

# POSSIBLE PREVENTION OF NEURODEVELOPMENTAL CONSEQUENCES OF VERTICAL HIV TRANSMISSION IN EARLY CHILDHOOD? A SYSTEMATIC REVIEW

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## SUMMARY

**Background:** Children infected with the Human Immunodeficiency Virus (HIV) exhibit the lowest neurodevelopmental scores. Mother-to-child-transmission prevention include perinatally and early antiretroviral therapy (ART) although long-term effects of in utero exposure to ART on neurodevelopment remain unclear. It was difficult to determine whether these reported neurodevelopmental scores were a direct result of HIV.

**Methods:** A systematic search was conducted to identify the environmental and neurobiological factors associated with HIV infection and their impact on neurodevelopment. It was carried out across four electronic databases: Scopus, PubMed, ProQuest and Cochrane Database of Systematic Reviews. We selected 15 articles published between 2012 and 2024.

**Results:** Regarding ART, 4 articles reported a positive effect of ART regardless of the age of initiation and duration. We couldn't identify caregiver distress as a risk factor.

**Conclusions:** Further research should include large cohort studies assessing long term consequences of ART exposition on children's neurodevelopment and impact of caregiver distress on child neurodevelopmental outcomes.

**Key words:** HIV - neurodevelopment/al – child – prevention - psychopathology

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## INTRODUCTION

Children infected with the Human Immunodeficiency Virus (HIV) exhibit the lowest scores in terms of neurodevelopment (Laughton et al. 2013). According to The Joint United Nations Program on HIV/AIDS (UNAIDS), the global number of children aged between 0 and 14 living with HIV in 2020 was 1.7 million. The main mode of HIV transmission in children is Mother-to-child-transmission (MTCT) and MTCT prevention include perinatally and early antiretroviral therapy (ART) although long-term effects of in utero exposure to ART on neurodevelopment remain unclear (Schnoll et al. 2021). Laughton et al. (2013) conclude that it was difficult to determine whether reported neurodevelopmental scores were a direct result of HIV since there is a scarcity of data regarding the effects of HIV infection on neurodevelopment of children. The critical phase of early childhood, as defined by the United Nations Children's Fund (UNICEF) to span from birth to 5 years, emerges as a pivotal timeframe for proactive interventions. In this study, we conduct a systematic review aiming to identify the environmental and neurobiological risk factors of neurodevelopmental disorders (NDD) in children aged 0 to 5 years who are living with HIV.

## SUBJECT AND METHOD

All analyses in this study were carried out in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al. 2009). Our search strategy was guided by the Patient-Intervention-Comparison-Outcome (PICO) question: "What are the risk factors associated with NDD in HIV-infected (HIV+) children aged 0 to 5 years, compared to those who are exposed (infected or not) during the same period?"

The systematic search was carried out across four electronic databases: Scopus, PubMed, ProQuest and Cochrane Database of Systematic Reviews. The search included articles published between 2012 and 2024. The authors screened the titles, abstracts, and full texts of the identified works. This screening process took place from July 2021 to September 2024.

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed: [https://www.crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42023411404](https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42023411404)

**Inclusion criteria:** randomized controlled trials, controlled clinical trials, cohort, case series, case-control, or cross-sectional studies, mean age under 5 years old children, infected by vertical transmission of

HIV with no history of neural or psychomotor anomalies were eligible for inclusion, an intervention intended to detect and prevent NDD, were included.

*Exclusion criteria:* articles published prior to 2012 (Figure 1).

## RESULTS

We selected 15 articles and 80% were conducted in sub-Saharan Africa (Table 1).

Most of the studies indicated that HIV+ children exhibited lower neurodevelopmental scores, particularly in cognitive and gross motor skills, compared to their respective comparison groups.

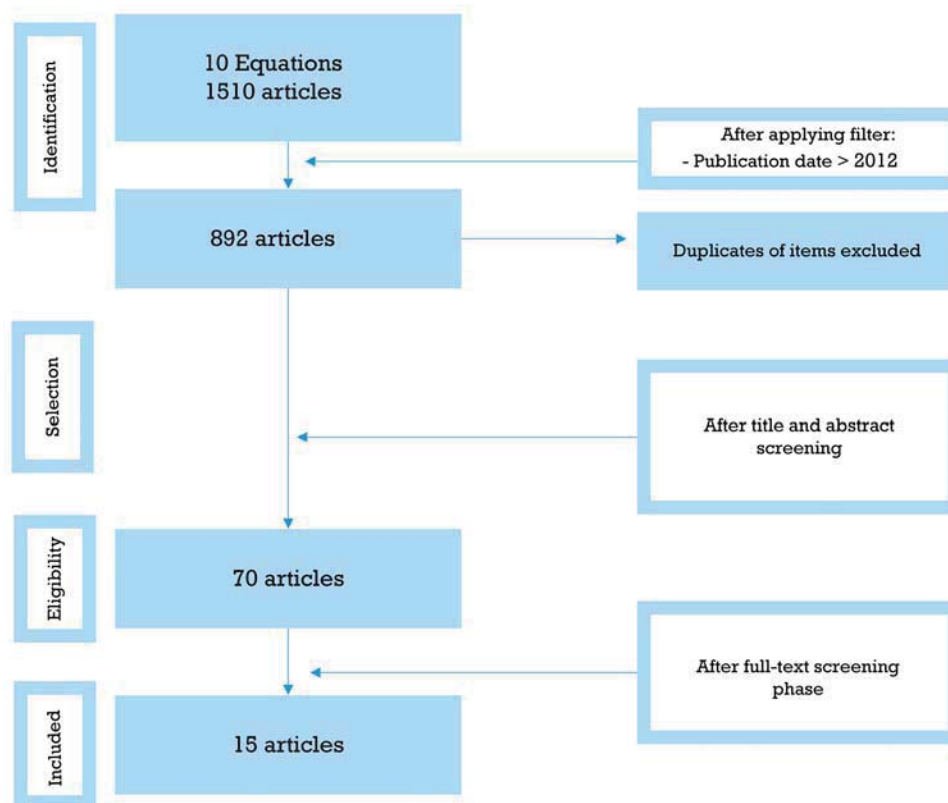
Data of our review didn't identify consensus regarding the effect of higher viral load on NDD development (Struyf et al. 2020; Strehlau et al. 2016; Benki-nugent et al. 2017; Chongwo et al. 2023).

Regarding ART, we identify a positive effect of ART on the neurodevelopmental scores, and it appears as positive regardless of the age of initiation and duration (Struyf et al. 2020; Potterton et al. 2016; Benki-Nugent et al. 2017; Laughton et al. 2019; Jantarabjenjakul et al. 2019). However, McHenry et al. (2018) systematic review reported a negative effect of ART. Regarding other significant risk factors of NDD associated with HIV infection, we identify a significant association between caregiver quality of care and neurodevelopmental outcomes, and we couldn't identify caregiver distress as a risk factor (Bass et al. 2016; Familiar et al. 2022; Mu oz et al. 2017). Our review identified also low levels of maternal education, a low socioeconomic status of the household, and the non-optimal health status of the caregiver (McHenry et al. 2019; Pamplona et al. 2019; Strehlau et al. 2016; Bass et al. 2017).

**Table 1.** Presentation of selected articles with studied location, number of studied children and Assessment Tools

Authors, year of publications	Location	Number of children	Child Development Assessment Tools
Bass et al. (2017)	Sub-Saharan Africa (Uganda)	118 children	MSEL, COAT, ECVT, The Behaviour Rating Inventory of Executive Function
Benki-Nugent et al. (2017)	Sub-Saharan Africa (Nairobi, Kenya)	165 children	Denver Developmental Screening Test
Chongwo et al. (2023)	Sub-Saharan Africa (Kilifi, Kenya)	153 children	A-not-B task, Wisconsin card sorting test, Number recall test, Big-small stroop test, Block design task, Picture vocabulary test
Dara et al. (2015)	Sub-Saharan Africa (Malawi)	33 children	BSID III
Familiar et al. (2021)	Sub-Saharan Africa (Uganda)	288 children	MSEL
Jantarabjenjakul et al. (2019)	Asia (Thailand)	150 children	MSEL
Laughton et al. (2019)	Sub-Saharan Africa (South Africa)	29 children	GMDS
McHenry et al. (2018)	20/45 from North America	/	BSID I ou II ou III
McHenry et al. (2019)	6/9 from Sub-Saharan Africa	/	/
Mu�oz et al. (2016)	South America (Lima, Peru)	14 children	ASQ-III
Pamplona et al. (2019)	South America (Brazil)	118 children	Denver-II test
Potterton et al. (2016)	Sub-Saharan Africa (South Africa)	68 children	GMSD
Strehlau et al. (2016)	Sub-Saharan Africa (South Africa)	195 children	ASQ
Strehlau et al. (2021)	Sub-Saharan Africa (South Africa)	161 children enrolled and 93 assessed with BSID-III	BSID III
Struyf et al. (2020)	Sub-Saharan Africa (Malawi)	555 children	BSID III BSID I ou II ou III

*Assessment Tools:* ASQ: Ages and States Questionnaire (% , < 75% = retarded); BSID III: The Bayley Scales of Infant Development Third Edition (The total score ranges from 40 to 160 and has a mean of 100 with a standard deviation of 15 (Bayley 2006). A total score below 89 indicates that the child is retarded (Bayley, 2006)); COAT: Color Object Association Test (number of items retained), Denver II-Test (score), ECVT: Early Childhood Vigilance Test (score); GMDS: The Griffiths mental development scales (The mean of the six sub-quotients and the GQ is 100 points (SD 16)); MSEL: Mullen Scales of Early Learning (total early learning score [M=100, SD=15])



**Figure 1.** PRISMA flow diagram. The diagram indicates the sequence of inclusion and exclusion of articles

## DISCUSSION

In this systematic review about prevention of NDD in HIV+ children aged 0 to 5 years, we found that HIV+ children had lower cognitive and gross motor skills scores compared to HEU children, which agrees with previous systematic review (Weddeburn et al. 2022). The Bayley Scales of Infant Development Third Edition (BSID-III) was the most frequently utilized tool in our review as Weddeburn et al. (2022) described when searching appropriate tools for developmental assessment in sub-Saharan African countries.

Our review couldn't identify exposure to HIV infection with or without ART as risks factors of NDD. Articles assessing long term consequences of ART on children found mixed results and confirmed our observation that actual evidence is insufficient to draw a firm conclusion (Schnoll et al. 2021). Schnoll et al. (2021) conduct controlled investigation of toxicity in human cells with stem cells technologies and we propose to investigate the impact of HIV with these technologies in today's context where ART permitted to decrease mortality rate of people living with HIV.

Interestingly, our review identified different psychosocial factors (non-optimal health status of the caregiver, quality of parental care and low socioeconomic status of the household) but the caregiver distress wasn't identified as a risk factor of NDD in HIV context. This surprising and possibly incomplete last result could be explained with the

challenge of maintaining distressed parent in long-term follow-up in HIV care resulting in a barrier to seek services for developmentally compromised children (Bhushan et al. 2022).

In an era where the dynamic interaction of environmental and genetic risks is no longer debated, our systematic review prompts us to propose interventions of mental health professionals. They could identify developmental disorders and coordinate psychosocial support within primary care settings, usually running cares in health-limited access countries.

### Strength and limits of our review

In our systematic review, owing to small sample sizes and lacks existing preventive literature, the conclusions drawn were constrained.

## CONCLUSION

Children infected with HIV exhibit the lowest scores in terms of neurodevelopment. It was difficult to determine whether these reported scores were a direct result of HIV. Our systematic review about prevention of NDD in HIV infected children aged 0 to 5 years, confirm that actual evidence is insufficient to draw a firm conclusion on long term consequences of ART. Interestingly, our review revealed different psychosocial factors, but the caregiver distress wasn't identified as a risk factor of NDD in HIV context. We

propose interventions of mental health professionals for identifying developmental disorders and coordinating psychosocial support. Further research should include large cohort studies assessing long term consequences of ART exposition on children's neurodevelopment and impact of caregiver distress on child neurodevelopmental outcomes.

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### Contribution of individual authors:

Johanna Muhigana formulated the first draft of the manuscript.

Rwego Antoine Gasasira contributed to the supervision of working hypothesis and data analysis.

H el ene Nicolis contributed to the supervision of working hypothesis, writing and editing the manuscript.

All authors approved the final version of the article before its submission.

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