancy and Paediatric HIV Cohort Collaboration further supported the periconception use of efavirenz during pregnancy.^{58,114}

Despite early concerns, efavirenz is a very widely used antiretroviral, and was previously part of the WHO first-line recommended regimen.¹¹⁵ In a cross-sectional analysis of the Tshipidi Plus Study, investigators reported in utero exposure to efavirenz-based ART was not associated with worse scores on cognitive or gross motor domains but in receptive language, Developmental Milestone Checklist language, fine motor, and the Profile of Social Emotional Development compared to non-EFV-based ART exposure.¹¹⁶ In a later longitudinal analysis of the SMARTT Study, an increased risk of microcephaly was associated with efavirenz exposure and worse neurodevelopmental assessments at ages 1 and 5 years.¹¹⁷ This was followed by another SMARTT report which described increased risk of microcephaly, seizures (febrile or not), ophthalmological disorders, and other neurological disorders in CHEU compared to CHUU, and higher risk in CHEU with efavirenz-exposure at conception compared to CHEU with no efavirenz-exposure during pregnancy.¹¹¹ Findings regarding the safety of efavirenz have been inconsistent, and although efavirenz is no longer the WHO first-line recommended regimen, it is still widely used for PVT in many countries.

Protease inhibitors

Protease inhibitor based regimens have been associated with an increased risk of preterm delivery in some

studies.^{51,118} Some protease inhibitors have also been implicated in developmental delay. Exposure to atazanavir during the second/third trimester was associated with a three-fold increased odds of late language emergence¹¹⁹ and with transient delays in socio-emotional development and language,^{120,121} although another study found no association between meconium atazanavir concentrations and early language delays.¹⁰³ In cell models, several protease inhibitors have been shown to induce oxidative stress and senescence in vascular cells, two potential mechanisms that could adversely affect neurological development.¹²² Current findings regarding the use of protease inhibitor based regimens are discordant. Studies observing an increased risk of preterm birth attributed to protease inhibitors are concerning, given the mediating effects this may have on child neurological development. Further research is needed to understand the safety of protease inhibitor-based regimens with respect to early and later child developmental outcomes.

Integrase strand transfer inhibitors

Dolutegravir has been recommended within first-line and second-line ART regimens for all populations globally since July 2018, reflecting its higher barrier to resistance, fewer side effects, and more effective viral suppression compared to efavirenz.¹²³ However, there was initially a note of caution for females of reproductive age, because of a potential safety signal for neural tube defects associated with periconception dolutegravir exposure from the Tsepamo Study in Botswana.⁵⁷ A subsequent analysis from this study found a significantly higher prevalence of neural tube defects for periconception dolutegravir-based ART versus non-dolutegravir ART at conception but with lower prevalence than initially reported,^{58,59} further supporting the WHO's recommendation of dolutegravir for all people living with HIV, including females of reproductive age.¹¹⁵ Other studies have reported reassuring results for the use of dolutegravir during pregnancy,¹²⁴ although a longitudinal analysis of the SMARTT study revealed increased risk of neurological disorders such as febrile seizure microcephaly, or other neurological or ophthalmological disorders after dolutegravir exposure.¹¹¹ Additionally, a recent study reported mitochondrial dysfunction in cells exposed to integrase strand transfer inhibitors dolutegravir and elvitegravir.¹²⁵ Surveillance studies looking at the effects of antiretrovirals remain important, especially as more antiretroviral integrase strand transfer inhibitors become available.

DISCUSSION

Beyond preventing infants from acquiring HIV, it is critical to ensure CHEU are supported to thrive in all elements of their growth and development. Our conceptual model illustrates the importance of universal risk factors for child neurological development. It also highlights how these factors may be more numerous than HIV-specific exposures and emphasizes their potential to impact CHEU at every point

of development. Notably, there remains a dearth of literature regarding the underlying mechanistic pathways and biological processes linking these HIV-specific and universal risk factors to child health outcomes.

In this review, studies from the pre-universal ART era demonstrated a significant association between HIV exposure and CHEU impaired development, although the effects of HIV exposure may differ between HICs and LMICs where maternal HIV disease severity, antiretroviral exposure, and infant feeding practices are different. Studies from the ART era have observed discordant findings on the development of CHEU: some suggest CHEU present with worse developmental outcomes than their unexposed counterparts, while other studies reported no differences (Table S1). Various studies from LMICs and HICs reassuringly observed similar developmental outcomes in CHEU with single, dual, or triple ART exposure (Table S2). Other studies demonstrated that exposure to specific antiretroviral drugs may be more likely to adversely affect development (Table S3). Concerns remain regarding language as many early and recent findings show poorer language development in CHEU compared to CHUU,^{28,90,91,96} sometimes incriminating specific antiretrovirals like didanosine, stavudine, and atazanavir.^{104,119-121}

This review demonstrates the highly heterogeneous literature examining potential effects of *in utero* and early life HIV/antiretroviral exposure on CHEU neurodevelopment and neurological outcomes. Overall, insights from the current literature are limited, as studies largely come from secondary analyses of vertical transmission studies, and are frequently restricted to the first 2 years of life, during which expressions of developmental delay may not be easily identified. Evidently, studies of longitudinal nature with larger sample sizes contribute largely to the literature because of their robust measures on CHEU development. However, early studies vary considerably regarding exposure/outcome definitions and measures, PVT strategies, and study populations, limiting their interpretability and comparability. Although the number of studies with validated measures is growing, there is also inconsistent use of standardized, validated assessment tools. Some studies also lack appropriate control groups or information on additional risk factors, such as socioeconomic conditions and infant feeding practices, which may confound or modify the relationship between HIV/antiretroviral exposure and CHEU developmental outcomes. This is further complicated by the

substantial changes in the management of HIV in pregnancy, as well as improved parental and child health in resource-limited settings. These observations highlight the need for coordinated definitions of exposure and outcomes, inclusion of demographic characteristics relevant in national contexts, monitoring of neurodevelopment beyond infancy, and reinforcement of specific methodological principles. Currently, international research groups are coordinating efforts in this respect to help integrate CHEU research (A Harmonized Infrastructure FOR Monitoring Health Outcomes of the HIV FREE Generation, CE 2020, personal communication). Collectively, this presents the prerequisites necessary to developing robust longitudinal and surveillance studies across various settings, as well as meta-analyses,²⁹ although we recognize that such an endeavour is challenging, owing to HIV-associated stigma and other factors.

There is an urgent need to better understand the potential origins and mechanistic pathways underlying CHEU impaired development, their long-term clinical significance, and the relative importance of ART exposure and universal risk factors in mediating these poor outcomes. Although administrative health data may provide useful information, this will be best accomplished by designing large prospective cohort studies, using careful methodological considerations and harmonized approaches to facilitate pooled analyses, as well as coordinated efforts to identify and implement effective interventions to reduce the burden of risk factors on CHEU health globally.

ACKNOWLEDGEMENTS

The authors have stated they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Observational studies comparing neurodevelopment in CHEU and CHUU

Table S2: Studies reporting CHEU neurodevelopment and ART exposure by LMICs and HICs

Table S3: Studies reporting CHEU neurological disorders and ARV drug regimens

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