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Neurodevelopmental Outcomes in Perinatally Acquired HIV: A Systematic Review and Meta-Analysis of Cognitive and Neuroimaging Findings

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 April 2026 and was last updated on 13 April 2026.

INTRODUCTION

Review question / Objective To systematically review and meta-analyze neurodevelopmental outcomes in children, adolescents, and young adults with perinatally acquired HIV (PHIV) compared with HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) controls. Specifically, (1) to pool cognitive outcomes across four pre-specified domains (global cognition, executive function, processing speed, and working memory) using random-effects meta-analysis; (2) to examine moderators including country income level and GNI per capita; and (3) to narratively synthesize CNS pathogenesis, neuroimaging biomarkers, and functional outcomes within a unified framework.

Rationale Neurodevelopmental outcomes (cognitive function, neuroimaging abnormalities, and functional impairment) in children, adolescents, and young adults with perinatally acquired HIV infection receiving combination antiretroviral therapy.

Condition being studied Neurodevelopmental outcomes (cognitive function, neuroimaging abnormalities, and functional impairment) in children, adolescents, and young adults with perinatally acquired HIV infection receiving combination antiretroviral therapy.

METHODS

Participant or population Children, adolescents, and young adults (mean age ≤ 26 years) with perinatally or vertically acquired HIV infection. Comparators included HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) controls.

Intervention Not applicable. This review examines the association between perinatal HIV infection (exposure) and neurodevelopmental outcomes. No specific intervention is evaluated. Evidence on combination antiretroviral therapy (cART) timing is synthesized narratively.

Comparator HIV-unexposed uninfected (HUU) children and HIV-exposed uninfected (HEU) children matched by age and setting. Additional comparators included sibling controls and population norms where available.

Study designs to be included Cross-sectional, cohort, case-control, and longitudinal observational studies published in the cART era (January 2006 onward). Randomized controlled trials reporting neurodevelopmental outcomes were also eligible. Reviews, editorials, case reports, and conference abstracts without adequate data were excluded.

Eligibility criteria This is another INPLASY form field – just paste directly from your §2.2:

Inclusion criteria: (1) Population: children, adolescents, or young adults (mean age ≤ 26 years) with perinatally or vertically acquired HIV; (2) Comparators: HIV-exposed uninfected (HEU), HIV-unexposed uninfected (HUU), siblings, or population norms; (3) Outcomes: standardized neurocognitive testing (executive function, processing speed, working memory, global cognition), neuroimaging (structural MRI, DTI, fMRI, MRS), CSF or plasma biomarkers of reservoir/inflammation/neuronal injury, psychiatric or behavioral symptoms, educational outcomes, or ART adherence/transition-related functioning; (4) Study design: cohort, cross-sectional, case-control, or longitudinal observational studies.

Exclusion criteria: Reviews, editorials, case reports, conference abstracts without adequate data, studies conducted prior to the cART era (before January 2006), and adult-predominant cohorts without separable PHIV data.

Information sources Five bibliographic databases were searched on 15 March 2026: MEDLINE/PubMed, Embase (Ovid), Web of Science Core Collection, Scopus, and PsycINFO (Ovid). Supplementary searches of bioRxiv and medRxiv preprint servers were performed on the same date. Reference lists of all included studies and three prior systematic reviews (Dahmani et al. 2024, Horton et al. 2025, Khobo et al. 2025) were hand-searched. No language restrictions were applied.

Main outcome(s) Pooled Hedges' g effect sizes from random-effects REML meta-analysis for four pre-specified cognitive domains: (1) global cognition, (2) executive function, (3) processing speed, and (4) working memory, each analyzed separately for PHIV versus HUU and PHIV versus HEU comparisons. Additional quantitative outcomes included digit span and Trail Making

Test Parts A and B. Heterogeneity was assessed with I^2 and τ^2 , and prediction intervals were reported for $k \geq 3$.

Quality assessment / Risk of bias analysis Risk of bias was assessed using Joanna Briggs Institute (JBI) critical appraisal checklists appropriate to each study design: the JBI Analytical Cross-Sectional Studies checklist (8 items) for cross-sectional studies and the JBI Checklist for Cohort Studies (11 items) for longitudinal cohort studies. Two reviewers (S.-K.C. and H.W.) independently rated each included study; discrepancies were resolved by discussion with a third reviewer (H.-P.W.). These assessments informed interpretation of heterogeneity, small-study bias, and the narrative synthesis.

Strategy of data synthesis Quantitative meta-analysis was performed using the metafor package (version 4.4) in R (version 4.3). Random-effects models with restricted maximum likelihood (REML) estimation were fit to precomputed study-level Hedges' g values using reported standard errors. For overlapping cohorts, one effect size per cohort, domain, and comparison was retained in the primary analysis. Pre-specified subgroup analyses examined high-income country (HIC) versus low- and middle-income country (LMIC) setting. Exploratory mixed-effects meta-regression examined GNI per capita as a continuous ecological moderator. Publication bias was assessed with funnel plots and Egger's regression for outcomes with $k \geq 10$. Sensitivity analyses included leave-one-out, AALPHI cohort wave replacement (Judd 2016 vs. Arenas-Pinto 2022), and construct-restricted executive-function analyses. Neuroimaging, biomarker, psychiatric, educational, and adherence outcomes were synthesized narratively following Synthesis Without Meta-analysis (SWiM) guidelines.

Subgroup analysis (1) Country income level: HIC versus LMIC subgroup meta-analyses were conducted for executive function, processing speed, and working memory versus HUU, with between-subgroup heterogeneity assessed by the Q-test for moderators (QM). (2) Comparator type: all four primary cognitive domains were analyzed separately for PHIV versus HUU and PHIV versus HEU comparisons. (3) Early ART: a planned subgroup meta-analysis by ART timing could not be meaningfully estimated because ART-initiation categories were sparsely and inconsistently reported across studies; ART-timing evidence was therefore synthesized narratively from randomized and longitudinal cohorts (CHER, PREDICT).

Sensitivity analysis (1) Leave-one-out analysis: each study was sequentially removed from HUU-referenced composite domain meta-analyses to assess whether any single study reversed the direction or significance of the pooled estimate. (2) AALPHI cohort wave replacement: for executive function and processing speed versus HUU, Judd et al. (2016) was retained as the primary AALPHI wave and Arenas-Pinto et al. (2022) was substituted as a sensitivity replacement to assess the impact of cohort-overlap adjudication. (3) Construct-restricted executive function: BRIEF-based or screening-derived executive measures were excluded to assess whether the pooled executive-function effect was robust to measurement heterogeneity, performed separately for HUU and HEU comparisons.

Country(ies) involved Taiwan.

Keywords perinatally acquired HIV; neurodevelopment; meta-analysis; executive function; processing speed; working memory; neuroimaging; systematic review.

Contributions of each author

Author 1 - Sheng-Kang Chiu - Investigation, data screening and selection, data extraction and validation, risk of bias assessment, writing – review and editing.

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Author 2 - Hsu-Pin Wang - Formal analysis, data extraction and validation, risk of bias assessment (third reviewer), writing – review and editing.

Author 3 - HSIHSIEN WEI - Conceptualization, methodology, investigation, data screening and selection, formal analysis, writing – original draft, supervision, project administration.

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