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Review Article

Exposure to HIV during pregnancy and child neuropsychomotor development: a scoping review

Exposição ao HIV durante a gestação e o desenvolvimento neuropsicomotor infantil: uma revisão de escopo
Exposición al VIH durante la gestación y el desarrollo neuropsicomotor infantil: una revisión de alcance

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ABSTRACT

Background and Objectives: Aiming to contribute to the elucidation of factors involved in neurodevelopmental alterations in children, whether infected or not, born to HIV-positive mothers, this study mapped the existing literature on the influence of HIV exposure during pregnancy on child neuropsychomotor development. **Methods:** This study is a scoping review registered on the Open Science Framework platform. An electronic search was conducted in the databases SciELO, PubMed, Embase, LILACS, Web of Science, CINAHL, BDTD, and the Open Gray repository, using descriptors related to child development and HIV. Additionally, a methodological quality assessment was performed. **Conclusion:** The analyzed studies indicate that HIV exposure during pregnancy is not a determinant of neuropsychomotor developmental alterations. Instead, HIV infection itself appears to be the critical factor due to the virus's impact on the central nervous system. Nevertheless, children exposed to HIV in utero but not infected may also experience developmental alterations, primarily influenced by environmental factors.

Keywords: *HIV. Acquired Immunodeficiency Syndrome. Child. Child Development.*

RESUMO

Justificativa e Objetivos: Visando contribuir para a elucidação dos fatores envolvidos nas alterações do neurodesenvolvimento de crianças, infectadas ou não, filhas de mães soropositivas para o HIV, este trabalho mapeou a literatura existente sobre a influência da exposição ao HIV durante a gestação no desenvolvimento neuropsicomotor infantil. **Método:** Revisão de escopo registrada na plataforma *Open Science Framework*. Foi realizada uma busca eletrônica nas bases de dados Scielo, PubMed, Embase, Lilacs, Web of Science, CINAHL, BDTD e no repositório *Open Gray* com descritores relacionados ao desenvolvimento infantil e ao HIV. Também foi realizada uma análise da qualidade metodológica. **Conclusão:** Os estudos analisados demonstraram que a exposição ao HIV durante a gestação não é determinante para alterações no desenvolvimento neuropsicomotor, e sim a própria infecção pelo HIV em virtude da ação do vírus no sistema nervoso central. Entretanto, crianças expostas ao HIV durante a gestação, mas não infectadas, também podem apresentar alterações do desenvolvimento, associadas principalmente a fatores ambientais.

Descritores: *HIV. Síndrome da Imunodeficiência Adquirida. Criança. Desenvolvimento Infantil.*

RESUMEN

Justificativa y Objetivos: Con el objetivo de contribuir a la elucidación de los factores involucrados en las alteraciones del neurodesarrollo en niños, ya sean infectados o no, nacidos de madres VIH positivas, este estudio realizó un mapeo de la literatura existente sobre la influencia de la exposición al VIH durante la gestación en el desarrollo neuropsicomotor infantil. **Método:** Se trata de una revisión de alcance registrada en la plataforma *Open Science Framework*. Se llevó a cabo una búsqueda electrónica en las bases de datos SciELO, PubMed, Embase, LILACS, Web of Science, CINAHL, BDTD y en el repositorio *Open Gray*, utilizando descriptores relacionados con el desarrollo infantil y el VIH. Además, se realizó un análisis de la calidad metodológica de los estudios incluidos. **Conclusión:** Los estudios analizados indican que la exposición al VIH durante la gestación no es un factor determinante en las alteraciones del desarrollo neuropsicomotor. En cambio, la infección por VIH en sí misma parece ser el elemento clave, debido a la acción del virus en el sistema nervioso central. No obstante, los niños expuestos al VIH en el período prenatal, pero no infectados, también pueden presentar alteraciones en el desarrollo, principalmente asociadas a factores ambientales.

Palabras Clave: *VIH. Síndrome de Inmunodeficiencia Adquirida. Niño. Desarrollo Infantil.*

INTRODUCTION

Childhood represents a fundamental stage of human development, as it is during this period that most neuropsychomotor development (NPMD) occurs. This process involves multiple aspects, including growth, neurological maturation, and the acquisition of behavioral, cognitive, and socio-emotional skills by the child. Several factors can influence neuropsychomotor development and are classified as intrinsic, when related to biological and genetic aspects, or extrinsic, when resulting from the environment in which the child is raised. Among the extrinsic factors, social and emotional aspects, maternal education level, family structure, and exclusive breastfeeding, among others, stand out.[8] In this way, child development results from processes involving complex neural pathways, which are susceptible to environmental, social, and potential pathological influences.[1,2]

Studies report that neurodevelopmental alterations in children infected with HIV are mainly due to the direct action of the virus on the central nervous system, given its neurotropism, but also to contributing factors related to maternal Aids (e.g., stage of the mother's illness, presence of opportunistic infections, nutritional status, among others), in addition to the use of alcohol and drugs during pregnancy, which can lead to prematurity, low birth weight, and longer hospitalization after birth. As well as socioeconomic conditions, such as the physical environment and unfavorable caregiving practices, including violence, orphanhood, lack of access to healthcare, social vulnerability, low educational level, and limited parental knowledge about child development.[3–6]

With the widespread access of pregnant women to antiretroviral therapy (ART), the number of children exposed to HIV during pregnancy but not infected has been increasing, and despite being limited, studies have also indicated neurodevelopmental alterations in these children.[7,8] However, the literature remains unclear regarding the prevalence of neurodevelopmental alterations when comparing HIV-exposed but uninfected children (HEU), HIV-exposed and infected children (HEI), and HIV-unexposed and uninfected children (HUU).

In this context and aiming to contribute to the elucidation of factors involved in neurodevelopmental alterations in children—whether infected or not—born to HIV-positive mothers, this study seeks to compile scientific literature on the topic, identify gaps, and systematically understand the main findings. Thus, the objective of this study was to map the existing literature on the influence of HIV exposure during pregnancy on child neuropsychomotor development.

METHODS

The present study follows a scoping review design and adhered to the recommendations of PRISMA-ScR and the Joanna Briggs Institute Manual for Evidence Synthesis for Scoping Reviews. The study was registered on the Open Science Framework (OSF) platform (10.17605/OSF.IO/3X69R).[9,10]

To address the research question and develop the eligibility criteria, the PCC strategy was used, where the Population refers to children aged zero to six years; the Concept, to neuropsychomotor development; and the Context, to children born to HIV-positive mothers during pregnancy. Thus, the guiding question was: “Do children aged zero to six years, born to HIV-positive mothers during pregnancy, present delays in neuropsychomotor development?”

The searches were conducted in PubMed, Embase, SciELO, LILACS, the Brazilian Digital Library of Theses and Dissertations (*Biblioteca Digital Brasileira de Teses e Dissertações* - BDTD), Web of Science, CINAHL, and OpenGrey on December 17, 2022, with no language restrictions, using the following strategy adapted for each database: ((Infant OR Child OR "Preschool Children") AND (HIV OR Aids OR "Human Immunodeficiency Virus" OR "Aids Virus" OR "HIV Infection") AND ("Child Development" OR "Infant Development" OR "Development, Infant" OR "Developmental Disabilities" OR "Disabilities, Developmental" OR "Developmental Disability" OR "Child Development Disorder" OR "Developmental Delay Disorders" OR "Child Development Deviations" OR "Child Development Deviation")).

The selection stage was carried out using the Rayyan tool by two blinded reviewers, through the reading of the title and abstract. In cases of discrepancies between the reviewers, a third reviewer was consulted. Subsequently, the texts were read in full, applying the following inclusion criteria: observational studies (cross-sectional and cohort), involving children aged between zero and six years, that assessed some domain of neuropsychomotor development and confirmed maternal HIV seropositivity during pregnancy.

For the extraction of results from the eligible studies, a data extraction spreadsheet was designed by the third reviewer and validated by the two reviewers. The results were individually extracted by the two reviewers and then compared and unified by the third reviewer. Possible discrepancies were resolved through consensus meetings, led by the third reviewer. The data extracted from the selected studies included the authors' names, year of publication, country where the research was conducted, sample characteristics, the tests or types of neurodevelopmental assessment used, and the main findings. The results were presented narratively in the text and through tables.

The methodological quality assessment was carried out by two reviewers, and in cases of discrepancies, a third reviewer was consulted. The research protocols from The Joanna Briggs Institute (10.46658/JBIMES-24-09) were used, specifically the Checklist for Analytical Cross Sectional Studies, consisting of eight questions, and the Checklist for Cohort Studies, consisting of eleven questions. In the final scoring of the Checklist for Analytical Cross Sectional Studies, the risk of bias can be considered high for studies that received up to 49% of the responses marked as "yes" (0 to 3.92), moderate when the study received 50% to 69% (4 to 5.52), and low when the study received more than 70% of the responses marked as "yes" (6.4 to 8 points). In the final scoring of the Checklist for Cohort Studies, the risk of bias can be considered high for studies that received up to 49% (0 to 5.39) of the responses marked as "yes," moderate when the study received 50% to 69% (5.5 to 7.59), and low when the study received more than 70% (7.7) of the responses marked as "yes".[10]

RESULTS E DISCUSSION

After the database search, 4,625 articles were found, with 682 duplicates removed. After exclusion based on title and abstract screening, 166 articles remained for full-text reading, of which 73 were selected (Figure 1).

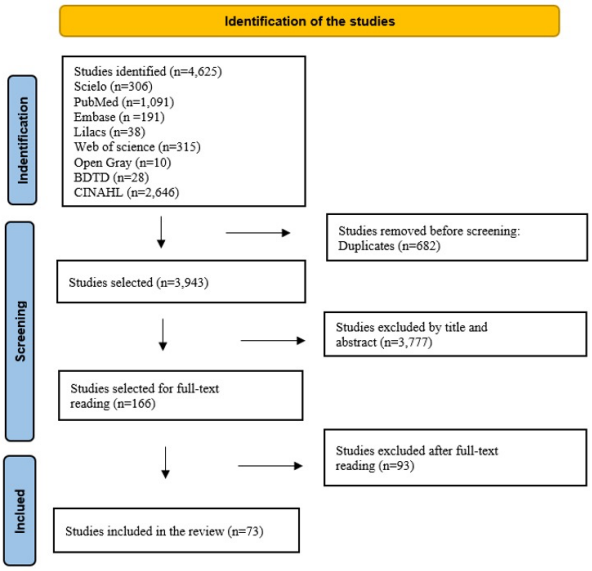

Figure 1. Flowchart of article search and selection.

The oldest study was from 1992 and the most recent from 2021. The studies were conducted on three continents — America, Africa, and Asia — in 20 different countries: South Africa,[12–31] Botswana,[32–35] Brazil,[36–39] Canada,[40–42] Colombia,[43] China,[44] United States,[45–50] United States and Puerto Rico,[51–55] Haiti,[56] India,[57] Iran,[58,59] Malawi,[60] Kenia,[61–64] Democratic Republic of the Congo,[65] Rwanda,[65] Thailand,[66,67] Tanzania,[68,69] Uganda,[11,70–75] Zaire, currently the Democratic Republic of the Congo,[76] Zâmbia,[76] Zimbabwe,[77–80]. Puerto Rico was counted as a country because it is an unincorporated territory of the United States, and Zaire was counted as Congo (Frame 1).

Frame 1. Articles included in the review.

Author (year)	Place	Sample	Protocols	Main Results
Aylward et al. (1992)[81]	United States	96 HEI = 12 HEU = 39 HUU = 45	BSID	Children in the HEI group showed significantly poorer performance in NPMD compared to children in the HEU and HUU groups.
Msellati et al. (1993)[67]	Rwanda	436 HEI = 50 HEU = 168 HUU = 218	Own Protocol	Children in the HEI group exhibited developmental delays more frequently than those in the HEU and HUU groups, with the delays being associated with the stage of Aids.
Chase et al. (1995)[45]	United States	51 HEI = 24 HEU = 27	BSID	The children were assessed at two time points. Motor delay was significantly worse in the HEI group at both time points, and cognitive delay was significantly worse in the HEI group at the second time point. Thus, early and persistent motor developmental delay, along with cognitive developmental deceleration, distinguish HEI from HEU.
Boivin et al. (1995)[76]	Zaire (Congo)	50 HEI = 14 HEU = 20 HUU = 16	ECSP and DDST	Children in the HEI group have significant deficits in NPMD compared to children in the HEU and HUU groups
Gay et al. (1995)[56]	Haiti	126 HEI = 28 HEU = 98	BSID	Over the first 24 months of life, the average developmental rate of infants in the HEI group is significantly slower than that of infants in the HEU group, with differences between the groups increasing over time.
Pollack et al. (1996)[49]	United States	91 HEI = 22 HEU = 42 HUU = 27	BSID	The delay in the NPMD for the HEI group, compared to the other groups, was first observed at 12 months and was correlated with the increase in viral load. It suggests that early intervention with potent antiretroviral agents aimed at reducing HIV viral load may mitigate the effects of HIV on growth and NPMD.
Drotar et al. (1999)[70]	Uganda	410 HEI = 61 HEU = 234 HUU = 115	BSID	The infants in the HEI group showed poorer performance on motor and cognitive assessments and experienced greater developmental deceleration compared to infants in the HEU and HUU groups.
Knight et al. (2000) [48]	United States	45 HEI = 20 HEU = 25	BSID	Infants in the HEI group had significantly lower BSID scores at baseline (cognitive development) and at follow-up (motor development) compared with those in the HEU group. When HIV infection and neurological deficits were considered together, HIV-positive children with neurological deficits scored significantly lower than HIV-positive children without neurological deficits and those in the HEU group, with and without neurological diagnoses. It suggests that CNS involvement is a critical pathway through which HIV affects the neurodevelopment of infants.
Chase et al. (2000)[55]	United States and Puerto Rico	595 HEI = 114 HEU = 481	BSID	A significant proportion of HEI children showed early cognitive and motor delay or decline, which may be important indicators for monitoring the early progression of HIV.
Smith et al. (2000)[54]	United States and Puerto Rico	114 HEI = 114	BSID	Early HIV infection increases the risk of developmental impairment during the first 30 months of life.

Author (year)	Place	Sample	Protocols	Main Results
Holditch-Davis et al. (2001)[47]	United States	81 HEU = 81	BSID-II	The quality of parenting and the consistency of the primary caregiver influence the developmental outcomes of HEU children.
Bruck et al. (2001)[39]	Brazil	150 HEI = 43 HEU = 40 HUU = 67	DDST and CAT/CLAMS	Hyperactivity, irritability, and hypotonia were the findings on neurological examination, with no statistical differences between the HEI and HEU groups. In the CAT/CLAMS, the developmental quotient of the HEI group was significantly lower than that of the other groups. The same occurred in the DDST, with the HEI group showing significantly more abnormalities than the HEU group.
Gontijo et al. (2001)[36]	Brazil	28 HEI = 11 HEU = 3 HUU = 14	DDST and BSID	HEI children exhibit NPMD delay compared to HUU children of the same age, socioeconomic level, and demographic conditions.
Blanchette et al. (2001)[40]	Canada	50 HEI = 25 HEU = 25	BSID	Infants in the HEI group had significantly lower motor and cognitive scores compared to infants in the HEU group, and abnormalities on CT scan were associated with these delays.
Llorente et al. (2003)[51]	United States and Puerto Rico	157 HEI = 157	BSID	It suggests that low cognitive and psychomotor scores at 4 months are significant predictors of early mortality in HEI children.
Alimenti et al. (2006)[41]	Canada	63 HEU = 39 HUU = 24	BSID-II	Exposure of HEU children to highly active antiretroviral therapy (HAART) is not associated with changes in developmental measures."
Lindsey et al. (2007)[50]	United States	1204 Pré-TARV HEI = 54 HEU = 221 Pós-TARV HEI = 91 HEU = 838	BSID	In the pre-ART era, the mean cognitive and motor scores in HEI children under one year of age were significantly lower than those of HEU children and remained lower up to two years of age. After ART became available, cognitive and motor functioning in HEI children under one year of age remained significantly lower than that of HEU children. However, in a context of declining scores among HEU children, there was evidence of only limited improvement among HEI children compared to their uninfected peers. Among children who underwent Bayley II assessments before and after starting ART, there was a trend toward improved mental and motor scores following initiation of antiretroviral therapy.
Baillieu et al. (2008)[12]	South Africa	40 HEI = 40	BSID-II	Eighty-five percent showed motor developmental delay and 82.5% showed language delay. In HEI children, cognitive delay may occur due to disease progression and structural brain damage, while language delay may be attributed to neurological impairment, cognitive delay, or environmental deprivation.
Gómez et al. (2009)[43]	Colombia	43 HEU = 23 HUU = 20	DDST-II and BSID-II	Intrauterine exposure to HIV and antiretrovirals in HEU infants does not cause changes in NPMD.
Van Rie et al. (2009)[65]	South Africa	160 HEI = 35 HEU = 35 HUU = 90	BSID-II	At baseline, HEI children had the lowest average developmental scores, HUU children had the highest, and HEU children had intermediate average scores. After 1 year of treatment, HEI children achieved average motor and cognitive scores similar to HEU children, although lower compared to HUU children.
Hokjindee et al. (2010)[66]	Thailand	143 HEU = 53 HEI = 2 SS = 88	DDST-II	The risk of developmental delay was present in 15.4% of the total sample, with nutritional deficiency being more common than delays in NPMD among children born to HIV+ mothers.
Potterton et al. (2010)[13]	South Africa	122 HEI in HSP = 60 HEI without HSP = 62	BSID-II	Cognitive and motor development were severely affected at the beginning of the study, with 52% of the children exhibiting severe cognitive delay and 72% exhibiting severe motor delay. Children in the Home Stimulation Programme (HSP) showed significantly greater improvement in cognitive and motor development over time compared to children in the other group.
Ramos et al. (2011)[38]	Brazil	12 HEU = 12	DDST-II	About 50% of the children evaluated were at risk of delayed NPMD, which may be related not only to biological factors, such as exposure to HIV and ART during pregnancy, but also to the presence of adverse environmental factors that compromise NPMD.
Kandawasvika et al. (2011)[80]	Zimbabwe	598 HEI = 65 HEU = 188 HUU = 287 SS = 58	BINS	The high risk of delay in NPMD was twice as high in the HEI group compared to uninfected infants.
Lowick et al. (2012)[24]	South Africa	60 HEI = 30 HUU = 30	GMDS-ER	There was a 7.88 times higher probability of severe delay in the HIV-infected group. Early initiation of ART in HIV-infected infants may improve cognitive function in this group; however, intervention strategies that optimise early cognitive development for all children in the area need to be urgently considered.
Sirois et al. (2013)[53]	United States and Puerto Rico	423 HEU = 374 HUU = 49	BSITD-III	The results demonstrate the safety of using ART during pregnancy and the prenatal period. The mean Bayley-III scores for HIV-exposed and unexposed infants were similar and within age expectations.
McDonald et al. (2013)[69]	Tanzania	311 HEI = 31 HEU = 280	BSID-II	Infant HIV status, gestational age at birth, stunting, and weight loss were significant and independent correlates of cognitive and psychomotor development among infants born to HIV-infected women.
Manji et al. (2014)[68]	Tanzania	206 HEU = 206	BSITD-III	Daily multivitamin supplementation for HIV-exposed infants does not substantially improve NPMD outcomes at 15 months.
Whitehead et al. (2014)[25]	South Africa	55 HEU = 29 HEI = 26	BSITD-III	This study suggests that HIV-positive infants are delayed when compared to HEU infants. HAART may help to prevent further delay; however, it does not reverse the neurological damage already present.
Brahmbhatt et al. (2014)[71]	Uganda	329 HEI = 116 HEU = 105 HUU = 108	MSEL and ELC	HEI children were more likely to have developmental deficits in NPMD, and prolonged ART use potentially mitigated some of the neurodevelopmental deficits.
Ngoma et al. (2014)[79]	Zambia	200 HEU = 97 HUU = 103	FSDQ and CAT/CLAMS	The study did not find any differences in NPMD between the groups, nor did it observe any adverse effects in HEU children exposed to ART in utero and during one year of breastfeeding.
Dara et al. (2015)[60]	Malawi	33 HEI =33	BSITD-III	The hypothesis of milder neuropathology in individuals infected with the HIV Tat^CS variant was not confirmed in the HEI cohort.
Benki-Nugent et al. (2015)[64]	Kenia	99 HEI = 99	DDST	HIV disease progression, poor growth, and inadequate response to ART were associated with an older age at achieving developmental milestones in HEI infants.
Bass et al. (2016)[72]	Uganda	339 HEI = 118 HEU = 221	MSEL	No difference was observed in NPMD between HEI and HEU children. The results indicate that the child's initial home environment is associated with general cognitive development. Complex environments in the context of poverty and HIV can impact cognition and neurodevelopment.
Boivin et al. (2017)[73]	Uganda	221 HEU = 221	MSEL	Although the Mediational Intervention for Sensitizing Caregivers (MISC) programme demonstrated an improvement in the quality of caregiving, it did not yield better cognitive outcomes in children compared with training in health and nutrition.
Chaudhury et. al. (2017)[32]	Botswana	670 HEU = 313 HUU = 357	BSITD-III and DMC	HEU children performed equally well on neurodevelopmental assessments at 24 months compared to the HUU group.
Silva et al. (2017)[37]	Brazil	80 HEU = 40 HUU = 40	BSITD-III	Infants exposed to HIV and antiretroviral therapy exhibited appropriate cognitive and motor development during the first 18 months. However, the lower scores found, particularly at the 8th and 18th months for cognitive development, may indicate future problems, highlighting the need for systematic monitoring of this population.
Smith et al. (2017)[42]	Canada	64 HEU = 64	Wechsler-III and Vineland-2 and VMI	The results suggest that children exposed to HIV and antiretroviral therapy in utero and early life may experience late NPMD changes.

Author (year)	Place	Sample	Protocols	Main Results
Rajan et al. (2017)[57]	India	50 HEU = 41 HEI = 9	DASII	The development of HEU children was negatively affected by lower socioeconomic status and the presence of weight loss. Furthermore, the development of HEI children was negatively influenced by the presence of stunting, opportunistic infections, advanced disease stage, and shorter ART duration. We conclude that, with optimal care, the HEU group can achieve normal development, whereas a significant proportion of HEI children may continue to experience delayed development.
Shariat et al. (2017)[59]	Iran	75 HEI = 28 HUU = 47	WHO Milestone Chart and ASQ	Some NPMD disorders in HEI children were more frequent than in HUU children but can be stabilized with the use of ART and family guidance.
Benki-Nugent et al. (2017)[63]	Kenia	155 HEI = 63 HUU = 92	DDST	HIV-infected infants with viral suppression on ART had better recovery of developmental milestones than those without suppression; however, deficits persisted compared to uninfected infants.
Dalili et al. (2018)[87]	Iran	39 HEU = 39	WHO Milestone Chart e ASQ	The prevalence of NPMD disorders, including delays in language, motor, and social domains, was common among HEU children. As various environmental factors may be involved in the etiology of neurodevelopmental disorders, postnatal control and prevention are necessary.
Laughton et al. (2018)[26]	South Africa	109 HEI = 36 HEU = 34 HUU = 39	GMDS	Five-year neurodevelopmental outcomes in HIV-infected children who received early, time-limited ART were similar to those of uninfected controls, except in visual perception, where their scores were lower.
Rodriguez et al. (2018a)[28]	South Africa	69 HEU = 69	BSITD-III	This study highlights that not living with the male partner, not disclosing one's HIV status, and experiencing postpartum depression predicted cognitive delay; and diminished prenatal male involvement predicted motor development delay.
Rodriguez et al. (2018)	South Africa	72 HEU = 67 HEI = 5	BSITD-III	Early exposure to postnatal intimate partner violence was associated with cognitive delay and receptive communication delay in infants.
Le Roux et al. (2018)[29]	South Africa	521 HEU = 215 HUU = 306	BSITD-III	Young HEU children may be at increased risk of cognitive and motor delay, despite universal maternal ART and breastfeeding. Preterm infants may be more vulnerable.
Springer et al. (2018)[30]	South Africa	96 HEU = 58 HUU = 38	BSITD-III	There was no difference in NPMD at 12 months between HEU and HUU children. However, slight differences in neurological assessments and vocalization patterns indicate the need for follow-up evaluation at a later age.
Chaudhury et al. (2018)[33]	Botswana	598 HEU = 598	BSITD-III DMC	The neurodevelopment of HEU children at 24 months does not differ based on in-utero exposure to ART. Maternal ART combined with breastfeeding does not appear to have an adverse effect on neurodevelopment.
Kacanek et al. (2018)[34]	Botswana	197 HEU = 197	BSITD-III	Neurodevelopmental outcomes at 24 months for HEU children born to mothers with CD4 ≥ 200 were similar between HEU children randomized to receive dual-NRTI–based ART and those randomized to receive triple-NRTI–based ART. This study showed that ART has low toxicity in the short-term follow-up.
Wu et al. (2018) [44]	China	500 HEU = 250 HUU = 250	BSITD-III	HIV-exposed but uninfected children had significantly lower Bayley-III scores than HUU children.
Gómez et al. (2018)[62]	Kenia	74 HEI= 74	MDAT	It evaluated the influence of ART initiated within the first 48 hours after birth on neurodevelopment at six months of age. The children made significant gains in neurological development during six months of ART. Children who experienced better growth and immune recovery showed greater improvement. Immediate initiation of ART may improve neurodevelopment, in addition to supporting immune recovery and growth.
Ruiseñor-Escudero et al. (2018)[7]	Uganda	308 HEI = 87 HEU = 221	MSEL and COAT and ECVT	Neurodevelopmental scores among children aged 2 to 5 years infected with HIV were similar for subtypes A and D, with few potential differences in language production and memory outcomes that favored subtype A.
Familiar et al. (2018)[75]	Uganda	215 HEU = 75 HUU = 140	MSEL	HIV exposure is associated with lower scores in infant cognitive development.
Mebrahtu et al. (2018)[83]	Zimbabwe	397 HEU = 381 HEI = 16	MSEL	The results show an association between maternal mood and stress levels and cognitive functioning in HEU children, specifically in expressive language and visual reception domains.
Cassidy et al. (2019)[35]	Botswana	493 HEU = 493	BSITD-III	HEU children exposed in utero to efavirenz-based ART may have a higher risk of neurodevelopmental and socio-emotional deficits compared to children exposed to conventional ART.
Alcaide et al. (2019)[31]	South Africa	80 HEU = 80	BSITD-III	The results showed a risk of cognitive developmental delay associated with the use of ART during pregnancy and intimate partner violence.
Le Roux et al. (2019)[14]	South Africa	214 HEU = 214	BSITD-III	Maternal cumulative HIV viremia during pregnancy may have adverse effects on neurodevelopment in HEU children.
Wedderburn et al. (2019)[15]	South Africa	At 6 months (n = 260) HEU = 61 HUU = 199 At 24 months (n = 732) HEU = 168 HUU = 564	BSITD-III	HEU children exposed in utero to maternal ART may have a higher risk of delays in receptive and expressive language development at 24 months compared to HUU children.
Pamplona et al. (2019)[84]	Brazil	118 HEU = 60 HUU = 58	DDST-II	Maternal HIV-1 infection negatively affected neuropsychomotor development in children, although other factors may have influenced this outcome. A child diagnosed with HIV had the worst outcomes.
Jantarabenjakul et al. (2019)[85]	Thailand	150 HEI = 50 (HEI = 27 children with immediate ART upon diagnosis and HEI = 23 late ART) HEU = 100	MSEL	Preschool-aged HEU children who initiated ART within the first 3 months of life exhibited a global developmental delay rate comparable to that of HUU children.
Cox et al. (2020)[16]	South Africa	60 HEU =30 HUU = 30	BSITD-III	In utero exposure to HIV and ART appears to have minimal impact on child development.
Cornelia de Beer et al. (2020)[17]	South Africa	81 HEU = 41 HUU = 40	Vineland-3	The developmental outcomes of HEU children during early childhood are not significantly different from those of the HUU group.
Gruver et al. (2020)[18]	South Africa	922 HEU = 257 HUU = 627 HEI = 38	K-ABC	The HEU group does not differ from the HUU group in their cognitive and language profiles between 4 and 6 years of age, but HEI children had significantly lower scores.
Springer et al. (2020)[19]	South Africa	59 HEU = 32 HUU = 27	BSID	HIV exposure did not confer additional risk to neurodevelopment. Growth delay was associated with increased behavioral problems, regardless of HIV exposure

Author (year)	Place	Sample	Protocols	Main Results
Strehlau et al. (2020)[20]	South Africa	49 HEU = 49	BSITD-III	No developmental delay was found at 12 months of age among HEU children exposed to maternal ART.
White et al. (2020)[21]	South Africa	54 HUU = 22 HEU = 32	GMCD	The main findings showed that there was no significant difference between HUU and HEU infants in the proportion who achieved neurodevelopmental milestones at 1–3 months of age. By 3–5 months of age, most infants achieved the expected developmental milestones. However, HUU infants exhibited difficulties with receptive language milestones, gross motor development, and play behavior during 1–3 months of age, whereas HEU infants faced challenges in fine motor milestones between 3–5 months.
Jao et al. (2020)[52]	United States and Puerto Rico	678 HEU = 678	BSITD-III	HEU children born to mothers with perinatally acquired HIV did not show an increased overall risk of cognitive developmental deficits during the first year of life, compared to HEU children born to mothers who did not acquire HIV perinatally. The differences (modest but significant) occurred in language and motor development.
Mebrahtu et al. (2020)[78]	Zimbabwe	514 WS = 514	MSEL	There is a strong association between NPMD alterations and children whose mothers have conditions such as depression and anxiety.
Ntozini et al. (2020)[77]	Zimbabwe	1380 HEU = 205 HUU = 1175	MDAT	Language and motor skills at two years of age were lower among HEU children compared to HUU children.
Sevenoaks et al. (2021)[22]	South Africa	267 HEU = 77 HUU = 190	BSITD-III	Maternal HIV infection is associated with immune dysregulation, with results indicating suppressed serum inflammatory markers in HIV-positive mothers and HEU children up to two years of age. Results also show that an altered immune system in HEU infants is associated with poorer motor development in children at two years.
Matseke et al. (2021)[23]	South Africa	160 WS = 160	BSITD-III	High levels of delay were detected in cognitive, communicative, fine motor, and gross motor development in children born to HIV-positive mothers.
Mchenry et al. (2021)[61]	Kenia	172 HEI = 24 HEU = 74 HUU = 74	BSITD-III	No statistically significant differences were found among the three groups (HEI, HEU, and HUU) in the assessed skills (cognition, expressive language, fine and gross motor), with the exception that children who were HIV+ were found to have higher receptive language scores than others.
Sirajee (2021)[11]	Uganda	170 HEU = 170	MDAT	Delayed growth in HEU children was associated with poorer attainment of developmental milestones at 18 months.

Abbreviations: HEI = HIV-positive children born to HIV-positive mothers during pregnancy // HEU = HIV-negative children born to HIV-positive mothers during pregnancy // HUU = HIV-negative children born to HIV-negative mothers during pregnancy // WS = children without serology, born to HIV-positive mothers // BSID = Bayley Scales of Infant Development // BSID-II = Bayley Scales of Infant Development, Second Edition // BSITD-III = Bayley Scales of Infant and Toddler Development, third edition // BINS = Bayley Infant Neurodevelopmental Screener // ECSP = Early Childhood Screening Profiles // DDST = Denver Developmental Screening Test // DDST- II = Denver II Development Screening Test //CAT/CLAMS = Clinical Linguistic and Auditory Milestone Scale // MSEL = Mullen Scales of Early Learning // ECSP = Early Childhood Screening Profiles // PLS-3 = Preschool Language Scale, Version 3 // VABS = Vineland Adaptive Behavior Scale // CAT/CLAMS = Capute Scales Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale // GMDS-ER = Griffiths Mental Development Scales-Extended Revised Version // ELC = Early Learning Composite // FSDQ = Capute Full-Scale Developmental Quotient // DMC = Development Milestones Checklist // DASII = Development Assessment scale for Indian Infants // Vineland-3 = Vineland Adaptive Behavior Scales, Third Edition // Wechsler-III = Wechsler Preschool and Primary Scale of Intelligence 3rd edition // Vineland-2 = Vineland Adaptive Behavior Scales 2nd edition // VMI = Developmental Test of Visuomotor Integration // WHO = World Health Organization Milestones Chart // ASQ = Age and Stage Questionnaire // GMCD = Guide for Monitoring Child Development // MDAT = Malawi Developmental Assessment Tool // COAT = Color Object Association Test // ECVT = Early Childhood Vigilance Test // K-ABC = Kaufman Assessment Battery for Children // GMDS = Griffiths Mental Development Scales // K-ABC = Kaufman Assessment Battery for Children // FSDQ = Capute Full-Scale Developmental Quotient // DASII = Development Assessment scale for Indian Infants // DMC = Development Milestones Checklist.

It was observed that the studies presented various configurations of study groups with the aim of analyzing neuropsychomotor development. A total of 18,043 children were evaluated, divided into groups according to the serological status of the child and the mother, as follows: HEI – HIV-positive children born to HIV-positive mothers during pregnancy (n = 2,119); HEU – HIV-negative children born to HIV-positive mothers during pregnancy (n = 9,624); HUU (control group) – HIV-negative children born to HIV-negative mothers (n = 5,481); and WS – children without HIV serology, born to HIV positive mothers (n = 820). The largest group consisted of HIV negative children born to HIV positive mothers.

The studies that compared HEI, HEU, and HUU numbered 12. Those that evaluated only HEI numbered seven; those that evaluated only HEU numbered 15; those that compared HEI with HEU numbered 12; those comparing HEI with HUU numbered six; and those comparing HEU with HUU numbered 18. And the studies that compared all three groups (HEI, HEU, and HUU) numbered 12, including one study with only WS, one comparing HEU, HEI, HUU and WS, and one study comparing HEU, HEI and WS.

To assess neuropsychomotor development, the majority of studies (60.3%, n = 44) used the Bayley Scales of Infant Development in various editions, followed by the Denver Developmental Screening Test (12.3%, n = 9) and the Mullen Scales of Early Learning (10.9%, n = 8). However, a variety of other protocols were also used, namely: Early Childhood Screening Profiles (ECSP); Preschool Language Scale, Version 3 (PLS 3); Vineland Adaptive Behavior Scale (VABS); Capute Scales Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS); Griffiths Mental Development Scales-Extended Revised Version (GMDS-ER); Early Learning Composite (ELC); Capute Full-Scale Developmental Quotient (FSDQ); Development Milestones Checklist (DMC); Development Assessment Scale for Indian Infants (DASII); Vineland Adaptive Behavior Scales, Third Edition (Vineland-3); Wechsler Preschool and Primary Scale of Intelligence 3rd edition (Wechsler-III); Vineland Adaptive Behavior Scales 2nd edition (Vineland-2); Developmental Test of Visuomotor

Integration (VMI); World Health Organization (WHO) Milestones Chart; Age and Stage Questionnaire (ASQ); Guide for Monitoring Child Development (GMCD); Malawi Developmental Assessment Tool (MDAT); Color Object Association Test (COAT); Early Childhood Vigilance Test (ECVT); Kaufman Assessment Battery for Children (K-ABC); Griffiths Mental Development Scales (GMDS).

Of the 73 studies included in this scoping review, 51 (69.9%) assessed children infected with HIV who were born to HIV-positive mothers, and in all of these studies, the children exhibited significant delays in NPMD, in comparison to both HEU and HUU children. When the studies assessing NPMD of HIV-negative children born to HIV-positive mothers were analyzed, the findings were controversial. Some studies observed NPMD alterations in HEU children when compared to HUU children, while others did not observe differences between the development of HEU and HUU children.

In the methodological quality assessment, the risk of bias was considered low in 69.9% of studies and moderate in 30.1%. (Table 2).

Table 2. Methodological quality assessment of the studies.

AUTHOR(YEAR)	TYPE	MQA	
Baillieu et al. (2008)	CACSS	5.75	Moderate
Van Rie et al. (2008)	CACSS	6.5	Low
Potterton et al. (2010)	CSS	8.5	Low
Hilburn et al. (2011)	CACSS	4.5	Moderate
Lowick et al. (2012)	CACSS	8.75	Low
Whitehead et al. (2014)	CCS	8.75	Low
Boyede et al. (2016)	CACSS	6.5	Low
Strehlau et al. (2016)	CCS	6.75	Moderate
Knox et al. (2018)	CCS	7	Moderate
Laughton et al. (2018)	CCS	10.25	Low
Rodriguez et al. (2018)	CACSS	7.5	Low
Rodriguez et al. (2018)	CACSS	8	Low
Roux et al. (2018)	CCS	9	Low
Springer et al. (2018)	CCS	8	Low
Alcaide et al. (2019)	CACSS	7.25	Low
Roux et al. (2019)	CCS	8.25	Low
Wedderburn et al. (2019)	CCS	9.5	Low
Cox et al. (2020)	CACSS	5.5	Moderate
Beer et al. (2020)	CACSS	6.5	Low
Gruver et al. (2020)	CACSS	8	Low
Rodriguez et al. (2020)	CACSS	7	Low
Springer et al. (2020)	CCS	9.25	Low
Streahlau et al. (2020)	CCS	8	Low
White et al. (2020)	CCS	8.75	Low
Sevenoaks et al. (2021)	CCS	10	Low
Matseke et al. (2021)	CCS	7.5	Moderate
Chaudhury et al. (2017)	CCS	10.25	Low
Chaudhury et al. (2018)	CCS	8	Low
Kacanek et al. (2018)	CCS	9	Low
Cassidy et al. (2019)	CCS	7	Moderate
Bruck et al. (2001)	CCS	7	Moderate
Gontijo et al. (2001)	CACSS	6	Moderate
Ramos et al. (2011)	CACSS	5	Moderate
Silva et al. (2017)	CACSS	6.5	Low
Pamplona et al. (2019)	CCS	8	Low
BlanHEUtte et al. (2001)	CACSS	5.25	Moderate
Alimenti et al. (2006)	CACSS	7.5	Low
Smith et al. (2017)	CCS	8.75	Low
Gómez et al. (2009)	CCS	8.5	Low
Wu et al. (2018)	CCS	7.75	Low
Aylward et al. (1992)	CCS	10	Low
Chase et al. (1995)	CCS	10	Low
Pollack et al. (1996)	CCS	8	Low
Knight et al. (2000)	CCS	9.5	Low
Holditch-Davis et al. (2001)	CCS	10.5	Low
Lindsey et al. (2007)	CCS	7	Moderate
Williams et al. (2010)	CCS	7	Moderate
Chase et al. (2000)	CCS	10.5	Low
Smith et al. (2000)	CCS	8	Low
Llorente et al. (2003)	CCS	10	Low
Sirois et al. (2013)	CCS	7.5	Moderate
Jao et al. (2020)	CCS	7.5	Moderate
Gay et al. (1995)	CCS	9	Low
Rajan et al. (2017)	CCS	8.25	Low
Shariat et al. (2017)	CCS	6.75	Moderate
Dalili et al. (2018)	CCS	7.25	Moderate
Dara et al. (2015)	CCS	10.5	Low
Nugent et al. (2015)	CCS	8	Low
Nugent et al. (2017)	CCS	10.25	Low
Gómez et al. (2018)	CCS	9	Low
Mchenry et al. (2021)	CACSS	6.25	Moderate
Van Rie et al. (2009)	CCS	7.25	Moderate
Msellati et al. (1993)	CCS	7.25	Moderate
Hokjindee et al. (2010)	CCS	8.25	Low
Jantarabenjakul et al. (2019)	CCS	8.75	Low
McGrath et al. (2006)	CCS	8	Low
McDonald et al. (2013)	CCS	8	Low
Manji et al. (2014)	CCS	9	Low
Drotar et al. (1999	CCS	9	Low
Brahmbhatt et al. (2014)	CCS	8.25	Low
Bass et al. (2016)	CCS	7.5	Moderate
Boivin et al. (2017)	CCS	8	Low

Abbreviations: MQA = Methodological quality assessment // Type = type of protocol used // CCS = checklist for cohort studies // CACSS = checklist for analytical cross-sectional studies.

This study aimed to understand how HIV influences neuropsychomotor development in both children who were exposed to the virus in utero and became infected, as well as in children who were only exposed in utero but did not become infected. For this purpose, the articles selected in this review present studies that evaluate the neuropsychomotor development of children who were exposed but uninfected (HEU), exposed and infected (HEI), and children who are neither exposed nor infected (HUU).

Among the groups addressed in this research, the most vulnerable to alterations in neuropsychomotor development (DNPM) was the group of children who were exposed to and infected with HIV and who were not using antiretroviral therapy. Several studies have demonstrated deficits in neurodevelopment in the HEI children. The studies that associated child development with the use of ART observed that the earlier the infant begins ART, the fewer the impairments in neuropsychomotor development (especially when the viral load becomes undetectable), and that even in cases of later initiation, ART is beneficial and helps prevent further delays, although it does not reverse neurological damage already present.[25,49,63]

Additionally, the studies show that developmental alterations can be identified as early as in the first months of life and are directly related to Aids

progression, such that they are even used as one of the parameters for monitoring disease evolution and severity and for classifying HIV infection according to the Centers for Disease Control and Prevention (CDC).[55,67]

Delay in neuropsychomotor development can occur due to disease progression and brain structural damage resulting from the direct action of the virus in the central nervous system, as well as exposure to environmental risk factors.[12] Studies have confirmed neurological deficits and the virus's damaging action in the CNS in infected children, linked to developmental alterations, demonstrating the neurotropism of the virus.[81,82]

To understand neuropsychomotor development and the mechanisms that can alter its progression, it is necessary to also analyze the factors that may influence this process beyond HIV itself. The researchers highlighted the effects of the home environment in which the child is raised within a context of poverty and HIV, socioeconomic status, maternal schooling, the child's nutritional status, maternal mood and stress levels in HIV-positive mothers, maternal depression, parental separation, maternal death, and low income on the overall cognitive development of infected infants.[56,72,83,84]

The authors emphasized the importance of strategies to reduce vertical transmission, promote child growth, prevent preterm birth, and ensure follow up monitoring of the development of these children.[36,48,69] The main way to reduce or even eliminate the influence of HIV on neuropsychomotor development in infected children nowadays is antiretroviral therapy (ART). According to the literature, when evaluating and comparing children exposed and infected with HIV who started ART early, with groups of uninfected HIV-exposed children and unexposed children over an extended period, it was shown that HEI had similar outcomes compared to HUU, even demonstrating restoration of neurodevelopment and viral suppression, thereby highlighting the importance of early intervention with ART. Other factors have been cited in this regard, such as the importance of nutritional and social support, as well as improvements in motor and cognitive development associated with early intervention.[23,63,85,65]

Several studies suggest that prenatal and postnatal exposure (up to the first 25 months of life in children exposed to HIV) to antiretroviral therapy is not associated with alterations in neuropsychomotor developmental skills.[20,26,29,34,41,42,79,86] A study conducted in Kenya that used delayed antiretroviral therapy intervention for a period of six months achieved significant gains in gross and fine motor functioning, growth, and immune system performance.[62] However, language and social functioning did not improve overall; even with the gains observed, the scores still remained below African norms, which corroborates findings from other studies. These studies help us understand how early intervention makes a difference, but also what benefits delayed intervention can bring.[50,71]

Although infants' exposure to an excess of medications brings benefits, it still requires caution due to their potential toxicity. The study conducted in Botswana enrolled a total of 493 children at 24 months of age to evaluate the neuropsychomotor development of HEU infants who had in utero exposure to Efavirenz (EFV)-based triple antiretroviral therapy. This study found an association between EFV exposure and reduced scores in receptive language as well as gross and fine motor skills.[35] A study evaluating children at around 24 months also found alterations in receptive and expressive language abilities among HEU children. When language skills are impaired, they are a strong risk factor for children exposed to HIV, as they lead to future learning disadvantages.[82,73]

The results of a Canadian study suggest that children with early exposure to ART may have inferior neurocognitive performance compared with their peers at the end of preschool.[24] The authors state that, despite ART and breastfeeding, children may have an increased risk of delay in cognitive and motor development. However, researchers cite that the use of ART during pregnancy, combined with breastfeeding, outweighs the possible risks for children exposed to HIV. However, the importance of programs for prevention of vertical transmission is emphasized. A study carried out in Zimbabwe with 540 children evaluated a vertical transmission prevention program, and the results showed a prevalence of 9.4% among the high risk HEI and HEU groups for neurodevelopmental impairment.[33,42,80]

Other studies have shown that antiretroviral therapy reduces the effects of HIV; however, when compared with HIV exposed children, a delay in neurodevelopment was observed.[42,45] A study that evaluated the neurodevelopment of children before the initiation of ART and after viral suppression promoted by the treatment identified a significant improvement in this aspect. However, a high prevalence of neurodevelopmental delays was observed, highlighting the need for additional interventions to enhance the outcomes achieved with ART. One example of an intervention that can help is the prevention program for mother-to-child transmission implemented in a 2010 study; this program encompassed everything from maternal antiretroviral therapy to free prenatal guidance courses for expectant mothers. Of the 143 children evaluated who participated in this program, only 2 (1.3%) tested positive for HIV. Another example is the home-based intervention program focused on caregiving, discussed by authors, which can bring

significant improvements to cognitive and motor development.[21,30,66]

When comparing the HEI and HEU groups, researchers reported that during the first two years, developmental delays occurred more frequently in infected children than in exposed children; these children even showed outcomes similar to those of uninfected and unexposed children.[57,67]

Unlike the group of HIV-exposed and infected children, where neurodevelopmental impairment is more prevalent, studies observe that HIV-exposed but uninfected children may exhibit more subtle changes or no neuropsychomotor development alterations. Some studies comparing HEU with HUU children assessed neurodevelopmental skills in children aged 12 months to 6 years, some of whom were socioeconomically matched and others were not, and no significant differences were found between the groups.[25,27,28,31,87]

However, other researchers focusing on children aged one month to two years exposed to HIV found significant differences demonstrating that HIV exposure can impair neuropsychomotor development skills, with alterations in the immune system associated with this impairment, highlighting the importance of early interventions for these children.[15,16,77]

An important issue for the group of HIV-exposed uninfected children is the biopsychosocial factors. Researchers have demonstrated that factors such as the presence of the father, antiretroviral use, intimate partner violence during and after pregnancy, parenting quality, maternal characteristics, caregiver consistency, maternal care quality, and common mental disorders (depression, anxiety, and somatic symptoms), when associated with HIV exposure in these children, can influence the skills that are part of the neuropsychomotor development.[17,47,75,78]

Despite the extensive literature on the subject and the quality of existing studies, researchers still cannot elucidate the true influence of HIV exposure and ART during pregnancy, as well as environmental factors, on the neurodevelopmental progress of HIV exposed, uninfected children; thus, new studies with greater control over the variables are needed. Given that the contributing factors remain unclear, it is important to highlight the need for long term monitoring of these babies who were exposed to HIV during in utero development, especially when we consider how rapidly ART use is expanding and the increasing variety of drugs being developed.

CONCLUSION

The studies analyzed showed that HIV exposure during pregnancy is not determinative of alterations in the neuropsychomotor development, instead, it is the HIV infection itself, given the action of the virus on the central nervous system. However, HIV-exposed children in utero, but uninfected, may also experience alterations in the neuropsychomotor development mainly associated with environmental factors, highlighting the importance of longitudinal monitoring of all children born to HIV-positive mothers, regardless of infection status.

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AUTHORS' CONTRIBUTIONS

Raphaela Barroso Guedes-Granzotti contributed to the conception, article design, critical analysis, and final draft of the article. **Matheus do Nascimentos Alves** contributed to the literature search, data collection, and writing of the article. **Lara Suzana de Oliveira Nunes** contributed to the literature search, data collection, and writing of the article. **Nathália Monteiro Santos** contributed to the literature search, data collection, and writing of the article. **Vinicius Nunes Araujo** contributed to the literature search, data collection, and writing of the article. **Carla Patrícia Hernandez Alves Ribeiro César** contributed to the conception, article design, critical analysis, and final draft of the article. **Kelly da Silva** contributed to the conception, article design, critical analysis, and final draft of the article.

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